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

Report of the Panel

Addendum

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

- Annex A: Add.1
- Annex B: Add.2
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ANNEX G

TRANSCRIPT OF THE PANEL'S JOINT MEETING WITH SCIENTIFIC EXPERTS ON 27-28 SEPTEMBER 2006

27 September 2006, morning

Chairman

1. Good morning. I would like to welcome the parties, the Panel's experts and representatives of international organizations to this joint meeting of the two Panels; the Panel on *United States – Continued Suspension of Obligations in the EC Hormones Dispute*, referred to as WT/DS320, and the Panel on *Canada – Continued Suspension of Obligations in the EC Hormones Dispute*, referred to as WT/DS321. The experts with us today are Dr. Boisseau, Professor Boobis, Dr. Cogliano, Professor De Brabander, Professor Guttenplan and Professor Sippell. We have representatives from the secretariats of the three international institutions: the Codex Alimentarius Commission, the Joint FAO/WHO Expert Committee on Food Additives, known as JECFA, and the International Agency for Research on Cancer, known as IARC. The representatives are Dr. Angelika Tritscher, WHO JECFA Secretary, and Dr. Annika Wennberg, FAO JECFA Secretary, Dr. Kazuaki Miyagishima, Codex Secretary, and Dr. Cogliano, one of the Panel six experts, who is also head of the IARC's Carcinogen Identification and Evaluation Group.

2. May I now invite the heads of delegations of each party to introduce themselves and the other members of their delegations. I would appreciate if you could submit the list of your delegations' members to the Panel secretary if you have not done this already. The European Communities first please.

European Communities

3. Good morning. My name is Theofanis Christoforou. I am Principal Legal Advisor of the European Commission in Brussels and I will be functioning as the head of delegation for these two days. If you agree each member of the delegation will introduce himself or herself.

4. Good morning. My name is Thomas Jürgensen – I work for the European Commission.

5. Good morning. My name is Sybilla Fries. I am from the Legal Service of the European Commission, now based in Geneva.

6. Good morning Chair. My name is Gudrun Gallhoff. I work for the European Commission Directorate General Health and Consumer Protection.

7. Good morning. Brian Marchant of the Commission, working for DG Trade.

8. Good morning. Lothar Ehring, European Commission, DG Trade.

9. Good morning. My name is Lars Berner and I am with the EC delegation here in Geneva.

10. Gentlemen, this was the delegation as such, the officials, lawyers and other advisors. Now we have a long list of experts with us and will also allow each one of them to present themselves, starting from Mr. Dan Sheehan.

11. Daniel Sheehan from Daniel M. Sheehan & Associates.

12. Annie Sasco from the University of Bordeaux, cancer epidemiologist.

13. Manfred Metzler, Professor of Food Chemistry, University of Karlsruhe, Germany.

14. Niels Skakkebaek, Medical Professor, Growth and Reproduction, Copenhagen University.

15. Henrik Leffers, Microbiologist, Growth and Reproduction, Copenhagen.

16. Professor François Andre from the National Veterinary School of Nantes, National Reference Laboratory for Hormones, Ministry of Agriculture.

17. Alain Paris from National Institute for Agronomic Research. I specialize in metabolism of steroids.

18. Professor Heinrich Meyer, Technical University of Munich. I am the Chair of biochemistry and physiology at the Technical University. Thank you.

19. I am Professor Frederik Vom Saal of the University of Columbia, Missouri in the United States.

20. With the delegation are also representatives of the member States of the European Community, and if you agree they will present themselves. Thank you.

21. Jukka Pesola, Counsellor, Permanent Commission of Finland.

22. I am Christian Forwick from the German Mission in Geneva.

23. I am Sebastian Keyserlingk from the German Ministry of Agriculture.

24. I am Anders Christiansen from the Danish Mission, Geneva.

25. Luca Burmeister, Danish Mission to Geneva.

26. Lukas Paul from the German Mission here in Geneva.

27. Cédric Pène from the French delegation in Geneva.

28. Blas Vicente, Spanish Mission in Geneva

Chairman

29. Thank you. The United States please.

United States

30. Good morning Mr. Chairman, members of the Panel. My name is Jay Taylor with the US Trade Representative's Office. To my left is Dan Hunter with the US Trade Representative's Office here in Geneva. To my right is Dr. Adele Turzillo with the Food and Drug Administration. To Adele's right is Steve Wolfson with the Environmental Protection Agency. To his right is Kelly Stange with the Foreign Agricultural Service. To her right is George York with the US Trade Representative's Office here in Geneva. Across the table from George is Dr. Ralph Cooper with the Environmental Protection Agency. Next to Dr. Cooper is Rita Kishore with the US Department of Agriculture Food Safety and Inspection Service. Next to Rita is Dr. Richard Ellis, Consultant,

formerly of the Food and Drug Administration. And next to Richard is Dr. Gregg Claycamp with the Food and Drug Administration. Thank you.

Chairman

31. Then I give the floor to Canada.

Canada

32. Thank you Mr. Chairman. I am Rambod Behboodi, First Secretary here at the Canadian Commission to the WTO. Counsel with me today who will argue this case are to my left Mr. Rob McDougall at the Trade Law Bureau, and to my right Mr. Kevin Thompson, also of the Trade Law Bureau of the Department of Foreign Affairs and International Trade. The rest of the members of the delegation, from the far left, there is Angela Webb who is the Paralegal, Dr. Don Grant who is adviser to the Government of Canada. Next to Mr. Thompson we have Dr. Jim MacNeil who is head of the Centre for Veterinary Drug Residues of the Canadian Food Inspection Agency. We also have Ms. Michele Cooper, First Secretary at the Canadian Mission and Mr. Vasken Khabayan, who is Second Secretary at the Canadian Mission, and across from me Mr. Evan Lewis of the Technical Barriers and Regulations Divisions of the Department of Foreign Affairs and International Trade, and Mr. Bill Bryson of the Department of Agriculture. Thank you.

Chairman

33. Thank you. I would like to continue by introducing the members of the Panels. On my right is Ambassador William Ehlers, who is Ambassador of Uruguay to India. On my left is Madam Claudia Orozco, who is a former senior official of the Colombian Government and who is now working in Brussels as an independent consultant. And myself, Tae-yul Cho, serving as Chair of these Panels. I am Ambassador and Deputy Representative in the Korean Mission here in Geneva. The two Panels are composed of the same individuals and in agreement with the parties, we are holding a joint meeting with the experts consulted by the Panels.

34. I would also like to introduce the Secretariat officials who will be assisting the Panel: Mr. Yves Renouf, Legal Officer to the Panel; Ms Xuewei Feng, Secretary to the Panel, and Ms Gretchen Stanton, Ms Serra Ayral and Ms Christiane Wolff from the Agriculture and Commodities Division of the WTO Secretariat. Finally I would like to inform the parties of the presence of Mr. Walters Nsoh, Intern in the Agriculture Division and Ms Esther Katende, an intern with the WTO Legal Affairs Division.

35. As you all know, further to the parties' common request, the Panel has decided to hold this meeting with the experts open for observation by the public through a closed circuit TV broadcast. I would also welcome those who are observing this meeting from another room at this moment. I would like to remind the viewers who are observing this Panel meeting that tape-recording or filming during the Panel meetings by anyone other than the WTO Secretariat is not permitted. In order to ensure an orderly proceeding and as a courtesy to everyone, I also request everybody, including those participating in the Panel meeting and those observing the meeting of the Panel, to turn off their mobile phones during the whole meeting.

36. In addition I would like to underline that the parties may request that the public microphones be switched off when any confidential material or information is being discussed. Finally, if the meeting is adjourned or suspended, I will specify the time at which it will resume for the benefit of those in this room, but also for those viewing this hearing from CR II.

37. May I also remind you that the meetings of panels in the WTO are tape-recorded and that at today's meeting as well as the meeting of tomorrow, English/Spanish/French simultaneous interpretation will be provided in relation to the public broadcast of this hearing through closed circuit television into Room CR II at the request of the parties. So please be sure to use the microphones when addressing the Panel and above all, speak slowly. I would like to express my sympathy with the interpreters for this meeting considering its extremely technical nature. I would also like to remind the experts and the parties that there are constraints and difficulties of interpretation and therefore technical language will be properly interpreted only if it is delivered at the reasonable pace. To the extent possible, any prepared notes or statements should be shared with the interpreters so as to facilitate their task and ensure accurate interpretation.

38. Turning to a brief history of the Panels' proceedings, I wish to recall that at its meeting of 17 February last year the Dispute Settlement Body decided in accordance with Article 6 of the Dispute Settlement Understanding to establish two Panels pursuant to requests of the European Communities. I further recall that the Panels held a joint first substantive meeting with the parties and third parties on 12-15 September 2005.

39. After its first substantive meeting, the Panel decided on 20 October last year to consult with experts who have specialized scientific expertise on the issue arising in this dispute. In consultation with the parties, the Panel adopted working procedures for its consultations with scientific and technical experts. These working procedures were communicated to the parties on 25 November 2005.

40. The Panel received suggestions from experts from three international organizations, namely, the Codex Alimentarius Commission, the Joint FAO/WHO Expert Committee on Food Additives, the IARC, and from the parties. Following consultations with the parties on the candidate experts, the Panel appointed, as I mentioned, Dr. Boisseau, Professor Boobis, Dr. Cogliano, Professor De Brabander, Professor Guttenplan and Professor Sippell to serve as scientific experts in this dispute.

41. In accordance with working procedures and after having considered the parties' comments, the Panel sent questions to the experts and international organizations on 13 April this year. The experts were requested to reply in writing by 12 June 2006, and these replies were communicated to the parties. Comments and counter-comments received from the parties and the expert replies were also provided to the experts in July.

42. The purpose of today's meeting is for the Panel to obtain further clarification of the scientific issues and to discuss the experts' written responses to the questions. The parties will also be given an opportunity to discuss the responses of the experts to the questions.

43. This two-day meeting will proceed in the following manner. Before proceeding with an examination of the specific scientific issues under consideration, the Panel will first give an opportunity to each expert and international organization representative to introduce themselves and make some brief introductory remarks, in particular in light of parties' written comments on their specific responses to these questions. But please bear in mind that these remarks should be kept as general as possible since we will subsequently discuss each issue in more detail.

44. Afterwards, the Panel intends to hold its discussions under five areas which are linked closely with the specific sections included in the written questions of the Panel to the experts. I will clarify the specific areas in a moment. For each of the five specific areas, I will open the floor to the parties to ask questions to the experts based on the written information and comments received thus far, addressed either to a specific expert or to the experts in general. The Panel would also pose some questions either at the beginning or following parties questions, depending on the issue. Once the question and answer process has been completed for one area, I will invite the experts and

international organization representatives to make some concluding remarks, if they so wish, before moving on to next area. In addition to the four predetermined areas, we have also foreseen a fifth area to address any other issues not covered by any of the four areas.

45. Concerning the questions by the parties to the experts, the Panel will proceed as follows. Under each section, the Panel will first give the European Communities the floor to ask questions to the experts. Thereafter, the United States and Canada will be given an opportunity to ask their questions to the experts, including any follow-up questions to those posed by the European Communities. After that, the European Communities will be given the opportunity to pose any follow-up questions to those posed by the US and Canada. The Panel is mindful that these are officially two proceedings and it will make sure that parties are given ample opportunities to ask questions necessary for a clear understanding of the facts. However, the Panel notes that the scientific issues are similar in both cases and would strongly encourage the parties to avoid duplicating questions. Please all keep in mind that this meeting has been convened primarily to hear the views of the experts and that parties will have ample opportunities to express their views at our meeting next week.

46. Finally, once we have covered all the five specific sections, I would like to give each expert and international organization representatives an opportunity to make concluding remarks based on the discussions held by that time. I am not intending to invite parties to make any concluding remarks during this meeting since they will have the chance to discuss any relevant points further during the Panel's second substantive meeting with parties scheduled for next Monday and Tuesday.

47. I would like to underline that the Panel may ask follow-up questions at any time during the proceedings. Moreover, although the Panel or the parties may address a question to one or more specific experts, all experts should feel free to respond to specific questions if they so wish. In making any remarks, both parties and experts are requested to minimize redundancy with what they have already submitted to the Panel in writing. I would also like to remind you all that experts and international organization representatives are expected to answer scientific and technical questions; they must refrain from addressing any legal issues, such as questions of interpretation of the SPS Agreement.

48. I would also like to recall that the purpose of today's meeting is to take advantage of the experts' presence to allow the Panel to gain a better understanding of the scientific issues before us. The Panel's experts have been selected after extensive consultations. I would like to express the Panel's appreciation for their contributions and their presence today. I am confident that the parties will also make the best of their expertise during these two days.

49. Let me also clarify that the Secretariat staff will prepare a summary of all the information provided by the experts and international organizations in their written responses to the questions as well as a transcript of the information provided by the experts and international organization representatives in the meeting today and tomorrow. Each expert will be asked to review this summary and the transcript and to confirm its accuracy. These will be part of the Panel's reports on these disputes.

50. Last but not least, I would like to recall that we the Panel members do not have scientific expertise. Therefore I would like to ask the experts to bear this in mind in replying to questions and explain issues in layman's terms, providing information on underlying concepts as necessary. In order to get a clearer picture with respect to the six hormones at issue, I would also like to invite all those taking the floor to clarify which of the six hormones their question or reply applies to.

51. Now I would like to introduce the five areas that I referred to earlier. In order to facilitate a focussed discussion, the Panel would like to structure the meeting under four specific areas which

relate to the Panel's original written questions: Area 1 relates to terms and definitions, which corresponds mainly to Section A of the Panel's written questions to experts; Area 2 is risk assessment techniques, which corresponds roughly to Section B of the Panel's questions and to some of the Panel's questions to international organizations; Area 3 is related to relevant scientific evidence, which corresponds roughly to Section D of the Panel's questions to experts; Area 4 relates to EC assessment of risks, corresponding roughly to Section C and some elements of Section D of the Panel's questions; and Area 5 is, as I mentioned, other – any follow-up questions that do not fit in the above categories.

52. In their replies, the experts may want to refer to various documents, including the parties' submissions and exhibits. These documents are either filed in the binders placed in the cupboard over there, or in the CD-Roms. The CD-Roms can be opened and viewed in the laptop computers near your seats. The Secretariat staff are ready to help you locate these documents if necessary.

53. Unless there are any comments or questions we can now proceed to hear the experts' brief introductory remarks. I will first give experts the floor in an alphabetic order, starting with Dr. Boisseau, which will be followed by the representatives of the international organizations. Dr. Boisseau, you have the floor.

Dr. Boisseau

54. Thank you, Mr. Chairman. Let me begin by apologizing for my voice – I caught a cold some time ago and I am afraid that my voice is not very clear, but I shall do my best to make myself understood. So, my name is Jacques Boisseau, and I withdrew from professional life four years ago. Before that, I directed the National Agency for Veterinary Medicinal Products (ANMAV) in France for 20 years. I was a member of the European Union's Committee for Veterinary Medicinal Products for 14 years and headed it for six years when it was still in Brussels. For 13 years I participated in all of the meetings of the JECFA, and had the honour to chair four of them and to be Vice-Chairman five times. Finally, for about 15 years I headed the French delegation to the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF). So, I specified in my curriculum vitae that in the above capacities, I had not done any scientific work on hormones, and that consequently, I had not published anything on the subject. I suppose that I have the honour to be part of this panel of experts thanks to my experience in assessing the safety of residues of veterinary drugs in food. I would like at this point to make three remarks that could be of help to the discussions that will be taking place over these two days.

55. The first comment is as follows: the experts have been given 64 precise questions, to which they were asked to provide precise answers. Consequently, I think that any comments on the replies of the experts, or criticism thereof, should focus on the replies in relation to the questions asked and not in relation to the questions that were not asked. Secondly, I think it is important that we should all have a common understanding of the risk analysis procedure. In other words, we should clarify together, and in agreement with each other, what pertains to the risk assessment procedure as opposed to the risk management procedure. We should be able, as well, to reach a common understanding of what a hazard is, and what a risk is. Finally, we should be able to adopt a common approach to what a qualitative risk assessment, is as opposed to what we might call a quantitative risk assessment. Finally – since I had meant to be brief – I think that we must clarify together the specificities of conducting a risk analysis for an endogenous substance as opposed to a risk analysis for xenobiotic substances. There we are, Mr. Chairman, thank you very much.

Chairman

56. Thank you. Professor Boobis, please.

Dr. Boobis

57. Thank you Mr. Chairman. My name is Alan Boobis. I am currently a professor of biochemical pharmacology at Imperial College London where I am also a director of the Department of Health Toxicology Unit. I originally trained in pharmacology at the University of Glasgow, but since 1976 have been involved in studies of xenobiotic metabolism of foreign compounds and in toxicology, particularly mechanisms of carcinogenesis of dietary contaminants. For the last 15 years I have played a role in national, regional and international advisory committees, as an independent member of a number of committees advising on the safety of chemicals, both pesticides, veterinary drugs and consumer products. I have published over 200 papers in peer reviewed journals, including a small number on issues of hormone research. I currently have two PhD students and a post-doctorate research fellow working on aspects of oestrogen toxicity.

58. I have very few comments to make specifically about the issue at hand today because I hold myself ready to expand upon my responses to the questions. I would just make one general comment at this time which is that in risk assessment it is important to recognize that it is not possible to establish safety with absolute certainty. Safety is a concept which is related to the probability of harm, and this is the reason that we use terms like "no appreciable risk". In risk assessment we don't have a concept of zero risk, because in strict scientific terms of risk assessment, risk is considered as a probability – the probability of harm based on the hazard of the compound and the specific conditions of exposure to the agent under consideration. Thank you.

Chairman

59. Thank you. Dr. Cogliano, please.

Dr. Cogliano

60. Thank you, Mr. Chairman, members of the Panel. My name is Vincent Cogliano. I am the Head of the IARC Monographs Programme at the International Agency for Research on Cancer in Lyon, France. The IARC monographs are a system of expert scientific reviews where we convene international working groups of scientific experts to evaluate the potential carcinogenicity of a variety of agents. They started out looking at chemical agents but since then have evolved to look at occupational exposures, chemical mixtures, lifestyle factors, physical and biological agents. Over the 35 year history of the Monographs Programme we have looked at over 900 agents and identified approximately 400 as potentially carcinogenic to humans, including 100 agents which are considered to be known to cause cancer in humans.

61. I am here perhaps in a double role; partially in my role at the International Agency for Research on Cancer but also as a member of the expert committee. Before coming to IARC I worked for nearly 20 years at the United States Environmental Protection Agency in Washington, DC where I was part of the Office of Research and Development assessing the health hazards of chemicals found in the environment. I am not going to make at this time any particular statements about risk assessment or risk but I do stand ready to assist the Panel in any way I can in answering any questions that come up today. Thank you.

Chairman

62. Thank you. Then I will give the floor to Professor De Brabander. Please.

Dr. De Brabander

63. Thank you, Mr. Chairman. My name is Hubert De Brabander. I know that my name is difficult to pronounce for non-Dutch speaking people, but we'll do our best. Maybe you can give me a nickname or something if you want to address me. I am from Belgium, from Ghent University, from the Faculty of Veterinary Medicine. I am trained as a chemist and during my PhD in chemistry I also obtained a degree in environmental chemistry, and concern for the environment will stay with me for the rest of my life. Then I was offered a position at the Faculty of Veterinary Medicine and I am still there as Head of Department of the Department of Veterinary Public Health and Food Safety. Over the years I worked mostly on analytical chemistry, residue analysis. I did a second PhD in analytical chemistry of food (aggregaat hoger onderwijs) and also a PhD in veterinary sciences. As you see my background is in analytical chemistry, but over the years I have become a little bit "veterinized", I should say. What I can offer to the Panel is my background, my experiences with residue analysis and practical experience in control of legal and illegal compounds. Thank you.

Chairman

64. Thank you. Professor Guttenplan.

Dr. Guttenplan

65. My name is Dr. Guttenplan. I have a PhD in chemistry but I have been working in biochemistry and carcinogenesis for over 30 years. I also have a Masters in public health and environmental sciences. I have been teaching biochemistry for a number of years and have been involved in carcinogenesis for 30 years. In responding to the questions I found one of the most difficult points to evaluate was the word "potential". Many times it arose – this is a potential carcinogen, this is a potential hazard – and this comes back to the notion of risk; almost any chemical can be toxic if the dose is high enough. I think this has been a very difficult area for the Panel to determine; what a dangerous dose is, and whether the doses of hormones that are in the cattle produce levels in humans that are dangerous. I am prepared to answer any questions during my responses throughout the day. Thank you.

Chairman

66. Thank you. Professor Sippell, please.

Dr. Sippell

67. Thank you, Mr. Chairman. I have prepared for introduction a few PowerPoint slides.[1] (May I have the first one.) Yes, there you see my affiliation; I am the only one of the experts who is a medical doctor, more specifically a Professor of Paediatrics, and I have been running the Division of Paediatric Endocrinology and Diabetology for now more than 25 years and also running a relatively highly-developed paediatric endocrinology lab. Our speciality is to do refined steroid analysis in very small samples from children, from premature babies to adult individuals.

68. (Next – just the first line of the second slide please.) I am a relative newcomer in the field and it is very interesting that this dispute has already been going on for more than a decade, and to my knowledge no paediatrician, let alone a paediatric endocrinologist, has been involved as a member of one of your expert committees. To my knowledge, neither has one of the very active scientific organizations been involved in these disputes, for example the Lawson Wilkins Paediatric Endocrine Society which serves North America, so not only United States but also Canada, or the European

[1] Dr. Sippell's slides are contained in Attachment 1 to this transcript.

Society for Paediatric Endocrinology. This fact is incomprehensible and paradoxical in view of the fact that prepubertal children are indisputably the most sensitive and vulnerable members of the population.

69. (Next point, yes, you can leave it there.) Children have the smallest body size but the longest life expectancy and I see (next please) my mission here as an advocate of and spokesperson for children and their specific needs. Just remember that children are not just small adults but something very special and they are our future, no doubt. Through my reading (can you go on) I got the impression that the validity of the supersensitive recombinant cell bioassay for oestradiol is a key issue in all the debate at stake. I would like to remind you that this supersensitive assay has been developed at the National Institutes of Health, the foremost and most refined research institution of the United States. And with our American colleagues – who in general really don't question the validity of this assay (can you go on please) the novel finding of significantly higher oestradiol levels – E2 stands for oestradiol, the female sexual steroid – in prepubertal girls than in boys readily explains fundamental features of human biology for the first time. Many questions that had not been answered before, basic biological questions, can be answered now by this quantum leap supersensitive assay of oestradiol in small biological samples. So for instance, the onset of puberty is on average one year earlier in girls than in boys. This is readily explained by a higher oestrogen input in girls endogenously, from the ovaries, which are not sleeping during pre-puberty but are active on a low level. The second aspect is the much faster bone maturation in girls than in boys, with a result that bone maturation is ready in girls on average at age 15, whereas it is mature at age 17 in boys.

70. (Next point.) Lower adult height in women than in men by a mean of 13 centimetres – in all populations men are taller than women. This can only be explained by this higher prepubertal oestrogen secretion in girls than in boys. (Next.) The higher weight for height or body mass index in girls than in boys at start of normal puberty is also readily explained by this. We have evidence that oestrogen exposure increases weight, and you can see in the next slide a piece of our own research. You can see on the left-hand side in the yellow box plot were 50 girls with central precocious puberty, in some of them puberty started at age two already, and at diagnosis they were already two standard deviations in weight above the mean for age and sex. So oestrogen exposure – in these cases endogenous oestrogen supersecretion – leads to increased weight. And we have shown that treatment of this disorder does not increase weight – you can see that the BMI standard deviation score stays stable or goes down.

71. (Next please, and I am coming to the end.) The incidence of central precocious puberty, as I told you, is about 10 times higher in girls than in boys. This is only explained by the fact that girls have prepubertally higher levels of oestrogen than boys. (Next.) I contrast, the incidence of constitutional delay of puberty is much more common in boys than in girls.

72. (And then the last slide.) Ethical considerations – they should always be kept in mind. To investigate whether eating hormone-treated beef elevates oestrogen levels in prepubertal children, tests cannot be performed in healthy children, because this would involve physical and psychological injury to them. (And the next.) Epidemiological studies comparing adverse effects in mass populations – and I have read in some of the comments that this is advocated – in healthy children eating beef from hormone-treated and untreated animals to compare them would also be unethical. We have to protect children from unnecessary clinical trials. This is not only (can you go on) written in the Declaration of Helsinki, but also in all good clinical practice guidelines and in the recent EU Parliament ruling on better medicines for children. I thank you for your attention.

Chairman

73. Thank you. I now request Dr. Miyagishima, the Codex representative, to take the floor.

Dr. Miyagishima

74. Thank you, Mr. Chairman, and I thank all the members of the Panel for having given the opportunity to the Secretariat of the Codex Alimentarius Commission to be invited to this Panel hearing. The Codex Alimentarius Commission is one of the three international standards-setting bodies explicitly enumerated in Annex A of the SPS Agreement. The Codex Alimentarius Commission was established in the early 1960s by FAO and WHO as an intergovernmental body operating under the auspices of these two parent organizations. The core business of Codex is to set international food standards and other related texts with the objective of protecting the health of consumers and ensuring fair practices in food trade. Codex, by setting international standards, acts as an international risk-management body, if I put it in the overall framework of risk analysis. Codex, as such, does not undertake any risk assessments but draws on the work done by FAO/WHO scientific bodies in that respect. The membership of the Codex Alimentarius Commission is open to all member states of FAO or WHO. Currently the Codex membership counts 174 countries, thus covering more or less 99 per cent of the world's population. Codex has one member organization, the European Community, which made a formal accession to Codex in November 2003. Codex' highest decision-making body is the Codex Alimentarius Commission, which used to meet every year after the creation of Codex, then the Commission turned to a biennial meeting rhythm, and since 2003 the Commission is again meeting every year.

75. The Commission adopts the final draft standards prepared by its subsidiary bodies, and Codex has 20-plus subsidiary bodies covering distinct speciality fields. In the 1980s, Codex decided to extend its activity area to cover the residues of veterinary drugs in food. Codex thus established the Codex Committee on Residues of Veterinary Drugs in Foods, known as CCRVDF. This Committee met for the first time in 1986 and continued to meet yearly until 1992; since then it is meeting more or less at the interval of 18 months. CCRVDF acts as a subsidiary body of the Codex Alimentarius Commission on matters related to the residues of veterinary drugs in food, and as mentioned earlier it does not conduct any risk assessments. It bases all recommendations that this Committee forwards to the Commission on the scientific advice given by JECFA. Of course JECFA covers a broader field than just the question of residues of veterinary drugs; it also covers food additives and contaminants and as such advises other subsidiary bodies of the Codex Alimentarius Commission.

76. Mr. Chairman, this is a brief outline of the history and the mission of the Codex Alimentarius Commission, and I am willing to provide further clarification or supplementary information with regard to the written information we have provided. I would like to stress the fact that we represent – together with the joint secretaries of JECFA – our respective organs and we do not, in my case, represent directly the member states. I would be most happy to reply on questions regarding procedures and facts, but I am rather reluctant to make any comments on those questions requiring value judgements or any analysis or assessment of scientific data. Thank you, Mr. Chairman.

Chairman

77. Thank you. May I now invite the JECFA representatives, Dr. Tritscher and Dr. Wennberg, to take the floor in turn and to make their introductory remarks.

Dr. Tritscher

78. Thank you, Mr. Chair. My name is Angelika Tritscher; I am from the World Health Organization here in Geneva. And within the WHO I work in the International Programme on Chemical Safety. Within the Programme I am responsible for the Chemicals in Food Programme. The main part of this Chemicals in Food Programme is to be the scientific secretariat to international expert bodies that perform risk assessment on chemical residues in food. We have two expert bodies, JECFA and JMPR. JMPR is the Joint Meeting on Pesticides Residues, but it is not of relevance here.

The other expert body, as already mentioned, is the Joint Expert Committee on Food Additives, which despite the name, as was already alluded to, deals not only with food additives but also with contaminants, natural toxins and veterinary drug residues in food.

79. Very brief to my training: I myself trained in food science – I have a Masters degree in food science and a PhD in biochemical toxicology. However, as was already mentioned, I am not here in a role as a scientific expert. My role here in this Panel is to explain JECFA procedures and risk assessment methodologies and definitions as scientific secretary to the committee.

80. Let me say a few words about JECFA, to explain what JECFA is. JECFA is an international independent scientific expert body. It is jointly administered by FAO and WHO. It is not a standing committee, so JECFA experts are invited for each meeting, depending on the compounds on the agenda and the tasks at hand. As was already explained, in the international arena of food safety, JECFA is the risk assessment body and does not deal by any means with risk management activities, which in the international arena are the responsibilities of Codex and its subsidiary bodies. As mentioned, JECFA is jointly administered by FAO and WHO, and FAO and WHO have complementary roles in administering this Committee and inviting respective experts. The role of the WHO secretariat, according to the role of the WHO, is to invite experts that perform toxicological evaluation of the available data and then together with FAO – and my colleagues from the FAO secretariat will explain in more detail the role of FAO and FAO experts overall – the risk assessment is performed. The WHO experts perform the toxicological evaluation.

81. JECFA first met 50 years ago – the first meeting was in 1956 – which means JECFA predates not only me but also the Codex Alimentarius Commission. Over the years, JECFA has really laid the ground work by developing the principles for how risk assessment of chemicals in food is done nowadays, both on the international and on national levels. Besides laying the groundwork, there is continuous improvement over the years, as published in the reports of each JECFA meeting. All publications of JECFA are publicly available, which nowadays luckily means on the internet, but also in print. We publish reports of each meeting that give the precise description of the data that allow the conclusion. Then we have toxicological monographs, published in the WHO Food Additives Series, that give a detailed description of the full toxicological database, including the full reference list. So far to the transparency of the outcome of the JECFA procedures. I will be glad to answer any questions there may be regarding JECFA procedures, in particular risk assessment methodologies and so forth. And with this I would like to give over to my colleague from the FAO. Thank you.

Dr. Wennberg

82. Thank you, Mr. Chairman. My name is Annika Wennberg, and as was said by my colleague Dr. Tritscher, I am the FAO JECFA Secretary. We work together; we have complementary roles to serve JECFA as the independent scientific committee in international settings. As was also mentioned, JECFA has been in place for some time, since 1956, and it actually started to evaluate veterinary drugs in 1987. The first meeting dedicated to veterinary drugs residues was held in 1987, and JECFA also started developing the general principles for the assessment of residues in veterinary drugs in food. Under the FAO constitution, JECFA is convened according to article 6, which lays down that the Conference of the Council of FAO may establish committees and working parties to study and report on matters pertaining to the purpose of the organization. These consist of individuals appointed in their personal capacity, because of their special competence in technical matters. Joint committees may also be established according to that article. This is the basis for the support of FAO to the work of JECFA.

83. I myself have a PhD in nutrition and metabolism from the medical faculty of Gothenburg in Sweden. I have also been involved in evaluations of veterinary drugs in my previous position as employee of the Medical Products Agency in Sweden. But I am here in my role as the JECFA

Secretary to respond to questions and clarifications that may be asked about the procedures and the principles of JECFA, not to respond to any questions on the substance matters. Thank you for inviting me and I will stop here.

Chairman

84. Thank you all for your introductory remarks and particularly for their brevity. I think that concludes our introductory part of this morning's session, and I now turn to the main business of today, the consideration of specific issues in the five areas I mentioned. On the first area I would like to let you know that the Panel would first like to pose some questions related to certain terms and concepts and definitions. I will pose our questions one by one, and after listening to the replies from the experts and from the parties, I will move on to the next question.

85. The Panel's first question is: Please explain the terms genotoxic, mutagenic and carcinogenic. How are they related? How do they differ? What are the consequences if a substance is genotoxic, mutagenic and/or carcinogenic? I would welcome any replies from any of the experts present, please.

Dr. Guttenplan

86. A genotoxic substance is one which damages DNA. Many genotoxic substances are mutagenic and many genotoxic substances are carcinogenic. Whether they pose a risk depends on the dose.

Chairman

87. Dr. Boobis.

Dr. Boobis

88. Just a further clarification of some of these terms. A carcinogenic compound is one that causes some abnormality of growth control and results in a tumour. It can arise from many different mechanisms. One of them is through direct damage to DNA, which is genotoxicity, and mutagenicity is a change in the sequence of the DNA caused by a genotoxin. So there are several different mechanisms of genotoxicity, some of them due to direct interaction with DNA.

Chairman

89. My colleagues asked if you could speak a bit more slowly.

Dr. Boobis

90. So there are many different mechanisms of genotoxicity, for example one can interfere with the mitotic spindle, which is the apparatus that determines how cells divide, or there could be direct modification of the DNA, which could lead to a mutation, a heritable change in the DNA. These mechanisms can give rise to cancer, but there are other possibilities, such as a mitogenic stimulus, something that stimulates the cells to divide. Perhaps random errors during normal replication can lead to the selection of cells which have a tumorigenic potential and could grow into a tumour. It is critical therefore in the risk assessment of something which produces cancer in an animal – which is simply a descriptive term, that is that we observe a tumour in an animal – that if possible we would determine the mode of action or mechanism leading to those tumours; and if the compound is shown to cause genotoxicity, if possible to determine how that compound caused genotoxicity. Not all genotoxicity is the same, because some of it is direct and some of it is indirect.

Chairman

91. Thank you. I am wondering whether any of our colleagues in the Panel have …

European Communities

92. Thank you, Chairman. Would you allow me to ask a clarifying question? The question is to the two scientists that have already expressed themselves, I think in particularly to Dr. Boobis. Dr. Boobis, in reply to question number two you have stated regarding genotoxic potential that the compound might be capable of causing genotoxicity, and then you say usually *in vivo*. You continue then to say it remains to be determined whether genotoxicity is indeed expressed *in vivo*. So there are a few words and each word of course changes specific meanings and significance. The question is, do we always need to find genotoxicity *in vivo*? Is it sometimes sufficient that we observe in large numbers of experiments genotoxicity *in vitro*, and are there examples of substances for which we have accepted that they are genotoxic on the basis of the large number of experiments *in vitro*? I don't quite understand what you mean, it remains to be determined whether genotoxicity is indeed expressed *in vivo*. Could you please elaborate and eventually …

Chairman

93. Before I give the floor to Dr. Boobis, may I remind the delegations that we will have further opportunities to exchange our discussions on the specific issues relating to risk assessment techniques and so on. So why don't you confine your questions to the terms and definitions at this moment, and then I will move on to the discussions in detail on the specific issues later.

European Communities

94. Chairman, my question then is simple. Do we always have to observe genotoxicity *in vivo* before we conclude that the substance is genotoxic? Thank you.

Chairman

95. Actually, I do have a question. I have a question on what is the meaning of *in vivo* studies and *in vitro* studies. May I ask the experts to respond to this question first before they respond to the question put forward by the EC. Dr. Boobis.

Dr. Boobis

96. Well, *in vitro* means outside of the body, usually in a cell-based system in a test tube or culture dish. *In vivo* means in the whole organism, the intact organism. And because of the many protective mechanisms, both metabolic and repair mechanisms, there is an accepted wisdom that the observation of a response *in vitro* in an isolated cell does not necessarily translate into a response in the whole animal. This is one of the reasons, as far as I am aware, that almost all test strategies for genotoxicity have in them a component that if one is performing a risk-based approach, one would seek to confirm a positive *in vitro* result with an OECD-accepted method *in vivo*, of which there are several.

Chairman

97. Could you respond to the question by the EC?

Dr. Boobis

98. It is pretty well embedded in that response, Mr. Chairman, that the potential is that there are indications of a positive *in vitro*, but that it is not actually described as an *in vivo* genotoxicant or a true genotoxicant with relevance to the risk of that compound until an appropriate study is conducted on mechanisms and an *in vivo* test to confirm that *in vitro* observation. There are examples of compounds which are clearly genotoxic *in vitro* where they are negative *in vivo*, and the risk assessment has proceeded on the basis that the genotoxicity is not expressed in the *in vivo* situation for one of a number of reasons.

Chairman

99. Thank you. You wish to ask a question?

United States

100. Thank you Mr. Chairman. Dr. Boobis, to follow up on your response, if I may. Could you please explain the relationship, if any, between genotoxicity and carcinogenicity? For example, if a compound is genotoxic, is it also carcinogenic?

Dr. Boobis

101. This is the reason I tried to distinguish between, in a narrow sense, genotoxicity and mutagenicity. The answer to the question, is a compound that's genotoxic always carcinogenic is clearly no. There are a number of compounds that cause genotoxicity in *in vitro* tests by mechanisms which are not expressed *in vivo* because of repair mechanisms and detoxification by enzymes of xenobiotic metabolism. What is clearer is that a compound that is a mutagen, a direct-acting, DNA-reactive mutagen, is frequently a carcinogen. But to say that a genotoxin equates to carcinogenicity is not correct and is the reason we place such weight on understanding the mechanisms of genotoxicity and the relevance of observations *in vitro* to the outcome *in vivo*.

Chairman

102. I also would like to remind the other experts that they are free to respond to any questions put forward by the Panel or by the parties. Regarding the parties' questions, I understand that each delegation has its own set of questions to be put forward to the experts on the terms and definitions. So I would appreciate it if you limit your questions at this moment to only those related to answers given by the experts, and then I will give the opportunity for each delegation to put forward its own set of questions to the experts under this particular item. Is this clear? OK. Then as a related question, we understand that experts' responses referred frequently to genotoxic and hormonal mechanisms. What does the term mechanism refer to in this context? And also, as a follow-up question, how a hormonal receptor operates and what hormonal receptor really means. These are two related questions from the Panel. I would give the floor to any of the experts. Dr. Boobis.

Dr. Boobis

103. I propose, if you will, to answer the first half and perhaps one of the other experts can answer the second half. In terms of mechanism, there is this concept that has evolved during the last ten years or more, led by the International Programme on Chemical Safety and others, to try to understand carcinogenicity in a deeper way than simply the observation of abnormalities of growth, which is after all what a tumour is. And this has led to this idea of a mode of action, and a mode of action is a series of key events which are necessary to lead to the formation of the tumour, and these key events comprise the biological changes induced by the chemical and subsequent events which then lead to

the development of cancer. In the case of a mechanism, it is the actual molecular events that are responsible for those changes. So a hormonal mechanism in that sense would mean that it is the endocrine or hormonal effect of the compound that leads subsequently to changes that result in the development of a tumour, whereas a genotoxic mechanism would be where there is a mechanism independent of the hormonal action that results in damage to the DNA directly that leads to the tumour. That is not to say that there aren't situations where both could apply, that there could be elements of more than one mechanism.

Chairman

104. Thank you. Dr. Cogliano, please.

Dr. Cogliano

105. Thank you very much. At the International Agency for Research on Cancer, the expert working groups have been using mechanisms to affect their evaluations of carcinogenicity for approximately 15 years. And the reason it is important to try to understand the mechanism if you can is that sometimes it lets you know that the events, the processes occurring in experimental animals, are relevant to humans, and in other cases it lets you know that the processes that are happening in experimental animals do not operate in humans. IARC has had experience in many cases elevating the concern because what is happening in experimental animals is relevant to humans, and in other cases it downgrades or discounts the evidence in experimental animals because it is not relevant to humans. These principles are spelled out in IARC's guidelines, called the preamble to the IARC monographs. I would also like to say that it is not always necessary to understand the mechanism. For example, many carcinogens, like asbestos, vinyl chloride, benzene were determined from epidemiological studies to cause cancer before anybody had any understanding of the mechanism by which they cause cancer. But when we do have an understanding of the mechanism, it helps us put the experimental evidence in better context about whether it could be predictive of humans or not.

Chairman

106. Thank you. Dr. Boobis.

Dr. Boobis

107. I would just like to add that one of the reasons that such weight is placed on understanding the mechanism and mode of action is that it can inform interpretation of a dose response, and that of course is one of the issues at hand in this dispute. If we understand how the tumour arises, we can also understand what the likely nature of a dose response is.

Chairman

108. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

109. A part of the question was the effects of different mechanisms on carcinogenesis, and we have already talked about the genotoxic effects. That is the direct damage to the DNA. A hormonal mechanism results in enhanced growth or proliferation of certain cells that are responsive to the hormones. You could have an incipient or a single cancer cell that might not grow during the lifetime of the organism, but in the presence of a stimulus such as a hormone, that cell might grow and then become a tumour. So these are basic differences in terminology and that is another reason why mechanism is important, to understand how these different compounds act.

Chairman

110. Thank you. Is any of the experts ready to respond to the second part of my question on what a hormonal receptor is and how it operates in terms of the hormonal mechanism. Dr. Guttenplan, please.

Dr. Guttenplan

111. Yes there are certain cells – my nametag fell down on my controller and I am listening in French and talking in English – alright that sounds better. There are certain cells that have on their surface, if you will, acceptor proteins that can accept oestrogen, and when they accept the oestrogen, they then start to grow, and that's an oestrogen receptor cell, what we call an oestrogen receptor-positive cell. So they would normally grow at a very slow rate or not at all, but in the presence of oestrogen they are stimulated to grow.

Chairman

112. Thank you. Any other follow-up questions? Yes, Dr. Boobis.

Dr. Boobis

113. It is also, I think, relevant that the endocrine system, the system that the hormones act within, is a network of hormones and a network of receptors, and is part of the normal physiological control mechanisms of the body. These hormones evolved as one of the processes whereby we can function as organisms. They are signalling molecules which are transported in the blood from remote sites of production to their sites of action, so they differ from some other signalling molecules which are produced locally. The important thing about a hormone is that it is actually distributed by the blood and is an essential part of normal physiology. So we are looking in terms of hormones as residues against an existing background of hormonal activity, certainly for the endogenous hormones, sorry, the natural hormones.

Chairman

114. Thank you. Dr. Sippell.

Dr. Sippell

115. Yes, I would like to add that this network Dr. Boobis was alluding to is particularly sensitive in children, more sensitive than in adults. And this is very important also in the receptor levels. Some receptor function is really much different from adult individuals in order to allow growth and development at puberty.

Chairman

116. Thank you. Dr. Guttenplan.

Dr. Guttenplan

117. Yes, it is probably obvious to most people, but I just mention a few of the well-known oestrogen receptive organs, which are the breasts, the prostate, the ovaries and the uterus. And a somewhat different comment on genotoxic effects which Dr. Sippell brought to my mind is that genotoxic effects can be a lot more effective if the cell is rapidly dividing, so children represent an

exceptionally sensitive population to genotoxic effects, too, not just hormonal effects on cell replication.

Chairman

118. Thank you. But why is it causing only prostate and breast cancer, other than ...

Dr. Guttenplan

119. Well, nobody is saying it only causes those, oestrogen is probably involved in ovarian cancer and uteran cancer.

Chairman

120. The next question is: what is marker residue? How is it established? And what is a bound residue? Why is it significant? Dr. De Brabander please

Dr. De Brabander

121. Would you repeat again the question, Mr. Chairman.

Chairman

122. What is a marker residue, how is established, what is a bound residue and why is it significant in this?

Dr. De Brabander

123. When a drug is given, or if a compound is given to a human being or to an animal, it is metabolized, and that metabolization is different according to the compound, also according to the species. When it is metabolized, it can be different for humans, it can be different for animals, it can be different in different animals, and if you want, and I go from the point of control, if you want to control that a given compound is administered, you have to look at the metabolite which you will find in a given matrix. What I call a matrix is urine, faeces, meat, whatever is available and you can measure. The marker residue is the residue which you will find. That is a general definition for me as control, it will be different if you look from a veterinary direction. And what is a bound residue? It can be a residue which is bound for example to tissues or to other compounds, so that you must use special techniques to extract it. Thank you.

Chairman

124. Before I give the floor to my colleagues, I will give the floor to Dr. Wennberg and Dr. Boisseau.

Dr. Wennberg

125. Thank you, Mr. Chairman. JECFA has also provided a definition for marker residue, which is in line with what Professor De Brabander has stated. It is a way to actually define what you want to analyse. It is the parent drug, or any of its metabolites, or a combination of these with a relation to the concentration of the total residues of the veterinary drugs in each of the tissues, i.e. the target tissues. What you want to measure is the level of the drug at any time between administration of the drug and the depletion of the residues to the safe level. So it means that to be able to recommend maximum residue limits which will be useful in the control of the safe use of the veterinary drug, you have to

have a method, an analytical method, which measures a chemical substance which relates to the veterinary drug that has been administered, either the drug itself, or a combination of the drug and metabolite, or a metabolite of the drug which is formed in the body of the animal. The definitions of bound residues are the residues which cannot be extracted by the method used to measure the residues of the drug in the tissue in question. There can be different ways of binding of chemical substances to various components of tissue, protein, fats, carbohydrates, etc., and the way to determine whether these residues should or should not be included in the residue definition is a matter to be determined on a case-by-case basis, depending on the behaviour of these bound residues, whether they can be released by enzymatic or other mechanisms, or whether they are actually completely bound and inactivated as such by their bondage to molecules in the tissue. Thank you.

Chairman

126. Thank you. Dr. Boisseau.

Dr. Boisseau

127. Thank you, Mr. Chairman. To begin with, a few words about marker residues. It is a challenge for those who perform evaluations to reconcile the frequent complexity of the metabolization of a substance, which can give rise to a multitude of derivatives of varying concentrations, and with the need for a simple control method. In other words, you have to be able to combine the two.

128. The purpose of toxicological evaluation is to identify, in terms of a toxicological effect that is deemed relevant for the evaluation of the products, all of the residues including the parent substance and the metabolites associated with this toxic aspect. Most of the time, metabolism does not yield one single residue associated with the toxic effect. Thus, to keep the control simple, it is necessary to identify among the residues the one that can be considered a marker residue – in other words the residue that reflects, according to the time in a given matrix, the evolution of all of the residues of concern. Thus, there must be a constant quantitative relationship over time between the marker residue content in a given tissue and total residues of concern – i.e. that are of interest in terms of the toxic effect in question – taken as a whole. As it is not usually possible, however the modern methods used, to analyse different substances at the same time, it is much easier to follow a single residue, the marker residue, which must reflect, over time, the concentration in a given tissue of all of the residues of concern in terms of toxic effect.

129. Now, as regards bound residues, these are what we call – and I do not wish to repeat what Doctor Wennberg has just said – residues that are covalently bound with macromolecules, and in that sense, are not bioavailable – i.e. they are not spontaneously available – as opposed to the so-called free residues, which are not bound to macromolecules. Since for the most part, these residues cannot be extracted, they are identifiable and quantifiable by so-called radioactive methods. Once the content of bound residues in a given tissue has been identified, we have to know what they signify, since the normal metabolism of a substance could lead to the complete degradation of that substance and the reincorporation of very simple monocarbonic elements, for example in the normal protein anabolism in particular. And where you have CO^2, for example, which is radioactive if it is the carbon of the CO^2 that is marked – it is not because this CO^2 is reincorporated in a protein synthesis that it will necessarily pose a safety problem for the consumer. In other words, the mere identification of a certain bound residue content does not necessarily mean that these bound residues pose a problem. Thus, it is up to those conducting the toxicological evaluations – and this is not easy – to go further in the identification of theses bound residues, of their possible release according to the methods that Doctor Wennberg has just mentioned, to see if these covalent bindings could have an impact on the biology of the cell in which they have taken place. Thank you Mr. Chairman.

Chairman

130. Thank you. I now give the floor to Madam Orozco – it is OK? Dr. Wennberg, would you like to take the floor? If that is not the case, Dr. Guttenplan.

Dr. Guttenplan

131. I would suggest for bound, at least the way it is being discussed now, that there should really be a descriptive term there, covalently bound, because bound can be somewhat ambiguous. It just means that it is contained very strongly in a tissue, whereas covalently bound basically means that it is unavailable.

Chairman

132. We have already heard some comments on bioavailability, but I would like you to further elaborate on what bioavailability is, and why is it relevant. Dr. Boobis.

Dr. Boobis

133. Bioavailability is the availability to the interior; the systemic circulation of a compound, in this case via the oral route of exposure, and it can be less than complete because the material is not physically available, for example it is bound covalently to the food matrix, because it does not cross the intestinal wall easily, so absorption is incomplete, or it is metabolized either in the small intestine, the site of absorption, or the liver; because the peculiarity of the anatomy of the digestive system is that almost everything that is absorbed across the small intestine into the circulation first goes through the liver before it gets into the body, and the liver has a tremendous capacity to metabolize compounds. And so for some compounds, drugs and dietary chemicals, it is possible for the small intestine and/or the liver to metabolize to less active or inactive products some or even all of what is being absorbed. So this means bioavailability is less than 100 per cent, what is available to have a biological effect on the body is less than what was anticipated based on the administered dose or the ingested dose. And so in this assessment one would like to know how similar are humans to the experimental animals for example in terms of bioavailability.

Chairman

134. Thank you. Dr. Sippell, please.

Dr. Sippell

135. Again the special case in children regarding bioavailability, as an example for instance we paediatricians or paediatric endocrinologists know very well that a twentieth of the daily dose of the natural oestradiols being used in adult women is already effective in prepubertal girls in stimulating growth, weight development and inducing puberty. So bioavailability is certainly in children much higher in many instances than in adult individuals, and the problem is that pure bioavailability studies which tell us which compound is being absorbed to which extent in a two-year-old or three-year-old or four-year-old child are simply not available because they are unethical to perform in healthy children.

Chairman

136. Thank you. Dr. Guttenplan.

Dr. Guttenplan

137. Another way of expressing bioavailability is to compare the blood dose that one would obtain by injecting the compound intravenously compared to what one actually obtains when one ingests the compound orally. So if you get a much lower effect orally than you would intravenously, you have much less bioavailable compounds.

Chairman

138. You wish to ask a question?

United States

139. Just a clarification, Mr. Chairman. Dr. Sippell, you mentioned, referenced a daily dose in women, can you clarify what dose you are talking about or what sort of treatment of women you were referring to?

Dr. Sippell

140. Daily replacement dose in women who for instance lack ovarian function.

United States

141. And what would the quantification of that dose be? Is there an estimate of the level of that dose in terms of quantity?

Dr. Sippell

142. I mean that's the amount necessary to replace endogenous oestradiol production which is not functioning or absent.

Chairman

143. Thank you.

European Communities

144. Chairman, clarification, what has been said previously by Dr. Boobis on this? Is it always necessary that – either through injection or oral absorption, in order to determine bioavailability – that the drug goes first through the clearing system, the liver, or is there another route which does not necessarily go through the liver? Is this also possible? And do you know if any of these substances enter the human body in that way?

Chairman

145. Dr. Boobis.

Dr. Boobis

146. There are other routes of course for absorption; a small amount will bypass the portal blood supply, which is the one that goes to the liver. It is possible that something could be absorbed into lymphatics. It very much depends upon the physicochemical properties of the agent that is being absorbed. Of course early on oestrogens were trialled in adult patients for therapeutic purposes and it

was apparent then, in those early studies, that there is a very substantial metabolism in the liver which made them unusable for nonhepatic targets in adult males, and this is the reason that they are given by other routes; to bypass that very extensive first-pass metabolism, pre-systemic, pre-absorption phase of metabolism. So there are data in adults. I mean I certainly take the point that has just been made by Dr. Sippell, that these data are not available in children, but in adults there are actually data in human subjects. But I would like to add an additional point about the ethical nature of the question of data gaps. There are studies that one could envisage to answer the question as to whether a child has similar or lower first-pass metabolism without giving a hormone. There could be oestradiol present in normal food; and we have done such studies on other compounds where it would be unethical to give the compound itself. But because it also occurs in low dosage as part of the natural diet it is possible with sophisticated analytical chemistry to design a natural experiment, which is that you just look at what is in the diet, measure what is in the blood and then determine whether there is any change. So one can think of experiments, if there is considered to be a data gap, to seek to address that data gap.

Chairman

147. Thank you. Now the floor is for Madam Orozco.

Ms Orozco

148. Yes, thank you. I had a question for Dr. Sippell, because I assume that something similar happens when you want to test or give drugs, medicines to children. You have to know what is the bioavailability, so how do you find out the bioavailability of other substances?

Dr. Sippell

149. That is indeed a very difficult question and there are special regulations to protect the integrity of children. You know, if they are not healthy, then you can do – with the informed consent of parents and guardians – you can do such studies, but you cannot take blood, for instance, just to study bioavailability. This is unethical.

Ms Orozco

150. Just one question. How do you find out what is the bioavailability of medicines that are being developed for children?

Dr. Sippell

151. Yes, that is a very very difficult question, and I am not a paediatric pharmacologist, but this is very much debated, how this can really be done. It cannot be properly studied as in experimental animals or in adult people.

Ms Orozco

152. Do you know how it has been done until now? Because if one goes to any pharmacy one will find a cough syrup for children, and someone has studied how much is its bioavailability in the child, because we know that one spoon or two spoons would be enough or too much.

Dr. Sippell

153. Most medications we prescribe or give to sick children are not licensed for, let's say, infants or young children, because there have never been done proper studies, as in adults. It is just by experience, by empiric, and that's a big big gap in our knowledge, that we for instance cannot do

metabolic studies in infants or in small children. You know the access to their circulation is so difficult, and if some of you have ever done a blood puncture in a premature infant or so, its really very very difficult, and I am not aware of any big trials which can, or have been applied, to study these bioavailability factors.

Ms Orozco

154. Just one last question. Nowadays a child, maybe two years old, might fall ill, might have an infection, might have a virus, and antibiotics are being suggested. So somehow until now someone has been able to find alternatives to find out more or less what bioavailability is, or at least to be able to estimate it drawn from something else. Do you know how?

Dr. Sippell

155. Exactly. We deduce from adults or from young adults, and of course observe any risks that are being observed, you know the reactions and so on, and in general this is of course explained to the parents and it's compassionate use, it's, as we call it, individual trial in a sick child. That's easy.

Ms Orozco

156. I am not asking about extreme cases, because there are situations where there is need to consent, but for example something which is daily occurrence, you go and you buy a syrup for coughing, or – it should not be, maybe, but it happens all the time – that antibiotics have been prescribed as a medicine, they are prescribed to a lot of children since a very early age, so it is common occurrence what I am talking about.

Dr. Sippell

157. This you can study of course with their metabolism, their absorbance and their bioavailability in sick children. You know that when a new antibiotic comes up, then of course we are doing studies in our patients. That is different from the healthy population in children. Do you understand what I mean?

Ms Orozco

158. Not really, because when a person, an adult, takes a child to a paediatrician because it's ill, the paediatrician will examine the child and conclude you need this or that. You go out from there, you go to a pharmacy, no one asks you anything; if it's known that that medicine at that dose is ok, there is no further clearance, so somehow the system has been able to identify ways to make sure to every consumer that it does not pose a problem. What I am trying to find out is: in the normal cases until now, how has society been able to estimate the absorption in a child?

Dr. Sippell

159. Just by guessing. Even the dosing is in many many instances pure empiric. In modern drugs its somewhat better, but in the past these old standard drugs have never been tested properly in clinical trials and therefore many of these drugs in Europe have lost their licence and have to be retested and this creates tremendous ethical problems. And that is a problem of paediatric pharmacology worldwide.

Chairman

160. I give the floor to Dr. Boobis first and then to the United States.

Dr. Boobis

161. Just in the interest of clarification, Chairman, I would like to make a couple of points. One is that it is important, when we are talking about children, we don't lump them all together, it is critical to recognize that an infant is not the same as a prepubertal child. There is a tremendous range of biology and physiology that changes from early childhood onwards to adulthood, and we have to treat them as distinct groups, and the effects of the hormones will vary as well depending upon the age. We don't use this term child to encompass everything under puberty.

162. And the second point is, it is actually possible for some compounds to design experiments that do not require you to take invasive measures. It is not necessary to take blood always to get some measure of what is in the circulation. Two examples would be a saliva sample, which could be acquired just by passive and non-invasive collection, and similarly the collection of excretions, particularly urine, where, if the compound is largely excreted as a parent or metabolite in the urine, one can get comparative information on bioavailability. So it is not always necessary to use invasive blood sampling techniques to get some indication of whether the compound is absorbed and the nature that the compound is absorbed in. It is just for clarification, if one is thinking about data gaps that might be filled in the future, for example. There are possible strategies that exist to do that.

Chairman

163. Thank you. The US.

United States

164. Thank you, Mr. Chairman. I think that Dr. Boobis just spoke to the point I wanted to raise. Thanks.

Chairman

165. Thank you. EC.

European Communities

166. Could we ask the representatives of the international organizations, in particular JECFA, whether this type of experiments for the residues of these substances which we are talking about here in children or in adults have been performed so that we know what one member of the Panel, Madam Orozco, was looking for, whether this has been done in this case, and why not. For example, when the United States has licensed these substances, why did it not look and why did it not perform these kind of experiments here for example. Thank you.

Chairman

167. Is the representative of JECFA ready to respond? You have the floor.

Dr. Tritscher

168. I don't think we are in a position here to give the detailed response as to exactly what type of data were submitted and looked at by JECFA in individual compounds, that is not our role here. And I would like to point out that JECFA is not a regulatory authority, so we are not talking about drug registration; it is not a registration authority, which is very different. Studies as were just referred to would have to be partially done and submitted to a regulatory authority that registers drugs for specific drug uses. JECFA looks at scientific data, toxicological data and human data, epidemiologic

or experimental studies of any kind that are submitted to the experts or that are publicly available in the published literature. And I am in no position now – I would have to go back to all the individual evaluations that have been done and that have been published in order to find out if any specific studies in children or young infants would have been performed. I am not aware of this.

Chairman

169. EC.

European Communities

170. Well, Madam, we are aware of what happened and we can tell you now; because, as you know, when JECFA evaluated these substances in 1988, all of the five substances, and in 1999 the three natural hormones and in 2000 for melengestrol acetate, we know from what we have seen that none of these experiments involved the kinds of experiments Madam Orozco was asking about. So we would appreciate if the member of JECFA goes back next week or the week after and has a look and can inform the Panel where this indeed has happened. We will give you the time to do that if necessary. Thank you.

Chairman

171. Thank you. Dr. Tritscher please.

Dr. Tritscher

172. With all due respect I am not sure what this really would contribute to go back on all these individual things if you already say that you also have an answer to that. The question is a different one to me: what is the relevance of this kind of study in light of the overall weight of evidence, in the light of the overall data that has been submitted and that has been looked at?

Chairman

173. May I remind delegations again we are now on the first area, on terms and definitions, so I would like you not to go into discussions on the other specific issues. EC.

European Communities

174. Chairman, this is all fine and we can let you go on asking questions, no problem, but please bear in mind that we will have other questions later on, and it is only for that purpose we intervene. We restrain ourselves from intervening really in order to give you the time which you think you need to clarify these questions, but we will have questions to ask on practically the same issues which are being discussed now. So with this understanding there is no problem from us of not asking questions now.

Chairman

175. Thank you. It is quite clear to the Panel. Dr. Boobis you would like to – thank you. And the next question from the Panel is very technical and I don't even know whether I can pronounce the terminology correctly but I will try. Please explain the units used in measuring hormone levels, for example in Dr. Boisseau's response to question 38 of the Panel, in particular please explain ng per ml is or pg per ml, ng per person per day, microgram per day, and how they are converted. Dr. Boobis.

Dr. Boobis

176. There are two main ways of expressing units – actually, I was going to introduce another unit which is micromoles, but I will stick to two at the moment. These are masses per unit volume, so the base would be grams per litre, where we have so much mass in grams per one litre of liquid. They are scaled to units of 10 according to the Système international, the SI units, so they go: micro is 10 to the minus 6 of a gram, nano is 10 to the minus 9, pico is 10 to the minus 12. In expressing dosages in an animal study or with respect to human exposure we often divide by the body weight, so we get so many nanograms per kilogram of body weight per day. So that is where the kilogram comes from, that is to normalize it to the weight, and that is because many effects scale from one species to another – although how much is open to discussion, but that is a scientific debate – on the basis of body weight. So, in other words, if we give a microgram to a mouse it is not equivalent to giving a microgram to a human, because a mouse is so small, so we divide by the body weight to get a body weight-normalized dose, which allows a better – not ideal, but better – comparison of dosage. I was going to introduce the micromole if you wish me to clarify that, which is based on molecular weight, so it essentially allows compounds to be compared on the basis of how many molecules of one to how many molecules of another. Because when you take a small molecule, one gram is going to represent more molecules than when you take a large molecule; and if it is interacting with a receptor it is the number of individual molecules that counts, not the absolute weight, so sometimes we express them in terms of moles. I agree it is a technical issue, discussion.

Ms Orozco

177. Just one clarification. This, for example, nanograms per millilitre – is it already normalized by body weight or is that a second stage?

Dr. Boobis

178. A separate stage. This is a concentration, nanograms per ml.

Chairman

179. Thank you. Dr. De Brabander please.

Dr. De Brabander

180. Thank you, Mr. Chairman. I used to teach analytical chemistry and residue analysis to veterinarians, so I developed something to help them understand these units and maybe it will help also the Panel, so it is just not technical. If you start from a lump of sugar which is approximately 6 grams and you put that lump of sugar in a can of coffee, which is approximately 0.6 litres, you have approximately 1 per cent. When you put it in a bucket of water, then you have 1 per cent, and we are familiar with that because in alcohol control we are in that unit, 0.5 per cent is the limit in Belgium. When you go down and you place the same lump of sugar in a truck which is bringing the gasoline to your home, you are in a range of what we say 1 ppm, one part per million, or 1 milligram per kilogram, or 1 microgram per gram. If you go down and you have it in an oil tanker then you are at a level of 1 ppb, or one nanogram per gram, that is to say one nanogram per millilitre. So if you go still down (you can go down and down further) then you go really to very very low concentrations, like if you can imagine that you have a soccer field and you have submerged it with water from 1 metre high, and you take 1,000 soccer fields and you put one lump of sugar in it then you are again a concentration factor of 1,000 times lower. Maybe that can help the Panel understand. It is not very technical, I know, but I try to make it comfortable for you.

Chairman

181. I agree with your point of view on layman's terms explanations, because it was much helpful for us to understand. Dr. Cogliano.

Dr. Cogliano

182. Thank you very much. I would like to address a little bit of the point about the difference between nanograms per millilitre and nanograms per person per day, because at IARC many times we look at all of the studies that are published in the scientific literature, and different investigators will report the doses in different ways, and we need to try to get some kind of common conversion. It helps us to understand, for example, why one study might be positive and another study might be negative. The positive study might have been conducted at 10 times higher dose, but the units are expressed differently. The third one there, the nanogram per person per day, gives a good example of why you do want to perhaps normalize the dose, because a nanogram in an adult woman is very different than a nanogram in an infant per day. You could perhaps normalize it by body weight, but there might be other ways of doing it. The first unit that you have on the board, nanograms per millilitre, is a different way of normalizing it. It is the concentration in the blood, so it is one nanogram per millilitre of blood, and maybe that is an equivalent concentration, maybe it's not.

183. This actually suggests also why mechanism is important. I think you heard earlier this morning from one of the experts that the rates at which cells are dividing is very important, if you have one nanogram per millilitre while cells are dividing very rapidly, that might have different effects than one nanogram per millilitre in an organ where the cells are not dividing very rapidly. So it is important to try to understand the mechanism, and which of these different units of concentration or dose or exposure is most relevant. Now frequently we don't know which is exactly the right one, and we make our best professional judgement on that. But I think – just to help everybody understand – the units that you have up there are really measurements of very different kinds, and it might take a mathematical model or a conversion formula to go from one to the other. But if we do know how to make those conversions, it can help us understand how a dose in different studies or in different populations might relate to each other.

Chairman

184. Thank you. Dr. Guttenplan.

Dr. Guttenplan

185. Just another way of maybe expressing what has been expressed before, a microgram per ml is one part per million, a nanogram per ml is one part per billion, and then if somebody consumes a ml of a compound that was one microgram per ml that person would consume one microgram of that compound for every ml. It may sound simplistic, but it might help people to understand some of these units.

Chairman

186. Thank you. Dr. Boobis.

Dr. Boobis

187. So just two additional points of clarification. Dr. Cogliano has already referred to the concentrations in blood, and the question was raised from the Panel earlier about normalization, they would not be normalized for body weight because – depending on the sensitivity of the receptor – it is

the circulating concentration that determines response, and so one microgram per ml in a human and one microgram per ml in a rat are essentially equivalent. They may not give the same response, depending on the receptor, but they are equivalent because they are distributed throughout the body. And the other point is that, on the nanogram versus picogram, just a simple point of explanation is that the reason we use these different terms, and it does cause a lot of confusion I recognize, is to avoid the situation of getting into a lot of zeros, so if one expressed something that in picograms was 0.00001, we would just convert it back down to the next appropriate unit, to make it a slightly more manageable number, and that happens in both directions, so it is a practical consideration there.

Chairman

188. Thank you. Dr. De Brabander.

Dr. De Brabander

189. Yes, for the benefit of the Panel I should also say that if you work with students, you learn that they have difficulties to work with those concentrations, they really need a training on that. You can put very difficult questions, and what may be interesting also for you is that you should not underestimate the psychological factor, which is coming with how you will say how the concentration is. For example, if you say it is "0.1 milligram per kilogram" it sounds less than if you said "100 micrograms per kilogram" – but both are the same. The psychological factor of expressing the concentration is very important and veterinary students should learn to see through that.

Chairman

190. If there are no other follow-up questions, then the Panel's last question on this item is: what are xenobiotics? Dr. Boobis.

Dr. Boobis

191. They are from the Greek root xeno, foreign; biotic, to the life, so they are compounds that are not produced naturally in the body, so they are a whole range of so-called foreign compounds. Usually we exclude from xenobiotics nutrients in the diet, so the essential nutrients in the diet like protein, carbohydrates etc. will not be classified as xenobiotics, but everything else, all the chemicals we are exposed to would be regarded as xenobiotics. It is simply a convenient way of lumping together an awful lot of different molecules.

Chairman

192. Dr. De Brabander.

Dr. De Brabander

193. I agree totally, but I would add to that, if you go through all animals and all human beings the definition of xenobiotic is a little bit different, because some components may occur naturally in some animals and not in other animals and not in human beings. We don't have to go into detail, but it can be confusing if you speak about xenobiotic, it can be xenobiotic in one species and not in another one, and also in certain conditions.

Chairman

194. Thank you for your clarification. This concludes the list of the Panel's questions on area 1, and I now give the floor to the parties to ask their own questions to the experts under this particular item. The floor is open. I will give the floor to the EC delegation first.

European Communities

195. Thank you, Chairman. So in this broad area of terms and definitions we have one question first addressed to experts, in particular Dr. Boobis and probably Dr. Guttenplan. Dr. Boobis says in his reply to question number 2, where the definition of steroidal oestrogens is provided, at the end of his reply, that these substances – steroidal oestrogens – act through oestrogen receptors, and my question is: is it really the only way they act, is it only through oestrogen receptors, or do they act through another mechanism, one or more?

Chairman

196. Thank you. Is Dr. Boobis or Dr. Guttenplan ready to respond? Dr. Guttenplan.

Dr. Guttenplan

197. The evidence that oestrogens act through a non-receptor mechanism is not strong. There have been a lot of studies of what we call *in vitro,* in test tube studies, but there is some recent evidence that has not been published yet which pretty much confirms that oestrogens can act by a genotoxic mechanism in humans. However, the level is very very low and you need supersensitive instruments to detect it.

Chairman

198. Dr. Boobis.

Dr. Boobis

199. I think it is important that we recognize that there is a difference between what a given oestrogenic compound can do and what we mean by oestrogenicity. So we can argue or discuss whether oestradiol has various properties, but some of those properties may be additional to its oestrogenic activities. Oestrogenicity is a defined biological term and it functions through specific biological pathways, which is not to say that some compounds which are oestrogenic cannot have other properties. So I think we need to make a distinction, we cannot lump everything that is oestrogenic into one chemical class and say that it always has other properties. It is absolutely clear that not all oestrogens have any genotoxicity, not all of them, some of them do, some of them don't. It is probably not a function of oestrogenicity that causes that effect, it is some other property that they have, in the case of oestradiol, it produces quinones; not all oestrogens can produce those structures.

European Communities

200. Gentlemen, I recall, if I may say so, in a statement by Dr. Guttenplan, that these steroidal products, oestrogens, do not act only through the receptor, may they act through another means? And this is my question. Because in his reply Dr. Boobis only says they act through receptors, oestrogen receptors, which is in fact not true. There may be another way in which they act.

Chairman

201. Dr. Boobis.

Dr. Boobis

202. There are examples of oestrogenic antagonists, that were designed to interact with oestrogen receptors for therapeutic purposes, and these compounds have been studied using the most sensitive methods known to man for interaction with DNA, accelerator mass spectrometry, and have been shown to be negative. Now what that shows to me is that the oestrogenic structure *per se* itself does not necessarily lead to the capacity for genotoxicity. I am not saying that some of these compounds might not do that, but I think it would be inappropriate to regard that as a property of their oestrogenicity. That is the point I am making.

Chairman

203. Thank you. Dr. Cogliano.

Dr. Cogliano

204. I would like to say that last year the IARC monographs evaluated combined oral contraceptives and hormone therapy that combined oestrogen and a progestogen at the same time. And the expert working group concluded that both of these kinds of exposures clearly did have receptor activities, but that there was also some evidence of genotoxicity and that it was possible that they acted both through a hormone receptor mechanism and a genotoxic mechanism. The evidence was that it is obvious that they do have a hormonal effect, but the expert working group at IARC last year did conclude that these oestrogens and progestogens that are used in birth-control pills and in hormone therapy could have some evidence of genotoxicity as well.

Chairman

205. Dr. Guttenplan.

Dr. Guttenplan

206. Just to elaborate on what Dr. Boobis said. The oestrogenicity has no direct relevance to the genotoxicity of the compound – different effects. And I think of all the compounds and hormones that are possibly present in beef, the only one that might have genotoxic effects is oestradiol, and these would be very weak but they might still be there.

Chairman

207. Thank you. Does the EC have more questions? EC.

European Communities

208. I would like to ask the experts if they could restate or provide again their views on the mutagenicity in this case and how that relates to genotoxicity, in particular the DNA damage? And what is the role in that respect, and the conclusions we can draw, if a product is or is not mutagenic for the purposes of genotoxicity? Thank you.

Chairman

209. Thank you. Dr. Guttenplan.

Dr. Guttenplan

210. A mutagenic substance alters the structure of the DNA permanently and heritably. So DNA has if you would, an alphabet. If even one letter of that alphabet is changed, you have a permanent heritable change in that DNA, which will be transmitted to future cellular generations. Very few mutations actually are deleterious, most mutations are innocuous. And then of those that have deleterious effects, very few of them are in growth control genes. So the probability of a substance that causes mutations also causing, say, a cancer-causing effect would be very small. An agent that damages DNA is a potential mutagen. That damage is mainly going to be repaired, but if a little bit does not get repaired or is misrepaired – there are DNA damage responses that make errors when they repair – then you can get a mutation. So a substance that damages DNA may give rise to mutations and it may be carcinogenic. As was elaborated before by Dr. Boobis, there are many mechanisms by which chemicals can cause cancer, genotoxicity is only one of them.

Chairman

211. Does that conclude the list of questions from the EC? I give the floor to the US. You have the floor.

United States

212. Thank you, Mr. Chairman. The United States has only one question, so I will keep this brief. I would ask Doctors Boobis, Boisseau and Guttenplan, who I think spoke on the terms and definitions section on similar issues, if you could please explain the difference between oestrogen and oestradiol 17-beta (17β).

Chairman

213. Dr. Boobis

Dr. Boobis

214. Oestradiol-17β is a specific compound. Amongst its properties it can bind to oestrogen receptors. Oestrogen is any compound with a steroidal structure that can bind to those receptors, so it is a class of compounds.

Chairman

215. Thank you. If that is all from the US, then I give the floor to ... Are there any experts to add to the comments made by Dr. Boobis on this question before I give the floor to Canada? If there are none then I will give the floor to the delegation of Canada.

Canada

216. Mr. Chairman, we have no questions at this time on the definitions. The discussions on the definitions has been very fruitful and clarified some of our questions. Thank you.

Chairman

217. Thank you. We have 30 minutes to go before lunch break, but given the time constraints I would like to move on to the next item, that is risk assessment techniques. As was the case for the first item on terms and definitions, the Panel will pose some questions first and then invite the parties to pose their own question to the experts. The Panel's first question is composed of three parts; one is: how are ADIs and MRLs determined? and how do JECFA and Codex interact? The floor is open to answers by the experts.

Dr. Tritscher

218. Thank you. I would like to start with the first part, on how ADIs are set, and the latter part I give over to my colleague. In this context I would like to refer to the basic document that explains how ADIs are set. I will make it very brief in my explanation, but it is explained in detail in Environmental Health Criteria 70, Principles for the Safety Assessment of Food Additives and Contaminants in Food, published by the World Health Organization in Geneva 1987. Again in the interest of time I will make it very brief and basic and then if there are additional questions I think I can explain later. ADI is an acceptable daily intake and is a chronic health-based guidance value. It denominates the amount that can be consumed over lifetime without appreciable health risk. As Dr. Boobis alluded to in the beginning, appreciable is not a legal term or anything like that in this sense, it just denominates the basic concept in toxicology that there is no zero risk, there is always some level of risk.

219. Now the accepted daily intake is established from the overall toxicological database. Experts review all available data, and since it's a chronic long-term guidance value the emphasis is on long-term studies. Mostly we talk about experimental studies from experimental animals that are treated under very defined circumstances and conditions with the specific compounds of interest. And from these studies no effect levels are determined; levels of exposure that do not lead to any adverse health effects in the test species. I have to add that sometimes of course there are also human data available that are also taken into consideration. From this no observed adverse effects level in the experimental studies it is then – with a number of uncertainty factors, or also called safety factors – extrapolated from experimental species, if we talk about animals, to the human situation. With another uncertainty or safety factor it is then taken into account that there is possibly broader variability in the response of the human population as compared to a more defined experimental setting, so that no observed effect level is divided by these combined safety or uncertainty factors in order to arrive at an acceptable daily intake level for the human population. Mr. Chairman, is this sufficient as a brief explanation for the Panel?

Chairman

220. Yes, I suppose so. May I ask Dr. Wennberg?

Dr. Wennberg

221. The acceptable daily intake is established by JECFA. To then go through the procedure which is used by JECFA since JECFA started to evaluate veterinary drugs, is to derive the MRLs from the data on the pharmacokinetics, the metabolism and depletion of the residues from the tissues after the last administration of the veterinary drugs in the animal in which the product is to be used. JECFA has developed a decision tree procedure to arrive at the maximum recommended maximum residue limit, which consists more or less of the following. As we were talking about the marker residue before, JECFA determines what is the most appropriate marker residue in the circumstances for the various tissues which have been chosen by JECFA to be included in a standard food basket to be consumed every day. This food basket consists of 300 grams muscle, which is meat, 100 grams

liver, 50 grams kidney, 50 grams fat, 1½ litres of milk, 100 grams of eggs and 20 grams of honey – in the case of milk and eggs and honey, if the product is to be used in lactating animals, laying hens and honeybees, respectively.

222. Then JECFA requires a study using a radio labelled compound, which means that the substance, the veterinary drug, is marked so that all the molecules of the substance can be found in an animal and compared to the amount of the marker residue which can be found by the analytical methods that I will come to later, which is used to analyse the marker residue. Then the recommendation of the MRL is an iterative process which has been described in our answer to question number 9, in that JECFA tries to find the balance of the values where, given the depletion of the residue from the various tissues, which can be different, as a marker residue can remain longer in the liver or longer in the fat or longer in the kidneys. So for the practical purposes of using veterinary drugs, to establish a time where all the residues, if they were targeted for the specific food basket, would be below the ADI. So to try to balance the different levels of the total residues to the marker residue with the different concentrations at different time points in the tissues of concern, JECFA is making these calculations to make the best fit. And if, for example, the first calculation results in that the sum of all the total residues are significantly above the acceptable daily intake, then of course one has to adjust the calculations to arrive at final recommendations of the maximum residue limits for the marker residue, which if the drug is used according to good practice or use of the veterinary drugs, as defined by Codex, would result in the total residues being below the ADI. And then I could remind maybe the Panel and the rest of the experts and the parties that the food basket that has been chosen by JECFA is quite a substantial amount of food from animal original to be consumed every day. So in a sense it is also an over-estimation of the consumption of residues.

Chairman

223. Thank you. So who is going to respond to the second part? Dr. Miyagishima please.

Dr. Miyagishima

224. Thank you, Mr. Chairman. Let me briefly explain how Codex interacts with JECFA. As I mentioned in my introductory remarks, Codex is a risk-management body and, contrary to the perception which some people have according to which everything starts with risk assessment and then is followed by risk management, in the Codex/JECFA system the story starts with risk management, and the first component of risk management, called preliminary risk management activities. First of all, in the specialised Committee of Codex dealing with residues of veterinary drugs in foods, CCRVDF, the discussion takes place as to what compounds in what foods may pose public-health risks or may lead to barriers in international trade. And the Codex members in this Committee discuss, among themselves, on what compounds new work should be started within the Codex system. Of course they take into account various factors, such as whether the product itself is available as a commercial product, whether good agricultural practice has been established that goes with the use of the compound, whether there are sufficient amounts of scientific work that would warrant sound assessments by JECFA. When these conditions are considered to be met, then the CCRVDF puts the compound on what we call the priority list for evaluation by JECFA, and this is sent to JECFA for evaluation. You can put in this list compounds that were already evaluated by JECFA in the past, or you can put a new compound that has never been evaluated by JECFA; you can nominate a compound for which the Codex has already established an MRL, or you can also include a compound for which no Codex MRL has been established. It is up to the CCRVDF to take various conditions into account and set priority for compound assessment.

225. After JECFA has conducted risk assessment on these compounds, and when the result, including the recommended MRL, is sent to CCRVDF, CCRVDF usually sends or circulates the recommended MRL at step 3 of the Codex step procedure; that is the step at which government

comments are invited. The comments made are considered and are looked at at a physical meeting of CCRVDF at step 4, and then MRLs usually follow the way through the final adoption at step 8; and of course at each step the Codex will have due regard to the scientific output of JECFA, but also take into account other factors that are deemed necessary to be looked at. And in this process there is interaction between Codex and the JECFA system. If Codex, namely CCRVDF, wants to have more information on certain issues, CCRVDF has the ability to ask those questions, either general or specific, to JECFA, and also Codex may request a particular type of risk assessment or scenario analysis and other kinds of supplementary information to JECFA, and it is up to JECFA to answer those questions. Thank you.

Chairman

226. Thank you. I understand that Dr. Boisseau would like to add. Before I give the floor to Dr. Boisseau, may I give the floor first to Dr. Tritscher please.

Dr. Tritscher

227. Thank you very much. Just to emphasize again the ADI and MRL and the interaction between JECFA and Codex. The ADI is established by JECFA; it is the outcome of the risk assessment, if you want, and it is not for discussion at the Codex, so that is a value that is established by the risk assessment body. The MRL as it is proposed by JECFA, is based on scientific studies and data that are made available to the expert body and that are evaluated by the risk assessment body, by JECFA, and then the MRLs are proposed to the respective Codex Committee, CCRVDF in that case. And then the risk management body, so the Codex, the CCRVDF is the risk management body, takes this proposal into account and can consider other factors in setting the final MRL. That is all it is, just to emphasize it again. Thank you.

Chairman

228. Thank you for your clarification. Dr. Boisseau has the floor.

Dr. Boisseau

229. Thank you, Mr. Chairman. I agree, of course, with what was just said by the three preceding speakers. I would simply like to add a few details. We are accustomed to saying that in order to determine an admissible daily intake, we perform an evaluation of the toxicological profile of the substance studied. In fact, toxicology is a somewhat narrow term, since the experts will focus not only on the toxicological effects, but will be looking for all of the undesirable effects which, in addition to the toxicology, could include physiological and microbiological effects. And for each study concerning one of these aspects – toxicological, physiological or other – the experts establish an intake that has no effect, and depending on the nature of the undesirable effect observed, they will allocate to that intake which has no effect an appropriate safety factor which may range from ten to 1,000, enabling them to obtain a series of acceptable daily intakes. Finally, the committee – the CVMP or the JECFA – will select the most restrictive of these daily intakes, in other words the one that is most protective of public health. So it is important to take account of the great variety of tests involved and the fact that at the end of the day, the daily intake selected is the one which is most protective of public health. You will probably ask later on about the safety factors considered throughout the process of determining the ADI and the MRL, so I will not address that issue now.

230. Let me add that usually, these toxicological studies are experimental studies that are conducted with the parent substance for practical reasons. But where feasible and justified in view of the toxicological profile of a given metabolite, this kind of study can also be conducted with a

metabolite whose toxicological or pharmacological profile could make it the limiting factor in terms of the evaluation of the safety of the residues.

231. Finally, I just wanted to add a word or two, if I may, on the distribution of the risk assessment and risk management tasks between the JECFA and the Codex. It is customary, in conducting a risk assessment of an environmental product, for the scientific committee to conclude its risk assessment with an indication of the probability of risk for a given population or sub-population. The residues of veterinary drugs are a somewhat special case, since we control the administration of veterinary drugs to animals, and the JECFA therefore goes beyond the mere appreciation of the risks, since that appreciation more or less stops with the determination of the ADI. With the determination of the MRLs, the JECFA is deliberately entering into the realm of risk management, since an MRL is a tool, a proposal to ensure that the ADI is not exceeded with regard to the standard food basket as mentioned a short while ago by Dr. Wennberg. This is a somewhat special case, since one can effectively manage the situation and the objective. The objective is not only to assess the risks, but also to minimise the risks to which consumers of foodstuffs of animal origin could be exposed.

232. However, this does not detract from the JECFA's responsibility for risk assessment and the responsibility of the Codex Committee (CCRVDF) for risk management, since when it comes to MRLs, the JECFA, which is a competent scientific committee qualified to make proposals, makes proposals only, while the risk manager – in this specific case the CCRVDF – is the one that takes a decision. In other words, the fact that the JECFA makes MRL proposals on the basis of the competence of its WHO or FAO experts does not mean that it can be accused of interfering in risk management. It is the decision maker that manages the risk, i.e. the CCRVDF with the Codex member states. Thank you.

Chairman

233. Thank you. Dr. Wennberg.

Dr. Wennberg

234. Thank you, Mr. Chairman. Yes, could I just add a few comments, also regarding the possibility of temporary MRLs, or is that another question that you have? So JECFA will make full recommendations for quantitative values for MRLs if there is adequate data to do so and if this is in accordance with the ADI. There may be instances where there is enough information to recommend MRLs, but the analytical method to determine these MRLs has not been sufficiently validated to the use in control laboratories worldwide. In such instances, as the process in Codex is quite long, JECFA may recommend temporary MRLs, and providing an opportunity for submission of additional information to a next meeting or a future meeting of JECFA for evaluation of the validation of the analytical method. This has happened on occasion. Also the Committee of JECFA may recommend MRLs not specified, or unnecessary as it was termed in very old reports, where there is a wide margin of safety of residues when compared to the ADIs, and which would mean that it is not necessary to control this substance when it is used in accordance with good veterinary practice, because the values will never come anywhere close to the ADI. And finally, of course, if there is not enough information for JECFA, and there are deficiencies in the data available to the Committee, they will of course not recommend MRLs and they never have recommended MRLs if there is no ADI established.

Chairman

235. What do you mean by temporary? When and under what conditions will temporary MRLs be terminated?

Dr. Wennberg

236. Temporary MRLs are recommended with a qualification that if the specified information, which is also specified in the report, is not submitted within a certain timeframe, then the MRL will not exist anymore. So if the JECFA Secretariat does not receive the required information, the appropriate following meeting of JECFA will take the decision that a temporary MRL will be revoked. And this information is transmitted to the CCRVDF and Codex.

Chairman

237. Thank you. As it is already ...

Ms Orozco

238. Just one qualification please. What kind of criteria are brought into consideration when an MRL is being considered; information that is different than the one that has been taken into account by JECFA? What kind of other criteria or other information is it taken into account by Codex?

Chairman

239. Dr. Miyagishima.

Dr. Miyagishima

240. Thank you very much. Indeed, within the Codex system there has been a lot of discussion that took place to better delineate those factors that can legitimately be taken into account when Codex elaborates texts. In fact the Codex Alimentarius Commission adopted in 1995 a statement of principle concerning the role of science in the Codex decision-making process and the extent to which other factors are taken into account. There are four paragraphs and these statements are reproduced in the Codex procedural manual. Later, in the year 2001 there were additional criteria adopted by the Commission that assist in the consideration of those other factors referred to in these statements, and this text is also included in the Codex procedural manual. Basically, the factors that may be considered as relevant for the protection of the consumers' health and/or for ensuring fair practices in the food trade can be taken into account and they can be moved by any members of the Codex bodies. It is up to the CCRVDF and ultimately to the Commission to weigh those factors and incorporate and take account of them in making a final decision. One could give some specific examples but I would rather not mention them at this stage. Thank you.

Chairman

241. US.

United States

242. Thank you Mr. Chairman. Just a quick follow-up on the response of the representative from JECFA, just a point of clarification. Did JECFA make full recommendations for MRLs for each of the six hormones involved in this dispute?

Chairman

243. Dr. Wennberg.

Dr. Wennberg

244. Thank you, Mr. Chairman. Well, the six hormones which are the matter of this dispute, as far as I understood, are oestradiol-17β, progesterone, testosterone, trenbolone acetate, zeranol and melengestrol acetate, is that correct? OK. So JECFA evaluated the three endogenous hormones, the first three ones, and on three occasions; in 1981 only for general considerations; in 1987, concluding that an ADI was unnecessary; and in 1999, establishing ADIs for all these three hormones. At the same time, a complete residue evaluation of these hormones was performed and is available in FAO Food and Nutrition Paper 41/12, and concluding that it was not necessary, on the basis of the residue data, to recommend full MRLs for these three hormones. As regards trenbolone acetate, JECFA evaluated this substance four times; in 1982, general considerations; in 1983, limited by good husbandry practice; and in 1987 and 1989, established first a temporary and then a full ADI. In the same way the residue data were evaluated and no MRLs were considered. No that is not correct. Can I have the lunch break to go back to the data and see about these three other substances, whether there were MRLs established for those?

Chairman

245. Sure. If you don't have the information now then you can do so. I would appreciate if you can respond to all the questions as briefly as possible. It is already 1 o'clock, so now I would like to have a lunch break and resume the discussions at 3 p.m. sharp in this room. I will see you all this afternoon at 3 p.m. Have a good lunch.

27 September 2006, afternoon

Chairman

246. [Beginning of tape] ... when our discussions were suspended, we were on the issues related to ADIs and MRLs and I believe that issues on this item, the risk assessment techniques, are at the heart of the discussions this afternoon. The Panel has a rather long list of questions, but as we understand it the parties are also very eager to put their own questions to the experts. I would like to be as brief as possible, not only in our answers and questions, but also I would appreciate if the experts will be very brief and succinct in their replies to the questions so that the parties can have more time to ask their own questions later.

247. The two follow-up questions regarding the first one I posed this morning also relate to ADI and MRLs, so I would combine these two questions together. My question is: does the ADI take into account the fact that some of the same hormones exist in other food and medicinal products and that therefore there are other sources of intake of the same compounds? The second one is: does the ADI take into account all uses of the hormones as veterinary drugs, including for example for zootechnical purposes? The floor is open for comments and replies, from JECFA first, and then I will give the floor to Dr. Boobis.

Dr. Tritscher

248. Thank you Mr. Chair. If I may ask, I happen to have slides on my computer that explain this and answer actually the two questions.[2] Just very quick, to the first question about the interactions of JECFA and Codex. This is illustrated here, but we have discussed, so JECFA as a risk assessment body interacts with the Codex as the risk management body. (Can I have the next slide please.) Now this illustrates what we actually do with the ADI and the exposure assessment, and this is to answer questions (b) and (c) that was just raised, if JECFA, in setting the ADI takes account of all possible

[2] Dr. Tritscher's slides are contained in Attachment 2 to this transcript.

exposures, to simplify the two questions. As I mentioned briefly earlier, the ADI, the acceptable daily intake, is the outcome of the toxicological evaluation, and as was mentioned earlier by one of the experts, in the case of veterinary drug residues, its toxicological effects, physiological effects, pharmacological effects, as well as microbiological effects are considered, and from that an ADI is derived.

249. Now the exposure assessment is then done separately from that, so in setting the ADI exposures are not considered. Exposure assessment is done separately in that the amount of the chemicals in the food times the amount of food consumed is considered, this is the exposure. And in the actual safety assurance you compare this estimated human exposure with the ADI, so if the estimated exposure is below the ADI, then the situation is OK, if the estimated exposure is above the ADI, then a risk management decision has to be taken. That can also be, from the risk assessment point of view, in the first step the refinement of the exposure assessment and so forth, so in an iterative process refining the exposure assessment and then comparing it with the ADI. Basically, and sure to answer the question, the exposure assessment is done separate of the ADI, so in a subsequent step the exposure has to be compared to the ADI in order to ensure safety of the overall food supply.

250. Very quickly a few comments on the international field, so from the perspective of JECFA. The exposure assessment in the case of veterinary drug residues, as my colleague from the FAO explained earlier, is based on a food basket diet, so on a model diet. In a national setting, exposure assessments can be done in a more refined way, because more specific data for that country would be available, for example with food consumption patterns and so forth. So in the international field, in the case of veterinary drugs we work with model diets in order to assess the estimated human exposure and to compare it with the ADI. And also, then the estimated exposure is compared with the MRLs that JECFA proposes in order to ensure that they are compatible with the ADI and hence they are compatible with public health. I would leave it at that and would ask you if you have any additional questions.

Chairman

251. Thank you. Dr. Boobis – ...yes, EC.

European Communities

252. To change the subject a bit right now, because all of the things that you have not been told is that there is a lot of data that you can't get because you don't have enough animals to do the testing, in many cases, and so there are assumptions made, what the dose-response curves looks like when there is no data, so it's a guess. These assumptions are a weak scientific statement and there are dozens of these assumptions, and one of them is that there is a threshold, a dose below which there are no adverse effects. A threshold is a theoretical concept and it is difficult or impossible to actually measure, because there really are not enough animals to be able to determine that there is a threshold or not. It would take thousands of animals and you could still find arguments that there are other data that suggest that these assumptions are not right. When there is a hormone that the body is making and is in circulation, and when you add more of the same kind of hormone, such as an oestrogen, you are just increasing the response that is already taking place, and in that case there cannot be a threshold. The threshold has already been exceeded by the concentration of hormones in the circulation. So this specific set of conditions results in dose-response curves that will have no threshold, and if there is no threshold, there is no safe dose, unlike the suggestion that there is an acceptable daily intake, and in a lot of cases an acceptable daily intake is legitimate, as long as there is not a counterpart to the chemical that you are giving and it does not exist naturally in the body, then you have the opportunity to at least justify an acceptable daily intake. But when those hormones are circulating and are already active and you add more hormones, particularly at lower doses, what you expect to get is an increase in the adverse effects, and under these conditions an ADI has no meaning

whatsoever. There will be risk at any dose no matter how low, and both Fred and I have demonstrated that at experimental studies and we have nobody that has been able to tell us or to show us where what we have done experimentally, and what we have done in terms of our conclusion, no one has shown us that it is wrong.

Chairman

253. US.

United States

254. Thank you, Mr. Chairman. Two quick points, one a point of clarification. The United States was under the impression that this was the opportunity of the parties to ask questions of the experts selected by the Panel rather than presenting evidence of perceived situations ourselves in response to Panel questions. On the second hand I would refer back to the Panel's e-mail or letter of last week noting that the evidentiary record in the proceedings had in fact been closed but for a showing of good cause to present new evidence, and we would note that a presentation of evidence as we just heard could fall within the ambit of that letter. Thank you.

Chairman

255. As I mentioned this morning, the purpose of this meeting is to request the experts to assist the Panel in discharging our duties as panellists, so it is quite clear to us. I also mentioned that parties will be given more opportunities to put their own questions at a later time in due course. So I would ask the delegation to limit their questions and comments or replies to those particularly related to questions put forward by the Panel. I give the floor to the delegation of Canada.

Canada

256. Thank you very much, Mr. Chairman. First of all, of course we want the Panel to get as much information they can out of this process and out of the experts as possible, and we certainly are not in any position, we don't want to limit the flow of information to you. But in the same vein as the questions raised by my US colleague, and we support the point, I guess as a matter of clarification, you mentioned questions may be put, I would like to know whether questions also includes arguments and expert testimony by members of the delegation of one of the disputing parties? I think, to the extent that we are talking about questions, that presumes that we are not talking about arguments or running monologues, or we don't want to get into a debate or discussion with the experts at this point, it would seem to me.

Chairman

257. Yes. As I made it clear in the opening statement this morning, the questions and comments have to be focussed on the information and replies given by the experts in written form. So I make it clear once again that the discussions that we are going to have this afternoon will also be focused on the information and comments and replies by the experts, without going further into the arguments on legal issues and those factual issues which have to be discussed next week on Monday and Tuesday. Is that clear to every delegation. OK. With that understanding …

Ms Orozco

258. Thank you, Mr. Chairman. I have a follow-up question to the information that has been presented by JECFA. In the case of hormones, for example, it is clear, as we have been told, that there are hormones in different types of food, so when you take establish the ADI, are you taking into

account the level of hormones that there is from the consumption of every product that contains hormones in an endogenous way?

Chairman

259. Dr. Boobis? JECFA, Dr. Tritscher

Dr. Tritscher

260. Just very quick. In the MRL derivation, the experimental studies are done in the actual food-producing animal, as it's called, so by default you have the levels that are measured in these studies contain endogenous levels of hormones as well, so if you want, by default they are included in this consideration.

Ms Orozco

261. Yes, but what I would like to understand is, it is the addition of all the hormones that you would intake in your diet, because I don't know if it is set by the product, by meat for example in this case, or if it takes into account all the intake of hormones, because you eat different things. That was the first part of the question, and I'll just explain to you the second part of the question, so I don't have to repeat so many times. In the same vein, do you take into account the intake of a veterinary residue that would exist of the same compound because of other reasons, so we have also seen that there are veterinary drugs that use hormones that are used for zootechnical treatments. Is that reflected in any way in the ADI?

Chairman

262. I would appreciate it if the replies would be right to the point, as succinct and as brief as possible, given the time constraint. OK?

Dr. Wennberg

263. OK. Thank you, Mr. Chairman. Well, the questions that are asked to JECFA from the CCRVDF are particular questions on the assessment of a particular residue or a veterinary drug, and it is used according to good veterinary practice. It's also said that for JECFA to assess a veterinary drug, it has to be authorized at least somewhere in the world, so there has to be a national authorization somewhere. I think we have to make it clear once again that JECFA is not a regulatory authority that authorizes the use of drugs. So the questions that are asked to JECFA are related, in this case of the natural endogenous hormones, to their use as production aids in cattle. So what JECFA has evaluated is first of all the toxicological evidence which enables JECFA to set ADIs, which is irrespective of the exposure, as we have just heard. And following on from that JECFA evaluated the concentrations of the hormones, as evidenced by the residue depletions studies and taking into account the endogenous concentrations of hormones in the meat.

264. Now, the endogenous concentrations of hormones in the meat are variable, and so its not possible to say that is X, Y or Z, because depending on the reproductive cycle of the animal, these levels vary. They can be high at certain times and low at certain times for the different hormones. So JECFA evaluated how much of the additional residues relating to the use of the hormones in question would represent in terms of the ADI, and we come to a very low figure, it's less than 2 per cent of the ADI for oestradiol, it's less than 0.03 per cent for progesterone and it's less than 0.2 per cent of the ADI for testosterone. That made the Committee conclude that it was not necessary to specify numerical MRLs and recommend MRLs not specified for these three natural hormones. Now, if you are using hormones, you can either use one hormone or you can use a combination, depending on

what kind of effect you would like to have. These uses are to be authorized by national authorities. JECFA does not enter to efficacy of the use of these hormones.

265. When you are using xenobiotic hormones which are not natural, these are also governed by national authorizations, how much you use and under which circumstances. And in these cases, as I was asked before the lunch break, I was going to come back with MRLs that JECFA had proposed, recommended for these substances. So for these substances, ADIs were set specifically for these substances, so they are not put together with other hormones, because the effects that were evaluated in the toxicological assessment enabled the Committee to set an ADI for these specific substances. So you don't consider all different hormones with different kinds of effects and different types of profiles in the same evaluation. So if you use one hormone, that's the hormone that you are using at this time. There may be combinations but if they are authorized on a national level that's it. So for the three xenobiotic hormones, JECFA set full MRLs, recommended full MRLs for all three of them. This is available publicly and unless the United States want me to actually give you the levels, I will make my intervention shorter by not mentioning them. If you have any further questions I will be happy to answer.

Chairman

266. Thank you. So are any other experts intending to add any more comments? EC.

European Communities

267. Gentlemen, I think there are other more simple and I hope more clear ways to reply to the question. Now this is given in the reply of JECFA to question No. 10; it is already in your files. So you will see that JECFA says that they do not take into account data on the intended or actual use and consumption – the way the substances are going to be used or consumed, they don't take data into account. It is in the file. This is the reply to the question, the second of the questions. How they are going to be used and how they are going to be consumed; they don't take this into account. This is a purely generic toxicological study, without consideration of where they will be used for. A body with good veterinary practice or not, whether they would be misused or not, there would be more implants, in one implant there will be more hormones, one, two, three or not, this is not considered. As the doctor has said, it's only a single substance that is analysed.

268. Now for the first question, again on the reply of JECFA to question number 10, you will see they speak about the so-called basket and whether there are intakes of the substances from other sources, and there you will see the basket consists mainly of steak, meat and muscle, meat and liver, meat and kidney and they have milk, eggs and honey, but of course it does not exhaust all the other possible sources which humans eat every day and from which intake of these hormones can come. This is the reply to the first question and it is explained also in the text. Thank you.

Ms Orozco

269. Excuse me, an interruption just for completeness. What other sources are you thinking about? You say that there other ways in the diet of humans, other than the food basket of JECFA, what other sources do you have?

European Communities

270. For example, speaking about butter, I can think of a list of substances a human eats every day. Some of them may contain more hormones, less hormones. Or other kind of meat. So these are things which – I understand it is difficult to devise a basket that is really representative, and the representative of JECFA has said they leave it to the national authorities to see, in each EC member

State, in each country, according to the nutrition habits probably. If one country eats some substances a little more than what is in the basket, they would have to be reviewed, these calculations. But certainly humans one day eat not only 300 grams muscle, 100 grams of liver or 100 grams of kidney and so on. So there are certainly other sources from which we take in these substances. This is not disputed in the science. And if you allow me to clarify, in reply to what has been said by the representative of JECFA – this is very important – the toxicological analysis takes into account a substance individually. We will come back later to this. None of the implants as far as we know consist of one substance only, there is more than one substance. It means the majority of the implants contain more than one of these hormones together, and the data which they have examined, they don't take this into account. The toxicological data they take into account, they don't examine the possible additive or synergistic effects of these implants, and these possible effects they have not been examined because it is not done. It has not been done before by the countries that have authorized these substances, for example. Thank you.

Chairman

271. Dr. Tritscher would like to add some more comments.

Dr. Tritscher

272. Yes, I have to respond to that and clarify a couple of points that were not exactly correct in the intervention by the EC. (May I kindly ask you to put up a second slide, what I have on JECFA MRL, that is what it is called.) This is just a little graph, an illustration how JECFA does residue evaluations. Just to illustrate that it is based on specific detailed studies in the food producing animal. (Thank you, that's it.) As I said earlier, so you have detailed studies in respective animal species for what the veterinary drug is intended to be used for. So by default, and that is what I tried to say earlier, you consider endogenously occurring hormones as well as the additional treatment, that is by default, because that is what you measure in the end if you measure a synthetic hormone for example. So based on these studies, the residues, the MRL, is derived. And then from the studies, from the median residue level in these defined studies according to good veterinary practice – this is very important because it is incorrect what was said before, that this is not considered, it is considered. Only studies that are field trials and studies that are performed under good veterinary practice. And we have a small definition, but the problem here is that there is no internationally agreed definition. But from these studies the median residue level is taken for the intake assessment according to the model food basket, as was correctly said.

273. Now this model food basket was constructed in a way to reflect exactly these commodities as animal-derived foods that may contain veterinary drug residues, and butter, for example, it is self-understanding that butter is covered by milk, because butter is milk fat. So there are all these different types of commodities that are covered in the model basket, in a way, to give you conservative – and conservative in our language means a high level – estimate, rather than going too low. And as I mentioned earlier, or what I tried to explain, is that JECFA has to consider a worldwide model, and I did by no means say that JECFA leaves it up to national authorities to do an exposure assessment. JECFA does do an exposure assessment based on this model diet, taking conservative assumptions to give them an idea of what the estimated exposure on the higher level could be. National authorities have the possibilities, based on refined data, to refine these intake assessments – to use data, additional data, that are adapted to, for example, national food consumption habits, or that are adapted to national registration for a specific purpose of this use of a veterinary drug, that is maybe only allowed in this country. So there may be additional exposure sources in a specific country that only that country can take into account, that cannot be taken into account if we have to give a recommendation on the international basis. Moreover, what this model basket reflects and the ADI reflects is a chronic exposure. We are not talking about somebody who eats half a beef on one day because there is a big wedding party somewhere, excuse me to talk like this, but just to say what we

are trying to do here is to get a conservative – in a public health protective way – a model that is sufficiently protective over a lifetime exposure. And I think that are most of the comments I wanted to make now. Thank you.

Chairman

274. Dr. Wennberg.

Dr. Wennberg

275. Yes. I have two more comments to make on this. The first one is on this model standard food basket. It is internationally accepted; it is also used in the EU. And the second comment is that the studies performed in the field trials which were evaluated by JECFA reflect the use of these products also in combination, if it was the case that these were the authorised uses in the particular country. So for the endogenous hormones, the combination in terms of the exposure was evaluated, and the additional exposure, based on the use of these hormones compared to the endogenous one in relation to the ADI for each of the substances was calculated. So I do not consider that JECFA only looked at one single hormone in one single instance. The ADI is of course specific for each substance, because there are specific endpoints which have been used for the establishment of the ADI with the no effect level. So you cannot combine different hormones which have different endpoints in terms of toxicology and say that you can lump them together and say that if I use this and this and this I get an increased toxicity. You have to look at each of the hormones and their endpoints, which is what the ADI is based on, to see whether there is a risk to public health or not.

Chairman

276. Thank you. OK. EC please.

European Communities

277. Mr. Chairman, I don't want to become polemic, but I think in the documentation of JECFA and Codex which we have seen, toxicological data, and the evaluations of combinations of implants have not been performed, as far as we know, not for all the substances which we are talking about here. So if the representative of Codex and JECFA think otherwise, we would like to see this paper. We have asked the United States and Canada to provide this paper; they didn't give them to us. So if they are claiming something, we need to see these studies, toxicological and residue studies, where they claim that the combinations of implants, where more than one hormone is contained and administered, has been performed. As far as we know they have not been done, not for all of them. If you allow me to come back on the first question replied by Dr. Tritscher, the basket, of course we have a basket similar to what Codex and JECFA have in their evaluation, but the point, I think, that the member of the Panel was trying to clarify is that we eat daily so many food products and otherwise which contain the same substances, or substances which have the same or similar toxicological effects and activities, and these of course are not taken into account. This is what we would like to clarify. There are so many other substances which have oestrogenic activity when they are consumed in food and this has not been examined. I don't know if it is feasible to be examined. I think it is difficult but it is not impossible and probably the countries which have authorized these hormones must have performed this before they authorized it. And later on we will give you precise reference to our assessment where we do mention this potential risk, possibly from these other sources. Thank you.

Chairman

278. Dr. Boobis.

Dr. Boobis

279. I don't propose to get into a long discussion at the moment on this issue, but I would just make the comment, since it has been raised, about the totality of exposure to oestrogenic compounds in our diet. There have been estimates of the total exposure to oestrogenic compounds, and by far the dominant source of those compounds is natural oestrogens which are produced by plants in our diet. These far outweigh the traces of oestrogens from other sources, either natural oestrogen coming from non-treated animals or the presence of growth-promoting hormones used to treat animals. That is not to say I have addressed the question of incremental risk, I assume that will come up later, but just to point out, in terms of the total burden of oestrogen exposure, this is a much broader question than just the hormones coming from beef, it would open up the whole question of nutritional exposure as well.

Chairman

280. If the JECFA representative is not in a position to clarify on the question posed by EC then can I ask the representatives to move on to the second part of the question. Am I right to understand that the second part of the question has not been fully responded?

Dr. Tritscher

281. Could you please repeat the second part of the question?

Chairman

282. Does the ADI take into account all uses of the hormones as veterinary drugs, including for example for zootechnical purposes? Dr. Boobis.

Dr. Boobis

283. I tried to emphasize this, and I think the joint secretariat has made this point, but it bears repeating. There are two different questions here, and we have tried to answer the specific question. The ADI is derived from toxicological information. We can argue about the security of the conclusions, but it does not consider, nor should it consider, exposure or the use patterns. It is based simply on the toxicological properties and the biological properties of the compound itself. You then come up with a health-based guidance value, the allowable daily intake, that is then compared with exposure. And the second question which one might pursue, and I think we have been, is to what extent are all different exposures taken into account, but that is a separate question from the ones on the board, Mr. Chairman, which is that the ADI does not take account of other uses nor should it.

Ms Orozco

284. Total exposure from food then should be taken into account during the exposure assessment?

Dr. Boobis

285. Yes, indeed. That is where it would come in if it was going to be taken into account. It does not come down the left-hand side of Dr. Tritscher's diagram, which is the ADI derivation based on the toxicology, it comes down on the right-hand side, which is exposure evaluation. And then it becomes a risk management question as to how broadly are you going to include exposures other than those that arise from GVP, good veterinary practice, because of course JECFA bases its evaluations on the use of the compound according to good veterinary practice.

Chairman

286. OK. I hope we can conclude the discussion on this question as early as possible. I will give the last chance to EC.

European Communities

287. Chairman, I am afraid we cannot conclude these discussions because we have a number of other questions, but I would agree with the first reply of Dr. Boobis, that the way the ADI is performed by JECFA does not take into account other use of these hormones, like zootechnical or therapeutic use. The claim is that they cannot do it, or they don't want to know that they may be used in that way, fine, but for the purposes of your consideration this is true, they do not take any, and this actually has been said in the reply of JECFA, which if you wish I can read today. The second question is the reply of Dr. Boobis about where exposure from other sources has come in. If the reply of Dr. Boobis were to be true, then what JECFA does is not correct, and I think that the reply is somewhere in between. It is not as clear-cut as JECFA present it or Dr. Boobis would like to present it, because it all depends what these other sources are and what they contain. And if it is biological activity, in this case we speak about carcinogenesis, it has to be taken into account in the first step, in hazard identification, it is not only the in exposure assessment that we need to consider it. So I think we will have the opportunity, if we go down the questions later on, to clarify this instead of dwelling now on this issue in a generic manner. But if you allow me – because my questions relate to the two questions which you have asked, the first before the lunch break and the second now – if you allow me to have three follow-up questions on this.

Chairman

288. Please do that at a later stage, as I mentioned earlier, because I think that the situation may be the same for other delegations too on the other specific questions.

European Communities

289. Well, I think, if you allow, I will ask at least one question of the three I have.

Chairman

290. OK. With the understanding of delegations, please go ahead.

European Communities

291. Chairman, in the reply of Codex to question number 4, for your consideration I only read the first sentence: There is no adopted Codex standard or related text on the risk assessment of residues .... So what is being talked about here – there is no standard about how to do this risk assessment, techniques and how you set the ADI and MRL. These are the methods used and developed by JECFA, but they are not presented in an assembly of an organ for adoption so that they become standards in the sense of the SPS Agreement. They are considered by some committees and JECFA and a few scientists, as they say, they are developed by individual persons who happen to sit on those committees and they thought that is the relevant model. But the truth is, and this is relevant for our case, there are no agreed international standards on how to do a risk assessment in that sense. The other questions I will keep for later on. Thank you.

Chairman

292. Thank you for your cooperation. Is it on a procedural matter, Canada?

Canada

293. I would simply – I did not hear a question there – but I would propose a question too. I think Drs. Boisseau and Boobis both spoke to the last point raised by the EC, on how safety assessments are conducted and the process by which that's done, and I wonder if they had any comments on the EC's last statement.

Chairman

294. Can I give the floor to Dr. Boobis.

Dr. Boobis

295. I think it is not entirely accurate to say that it was a few scientists at JECFA who developed risk-assessment methodology; this evolved out of the National Academy in the US. It has been developed by the International Programme on Chemical Safety and is the cornerstone of risk assessments by almost everybody. The four-step risk assessment paradigm, as we call it, – hazard identification, hazard characterization, exposure assessment and risk characterization – is very very widely use. It has been endorsed by essentially everybody conducting risk assessment on expert bodies. There has been lots of discussion about whether or not this is applicable to veterinary residues. The view widely held is that there is nothing fundamentally different about the philosophy of evaluating risk of a veterinary residue, as opposed to any other specifics about the exposure assessment; one has to work out the residues in meat from treated animals, but that is a technical detail, as opposed to the overall philosophy that underlies the strategy. So I think that it is not accurate to say that this is something that has been cooked up or produced by JECFA in an informal manner, it has been widely validated by many organizations. And in fact I believe it is in the Codex Manual as well, at least allusion to the general principles.

Chairman

296. If Canada's point is not related to the procedural one, can I give the floor to the experts first, because I saw their flags were raised before you did. Dr. Boisseau and then Dr. Miyagishima.

Dr. Boisseau

297. Thank you, Mr. Chairman. I am sorry, but there were many questions in rapid succession, and I wanted to take the floor following the statement by the European Union to the effect that ultimately, there were various utilizations that the ADI could not take into account. I think we have to be fairly precise on terminology, because otherwise we will be going round in circles like this for hours, without getting anywhere. The ADI has nothing to do with exposures, as Dr. Boobis quite rightly said. The ADI does not need to take account of exposures, it is the logical conclusion of a toxicological evaluation. By "toxicology", we may also mean "pharmacology" or any adverse effect. In any case, it is important that we bear this in mind. Now, we must not confuse the Theoretical Maximum Daily Intake (TMDI) with the daily amount ingested which is the sum of the amounts actually ingested from different sources, and we compare, as the joint secretariat said this morning, I think, the amount ingested with the ADI. So we must stop linking the ADI with the amounts ingested, otherwise I can see no way out.

298. Secondly, regarding the standards and the protocol that we have just spoken of, there is currently a cascade protocol, so to speak. We have, today, a general structure for risk analysis and risk assessment. However, it is true that the JECFA applied this risk assessment to the consumer safety assessment of veterinary drug residues, with the exception of antimicrobials, for several years without a detailed assessment protocol – that work has been going on for a number of years within the

JECFA. However, before the work was done, this protocol was perfectly well established in the minds of all those throughout the world who, at the JECFA or EU level (I am thinking of the CVMPs), use the same methods. Moreover, it was the same people working in the different bodies, so we can hardly say today that this work was done more or less according to the mood of the moment. There was a consensus on the way that this methodology for assessing the safety of veterinary drug residues should be applied. It was neither written, nor formally adopted, but the methodology was perfectly operational and universally accepted. Thank you.

Chairman

299. Thank you. Dr. Miyagishima.

Dr. Miyagishima

300. Thank you, Mr. Chairman. I would like to add some clarification as to what is meant by the Codex reply to question number 4. We did confirm that there is no adopted Codex standard or related text on the risk assessment of residues of veterinary drugs. When we call something a standard or related text, that means any text that is part of the Codex Alimentarius. The Codex Alimentarius is a collection of adopted standards and related texts that are there for guidance or for use by governments. In this particular case the Codex relies on JECFA, and Codex uses primarily MRLs as a tool for risk management. Codex in this sense has not attempted to provide guidelines for governments to conduct risk assessment, because JECFA does the business.

301. This is the reason why the document on risk assessment policy and the whole risk analysis framework related to the work of CCRVDF, which is now in elaboration, is not meant for inclusion in the Codex Alimentarius even if after it has been adopted by the Commission in the future. It will be eventually included in the Codex Procedural Manual, because the document describes the way the Codex interacts with JECFA. So the scope of the document has no links with the guidance Codex intends to provide to governments. This is the reason why the Codex replied that there is no risk assessment guidance within the Codex Alimentarius. In other areas such as microbiological risks in foods, the Codex has taken a different approach, and the Commission adopted risk assessment guidelines which have been included in the Codex Alimentarius. But with the approach the CCRVDF has taken, and the Codex Commission has taken so far, there has been no need for providing guidance to governments directly in terms of risk assessment techniques. Thank you.

Chairman

302. Thank you. EC – sorry, I forgot that the Canadian delegation has raised its flag. Canada.

Canada

303. Thank you, Mr. Chairman. It is always illuminating and interesting to listen to my friend Mr. Christoforou, so I didn't want to deprive him of the podium. But I think, as this exchange demonstrated, in fact it was immediately after the intervention of my American friend who put the statement into the form of a question, we can actually have a very fruitful contribution from the experts when instead of making statements and arguments we put simple questions to them. And I hope that my EC colleague will respect your guidance and in fact your initial statements about the way this process is to be made, which is that at this point instead of making arguments it's better to simply put clarification questions. And if later on, on Monday and Tuesday, we have arguments to make, we will make them. Thank you.

European Communities

304. Chairman, there are two clarifications, and I will not continue this now. It is another thing to speak about the four stages of risk assessment to which Dr. Boobis has referred, risk identification, risk characterization, dose exposure, risk characterization, that is true. But here we were not talking about these four steps of what is a risk assessment and how to do it, we were talking about the ADI, and the maximum limits. For this concept Dr. Boisseau says there were a few scientists, it was probably already before considered and was taken into account in JECFA, but there are no internationally agreed standards about this concept. This is what I want to clarify. The question was relating to ADI and MRL not only four steps. With this we agree, of course, and we claim we can follow these four steps of the risk assessment, but that was not the point, if you allow me to clarify. The second question is: Dr. Boisseau himself has said there are no agreements to the national standards, in JECFA or otherwise, how to define this concept of ADI and MRL. There are questions one may ask about the details or some other important aspect of this, so that is what I wanted also to clarify. Dr. Boobis said that it all started from the United States National Academy publications, this is all fine. But for you to understand, there is the Codex Alimentarius Commission, which is the members of the committee adopting texts, where the four steps of risk assessment have been presented and have been adopted and have been accepted. That's fine. But in JECFA there is no plenary of members of the WTO, for example, where they meet, and they take the papers of JECFA, and they say yes, they are well done, and we accept and adopt them. This does not exist in JECFA. And all these papers, as I said, they are publications without legal status in terms of the SPS Agreement. I think that it is as simple as that, I don't want to confuse the scientists about this, and I certainly would agree with my colleague from Canada that we would have the time to clarify this on Monday and Tuesday; simply then, on Monday and Tuesday, the experts will not be here, so we need to take advantage of their presence here as well. Thank you.

Chairman

305. I would ask the representative of JECFA to respond to that question, not in the context of the legal analysis of the SPS Agreement, but in the context of the work you are doing in JECFA and Codex. I give the floor to Dr. Tritscher.

Dr. Tritscher

306. Thank you. Again, it's not correct the way it was just presented by the representative of the EC, because specifically the ADI concept, how it is defined, and how this arrives, and how to go about to get to an ADI, is exactly described, as I said earlier, in the Environmental Health Criteria document No. 70, Principles for the Safety Assessment of Food Additives and Contaminants in Food. This is the document that was elaborated by a large group of international scientists convened through the International Programme on Chemical Safety. It is a consensus document of an international independent expert scientific panel published in 1987, and this is the basis on how to derive an ADI. An ADI cannot be derived if you don't follow the risk assessment steps as they were defined, so you cannot disconnect an ADI from the risk assessment procedure, the defined steps of hazard identification and hazard characterization. So again, this was not a correct statement. You cannot devise an ADI without following risk assessment steps. Generally this is the basis, and any of the national expert bodies, regional expert bodies, use exactly the same principles and the same methodology, let it be the European Food Safety Authority, former SCF committee, let it be the US FDA or whoever. This is the basis for this IPCS document published at WHO in 1987 and every follow-up from this. Going to JECFA – JECFA is not just a handful of people sitting there and having fun. JECFA is a scientific peer review panel, independent scientific experts that are an international peer review panel. Everybody talks about peer review now. So what JECFA does, they use all the evidence that is available, scrutinize and discuss it to come to a conclusion, based on all the available evidence. Again JECFA works on a consensus basis to the extent possible; if it is not

possible there will be a minority opinion presented. That has not been the case to my knowledge in the veterinary drug field; in the 50 year history of JECFA it only happened twice. So it is the highest level expert body in this field that performs a peer review of all available information. And just saying it is a handful of people sitting together doing something, sorry if I am reacting like this, but I find this rather offensive towards the experts that dedicate their time to do this work in the international context for public health protection purposes. Thank you.

Chairman

307. Dr. Miyagishima.

Dr. Miyagishima

308. Thank you, Mr. Chairman. I will be very brief. I just wanted to clarify that there is an internationally agreed document that governs the whole framework of risk analysis within Codex, which is the Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius. This text was adopted in 2003 and is now part of the Codex Procedural Manual that applies not only to the work of the Commission but all subsidiary bodies. And as Dr. Boisseau mentioned, CCRVDF has now finalized the document called Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Food, and this document is awaiting the final endorsement by the Commission. But it does not mean that CCRVDF is now trying to reinvent the wheel; basically this document describes the standing practice applied by CCRVDF from its inception. Of course, risk analysis is a continuing process and Codex is trying to evolve with more fine-tuning about risk analysis, but basically this document describes the ongoing and established practice followed by CCRVDF. In essence, the basic framework of how JECFA does its work and how its work is treated by Codex has not changed substantively since the beginning of the Codex work in this area. Thank you.

Chairman

309. Thank you. I think the replies are good enough for the Panel to clarify all the issues at hand. So now I would like to move on to the next question, that is purely procedural in nature again. The question is: How does the work of IARC feed into the work of JECFA and Codex? How was this done in the case of hormones at issue? May I ask this question to Dr. Tritscher or Dr. Cogliano? Dr. Cogliano.

Dr. Cogliano

310. IARC convenes its own working groups to evaluate the carcinogenicity of various agents. They have evaluations of steroidal oestrogens as carcinogenic to humans, non-steroidal oestrogens as well, and also oestrogen as used in hormone therapy, and oestrogens and progestogens in combination, as they are used in hormone therapy or in oral contraceptives. There is also an evaluation of oestradiol-17β as carcinogenic in experimental animals, and there is an evaluation of testosterone as carcinogenic in experimental animals. IARC publishes those in the form of monographs, and they are available to be used by JECFA or any other body that is interested in making a decision about those agents.

Chairman

311. Has the representative of IARC ever been invited by JECFA to the Committee meetings?

Dr. Cogliano

312. I have not personally been, but Jerry Rice, my predecessor, might have been. I was there for something about expert advice, but I have not been there to evaluate any chemicals.

Dr. Tritscher

313. IARC is also a WHO organization. We invite the IARC representative to JECFA meetings every time when there are contaminants and relevant substances evaluated. We are not talking about food additives in the context of IARC. What IARC does; IARC does cancer classification, so in the IARC assessments the focus is on the carcinogenicity or potential carcinogenicity of the compounds. How the work feeds in was already basically answered. IARC publishes their work in monographs, so does JECFA, and we base – depending on which one comes timely first is the starting point of the work of the other, so we take each other's work into consideration. Thank you.

Chairman

314. Thank you. Dr. Boobis.

Dr. Boobis

315. To expand on that a little bit, when JECFA discussed the hormones, the natural hormones, for the fifty-second meeting there was a staff member of IARC present who was an adviser, a temporary adviser, and we were fortunate that we had access not only to the published reports, but some of the information about to be published, and in fact, if you read the technical documents from JECFA, it was made clear that the IARC evaluation and some of the information they had put together formed an important part of the deliberations of the Joint Committee.

Chairman

316. Thank you. EC.

European Communities

317. Chairman, I have one question to both representatives of JECFA, actually Codex as well, and the International Agency for Research on Cancer. The International Agency for Research on Cancer has classified, as you know, oestrogen and oestradiol in the first group, which is the proven carcinogens of humans, and they have classified the other two in the second category, group 2A and 2B. So I would like to ask JECFA, how it is possible, since they are interacting, these two international organizations, that JECFA comes to the conclusion they are not proven carcinogens – I am speaking about oestradiol – whereas the International Agency for Research of Cancer has come to a different conclusion. I would like to know: is it because they use different data, do they use different toxicological studies, do they take other considerations into account which make for this different outcome? Because I guess you would like to know as we do, since we take the advice of these two groups into account, which one of the two to follow. One says oestradiol is a probable carcinogen, the other says no, there is a threshold, there is no risk. I simplify, but this is the end result. Thank you.

Chairman

318. I see many flags raised, so I will give the floor the JECFA first, and then Codex, and then Dr. Boobis.

Dr. Tritscher

319. Thank you. There are many things mixed up now in this statement. So JECFA and IARC are doing two different things. First of all I have to clarify that JECFA never said oestradiol is not a carcinogen, you will not find this anywhere in any JECFA publication. IARC does, as I said, cancer classification; it is a totally different thing than what JECFA does in doing risk assessment, and my colleague from IARC will explain what it means, what their work really means to cancer classification. A compound being a carcinogen does not preclude it from a safety assessment being performed and an acceptable daily intake or tolerable daily intake being set. Again, those are not mutually exclusive things. Sorry, let me say it like this: JECFA has evaluated several compounds that have carcinogenic properties and have still been able to set an ADI or a TDI.

Ms Orozco

320. Sorry, can I interrupt you there for asking you for an example of other compounds in a similar situation.

Dr. Tritscher

321. Contaminants in food like the chloropropanols for example, monochlorpropandiol and DCP. I think I will leave it at that in the interest of time, because I know that ...

Chairman

322. Thank you. Dr. Miyagishima.

Dr. Miyagishima

323. Simply to say that there is no standing or institutional linkage between the Codex system and the IARC. Of course, to the extent that the work of IARC is beneficial to the work conducted by the Joint FAO/WHO bodies, such as JECFA, it is up to JECFA to draw any useful elements from the work of IARC. But there is no direct link between Codex and IARC. Thank you.

Chairman

324. Dr. Boobis and Dr. Cogliano.

Dr. Boobis

325. Well, it is just to emphasize the point that in the view of JECFA it is necessary to consider the mechanism and mode of action for the carcinogenicity, because, as we alluded to earlier, there are many different ways in which one can generate a tumorigenic response. I am sure tomorrow we will discuss exactly how oestrogens cause cancer, but as a philosophical point at the moment, just to clarify the point that Dr. Tritscher made, simply because a compound causes experimental cancer in an animal, or even at high doses in humans, does not necessarily and automatically mean that it is not possible to establish a safe level of exposure. JECFA sought to do that for the hormones. One can argue whether it came to the right conclusions, but it was on the basis of consideration of the mode of action and the mechanism of the carcinogenicity. As already stated, at no point did we ever exclude evidence which was readily available at that time, in 2000 and 1999, that in humans at certain levels of exposure oestrogens could cause cancer in endocrine sensitive tissues.

Chairman

326. Thank you. Dr. Cogliano.

Dr. Cogliano

327. I put my flag up just to make one correction. IARC has classified oestradiol 17β as possibly carcinogenic based on sufficient evidence in experimental animals. The agents that are known to be carcinogenic in humans are the steroidal oestrogens, non-steroidal oestrogens and various oestrogen-progestin combinations as used either as birth-control pills or menopausal therapy.

Chairman

328. Thank you. EC.

European Communities

329. Chairman, I think it would be useful if we take a little bit of time on this issue, because it is interesting to know the scientific basis upon which the International Agency for Research on Cancer re-examine partly the same documentation that is available, the toxicological studies and the profile in the mode of action in these substances. And I understand by reading the International Agency for Research on Cancer monographs that they consider that oestradiol, oestrogen and oestradiol-17β not only act through receptor mediation but also they consider them to be genotoxic. This problem, this toxicological assessment of this substance and the other natural hormones – I need to clarify, the International Agency for Research on Cancer, it has not examined the synthetic hormones, but they have examined the three natural. Partly the same studies have been evaluated by JECFA as well, and as you see, they dispute, they go through – if you take and read the opinion of JECFA and Codex subsequently, which is taken out and published – they go through the data, but the ultimate conclusion is that oestradiol has a genotoxic potential, but they do not define it as genotoxic in the sense that the evidence is sufficient. As Dr. Cogliano has said, they thought the evidence was sufficient to define as carcinogenic in humans. So I am still wondering and I would like, as a lawyer, and I hope you as well, to know why on this crucial aspect the International Agency for Research on Cancer comes to a different conclusion for oestradiol, and they also come to different conclusions for progesterone in particular and testosterone as well, than the conclusions obtained by JECFA. I am not trying to fudge the issues, no. But the truth is that part of the scientific documentation is examined by the two bodies, and the conclusions and toxicological conclusions they reach are very important, and I have the feeling, and we have the feeling here, that they are not getting to the same conclusion on that aspect. Dr. Boobis said that he does not, JECFA does not dispute that oestradiol is carcinogenic, fine, but the method by which we define oestradiol as a possible human carcinogen is also important, and I hope it is clear what I am asking the two or the three delegates to clarify. Thank you.

Chairman

330. The Panel's intention in putting forward these questions was purely procedural, as I mentioned, and I think the comment you made is rather stretching out to the substantive issues to be discussed later on, in due course, through exchanges of questions and answers on different issues. I hope we can conclude discussion on this question here and then come back, if necessary, in due course. OK. Then the next question of the Panel is rather broad in concept, or which may capture the broader picture of the issues at hand. The question is: how much scientific evidence is needed for a valid risk assessment? What is normally done if data in a specific area are incomplete? How is scientific uncertainty addressed? The floor is open to any expert to respond. Dr. Boisseau.

Dr. Boisseau

331. Thank you, Mr. Chairman. There are two hypothetical possibilities here: either the necessary scientific data is lacking to the point where the risk assessment cannot be completed – in which case the required data is requested so that the risk assessment can be continued; or a committee, the JECFA – but it could just as well be the CVMP – considers that the necessary data has been gathered and is available, but since there is an element of uncertainty in any piece of scientific data owing either to the experimental protocol used or the obsolescence of the method used, or with the number of animals involved, it uses safety factors to ensure that the evaluation results in proper protection of public health. Thank you.

Chairman

332. Thank you. Any other additional comments from the experts. If there are no follow-up questions from parties, then can I move on to the next, please. Madam Orozco.

Ms Orozco

333. I would like to ask a follow-up question, because I am not quite sure. The question has two elements that we would like to clarify: What would be the procedure when the data is incomplete? And what would be the procedure when there is uncertainty about the science?

Chairman

334. Dr. Tritscher.

Dr. Tritscher

335. Again, very quick, to the completeness of the database; if you want to look at chronic intakes or setting an ADI of course you need sufficient long-term studies that allow an extrapolation or an assessment of the compound. If it is a compound like the hormones, with hormonal effect, you would definitely require reproductive and developmental studies to check specific effects. Again, what Professor Boobis mentioned a couple of times already is that JECFA puts great emphasis on the mode of action of the compound. That's part of the first question, sorry that I am going back, but then the rest is better understood. To the question how much scientific evidence is needed, it is not a check box, it is not a list that then is then just checked off. There are certain basic studies that need to be available; over and above that, it is on a case-by-case basis. Depending on the toxicological profile or the suspected profile of the compound, you would require certain studies. If these studies are not available, if there are significant – now I am going to the follow-up question – if significant data gaps are identified by the Committee, then these have to be clearly identified. For example, there is concern for reproductive effects, however there is no reproductive study performed, that would preclude a safety assessment on that compound, and it would be clearly identified what the significant data gaps are, and the conclusion would be that there cannot be a safety assessment performed on this compound if there is a significant data gap. If the data gaps are considered to be minor, in the sense that a safety assessment could be performed to still be public health protective, however additional data would be required, then there is the option to set a temporary ADI, and then there would be a specific definition of what additional data would be required in order to fill these minor data gaps. A temporary ADI usually has a limited lifespan, meaning the data requirements would have a date attached to them. If a temporary ADI is set, so minor data gaps that are clearly identified are there, then what usually happens is that there are additional safety factors, uncertainty factors, added on to have an extra level of safety added and to take this additional uncertainty into account. Thank you.

Chairman

336. Dr. Wennberg and then the EC.

Dr. Wennberg

337. Thank you, Mr. Chairman. Just short on the residue part. I already alluded to the requirements related to the data needed to perform an evaluation of the residue in the animals in question. When I was talking about how to set MRLs – I am not going to go into that any further – and similarly applying, which I also mentioned before, is that if there are minor gaps in the validation of the analytical method to be used in residue control, for example, JECFA could consider to set temporary MRLs, but we already talked about that.

Chairman

338. EC.

European Communities

339. Chairman, two brief statements and I think we can be more concrete. If you look at the 1987, 1988 evaluation by JECFA of the three natural hormones, they thought at the time that they had a complete set of data, they made the evaluation, but they did not fix an ADI because they thought the data was complete and there was no risk, because of the wide margin of safety, as they call it. JECFA has re-evaluated the three natural hormones again in 1999, and they came to a different conclusion, that this time it was necessary to fix an ADI, because data apparently changed, were more complete. Now, the United States, in its reply to the comments made by the experts and by the European Community, interprets why JECFA fixed in 1999 an ADI is because the data were now complete. This is the terminology, I can find the correct quotation if necessary. Whereas the reply of Dr. Boisseau, why they fixed an ADI for the first time in 1999, is in order to be more convincing. I can find the correct quotation as well. So there is quite an uncertainty in the way JECFA proceeds. The point is, and this comes to the second question asked by Madam Orozco – practically there is no room to take into account uncertainty in JECFA, because they think that they can address uncertainty through the so-called safety factor. By applying the so-called safety factor, sometimes it's 100, 200 or 1,000 times, they think they can take into account uncertainty in the data, but at least the way we understand scientific uncertainty is different. And I would like to know instances where – if there are, there are really very few, very very few in the history of JECFA – where they came to the conclusion that for a substance we do not have sufficient data to propose an ADI or an MRL. And I should give you another example which is also pertinent in this case, the case of carbadox, and I will only mention it and not go on into the details. We were arguing the data were not sufficient in 1996, nevertheless JECFA proposed a provisional, as they call it, a provisional ADI and MRL, and ten years later on Canada, for example, has agreed that the data were not enough and were wrongly interpreted. So I think these questions are very important. Is there any room in the JECFA procedure and the risk assessment to take into account scientific uncertainties what the real scientists understand what is scientific uncertainty? And our feeling is that there is very limited room for that and I don't thing they actually do it. Thank you.

Chairman

340. Thank you. US.

United States

341. Thank you, Mr. Chairman. I again had a very difficult time discerning a question in the last statement by the EC, but there were quite a lot of factual assertions made in the course of that "question". I was wondering if, maybe we could open up the EC's comments to the experts who have spoken on the issue of ADIs and the JECFA/Codex/IARC work. So I would propose that Doctors Boobis, Boisseau, Cogliano and Dr. Tritscher respond to several of the factual statements made by the EC in its last comments.

Chairman

342. Well, before I give the floor to the experts, may I remind you again this is the session for the Panel to put the questions, and we are allowing the parties to ask additional questions in relation to those questions posed by the Panel. So we are not going to make any statements from the Panel or from the parties at this particular moment, and I would urge the delegations to refrain from making any statement and rather focus on the questions put forward by the Panel and replies given by the experts. With that I will give the floor to Drs. Boisseau and Boobis.

Dr. Boisseau

343. Thank you, Mr. Chairman. I will try to keep my reply to the EC intervention brief. Science is a discipline which is constantly evolving. When we manage to resolve a problem, we generally find that there is another problem hidden behind it, and so on ad infinitum. The assessment of the safety of veterinary drug residues is a pragmatic system, because the proper use of veterinary drugs depends on its conclusions. We need to be able to decide, at any given moment, whether we should think of reconsidering an assessment in the light of scientific developments. But we cannot constantly delay that decision, or otherwise it can turn into a Sisyphean challenge. When the EU speaks of these scientific uncertainties, it is the general protocol that is being called into question. We must understand that the committees, the JECFA and the CVMP, work on the basis of the data available. Where do these data come from? Generally from the industrialists that provide them. In the end, there is very little, relatively speaking, in the way of data, from independent bodies. So ultimately, it is going to be necessary, in the light of the information available – if it is sufficient – to make proposals that it will be up to the Codex to accept or reject. If not, none of what we call old molecules will ever be evaluated and they will have to be withdrawn from the market, since no one will support them. The same applies to the developing countries. There are substances which are very important for the developing countries, but which represent a minor market. Most of the time, although their files are not complete the JECFA tries to conduct these evaluations on the basis of the data available and using appropriate safety factors to recommend ADI and MRL standards to the CCRVDF, that guarantee public health. Thus, I think it is important to remember that the approach is a pragmatic one.

344. As regards what happened in the re-evaluation of natural hormones in 1999, I maintain what I wrote, namely that during the preceding re-evaluation, the margin of safety between what might have been envisaged as an ADI and the daily amount ingested seemed to the JECFA to be such that it did not appear necessary to determine ADIs, and its conclusion at the time was: ADIs not necessary; MRLs not necessary. It emerged that there was a problem of communication, because as a result this margin of safety did not appear; and the JECFA, of its own accord – this was not requested by the CCRVDF – reverted to this evaluation, for which, in fact, it had access to a whole data package. Please excuse me, I made a mistake in my previous reply: there were indeed new data in connection with the data package which the FDA placed at the disposal of the JECFA, and which helped, as it were, to determine more precisely this margin of safety between an ADI that was established at that time and the theoretical daily intake of residues. The JECFA once again determined that it was not necessary to establish the MRLs since the margin of safety was still sufficient. In other words, the

evaluation remained unchanged, and it is not really the availability of new data that led the JECFA to reconsider its previous evaluation – it was only that the JECFA wanted to be more transparent, more explicit. The CCRVDF did not want to take account of this new re-evaluation which yielded the same results and which it had not itself requested. Thank you.

Chairman

345. Thank you. Dr. Boobis.

Dr. Boobis

346. Just from my own personal perspective, and I am not necessarily speaking for JECFA or anybody else here, I think it is probably fair to say that when conducting a risk assessment, we are not really looking to see if a data package is complete as to as much as whether it is adequate for the purpose, because I agree entirely with everything that Dr. Boisseau has just said, that science moves on, and it would be complacent for a risk assessment body to assume that it knew everything about a substance at a particular point in time. We have to work within the available information, and the question we ask is: do we have sufficient information at this point to conduct a risk assessment? – not: is the data complete and are there no scientific questions remaining to be answered. And I would add that there are numerous examples in the JECFA monographs of substances where it was not possible to establish an ADI on the basis of incomplete data; that has been done on several occasions.

Chairman

347. Thank you. Dr. Tritscher.

Dr. Tritscher

348. I would like to comment on the aspect of uncertainty and if or if not uncertainty is taken into account by JECFA assessments. It is correct that scientific uncertainty is difficult to quantify very often, and the scientific community is still debating. There is a lot of debate currently going on to better quantify uncertainty in the database, to give a better information to the risk manager as to the confidence on the conclusions that are reached. As the delegate of the EC said, real scientists even have problems to define scientific uncertainty. The experts working in JECFA are also real scientists and they also have problems with that. However, it is always taken into account and, very briefly, there are two aspects that need to be separated out, that is uncertainty and variability. Uncertainty is what we don't know, and variability is variation in a response between individuals, between species. Those are two different concepts and both need to be considered. Uncertainties as to extrapolations from model systems to the real-life situation and so forth, they are taken into account by safety factors that are also called uncertainty factors. Now there are default factors that have been used by everybody, by all the expert bodies since the inception of the invention of the ADI, and now increasingly efforts are undertaken to go away from default uncertainty factors to data-derived uncertainty factors, meaning to put more science into the derivation of these factors to take account of true uncertainties, if possible, if the data are available. That is the concept of the chemical specific adjustment factors. Again, a concept that was developed by Andy Renwick, I think, originally, but the International Programme on Chemical Safety has published on that and the Expert Committees like JECFA and JMPR are trying to apply this concept where possible, meaning where data are available to extrapolate, for example from the animal to the human situation. So it is factually entirely incorrect to say that JECFA does not take uncertainty into account. Thank you.

Chairman

349. Thank you. I think the comments just made by Dr. Boobis and Dr. Tritscher have already answered the Panel's next follow-up question, but I would appreciate it if any other experts would further elaborate on this particular question, that is: how would you distinguish between insufficiency of science evidence and scientific uncertainty? Could you rephrase your comments in more clear terms to distinguish between these two concepts. Dr. Cogliano.

Dr. Cogliano

350. Yes. I want to start by agreeing with Dr. Boobis's comment that it is not so much a matter of being incomplete. But I would also point out that there are several kinds of uncertainty. There are uncertainties as to, for example, what is a null-effect level in animals, or a safe dose; or how would you extrapolate between animals and humans. There are also wider uncertainties about – are the animals predictive at all of humans, or is a single chemical fed to an animal predictive of the human situation? There are very different levels of uncertainty and I think that the way some types of uncertainty are addressed is by trying to quantify them, by trying to get data derived from chemical-specific uncertainty factors. Some forms of uncertainty are addressed by general assumptions, like we will assume animal results are relevant to humans unless we had the data to show otherwise. So that is another approach to dealing with uncertainty, to take a conservative approach and say that we will assume that these study results are useful. And I think that as risk assessment evolves there are more and more questions that are asked. We are now asking more questions; once we understand the mechanisms we start to ask: what is the range of variability in human populations and who is likely to be more susceptible? These are concepts that IARC monographs are trying to address more in the future, but they had not really been questions that were routinely asked 20 or 30 years ago. I think that what we do with uncertainty does evolve over time and there are different forms of uncertainty that do get different approaches. Some are very quantitative and some are much more qualitative. I think I will leave it at that since more specific questions – it's a very broad-ranging field, I think, to try to really answer in a few words. I think there can be whole books written on uncertainty and how to deal with it.

Ms Orozco

351. Simply, if you have similar explanation as to what is or what's not sufficiency of scientific evidence?

Dr. Cogliano

352. Let me try to answer that in the context of the monographs. If we don't have epidemiological studies, good epidemiological studies, we will say we have inadequate information, and then the evaluation will proceed looking at the animal studies. If we have good bioassays, we will make our conclusion that something is probably carcinogenic or possibly carcinogenic or not based on the animal studies. If we don't have good animal studies or good human studies, we have inadequate information, and we would end with saying we cannot classify this substance. So we do want to have either epidemiological studies or animal bioassays. Now let's shift to the mechanism field. If we don't have a good mechanistic understanding, that will not stop us from classifying the substance; we will classify the substance based on the human and the animal studies, even if we do not understand the mechanism. So having epidemiology or animal bioassays, that's a requirement to come up with a classification. Not having mechanistic studies – its nice to have that, it contributes to our understanding, but it does not stop us from a classification. So I guess you could say what we need, and IARC usually has, are some animal bioassays or some epidemiological studies and then we will proceed with a classification. If the rest of the database is somewhat lacking, that does not affect the classification. Now I should mention that IARC does not come up with safe levels of exposure and

uncertainty factors. So our uncertainty analysis is really different from what JECFA would do or someone else trying to come up with a safe level for consumption in foods.

Chairman

353. Let me put this question to all of the experts. If there is scientific uncertainty, would you all agree that there is always insufficiency of scientific evidence, or, even if there is scientific uncertainty, may there be a situation where scientific evidence is sufficient in terms of risk assessment? Dr. Boobis.

Dr. Boobis

354. I will try and answer that question in a slightly different way, if I may, which is just following on from the comments of Dr. Cogliano. Where there is scientific uncertainty, we would tend to adopt a worst case default in extrapolating the data to take account of that, so we will use the most sensitive endpoint in the most sensitive species for the extrapolation purposes of a risk assessment, assuming that it is relevant to humans and assuming that humans are going to be more sensitive than animals. Now that is a fairly conservative assumption, based on the totality of scientific information available to us at this time. The insufficiency of scientific evidence, I would say, as has been indicated, could be trivial, it could be that just one test is not there and we can fill in, but it could be substantial. For example, there might not be a reproductive toxicity study for a compound that women of child-bearing age would be exposed to, in which case we would consider that a major insufficiency of data, not a scientific uncertainty, just an absence of data, and we would not proceed without filling that data gap. So I think they are rather different issues; one we can handle with taking conservative defaults, for the other we really need information to allow us to proceed.

Chairman

355. Thank you. Dr. Boisseau, Dr. Cogliano and then Dr. De Brabander.

Dr. Boisseau

356. Thank you, Mr. Chairman. I am afraid it will be difficult to reply to the question you have just asked. I can repeat what I said, namely that if there is a major insufficiency of scientific data, as Dr. Boobis just mentioned, we cannot go any further in the evaluation of the safety of residues of veterinary drugs. There are other cases where scientific uncertainty with regard to less important data would not prevent a conclusion from being reached with a safety factor that would provide for adequate protection of public health. Beyond that, it is impossible to draw up a table with two columns showing what constitutes insufficiency and uncertainty. All we have is specific cases, we can provide the odd example. We could speak of insufficiency in the case of suspicious results of short-term mutigenicity tests without a supplementary carcinogenicity test or without any studies involving radio-labelled elements for a tissue depletion or a metabolism study. That is an insufficiency. We can give you a few examples, but there will always be cases that do not fit the examples. The reply that I am tempted to give you is that a distinction must be drawn between an individual evaluation, whatever the competence of the expert involved, and a collective evaluation conducted by a committee of competent experts, be it the JECFA, the CVMP, or another committee. We must not underestimate the notion of collective evaluation. When 30 or so experts reach a consensus that there is an insufficiency of data or that a scientific uncertainty can be managed through safety factors, I think that we can be fairly confident – this is a collective approach.

Chairman

357. Thank you. Dr. Cogliano.

Dr. Cogliano

358. I was going to respond. I think similarly – it really depends on what the question is, for example: does tobacco cause cancer? I think the answer is unequivocally yes. Are there uncertainties or are there things we don't know, for example I was asked the question earlier, am I going to get cancer if I smoke for only five years, or only one year, or only two cigarettes a day? We don't really know exactly the shape of the dose-response curve. But we do know enough to know that from a public health point of view tobacco is definitely harmful and we should take steps to curb smoking. There are always going to be uncertainties or things we don't know at the fringes. What happens if we smoke and we also work in a dusty environment, what happens if we smoke and we have vitamin deficiencies, these are the niceties that scientists will say are uncertainties, and there are things that we would like to know more about. So I think when you are asking about insufficiency of evidence it is really: insufficient for what purpose, and what is the question you are trying to ask? In some cases the data set can be absolutely conclusive that tobacco is harmful, but without necessarily answering every single question: what about in combination with this or in combination with that or two cigarettes a day? So yes, keep in mind the purpose, and data sets are always sufficient to answer some questions and there is always more that you could know if you wanted to answer everything.

Chairman

359. Thank you. Dr. De Brabander.

Dr. De Brabander

360. Thank you, Mr. Chairman. As you know, I am layman in that area of risk assessment, but in answering this question I really want to make some remark on a question which is important to me and perhaps for the whole system. I agree that science grows continually, we always have new evidence. I also agree that there are internationally recognized items to make the risk assessment for veterinary drugs, but when you as a human being take medicine, or you give a veterinary drug to an animal, it is in order to cure it from a disease, and when you take a medicine, you always balance the profit of taking a medicine against the risks, because every medicine has its side effects, against the profit of being healed. So the question I ask: by scientific uncertainty, if you are using hormones, what is the counterbalance of using hormones except of profit, money?

Chairman

361. Thank you. Any other – EC.

European Communities

362. Thank you, Chair. A simple question. In the view of all experts, perhaps, and whoever wants to reply on this: is direct genotoxicity of oestrogens an issue on which there exists scientific uncertainty?

Chairman

363. The floor is open. Dr. Cogliano.

Dr. Cogliano

364. Yes, I think there is scientific uncertainty. One of the exhibits you have was the summary of the most recent monograph meeting on the oestrogen/progestogen combinations, either as birth-control pills or as menopausal therapies. And as I mentioned earlier this morning, a hormonal

mechanism is clearly operating, but there was some evidence that there could be genotoxicity operating; it's not as strong. It was not the entire working group that put a lot of credence in it, but enough members of the working group thought that there was some possibility of genotoxic action that our summary does have a paragraph for each of those two types of exposures that mentions that there could be some genotoxic activity as part of the cancer mechanism. I think that is an area of continuing research and obviously more will be known later.

Chairman

365. Thank you. Dr. Guttenplan.

Dr. Guttenplan

366. I think qualitatively one can say that there is very little uncertainty in the fact that oestrogen is genotoxic, however quantitatively I think there is a lot of scientific uncertainty. I don't think we can really estimate the risk at this point from such low levels of genotoxic effects.

Chairman

367. EC.

European Communities

368. Mr. Chairman, I think that this is a very important question and we may replicate the examples where we would like to ask the scientists, all of them, where there is scientific uncertainty and where it comes from. Does it come from the lack of sufficient evidence, as you say in your question, or does it come from, as I would put it, from evidence which is there on the table but it is conflicting? One does not agree with the other evidence? And I think there is a very important causal relationship between these two concepts. Our suggestion is – and I would like to see if the experts agree or disagree – we would say, and we have said in our submissions to the Panel, if the evidence is insufficient, then I think practically always there will be scientific uncertainty, because the evidence is not sufficient. Dr. Boobis has said: if it is a major insufficiency; but it is a value judgement, whether the insufficiency is small, higher or major. Our suggestion to go about this issue is, if the data are not sufficient, there is scientific uncertainty. But this is not all, and it is not the most important in this case as well, because as Dr. Cogliano and Dr. Guttenplan have said, qualitatively there is no doubt that oestrogens are genotoxic or carcinogenic, but the evidence is not sufficient in terms of quantity. And there we will also propose to the Panel – and if the experts agree or disagree they can say so – but when there are conflicting interpretations of the evidence that is available, still we will argue that there is scientific uncertainty. Thank you.

Chairman

369. Thank you. I think the EC's comments are somewhat related to the questions that the Panel are going to put forward later, so I would appreciate it if the experts would respond to the EC's comments when they respond to the Panel's questions, and then I will give the floor to the US.

United States

370. Thank you, Mr. Chairman, I want to interject. I feel with the last question from the EC we have strayed into the scientific evidentiary discussions of tomorrow, and I just wanted to raise that point clearly. The EC's assertion that these hormones function by a genotoxic mechanism at relevant exposure levels is critical to their arguments, and I would propose either the United States can go

forward with its questions on genotoxicity and the scientific evidence, or that we hold back until tomorrow at the time the Chair had set aside to discuss the scientific elements of the case.

Chairman

371. OK. In connection with that comment, may I propose to the delegations: why don't we go through all the Panel's questions as quickly as possible, and then based upon the answers and replies and comments from the experts on all these questions put forward by the Panel we can have more structured discussions by the parties, more elaborate questions on these basic discussions. So that we do not duplicate or repeat discussions we had already. I think that would be a more structured way of debate for today and tomorrow. So I would request the understanding of the delegations by way of refraining from putting many additional follow-up questions on the issues at hand. Are there any comments or replies from the experts? Dr. Boobis.

Dr. Boobis

372. I appreciate your comments, Chairman, and will not enter into discussion about the evidence. I just wanted to make a general point, which is that it would be a mistake to think that risk assessment results in the complete and absolute agreement of everybody in the risk assessment. The nature of the evidence available on science in general is such that we will never get a uniform interpretation. What happens generally is that there is a consensus and if necessary the adoption of defaults which are conservative to allow us to move forward. Seeking unanimity on the interpretation of all the data is futile because it will not happen.

Chairman

373. Thank you. Let me put the Panel's next follow-up questions, two questions at the same time. The first is: at what step in a risk analysis is a determination made whether the available evidence is sufficient to undertake a risk assessment? The second is: at what step of risk analysis does one factor in the level of protection to be achieved by an SPS measure? Any expert? Dr. Boobis.

Dr. Boobis

374. Could I just ask you, Chairman, to repeat the second half of that question?

Chairman

375. The second one is: at what step of a risk analysis does one sector in the level of protection to be achieved by an SPS measure? I would rephrase the last part of the second question as: by a health protection measures, instead of SPS measure. Dr. Cogliano.

Dr. Cogliano

376. I would actually still like to clarify that. It seems to me the level of protection is something that was discussed earlier as part of risk management, and I am not sure that it is part of the risk assessment. Well, risk analysis, then, is a new term we have not talked about. We have talked in terms of risk assessment; is risk analysis being used to mean risk assessment?

Chairman

377. I don't want to go into the detailed legal issues which will be the focus of our discussion next week, but there is a difference in the terminology of risk assessment and management, and there is a

broader concept of risk assessment, risk analysis, so I think it would be better to avoid that discussion at this time, and I give the floor to Dr. Tritscher.

Dr. Tritscher

378. So at what step in the risk analysis is a determination made about the sufficiency of the data to undertake a risk assessment? In the ideal case you would have a step that's called problem formulation, when you really formulate the question, what is the concern, what is the question that the risk assessor should answer, which is followed. Now, there are different terms used – a preliminary risk profile – this is a step where you really look what kind of data are available. Now in the international field, in the context of JECFA and Codex, these steps have not been formalized as such, not in that level of detail, the way I have just described it. What happens is, the Codex Committee, CCRVDF, poses fairly simple, if you allow me to say it that way, a simple questions to JECFA, asks JECFA to perform a safety assessment or a risk assessment on a specific veterinary drug when used according to good veterinary practice. And at that point it goes over to the risk-assessment body, and the risk-assessment body, JECFA in that case, puts out a call for data and performs literature searches, the experts perform literature searches on all publicly available date. Now in the concrete case of JECFA, in the preparation of the meeting, a designated expert reviews the available database and prepares what we call a draft working paper as a basis of the discussion of the Committee at the meeting. If at that point the expert determines that the data are insufficient to allow an assessment, that would be recorded as such, and why the insufficiency is there, or what other significant data there is. So the working paper would lay that out, and then, when the actual JECFA meeting takes place, the Committee would discuss that as such. So to answer the first question, in the context of the JECFA/Codex system – in what step of the risk analysis paradigm – in this case it is at the risk assessment step. So JECFA makes that decision if the database is sufficient, as it concerns us, as opinion of an international expert panel.

379. At what step of the risk analysis does one factor in the level of protection? Now the level of protection is a term that comes from the microbiological area and is not as such used that much in the chemical area and in the context of chemicals in food, also veterinary drugs we are now talking about, where the risk assessment is performed to set an ADI. What that actually means, what an ADI is, what is done is to set a level of no apparent risk on the basis of the available data. So it is a little bit like an acceptable level of protection, like some other agencies or authorities or expert bodies do, in a sense, that one additional cancer case in a million population would be an acceptable level of risk. This is clearly a risk-management decision. The risk manager would have to define this for the risk-assessment body, to go to a certain level of protection. If we are talking about an ADI, setting of an ADI, this is not the concept. What the concept behind there is, to set – again, I repeat – a level of no apparent risk. This is a chronic acceptable intake level without – this famous term – appreciable health risk.

Chairman

380. Thank you. Dr. Miyagishima.

Dr. Miyagishima

381. Thank you, Mr. Chairman. I will speak only to the first question because I still have some difficulty in understanding the meaning of the second question. The determination, or any judgement as to the sufficiency or insufficiency of data to undertake risk assessment, may well take place within the risk-assessment programme. For instance, JECFA may come to a conclusion that the scientific data is insufficient to undertake a complete risk assessment, and they may abort their undertaking at that stage. There are also cases where the risk managers, in this case the Codex Alimentarius Commission, may already foresee the insufficiency of scientific data and yet the Commission may

still ask the JECFA to attempt to undertake a risk assessment, or the Commission may decide not to waste the resources of JECFA and opt for another risk management options that would not require stringent risk assessment, for instance the development of a code of practice, rather than numerical standards, could be an option. There may be other options. I must say that there are cases where risk managers make some judgements on this point. Thank you.

Chairman

382. Thank you. Then could you also explain what a deterministic approach to risk assessment is, and what other approaches are there? And in relation to that: what is a so-called hazard-based approach, and under which circumstances is that approach used? I would welcome the replies from the experts to these comments in combination. If there are no specific – Dr. Tritscher.

Dr. Tritscher

383. I can try to give you the very very brief description, but there are also written comments to the deterministic versus probabilistic, if this is what is meant in this sense. I am sorry, but sometimes it's not that clear what is really behind the question. Deterministic approach to risk assessment means that we are using point estimates – high-level consumer, mean-level consumer – on the exposure assessment, individual points on the dose-response curve, whereas probabilistic takes distribution into account – like I explained earlier, you have variability in responses, and to take this into account is a much more complex way of doing risk assessments. I am not aware that even on the national level really probabilistic risk assessments are performed. This is highly complex and is not routinely done. Increasingly probabilistic exposure assessments are done, meaning where one takes into account the variation of levels of different chemicals in food and the variation of consumption patterns, variation in portions of what people eat. That is increasingly taken into account; whereas when it is just a point estimate, what is the mean level of occurrence, what is the mean portion size. Taking also probabilistic approaches into account on the toxicological side, if you would think about the graphs that I had, so that, going down the left arm of the graph, taking also distributions into account is highly complex and definitely not done routinely, and – other than, let's say, in the scientific experimental field – I am not aware that this is done in the regulatory field. Again, on the international basis, in the context of JECFA we are basically bound to use deterministic approaches, because we basically have to cover scenarios for the whole world. However, again, having said this, the increase in the efforts now, at least on the exposure assessment, we try to take distributions into account. And I do not understand the second question, what is the hazard-based approach. Any risk assessment starts with the hazard, it is the hazard-based approach, so apologies, I do not understand the question.

Chairman

384. As I understand it, that terminology was used by one of the experts or parties in their replies or submissions, which I cannot identify for the moment. Dr. Boobis.

Dr. Boobis

385. Well, I suspect, what Dr. Tritscher has just explained is exactly what I understand by deterministic versus probabilistic, but I have a suspicion that something different is meant here. Obviously we are trying to get to a different place, so that deterministic is where we use point estimates, conservative assumptions, but the underlying assumption, based on analysis of the data, is that there is a point at which one can reach a safe level of exposure, an acceptable level of exposure, and so that is the basis for arriving at an ADI based on point estimates. One could do it in different ways, probabilistic, which is much more complex. But I think that what this is to be contrasted with is the idea that there isn't a safe level of exposure and what one could use under such circumstances is

what is called quantitative risk assessment, extrapolating down levels of exposure, where one gets to a level where there is still a risk, but the risk, in the view of the risk manager, is considered acceptable. Now that is not an approach that JECFA has used before for veterinary drug residues. A hazard-based approach, I would imagine, is a qualitative risk assessment, if you like, where one stops once one has identified a hazard that is deemed unacceptable. So, for example, the compound is shown to be direct-acting genotoxicant; this is considered unacceptable at any level of exposure, permitting exposure would not be appropriate, and then one stops the risk assessment at that point. So it does not need to take account of exposure, because any level of exposure is deemed to be of concern. There are some who argue that certain other endpoints, such as certain types of neurotoxicity, would fall into that category as well. There are intermediate positions, which is that even if there is such a hazard, one could think about what is the margin of exposure, or what is the exposure with respect to the so-called threshold of toxicological concern. These are newer strategies which have been designed to deal with endpoints which may not have a discernible threshold, but where some exposure may be unavoidable, for example a contaminant, and so we have to determine whether we need to prioritize resources to bring exposure down to lower than that. The issue of veterinary drug residues, which are compounds that are added intentionally to animals, is a wider discussion and I won't even enter into that here because it is outside of the thrust of the question.

Chairman

386. I think I did understand the issues but could you repeat once again, but in a much briefer way, the difference between deterministic and probabilistic approaches.

Dr. Boobis

387. I am not sure that that is helpful here, Mr. Chairman. The deterministic approach is to use single estimates of, for example, the toxicological no observable adverse effect level, the exposure level etc. One uses conservative assumptions for those values. The probabilistic approach is to take distributions of those values and try to get closer to the real world situation. We are not all exposed to the highest level of residues our entire lifetime and with the sensitivity of the most sensitive animal, and the most sensitive endpoint. So we can use distributions of those values, multiply them together, and say the probability of an individual lying on the curve is X, very low, medium, high, whatever. And then that requires the risk manager to take a decision as to a percentile of the population they wish to protect, because you never reach a 100 per cent on a distribution curve.

Chairman

388. Thank you. If there are no other follow-up questions, let me put the next question. If a substance is genotoxic, can a threshold be established? If there are any substances for which no threshold can be established, how does this affect the conduct of a risk assessment for such a substance, and what happens to the four steps? Dr. Boobis.

Dr. Boobis

389. There are substances for which there are thresholds for genotoxicity; it depends on how it causes the genotoxicity. For example, it may be acting indirectly through the apparatus that allows cells to divide, the so-called spindle apparatus, which is actually a protein which allows the DNA to segregate during cell division. And it has been shown that inhibition of that process has a clear threshold, and there are some pesticides which have been regulated accordingly. It is deemed that it is possible to adopt a deterministic approach for such compounds, with an allowable daily intake because there is a threshold. Most thresholds are demonstrated experimentally, mechanistically and *in vivo*. Whether there is a threshold can be established on the basis of scientific evaluation of the underlying mechanisms but not just on the observable data. I think it would be fair to say that the

conduct of the risk assessment would depend upon the purposes of the risk assessment. If it was a contaminant, there would still be the need to proceed to determine where is the level of exposure relative to the level of concern. If it was a veterinary drug residue, then one might consider that it would not be acceptable to allow a non-thresholded compound to be present in the diet. But it is very much at the discretion and direction, I would say, of the risk manager as to how one would proceed.

Chairman

390. When it comes to the question of establishing a threshold, what is the difference between a genotoxic substance and a substance with genotoxic potential? When a substance is genotoxic, by definition, and is there any possibility of not being able to set a threshold?

Dr. Boobis

391. Yes, absolutely. If it was shown to be a direct-acting genotoxicant which caused mutation, and there was an indication that that also occurred *in vivo,* then it's very likely one would conclude that it was not possible to identify a threshold. There are one or two rare examples of compounds which are direct-acting genotoxicants, which because of metabolic reasons there is considered to be an *in vivo* threshold, but they are very very rare. As I said before, and as others have said on this side of the table, it very much depends on examination of the underlying data and the scientific interpretation of that data as to where one gets to in considering the significance of genotoxicity, and whether or not one can establish a threshold for that compound. There are no absolutes in this.

Chairman

392. Dr. Guttenplan.

Dr. Guttenplan

393. Most genotoxic compounds that we know of now are of the type that directly damage DNA and cause mutations, and they don't exhibit a threshold. In terms of risk assessment then, the critical factor would be exposure. If exposure is near zero, then whether there is a threshold or not, it does not make a difference, you are not exposed, there is no risk. But determining the exposure is then critical in the case of a compound that exhibits no threshold. Now many of these genotoxic compounds, from what we can determine in animals, do not have, and this was discussed before, a linear dose-response curve. So determining risk from a compound without a threshold, where you don't know the dose response at the low levels, requires a fairly high level of extrapolation, and there is going to be a larger uncertainty, and that is one reason for the uncertainty factors.

Chairman

394. Thank you. Any additional questions from the Panel.

Ms Orozco

395. I would please ask Mr. Guttenplan to repeat what he has just said, because I am trying to think through, and I am not sure that I did understand.

Dr. Guttenplan

396. Well, let me see if I can recapitulate. Yes, the type of genotoxic agent that damages DNA and causes mutations, as opposed to the spindle-active compound that has a threshold, is not going to have a threshold. And then its risk is largely going to be determined by how effective it is as a

genotoxicant and the exposure level. If you are not exposed, or the exposure is very low, then the risk may be insignificant. However – yes.

Ms Orozco

397. Sorry to interrupt, but if I allow you to end, then I will ask you to start again. Exactly this is the point where I lost you. If the premise is that a genotoxic substance can create damage to DNA, why do you say that at low exposures that changes?

Dr. Guttenplan

398. I didn't say it changes. I said that there may be no appreciable risk. We have naturally occurring substances within our bodies that cause DNA damage, they are always there. Oestrogens may be in that class of compounds. We live with this. You cannot do anything about that background. That small amount that comes from a genotoxic agent if the exposure is very low may be insignificant in comparison to the natural background.

Chairman

399. Thank you. If there are no other additional follow-up ... Dr. Cogliano.

Dr. Cogliano

400. Can I try the same thing with an example we had two years ago at IARC, with formaldehyde, and that's again another substance that is carcinogenic to humans. It is genotoxic and there was a lot of discussion about what is the shape of the dose-response curve as you get down to lower doses. And when you have no threshold basically it means your dose-response curve goes down in some shape, but it does not go hit the x axis and be flat. A threshold means your low dose is a flat 0, and then it goes up after some threshold dose. No threshold means that as soon as you leave zero you are going to have some risk. Now, so what Dr. Guttenplan said, at very low doses, you also have very low risk. Now the question is, we don't really know, there is uncertainty about the shape of the dose-response curve at the lowest doses, and this is what came out in the modelling that was discussed at the IARC meeting on formaldehyde. Possibly you could have a dose-response curve that goes linear all the way down to zero. Possibly you could have a dose-response curve that is very steep at high doses and then at low doses it still goes down in a straight line, or you could have something that is curved all the way down but it is still slightly above zero for any finite dose. The point is, we don't have studies that are powerful enough to tell us what is happening at the lowest of the low doses. So there is some uncertainty. But when you have no threshold, it means you are not looking for a dose where you are absolutely safe, what you are looking for is a dose where you have some low level of risk. And you do your best to try to describe that dose-response curve as low as you can, but at some point you still have uncertainty and you cannot with any degree of confidence say what is the shape in this very very low range. Does that help any?

Ms Orozco

401. Up to your last sentence there I got it. You were saying – and thank you for the effort too, to explain this important element – if there is a threshold, it means that a dose that is lower than your threshold does not pose any apparent risk?

Dr. Cogliano

402. That's right. The risk curve is flat up to a threshold dose, and then it begins to rise, so below that dose, yes, your risk is zero.

Ms Orozco

403. So why is it important to know what happens below that dose?

Dr. Cogliano

404. That's if you have a threshold, it's not important to know; but if you cannot establish a threshold, you may have some level of risk, and we were really talking about cases where we cannot establish a threshold and there is uncertainty about whether the dose-response curve is going down with some undefined shape, and how low is that risk at the lowest of doses.

Ms Orozco

405. And when is it that you cannot establish a threshold? Is it because of the mechanism?

Dr. Cogliano

406. Yes, the mechanism gives us clues as to whether something has a threshold. I think it has been stated by a couple of people that a direct-acting mutagen is not likely to have a threshold.

Chairman

407. I think my follow-up question is also related to the question which has been responded to just now. Would you clarify the difference between linear and non-linear situations, which are referred to by the parties? When would it not be feasible to set this threshold below which there is no appreciable risk?

Dr. Cogliano

408. Linear simply means the dose-response curve goes down at low doses at a straight line. Its not a straight line all the way up to past 100 per cent risk, its going to level off. But at low doses, linear means the risk is proportional to dose, and at any level of dose higher than zero there will be a risk higher than zero. Non-linear means the curve has some other shape and that's what is really problematic, because at those low doses, we don't have enough animals or our epidemiological studies are not big enough to observe what happens at one picogram of exposure. With a typical animal study with 50 animals, the lowest you can observe is a 2 per cent risk. With an epidemiological study that's got 10,000 people, the lowest you can observe is the one in 10,000 risk, but you still don't know if there is some lower level of risk at lower exposure levels. So the problem is that when you have a non-linear dose-response curve, you really don't know the exact shape at low doses, and that's where we get into what Dr. Boobis had said; we take conservative assumptions and try to predict what is the worst it can be, because we really can't precisely specify what the risk is there, so we say, well, the highest it could be is this, and then a risk manager has to decide if that is an acceptable level of risk, given all of the other factors that a risk manager thinks about.

Chairman

409. Even in the linear situation could there be a situation where the threshold cannot be established?

Dr. Cogliano

410. In the linear situation we do not have a threshold. Threshold means it's flat at zero and then starts to go up, like a hockey stick perhaps, it's flat against the ice and then it goes up to the person's

hand. Linear means it is just a straight line from the origin of the graph and there is a risk at the lowest of doses. Now that risk can be very very very small, and if exposure is very very very small the risk is very very very small, but the risk is not zero. I think that is the distinction between linear and a threshold kind of response.

Chairman

411. It may be linear, but it never hits the bottom, zero. After all it has to be flat at some point.

Dr. Cogliano

412. I don't think there is consensus that it has to be flat at some point. I think that is one of the scientific arguments a lot of risk assessors have, about whether everything has a threshold or not. I think there is a consensus that there can be low levels where risks are very very low, and some people will say the risks are zero.

Chairman

413. Dr. Guttenplan?

Dr. Guttenplan

414. Yes, the problem is in the second question. That question says: when would it not be feasible to set a threshold below which there is no appreciable risk? And that is the question; what do you consider appreciable? One in a million, one in a thousand?

Chairman

415. Well, actually, that is the Panel's next question (laughter). Let us go directly on to that question: what is appreciable risk, no appreciable risk, no apparent risk, zero risk, no additive risks, no adverse effects – what are the differences between all these terms?

Dr. Guttenplan

416. Lets see all the terms and then (laughing). As far as what is an appreciable risk, I think that is up to the risk management to decide, what they consider appreciable and acceptable. If there are many compounds with additive risk, and if you have several compounds, each has a risk, and each risk is independent, then they are additive.

Chairman

417. But if the appreciable risk is a concept related to risk management rather than the risk assessment, then it could vary depending on the level of protection chosen by each country.

Dr. Guttenplan

418. Exactly, yes.

Chairman

419. Then there would be no objective criteria at all. It could vary from zero to ...

Dr. Guttenplan

420. In performing a risk assessment you can come up with a number, but which number in terms of risk a country wants to use is up to their own individuals, is up to their own risk managers.

Chairman

421. Dr. Boobis.

Dr. Boobis

422. I think part of the confusion is the innate self-preservation of scientists who don't want to commit themselves to absolutes. Most of those terms there generally have similar meanings, no appreciable risk, no apparent risk, zero risk, no adverse effects, maybe not the one no additive risk, we can talk about that later. And I will just try to explain why it is we use this term quite frequently, no appreciable risk. First of all, it is true, the level of protection is set by the risk manager, in that by usage and by adoption there is an implicit if not explicit level of protection for a thresholded residue, and that is how we set the ADIs as has been explained, based on default assumptions on the safety factors that are in common use. This provides, de facto, a certain level of protection. That level of protection, to this date, has been accepted by the risk manager as being appropriate, because they accept the risk assessments, and the assumptions that are in those risk assessments are clearly laid out, if we are using a safety factor default of 100 in the absence of other information. We don't call it zero risk usually, we call it no appreciable risk, and I am talking here only about compounds which have a threshold. And the reason we call it no appreciable risk is because of the two extrapolation factors we talked about, one to extrapolate from experimental animals to humans, and one to allow for human variability.

423. And we are really talking about two different thresholds. The first threshold is the threshold in a dose-response curve, and really we have been talking about that largely today, that is when we talk about thresholds, that somewhere on the dose-response curve we reach a low dose and there is no response below that dose. But the second threshold is a population threshold, that within a population there is a variability in sensitivity, and that second threshold is the one that makes toxicologists and risk assessors reluctant to say zero risk, because we cannot say with absolute certainty, within a population of 6 billion human beings at the present, that there is not somebody somewhere under a given set of particular circumstances that might not be ultra-sensitive, so we hedge our bets if you like and say no appreciable risk. We are protecting a very very large percentile if not the entire population. I would stress, however, this does not mean to say we are not protecting certain sections of the population such as the young or the elderly, because they are definable groups and the risk assessment takes account, to the extent it can, of such subgroups within the population. We can discuss how we do that, I assume later today or tomorrow, but I am talking about a rare sensitive individual, not the population.

Chairman

424. OK. We also have related questions on the terms such as additive risk, additional risk, aggregate risk and cumulative risk. So would you explain further the differences.

Dr. Boobis

425. Additive risk. Could we maybe have those terms – OK. Aggregate risk and cumulative risk have come to mean something by definitions that were devised by the US. They defined what is meant by aggregate and cumulative risk, it is not an intuitive meaning, it is not a meaning that would automatically be understood from the words themselves, so I must stress that. So what we mean by

aggregate risk is, simply by convention, a lot of people use the term in that way, the same for cumulative risk, so that is just to clarify that. Aggregate risk in the sense that it has been defined under the Food Quality Protection Act, where this came from, is the risk from all sources of exposure to the same substance. We were talking earlier about, if we think of just oestradiol, all the different possible sources of exposure to oestradiol; if we were doing an aggregate risk assessment, we would add up all those sources together. A cumulative risk is thinking about substances which might act on the same target, so, in the case of hormones, all possible oestrogenic substances acting on the oestrogen receptor, we would have to think about exposure to all of those compounds by all different routes, and find some way of combining them. You would not just add up the amounts, because a phyto-oestrogen is going to be a lot less potent than oestradiol; diethylstilbestrol is more potent than oestradiol, so you have to normalize them for potency, which is a technical issue in respect of conducting a cumulative risk assessment. Additive risk is additional risk or risks over and above the background level of risks that already exists.

Chairman

426. So all these terms are not necessarily limited to the problems arising from the long latency period.

Dr. Boobis

427. No, they don't relate to it at all.

Chairman

428. OK, thank you.

Ms Orozco

429. Just one question. Aggregate risks – that was for Dr. Boobis.

Chairman

430. OK, we will continue to the next question and then come back to this question again. Our next question is: what are the components of a qualitative risk assessment compared with a quantitative risk assessment? Could you please clarify whether in your view the four steps of risk assessment as defined by Codex and JECFA are not applicable for qualitative risk assessment? Maybe this question could be addressed particularly to Dr. Cogliano. The EC indicated that it has carried out a qualitative dose-response assessment. We would appreciate it if the experts could provide their views about this argument, and probably the EC may also want to respond to this particular part of the question.

Dr. Cogliano

431. I would say qualitative risk assessment could be described as what IARC does when we come up with a determination that an agent is carcinogenic to humans or probably not carcinogenic to humans. It's simply the statement that a hazard does exist, without trying to further characterize that hazard as to dose level or duration of exposure of susceptible populations. This qualitative risk assessment can be a more quantitative risk assessment that could include developing dose-response relationships, establishing levels where you don't see adverse health effects, measuring exposure and comparing the exposure to the dose-response curve. So I would say, any time you are starting to get into dose-response curves and into exposure levels, you are getting into the quantitative risk

assessment; the qualitative risk assessment is just the establishment of whether a hazard exists, whether something causes cancer.

Chairman

432. You have a question?

Mr. Ehlers

433. Well actually, and I thank you for that answer, it goes on to the last part of our question. It would seem then that to say that a qualitative risk assessment, if it is qualitative, then a dose response is a contradiction, because a dose response requires quantitative, and that is why this part of the question was put in. Can you carry out a qualitative dose-response assessment if the dose is quantitative by nature? That is what we are trying to get at.

Dr. Cogliano

434. When IARC does its qualitative evaluations that end up in simply a statement that an agent is carcinogenic or possibly carcinogenic, or probably not carcinogenic, it does look at dose-response relationships because, for example in an epidemiological study or an animal study, if high levels of exposure give you higher levels of risk, that increases your confidence that you do have a carcinogen. If you had a dose-response curve that went up and down, you are not sure what you have. And so we do look at dose-response relationships. What distinguishes qualitative from quantitative risk assessment is how the conclusion is expressed. IARC expresses the conclusion by saying this agent is carcinogenic to humans or this agent is probably carcinogenic to humans, but we don't get into if it's a dose-response relationship that's linear, that there's a safe dose; that's part of the quantitative risk assessment later. So I think I would refine my first answer by saying that the difference between qualitative and quantitative is how you express your conclusions, and if your conclusions have any element of a safe dose, dose-response curve, susceptible populations, then I think you have gotten into a more quantitative assessment.

Chairman

435. So the same requirements and steps and components should be applied to the qualitative risk assessment even though their conclusion may be made in the form of a qualitative decision rather than quantifying?

Dr. Cogliano

436. I would express it this way. The qualitative risk assessment is the first of the four steps, it's the hazard identification phase. When IARC says this agent is carcinogenic to humans, we have identified a hazard. If IARC says this agent is probably not carcinogenic to humans, we have made a hazard statement that this agent probably is not a hazard, at least for cancer.

Chairman

437. Do you mean that when it comes to a qualitative assessment, stopping at the first step of the four steps could satisfy the requirements of risk assessment? I will give the floor to Dr. Boobis and then ...

Dr. Cogliano

438. I think there are cases where calling something a carcinogenic hazard has led an agency to make a decision just on the qualitative element alone. But I think many agencies still prefer to see a quantitative risk assessment that they will then carry out, based on the exposures in their country, to determine what to do. The reason IARC does the qualitative assessment only is that we really don't have the resources or the expertise to identify all the types of exposures in every country, and there does seem to be a need for an authoritative statement about what is carcinogenic and what we don't feel right now is carcinogenic. But then the next step is for national agencies or local agencies to look at their local exposure situation and compare it with a dose-response relationship or safe dose and make a determination about whether some action should or should not be taken.

Chairman

439. If we follow your views, then there would be no need to get into the exposure assessment by way of doing qualitative or quantitative dose-response assessment.

Dr. Cogliano

440. In some cases no. I would say for example cigarette smoking; I am not aware of any dose-response assessment that says your risk per cigarette you smoke is X. I think the totality of the evidence about smoking, that it causes, I think, 16 different types of cancer in the most recent IARC monograph, and just the consistency of positive results everywhere, I think is enough to have caused action to be taken. But smoking obviously is a very extreme case about having a lot data and a case where qualitative assessment is in itself sufficient to take an action.

Chairman

441. Thank you. Dr. Boobis and Dr. Tritscher.

Dr. Boobis

442. Well, I think that it does depend upon why the risk assessment is being conducted and what the risk manager requested, and in the case of a veterinary drug residue, one is seeking to determine whether residues at the level that occur in the diet are considered to be without appreciable harm or risk. And if a mechanistic consideration led to the conclusion that the hazard was such that the dose response was going to be linear, there is no threshold as we discussed just before, then it might be that one would stop the risk assessment at that point. But that would be an unusual circumstance, and in most circumstances one would want to understand the relationship between the hazard and the level of exposure that was occurring. For that reason one would progress at least to a semi-quantitative evaluation of the exposure and risk, rather than just stopping at a simple identification of hazard.

Chairman

443. Dr. Guttenplan.

Dr. Guttenplan

444. Yes. The comment was made, if you have a dose-response curve for an animal, you have a quantitative dose, why isn't that a quantitative risk assessment. Usually when you are testing a carcinogen in animals, you will test in both sexes at several doses and often in several species, and you will get different dose responses in each one of those. So just having a number for a particular animal species is not enough to produce a quantitative risk assessment.

Chairman

445. We have ten minutes before 6 o'clock so I think the Panel has – OK sure.

Ms Orozco

446. Sorry, I go back to something that was being mentioned, the aggregate risk. If you talk about evaluating aggregate risk, what that does is to modify the scope of the risk assessment, if I understand you well?

Dr. Boobis

447. It does indeed, because one of the big questions that has to be asked is how widely do you cast the net for all exposures? Do you include therapeutic application of the same drug used in deliberate administration to patients? Whose responsibility is it to take account of all the different sources of exposure? And these are very difficult questions, and on the international scene are particularly problematical because the totality of exposure will vary with the circumstances of the region, and that is one of the reasons that it has been very difficult up till now to conduct aggregate risk assessments globally. And I would add we are still struggling with this, we have not answered these questions yet, we have not reached solutions yet.

Chairman

448. EC.

European Communities

449. Gentlemen, I would not intervene, since you say the EC, that we have carried out a quantitative dose-response assessment. And I would request the scientists tonight that they have a look at our risk assessment and we can take up the subject tomorrow. We said we have carried out a dose response, in particular for the children, and I would request the scientists to have a look at our 1999 first risk assessment. We have done this for all the hormones, the six hormones. It is on page 36, 37 and 38 for oestradiol and there are corresponding pages for the other hormones, and then we can take up this issue tomorrow. I am not posing a question now, but I would request, because it is not true that we have carried out only a qualitative dose-response assessment. We explain we have examined the ADIs and the rest proposed by JECFA and those levels demanded by the US. We have tried to go through this dose-response quantitative assessment, in particular for children. As far as the genotoxicity of these substances, it is true we have made a qualitative dose-response assessment. But it is not true we did not try to do a quantitative risk assessment, and I give these pages for oestradiol but there are comparable pages for each of these six hormones. They are in our 1999 first risk assessment. They are in the documentation of all the experts. So please have a look tonight to see. We did not stop at the hazard identification, that's not true.

Chairman

450. Well, we are here not to make a decision, we are just getting advice from the scientific experts. I was expecting to see the representative of JECFA, Dr. Tritscher raised her flag on this question. We are wondering whether JECFA has done qualitative or quantitative assessments for these hormones at issue, and I am wondering whether JECFA agrees that the hazard identification alone equals a qualitative risk assessment.

Dr. Tritscher

451. Thank you. I had actually taken down my flag because I thought that we had clarified or had moved on, but it really addresses the last point here on the slide and we may have contributed in our response a little bit to the confusion in this context. So it is in the context of dose-response assessments, and dose-response assessment is an integral part of each risk assessment. Now this can be done qualitatively or quantitatively, and I tried to explain what we mean with that. In a qualitative sense, a dose-response assessment is simply determination of a no effect level. One looks at all the measured effects, identifies the dose where one sees an adverse effect, goes one step lower, the next dose lower is the no effect level. The outcome is a number, in that sense it is quantitative, that may be the confusion, but it is not doing a complete quantitative mathematical dose-response analysis, taking all the points of the dose-response curves into account. This is what we meant with the quantitative dose-response assessment. But even a derivation of a no-effect level and derivation of an ADI considers dose-response assessment, but not in a mathematical quantitative modelling way. Sorry if that raised any confusion in that context. Regarding the six hormones, JECFA did identify the no-effect levels and derived an ADI, so in the terminology, the way I introduced it, which may be a little bit misleading, this would be a qualitative dose-response assessment.

Chairman

452. Am I right to understand your comment as saying that even in the qualitative assessment you have gone through all these four steps of risk assessment?

Dr. Tritscher

453. Yes; that is the short answer. Hazard identification is not a risk assessment, a risk assessment comprises the four steps, and one can simplify it, the hazard identification and hazard characterization steps are often done together, or can be done together. This is the toxicological assessment, again, the left arm; the right arm is the exposure assessment. The integration of the outcome of these two assessments is the actual risk characterization step and yes, JECFA has done this.

Chairman

454. Thank you. Dr. Boisseau.

Dr. Boisseau

455. Please excuse me, Mr. Chairman, but I had raised my flag following the Panel's question on cumulative risk. In Dr. Boobis' example, the cumulative use of the same substance as an additive and as a veterinary drug theoretically poses a complex risk assessment problem. In practice, there may be no problem. I think we need to be fairly pragmatic, because whereas a growth promoter may be used repeatedly or even continuously, the same substance used for therapeutic purposes may only be used on a one-off basis. The evaluation of the safety of residues is something which, according to the ADI definition, is done on a long-term basis. In other words, supplementary ingestion of residues in connection with the one-off therapeutic administration of veterinary drugs is relatively less important in terms of exposing consumers to the residues of that substance. Furthermore, we must not forget that therapeutic application is not oblivious of public health. There is what is known as the waiting time. Consequently, the possible supplementary ingestion of a given substance administered therapeutically can often be considered negligible. Thank you.

Chairman

456. Thank you. Dr. Miyagishima.

Dr. Miyagishima

457. Thank you, Mr. Chairman. The Codex Commission as such does not conduct any risk assessment, but it has expressed its position on risk assessment, and this is found in the Codex Working Principles for Risk Analysis for Application in the Framework of Codex Alimentarius. Paragraph 20 of this document states that risk assessment should be based on all available scientific data. Risk assessment should use available quantitative information to the greatest extent possible. Risk assessment may also take into account qualitative information. Therefore I think that one could interpret this phrase as the desire of the Codex Commission that risk assessors use as much quantitative information as possible, whether it is in the framework of what can be seen as a qualitative risk assessment or quantitative risk assessment. Thank you.

Chairman

458. May I give the floor to Dr. Guttenplan before I give the floor to EC.

Dr. Guttenplan

459. The term cumulative risk assessment has come up, and one way that could be interpreted is the accrual of damage or mutations; if one is talking about a genotoxic substance over time. One can estimate, for instance, for certain number of years smoked you will increase your risk of lung cancer by a certain amount, or for a certain number of years of taking oestrogen replacement therapy you will increase the risk of breast cancer by a certain amount. So this is an example of a cumulative risk assessment. The longer you are exposed the greater your risk.

Chairman

460. EC has the floor.

European Communities

461. Chairman, just a quick clarification and a question to JECFA. When you identify a substance as being directly genotoxic, do you go on in your risk assessment or you stop at hazard identification? Thank you.

Chairman

462. Dr. Tritscher.

Dr. Tritscher

463. It depends, it is very difficult, again, to answer very generally on these questions, it depends very much on the mechanism, again, as was explained in detail further. With respect to oestradiol, since this was the example used in this context, and I have to correct a statement that was made earlier by the EC, JECFA stated in the report of the fifty-second meeting that the Committee, JECFA in that case, concluded that oestradiol has genotoxic potential – it is worded that way on purpose, because of the scientific uncertainty that was alluded to earlier by the experts, and I am not in a position to comment on the content there. And in that case, the risk assessment was taken further in the sense that all other information is being looked at, in particular with compounds that have a genotoxic potential. One has to, of course, as a next step look if there are cancer bioassays, does the chemical cause cancer in animal studies, in the long-term studies or not. So it is the totality of the information that has to be taken into consideration before drawing any final conclusions.

Chairman

464. EC.

European Communities

465. Sorry, I did it on purpose not to ask specifically about oestradiol, because the views of JECFA are known as genotoxic potential on this one. If you without uncertainty identify a substance as being directly genotoxic, do you then go on?

Dr. Tritscher

466. Yes, again, the answer is exactly the same. One has to take the totality of the information into account.

European Communities

467. Gentlemen, the question is if you follow the four steps if the substance – we are not talking now for this question for oestradiol – in general, if you come to the conclusion, and we are not talking about uncertainty, if you come to the definite conclusion that a substance is genotoxic, would you still go on doing the four steps?

Dr. Tritscher

468. I would say yes. It depends on what level of detail you go into. But now I have to, apologies for the time, but I have to explain a little bit longer, because its very different if we are talking about compounds that are added to foods for a specific purpose, or if we talk about unintentional and potentially unavoidable contaminants, that is a very different story. But traditionally in the food safety assessment area for compounds that have been added intentionally to food, veterinary drug residues, pesticides, what have you, if there is in *in vitro*, *in vivo* studies a clear-cut conclusion that the compounds are genotoxic, and traditionally no formal risk assessment was performed in a sense, not quantitating it and so forth, but the recommendation, and I guess that is what you want to hear now, that's what you are alluding to, is invoking the so-called ALARA principle, meaning that exposure to compounds that are unwanted in food should be reduced to as low as reasonably achievable. Again, one has to differentiate between unintentional compounds and intentional compounds, to say very briefly, and it is up to the risk management to make decisions on the regulatory level what to do to reduce exposure. For example, with compounds that are added, like veterinary drugs, one can make different legislative ruling than for example for contaminants.

469. Now going back to the contaminants, JECFA as well as EFSA, the European Food Safety Authority, and then together in a joint EFSA/WHO effort, is trying to go a step further to get away from this ALARA principle, to give more advice to the risk managers for contaminants in food that have genotoxic and carcinogenic properties, which includes compounds where you cannot necessarily make the link; there are genotoxic properties, carcinogenic properties, not necessarily linking that the carcinogenic mechanism, the carcinogenicity has to be provoked by genotoxic mechanisms. In order to give better directions to the risk managers as to which compounds are really of public health concern – so where to put your efforts, for management measures, for public health protection, the concept of the margin of exposure has been now formalized. I want to say it is not a new concept, but formalizing it, which compares certain effect levels for model studies with the estimated human exposure, and the larger the difference between those two, the lower the public health concern. By formalizing this approach, this allows comparison between different compounds, and gives some indication which are of more concern to health than other compounds. But having said this, I have to

emphasize again this is a concept that JECFA applied or developed a formalized approach now, and it is applied only to contaminants. Thank you.

Chairman

470. Even if in seven minutes it's already 6 o'clock, I think this is a rather important issue, so I will continue until we complete discussion on this particular issue this evening. I am wondering whether interpreters are available until that time.

Interpreter

471. Could you tell me how long you might expect to last, how much longer you would like us to be here? I will have to check. I think that is alright but I will check with my superior. Thank you.

Chairman

472. May I request each one of the experts to be as brief as possible in his or her response to this question. Dr. Boobis.

Dr. Boobis

473. Briefly, just from an independent scientific perspective, regardless of whether I participate in JECFA or not, if I was talking about a veterinary drug which was generating a residue and were evaluating that compound and it was shown to be a DNA reactive mutagen which was expressed *in vivo,* I would consider it unnecessary to proceed with the risk assessment, with a proviso that for any reason the risk manager did not ask for some scenario evaluation. For example, it might be that there was a particular essentiality for that compound and the risk manager might say well, what is the margin of safety, along the lines Dr. Tritscher has just outlined, it would be possible to conduct a risk assessment on that basis.

Chairman

474. Thank you. I saw many flags raised a few minutes ago. EC.

European Communities

475. Gentlemen, we are grateful for the intervention of Dr. Boobis, because on the basis of what we have been hearing from the representative of JECFA, then an exposure assessment in that situation, that means where you had a genotoxic substance, defined and uncontested, you only need to count how many people will die definitely, and the question is why you are supposed to do it, because this is the question, why you are going to go along with the risk assessment if you know that the substance is genotoxic? And by the way, I would like to ask, how are you going to do it since you don't know if there is no threshold there? So I appreciate the intervention, because it clarified the situation.

Chairman

476. Thank you. Dr. Boobis.

Dr. Boobis

477. I regret that I have been misrepresented, Chairman. I have chosen my words with extreme care – I would like to repeat, I said a DNA reactive mutagen. I would also like to point out, although

we have not got into this yet, when JECFA evaluated the specific compound in question – and what my answer was was a general answer – the specifics are that they did not conclude that that compound was a DNA reactive mutagen, which is the reason why JECFA was able to proceed with this risk assessment, it felt it was appropriate to do so. These are different scenarios. As I stressed before, and I do again, it depends entirely upon the conclusions that an evaluation of the data lead to as to how you proceed.

Chairman

478. Thank you. Dr. Boisseau, and I will conclude

Dr. Boisseau

479. Yes, thank you Mr. Chairman. I simply want to mention, since we are speaking of general principles, that it is obvious that if a product has been shown to be mutagenic following a series of tests, it will be mutagenic for the target animal. But we are not talking about a target animal, we are talking about the consumer, so that the risk remains for the consumer to the extent that the mutagenic product is present as a residue. Imagine a parent substance that is definitively mutagenic but that is completely metabolized: I have in mind carbodox, for example. The substance, which is toxic as such, may not ultimately generate toxic residues in the foodstuff. So the evaluation must always be comprehensive, and indeed, stopping an evaluation as soon as a hazard has been detected, without trying to evaluate the possible risk for public health, is a procedural shortcut that could lead to an erroneous assessment of the risks without necessarily providing a comprehensive and reasoned view of the case as a whole.

Chairman

480. Thank you. We do have some more questions that, I am sure, will be asked by the parties, because some them have already made comments in relation to conflicting evidence on the table and so on. So I would rather stop our discussions this afternoon here and see you tomorrow morning at 10 o'clock in this room. But before I adjourn the meeting – excuse me, there was a request from my colleague in the Panel to go on. Instead of getting into the question and answer session again, on the remaining questions, I just want to put the questions verbally so that you can consider these questions for the discussion tomorrow morning in responding to the questions posed by the parties.

481. Our question was on the weight of evidence approach, which was, to my knowledge, used by Dr. Boobis, and the remaining two questions are: please comment on the EC statement in its comments on question 19, where it states that it has a standing request to review the hormones at issue. The last question is about Codex and JECFA. In response to question 3, Codex makes reference to ongoing work regarding risk analysis principles applied by the Codex Committee on Residues of Veterinary Drugs in Food and risk-assessment policy for the setting of MRLs in food. Do you expect major changes to Codex/JECFA work in this area once these documents are adopted? These are the remaining questions for your consideration at tomorrow morning's session.

482. Thank you for your cooperation, and I particularly appreciate the patience and cooperation of the interpreters for staying with us until this time and I hope you will have a good evening and see you tomorrow morning at 10 o'clock sharp in this room.

28 September 2006, morning

Chairman

483. Good morning. I hope you all had a good sleep last night and, for those who have travelled a long way from another continent, recovered from the jetlag, I hope.

484. This morning we are going to continue the remaining questions on area 2. As you may recall, before we adjourned the meeting yesterday afternoon, the Panel read out three questions, the question, Nos. 18 and 23 and 24, which you might have noticed on the screen, but we believe that 24 has already been answered by JECFA representative, so I hope we can start with the experts' replies to the Panel's questions 18 and 24.

485. For your reference I will read out the questions once again: could you please explain what the weight of evidence approach is? And the other one is: please comment on the EC statement in its comments on question 19 where it states that it has a standing request to review the hormones at issue. These are two remaining questions of the Panel on which we expect the replies from the experts at the beginning of this morning's session. And then, as I mentioned in my opening statement yesterday morning, the Panel will invite parties to pose their own questions to the experts on the area 2 items. And on area 3, the Panel has the intention to let the parties go first with their own questions and then the Panel will follow up the questions already posed by the parties. And I would like to remind the delegations that we have a time-limit to finish our business until the end of this session. And also I would like the delegations to know that one of the JECFA representatives, Dr. Tritscher, has a prior engagement this afternoon, so she has to leave after the lunch break. So we have to finish our discussions on the remaining questions under area 2 and, if possible, all the questions under area 3, that is scientific evidence, and there are many JECFA-related issues even under area 3. So I hope we can conclude our discussions on area 2 and area 3 this morning so that we can move into the remaining areas, that is EC's risk assessment and others. So, all in all, time is very constrained, so I hope the parties will be very strict in selecting the questions of their own, so that they can economize the time given during the remaining meeting today. Before Dr. Tritscher leaves this afternoon, parties are requested to pose questions on JECFA-related issues this morning, even if that falls into the category under area 3, that is scientific evidence. I am not sure whether I was quite clear to the delegations.

486. OK, with that understanding may I ask the experts to respond to the Panel's questions on Nos. 18 and 23. Dr. Boobis.

Dr. Boobis

487. Mr. Chairman, I would like to address the issue of weight of evidence. The weight of evidence is the evaluation of the available information about a particular toxicological endpoint, taking into account factors such as the adequacy and number of available studies and the consistency of results across studies. It is not an issue of seeking to weight one person's opinion against another. It is a specific situation where one is faced with a large body of information on a particular endpoint, and we can talk about, for example, genotoxicity. Where there are multiple tests of genotoxicity, and the results of those tests are not entirely consistent, a weight of evidence approach requires an examination of the quality of each study individually – because sometimes the studies will not all be done to the same standards – and the consistency across those studies, and then eventually an evaluation of what is the totality of the evidence telling us about that endpoint. Thank you.

Chairman

488. Thank you. Any others – Dr. Boisseau.

Dr. Boisseau

489. Thank you, Mr. Chairman. I would like to support what has just been said by Dr. Boobis concerning the genotoxicity and mutagenicity tests. In fact, these tests currently pose a double problem, I think. Over the past twenty years, the number of such tests has increased considerably, with the inevitable result that since we are using a greater number of tests to study a substance, the chances of our ending up with a positive result obviously increase accordingly. The second problem is that these tests, which have flourished over the past few years, have not always been validated according to internationally accepted criteria – so that whereas fifteen years ago when a committee of experts considered the results of a series of what was usually four tests, two *in vitro* and two *in vivo*, where there were one or two positive tests it was not too difficult to declare the substance genotoxic or mutagenic, today we always have one or two positive tests and two or three dubious tests out of a total of fifteen; and when the tests used have not necessarily all been validated, it is easy to understand that the willingness of a committee of experts to declare the substance genotoxic or mutagenic is not very strong. Thank you Mr. Chairman.

Chairman

490. If there are no other additional comments, then shall I move into the next – OK, then I will open the floor for EC.

European Communities

491. Thank you. Without wishing to prolong the debate, I would like to ask the scientists which have responded and also the other scientists which have not taken the floor: the United States 2002 National Carcinogenesis Reports have classified oestrogen and oestradiol as capable of causing direct and indirect damage, cancer. This is part of the file we have submitted to the Panel and you must have it. Is it clear? The question then is: in your conception of the weight of the evidence approach, where would you place this United States National Carcinogenesis Report? Why is it not part of the weight of the evidence?

Chairman

492. Dr. Boobis.

Dr. Boobis

493. The report on carcinogenicity of the United States is the consequence and evaluation of the data, it is a conclusion. The weight of evidence approach requires a de novo evaluation of the data, so you don't use somebody else's conclusion in a weight of evidence approach. You may ask the question why does one reach a different conclusion, that is a perfectly justifiable question, but it is not appropriate to take other people's conclusions in a weight of evidence evaluation of the data.

Chairman

494. US and then EC.

United States

495. Thank you, Mr. Chairman. I would like to follow up on Dr. Boobis's comments and on the EC citation to the 2002 US report on carcinogens, and actually this is a question to Dr. Boobis with a short lead in. The EC has cited this report as evidence that steroidal oestrogens *per se* are known to be human carcinogens, and as you might be aware if you have looked at this report, the conclusions

rely heavily on an evaluation conducted by IARC in 1999 entitled Post-Menopausal Oestrogen Therapy. Dr. Boobis, if you are familiar with the US report on carcinogens and these IARC monographs, can you comment on the relevance of these reports to the specific risk alleged by the EC, which is that posed by oestradiol 17 β residues in beef and beef products?

Chairman

496. Dr. Boobis.

Dr. Boobis

497. I am certainly familiar with the IARC evaluation and familiar to some extent with the RC. As I understand it, the conclusion was that oestradiol-17β was a likely human carcinogen; but neither of those reports, as I understand it, said that genotoxicity was the mode of action. And, based both on the evidence of other bodies and also on its own primary evaluation of the epidemiology – because at that meeting there were distinguished international epidemiologists present who did their own evaluation of the world's literature on the possibility of a risk of cancer from exposure of humans to oestradiol-17β – JECFA accepted at that time that was a risk. But, and it is a very big but, the conclusion was that this was not associated with genotoxicity. And critical to the JECFA evaluation was the relative level of exposure, and the conclusions of JECFA were based on an evaluation of the exposure that was likely to occur from the use of the hormones in beef-producing animals.

Chairman

498. Thank you. EC.

European Communities

499. Thank you, Chair. A simple question, going back to the weight of evidence and the explanation given by Professor Boobis. I would just like to know whether you mean to say that the weight of evidence approach involves interpretation of data of the kind you have explained in your reply to question 52. Thank you.

Chairman

500. Dr. Boobis. Is Dr. Boobis ready to respond?

Dr. Boobis

501. In fact, the IPCS report to which I refer did use a weight of evidence strategy. I was using weight of evidence in a narrower sense in my earlier response in that we were very much focussed – and this is common practice when one is dealing with multiple studies on the same endpoints, or related endpoints, one has to have some process to determine what is the consensus picture of that data set. This is not a question of what people think and minority opinions, it is a question of looking at the data, and we had an expert genotoxicity person with us at that meeting to help us to evaluate the quality of the studies and the likelihood of outcome. Now when one looks at genotoxicity testing, some tests are more prone to artifactual results than others. So an Ames test, the bacterial test for mutagenicity, is generally a very reliable indicator of DNA damage, because there are few ways in which one can generate an artifact if the test is done to a reasonable standard. If one looks at some other tests, toxicity and other methods of interfering with a cell can influence the endpoint, so it is very important that one looks under the conditions of the protocol of the study as to the reliance that one is placing on the endpoint of that study. When one looks at 100 studies of genotoxicity, for most compounds one can find the odd positive, even for a genuinely negative substance. And so that is

what I mean by the weight of evidence. If you have 99 negative studies all done well, one study done badly which gives a positive, what is the weight of evidence? The compound is negative. I am not arguing this is the case with oestradiol-17β, is was not quite as clear-cut, but using a weight of evidence approach, the committee was able to reach a conclusion as to what the genotoxicity was telling us, and that was the case for many other organizations that have looked at the body of evidence available for this compound's genotoxicity. There is an element of interpretation of the quality of the study, I accept, but that is why you have experts on the evaluation committee.

Chairman

502. EC.

European Communities

503. So Dr. Boobis and also the other scientists, do you accept that different groups of scientists can view the same set of data and reach different conclusions to that question?

Chairman

504. Dr. Boobis.

Dr. Boobis

505. The simple answer is yes, one can always get different interpretations with the same dataset, but some datasets are more likely to give a consistent answer than others for most people, if that makes sense. So the example I gave earlier of 99 good studies giving a negative, or let's put it the other way around, 99 good studies giving a positive and one bad study giving a negative, one would hope that the vast majority of people looking at that dataset would reach the same conclusion. It is just possible that somebody would say that the negative study is the one we should put the weight on.

Chairman

506. Let me give the floor to Dr. Guttenplan and Dr. Boisseau first.

Dr. Guttenplan

507. Yes, I guess I want to answer some of the questions. I think it is probably fair to say that most of the agencies that look at or have looked at these compounds or other compounds use a weight-of-evidence approach. I think that is true of the National Toxicology Program Report on Carcinogens, it is certainly true of the IARC monographs. It means that you get a lot of experts together and they look at the positive and the negative studies, they consider multiple interpretations, they try to weigh which studies should contribute most to the evaluation and come up with a reasonable judgement. Also, as Dr. Boobis said, it is possible for different groups of experts to come to different opinions. That is why we invite groups of experts, so that we are not too dependent on any one person's opinion. And in most cases when the IARC monographs programme looks at data, they do have a consensus, although there are cases where the dataset is sufficiently mixed that there is a close vote. So there are some cases where the overall signal about whether something is carcinogenic is an issue. I don't think that is the case with steroidal oestrogens, I think many bodies have said that steroidal oestrogens are carcinogenic. I think that the next level down of questions is: How is it carcinogenic? Is it carcinogenic through a hormonal mechanism, through a genotoxic mechanism, only one of them, possibly a mixture of both? And I think that there is some uncertainty and there is some difference of opinion among the experts. So in that case it is possible for different groups of people to reach different evaluations.

Chairman

508. Thank you. Dr. Boisseau.

Dr. Boisseau

509. Thank you, Mr. Chairman. I would go along with what was just said. The fact is that expert committees are currently issuing different opinions in the area of genotoxicity, perhaps because they are focusing more on the results. I am convinced that if we brought together competent and independent experts and if they began by objectively evaluating the validity of the methods, there would be far fewer problems with the results that those methods produce. I do not think that we place enough emphasis on the validity of the methods. Secondly, to favour consensus, it is important to know what these short-term mutagenicity or toxicity tests can produce and what they cannot produce in order to avoid erroneous interpretations depending on the results obtained. Clearly these techniques are used with large quantities of the substance that have nothing to do with residue content. This is particularly true of *in vitro* methods: they are conducted in conditions which do not reflect the fate of a substance in an organism, determined by pharmacokinetics and the metabolism – they are merely screening tests, and nothing more. They cannot, under any circumstances, lead to a determination of dose effects, and at best, they can only provide information on the mechanisms of action. Thus, if the experts focus on the validity of the methods, on what these methods can produce and what they cannot produce, I am convinced that there would be much more consensus on the interpretation of the results of the methods. Thank you.

Chairman

510. I have a procedural question. What if there are conflicting views, half and half, or almost half and half, among the experts participating in the JECFA Committee? What is the decision-making process in that case? Do they still make conclusions on the issues that do not provide any sufficient scientific evidence, or avoid making decisions and refer it to the next committee or to a later stage? Dr. Boobis.

Dr. Boobis

511. First of all, Chairman, this is a hypothetical question, because it has not occurred. I want to make that clear. The JECFA Committee – at least as far back as 1997 – have been able to reach an agreed position on all the questions before them. In the event that there was a disagreement, there would be two possible options – one would be not to proceed further and seek further evidence, and the other would be, as has been indicated already by the secretariat, if the majority was of one view and a minority was of another view, to issue a so-called minority opinion or minority report as well, which reflects a contrary view on the interpretation of the data. As I said earlier, this has not happened, there was unanimity. Generally what happens is that there is a discussion, there may be varying interpretations of a dataset, the experts get together over the period of a meeting and explore the various possibilities, bringing new information, or new insights and reach a common position, and that has worked generally very successfully in the evaluation of the compounds over the last 10 years I have been involved in JECFA. Thank you.

Chairman

512. Are all these decisions made by consensus, or sometimes by voting?

Dr. Boobis

513. At JECFA the decisions have always been made by consensus, to my knowledge no vote has been necessary.

Chairman

514. Dr. Tritscher.

Dr. Tritscher

515. Thank you. I have to explain a little bit what I did not do in the beginning, what the role of JECFA is within the WHO Constitution. JECFA is an Expert Committee, and expert committees are the highest level scientific expert groups that exist within the WHO Constitution, and there are very strict rules for scientific groups. And as I said, an expert committee is the highest-level committee with very stringent rules with respect also to the selection of the experts and so forth. With regard to decision-making, it is the basic documents of the WHO which lay out the rules for expert committees, which are convened to develop a recommendation to the Director General for his or her decision. It is made very clear that scientific decisions are not subject to vote, that is very clear. And as Professor Boobis said, your question is indeed a hypothetical one because the whole purpose of an international expert committee is to reach a conclusion. If theoretically there would be a situation where you have a 50/50, 60/40 or very close decision, and then it is in the discretion of the Chairman on how to proceed. If it appears that no consensus opinion will be reached, then that subject would not be concluded on. If there is a minority, then there are also very clear rules, and there is the option that if it is not possible to reach consensus, a minority opinion can be expressed, and has to be expressed, if there is no consensus. And again, this minority opinion is published in the report, with the names of the experts having this minority opinion and a clear description of their rationale and their opinions. Thank you.

Chairman

516. Dr. Wennberg.

Dr. Wennberg

517. Thank you, Mr. Chairman. Yes, as I was explaining yesterday, the existence of scientific committees is also laid down in the basic text of the Food and Agricultural Organization of the United Nations, and as Dr. Tritscher explained, the same rules apply to the experts which participate in expert committees called by FAO to help the international scientific committees to elaborate on scientific issues. And may I also say that as far as the expertise is concerned, there is a transparent procedure in how these experts are called upon, are selected, are put on rosters which are agreed by the Director-General of FAO and by the member countries from where these experts are coming, and the experts have to sign a declaration of interests for every meeting in which they participate, and these declarations of interests are filed by the Organization. Thank you.

Chairman

518. Thank you. EC.

European Communities

519. Chairman, can I make a short statement instead of a question, or it is both. A clarification for Dr. Boobis. In the United States 2002 carcinogenesis report, is it not true that they examined and

declared oestradiol as a direct and indirect genotoxic substance? They have also said, and I can read, veterinary use of oestradiol estrogens to promote growth and treat illness of animals can increase oestrogens in tissues of food-producing animals to above their normal levels. This is in the report. They didn't make just a general finding, they have linked it to the residues from meat of animals treated with hormones for growth promotion, it is written in the text. And later on we come to the more precise question of the growth response. Thank you.

Chairman

520. US.

United States

521. Thank you, Mr. Chairman. I think you know that the issue that the EC has raised is one that we can discuss on Monday of next week when we discuss these issues. But I would note that the statement made by the EC is nowhere linked, in that report, to the carcinogenic effect that the EC seems to be alluding to. So just as a point of clarification, and perhaps any of the experts who have read the report would like to speak to that issue.

Chairman

522. OK. Question 23 regarding the EC statement that it has a standing request to review the hormones at issue has not been answered by the experts or the JECFA representatives. Dr. Miyagishima.

Dr. Miyagishima

523. Thank you, Mr. Chairman. Yesterday I explained briefly how the Codex Committee on Residues of Veterinary Drugs in Foods operates, but please let me reiterate what I explained yesterday a little bit, and answer the question posed. CCRVDF uses the so-called priority list as a means of communication with JECFA. Prior to each meeting of CCRVDF, the Codex Secretariat circulates or distributes a circular letter to all Codex members and observers, and this circular letter invites any nominations of compounds for evaluation or re-evaluation. The comments or proposals received in reply to the circular letter are usually considered by an ad hoc working group that meets the day prior to the beginning of the CCRVDF session. The discussion and conclusions of the ad hoc working group are presented to the plenary session of CCRVDF where the final decision takes place as to what compounds should be included in the priority list and then communicated to JECFA.

524. Now, with regard to the five substances for which the Codex established MRLs, that is, oestradiol-17β, progesterone, testosterone, trenbolone acetate and zeranol, the only reference found in the reports of CCRVDF is the intervention made by the European Commission – which was an observer at that time, participating in CCRVDF – on behalf of the European Community, at the eleventh session in 1998. The European Community requested that the re-evaluation of these five substances that was being scheduled in 1999 be deferred to a later session of JECFA, in view of substantial studies that were being prepared by the European Union at that point of time. Since 1999, CCRVDF has met five times, as I explained, at the interval of approximately 18 months. In the reports of CCRVDF, there is no record of proposals, either from the European Community or from member States of the European Community, to include these five substances in the priority list for re-evaluation by JECFA. With regard to melengestrol acetate, it was included in the priority list for recalculation of MRLs and TMDI by the fifteenth session of CCRVDF that met in 2005. However, the request did not come from the European Community, but came from an industry observer present at the meeting. These are the records found in the reports of CCRVDF, and given the fact that Codex rules or internal procedures allow for any member to go on record for any decisions taken by

CCRVDF contrary to its wish, it is unlikely, reading from the reports of CCRVDF, that a request was made from the European Community for re-evaluation or evaluation of these substances. Thank you.

Chairman

525. Thank you. Madam Orozco.

Ms Orozco

526. Thank you, Mr. Chairman. I have two follow-up questions, one to the EC, as to what they means by a standing request to review the hormones at issue, because that has been stated in some of your documents. I would like clarification as to what the actions are, or how this request has been submitted. And second, I have a follow-up question to the Codex representative as to what was the answer, and the reasons for the answer to that intervention by EC requesting postponement of the re-evaluation. Thank you.

European Communities

527. Mr. Chairman, I can be very brief on this. We have sent to the Panel Exhibit No. 63, where we have attached the exchange of letters we had with the JECFA and Codex secretariat. In the last letter, the reply of the joint secretariat, it is stated that we had been requesting JECFA to postpone the re-evaluation of 1999, which nobody has requested. It was coming from the secretariat themselves, which is a very rare procedure to apply. And we have requested them to postpone because the new data was coming. And they have replied to this letter that once the new data becomes available we will review them, and they conclude we will be happy to place again these substances on the agenda of a future meeting of JECFA. And the issue was left there. We never said after the re-evaluation don't do it, it was there on the table since we were communicating on this question since 1999. It is true we didn't put it on a priority list subsequently, but the understanding was, at least this is how I understood it, that when the new data become available, they will review that. And the truth is, when they presented the 1999 evaluation to the Codex Committee, they said we did not ask you to re-evaluate, and they didn't consider that. So I think it would be reasonable, in the light of these letters which we have exchanged, and the promise that they will be happy to place again these substances on the agenda, they would have done it. That is all, it's no more than that. Thank you.

Chairman

528. Thank you. Dr. Miyagishima.

Dr. Miyagishima

529. Thank you, Mr. Chairman. Just to complement my previous intervention by saying that the latest session of CCRVDF actually met earlier this year, and there was a circular letter, Codex circular letter 2005/43, was circulated in September 2005 to invite nominations for compounds for evaluation, with a deadline of 28 February 2006. No replies were received from any member or observer. Thank you.

European Communities

530. Excuse me. I have the question for Codex and for JECFA as to what was the answer to the intervention made by the EC observer referring to the deferral of the re-evaluation.

Dr. Miyagishima

531. The request from the European Commission made at the eleventh session of CCRVDF was duly recorded in the report of that particular session and as such it was brought to the attention of the JECFA secretariat, and that was the action taken by the Codex side.

Chairman

532. Thank you. Dr. Wennberg.

Dr. Wennberg

533. Thank you, Mr. Chairman. The JECFA secretariat and the exchange of the letters that was talked about – the reason why JECFA put the substances on the agenda of JECFA was that there was new important epidemiological data that had become available since these substances had been evaluated in 1987. The JECFA secretariat may place any substance on the agenda for re-evaluation, even though no outside request has been received. It is not permissible that the JECFA secretariat should postpone a re-evaluation of a substance when new important information has come to the attention of the secretariat – let's make that clear. The second point I would like to make is that the procedure to put substances on the agenda of JECFA, through the CCRVDF, is open to all members of Codex and even observers, as we have heard. So it's not because there is a letter responding to this request for postponing a re-evaluation that the secretariat would issue a call for data for re-evaluation of the substances when there is no explicit request from a member of Codex to do so. The procedures have been very well explained by Dr. Miyagishima and they are followed by everybody. The secretariat never received any information on the studies, the studies themselves, or the study report from the EC. Thank you.

Chairman

534. Thank you. Dr. Tritscher.

Dr. Tritscher

535. Just to add to what my colleague already said, it's really that there are three main routes or main ways for a compound to get on the agenda of JECFA; through the priorities working group in CCRVDF, but also requests from FAO and WHO member States can be brought forward directly to the JECFA secretariat with the request for evaluation or re-evaluation, with justification, data availability and this kind of information. And the third is that the JECFA secretariat can re-schedule the re-evaluation of a compound if they are made aware that there is significant new data available. What that requires usually is that these data are really made available, not just saying that there are new data, here it is, but there has to be a very clear list of what type of data, to allow, with the help of experts often, to judge if this is justified, if the data are significant enough to justify a re-evaluation. And it is not correct that this is an extremely rare procedure. Sorry, there is one other way for compounds to be nominated for evaluation; it is actually through specific FAO and WHO programmes themselves. It is commonly the case that, for example for the WHO drinking water guideline programmes, compounds are requested for evaluation through JECFA or through JMPR for pesticides. And although the main route for nomination of compounds for evaluation is through the Codex Committee, it is not correct to say on the other side that it is extremely rare; it really happens frequently. Thank you.

Chairman

536. We now invite the delegations to pose their questions. Starting with EC.

European Communities

537. Thank you, Chairman. So we move now to another area.

Chairman

538. Another area, you mean area 3, or are we still in the risk assessment techniques? Have you exhausted all your questions on item 2? Do the US and Canada have any questions on risk assessment techniques? Canada.

Canada

539. Thank you, Mr. Chair. Our questions are just clarifications on some of the answers that have been provided. First for Dr. Cogliano. You said yesterday that IARC conducts qualitative risk assessments in that it stops after identifying a hazard. You also said that it's qualitative because of the way it expresses its conclusion as possibly carcinogenic or a known carcinogen. My question is, then, can you use the qualitative conclusions of a JECFA monograph to evaluate the potential for occurrence of the hazard that is identified for given exposure scenarios? Perhaps – you are going to answer that one first then.

Chairman

540. Thank you. Dr. Cogliano.

Dr. Cogliano

541. It is true, the IARC monographs do stop with a statement that something is carcinogenic or probably not carcinogenic to humans. That can be enough, depending on the structure in which you make a decision. The monographs on different forms of tobacco were enough for WHO to conduct its framework convention on tobacco control. It does not give you dose-response information about what is happening at lower doses; it will simply tell you what are the substances for which carcinogenicity should be considered, and then different decision-making authorities will have to decide whether that evidence is sufficient for them to make a decision, or whether they do need to conduct further analysis.

Chairman

542. Thank you. Canada.

Canada

543. On its own, then, the conclusion is not useful for evaluating occurrence in a specific exposure scenario though, is that what I understand? It might lead other authorities to determine in specific circumstances whether there is a risk that that particular hazard would occur.

Dr. Cogliano

544. Yes. Other authorities would need to determine whether there is a risk. Now occurrence is a different matter. Occurrence simply means is there some exposure to the chemical through some particular pathway. The IARC monographs do attempt to identify the different types of exposures people encounter, whether it is occupational exposure, whether something is found in food, whether something is widespread in the environment; so the monographs identify occurrence, but not the

specific levels of exposure in a particular population. There are a lot of terms, like occurrence, exposure, risk and I'm trying to be precise here.

Chairman

545. Thank you. Is that all Canada?

Canada

546. I have just two more questions. Dr. Boobis, you explained the difference between deterministic approaches and probabilistic approaches to risk assessments. I wonder if you could comment further on – I think in fact you did comment on – which approach is more often used, but if you could further comment on which is the more conservative of the approaches.

Chairman

547. Dr. Boobis.

Dr. Boobis

548. In terms of the toxicological side, the hazard side, of risk assessment, the probabilistic approach has only very rarely been used. We almost always use a deterministic approach. In terms of the exposure side, the majority of risk assessments have also used deterministic approaches, although increasingly people are using probabilistic approaches. Where data have been obtained, it is quite clear that almost always the deterministic approach is more conservative than the probabilistic approach, and sometimes by orders of magnitude.

Chairman

549. Thank you. Canada.

Canada

550. A final question then, Mr. Chairman, and this would go to the representatives of the JECFA secretariat, or I guess any other expert that is familiar with the operation. In light of the suggestion by the EC in its comments that JECFA takes for granted all the unpublished data from industry, I wonder if you could describe the steps that JECFA takes to verify the quality and sufficiency of the preparatory data it receives from industry. Thank you.

Dr. Tritscher

551. Thank you. I don't understand what is meant with taking for granted, maybe that has to be explained later if I am not addressing what is actually meant with that. When compounds are put on the agenda, the JECFA secretariat publishes a call for data on the internet that goes out publicly to everybody. With compounds that are commercially produced and sold, very often important toxicological information is proprietary information and is not publicly available. This information is submitted by the company to the JECFA secretariat, and JECFA requests the complete study reports, so not the summaries or the conclusions or what have you, but the complete detailed individual reports with all the details, individual numbers, individual data, completely the whole set of information. And in addition, all the experts perform literature searches using standard techniques in order to, in addition to the non-publicly submitted information, to take into account everything that is publicly available in the public domain as relevant scientific information. The data that are submitted are scrutinized in detail by the JECFA experts, in particular with respect to quality of the study. There

are criteria with respect to good laboratory practice that are very well defined. Modern newer studies have a statement to that effect, a legal statement, quality assurance statements, statements regarding good laboratory practice in their study reports. All those studies before these methods were implemented very often do not have such official quality-assurance statements and so forth. And then it is the responsibility of the experts to scrutinize in detail the study reports, if current good laboratory practice techniques have been followed. That means characterization of the test material, appropriate analytical methodology and any kind of really basic information that is available. If this is not available, if it is concluded that a study was not conducted according to what would be called good laboratory practice; it does not necessarily discredit the study as such. Sometimes these studies can still contain important information, in particular if you talk, as was explained earlier, in the context of the weight of evidence approach. Sometimes such studies still give important information, but one would not base an evaluation on such studies. It is in the overall context of evaluating the whole database. And again, all the data that are submitted are scrutinized in detail, checked for accuracy and then summarized and described in detail. I hope this addresses the question.

Chairman

552. Canada.

Canada

553. That concludes our questions on item 2. Thank you.

Chairman

554. Thank you very much. May I now invite the EC to pose questions on item 3, scientific evidence. Please go ahead.

European Communities

555. Thank you, Chairman. I would like to come back to the issue of the most sensitive segment of the population, in particular prepubertal children, and I would like to ask Dr. Sippell, for example, whether the values which we have seen yesterday on the screen from JECFA are the values for prepubertal girls and boys which are their actual production rate, daily production rate, or whether they are based on the detection limits of the assays used for the calculation.

Chairman

556. Dr. Sippell.

Dr. Sippell

557. As far as I could see the official production rates, and it is difficult to calculate exact production rates in prepubertal children because first you have to have a true level of endogenous production, blood levels, so that you can calculate the production rate. They have been based on the, so to speak, traditional levels measured by radio immuno assays, and usually by radio immuno assays without prior extraction. We all know that the sensitivity of such procedures is not enough compared with more modern techniques, so to speak, the extractive procedures involving radio immuno assays, but even more modern molecular base techniques like recombinant cell bioassays, of oestrogen, oestradiol or oestrogen activity. And these, as I have pointed out in my answers to the Panel, are significantly below the levels previously thought, and by that the production rate now is significant lower. And this of course implies that any risk from exogenous sources, for example beef treated with hormones, treated with oestradiol-17β, is much higher.

Chairman

558. Thank you. EC.

European Communities

559. You have also made reference yesterday to the latest method in the USA to calculate the daily production rates, and you made a reference to the assay of the group of Klein which became relevant after the evaluation made by JECFA, so does this in your view put in doubt the validity of the values given in JECFA, and I am precise as to the potential risk for prepubertal children from eating meat treated with hormones for growth promotion. It's an important point to clarify in my view. Thank you.

Chairman

560. Dr. Sippell.

Dr. Sippell

561. Yes, that's indeed the case. This ultra-sensitive assay has been recently confirmed, its validity has been confirmed by another lab, you know the Klein methodology. The main author is George Chrousos, by the way, who was for many many years director of the children's section at the National Institutes of Health, and this new supersensitive assay has been confirmed by another laboratory which also is very well-known and considered to be very thorough and applying good laboratory practices, of course; that is the lab of Professor Charles Sultan in Montpellier, and coming to quite similar levels and, as I said yesterday in my introduction, many basic biological features can only be explained by the validity of these supersensitive oestradiol assays. There is no other explanation among scientists, among paediatric endocrinologists, than very very low levels, significantly higher levels of secretion in prepubertal girls, significantly higher than in prepubertal boys. Therefore there is no doubt, as I told yesterday already, there is no doubt among the scientists, also in the United States and Canada, that this is really the case, and this supersensitive assay is not being put into doubt really by the experts I have been speaking to. Therefore, there really is concern that the exogenous load from, for instance, oestradiol-17β, might be significant.

Chairman

562. I will give the floor to the US and then back to EC.

United States

563. Thank you, Mr. Chairman. Just as a point of clarification, to the best of our knowledge the Klein assay has not been used subsequent to its 1994 publication for regulatory purposes. But beside that point, I think there are two important questions here, one of which I would like to pose to the experts generally, which is: what does it mean when an assay is validated? And I think the follow-up to that is an appropriate question for Dr. Boobis, which is: given the considerable debate in these proceedings regarding blood levels of oestradiol in prepubertal children, and given the EC's heavy reliance on the Klein assay which purportedly shows lower circulating levels of oestrogen, I was wondering if in Dr. Boobis's opinion the Klein assay indeed establishes that circulating oestrogen levels in prepubertal children are lower than previous reported, and whether that assay has indeed been validated by the evidence that is on the record? So a two-part question, one to all the experts – what does it mean to validate an assay? and then secondly – has the Klein assay indeed been validated? – to Dr. Boobis.

Chairman

564. Is any expert prepared to answer the first part of the question? Dr. Guttenplan, please.

Dr. Guttenplan

565. If an assay has been confirmed independently in a number of laboratories, I would consider that validated.

Chairman

566. Dr. Boobis.

Dr. Boobis

567. I am not an expert on residues, and there are people here who can speak on this better than me, but as I understand it, in residue analysis the process required for assay validation to measure and analyse biological samples for regulatory purposes is fairly well defined and consists of a number of steps, such as ruggedness, precision, sensitivity, reproducibility, transferability, availability of standards, etc. etc. There is a procedure which the chemical societies have agreed internationally, that before an assay can be described as validated, as opposed to fit for purpose, these are different things, that for validation it has to undergo this procedure which has been recognized as a systematic analysis of the different performance characteristics of the assay.

Chairman

568. Dr. De Brabander, please.

Dr. De Brabander

569. Yes, I agree with what Dr. Boobis said, it completely described what validation is of a analytical method. Of course I don't have experiences with assays for very low amounts of oestrogen in blood, we don't work in blood, but it is completely described. The most essential thing is specificity – that you are really measuring what comes up, and in that respect yesterday we talked about qualitative and quantitative methods in risk assessment, we have the same nomenclature in analytical chemistry, qualitative and quantitative methods, and both are always mixed. Every quantification needs a qualification; you must be sure of what you are counting; the specificity of the method is extremely important. And also, if you have a qualitative method, you get always a signal and you get some kind of quantification, but it is only qualitative and again, you will have to fit the rules for quantification, a calibration curve etc. etc. I can put at your disposition a number of papers on validation, but I don't think we will start a discussion on validation as it is strictly described.

Chairman

570. Thank you very much. Any other experts? US.

United States

571. And then, just as a follow-up, if in Dr. Boobis's opinion the Klein assay has indeed been validated by any of the evidence that is on the record.

Dr. Boobis

572. Not to my knowledge. I would just comment on my concerns about the Klein assay. There is a review published in the Journal of Paediatric Endocrinology and Metabolism in July of this year by the Klein laboratory, or with Klein as an author I should say, and it states in the review summary: prepubertal boys have oestradiol levels of 0.4 plus or minus 1.1 picograms per ml – which is somewhat higher than the level that was reported in the 1994 paper, which was 0.08 picograms per ml, that is significantly different. Now the Klein assay uses a recombinant assay in yeast with the human oestrogen receptor and therefore it is not specific to oestradiol-17β; if it is, there is something strange about the biology, because one would not imagine that that receptor could discriminate between different oestrogens with absolute certainty, because otherwise the whole concept of oestrogenicity would not work. There are extraction procedures in the assay which might help select out certain compounds or others. Having looked at the characteristics of the assay, I find it extraordinarily difficult to understand why that assay would be so specific, or so sensitive, to oestradiol as opposed to other oestrogen agonists. There are other assays based on the recombinant oestrogen receptor; one of them utilizes a mammalian cell, not a yeast cell, and it is by Dr. Paris's laboratory. They have reported, using this assay, levels of oestradiol, of I think a couple of picograms per ml, yes, 1.44 picograms per ml. So we can see now that using these recombinant assays there is a variation from below 0.1 to 0.4, to 1.4, so that my view, having looked at these data is that, first of all, the recombinant assay has not yet been validated adequately, but secondly there is evidence, when one looks at these data, to suggest that the circulating levels of oestradiol in male children are lower than previously thought, I would accept that, but I would not think they are as low as in the original publication by Klein *et al,* because there have been numerous publications since then using a variety of assays which suggest that the levels are certainly higher than those very low levels first reported.

Chairman

573. Can I give the EC and then Dr. ...

European Communities

574. Gentlemen, I think we have a different interpretation of the data, and we will review references made by Dr. Boobis and will reply to that on Monday and Tuesday, but we understand that all the latest assays, and the one mentioned by Dr. Sippell later on, from the professors in Montpellier, they confirm that the level of oestrogen is much much lower, many more times lower than the ones reported in the JECFA report. There is no doubt, and even Dr. Boobis in his reply says in the first sentence of his replies that there is no doubt today that the levels are much lower. This minor difference to which he has made reference, they are not statistically different important differences, they are minor differences which sometimes you observe in the assays, and if you normalize the assays, you will see the values you expressed in the different assays, you will see there is no doubt about it, that it is significantly lower. But I have to move on from that debate and come back again to Dr. Sippell, and other scientists may come in, for example. In the risk assessments which the European Communities has performed and which you have in your files – and I refer to our 1999 and again to 2002 assessments – do you think that the European Communities has attempted to evaluate the risk for the prepubertal children from exposure to these hormones, taking into account these latest values which have been measured by the most sensitive assays?

Chairman

575. Dr. Sippell.

Dr. Sippell

576. I think that the risk is, and I have read several papers on that and also from my clinical experience, that as I pointed out yesterday, the levels probably are still lower than what has been measured by a radio immuno assay, and that the recombinant assays, they might differ, but they are with a lot of indirect evidence much closer to the truth than the traditional assays that we are all using nowadays in a routine lab. And if you calculate, then the exposure certainly is much higher if you have the low levels with the recombinant assays as a basis, and therefore I think some people have calculated that as little as 10 grams of meat ingested per day for a prepubertal boy might be or will be above his own production rate, and this is something one should consider.

Chairman

577. Excuse me, I don't think the US questions have been fully answered, so may I invite experts other than Dr. Boobis to add their comments on the first part of the US question and then move into the second part of the question. Is there any expert who is willing to add comments on the first part, on validated or not.

Dr. De Brabander

578. Well, as I said, there are rules for validation and normally if a lab performs well it is controlled by some organization. I don't know, I tell just for Belgium, you have the Belgian accreditation system, and labs who work in accreditation regularly have inspection from auditors. I have experience with that because I am an auditor myself, trained as an auditor, and when I go to a lab and they have qualitative methods (of course you don't test every method every time) I ask samples to be analysed. For example if it is urine and they have a method for testing urine, I ask them to prepare some samples of urine and I ask the components and then I take out amounts of the components and put them into the urine and then say do the test and show me the results. And then you can say that your method is validated. Of course, there are rules on paper – but in practice you can see if it works. And if it does not work, you can get the feedback to the lab – that's not in order, you should do that; that being the validation. It is not that you just have paperwork, there is control, and if you have a lab that works on GLP or accreditation, you have laboratory control on the results. In addition, maybe what was said, that a method is good when it is done in two labs, we use that also, performing analysis in two labs, and you see that for us chemists is it normal that if you get, for example, one ppb in one lab and two ppb in another lab, that's nearly the same. They are using slightly different procedures and it is within the variation of the method. And there is also evidence for that; there is a curve published by Horwitz, from the United States, who says that the uncertainty goes up when the concentration goes down.[3] The lower the concentration, the more difficult. Of course, you can understand that it is really impossible to have exactly the same figure. So the figure may vary a little bit within ranges, giving the same results.

Chairman

579. One follow-up question. In order for this scientific data by one laboratory to be validated, do we need a kind of endorsement by another laboratory or a number of laboratories on the same data?

Dr. De Brabander

580. No, it is not necessary, you have different systems, like I said, you have an accreditation organism who control that your lab is accredited. Within the accreditation you are also obliged to do

[3] W. Horwitz, L.R. Kamps, K.W. Boyer, J.A.O.A.C. 63 (1980) 1344-1354. (Reference provided subsequently).

ring tests. There are organisms who will prepare samples with certain amounts of components, the laboratories that are accredited need to analyse those samples and produce results. If your results are outside of a certain z-score[4], as they call it, outside the normal range, you are alerted, and if you come, during an accreditation audit, you can ask: can you give me the results of your ring test, how have you done for that component, how have you performed for that component, you can control that. And that's not another laboratory, that's an organization who controls it. I hope that answers your question.

Chairman

581. Dr. Boisseau.

Dr. Boisseau

582. Thank you, Mr. Chairman. Yes, I would like to confirm what Dr. De Brabander just said. However, we are talking about two different things here. We need to draw a proper distinction between the accreditation of a laboratory and the validation of a method. Dr. De Brabander has just spoken of an accreditation, and I have nothing to add to what he said. But, the question that was asked concerned the validation of a method. Dr. Boobis had reminded us of all the internationally recognized criteria for validating a method, and as Dr. De Brabander said, it is well known that the lower the target in terms of concentration, the greater the uncertainty and the lower the reproducibility and the reliability of the method – this is well known. There are two ways of validating a method: there is intra-laboratory validation, which takes place within one and the same laboratory, i.e. it is the same laboratory that repeats a certain number of dosages at different periods with different technicians, and if the results fall within an accepted range, the validation takes place within the laboratory. But more importantly, there is inter-laboratory validation, in which a certain number of laboratories are selected within the framework of what is known as a circular test, and the method is tested for precision, reproducibility, reliability, and what is also known as strength to see if it is exportable from one laboratory to another. Thank you Mr. Chairman.

Chairman

583. Thank you. Ambassador Ehlers has a follow-up question.

Mr. Ehlers

584. Thank you very much. The question has basically three elements. The first one is: do these hormones accumulate in the body or does the body eliminate them in total or in part? If so, do the adverse effects depend on this accumulation or not? And thirdly, if they do, then if you start with a lower endogenous level, would you not say that the risk also diminishes? Thank you.

Chairman

585. Dr. Boobis.

Dr. Boobis

586. The hormones don't accumulate to any appreciable extent in the body because of the natural production of similar or the same hormones, and these hormones would not be able to function if they accumulated in the body. So we have evolved mechanisms to allow the turnover of the hormones.

[4] In statistics, a standard score (also called *z*-score or normal score) is a dimensionless quantity derived by subtracting the population mean from an individual (raw) score and then dividing the difference by the population standard deviation. (Explanation provided subsequently).

All hormones have to have a turnover so that we can switch on and switch off the signalling pathway as necessary to off-regulate or down-regulate the target receptor system, and that would be true of the xenobiotic exposure to the hormones as well, because once they are in the body, the natural hormones are indistinguishable from the native hormones and would be eliminated by the same processes.

Chairman

587. Dr. Sippell.

Dr. Sippell

588. Again, the special situation in children before puberty – there is evidence that for instance secretion of sex steroids is pulsatile on a very very low level and that the sensitivity of the organism is such that these extremely low levels are being picked up and being recorded in the centres, in the hypothalamus, so in the brain, and also in the pituitary for regulation, also for imprinting. And we know that prepubertal boys or prepubertal girls, in case of oestradiol, are particularly sensitive to very very low exogenous levels of oestrogens. We have, for instance, the natural example of Turner syndrome girls who lack ovaries and thereby ovarian function and thereby have no endogenous oestrogens. And we know that with as little as 25 nanograms per kilogram body weight per day we can promote growth in these poorly-growing girls. So I think if you make the point that levels are very low, then at the same time sensitivity is of course adjusted to these low levels, which has to be taken into account also for exogenous exposure.

Chairman

589. Yes please …

Mr. Ehlers

590. Yes, thank you, I followed that explanation and there is part of my question that has not been answered yet, maybe somebody can do it. That is – since the body eliminates, then there is no accumulation, or if it is only temporary until the body has done its work, the adverse effects then do not depend on that. But you were trying to say that the fact of starting at a lower level does not diminish the risk but it keeps it at the same rate.

Chairman

591. May I give the floor to Madam Orozco to follow-up on the question.

Ms Orozco

592. Would there be any comments to the follow-up question of my colleague before I change the subject? Because I would ...

Chairman

593. I will give the floor to the US first and then the EC. EC.

European Communities

594. When we started the meeting, if we think of a fair distribution of time, I think they have been asking quite a lot of questions and we don't have the time to ask our questions.

United States

595. I think this is a very quick question if the Panel will indulge. Yes, it is related to Dr. Sippell's response. Very quickly for the members of the expert panel who have had experience in JECFA, that is Dr. Boobis, Dr. Tritscher, Dr. Boisseau, Dr. Wennberg, I am wondering, does JECFA in its evaluations take into account populations such as prepubertal children or sensitive populations, and how do they do that?

Dr. Tritscher

596. It's a basic principle of every risk assessment to take – it's a general remark – to take into account sensitive subpopulations, it's a basic principle. Because that is the part of the population that you want to protect with what you are doing, and this is based on the availability of data, what is taken into account. But it is definitely it's the goal of the risk assessment to identify who would be the most susceptible, the most sensitive part of the population, and that is the part of the population that the risk assessment is targeted to.

Ms Orozco

597. Just a quick follow-up question: how was it done in the 1990 evaluation?

Dr. Tritscher

598. I cannot respond to that question. I am not entitled to respond to that, sorry.

Chairman

599. Dr. Boobis.

Dr. Boobis

600. The Committee had available to it studies conducted in developing animals, where one of the assumptions is, based on research and scientific information, that the basic physiology of the test species that were used has a similarity to that in humans, and based on an evaluation of effects in those sensitive life stages, together with the other available information, the Committee concluded that it had been possible to evaluate the risks to all susceptible populations.

Ms Orozco

601. One more question, Dr. Boobis. How was the endpoint chosen in the 1990 evaluation?

Dr. Boobis

602. One of the hallmarks of a toxicological evaluation is that we don't focus on a specific endpoint because of the concern that we would miss something. So we use, as much as possible, to start with a so-called holistic approach, so we look at the totality of effects, evaluating multiple endpoints for the possibility of a compound-related effect. So in this case we looked at reproductive outcomes, we looked at the developmental effects and we looked at a range of other effects that were the normal hallmarks of reproduction and development in an animal.

Ms Orozco

603. Just one more question. The ADI that has been established – is that protection enough if you would take into account the new data about sensitivity of prepubertal children?

Dr. Boobis

604. I have done a calculation, which was in my responses to the questions, based on what I consider a consensus concentration that was somewhat higher than the lowest concentration, but was still significantly lower than that originally reported, and I calculated that the ADI would still be protective. I should add that what has not been mentioned so far is that we should not just take the external exposure and assume this translates into an internal dose or concentration. There are two factors which go against this. One is the pre-systemic metabolism we mentioned earlier – I think it was assumed this was 100 per cent in the EC evaluation, sorry, zero per cent, it was all absorbed. Whilst I accept that it is likely lower than in an adult, it will be very unlikely to reach zero per cent, particularly after the first week of life, and there will not be exposure to the hormones in meat in the first week of life as I understand it. And the second is that the hormone is not circulating completely free, a very appreciable amount is bound to sex hormone binding globulin and other proteins and there is good evidence that only the non-bound form is able to cross cell membranes and interact with the oestrogen receptor, and so that will reduce the circulating concentration as well. So that one has to consider those aspects in the evaluation.

Chairman

605. OK. Canada wanted to ask a related question quickly and then we move back to EC.

Canada

606. Yesterday there was some discussion about the extent to which the human population is exposed to exogenous sources of hormones in their diet, and Dr. Boobis yesterday indicated that there was a significant amount of exposure to oestrogens or to phyto-oestrogens or oestrogens in plant material, and my question then to the experts is: in establishing the ADI, is the extent of exposure to exogenous hormones taken into consideration, particularly in the diet of a prepubertal person, and is there any evidence that in the normal food, a diet with a normal food consumption, that prepubertal boys are at risk from exposure to exogenous hormones?

Chairman

607. Thank you. Dr. Sippell.

Dr. Sippell

608. I can be very brief. I believe that nobody has ever investigated this probably, also due to the fact that this is extremely difficult, also ethically, as I pointed out yesterday.

Chairman

609. OK. One more.

Canada

610. Dr. Sippell, in 2001, I believe, you co-authored an article that was looking into precocious puberty and you indicated, I believe, in your conclusion that there was no evidence in the literature

that exogenous exposure to oestrogens led to pseudo puberty, which is to be distinguished from central puberty. But I wonder if you could elaborate on that conclusion that there was no evidence in the literature to suggest that exogenous exposure to oestrogens cause precocious puberty?

Dr. Sippell

611. Yes. This was, as you just said, more than six years back – I think that meeting was in 1999 – and this was a review article, so we combined a little bit of our own research with the opinions published in the periodic review literature. And at that time we came to that conclusion. Since then the acceptance of the significance of the supersensitive oestradiol assays within paediatric endocrinology increased tremendously because, as I said before, it for the first time gave an explanation for basic physiological peculiarities which we did not understand before, and therefore there has been really a change of our understanding since then, and therefore my opinion now is quite different from that opinion in the one review article you cited.

Chairman

612. I will give the floor to the EC.

European Communities

613. Chairman, I said that I had two related questions to ask. First, it is not disputed that oestradiol produces a number of metabolized and other substances when administered to animals, and quite a substantial part of this is in the form of this so-called fatty esters, or lipoidal esters, which are thought to be eight times more potent than oestrogen itself, and we know that from the review of JECFA papers that the potential risk from these esters have not been taken into account in order to measure the effects on the humans when they are administered This goes back to Dr. Boobis, to what he said. He explained how they have taken into account the prepubertal children. Here we are not talking about developing animals, that's not the point, the point here we are talking about is developing human beings, boys and girls, and we cannot extrapolate from developing animals, which we know nothing about their organism, and draw a conclusion about human beings which nowadays it is internationally agreed, and Dr. Boobis has also said, that is at a much lower level of production. By the way, we have gone through the JECFA report and we didn't see any reference to developing animals. They have done the classical type of tests which are on animals, as they do it, and so all this is really questionable, and if there is any different view, then all the scientists can take the floor. The most important metabolite, which accumulates in the fat of meat, the fatty esters, which are more important, they are not taken into account. You cannot extrapolate for young animals, here we are talking about human beings, and this has not been done. And Dr. Sippell has confirmed, and if you would like to intervene, if you wish to explain why this is significant, and I posed the question in the beginning, we have provided the evidence, it is our 1999 and 2000 risk assessments. We have tried to estimate what would be the effects on prepubertal boys and girls, taking into account these recent findings from the residues in meat treated with hormones, under normal exposure conditions. And here we are talking about normal exposure conditions, we are not talking about other kinds of exposure which make up from misuse and abuse, we will come back to that later on, that is not the question. Here we are talking about normal exposure conditions. Thank you.

Ms Orozco

614. I would like to ask, because I think it is a very important issue that is being touched right now and it was asked before, and I would like to hear answers from as many experts as we have, as to whether the EC evaluated the risk to prepubertal children from the exposure of eating meat from treated animals. I think that is a very important question for the parties and for the Panel on which to hear views from the experts, please. And I am talking about the risk assessment, that is the three

Opinions that have been submitted by the EC and the supporting studies, I think that is the limit of their assessment for the purposes of this exercise.

Chairman

615. Dr. Boobis.

Dr. Boobis

616. The EC estimated the possible exposure of prepubertal children to food-derived hormones making a number of assumptions which we could debate here; they were certainly conservative, let's put it that way. For example, that everything that they were exposed to would be absorbed into the circulation – that is a conservative assumption, you could not get more than that but you could certainly get less than that. But what was not done was to consider what would the actual risk be, this was an exposure evaluation, I could not find in the documentation what the adverse effect that they were comparing that exposure to would be. So certainly they have done an evaluation of potential exposure, with certain assumptions, but I could not see how that was a complete risk assessment in those populations. Just to add, if they wish to refer to page 70 of technical document 43 of JECFA, you will find reference to the reproductive toxicity studies that were available for evaluation.

Chairman

617. Turning to the JECFA recommendations, how would you comment on Dr. Sippell's response indicating that scientific material referred to by the EC requires the revision of the Codex recommendation with respect to oestradiol. In the replies of Dr. Sippell to the Panel's question 42 there was a statement that scientific material referred to by the EC requires the revision of the Codex recommendations with respect to oestradiol. This a comment by Dr. Sippell. Are any other experts willing to add their own comments on this statement? If none, EC.

European Communities

618. Chairman, I think we can provisionally make a little connection to this issue by making reference to the dose response, which is also important to understand, because children indeed are a very sensitive segment of the population, this is not disputed, and it is not disputed that they have much more lower level of endogenous production. And it has been said yesterday, for example, that here we are not talking about zero risk because the risk is non-appreciable, but the concept non-appreciable does not mean zero risk. There is some risk and we have heard that it is not possible to calculate it exactly because the shape of the curve is not clearly defined, we don't know how it is defined. We have evidence and the scientists which are around me can take the floor if they wish to explain in more detail. The question is the following: we know and we have observed – the scientists and experts and the studies which we have submitted to the Panel and in our risk assessment – with the exposure already to the background levels, endogenously produced, we observe a biological action, several biological actions on the organism of young children. Some of them may lead even to cancer, this is not also disputed. So the question is: since we know this already and we have evidence, a few molecules, one or two or three, in the experiments already initiate the cells to grow and proliferate and divide, the question is how does this enter into the risk assessment of JECFA in this particular case of residues in meat from animals treated with hormones for growth promotion? This is a very specific question. Because we have tried to take this into account in our risk assessment and came to the conclusion which is now in our documentation. The point I make is I don't want to fudge the issue, this is taken into account on page 70. It is very precise, knowing that a very small, limited number of molecules, one or two, have a biological action on the organs of young boys and children. Why was this not taken into account when JECFA has evaluated these hormones? And is

this an important element to take into account in the light of the new evidence which is now available, for example, by JECFA?

Chairman

619. Dr. Boobis first and then US.

Dr. Boobis

620. Chairman, I must seek clarification. I am not clear yet whether the question relates to the DNA reactivity of oestradiol or to the hormonal effects of oestradiol. So far, what Dr. Sippell was talking about, as I understand it, was the hormonal effects. The genotoxicity argument is an additional argument and I was not clear in my own mind as to what was being asked by the EC.

Chairman

621. Would you like to clarify first?

European Communities

622. Chairman, the debate about the genotoxicity data is separate indeed, in our statement, what we are discussing here is about the hormonal effects, the effects through the hormone receptors' mediation.

Chairman

623. Thank you. Dr. Boisseau.

Dr. Boisseau

624. Thank you, Mr. Chairman. When it comes to the hormonal effect on pre-pubertal children exposed to hormone residues, and I am speaking of natural hormones, I think we need to recall the context of these discussions and to separate oestradiol, for example, from a xenobiotic, because when we say that an adult or young person is exposed to residues, we need to know what residues we are talking about. Since there is an endogenous production in the animals consumed for which we need to make allowances, what we are talking about is the additional residues linked to the treatment. Even if there is no treatment, there is in any case a basic level of residues that are natural. So what I want to know is, in view of these well-known variations in residues that are naturally present in meat, what is the risk already identified in connection with these residues alone and what is the additional risk linked to the supplementary residues resulting from the treatment. Oestradiol must not be treated as a xenobiotic on an all or nothing basis. The problem of oestradiol is that whether or not there has been treatment, we are still exposed to residues, and we must not forgot those residues.

Chairman

625. US.

Mr. Ehlers

626. Thank you. That is similar to what I was going to ask, not only about beef but about other sources, eggs or vegetables or others that also have hormones that come into our – or to children's, for that matter – diet. Do we have to stop their consumption of all of those also? Because if the effect is very great by just a few molecules, then it is not only the beef that is treated with these hormones, but

all other sources should also be stopped. Do we have to set an age limit for consumption of any beef, any eggs, any broccoli or whatever other source of these hormones exists in nature?

Chairman

627. Any experts? Dr. Guttenplan, please.

Dr. Guttenplan

628. Not a direct answer but a clarification. When the term "a few molecules" is used, that really is a simplification. It is not a few molecules, it's a small number of molecules per unit of whatever unit, usually its weight that you are talking about. So it isn't that if you have one or two molecules you are going to have a biological effect, it's basically a low concentration, I think this is what the EC is referring to, and not a few molecules.

Chairman

629. But still the question remains to be answered. No expert? Dr. De Brabander please.

Dr. De Brabander

630. I cannot comment on risk assessment because I am not a specialist in risk assessment, I would just comment on the broccoli Mr. Ehlers mentioned. You know that for young children all kinds of these things should not be given because they contain some natural thyreostats which are not good for young children – for thyroid function, yes. Some food should be forbidden for young children, including broccoli.

European Communities

631. Chairman, here the point is that there is no valid reason to overburden the human body, in particular of young children, with other sources, exogenous sources of these substances if it is not necessary. Normally we do it with children when it is for medical treatment, when there is a necessity; here there is no necessity to do it. But I would like to ask Dr. Guttenplan, and his qualification was very useful, this small quantity of molecules that you said, would they be present taking into account the ADI which has been fixed and the MRLs, if that quantity has just been fixed by JECFA, would that be sufficient to agree that a small number of molecules can indeed initiate or promote cancer? Would that be sufficient in the small quantity which has been defined as an ADI or an MRL?

Dr. Guttenplan

632. You are asking whether the ADI that is currently accepted is sufficient to protect against cancer. Is that the question?

European Communities

633. Yes, we have turned the question another way. My question was: if we agree that a small number of molecules, not one, two or three as you said but nevertheless a small set of molecules, can indeed initiate biological action, cells brought into separation and division, would the quantity which is included in the ADI from the residues in meat treated with hormones, would that quantity of molecules that can come from the absorption of these residues be sufficient to give rise to this kind of biological action when eaten?

Dr. Guttenplan

634. If you are talking about cancer, I don't believe there is a risk from consumption below the ADI for cancer. Those low levels might have a greater effect on developmental abnormalities in children though – I think Dr. Sippell has commented on that already.

European Communities

635. So you would agree that there would be other developmental effects on children, but probably you don't know if that will be leading eventually to cancer?

Dr. Guttenplan

636. I don't think that the levels that produce developmental effects in children, that might produce developmental effects in children, would be sufficient to induce cancer later in life.

Chairman

637. Dr. Boisseau would like to add?

Dr. Boisseau

638. Thank you, Mr. Chairman. Very quickly, the statement by the European Communities that there is no reason to overburden an intake of residues clearly has to do with risk management. Here, we are talking about risk assessment, and I think it is important to separate the two concepts. When we say that a few molecules could possibly generate tumours, excuse me for saying so, but we are talking of induced hormonal cancers. I think that there is currently a consensus that cancer associated with hormonal activity can give rise to a threshold, so we must stop speaking of a few molecules, since in the case at issue, we are not talking about induction, we are talking about genotoxicity, in other words promotion. And I think that there is a consensus on the fact that there is a threshold effect: this has been confirmed in writing by many committees. Thank you.

Chairman

639. The focus of our discussion at this point of time is scientific evidence in terms of risk assessment in general. Dr. Wennberg would like to ...

Dr. Wennberg

640. Just to recapitulate what I was saying yesterday about the additional residues that could be calculated from the residue depletion studies, where there were animals which were treated and animals that were not treated, the concentrations of the three natural hormones were analysed – what the excess amount of hormone would be in the beef – and compared to the ADI. The figures which are in the JECFA report and also in our report to the Panel say that the total oestrogen highest excess would be in the range of less than 4 per cent of the ADI, so that is a very small amount of the ADI. For the progesterone, the additional residues from the treatment would be 0.003 per cent of the ADI for progesterone, and for testosterone it would represent around 0.2 per cent of the ADI for testosterone. So we are talking about, in these studies, where there were control animals and treated animals, where there was variability in the natural hormonal discharge from these animals, that it is quite a small amount which could be considered additive to the natural background levels.

Chairman

641. Thank you. Yes.

European Communities

642. I would like to ask the representative of JECFA, do you know the date of these studies? Since when do they date? Because we know that these data date from the 1970s and 1980s. Could you give us the date of the studies to which you refer? We have been asking for this data, to see them.

Dr. Wennberg

643. These studies are available publicly reviewed by the committee with individual animals so you could have studied them all by yourself in FAO Food and Nutrition Paper 41/12. These are studies which were provided to the committee by the Food and Drug Administration of the United States and were the studies that were used for the authorizations for particular products containing these substances. If you consider that these studies were not sufficient for the authorization of these hormones in the United States, I think you should ask the questions to the United States. Thank you.

Ms Orozco

644. Excuse me, I have a follow-up question, please. What is the date of the residues data JEFCA used in the re-evaluation report of 1999? Or maybe, because we don't need a list of all the information used, but maybe to cut short the question, did you have new residues data for the 1999 re-evaluation? Did you use any residues data that was not used before?

Dr. Wennberg

645. Yes, as I was saying, for the 1999 evaluation the data that was reviewed, that was not reviewed before, was the complete set of residue depletion studies that were provided by the Food and Drug Administration of the United States. Now these had not been evaluated before by JECFA.

European Communities

646. Chairman, on this point, because this is important. I refer, and it should be in the records of the Panel, to Canada's Exhibits 17, which is the residues analysis monograph prepared for the 1999 evaluation by JECFA. It is on the record. Canada's Exhibit 17 and I refer to pages 88 and 89, where the studies upon which the evaluation was based are cited. And I don't see any of these studies cited here that it is more recent than 1989, they all date to 1979, 1982, and quite a number of them are undated and unpublished, so presumably they date from the 1970s and 1980s. I don't see any studies of the date which the representative of JECFA and Codex cite now. It is on the record.

Mr. Ehlers

647. Thank you very much. I would like to add another point to this. First of all, of course, what is at stake here is not the JECFA studies themselves but rather the EC risk assessment, that is what we have to study. But perhaps the question more likely should be whether since the 1999 study to now new information has come to light that would question, undermine or require that a re-evaluation be made now in the light of new information that has appeared since that re-evaluation of 1999. So this would be my question to everybody. Has new information come to light, new studies, that would indicate that the basis for the 1999 re-evaluation has changed so much that a new evaluation is needed now? Thank you.

Chairman

648. Thank you. In addition to that I am posing this question to JECFA: whether or not the new data available in the 1999 assessment were publicly available since that time? In order to know what was the reason why the EC has not received all these data materials since that time.

Dr. Wennberg

649. Thank you, Mr. Chairman, but I think that we are in the wrong, reverse sort of situation here. It is not for JECFA to submit data to the EC, it's for the EC to submit data to JECFA if they want JECFA to evaluate anything. So the data which are the basis for these percentages that I was quoting before are available in the report of JECFA, so they are available to everybody and not only to JECFA. That is the point of JECFA, to publish the evaluations.

Chairman

650. Does this include the new data that is not those produced in the 1960s and 1970s?

Dr. Wennberg

651. Well, as I now look at the reference list, many of these studies are from the 1980s and some are from late 1970s, some are not dated, but it's not true to say that they are all from the 1960s and 1970s. But may I also say that even if they were older, if the methodology that was used, and if the methods had been validated properly, there is no reason to discredit any studies because they were done a long time ago.

Chairman

652. But my question was that JECFA said that new data were also reviewed and that all those data were publicly made available. I am wondering whether those new data were also publicly made available. If that is the case, then there is no reason why the EC is continuing to claim that it has not received any new data other than that from the 1960s and 1970s.

Dr. Wennberg

653. The data that was evaluated by JECFA in 1999 as concerned the residues part are the data which had not been previously evaluated by JECFA. JECFA does not produce studies themselves, JECFA receives data from various sources, as we have explained before, from companies, from governments, from other institutions perhaps, and so what JECFA received and evaluated in 1999 was the complete residue dossier for these particular products, which are mentioned by name here in the report, from the Food and Drug Administration in the United States to JECFA. That was new data. It does not mean that all this data was produced in 1999, it means that the data was made available to JECFA for this evaluation, and there are studies from 1986, I read here in the reference list, 1979, 1982, 1983, 1989 and so on and so forth. I don't think I have to go further on this issue.

Chairman

654. Dr. Tritscher.

Dr. Tritscher

655. I would like to add just some general comments. As we have explained in our response to question No. 13, I refer to page 12 in our response, all documents from JECFA are published and are

publicly available in the public domain, all JECFA assessments, and I think that is one of the features of JECFA, to write very detailed monographs with very detailed descriptions of the database and complete references. In general, all these documentations are available within a timeframe from 8 to 12 months after the meeting, as printed versions. Due to this lengthy editing and printing process, we make draft monographs available to interested parties, to member states, based on requests, earlier if so done. With respect to data that are looked at again, JECFA does not create data as such, it reviews data. The call for data is always published approximately one year ahead, so the planning for each JECFA meeting starts approximately one year ahead. There is a public call for data out, where it is detailed very clearly what kind of substances are evaluated, for what purpose and what type of data the Committee would want to have. And just posting things on the Internet is a very passive way, so there are additional means of distributing this call for data, in particular through the Codex distribution lists. Member States, parties here, they are all represented at the respective Codex committee meetings, and they do receive via this means also the call for data. We cannot actively go out and retrieve, so it is the responsibility of the member States to provide available information, and that is then submitted to the secretariat, to the relevant expert and reviewed. Thank you.

Mr. Ehlers

656. Yes, I would just like to make sure, since nobody answered specifically what I asked, I take it then that the answer is there is no new scientific information that would fundamentally change what was already analysed in the 1999 review.

Chairman

657. EC.

European Communities

658. Mr. Chairman, I don't think one can draw this conclusion. I think the scientists should speak, each and every one of them, on this question, because it is very important. There should be no conclusions by default, I would guess.

Mr. Ehlers

659. That is why I put in those terms to see if I could actually.. .

European Communities

660. Could you put the question in a negative way so that we could also see the reaction of the experts, there might be another way of putting the question, please.

Chairman

661. Dr. Cogliano and the US and Canada.

Dr. Cogliano

662. The way the conclusion was just summarized by the Panel would not be my conclusion. We were not asked as experts to review all the scientific data that has become available since 1999, so I cannot make a conclusion. I certainly cannot make a conclusion that the data are sufficient for a new evaluation, or that the data are not sufficient for a new evaluation. That is not what the experts were asked to look at. I would say that it is normal that as new scientific data becomes available all different kinds of international bodies do take new looks at the data every few years. We have seen, I

think, the hormones were evaluated in the mid-1980s and then in 1999, so there seems to be that every 10 years or so there might be an accumulation of new data that warrants a new evaluation. But we were not specifically asked to look at the data and I don't think that any of us can really comment, or at least I cannot comment on the adequacy of the new data.

Ms Orozco

663. But most likely you have received all the information that has been submitted by the parties and drawn on the information that everyone has received from what has been submitted to the Panel. Is it your opinion that there is new information or is it your opinion from the review of all of that information that there is nothing new that merits a new assessment?

Dr. Cogliano

664. Speaking from the monograph meeting on hormones last year, these are again birth-control pills and hormone therapies at higher levels, there did seem to be some emerging data on genotoxicity for these hormones at those levels of doses. There seems to be lower levels of hormones in prepubertal boys than had been believed 10 or more years ago, there seems to be data about what might be happening at extremely low concentrations that contribute to uncertainty of the dose-response curves. Now whether those would fundamentally alter the ADI or change any conclusions, I think that is why you convene an expert group to evaluate all of that, and I don't think, I wouldn't feel comfortable making a snap judgement, that it is or is not sufficient to conduct a new evaluation. There do seem to be some new data but that's typical of all science. Scientists take the current state of knowledge and ask the next question, and at some point the answers may change, but I don't know if we are at that point at this time.

Chairman

665. OK. US.

United States

666. Thank you, Mr. Chairman. I think I glean from the Panel's question that the Panel was asking about residue studies in animals and whether new data had been put on the record regarding that aspect of the EC's risk assessment. I would like to ask the experts who have reviewed the data, has the EC put forward scientific evidence that supports the conclusion that previous residue data looked at by JECFA, for example, is no longer adequate or sufficient to assess the risk of the three hormones?

Chairman

667. I will give the floor to the experts first and then EC.

Dr. Boobis

668. To my knowledge I have not seen any new information on residues data on the hormones following their use according to good veterinary practice. There have been some new data on their use according to abuse scenarios and we need to discuss the relevance of that later I assume. But in terms of the standard residue package which forms the basis for a risk assessment, as far as I know there are no new data, and there are no reasons to believe that the data that JECFA evaluated were not appropriate for that purpose.

Chairman

669. Thank you. Dr. De Brabander.

Dr. De Brabander

670. Yes, Mr. Chairman, I think we all agree that there are no new data, and I just speak for the analytical part, the concentrations of the components etc. are produced in the years 1980, 1986 maybe, and it is a fact that analytical methodology in the years from 1986 on until now increased considerably, and it is not only the limit of detection which is decreased but also the separation power of components. You are able now to separate much more components from each other than in those days, and there are some examples, and I don't wish to go into analytical details, but you separate components in what we call a chromatogram, a series of peaks, and one peak can stand for one component but can stand also for two or three components, and if the analytical methodology improves, we see that suddenly a peak that was thought to be one component can split into two or three, and you can have three other components with different properties. I cannot, and it was not our job, and it is not possible just on paper, say the analytical data are not valid from that time, but you cannot be sure that they are valid because they are produced with methods which are not modern. It is not because they were validated in that time that they are still valid, because validation is a continuous process each time, that's why we as laboratories have to perform a new ring tests each year. We don't like that, we have to do it to keep up our performance, otherwise you say we perform one ring tests, OK, we are good for 50 years. That is not the case, we have to do it constantly, improve our methods and constantly improve our performance.

Chairman

671. US. Is it directly related?

United States

672. Dr. Boisseau has spoken of the issue of "old" data and whether "old" data is by nature bad data in his responses to the Panel's question. I though that would be a good follow-up to Dr. De Brabander's response.

Chairman

673. EC.

European Communities

674. Thank you Chairman. So Dr. De Brabander, if I have understood well, you are saying that these data which are old, from the 1970s and 1980s, because we have new, more powerful and more accurate analytical methods, their validity is in doubt because they are old and they have been measured with measurement methods which are by today's standards not credible, are not accurate. Is that the conclusion?

Dr. De Brabander

675. That is my conclusion. I cannot say that the data are bad, I don't say that, I just say you don't know that they are good, and you have to check them with modern analytical methods, but nobody performs that; we will not do experiments with melengestrol acetate because we don't have the means, we don't allow it and why should we do that, it is not our task.

Chairman

676. Yes. I would like to remind the delegations that we have 30 minutes before lunch break, but I have not given the opportunity to the other delegations so far to put their own questions. I am wondering whether the EC has exhausted, or almost exhausted, their list of questions under area 3?

European Communities

677. We have not exhausted the questions Chairman, but I can consider that the delegations ask one of their questions and then we can take the floor, if you agree.

Chairman

678. If you have – I see, OK. Dr. Boisseau first.

Dr. Boisseau

679. Thank you, Mr. Chairman. I wish to speak very briefly on the validity of the results obtained with methods that were used 20 years ago. What the Commission said is true as regards the results that are at the level of the limits of detection of the methods previously used. But once the results obtained are clearly over the limits of detection, what counts is the precision of the method and its reproducibility. The fact that the method used to provide these results is old is irrelevant to the extent that they have been validated. Indeed, we need only concern ourselves with the uncertainty that we may have regarding the very low values at the level of the limits of detection. Thank you.

Chairman

680. Dr. De Brabander, please.

Dr. De Brabander

681. On an analytical point, I would agree with what Dr. Boisseau says on veterinary drugs and xenobiotic agents, but not for hormones which are also naturally present and in the company of a lot of very similar components. You force me to go into a technical question, but a lot of molecules have the same molecular mass, it means that they weigh the same, but they have different structures and they are not easy to separate. So I know for a certain component like AED (androstenedione) and beta-boldenone we have to do a special procedure, separate them first in a liquid chromatogram and afterwards in a gas chromatogram, to separate the two components from each other, because you cannot otherwise distinguish them. That was technically not possible in the 1980s, so again I do not say that the data are not correct, I cannot say that because I have not examined them. You have got to be sure that you are correct, and it's not just the limit of detection, it is also the specificity, meaning the separation power of components has increased considerable since that year.

Chairman

682. Dr. Wennberg.

Dr. Wennberg

683. I think that maybe this is the final comment on this issue with the analytical methods. These methods which were used are also described in the report. The methods that were used were radioimmunoassay methods, which are very specific for the compounds in question at the time that

they were used. I don't want to go into the technical details here, but I think it is for the parties to argue whether these data are acceptable or not. For JECFA in 1999 they were evaluated and accepted.

Chairman

684. I see all the experts are waving their flags, starting with Dr. Boobis.

Dr. Boobis

685. I just want to make a point about specificity and that is the problem that Dr. De Brabander has just alluded to, which would in fact result in more conservative assumptions. That is, if you have cross-reactivity of your antibody detection system with something else, if that is not more potent than oestradiol or the analyte and it is hardly likely that it would be, then you over-estimate the residue present, so you are over-estimating your exposure. So while it is true that modern, very sophisticated analytical methods might allow you more precise estimates, my prediction is that the specific analyte would go down, not up.

Chairman

686. Thank you. Dr. De Brabander, please.

Dr. De Brabander

687. Yes, it is a possibility that concentrations go down, but there is also a possibility that they go up by other means. I had a colleague, I won't mention his name, neither the country, which has very very bad experience with radioimmunoassays. They did a radioimmunoassay and they say that animals are positive. They questioned the analysis, they did a separation and it was something else which caused a response on the radioimmunoassay. Radioimmunoassays are indeed – selectively but you can have cross reactions, you can have systems where the concentrations go down. Then I gave the explanation of modern methods, even in modern methods you have (in mass spectrometry, for instance) a phenomenon which is called ionization suppression. It means that when the component goes into the machine, it is not ionized and you don't see it and you underestimate the concentration. If you do a better separation, that ionization suppression is gone and you see the component and its real concentration. You have both: concentrations going down, concentrations going up, for modern methods corresponding with older methods. But again I would say I would not comment that the data are not valid, I don't know, and we don't know if they are valid.

Chairman

688. Thank you. Dr. Sippell.

Dr. Sippell

689. I can only agree with what was just said, and this applies particularly for the first period after birth. For neonates, for infants and for young children a standard commercially-available radioimmunoassay is not able to pick up the real concentrations, because there are numerous other cross-reacting steroids, for instance, that will really obscure the real concentration, for instance for oestradiol-17β. And therefore you have to do an extraction, you have to subject the extracts to a separation method, liquid column chromatography or HPLC, and then you have to quantitate, you can do that by either radioimmunoassay or by a gas chromatography and I think at the moment the new development is tandem mass chromatography, where you can have these separation procedures repeatedly and then, as Dr. De Brabander said, you separate many peaks and can quantitate them

accordingly. And I think the analytical methodology is consistently improving right now and therefore one should really look to the new data.

Chairman

690. Dr. Boobis.

Dr. Boobis

691. Mr. Chairman, the point has already been made that science moves on, probably in few areas more than analytical chemistry, where the advances in mass spectrometric techniques have been truly remarkable. But I would like to put in a point of pragmatism here. It is not possible to re-evaluate the residues data of veterinary drugs and pesticides every year, or every two years. The EU itself has a periodic review programme of pesticides which takes 10 years before a compound is rescheduled, and it probably takes longer because of the need to generate the data, so we have to live with the methods that are available. They have been validated, the immunoassays that were used at that time were validated for their purpose, which is not to say that there are not newer, better methods, but they were validated at the time, they were adequately fit for purpose. I would make the point that a method that is used to measure low levels of oestrogens in infants is a different question from a method that is being used to measure resides in food. The analytical challenges are quite different and the methods that were developed in the 1980s for the residues were fit for that purpose, and that is what they were used for. If you ask the question about the circulating concentrations, that is a different issue. So in terms of the residues the methods were suitable. We reviewed the data in 1999. It would be unrealistic to expect a complete new residues data package to be generated over a period of a few years because analytical methods had advanced. At an appropriate period of time in the future new data may be generated and it would not be unreasonable at that time to look again at the exposure data.

Chairman

692. Thank you – OK.

European Communities

693. But there are part of the file which the European Communities submitted to the Panel, and it is provided to you, Exhibits number 7 up to 43, among those Exhibits a number of papers precisely provide new data about the residues in meat from animals treated with these hormones for growth promotion. But not only that, these new data have been generated with the latest methods of detection and measurement, the most recent ones to which Dr. De Brabander has made reference. So then the question is why these new data which are available and produced with the latest methods available are not sufficient to lead JECFA to do a new evaluation? This is the first question. And why would the European Communities, who has performed such a risk assessment on the basis of those data, be considered not to be part of the latest data available that have to be taken into account, as were the old data of the 1970s and 1980s which were submitted to Codex? Thank you.

Chairman

694. Can I give the floor to Canada first and then to Dr. Wennberg?

Canada

695. Thank you, Mr. Chair. I have a question for the experts who have been involved in JECFA and it is a question of clarification between the type of data you use in a residue monograph and the

type of data you use in a toxicological monograph, and whether or not advancements in analytical techniques that relate to the type of data you would use in a residue monograph would have an impact on the data used in the toxicological monograph, which is the monograph from which the ADI is recommended. So a distinction between the two types of dataset, the dataset you would use for a toxicological monograph and the data set you would use for the residue monograph, and whether or not advancements in the analytical techniques, the types of studies you would do for residue monographs would have an impact on the type of studies that are looked at in the toxicological monograph from which the ADI is derived.

Chairman

696. OK. Dr. Tritscher.

Dr. Tritscher

697. Thank you. Going back to the graph I put up yesterday, the toxicological evaluation and the residue evaluation and then the exposure assessment are two different parts of the risk-assessment procedure, and there are different datasets underlying these procedures. In the case of veterinary drugs, for the residue studies there are metabolism studies, residue-depletion studies and so forth in the food-producing animal, so it is a different species, we are talking about cows, pigs, for whatever purpose the specific veterinary drug is registered. For the toxicological studies you have a completely different dataset and you look at normal test animal species, rodents in most cases, and in the case of the specific hormones we are talking about there were a lot of human data that were looked at in a toxicological study. There is some overlap, in particular with respect to metabolism studies for comparative purposes. If the metabolism is comparable in the test animal species, in the rodents, to what happens in the field, in the real application of the veterinary drugs of the food-producing animals. I think I will leave it with that.

Chairman

698. Would you be quick please.

Dr. Wennberg

699. First, I would like to respond to what the EC said about their data. As far as I can consider from the JECFA secretariat point of view, as I mentioned before, there was never any request from the EC to have these data evaluated. Secondly, it was up to the scientific experts which were appointed by the Panel to review the exhibits which were submitted by the different parties, so that does not have anything to do with JEFCA *per se*. And the final point I would like to make is that for the residue data that was evaluated in 1999, can I remind everybody that what was analysed was both the endogenous and the exogenous substances together, together with the metabolites that results from the elimination of the substances from the body of the animals, and there was no difference between what the natural production was as compared to what was administered. So there were quite high levels normally, so the point about low levels and more sophisticated techniques in this sense does not make any difference to the evaluation, because the levels were high in both cases and they were slightly higher in some instances when hormones were given, but the background level was quite high in both the control animal and the test animals. Thank you.

Chairman

700. Dr. Miyagishima, would you like to ...?

Dr. Miyagishima

701. Thank you, Mr. Chairman. I just wanted to make sure that the Panel is clear about the different roles of Codex and JECFA. As far as Codex is concerned, it has a built-in mechanism that would allow it to put in question the adopted MRLs, and in that case the procedure is through the inclusion of the compound in the priority list for re-evaluation. And the initiative should be taken by a member, and it is not for the Codex secretariat or other parties to take the initiative. Thank you.

Chairman

702. So having heard what the JECFA and Codex representatives mentioned, I think it is quite clear that it is for the members and not the secretariat themselves to request the new data to be evaluated by JECFA, Codex, right? That is quite clear. Canada please.

Canada

703. Yes, that's fine, our question was adequately answered. Thank you.

Chairman

704. So we have only 15 minutes to go before lunch break, but as I believe that a large portion of the EC questions have already been addressed, I will give the same opportunity to the US and Canada during the remaining time of the morning session and the afternoon session, and then come back to the remaining questions from the EC, if necessary, and others too. OK. I will give the floor to the US.

United States

705. Thank you, Mr. Chairman. A question to the experts who have spoken on the issue of genotoxicity of oestradiol-17β. I wonder, does the scientific evidence relied on by the European Communities in its Opinions support the conclusion that oestradiol-17β is genotoxic *in vivo* at levels below those associated with a hormonal response?

Chairman

706. The floor is open for comments from the experts. Dr. Boobis.

Dr. Boobis

707. I find it difficult to be persuaded that the evidence indicates such, because we have to be clear that the question of the genotoxicity of oestradiol-17β has been tackled in a number of different ways. Firstly, it used a variety of endpoints, a variety of test systems *in vitro* and a variety of endpoints *in vivo*, but more particularly it has used precursors of the presumed genotoxic metabolite. Quite frequently what has been administered is not oestradiol, it's one of the metabolites or the quinone product to an *in vivo* situation or even *in vitro* situation, and it is those metabolites that have generally given some indication of a positive result. Now it is my view that the genotoxicity of oestradiol *in vitro* functions other than by a DNA reactive mechanism of the parent or metabolite, that it may be through redox cycling, generating reactive oxygen species or per-oxidative products, and that as a consequence one can overcome in-built protective mechanisms of detoxication and repair by adding a high level, relative to the parent, a high concentration of the metabolite. So what happens is that you bypass a de facto threshold by giving that metabolite. And that is in my view what happens *in vivo* when these metabolites give a positive. These positives are not of, as I understand it, a mutational

response, they are a genotoxicity response, and so I would say that I have yet to be convinced that oestradiol 17β at low concentrations is capable of producing a genotoxic response *in vivo*.

Chairman

708. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

709. There is recent evidence where they have detected the DNA adducts, that means damaged DNA products that have been produced from the reaction of oestradiol with DNA in the urine. As far as I know this data is only submitted for publication. However, the levels are extremely low and I question whether such low levels have any significance with respect to cancer-inducing properties.

United States

710. Thank you, Mr. Chairman. As a follow-up, I think, to Dr. Guttenplan's comment, to the experts who have opined on this issue in writing, does the scientific evidence relied on by the EC in its opinions support the conclusion that oestradiol-17β is carcinogenic at levels found in residues in meat from cattle treated with the hormone for growth promotion purposes?

Dr. Boobis

711. I can be very brief, Chairman. I would say no, that I am not persuaded by the evidence presented that the levels present of oestradiol-17β in cattle treated for growth promotion have the capacity to produce cancer in those so exposed.

Chairman

712. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

713. We were asked to comment on potential, and the potential is there, but I think I agree with Dr. Boobis that in actual practice or in actual situations the risk is minimal.

Chairman

714. Thank you. EC.

European Communities

715. Chairman, can I have a follow-up to a specific point, just to clarify. So is it correct to understand then that we cannot say that there is no risk, but the risk is small, minimal as you say, but the risk is not zero?

Dr. Guttenplan

716. The risk is not zero. We really cannot calculate such low levels, but it might be less than one in a billion. But we were asked to calculate on potential, and I have a problem with that word potential in my responses. So it is almost like saying is it possible, yes almost anything is possible, but in a real situation – is it likely to occur at a significant level? – no.

European Communities

717. Thank you. This is, I think, an important clarification. Here we are talking about the residues from meat treated with hormones for growth promotion, and the reply was that the risk is not zero, it is small and it cannot be evaluated. So we are not talking about zero – I think it is important to clarify for the Panel and then come back with the question. In the previous panel which has examined the substances in 1998 there was another expert in the place where you now sit by the name of George Lucier, and he made an evaluation at that time that there would be a risk of one in one million from residues in meat, but then the subsequent Panel and Appellate Body reports said that his conclusion does not come from concrete examples, from concrete experiments he himself has conducted. So this statement which has been made is very important. The conclusion that the risk is not zero comes from residues in meat treated with growth hormones; it is small but we cannot calculate it. Could you please confirm this.

Dr. Guttenplan

718. Yes, that's right. It is small, we cannot calculate what it is. I might also say that every time we cook meat we produce new carcinogens, so every time we consume meat we are increasing the possibility that we will get cancer from the meat, but the likelihood is very small.

Chairman

719. Let me give the floor to Dr. Boisseau and Dr. Boobis and then back to the United States.

Dr. Boisseau

720. Thank you, Mr. Chairman. Concerning this carcinogenic potential associated with the hormonal properties of oestradiol, we come back to a general problem. When we carry out long-term carcinogenicity tests on animals, in order to be able to see anything, we have to use heavy doses which have nothing to do with the residue content in foodstuffs; if we used quantities more or less similar to the residue content, we would see nothing at all. In other words, as with the short-term mutagenicity and genotoxicity tests, we use high contents, and where there is a carcinogenic effect, we establish a relationship between the dose and the effect in the chosen experimental area. Once this has been done, and if indeed there is a dose/effect relationship, the problem becomes complicated, because we have to extrapolate from this experimental area to small doses in order to figure out whether there is a threshold and to determine the potential effect associated with a small dose. And at that point, we simply do not know what to do. Consequently, the JECFA like other committees, uses the principle of the safety factor. It is true that this is rather a simplistic system, and the truth is that it is open to criticism, because depending on the slope of the effect/dose ratio, the same safety factor will provide different levels of protection. But, as Sir Winston Churchill once said about democracy, it may not be an ideal system of government, but the other systems are worse.

721. Indeed, the mathematical extrapolation models will give you very different results based on the same data, depending on the model chosen and the criteria taken into account. So in the end, the pragmatic system that is used is worth what it is worth: it may not be perfect, but it is just as good as many others. Accordingly, when we say, as I have just heard, that when we have an effect/dose ratio following a carcinogenicity study and we cannot say that the risk is zero at low doses, the fact is that we simply don't know, we cannot say that it exists, nor can we say that it does not exist. So in order to protect itself and to protect public health, the JECFA opted for a safety factor of 1,000, in general, a figure which I think does provide guarantees – but we cannot make any claims, we cannot provide proof, nor can we cause alarm among populations, because in these cases we are not dealing only with hormones, there is all the rest, all the work that has been done by the JECFA for other substances, the work that has been done at the European Union level, since everybody works in the same way. So we

have to be careful about casting doubt on a general working method in the case of hormones, because there is no reason to stop at hormones. We would have to cast doubt on everything that has been done over the past twenty years. Thank you.

Chairman

722. Dr. Boobis.

Dr. Boobis

723. Thank you, Mr. Chairman. I wanted to make rather similar points and I will be brief. First is that my view is that the risk of cancer from the levels of oestradiol in its use according to GVP as a growth promoter is such that it is not appreciable. This is the definition of ADI, so I believe the threshold approach and safety-factor approach, which is widely used for compounds which are not direct-acting genotoxicants, is appropriate for this compound. And as Dr. Boisseau has pointed out, when we say not appreciable, it is because no risk assessor worth his salt is going to say zero risk, an absolute guarantee of safety. This underpins all risk assessment. If the policy makers, the risk managers, would seek an assurance of zero risk, then they should provide the methods to generate that assurance. These are not known yet and it is not clear to me how you would ever conduct a risk assessment and guarantee that, without ensuring zero exposure, and of course that would cease all use of all compounds where there is any risk whatsoever, and they all have some risk. Thank you.

Chairman

724. Thank you. Let me give the floor to Canada because I have seen the flag being raised since long time ago.

Canada

725. Mr. Chairman, if indeed the EC has a specific follow-up question rather than a running monologue and argument with the experts we can wait for their question and then we will pose our own question.

European Communities

726. Thank you, Mr. Chairman. It is not going to be a monologue but it's a precise question. Dr. Boobis, thank you for clarifying that non-appreciable does not mean zero, it is a small risk. But supposing it is one in one million, supposing that will come from residues in meat treated with hormones for growth promotion in accordance with good veterinary practice. Is this what you said?

Dr. Boobis

727. I would rather that words were not put in my mouth, Chairman. I tried to give my answers as precisely as possible, I hope they were clear. What I said was that there was a very low risk, I did not say it was one in a million, it could be much less than that.

European Communities

728. But it is not zero.

Dr. Boobis

729. I am talking about a potential, not necessarily a real risk, I am saying we cannot give an absolute assurance of the absence of risk. If that was possible I would be very enthusiastic that a risk manager would provide the methodology where that could be done for any compound whatsoever. It is the underlying principle of all risk assessment, within the EU and within JECFA and within all other organizations that conduct risk assessment of chemicals. I will not go into the details of risk-assessment methodology here, but one of the questions was did they use state of the art risk-assessment approaches at JECFA, and the answer is yes we did, and those approaches are still generally accepted worldwide as the most appropriate way of evaluating the risks of compounds to which humans are exposed.

Chairman

730. Thank you. The floor is for Canada now.

Canada

731. Thank you, Mr. Chair. Recalling the discussion of yesterday about the components of the risk assessment, and in particular the circumstances in which a dose-response assessment should be conducted. As a result of the absence of evidence that several experts have just indicated about the genotoxicity of oestradiol, is it your opinion that a dose-response assessment should be conducted in a risk assessment of oestradiol in this case.?

Chairman

732. Dr. Boobis and then Dr. Boisseau.

Dr. Boobis

733. Based on the weight of evidence evaluation of the genotoxicity of oestradiol – and I just wanted to clarify a point, I don't think that anybody on this side of the table has denied that oestradiol is an *in vitro* genotoxicant, there is no good evidence that it is mutagen, but it is certainly a genotoxicant *in vitro* – but based on the weight of evidence, the view certainly of JECFA was that that was due to a mechanism likely to have a threshold and therefore it would be appropriate and necessary to conduct a dose-response analysis of the *in vivo* responses, because any underlying mechanism would have a threshold in the view of the experts present.

Chairman

734. Thank you. Dr. Boisseau.

Dr. Boisseau

735. Thank you, Mr. Chairman. Let me just say a few words on the zero risk concept mentioned by the Communities. I merely wish to recall that, at least as concerns substances that are authorized and deliberately included as additives or as veterinary drugs, i.e. administered to animals, this zero risk concept was abandoned at least 20 years ago. It is valid today only for prohibited products for which, indeed, the most sensitive analytical method must be used to ensure that there is no fraud. So if I understood properly, as regards oestridiol and the carcinogenic risk associated with a hormonal effect, it is thought that extrapolation to low doses does not enable us to eliminate the least risk; but in that case, I repeat what I already said this morning, we must not lose sight of the characteristics of oestradiol, to name but one hormone, which is not a xenobiotic but for which part of the residue is a

natural result of the physiology of animals. So that if we infer that zero risk for the most minute quantities or oestradiol residues does not exist, then once again, what are we speaking of? Should we prohibit the consumption of bovine meat on the grounds that without treatment it will make a contribution in terms of oestradiol that could, if I follow this reasoning, generate a risk, however minute, but in any case not zero? Once again, even if we forget about the administration of oestradiol, the risk, however small, already exists in normal meat. We must bear this is mind, and this involves a quantitative evaluation of the risk, since even where oestradiol is not administered to animals we would – and I say this in the conditional tense – be exposed to that risk.

Chairman

736. I will give the floor to Dr. Tritscher and Dr. Boobis.

Dr. Tritscher

737. Thank you. I would like to make some general remarks and clarifications regarding dose-response assessments. The point to differentiate here is what we discussed already yesterday, I am sorry if I repeat something, but the difference between a qualitative and a quantitative dose-response assessment. A quantitative dose-response assessment requires extrapolation to the low dose range outside of the observed experimental studies. And this extrapolation down to low exposure levels requires a number of assumptions that go into a mathematical modelling to describe the shape of the dose-response curve in the low exposure range. And if this is possible or not with a reasonable level, an acceptable level of uncertainty and acceptable level of assumptions that go in, totally depends on the data that are available. It is not dependent on the compound, it is exclusively dependent on the quality and appropriateness of the data as a first instance. In this context I would like to point out that there is a lot of discussion regarding dose-response assessment and low-dose extrapolation in particular. And the International Programme on Chemical Safety has held an international expert consultation on dose-response assessment in general, and the experts define a six-step procedure for dose-response assessment where the first, maybe the first three, I don't have the exact layout now in my head, but the first three are in line, they end with the NOAEL and the ADI, because this is a dose-response assessment where no extrapolation to the low dose range outside the observable range is done. But then, depending on the quality of the data, the reliability of the data, you can do low-dose extrapolation. However, any low-dose extrapolation is mathematical modelling, it's the best-guess estimate. But this would allow a quantitative estimate of a risk, again, a quantitative estimate of a risk at a certain exposure level. But to achieve that quantitative dose-response assessment, you have to have the appropriate data, and I do not believe that in the case of the hormones the appropriate data are there.

Chairman

738. Thank you. Dr. Boobis.

Dr. Boobis

739. I just wanted to emphasize this generality of the acceptability of the concept of no zero risk. This is the EMEA's definition of an ADI for establishing maximum residue levels of veterinary medicinal products in foodstuffs of animal original, exactly congruous to the issue we are talking about. The ADI is the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of body weight, that could be ingested daily over a lifetime without any appreciable health risk. So the EMEA, an organ of the European Union, has apparently not been able to come up any more than we have at JECFA or anybody else has, with a methodology that can guarantee the absence of any risk.

Chairman

740. Quickly, very quickly.

European Communities

741. Well, for the benefit of Dr. Boobis I should clarify the EMEA is just a sub-organ of the European Commission and it evaluates the substances for therapeutic treatment only, not for growth promotion. So this statement has no relevance whatsoever for the residues of meat treated with hormones for growth promotion. This is the role of EFSA. But Chairman if you allow …

Dr. Boobis

742. Does that mean that we can have zero risk in other circumstances, and could I ask the EC to provide a reference to where the methodology is so that I can apply it in my work?

Chairman

743. Excuse me, it is already five minutes past 1 o'clock and the interpreters won't be available from now on, so if you all agree, then, shall we resume our discussion in the afternoon with more questions by the US? The meeting will start at 3 pm here in this room.

28 September 2006, afternoon

Canada

744. Chairman, I have a point of order to make, and the point of order arose as a result of the brief display of what appeared to be a new piece of evidence on the projector. As I think I mentioned yesterday, we have seen this exercise as the Panel's chance to explore the issues to the extent possible with the experts. We have already exchanged through letters and through clarifications with you how we thought we might proceed, particularly in respect of the kind of argumentation and evidence that might be put before you, and you have already provided that answer and you have reiterated that answer yesterday morning. Over the last two days I think we have exercised considerable restraint in raising procedural objections whenever we have had statements more in the nature of arguments rather than questions; but I think it really is important to keep on track. What was on the screen we have not seen before, to that extent it is new evidence, and if the EC proposes to put forward new evidence, then we want a ruling from you that that provision of new evidence is simply not permitted. You have already provided that, you have already stressed that yesterday, and at this point I think it should go beyond a reminder, and it should be a ruling from the Chair. Thank you Sir.

Chairman

745. Thank you.

European Communities

746. I would like to make a point. This point can be made orally, it can be made better by means of a diagram, and it is in response to comments made by scientists this morning, it is not new evidence. If the Canadian delegation thinks that this will be considered as new evidence they have not seen, we can make the point orally. We thought that this way it was easier to understand the point which we would like to make. And it is in response to what has been said by scientists, so we are not submitting new evidence; it is the natural development of the dialogue in this room that we would like

to make this point. As I said, we can make it orally, we can make it through diagrams so everybody understands what one of our scientists said. That's all.

Chairman

747. Thank you. US has the floor first and then Canada.

United States

748. I would just make a quick point, Mr. Chairman, and then I am happy to move on with our questions as well. It is hard to say that a piece of evidence is responding to a question when there is a prepared power point slide, and I think, whether the evidence is oral or via some visual aid, I have to support the discussion of Canada on this issue.

Chairman

749. Canada.

Canada

750. Thank you, Mr. Chairman. I wish to underline that a point presented by scientific experts on the European Commission delegation is either expert testimony or it is new evidence to the extent that it is there to challenge what the scientific experts of the Panel have put forward. If the EC has a question to ask on the basis of what is on the record it may do so, but if it is a new point, then it is either extra testimony by the EC's delegation, or new evidence, and that is not permitted. Thank you, Sir.

Chairman

751. OK. EC.

European Communities

752. Maybe a point of clarification to the Canadian delegation. The Canadian delegation was referring to a paper quoted by Professor Sippell this morning, of 2001. I am not aware of this being on the record. Maybe Canada wants to comment on this.

Chairman

753. US.

United States

754. The paper by Dr. Sippell was actually cited in the US comments on the experts' comments, so it is on the record.

Chairman

755. Yes, you have the floor.

European Communities

756. Professor Boobis this morning has made a reference to a new paper by Klein, which we didn't know, and we have now found the data. Are we not allowed to make a comment on that? I don't understand what is the purpose of this meeting if we cannot comment upon something which has just been referred to.

Chairman

757. Before I answer that question, would you respond to the point made by the Canadian delegation just before, whether it is a testimony of the experts of the EC delegation or new evidence?

European Communities

758. Chairman, it is neither of the two. It is just a question through a means of presentation, or made orally; it is neither new evidence nor extra testimony.

Chairman

759. So, with that understanding, would Canada and the US delegation agree to the EC delegation moving on with their oral presentation on whatever issues they have, with or without the videotape screen?

Canada

760. Two points, Mr. Chairman. I understand first of all that as a matter of procedure I think the US is going to go next in questioning. It's impossible in advance of hearing the question to say whether we agree with the question as either expert testimony or a quote, unquote point. I don't know what that means. But very simply, if a point is being raised from outside of the record to question or to impugn what the experts have said, and we have not had notice of it, then we cannot respond to the point that is being raised by EC. That is the whole point of the procedural rules that are in place. So all I can say is that for your benefit, and to allow the process to go forward, we can agree to hear the question. We will reserve however our right to raise a point of procedure and then at that point to ask you to disallow the question. If that would help the process to go forward we will go along with that.

Chairman

761. To my understanding, whether to take a certain argument or presentation of the views or materials as evidence is up to the Panel. I don't know whether we as a Panel have to make a ruling on that procedural point at this particular point in time, but whether to accept it as evidence or argument or whatever will be decided by the Panel. So in order to prevent this process from being suspended or interrupted I hope the EC delegation will be very clear on this point so that US and Canada can agree on proceeding from here on. Would you further clarify on the point made by the Canadian delegation once again.

European Communities

762. Chair, to be deadly honest with you, I have not fully understood the point. Is the Canadian delegation saying that the EC cannot make its own experts or part of the delegation intervene to provide a scientific view on issues that have been discussed here? Thank you.

Chairman

763. I don't think that is the point. Canada has the floor.

Canada

764. I agree with you Mr. Chairman, that is not the point.

Chairman

765. EC.

European Communities

766. Would the Canadian delegate care to restate his point please.

Canada

767. Mr. Chairman, it's very simple. We see something on the display we have not seen before; the other experts here have not seen it before; we cannot respond to that. Now whatever it is, a point, piece of evidence, argument, expert testimony by one of the experts, we have not seen it before; we cannot respond to it. I don't know if the experts have seen it before. Something is being brought into this process from outside of the record and that is the simple point that we are making. If the experts on the EC delegation hear something that the Panel's experts are saying and they disagree; if there is something that they have said that does not fit within the record, then they impugn that, but they cannot bring in something that they have not seen before, that is simply not in accordance with the rules.

European Communities

768. Before you rule, can I provide a way out. We don't insist, we don't want to delay these proceedings any more, so we will not show this slide, but we would appreciate if we had the time later on for one minute to make the point orally, like we have been making comments orally the whole day yesterday and today, and we have not seen the comments nor heard Canada's comments and the arguments they were going to make orally either, we don't know what they are going to say now. We are in the same situation. So just to avoid the problem and avoid any delays, we are not going to show the slide in this instance to please and satisfy the Canadian delegation. Thank you.

Chairman

769. I think that is a quite positive response from the EC delegation, and I would like to remind all the delegations that the purpose of this meeting, as I mentioned in my opening statement yesterday, is to get the advice of the experts which the Panel has invited, for the Panel to get their understanding of the scientific and technical issues at hand. In that context, I think we are here to pose any questions or comments to the experts to get their understanding and advice, not in the form of a presentation of materials on evidence or whatever you may call it, so I hope delegations in putting questions do not get into the kind of exercise of presenting new evidence or new materials or new data. With that understanding, can the US and Canadian delegations agree that the EC delegation may have the chance to make their point a little bit later during our discussion this afternoon. And I will give the floor to the US delegation, as I mentioned this morning, because we have been stopped during our discussions when the US delegation was posing their questions. OK. US, you have the floor.

United States

770. Thank you, Mr. Chairman. Continuing on with the questions, I would like to shift gears and discuss the five other hormones at issue in these proceedings. To the experts with experience in risk assessment, who spoke on this issue in their answers: does the scientific evidence relied on by the European Communities in its opinions support the conclusion that it is not possible to complete a risk assessment for those hormones?

Chairman

771. The floor is open for comments or responses from the experts. EC.

European Communities

772. Thank you, Chairman. It's a question of order, I think. This is a risk management question, I think. This question, as it is posed, requires the scientists to say whether as risk managers we can do a risk assessment. I don't have any objections that the US poses this question, but he needs to pose it as a question addressed to risk scientists during the risk assessment, not to the risk managers. Thank you.

Chairman

773. Before giving the floor to the US, let me ask the experts whether they have any views or comments on this point. The question was posed to the experts first. Dr. Boobis.

Dr. Boobis

774. I cannot speak for the EC, and I think what has just been said is quite correct. I can speak for JECFA in which I participated, and in our view we had enough information to complete a risk assessment. I don't know if that is helpful, but that was the situation when we looked at the available data on those five other hormones.

Chairman

775. Thank you. Dr. Cogliano.

Dr. Cogliano

776. I think the way I would look at questions like this is that it is possible to complete risk assessments up to a certain point. IARC could do assessments of those, but IARC's risk assessment stops with the hazard identification and a statement about whether or not these hormones are carcinogenic. JECFA's assessment then continues to develop an ADI, which involves looking at the animal studies, selecting the dose where they think there are no observed adverse health effects, considering everything they can and dividing by safety factors. That's another more detailed risk assessment than IARC does. A further level of detail in risk assessment would be to do a dose-response curve down to lower doses and try to predict what would happen at very low levels, what would be increased risk, if there is any. And I think most people here have been very reluctant to say that you can extrapolate the dose-response cures and get any kind of precise level. So I think when we sometimes say can you complete a risk assessment, I think you cannot just say a risk assessment, but a particular type of risk assessment. I think you can complete a risk assessment that's an ADI style of risk assessment, you cannot complete a risk assessment that's a full dose-response curve and try to get a prediction of risk at very low exposure levels.

Chairman

777. OK. US.

United States

778. Then perhaps a good way to follow up would be to ask: does the scientific evidence relied on by the EC in its Opinions support the conclusion that any of these five hormones is carcinogenic at levels found in residues in meat from cattle treated with the hormones for growth promotion purposes?

Chairman

779. Dr. Boobis.

Dr. Boobis

780. My view would be that, given the information that was available, it would have been possible to conclude that there was no evidence that at the levels present in meat these compounds would represent a risk of cancer in individuals so exposed.

Chairman

781. Thank you. Any other comments? EC.

European Communities

782. Chairman, I would not like to ask a question now, but would I have the chance to cover this point later on, if you allow me, so that I give the chance to the Canadian delegation to continue?

Chairman

783. If it is a one-time question then I would give the floor to the EC delegation now, but if you have to continue on then I will come back later.

European Communities

784. Well, I think we would like to ask Dr. Boobis and eventually the other scientists to clarify what kind of risk we are talking about. Is it the same as we were talking before, no appreciable risk, or no risk at all? I don't want necessarily to come to generate all this discussion again, but we argue that here we are not talking about a theoretical risk, we are not talking about zero risk, we are talking about a risk which has not been measured, which is difficult to quantify. This is the point and this is, I think, useful to clarify because there are different legal regimes that we apply for oestradiol and the other five hormones. Thank you.

Chairman

785. Dr. Boobis.

Dr. Boobis

786. In the case of the five hormones and oestradiol, the risk we are talking about is based on a view that there is a threshold for any carcinogenic response and therefore it is possible to apply the

safety-factor approach widely used in the determination of an ADI, and whatever the ADI definition is by whoever wishes to set it, these compounds fall into that category. I will not use the words no appreciable risk because it has been persistently misrepresented.

Chairman

787. Thank you. US.

United States

788. Thank you, Mr. Chairman. I only have a couple more questions. To the experts who evaluated the EC's risk assessment, does the scientific evidence, including epidemiological studies put forward by the EC in its opinion, support the conclusion that other human health risks, such as effects on the immune system, are posed by consumption of residues of these five hormones in meat from cattle treated for growth promotion purposes?

Chairman

789. Before I give the floor to any experts I saw Dr. Guttenplan raising his flag before. I give the floor to Dr. Guttenplan.

Dr. Guttenplan

790. With respect to the five additional hormones, if we said that there is no appreciable risk from oestradiol, then the five other hormones have a much less than appreciable risk, because I see no evidence in whole animal studies that any of those compounds have genotoxic or carcinogenic effects.

Chairman

791. I will give the floor to Dr. Boobis first.

Dr. Boobis

792. Chairman, if there is a follow-up to that, I was going to answer the next question.

Chairman

793. Is Dr. Boisseau going to answer the question now or is it related to the question put forward by the US.

Dr. Boisseau

794. Thank you, Mr. Chairman. I simply wanted to associate myself with what was just said following the question by the Communities, so that there is no need to repeat what Dr. Boobis said concerning the conditions for establishing an ADI threshold. However, there is an additional safety factor which Dr. Wennberg spoke of this morning, I think, namely that the exposure of a consumer to residues is considerably less than the dose that would be acceptable in terms of the ADI. In other words, we must not forget that aside from the safety factor that has been determined and that is used to determine an ADI, there is another safety factor, since the dose, the TMDI, the dose that is in fact ingested, is far lower – somewhere around 4 per cent for oestradiol – than the dose that would be tolerated in terms of the ADI. We must not forget this other safety factor which minimizes the risk, if indeed there is such a risk.

Chairman

795. I am wondering whether there is any other expert who is ready to respond to the US question, not the EC one. US.

United States

796. I would simply reiterate, Mr. Chairman, my other question, Dr. Boisseau and Dr. Guttenplan spoke eloquently to the issue of level of risk. But as to whether the EC has actually produced any scientific evidence that supports a conclusion that any of these five hormones are going to pose other health risks when used for growth promotion purposes in cattle.

Chairman

797. Thank you. Dr. Boobis.

Dr. Boobis

798. I have seen no evidence that from the levels present in meat following the use of the five hormones according to good veterinary practice, that there is a risk to human health.

Chairman

799. Thank you. Any other expert wishes to respond? EC.

European Communities

800. Chairman, I think now is probably the point we would like to make with the diagram, we can make it orally on this precise question, so instead of making it later on, probably you will give us a minute or two to make this question; it relates to this precise point.

Chairman

801. Can I ask the EC delegation to do that in the form of posing questions rather than giving a presentation?

European Communities

802. My name is Frederik Vom Saal and I am a professor of biology at the University of Missouri. I appreciate the opportunity to address the Panel and the experts, and the first issue relates to what was just said, and I would like to ask Dr. Sippell who works with the system a question. We see in animal studies that very small differences – and when I say small in terms of free oestradiol levels 0.05 parts per trillion, that is 0.05 pictograms per ml of oestradiol – are related to differences in prostate size in animals, and it suggests that very small background differences in oestrogen are related to differences between individuals, and we know that individuals have different levels of oestrogen and different response to them, and when we give extra oestrogen to these animals, the amount of response of the animal is greater in the animal with the greatest amount of background level of oestrogen, and that shows that there is in fact no threshold, because the endogenous amount of hormone is already above the threshold and the added amount of hormone in again a phenomenally small amount, below a part per trillion, is detectible against this very small background amount. So I would ask Dr. Sippell whether he really believes that when you are eating meat that has oestrogens in it, is the background level against which it is operating to be considered zero the way it is in a typical risk assessment in calculating an acceptable daily intake, or is the endogenous amount already above threshold and any

amount added to that is just going to add to the risk and the types of effects caused by the endogenous hormone? Is this a question that you can answer?

Chairman

803. Dr. Sippell.

Dr. Sippell

804. It is, of course, difficult to answer such a question as a clinician, but from the experience we have with the low levels, I mentioned this several times before, with the extremely low levels that have been measured by these new recombinant assays, it is conceivable really that this extra burden of oestradiol poses a risk to very small children and particularly prepubertal boys, and this is in line with the very very high sensitivity of prepubertal children to oestrogens induced for other purposes. I mean, lets say, I mentioned the example of Turner girls, whom you treat with really minute amounts of oestradiol.

Ms Orozco

805. I would like to take advantage of your knowledge to pose a question. If such minute amounts of additional oestrogens create an appreciable or more than appreciable risk in your view, why we don't we seem to see effects in prepubertal children or at a later stage in their lives from eating eggs, meat and milk?

Dr. Sippell

806. That's actually an excellent question. One of the important parts of the answer to that is to ask whether there have been changes in human health trends over the past 50 years associated with the beginning of the use of the very large number of different types of estrogenic chemicals that children are now exposed to that they weren't before World War II when most of these chemicals began to be used. And if you look at human health events such as breast cancer and related diseases (for instance, gonadal cancer, genital malformation).

Ms Orozco

807. So that we talk about the same things, I am not talking about chemicals and residues of chemicals, but I am talking about the hormonal component that it is naturally present in food derived from animals.

Dr. Sippell

808. I guess my response to that would be that they are part of a mix of additional chemicals that humans are exposed to now that were not being used 40 years ago, and it is not really possible, for somebody in epidemiology for instance, to state the added risk, the increase in the incidence in breast cancer, in prostate cancer, in obesity – all of the types of things that are related to oestrogen are only associated with one particular source, but each of these sources of oestrogen increase the risk. Each of them independently and they add together, and everything you do to reduce one of those sources of risk reduces the overall risk. So the answer to your question is the evidence from human health trends that practically every oestrogen-related disease has increased, associated with the use of these types of chemicals in products.

Chairman

809. I will give the floor to Dr. Boobis and Dr. Sippell and Dr. Boisseau to respond.

Dr. Boobis

810. Mr. Chairman, just in the interest of clarity I would like to make a brief point, which is that the issue of the effects of endocrine disrupting chemicals found in our environment is one of the most complex and controversial issues in biology today. There is absolutely no clear consensus among scientists; very reputable scientists have different perspectives because the heterogeneity of the data is extreme. There have been a number of international respected reviews which have reported that they could find no direct evidence of harmful effects. I recognize that the absence of evidence is not evidence of absence, which is why I choose my words carefully, but I just wanted to say that we are opening up a very major issue which, as an expert on this group, I have not had the opportunity, nor was I asked, to explore in response to the questions addressed. I would also add that it does not appear to me that the EC used such a consideration in their risk assessment; I can find nowhere reference to some of these papers which were published prior to the EC risk assessment.

Chairman

811. Thank you. Dr. Sippell.

Dr. Sippell

812. In view of the fact that we just lack epidemiological studies in children eating normal meat to be compared with those eating hormone-treated meat, we can at the moment rely only on indirect evidence. And if we talk to our American paediatric endocrinology colleagues, they always report us, and this has been published, that the mean age of start of puberty in girls is lower in the United States – particularly in the not so well-off children, particularly those from black background and Hispanic background – than in Europe. Everybody here in the room knows that the problem of childhood obesity is the highest in the United States on earth, and it is increasing in Europe now, but luckily at a lower rate, and there are some other not so obvious indirect pieces of evidence.

Chairman

813. Thank you. Dr. Boisseau.

Dr. Boisseau

814. Thank you, Mr. Chairman. Just a question for the scientist who spoke for the Communities. He said that there was a trend revealed by an epidemiological study. In his view, is there an actual correlation between this trend and the use of growth hormones in the country of which he was speaking, given that over the past 20 years, although consumption of meat has been steadily increasing, people have been living longer and longer? Is the epidemiological study to which he refers discriminating enough to be able to establish a correlation between the observed effect and the cause?

Chairman

815. EC.

European Communities

816. That's an interesting question. Of course in many epidemiological studies establishing carcinogenic effects is very difficult. But one of the important issues is that associated with the use of these chemicals. There have been very recent trends, such as what was just pointed out by Dr. Sippell – a change in the incidence of puberty which is clearly oestrogen driven, and changes in obesity that have been related to oestrogen. And so associated with the use of these chemicals in beef we do have public-health data that suggest an increase in incidences of abnormalities, and again I agree with Dr. Boobis, the absence of evidence cannot be taken as evidence for the absence of harm, and we have to be careful when studies have not been done to assume that that means that there is no effect. [change of speaker.] Chairman, for the benefit of Dr. Boobis, can I refer him to our risk assessment of 1999, it is on page 20 of our risk assessment, under sections 2.3.2.3, where precisely Professor Vom Saal is cited for his research in the risk assessment, his name appears in the risk assessment, and there is precisely the title of this section is called "The Issue of Dose", and we go through this argument in our risk assessment, so it is not true that we have not included that in our risk assessment, and it goes on for two pages. It is on page 20. Thank you.

Chairman

817. Dr. Boisseau would like to have the floor.

Dr. Boisseau

818. Thank you, Mr. Chairman. Just a quick word on what Dr. Sippell said concerning the clear trend towards obesity among children in the United States. He also pointed out that the situation was getting worse in Europe, in the countries where growth hormones are prohibited and are not used. This brings me back to my question concerning the capacity for discrimination of epidemiological studies, since under two different systems – an American system where growth hormones are used and a European system where they are not used – we note that when it comes to obesity in children there may be a delayed effect in Europe, but the trend is similar.

Chairman

819. Dr. Sippell.

Dr. Sippell

820. But the obesity trend in Europe is at a much much lower rate, so the data from the (US) Centre for Disease Control – I think most of you are familiar with that map of the United States, where year by year the colour is getting darker in almost every state of the United States, in virtually every state. If you compare this with Europe, the rate of progression is much higher (in the USA).

Chairman

821. Before we further proceed, as I mentioned, given the time constraint I may not be able to give you a coffee break during this afternoon's session, but for your information, the snack bar will be open for services for us from 5 to 5.30 so please feel free to get coffees during our conversations. OK. And for your information, three of our experts have to leave this evening by 7 o'clock so I hope we can conclude our discussions by 6, but not beyond 7 o'clock at all. With that I will give the floor to EC.

European Communities

822. Chairman, we have promised to the Panel that we will do our best to finish indeed by the time you have alluded to, but there may be questions we really would like to ask, and you appreciate that this is an important occasion to clarify these issues. If we don't manage by then, what are we going to do?

Chairman

823. So that I hope all the delegations will cooperate with the Panel and experts so that we can complete the discussions before some of the experts leave. Without your full cooperation we cannot finish our business.

United States

824. Shall I continue with questions, Mr. Chairman?

Chairman

825. Please, US, go ahead.

United States

826. I only have one more question, actually, to keep things short, and it was interesting that there was a long debate on oestradiol when the question I asked was about the five provisionally banned hormones, and they are not involved in this debate whatsoever. To the experts who have opined on this issue, do any of the scientific materials presented by the EC in its opinions support the conclusion that bovine ears containing hormone implants enter the human food supply in the United States? If so, what is this evidence?

Chairman

827. Can I ask any of the experts to respond. There seems to be none

European Communities

828. Is it part of any of our areas of expertise to be able to trace what happens to bovine ears in the United States. I mean it is not in my area of expertise.

United States

829. Perhaps I can clarify it, Mr. Chairman. The EC in its 1999 opinion has a section under its misuse section that claims there is a risk from implants in bovine ears being processed into the human food supply, and I am wondering if the experts are aware of any evidence put forward in that Opinion that supports that hypothetical situation?

Chairman

830. No experts ready to respond. Dr. Boobis.

Dr. Boobis

831. I could find no direct evidence for such an occurrence. I found studies which explored the implications should it occur, but I could find no direct study of such an occurrence. I am not an expert and I could not say how this would be done, but in reading the literature provided, the materials provided, I could not find a specific study in which that had been investigated with the results presented.

Chairman

832. Thank you. EC.

European Communities

833. Chairman, probably the scientists have not understood, and if you allow me I would like to come in on this point because I think that it is an important point. We have submitted a number of Exhibits to the Panel and they are also mentioned in our risk assessment. The point is whether there are estimations or not how sure are we today that good veterinary practice is always respected in the United States, and in the evidence we have provided there are instances where good veterinary practice has not been observed. We have done specific inspections in the United States by our veterinarians; they came up with a written report which has been submitted to the United States and Canada, they are aware of this report, that identifies clear instances of the use and misuse, and I can refer to Exhibits 50, 52, 65, 67, 68.

Chairman

834. Is that question posed to the experts or to the US delegation? I am afraid that the experts may not be in a position to respond to that question. Canada.

Canada

835. I don't want to cut off the US questions, if the US has any more questions or any follow-ups. We have a number of questions, with your permission.

Chairman

836. OK. Please go ahead, Canada has the floor.

Canada

837. I think we are going to start with a follow-up on this point. [change of speaker] Yes, Dr. Boisseau in his answer to one of the definitions under the terms and definitions section indicated in describing these hormones that the hormones are implanted in the ear and that the ear is discarded, and the comment of the European Communities on this was that he should have said the ear should be discarded. But I wonder if Dr. Boisseau could give some explanation as to the operating procedures, if you will, in a slaughterhouse that are typically adopted so as to prevent or minimize the extent to which contaminants enter the food chain. And here perhaps not just a reference simply to the ear but to other types of contaminants like faeces, hair, hide, and those sorts of things.

Chairman

838. Thank you. Dr. Boisseau.

Dr. Boisseau

839. Thank you, Mr Chairman. I apologize, but since I am neither a veterinary doctor nor an inspector, I am unable to answer that question. I am terribly sorry.

Chairman

840. Canada.

Canada

841. OK. We have a couple of other questions on a separate issue. [change of speaker] Thank you, Mr. Chair, I have to take us back a little bit in the discussions, my apologies for reverting to an earlier question that came up only indirectly in some of the answers from the experts; it might be important to get some more information on this. In the comments from the experts they referred to homeostatic control or what might be also referred to as balancing systems. Perhaps a few experts could comment on the function of those balancing systems and further describe the implications of these systems for low doses of oestradiol received from meat from treated animals. Thank you.

Chairman

842. Thank you. Any comment? Dr. Boobis, please.

Dr. Boobis

843. Well, as indicated earlier, the endocrine system of which the estrogenic system is part plays a critical role in a number of physiological functions and Dr. Sippell has described some of these very clearly. We have also heard that we are subject to natural oestrogens in our diet and we have been for a long time. We have also heard that oestradiol levels can vary or fluctuate, and because of the criticality of the signalling system, it is important that the body is able to balance the levels of oestradiol against that required to produce the responses necessary. And so in general terms there is a system of checks and balances where the turnover of the hormone – any excess hormone tends to be balanced out to some extent. That is part of the role of the binding hormones, sex hormone binding globulin SHBG, it binds a large percentage of the free oestradiol in the circulation normally. And so the homeostasis is a way of preventing extraneous sources from completely unbalancing a tightly regulated system. That is just a general description, I am not saying that that is always the case under all circumstances at all life stages, but that is a general description of the homeostatic regulation of these systems.

Chairman

844. Thank you. Dr. Sippell.

Dr. Sippell

845. I only agree, but there are instances and reports, of course case reports, not epidemiological studies, that for instance children who are exposed to oestrogen-containing ointments, for example, which are being wrongly prescribed, and I have observed personally such cases, young girls get breast development and get a growth spurt and have changes in their behaviour and after this effect has been detected and the cause of that effect has been stopped, then, because the body and the hypothalamus of course react to the withdrawal of this exogenous source very sensibly, then this young girl enters into central precocious puberty, which then creates another problem. So precocious pseudo puberty caused by oestrogens from outside, if this is being stopped then the body reacts with central

precocious puberty, and this to our understanding might be the underlying mechanism why chronic low-dose oestrogen exposure to prepubertal children might result in an early onset of puberty. And, just to give you another example, several other observations have been made with DDT exposure in young children that have been adopted (from the Third World) to European countries, and in them also a high incidence of precocious-central puberty has been observed, after withdrawal of this exogenous oestrogenic compound.

Chairman

846. Dr. Boobis and then to Dr. Guttenplan.

Dr. Boobis

847. I just wanted to make a comment, Chairman, about the observational studies suggesting changes in, for example, the instance of precocious puberty and how that might be associated with the levels of hormones in meat. But as any epidemiologist would be happy to explain, there is a serious danger in trying to compare disease trends in two different countries because of the substantial differences that can exist. It is always possible to point to one factor and say it might be responsible, and of course it might be, we cannot say, but that is one of the reasons that in a risk assessment we tend to base our conclusions on evidence and not on speculation. And in the case, for example, of US versus Europe, we can all point to very many differences, any number of which can explain differences in disease trends, and it's impossible to say that it is due to levels of the hormone, and in fact it is less likely to be due to that than to some other clearly discernable differences between those populations. And on the homeostatic question, I would just add this is very much a question of dose. Toxicity or adverse effect is sometimes described as the breaking of homeostasis, you exceed the level within which the body is able to compensate by homeostatic regulation and then you begin to generate adverse effects.

Chairman

848. Dr. Sippell.

Dr. Sippell

849. Very briefly. If I understand the literature correctly all these homeostatic experiments have been derived from adult individuals, and not from prepubertal or very young children, and I wonder whether these mechanisms are the same in the young child as they are in the adult. And you just said, those case reports have been put together by speculation, this is really not the case, the levels have been measured in these individuals, in these patients, because they are patients and we are allowed to measure at least in them.

Chairman

850. With the understanding of Dr. Guttenplan, may I give the floor to Dr. Boobis to respond first.

Dr. Boobis

851. I certainly did not suggest that the case reports were speculation. I am talking about the differences in trends between the US and Europe, and that the linkage is the growth hormones in meat. That is speculation because we have no evidence for that. It might be biologically plausible speculation to some, but it is speculation; there is no direct evidence for that.

Chairman

852. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

853. I actually was going to respond to the homeostatic question, but just to comment on Dr. Boobis's last comment. Maybe it is not speculation, but often, the term that's used is it's consistent with. So yes, the trends, the time trends in different countries are consistent with the effect of oestrogens, but they are consistent with a lot of other trends too. So I would not say it's speculation, but on the other hand there is certainly no direct evidence that one particular component is responsible for a time trend in oestrogenic or prepubertal effects. With respect to the homeostatic control, at least in experimental animals it's very easy to exceed that. There have been many studies published on animals where oestrogens were administered by all different routes, and you get oestrogenic effects. So homeostatic mechanisms act, but they are not 100 per cent effective.

Chairman

854. EC.

European Communities

855. Chairman, on this point, I think it was a very useful clarification by Dr. Guttenplan. So do I understand correctly then, when you say it is consistent with, that means it is one possible explanation why we observe it. We cannot say this is the only one, but it can be one of the explanations why. That is your statement?

Dr. Guttenplan

856. That is correct.

European Communities

857. Thank you.

Chairman

858. Thank you. I am sorry, sometimes I don't notice the flag of the Canadian delegation. I give the floor to Canada now.

Canada

859. Thank you. We don't usually tend to be as noisy as some of our friends. I just wanted to ask a point of clarification. First of all I should say that in the Canadian diplomatic service Brussels is usually known as a 10 kilogram posting; that is to say that in the first year on average everyone who gets posted there adds about 10 kilos. I am not sure that this is anything to do with levels of hormones in Belgian beef, but it may have something to do with the levels of butter. The question I had was with respect to Dr. Sippell's instances and reports; I understand that he mentioned something about children who are exposed to oestrogen-containing ointments, and I'm far from being an expert in this area or indeed even remotely close to being a scientist, but I gather that ointments are a different means of getting a particular drug into your system than eating something, considering that there is, well, the intestinal tract that about 9 meters long and things happen to it in a different way than when you put an ointment on. So I wonder about the relevance of that, and the other thing of course is that I

go back to what Dr. Boobis mentioned and Ms Orozco, that these oestrogens or oestrogen-like compounds can be found in many green plants. I mean is there any observation, any instance of a boy turning into a girl as a result of eating too much broccoli? You know, that is the kind of information that perhaps we are lacking. But my specific question was to Dr. Sippell in respect of the ointment. Is there not a difference between ointments and taking something orally?

Dr. Sippell

860. May I answer to that very briefly. Oestradiol-17β is a highly lipophilic substance which means that it is being absorbed almost 100 per cent by an infant's skin, more than by the intestinal tract. And this is long known to paediatricians and to endocrinologists, and as a matter of fact for instance testosterone replacement in adult men now is being done by topical gels and creams and ointments.

Canada

861. Thank you, Dr. Sippell, you have made exactly the point I wanted to make. Thank you.

Chairman

862. Thank you. Does this exhaust the list of questions from Canada?

Canada

863. In light of the discussion about consistent with and relationships between a consumption of hormone residues in meat from treated animals and the early-on set of puberty, if I recall correctly there was some mention of the fact that the incidence of early puberty in females of African-American descent was higher than in other sub-populations, and my question is: is there any evidence to suggest that this sub-population consumes more hormone-treated meat than other sub-populations? And if the evidence was that they didn't consume more, that they consumed on average the same, then would that not be evidence that the exposure to hormone-treated beef is consistent with a conclusion that it has no impact whatsoever on the early onset of puberty, because the early onset of puberty is occurring for other reasons?

Chairman

864. Dr. Sippell.

Dr. Sippell

865. Unfortunately there are no epidemiological data to prove or to discard this very question, but there is indirect evidence. There has just been a new study in Germany where they compared the eating habits of children in different levels of the population, high-income, middle-income, low-income families, and they found out that children from low-income families consumed considerably more junk food, so-to-speak, and also higher amounts than an average-income-family child or a high-income-family child. For instance because they don't even have a common meal at home. Unfortunately we don't have such scientifically-sound data, but this might very well relate it with the increasing obesity. And we also know that fat tissues really aromatize, so convert androgens from the adrenals to oestrogens. So those (fat) kids have an additional source of oestrogens entering (from increased adrenal androgens) that turns them into early puberty.

Chairman

866. Dr. Guttenplan.

Dr. Guttenplan

867. Just as I mentioned the term consistent with, I would say studies or at least the statistics among the black and Hispanic community are inconsistent with the hypothesis that oestrogen in beef is responsible for prepubertal and other oestrogenic effects, because I would guess, and I am not sure about this, that consumption of beef by lower socioeconomic status individuals is lower, because beef is expensive. If you look at what is ordered at McDonalds, it is French fries and Coca Cola.

Chairman

868. Thank you. Our discussion is going too far beyond the issues of our constitution here, the focus of our discussions is whether or not the scientific evidence is sufficient in terms of risk assessment of hormone-treated beef consumption. So I think in order to focus our discussion on the subject at hand, I hope the delegations and parties and experts may not go beyond this range of discussions here.

Ms Orozco

869. Mr. Chairman, in order to bring back the discussion to the problem that we need to solve, I would like to come back to a question that was raised, I think, by the United States some moments ago, and I would like to ask the experts if they can please one by one express opinions, because the time is running and you will go away and we will have to decide, and we need your best judgements. With respect to the five hormones, progesterone, testosterone, trenbolone, zeranol and melengestrol acetate, was the existing evidence, the existing scientific information sufficient to complete the risk assessment? We started to answer that question, and I would like to go back to that question, and in those cases where you think the information was not enough, if you can identify what in your view would be missing, or if the information would be enough to complete the risk assessment. I think Dr. Cogliano was answering and was explaining that it depends on what type of risk assessment. The type of risk assessment that we have in mind is the completion of four steps that are common to risk assessments nowadays. So I would really appreciate if we can go back and try to address those two points of that question.

Chairman

870. The floor is open. Dr. Cogliano.

Dr. Cogliano

871. I would say that if you are going to do a JECFA-style ADI, the data are sufficient to do all four steps of the risk assessment. If you wanted to do a low-dose prediction of risk at levels you might find in hormone-treated meat, the data are not sufficient because you cannot estimate that dose-response curve with any kind of certainty. I think I would like to get away from the idea "is something sufficient to show a risk from a particular kind of low-dose exposure", because I think in many cases, in industrial chemicals for example, we get data from occupational studies or from high-dose experimental studies, we conclude that a risk is possible at lower doses and we take action without asking the question – do we have evidence that eating fish from the Hudson river is going to increase your burden of something? People don't often do studies at very low levels; we know what we know about hormones often from high-dose studies in animals, or from large studies in human populations, generally of people who have taken higher doses. I think that I see a disconnect in the

way the scientists like to talk about something and the way the lawyers can phrase questions, because I can answer that, no, the data do not demonstrate that there is a risk from consuming hormone-treated meat. I can also say, yes, the data are consistent with the possible risk, and I think it is the way these questions are phrased. I go back to your question about: are the data sufficient to do a risk assessment? If I were to assume a threshold exists, the data are sufficient to do the kind of – take a no-effect level and divide it by 100 or 1,000. If I were not to assume a threshold, the data are not sufficient for me to describe the low-dose risk and to predict whether it is one in a billion or one in 5 trillion; what the risk is from eating hormone-treated meat, because I cannot estimate that dose-response curve. That's more the way I would think about it: in the language of science rather than phrasing a question to elicit a yes answer or a no answer.

Chairman

872. Dr. Boobis.

Dr. Boobis

873. In my opinion there are sufficient data on all of these hormones to perform a risk assessment and the data support it. In deterministic risk assessment, which means there is no requirement to extrapolate to very low levels of exposure, we can establish an ADI and compare this with the estimated human exposure, and when this was done, the exposure, as you heard from the JECFA secretariat, is only a tiny fraction of that ADI, and so the risk assessment was possible.

Chairman

874. Thank you. Dr. De Brabander.

Dr. De Brabander

875. Yes, Mr. Chairman, I was a little bit, more than a little bit, surprised about the question put by the United States about the implants in the ear. If implants in the ear should enter the food chain, that should not be very well, I think. But it was linked to good veterinary practice and the application of good veterinary practice, and there was put in evidence, and I cite EC-12 here, that meat which was imported from a hormone-free programme in the United States and analysed in European labs still contains hormones, first, and secondly contains hormones which were not allowed for the type of animal. Those are facts. So I would ask – I am not in a position to ask questions to you, I think, Mr. Chairman – you could ask, if there are such findings in an hormone-free programme, what should be the findings in a not hormone-free programme? And that is the question. All we heard from JECFA is all the data we are talking about, I won't go into risk assessment because I am not a specialists in it, but it always said it has to be according to good veterinary practice, and here clearly shown from data, from evidence, that even in an hormone-free programme good veterinary practice is not followed. So can we be sure that good veterinary practice is followed in a not hormone-free programme? And as I answered, there are more products that can be used for growth-promotion than just hormones, and it can add an effect above the hormones. And if there is no monitoring for them, how can you be sure that they are not being used and that good veterinary practice is used?

Chairman

876. On this point? Thank you.

European Communities

877. Well, I would like to ask, because it is part of the evidence. Dr. De Brabander, if hormones, for example in the United States – we know they are sold over the counter. Really, is that good veterinary practice in your view?

Dr. De Brabander

878. In my view not. Normally in Europe we have a very strict regulation and that is one of our problems in the laboratories, that it practically causes a lot of paperwork for us to have just a standard for analyzing samples. If we would have all the standards, 20 milligrams, 10 milligrams of them, which would not be enough to anabolize a fly or mouse or something alike and it can just be used for analytical purposes. We have to fill in piles of papers and in other places they are sold freely.

Chairman

879. Thank you. Do you want the floor now?

United States

880. I don't want to get in the way of Madam Orozco's question -- this is sort of a distraction from that. The United States looks forward to speaking of these issues probably on Monday, when we get into the evidence that has been provided here today. I would make two comments though, one of which was the United States question whether implants in ears had found their way into the food chain. This is a conclusion, a scenario that the EC's 1999 opinion postulates. There simply is no evidence of that. There is nothing there in the Opinion that demonstrates this conclusion. Now if occasional situations where the US hormone-free programme had incidences of meat that was outside of normal ranges, the United States, we feel, and as we are ready to discuss on Monday, has a very robust system, and finding problems, addressing problems, and taking care of them within a regulatory structure, I think, is the utmost attempt to achieve good veterinary practice, rather than evidence against achieving good veterinary practice. And again I look forward to going into that in great detail. I would note that on the other hand the EC, which has chosen to ban these materials, has a well-documented black market for their use per the Stephany paper that the United States has presented. So, when we talk about failure of good veterinary practice, I think this is a fairly complex discussion that maybe these most recent comments oversimplified a little bit.

Chairman

881. I will give the floor to Canada.

Canada

882. Yes, I would like to ask a follow-up question to Dr. De Brabander's comments, and that is: are you familiar with the Canadian Food Inspection Agency National Chemical Residue Monitoring Programme, and have you had an opportunity to review the results of that Programme for, let's say, the last five years?

Dr. De Brabander

883. No, I'm not, that is simple. I am a chemist, I am working in a lab, involved in routine control, I'm not inspector, a veterinary inspector, and not a European inspector, but there are.

Canada

884. So you don't have any expertise to share with this Panel as to the control mechanisms in place in Canada to minimize or to prevent misuse and abuse of these hormones.

United States

885. We will just follow-up, Mr. Chairman, and ask the same question of the US system of controls.

Dr. De Brabander

886. I think the question is beyond our role as an expert. As an expert we have been asked to examine the papers, and my role is not going inspecting in the United States, neither in Canada. But evidence is here. I was involved in problems with the import of American pork meat. I was asked by the USDA to perform some analysis and some studies on that phenomenon, from which there was evidence from urine that also pork should be treated with hormones. That I have practical experiences in.

Chairman

887. I think Canada has been interrupted so many times while you were posing questions; I am wondering whether Canada has exhausted its list of questions.

Canada

888. We just have one more question on detection methods of residues and perhaps we can ask this question. I think this question follows on one of the Panel's question and it was answered by both Dr. De Brabander and Dr. Boisseau. And the question is that if you have a Codex MRL, a maximum residue limit that has been adopted by Codex, and you have a detection method that is of a sufficient limit of quantification so as to be able to detect residues at that MRL, so for instance an MRL of 10 micrograms per kilogram, and your detection method has a limit of quantification, about, say, half that, 5 micrograms per kilogram, the fact that you have developed more sophisticated analytical methods that now have a lower limit of quantification, lets say a limit of quantification now of 1 microgram per kilogram, does that mean that the other type of detection method, assuming that it was fit for purpose, that that other detection method is no longer fit for purpose? That's my question.

Dr. De Brabander

889. That goes into very technical details of analysis, technical terms like recovery. What is recovery? Recovery is if you take a piece of meat and you mix it with methanol for example and you add hormones to it, how much do you recover. And that is very dependent upon your analytical technique, and in most cases when you do that your recovery is low, so if you have an MRL of 10 and your recovery is less than 50 per cent, you cannot detect a residue at all. It's that simple. Furthermore, you should be certain that you detect the component in the right form. Certain components may be bound, maybe in another form than you detected. You must be sure that you free them, so it is a question which you can hold a conference on, I think, and maybe I should take a comparison with cars. If you drive at 100 kilometres an hour and you drive it with a car which just is able to get that maximum speed limit you are not comfortable, but if you drive a Ferrari or another racing car who can get up to 220 kilometres, then you drive safely at 100. It's a little bit the same with the analytical technique, if you have an analytical technique that is capable of 1 ppd or 0.5 ppd comfortably, then you can more easily and more correctly measure your MRL. I hope I was clear in that for you.

Chairman

890. Dr. Sippell.

Dr. Sippell

891. And this is just the follow-up to answer your question regarding the situation in children. We just don't have yet everywhere where it would be necessary the methodology, the analytical tools to measure as sensitively as we should do it, and therefore I think that the data available are insufficient. And I also already said before that due to ethical constraints I don't expect that we will get the data we need to answer these questions in the near future.

Chairman

892. Dr. Boisseau.

Dr. Boisseau

893. Thank you, Mr. Chairman. I would like to revert to the question concerning the methods of analysis. I have already answered, but since the question has re-emerged, I'll answer once again. We have to decide what we are talking about. The initial hypothesis was that there was an adequate method to control the established maximum residue limit, i.e. that this method must have been validated. This means, in particular, that the limit of quantification is compatible with the ADI value. I am not speaking of the limit of detection, which is lower, but rather of the limit of quantification. Moreover, this method needs to meet a certain number of criteria defined by the ISO standards such as reliability, reproducibility, precision, linearity in a given range of concentration etc. Assuming this method of analysis has been validated, it must also be practicable. Since any analysis has a cost, it is not necessarily a good idea to choose an ultra-sophisticated method, since what counts is to be able to ensure that the controls are economically reasonable. So if a method meets all of the criteria, there is no point in using a more recent and more sophisticated method. If other laboratories choose to use such methods, that is fine with me, but if a control laboratory is operational and produces good results for the control of that MRL with a method that may be ten years old but that works, I see no reason why it should be changed. The point of the MRL is that it offers the possibility of stopping this rush towards ever-better performance of methods of analysis, since analysts, like scientists, appear to have an infinite capacity to improve, to do more, to be more precise, to be more sensitive, and in general, this means higher and higher costs. Where there is no need, there is no point in investing in that area.

Dr. Boobis

894. I wanted to come back to this question of the sufficiency of information and the correct comments from one of my colleagues that it is highly unlikely we will be able to get information in children of the sort that would be suitable for a risk assessment because of ethical reasons. And this is for oestrogenic or hormonally-active substances. I just want to reflect on the implications of that, because it implies we cannot proceed with a risk assessment without information that cannot be achieved or acquired, and that if we add to that the argument that there is no bottom end to the dose-response curve for oestrogen, and we look at the range of compounds and the range of potencies of hormonally active substances – this is a very diverse and wide-range of materials – does that imply that it is impossible to conduct a risk assessment on any of those materials? I do not believe that is the case. I believe that with a fundamental understanding of biology and appropriate model systems we can make intelligent deductions about the likely risk to the population. That is not to say that there may not be some gaps in scientific knowledge and that there may be severe gaps, but the implication that we can never proceed without information in the target population of children means that we are going to be completely blocked from dealing with these compounds, and these compounds, as I said a

minute ago, are an extraordinarily wide range of compounds, because we have this idea that there is no zero risk for an endocrine-active material.

Chairman

895. Thank you. Dr. Miyagishima first.

Dr. Miyagishima

896. Thank you, Mr. Chairman. I would like to clarify that the terms of reference of Codex on residues of veterinary drugs in foods currently include consideration of methods of sampling and analysis for the determination of veterinary drug residues in foods. And there is a document called Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs. This is not a document which is located in the Codex Alimentarius in a strict sense, but this is a list of methods that are considered to be useful for governments to check that residues in food samples are in compliance with the Codex MRLs. Currently in this compendium there are no methods mentioned for the determination of oestradiol, progesterone or testosterone. This is consistent with the fact that there are no numerical MRLs in place within the Codex Alimentarius. However, this compendium recommends method of analysis for trenbolone acetate and zeranol, for which there exist Codex MRLs, and for melengestrol acetate, for which the draft MRL is currently at step 7 of the Codex elaboration procedure.

Chairman

897. Thank you. Dr. De Brabander.

Dr. De Brabander

898. Just a small clarification, Mr. Chairman, on what Dr. Boisseau said about the MRL. He said that the MRL was installed to stop the race for lower concentrations. Am I correct? And I thought hearing from the JECFA that the MRL was really based on toxicological evidence, it had nothing to do with an analytical technique. I was not aware that they want to stop chemists of doing our work better and better.

Chairman

899. Thank you. No comments from the experts, then I will give the floor to EC.

European Communities

900. Chairman, I would like to take the floor and ask Dr. Boobis – because in his reply to question 64, precisely as he has said, and it is very important in my view to understand, that the level obtained in a residual risk has never been quantified, but is considered to be acceptable to society. So – if I say something wrong, please, Dr. Boobis, correct me – that means he is making a value judgement for himself. He accepts that the residual risk has never been quantified, but he then goes on, every scientist, not a risk manager, every scientist to suggest that this is acceptable to society. And my simple question is: do you think it is a proper position to take of the scientists who are supposed to do a risk assessment in the strict sense? For example this is mentioned in the Codex Manual of Procedure. If I have misinterpreted what you wish to say please clarify it. Thank you.

Dr. Boobis

901. I will clarify. You completely misrepresent what I said and misunderstood my meaning.

European Communities

902. Could you explain then what is the meaning of what you said?

Dr. Boobis

903. Because the risk assessments of JECFA are adopted by Codex, it is implicit that they as risk managers have accepted and established the level of risk that is acceptable for society. This is nothing that JECFA says; it uses a procedure which is acceptable throughout the world, is used by the EU itself to establish ADIs. Implicit in that procedure is therefore the recognition of the level of risk that is represented by that process. It is not my judgement, it is the judgement of risk managers, I am simply interpreting what the risk manager's conclusions must be to allow us to do the risk assessment according to the principles that have been accepted throughout the world. And I stress again, I am not making a value judgement here.

Chairman

904. Thank you. Dr. Boisseau.

Dr. Boisseau

905. Because the question that has been asked is really quite important in terms of principles, I would like to back up what Dr. Boobis has just said. The experts in the JECFA, in particular – but the same applies to the CVMP – do not define a socially acceptable level of risk. They have a working method which uses – within the framework of a deterministic approach – a certain number of safety factors. I note, moreover, that although I made this suggestion yesterday, there was no mention of the chain of safety factors used throughout the procedure up to the determination of the MRLs. There is a whole series of factors, and it is a shame not to bear them in mind, because this would perhaps give us a better idea of the protection provided by the method used by the different scientific committees. Once again, the scientist in charge of risk assessment does not determine beforehand what a socially acceptable risk is, and it is not his job to do so. He makes recommendations on the basis of a methodology which, although not written out, is known to all and used everywhere. At the Codex level, the CCRVDF (the risk management body), fully aware of the method, was perfectly capable of accepting or not accepting the ADIs or the MRLs. We need to distinguish, when it comes to risk management, between those who make the proposals and those who end up deciding. The risk managers are those who decide – they are not the ones who propose. The same is true in other agencies, such as the AFSSA (French Agency for Food Safety), where I worked. As the Agency responsible for assessing all risks connected with food, it often made proposals with respect to management, but it was ultimately the Ministry that decided, and never was the AFSSA criticized for the proposals it may have made in the area of risk management.

Chairman

906. Well, before I give the floor to the delegations, I would like to remind all the delegations that discussions should not escalate to the point of making any offensive remarks in the posing of questions. And I believe that the parties have exhausted their list of questions by now. If that is the case, then I will give the floor to my colleagues in the Panel so that we can also pose questions on area 3, and with that understanding I am wondering whether – the US still wants the floor? OK. Canada has the floor.

Canada

907. Thank you. We just have a couple of more questions for Dr. De Brabander, and this is in relation to your comments that in your opinion there are economic incentives to illegally use

hormones, and I would just like to ask you a few questions on this. At one point in your advice you indicated that hormones can negatively affect behaviour, and my question to you is if you add increasing amounts of hormones to cows, does that increasingly affect their behaviour? And I believe you have mentioned at one point that it makes the cattle more aggressive. So does increasing the amount of hormone increase the level of aggressivity?

Dr. De Brabander

908. I think that is a little bit more than I said, what you take out of my words. I said that hormones may influence behaviour, and there are experiments, not with cattle but with rats, where hormones were added which made them more aggressive. That's right, that's known, that's facts, just facts. I don't know of experiments of a dose-response curve of aggressivity against hormones, and certainly not in cattle. Such experiments we would not do in Europe, not in Belgium, because of ethical reasons. For each animal experiment we have to do we also have to fill in a couple of papers, a number of papers. Luckily at our school we have our own ethical committee, a committee which is controlled, which assesses what experiments must be done, what can be done. I cannot answer your question because it is too far gone, the only thing I said is they really will influence behaviour and that is known in test animals.

Canada

909. Thank you. My question was: if you add more, do you expect to see some sort of a relationship between the effect of behaviour and the amount of hormones, so that if you add more hormones, if you multiply the dose, if you add considerably more hormone than what is recommended, whether this is likely to have an adverse effect on the level of aggression in the animal?

Dr. De Brabander

910. That is too a complex question to answer here on the floor, I think. I think it is a subject for a research programme, and certainly there are people who would like to carry out that programme, but we cannot answer that. I have just said they have an influence on behaviour, that's qualitatively, quantitatively that's not to answer at this moment.

Canada

911. OK. Thank you. I just have another question for Dr. De Brabander. Do you know whether or not the administration of hormones or the overdosing of hormones has an effect on the carcass grade quality – and by that I mean the quality grade of the meat, grade A, US grade A, US double grade A, triple grade A? I take it that the grade is related to the amount of marbling, to the amount of fat distribution, in the carcass. Does administering more hormones than is recommended have an impact on that grade?

Dr. De Brabander

912. Yes. That is also difficult to answer having studied these papers. What I have said is not the addition of more hormones, what I said was there are other components, and I mentioned here zilpaterol, a beta agonist of the third generation which is legal in Mexico, and I mentioned an experiment with zilpaterol I was looking at literature for zilpaterol because we have to monitor it and bring it into line with other beta agonists monitoring programmes. We found out that experiments with zilpaterol were done, and to my surprise the blank animals were not blank animals, but were animals treated with the regular US hormones and they had an extra profit. So if you ask: are there

incentives to use other growth promoters, yes there are, and the same incentives that's the same everywhere in the world: money.

Chairman

913. I think it is our turn, but before I give the floor to my colleague, the floor is for the EC. A quick question.

European Communities

914. Chairman, I would like to say that we have a couple of questions more to ask on this area. I don't know if now is the moment or later.

Chairman

915. Yes, please go ahead.

European Communities

916. Thank you. That question relates to the discussion ... (end of tape) ... concerning the genotoxicity and whether the evidence which we have, which is reported in our risk assessment and subsequent papers which we have submitted, of genotoxicity *in vivo* – because Dr. Boobis has made a statement just before the break saying that in his opinion the evidence is not convincing, I think that is more or less what he has used. So I would like on this precise point, because he made a reference to some papers, to give the floor, with your permission, to one of our scientists to make a short statement and then probably ask a question on this precise point – it's Dr. Metzler. Thank you.

Chairman

917. There is a question to be posed to Dr. Boobis? OK go ahead.

European Communities

918. Thank you, Mr. Chairman. It has been stated that there is not sufficient evidence for the mutagenicity of oestradiol and its metabolites *in vivo*. Before I go into this question, let me just reiterate that we all agree, I think, that, first, the DNA-directed mutagenicity of oestradiol is not due to the oestradiol molecule itself but to one or several of its metabolites which need to be formed. Secondly, these reactive metabolites, which bind to DNA, causing DNA adducts, are weak mutagens, as has been shown in *in vitro* studies. Despite this fact, to my knowledge there are three studies demonstrating *in vivo* mutagenicity of these metabolites and also of oestradiol, one study in mice and two studies in rats. As Dr. Boobis has correctly stated, in most of the studies the metabolite under suspicion for causing mutagenicity has been tested, but in one of the studies in rats, also in addition to this metabolite, E_2, oestradiol itself has been administered to the rat and led to an increased mutation frequency in the mammary gland. So there are three *in vivo* studies on the mutagenicity of oestradiol and its metabolites. And let me just add one little piece of *in vivo* evidence; there is a paper that has demonstrated that the very adducts of reactive oestradiol metabolite that have been shown mutagenic in cell culture studies *in vitro* is present in the human target tissue, the human breast. These adducts have been demonstrated to be there, and this demonstrates, in my view, that even in normal women these adducts are formed, and in my view obviously any additional oestradiol would increase the frequency of these *in vivo* adducts. Thank you.

Chairman

919. Dr. Boisseau – US first.

United States

920. Thank you, Mr. Chairman. I would just make one point. If the experts are going to respond to this, I would hope that they would discuss the levels of hormone that were used in the studies that were just were referred to. I think we may find that the levels used in these studies are exponentially higher or greatly higher than those that are relevant to the subject matter at hand, which is hormone residues in meat, but I leave that to the experts if they are indeed going to respond to this statement. Not to the EC's expert but to …

Chairman

921. Right, thank you, that is clear. I will give the floor to Dr. Boisseau first and then to Dr. Boobis.

Dr. Boisseau

922. Thank you, Mr. Chairman. When we revert to this series of short-term tests to suggest, or conclude, that oestradiol is associated with genotoxicity, potential genotoxicity or mutagenicity, this means that we credit oestradiol with the capacity to induce tumours through a channel other than the hormonal effect. Since the short-term tests are screening tests, these hypotheses, which are perfectly valid with respect to the results of the short-term tests, need to be confirmed through studies on animals, experimental carcinogenicity studies. So this leads me to a question for Dr. Boobis, who is a specialist in this area: have the experimental carcinogenicity tests – 18 months on mice and two years on rats – been able to identify the appearance or increase of tumours in non-hormonally-dependent tissues which are predictive of the same tumours in human beings? In other words, did any tumours appear or develop in non-hormonally dependent organs in animals whose physiological and metabolic characteristics were such that what was taking place in animals was predictive of what could take place in human beings? Thank you Mr. Chairman.

Chairman

923. Thank you. Dr. Boobis.

Dr. Boobis

924. I was just concerned to identify the three studies mentioned by the EC, so that I can look at them. You mentioned three studies that were positive *in vivo*, I would like to know what they were. Thank you.

European Communities

925. May I answer that question? They were cited in EC Exhibit 125, so they have been provided.

Dr. Boobis

926. Authors of those papers, to help me find them?

European Communities

927. The first author is Cavalieri, and I think Professor Guttenplan is also on the author list. I am sorry, there are a number of authors and I cannot remember all of them but there are seven or ...

Chairman

928. Dr. Boobis, do you need some time? Dr. Boobis, I think the secretariat may provide you with the relevant materials. OK. So in the meantime, can I give the floor to the EC to respond to the question put forward by Dr. Boisseau? Dr. Boisseau please.

Dr. Boisseau

929. Excuse me, Mr. Chairman. I had directed my question to Dr. Boobis, and not to the Communities.

Chairman

930. Thank you.

Dr. Boobis

931. Chairman, what I have in front of me at the moment is EC 125, an unpublished review. Is that correct?

European Communities

932. The draft you have is the prepublication available for the internet and it has been published and it has appeared in the meantime, in August 2006.

Chairman

933. Thank you.

European Communities

934. It's a review and it contains also original data on later pages.

Chairman

935. Please go ahead, Dr. Boobis.

Dr. Boobis

936. I have not had time to evaluate these date. This is a recent review, I hear that it came out less than six weeks ago, I have not been in my office for much of that time, I have not had time to read this paper. If possible I will look at it and maybe be able to have a comment in the next half hour.

Chairman

937. Thank you very much. I would appreciate it if you could do so. Does the EC want the floor?

European Communities

938. I think we are satisfied with the reply and we would appreciate it if there is a reply later on. Thank you.

Dr. Boisseau

939. Thank you, Mr. Chairman. Without wishing to harass Dr. Boobis, could I ask him please to answer the question that I directed to him – or perhaps he did not hear it; he may have been looking at the documents that he had just received from the Communities.

Chairman

940. Before I give the floor – Canada has the floor.

Canada

941. My apologies for interrupting the flow of discussions. It is simply a point of clarification. My colleagues tell me that the document as published may well be slightly different or different in certain key aspects, however way one looks at it, from the documents as a draft that has been put in evidence. So I just want to confirm whether in fact those who are familiar with the published version can guarantee to us, talking about appreciable risk, if they can guarantee to us that the document as published is in fact the one that we have in our possession, or alternatively what the differences are. We would like to know if in fact the reference made is to the published article or to the draft article. You will forgive the confusion here, but I think a better precision is probably useful, and we don't want Dr. Boobis to review a document that in fact may not be the document to which reference is being made.

Chairman

942. I think regarding that question we can benefit from the response or comments by Dr. Guttenplan, because he was one of the co-authors. We can ask Dr. Guttenplan to clarify on that point later maybe. Is the US point also related to this one?

United States

943. Simply to say that I was going to try to assist Dr. Boobis in his search. I think a relevant section to look at is section 5.2.1 in that study. There are a couple of paragraphs there that might shed some light on the methodology and how it actually relates to this dispute. That assumes I am looking at the unpublished version that – oh I am looking at a published version, I am not sure which version the EC's Exhibit is.

Chairman

944. EC has the floor.

European Communities

945. Chairman, if you see with our comments on the comments of the parties which we have sent on 12 July, it is all these papers cited by Dr. Boisseau, Dr. Metzler, they are cited there in our comments to question 13. So this has already been sent to the Panel, and the other papers as well, at least on 12 July when we submitted these papers. You will see them clearly cited, all the three papers have been mentioned. Thank you.

Chairman

946. Thank you for that clarification. I am afraid that Dr. Guttenplan was out of the meeting room for around ten minutes, so I am wondering whether he has followed the discussions so far?

Dr. Guttenplan

947. No, I haven't.

Chairman

948. Maybe the EC can briefly explain what he mentioned again.

European Communities

949. Well I can answer that question, I think, if I understood correctly. What has been submitted in May or June or in July was the pre-publication, and the pre-publication means it is not a draft, but it's the final paper that appears on the internet, because the Journal where it is published usually appears two or three months later. So it is identical and it has appeared in the Journal now in August and I would be happy give you the reference, which is volume 1766, pages 63 to 78, Biochem. Biophys. Acta., as is already on the pre-publication.

Chairman

950. So, until we reach the time when Dr. Boobis is ready to respond to that particular point, shall we move on to the next item on EC's risk assessment? If we have wound up the discussions on area 3, I will give the floor to the EC first to put questions on section 4. EC has the floor.

European Communities

951. Chairman. With your permission, while Dr. Guttenplan was away, I think a member of the Panel, Madam Orozco, has posed the question on the sufficiency of the evidence, and I think practically all the scientists have replied, I thought, except Dr. Guttenplan, if I am not mistaken. So could you please make sure that we have the views of all the experts on this issue, and probably, if I may suggest, that Madam Orozco repeats the question again if possible. Thank you.

Ms Orozco

952. Yes, Mr. Chairman and the experts who are assisting the Panel, I posed a question and I would appreciate answers as complete as possible, because we have a situation where the European Communities has stated that in their view they did not have sufficient evidence, sufficient information, to be able to carry out a full risk assessment on the five hormones other than oestradiol-17β. I have posed the question and I have asked your views as to whether or not the information that is available is sufficient to carry out the four-step risk assessment that we are talking about.

Dr. Guttenplan

953. These are the five hormones in addition to oestradiol? I don't know about a full risk assessment, but I think there is enough data to carry out a risk assessment as Dr. Cogliano refers to.

Ms Orozco

954. Because the terms are not always used in the same sense, what we are talking about is the four steps of a risk assessment, or a risk assessment that for some good reason does not have them, but in principle we are talking about a risk assessment that would have a hazard identification, that would have a hazard characterization, that would have an exposure assessment and that would have a risk characterization step. Whether or not the information that is available would be enough. If not, what is it in your view that is missing to be able to carry out a full risk assessment?

Dr. Guttenplan

955. I think there is sufficient information out there.

Chairman

956. Thank you. Dr. Boisseau.

Dr. Boisseau

957. I am going to answer along the same lines as Dr. Guttenplan, in that the method usually applied by the JECFA is considered satisfactory because it is a deterministic method. Now, if we are talking about a probabilistic method with effect–dose extrapolation to low doses, the data may not be sufficient. Consequently, my reply to Mrs Orozco's question is that my answer depends on the method applied by the JECFA.

Chairman

958. Thank you. Dr. Boobis.

Dr. Boobis

959. I have a comment on one of the studies that were referred to recently. Would you be prepared to listen to that now? A comment on one of the genotoxicity studies that were referred to a moment ago. This is an *in vivo* study of oestradiol. I note that it was a high dose – it was toxic – and that the mutational spectrum, which is a very important measure of the underlying mechanism whereby the interaction with DNA was occurring, was not significantly different from the control animals, and that the 4-hydroxy-oestradiol, which was the presumed metabolite, as Dr. Metzler has just pointed out – a possibility that the parent is not itself responsible but a metabolite – had a quite different mutational spectrum. So my view would be that this study is not sufficient at the present time to override the conclusions that we had come to earlier, that low doses of oestradiol do no cause a mutagenic response *in vivo*.

Chairman

960. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

961. The mutational spectrum for 4-hydroxy-oestradiol was different in the control.

Dr. Boobis

962. I stipulated that the mutational spectrum for 4-hydroxy-oestradiol was different from the control, but that of oestradiol was not, and if the hypothesis was that the effect of oestradiol in producing that response is through the 4-hydroxy metabolite, the anticipation would be that there would not be a very big difference in the mutational spectrum; there was.

Dr. Guttenplan

963. Well, we don't know how much of the oestradiol gets converted to the 4-hydroxyoestradiol, and it has been detected *in vivo,* or at least the conjugates have, in breast tissue from human women, and we know that that gives a different mutational spectrum than the control.

Chairman

964. Thank you.

Dr. Boobis

965. Could I just respond, please? But the problem I am having, Chairman, is that the compound we are concerned about is oestradiol. I can find no difference in the mutational spectrum, which is a signature of the response to the DNA, from the control. So it may be exaggerating something that is going on naturally, and I would repeat that the dose of oestradiol used in these studies was so toxic that not all the animals actually survived.

Dr. Guttenplan

966. Yes, this is a common problem with any toxicological study, you have to increase the dose in order to see something that is significant in the animals, you don't have enough animals to do the experiment if you were to use an environmental dose. So this is nothing different than what is done in usual toxicological studies.

Dr. Boobis

967. There have been guidelines established for dose setting in studies in which mutational responses have been observed *in vivo.* I do not believe that any of those guidelines recommend going up to doses which are lethal. There is supposed to be some slight evidence of toxicity at the top dose, but by no means lethality, so this would be a heroic study.

Dr. Guttenplan

968. 4-Hydroxyoestradiol was not toxic though, just oestradiol alone, and often this is what you do, you test the presumed active metabolite. And this is often done, this is classical studies in metabolism of benzpyrene, as you are familiar, which were eventually done with the end product.

Chairman

969. One last chance for Dr. Boobis.

Dr. Boobis

970. I agree entirely with what was just said. In the case against benzpyrene, however, the parent compound and the metabolite produced the same mutational spectrum, therefore confirming the likely

involvement of the metabolite in the response. Here, when we see a different mutational spectrum, the interpretation for me is: something else is going on; and it certainly does not confirm, it by no means confirms, the involvement of that metabolite. It may be that there was too low a level, but these data cannot be used to confirm that metabolite's involvement in response to the parent compound. That's all I was saying.

Chairman

971. Well, we have spent more than two hours already and we still have the most important issue of our consideration this afternoon, so I think it is better for us to move on to the next section on the EC's risk assessment, and then I will give the floor to the EC first to ask questions to the experts. You have the floor, EC.

European Communities

972. One question I would like to ask the experts, and in particular probably Dr. Guttenplan or Dr. Boisseau, is that, as we know these substances, the implants contain several of these hormones that, as we were told, they practically never are administered as a single substance, and Dr. Boisseau in his reply has confirmed that. The toxicological evaluation was made on an individual substance. Now how important do you think it is to know the possible synergistic effects, given that the actual administration of these implants involves more than one of these hormones? Thank you.

Chairman

973. Thank you. Dr. Guttenplan.

Dr. Guttenplan

974. I think that the biological effects of oestradiol so overwhelm the other effects that I would not be concerned with any synergistic effects.

Chairman

975. Is any other expert prepared to respond? If none, the EC has the floor.

European Communities

976. Chairman, it is not entirely clear how the current section differs from the previous one. In your instructions, your indications, you said section (c) and part of section (d), so I would like to discuss a specific aspect of the EC risk assessment which was discussed under the previous section. If you allow me to ask a question to Dr. Guttenplan.

Chairman

977. Sure. There is no clear-cut dividing line between these two areas. You can put whatever questions you feel are necessary.

European Communities

978. Thank you. It is just that, if I understood correctly, Dr. Guttenplan, you said that the scientific evidence on the five hormones was sufficient to conduct a risk assessment. In your reply to questions 61 and 62 you actually state differently, so could you explain the differences? There is a whole

bullet-point list of gaps you have identified, and in your reply to question 61 you speak of an assessment for melengestrol acetate which seems sound for example. Could you explain?

Dr. Guttenplan

979. That means that the risk assessment was alright.

European Communities

980. Would you care to elaborate on the gaps you have identified and question 62?

Dr. Guttenplan

981. Yes, on subsequent reading I could not find anything to indicate adverse effects, and I now think that risk assessment is alright.

European Communities

982. Can I reformulate the question? Because I think probably we have an issue of understanding each other. Can I ask, Dr. Guttenplan, whether your reply to question 61 is correct as you see it today?

Dr. Guttenplan

983. Well, I said the ability varies between compounds, but that does not mean you can't make a risk assessment, it just means the accuracy of the risk assessment is different.

European Communities

984. You also say, for example, that it does not appear that accurate ADIs can be established at this point.

Dr. Guttenplan

985. Well accurate means – if it's not accurate, there is just a larger range, but you can still do a risk assessment.

Chairman

986. I will give the floor to the US.

United States

987. Thank you, Mr. Chairman. Dr. Guttenplan actually spoke to our question, which was whether these particular items he had identified in this question actually prevented the conduct of a risk assessment, which is entirely separate from whether there are certain small gaps, whether you can actually conduct a proper risk assessment.

Chairman

988. EC, please, go ahead.

European Communities

989. Chairman, we have asked previously a question about the fact that the hormones are administered in combinations containing more of these hormones, and only Dr. Guttenplan has replied. Probably Dr. Boisseau would like to give a reply. Would it be necessary to have an assessment that takes into account the real administration of these hormones and not the individual compounds in question?

Chairman

990. Dr. Boisseau, please.

Dr. Boisseau

991. The same type of study was conducted for trenbolone, which, if I recall, is administered jointly with oestradiol, and no particular potentiation effects emerged. These studies of combinations of hormones were not conducted for all hormones. The JECFA considered that since the receptors were not the same and the biological properties were not the same, the prospects of a hormonal potentiation effect through the action of another hormone was unlikely. So if I am not mistaken, toxicological studies were made only for trenbolone. That is all I can say.

Chairman

992. Thank you. I would like to thank Dr. Wennberg and Dr. Miyagishima for their contributions and presence in this meeting. I would like to let the delegations know that they are leaving. Thank you. The floor is for the EC again.

European Communities

993. Chairman, I would not ask a question now; we will wait for the other part before we intervene.

Chairman

994. OK, good news. US has the floor.

United States

995. Thank you, Mr. Chairman. A question for all of the experts who have looked at the EC's risk assessment and have comprehension of the four steps of risk assessment; hazard identification, hazard characterization, exposure assessment and risk characterization. In light of these components, have you identified any deficiencies in the EC's opinion relating to oestradiol-17β?

Chairman

996. Thank you. Any volunteers? Dr. Boobis.

Dr. Boobis

997. Well, in looking at the four stages of risk assessment, as we have heard earlier, for various reasons the EC evaluation tended to focus more on the hazard identification side. There was some hazards characterization but it was not completed and, as far as I could gather, there was no

independent exposure assessments undertaken. And so, from the perspective of the four stages, it would certainly not be regarded as a complete risk assessment.

Chairman

998. Dr. Boisseau?

Dr. Boisseau

999. I concur with Dr. Boobis.

Chairman

1000. Thank you. EC?

European Communities

1001. Can we follow up on this? Dr. Boobis, is your reply based on the assumption that there would be a threshold, so that your reply would actually not apply in the case of direct genotoxicity?

Dr. Boobis

1002. That is partially correct, but I would have anticipated some exploration of the type of genotoxicity and whether it did have a threshold, and that does not seem to have been carried out very rigorously and there was not what I call the weight of evidence, a sort of balancing of the quality of the studies and the endpoints that they were responding to.

Chairman

1003. Dr. Boisseau.

Dr. Boisseau

1004. Thank you, Mr. Chairman. We always seem to come back to the problem of thresholds. Once again, short-term tests that can show a genotoxic or mutagenic potential are not intended for determining thresholds. If we really want to know whether this potential is real, it needs to be confirmed by long-term carcinogenicity tests. So I come back to my question to Dr. Boobis: in the long-term tests on mice and rats, was it possible to identify tumours in non-hormonally dependent organs that could confirm a mutagenic potential observed in short-term tests, and if so are such tumours in non-hormonally dependent animal organs predictive of what could happen in human beings?

Chairman

1005. Thank you. Dr. Boobis.

Dr. Boobis

1006. Apologies, Chairman, I did not catch that question to respond to earlier. From my knowledge, the studies in rodents have not shown any target tissues for carcinogenicity which are not hormonally dependent and that these tissues are targets one would have anticipated for an oestrogenically active substance. That is the factual evidence.

Chairman

1007. Do these answer the question by the US?

United States

1008. Yes, Mr. Chairman, thank you.

Chairman

1009. No further questions from the US? What about Canada?

Canada

1010. No further questions from Canada.

Chairman

1011. Thank you. I give the floor to the EC.

European Communities

1012. Thank you, Chair. On this last reply of Dr. Boobis we would like to intervene, and I would like to give the floor to Dr. Alain Paris who would like to respond to this please. [Change of speaker.] Out of courtesy towards Dr. Boisseau, I am going to speak in French. I am surprised at the division that has appeared, with regard to the action of oestrogens and their effects, between what passes through the oestrogen receptors and what passes via genotoxicity phenomena. To revert to the genotoxicity phenomenon, this is essentially a random process; and I wonder about the deterministic approach, as mentioned earlier, which would appear to be more efficient than the probabilistic approach, in that the deterministic approach, in my opinion, is incapable of taking account of all of these random phenomena.

Chairman

1013. Thank you. Dr. Boisseau.

Dr. Boisseau

1014. Thank you, Mr. Chairman. I am no specialist in these areas, but reverting to what you said, and I agree with you, a phenomenon based on genotoxicity or mutogenicity is random, which means that this genotoxic potential, if it exists, should, in a carcinogenicity study, provoke tumours which should concern a certain number of tissues in a random manner and not only those which are hormonally dependent. Hence my question earlier on, which was answered. For the moment, the only tissues affected by the development of tumours are hormonally dependent. This does not support the idea of a non-hormonal genotoxic-type mechanism. Finally, the statistical evaluation of the effect of small doses is another problem.

Chairman

1015. Thank you. Dr. Guttenplan please.

Dr. Guttenplan

1016. The genotoxic effects, at least the mutagenic effects, are also dependent on cell proliferation, and sometimes they are extremely dependent on cell proliferation, so that hormonally-sensitive tissues in the event of a random distribution of a genotoxic effect are going to show the first genotoxic effects. So it is not surprising that you see effects in animals in hormonal-sensitive tissues. Of course one could make the same arguments for a non-hormonal mechanism, too. On the other hand, one could make the same argument on a hormonal model as a genotoxic model, but even the hormonal model is dependent on mutagenic effects; it is just spontaneously occurring and not as a result of the oestrogen.

Chairman

1017. Dr. Boobis, would you like to ...? EC has the floor.

European Communities

1018. If you allow us to come in on this again, Alain Paris. [change of speaker.] Probably, the tumours that are detected, with regard to the administration of oestrogens, are revealed in a terminal stimulation process, and here we are combining initiation and promotion phenomena, knowing that promotion is extremely dependent on the oestrogen receptor. But this comes on top of the very premature initiation phenomenon which takes place via the activation, the bioactivation of the oestradiol molecule or its principal metabolites that will be found as residues, particularly oestradiol alpha.

Chairman

1019. Thank you. Dr. Boobis ... The United States have the floor.

United States

1020. I don't mean to interrupt Dr. Boobis, I was just going to note that I failed to discern a question in the statement that was just made and refer back to Canada's statement from earlier in the meeting regarding submission of evidence, and whether we are asking questions of the panel of experts that the Panel has comprised or whether the parties are providing evidence through their own experts at this point. Thank you.

Dr. Boobis

1021. I was going to make a somewhat similar comment. We are getting into the realms of interpretation of data. My view is that the data are interpretable as a non-mutagenic genotoxicity *in vivo,* if there is any response, with a threshold. Others have chosen to interpret the data differently. I was asked here for my opinion, my scientific opinion, based on the totality of the evidence. That is my opinion. So when we get into a discussion about the relevance of initiation and promotion in endocrine tumours, it critically depends upon the interpretation of the effects seen of these compounds. As I have just said, my view is that they do not support an *in vivo* initiation mechanism.

Chairman

1022. Thank you. Dr. Cogliano.

Dr. Cogliano

1023. Thank you. I think the comment that a lot of this is a question of interpretation, as Dr. Boobis has just said, is actually the heart of the scientific disagreement that we see here. I actually am not competent to tell whether there is or is not a threshold, but I can tell from my long experience in risk assessment that that is the fundamental scientific argument that is going on here. And so to be as helpful as I can to the Panel, the JECFA assessment felt that a threshold could be assumed even though there is some evidence of genotoxicity, because they felt that a hormonal mechanism was likely what was going on. Therefore they assumed there was a threshold and they computed the ADI and they went forward with an assessment. And it seems to me from reading the papers submitted by the European Commission as well as the arguments we have heard the last two days, they are unwilling to assume that there is a threshold. Sometimes I think the argument has been that because there may be some genotoxicity they are unwilling to assume a threshold, and sometimes I think they are unwilling to assume a threshold because there may be some other effects of these chemicals at low doses, but because they are unwilling to assume a threshold they say they cannot do a risk assessment because they cannot really predict a dose-response curve. Now I think those are the scientific arguments on both sides. I think that the way we phrase questions sometimes leads you to an answer of yes or an answer of no, but I think that is really the fundamental scientific issue that marks the difference between the JECFA assessment and the EC assessment; the willingness to conclude that there is a threshold for these compounds.

Ms Orozco

1024. Dr. Cogliano, I don't want to sound legalistic, but is that disagreement arbitrary? I am sorry, but we have to find ways to assess what has been done and sometimes there is a fair amount of information whereby professionals can disagree, scientists can disagree; other times the amount of information, the quality of the information, might not allow those variations. So what would be your assessment?

Dr. Cogliano

1025. I don't want you to put the word arbitrary in my mouth because I know that means something to lawyers and I don't fully understand what it means, but I would say it is a long-standing area of disagreement among scientists for many years about whether there are thresholds for carcinogens by different mechanisms. And the reason it is a controversy, I think, is the assumptions that scientists bring to risk assessment. There really are no data, we have heard that you cannot scientifically firmly establish that there is a threshold, but there are a lot of clues that a lot of scientists conclude that there is a threshold. But I think it really is an area of legitimate scientific disagreement that has gone on for many years. I don't wish to characterize that as arbitrary, I think it is more a matter of professional scientific judgement.

Ms Orozco

1026. … of course, legitimacy or reasonableness ...

Dr. Cogliano

1027. I don't think that there is a set of studies that can be done that will convince everybody one way or the other of a threshold or lack of a threshold.

Chairman

1028. I think this is also related to the so-called long-term latency period and cumulative effects arising from the cumulative exposure to the hormones at issue. I don't know whether or not the DNA repair mechanism is effective enough to deal with these kinds of long-term adverse effects. This is one thing I would like to hear from the experts. Dr. Boobis.

Dr. Boobis

1029. Well, of course experimentally when we are looking at the carcinogenic potential in animal models we dose the animals for what we call the lifetime, I mean it is not actually the full lifetime but it is a very substantial portion of a lifetime, two years in rats and 18 months in mice, and during that time any latency should be revealed. It takes into account accumulation of damage, DNA repair and any other components that might lead to a progression of effects, and indeed cancer is a multi-step process. It is well established now that you need several different overlapping stages before you get a malignant tumour and therefore these are encompassed within the scope of an experimental model. In the epidemiology studies one would have to look over a period of several decades to be able to account for such latency if the endpoint of concern was cancer.

Chairman

1030. What if DNA damage is done because of reasons we are not aware of due to the scientific uncertainty in the contemporary world and the adverse effects appear 30 or 40 years later; are current risk assessment techniques or mechanisms safe enough to deal with these kinds of problems? Dr. Boobis.

Dr. Boobis

1031. The paradigm we have, and there is some evidence to justify the case that this is a reasonable assumption, is that the effects observed scale to the lifetime of the organism, and so that is one of the reasons we use shorter-lived organisms in our toxicological testing. We use rats and mice which live for a couple of years; otherwise we would have to test for a lifetime in a longer-lived species which might be 40 or 50 years. So we are working on the principle that effects that are not evident within the lifetime of a rodent would not be evident, all other things being equal, within the lifetime of a human being. And there is actually very good evidence that that is the case. For a number of carcinogens that IARC have evaluated it takes approximately a quarter of a lifetime after an initial exposure for those tumours to become apparent, and that is true in rodents, it's true in dogs and it's true in humans. So I thing that the paradigm is reasonable that if there is going to be an effect manifest over a lifetime, it will be revealed in those experimental systems and therefore be predictive of lifetime effects in humans by and large.

Chairman

1032. Thank you. Dr. Boisseau and Dr. Guttenplan.

Dr. Boisseau

1033. Thank you, Mr. Chairman. I would like to go back to what Dr. Boobis has just said. If the protocol he has described permits us, where the experimental tests yield positive results, to predict an obvious effect on human beings after a reasonable period of time, why is it, if we are pleading for an absence of thresholds for this kind of oestrogen-related cancer, that the human epidemiological studies that have developed exponentially over the last twenty years have not been able to make any headway in highlighting this type of cancer?

Chairman

1034. Thank you. Dr. Guttenplan, please.

Dr. Guttenplan

1035. Actually, two points. You mention DNA repair in long-term tests. When DNA is damaged, DNA repair usually occurs relatively rapidly within hours and days. If the cell divides before repair occurs, you have a mutation. At least – I should not say that. If it divides and if the damage is of such a type that division does not produce an accurate reproduction of the original DNA molecule, then a mutation can result. Mutation is permanent, it cannot go away, and so once that has happened, there is some increased level of risk. But, as I mentioned before, most mutations are innocuous, most genes in which mutations occur are not going to result in, say, cancer or another adverse biological effect. So DNA repair takes care of most damage, but once the damage has occurred and has not been repaired before the cell divides it is permanent damage. As far as the threshold of oestrogens, and this I sort of throw out to the experts, if one assumes that there is a hormonal cause of cancer as a result of oestrogens as opposed to a genotoxic cause, the hormonal cause is assumed to result from pre-existing mutations, and then those pre-existing mutations, those cells containing the pre-existing mutations, are caused to turnover and divide because of the oestrogen stimulation. Unless there is a threshold for oestrogen stimulation, there should not be a threshold then for the hormonal effects of oestrogen, because the genotoxic effects, the effects of oestrogen, are indirectly genotoxic effects, they are promoting genotoxic effects. Now I don't know if there is a threshold for oestrogen receptors, I just throw that out as a piece of information.

Chairman

1036. Thank you. Dr. Boobis.

Dr. Boobis

1037. There is, and we have measured it. Endocrine-sensitive cells have a threshold for the mitogenic effects of oestradiol, it is absolutely clear, and we are not the only people, there have been many such studies to demonstrate that. I am talking about the mitogenic effects, I mean there are other effects that have been mentioned here and I am not qualified to discuss them in detail, but in terms of the mitogenic effect on, for example, the mammary gland, which is one of the targets we are considerably concerned about, there is a clear threshold for cell division. And that makes a lot of sense, you would not want circulating oestrogen to be stimulating cell division at whatever level it was, it has to be part of this homeostatic regulatory mechanism that allows the body to signal cell division when necessary by up-regulating the level of oestrogens.

Chairman

1038. Thank you. EC.

European Communities

1039. Chairman, we do appreciate the questions you have posed, they have been very appropriate in our view, and we have a number of scientists from our side – since we don't have other questions, we can make a statement in the form of a question, because they would like to intervene. These are important issues. There will be no new evidence, just comments on what has been said to clarify our debate.

Chairman

1040. Comments once again in the form of questions?

European Communities

1041. Yes. – Dr. Boobis, in the comments you have made, you refer to receptor-mediated events as thresholded and then be able to use them to create an acceptable daily intake. It is very clear that in the very low dose range oestrogen binds to oestrogen receptors, and then as the number of receptors are occupied, the receptors are inhibited as the dose of oestrogen goes up, until that response goes away, that is called the biphasic dose-response curve that has been known for 50 years. Then oestradiol begins to bind to androgen receptors, beginning to stimulate and inhibit an entirely different set of genes and an entirely different set of responses. If you begin your dose-response curve at a very high dose, what you will do is come to the bottom of a very bizarre set of events, that is the binding of oestrogen to androgen receptors. You will then use that as your NOAEL and calculate an ADI from it and completely miss the whole bottom part of the dose-response curve that is qualitatively different and completely unpredicted by what happens at the top part, and aside from the fact that you have an endogenous level of oestrogen that the oestrogen is operating against which argues against the threshold issue, could you explain how you can calculate an accurate ADI off of a hormone that operates through multiple mechanisms across a very wide dose-response curve that is never examined in a risk assessment study?

Chairman

1042. Dr. Boobis.

Dr. Boobis

1043. Mr. Chairman, do you wish me to answer this?

Chairman

1044. It's up to you.

Dr. Boobis

1045. I'll have a go. There are three components, one is the question of a threshold. I am sure Professor Vom Saal is familiar with the recent studies using transcriptomic experiments, looking at the totality of a gene expression profile in hormonally sensitive tissue, and there has been a clear threshold for every single gene transcript in those studies demonstrated. It is difficult therefore to understand how one can argue against a threshold. In our own studies using proteomic approaches, looking at the proteins that change within the cell, we have come to an identical conclusion. There are concentrations or doses of oestradiol-17β below which nothing changes – nothing. In answer to the second part of the question, how did we find a dose, a NOAEL where we could proceed to set an ADI. I said earlier it is based on a more holistic evaluation of the data. We are not concerned primarily with an intermediate response, we are concerned with adverse responses. What is the outcome for the organism, is there an adverse effect on reproduction, development, carcinogenicity? Based on such considerations on the totality of the available data we were content that we could identify a no-observable, and I stress this is by definition a no-observable adverse, and again I stress adverse, effect level. And this is the paradigm as adopted by all risk assessment bodies throughout the world. Thank you.

Chairman

1046. Thank you. Yes, EC.

European Communities

1047. Would I be able to ask a question back from that? The point here is that at the very very high end of the dose-response curve you are looking at adverse effects mediated through an entirely different system than the system that oestradiol operates through in a dose range a thousand times or so below the dose range that you are actually testing in your risk assessment, and I do agree that you are seeing adverse effects and that they will go away, the problem is that you then are not aware that there is a whole other set of adverse effects that can occur down below that, and I totally agree that there are different thresholds for turning on genes, and the endogenous level of oestradiol is high enough to exceed every single one of them. And that as you are adding extra oestradiol, you are altering the whole profile of genes that are expressed, and there was a PNAS paper by Toshi Shioda last year that showed that in exquisite detail.

Chairman

1048. Dr. Boobis.

Dr. Boobis

1049. The studies I mentioned were against the background of normal oestrogen levels. There were several papers published in the last three years showing that against that background there is no change from the control level in any transcript. As far as this ultra-low, U-shaped dose response curve is concerned, I would simply say that, as I mentioned earlier, this is one of those areas where there is considerable scientific controversy and I really don't think we can resolve it here; it is a major issue of controversial information. I could point to papers which show other results. Professor Vom Saal can point to many papers supporting his argument, quite correct. But as I say, currently, I think, it is fair to say within the scientific community it is an unresolved question.

Chairman

1050. Thank you. We have no confusion about that. Well, I don't know whether we have to continue this discussion on this particular point that this hour; we have 15 minutes to go before six o'clock. One question for EC.

European Communities

1051. Chairman, if you allow me, I will give the floor to one of our scientists who would like also to make one more point, this is Madam Annie Sasco, who is the expert on epidemiology.

European Communities

1052. OK. So I will be brief. I just want to make a point because it has been asked why did epidemiology fail to find any effect; and I am not sure epidemiology failed completely. Epidemiology, which is a study of the occurrence of disease and risk factors in populations, can be done at two levels. Levels of populations – and this was already discussed this morning when you looked at rates of disease potentially linked with hormonal factors in different countries. And this evidence is consistent with the hypothesis that these products may increase the risk of hormonal-dependent cancer, but there may be alternative explanations. And it's very complex, because cancer is a multi-factorial disease, so even beyond hormones there are also factors, other risk factors, which

intervene and play a role. It has long latency, we have to study for example diet 30 years ago to find the effect today, and therefore these population comparisons are just putting in some information that are not definitive. And the same can be said about time trends, and we have seen in most countries of the world we are still seeing increases in hormonal-dependent cancers, but the countries at the top of the scale are countries where these products have been used.

1053. The difficulty with these population statistics leads to the second type of epidemiological studies, where comparison is being done at the level of individuals; so we want to try to find out whether the people who have been exposed to these products are the ones getting cancer today. But when we look at an exposure like the one we are discussing, it is exceedingly difficult to do it, because all countries have been exposed, France as a whole country at the same time was exposed when this product was used, in the US almost everyone is exposed, so it's very difficult within a country to find differences and exposures between individuals, and I guess that is one of the reasons why it has not been attempted, because it will be a difficult exercise. But I think it could be attempted, at least in countries like the US, if we could identify population groups who only eat hormone-free meat and compare them with the ones eating hormone-treated meat. So I think we should not say that epidemiology will never be able to do it, it would be very difficult to do it, but maybe it could be attempted, and only now, because we needed to have 20 years, 30 years of exposure before we can see an impact. But I think for the whole topic, if we look at the effects on puberty, then in a way, from an epidemiology point of view it will be easier to see it, because we have to wait less years and maybe also because the difference is greater.

Chairman

1054. Thank you. Canada.

Canada

1055. Thank you, Mr. Chairman. I am very sorry to make this point so late in the day. Was that an argument, was that a statement, was that an expert testimony, was there a question in there somewhere for the experts? We are here at this point to hear from the experts, not from the EC delegation. We have heard enough, 19 volumes of evidence I understand, could you please clarify the role, even at this late hour, so that the time is not taken up by monologues.

Chairman

1056. I have no intention to further continue this discussion, so in the way of exchanging the views from the experts, the Panel has invited in experts in each delegation. So just leave this matter to the Panel with confidence and trust, and then I would like to give the floor to the US.

United States

1057. Thank you, Mr. Chairman. That was an interesting statement. I would note that the Panel expressly asked this question to the experts in question 26; it asked, which is relevant for this dispute, what the EC did in its purported risk assessment regarding epidemiological studies. And I think that Dr. Boisseau, Dr. Boobis, Dr. Coligano and Dr. Guttenplan all spoke to this issue. I won't put words in their mouths; if they would like to reiterate their answers to that question, they are welcome, but otherwise I would just note that this question has been asked and answered in the written responses.

Chairman

1058. So if delegations have no further questions or comments to be put to the experts, I have the intention of giving the floor to each and every expert to make concluding remarks if they so wish before we conclude our meeting this afternoon. The floor is yours, distinguished experts. Dr. Boobis.

Dr. Boobis

1059. Thank you Mr. Chairman. I have no specific comments. I hope that I have answered the questions put to me as clearly and succinctly as possible. I do believe that the information I provided in my written responses amplifies a number of those questions and hopefully will be a source of information as well to the Panel in their deliberations next week, and I thank you for your consideration and attention.

Chairman

1060. Thank you. Dr. Guttenplan first.

Dr. Guttenplan

1061. Although I have mentioned genotoxic effects of oestrogens, I would like to point out that in an adult woman, typical levels of oestrogen are 180 to 2,000 picomols per litre, and this is going to occur over their lifetime with the exception of menopausal state and pre-pubescence state. They are only about 2 in girls. So the potential genotoxic damage that is done in an adult would overwhelm that that could be done in a child. However, in boys the levels are even lower, and there I think we have to worry about developmental effects, and there has been less said on that – Dr. Sippell has been the major proponent of that – and I still think that these could be investigated epidemiologically or in some type of study. We might, as Dr. Boobis suggested, need a surrogate, perhaps saliva or urine, but I think it is perhaps the most important issue to address is the sensitivity of children. I should also mention hormone-sensitive cancers in post-menopausal women, it could be another concern. Post-menopausal women have levels of oestrogen that are similar to those of pre-pubescent girls, and if those levels are significantly elevated and you have a hormonal-sensitive cancer, you might be increasing the risk.

Chairman

1062. Thank you. Dr. Sippell.

Dr. Sippell

1063. I just would like to add that after these two days and hearing all the other experts' further comments to their written answers, I think that as much as children are concerned, we know really by no means enough and the data are really insufficient to tell or to be confident that this additional exposure from hormone-treated meat poses no risk. I am very much concerned.

Chairman

1064. Thank you. Dr. Boisseau.

Dr. Boisseau

1065. Thank you, Mr. Chairman. Over these past two days, I have done my best to provide as many clarifications as possible, responding to questions on the methodology used in the different expert

groups, in particular the JECFA which I know well. I insisted on the fact that the evaluation is a collective evaluation, conducted by competent and independent experts. This method, even if it has not been formalized or officially adopted, was known to everyone, and used practically throughout the world in the same way for all of the substances that were evaluated. I think that the hormones of which we have spoken were given special attention, and the data used were sufficient to enable us to come up with a risk assessment. Having said this, an assessment can always be updated to take account of scientific progress. Thank you Mr. Chairman.

Chairman

1066. Thank you. Dr. Coligano.

Dr. Coligano

1067. Thank you very much. I found these last two days extremely interesting and stimulating. I think that there are times I'm glad that I am in science and not in law, but I am sure that the rest of you are probably glad that you are in law and not in science. And I think what we are seeing here is the messiness of science as the data begin to accumulate but are not really sufficiently definitive to convince the entire scientific community, the way they are perhaps for something like tobacco smoking. And actually I think that the last comment that the leader of the US delegation made about question 26; our responses are emblematic of where these are. Question 26 was what are the differences between breast cancer and prostate cancer between the US and Europe; are they due to this factor? My own response was that it's one plausible cause but that there are many factors for breast cancer and the epidemiological studies cannot at this point sort out the difference between other dietary factors, physical activity, ethnic differences between the different countries, to be able to attribute causality to any particular cause with any reasonable confidence. So we are at this stage where we have suggestions but we cannot really resolve them, and I think that is what you see the scientists trying to struggle with. And when science is in this phase you will find scientists on both sides of issues, as we just heard about ten minutes ago. The idea of low dose effects of this is one of the major scientific controversies, and you do see scientists point to many studies on both sides of the issue, and it's not like going to be resolved any time soon. But I hope you have gotten a sense of the range of scientific thought, I think you actually can see that among the experts in the written answers and in these discussions. And I hope we have been helpful and I wish you luck in going on to making a decision on this important issue.

Chairman

1068. Thank you. Dr. De Brabander.

Dr. De Brabander

1069. A small final remark, Mr. Chairman. There is a lot said about risk assessment and I realize that indeed I was unable to help you very much on that item because I am an analytical chemist and control chemist, but as I expressed in my answers, I think there is more than human health only, and then the following of good veterinary practice only, there is also the influence of hormones on the behaviour of animals and animal welfare, there is also a concern about the environment. And I think in the future, concern with the environment will be more and more important, wherever it is in the world, and these are items I want to state in my final statement. Thank you.

Chairman

1070. Thank you all very much for your contribution and active engagement in the discussion on the issues at hand. I am particularly grateful for your patience, sitting with us for two full consecutive

days, even without having one minute coffee break. It was really difficult for us physically also. I myself, and I think the same is true of my colleagues in the Panel, we have learned a lot from our two-day meeting, even though I must confess that I did not fully digest your comments and replies on the technical issues; but I was very much impressed by the depth of the expertise and breadth of the knowledge you have brought to the area of your expertise, and I think it will greatly contribute to the Panel's work in the future. In the opening statement yesterday afternoon I stated that the Secretariat will provide a summary of the information and a transcript of the meeting for today and tomorrow. The Secretariat will do their best to make a transcript of the two-days meeting, but given the complexity of the issues and the difficulty to digest the terminology used during the meetings, they cannot be quite sure about whether they can make a complete transcript of the meeting. So at this point of time, the only thing I can say to you is that they will do their best to prepare that, but not with a 100 per cent guarantee. I don't know whether my colleagues in the Panel have additional comments before we conclude our meeting. Then I will conclude this two-day expert meeting now and the Panel will be meeting with the parties next week, starting on Monday, 2 October at 10 am. The meeting will be held in the same room as today. The meeting of the Panel with the experts is concluded. Thank you very much for all your contributions. Any point? Canada.

Canada

1071. Thank you, Mr. Chairman. Just a very simple question. Would the parties be provided with the transcript when it is provided?

Chairman

1072. I have been advised by the Secretariat that if the transcript is prepared, then it will be sent to the parties and experts for their comments.

Attachment 1

Slides shown by Dr. Sippell

WTO Panel on Hormones

Geneva, 27th & 28th September 2006

Paediatric Aspects

Wolfgang G. Sippell, MD, PhD

Professor of Paediatrics

Head, Division of Paediatric Endocrinology & Diabetology

Dept. of Paediatrics, Christian-Albrechts-Universität zu Kiel

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WTO Panel on Hormones
Geneva, 27th & 28th September 2006

- Although this dispute has already been going on for more than a decade, to my knowledge no paediatrician, let alone a paediatric endocrinologist, has been involved as a member on one of the expert committees.
- This is incomprehensible and paradoxical in view of the fact that prepubertal children are indisputably the most sensitive and vulnerable members of the population (smallest body size, longest life expectancy).
- I see my mission here as advocate of and spokesperson for children and their specific needs:

Children are not just small adults, but something very special!
They are our future!

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Factors supporting the validity of the supersensitive RCBA for Estradiol (E_2) developed at the N.I.H., U.S.A. (Klein et al. 1994)

The novel finding of significantly higher (~8x) E_2 levels in prepubertal girls than in boys readily explains fundamental features of human biology for the first time:
(1)

- Earlier onset of puberty in girls than in boys (mean 1 year)
- Faster bone maturation in girls than in boys
- Lower adult height in women than in men (mean 13 cm)

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Factors supporting the validity of the supersensitive RCBA for Estradiol (E_2) developed at the N.I.H., U.S.A. (Klein et al. 1994)

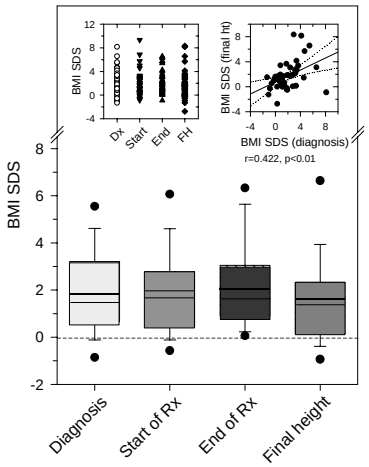
The novel finding of significantly higher (~8x) E_2 levels in prepubertal girls than in boys readily explains fundamental features of human biology for the first time:
(2)

- Higher weight for height/BMI in girls than in boys at start of normal puberty

WTO Panel on Hormones
Geneva, 27th & 28th September 2006

Chronic estrogen excess increases BMI in children

CPP Girls during/after GnRHa Treatment:
Weight Development (BMI – SDS) until Final Height



(N = 52)

Heger/Partsch/Sippell, JCEM 1999

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The novel finding of significantly higher (~8x) E_2 levels in prepubertal girls than in boys readily explains fundamental features of human biology for the first time:
(2)

- Higher weight for height/BMI in girls than in boys at start of normal puberty
- Incidence of Central Precocious Puberty (CPP) about 10x higher in girls than in boys
- Incidence of Constitutional Delay of Puberty much more common in boys than in girls

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Ethical considerations

- For ethical reasons studies to investigate whether eating hormone-treated beef elevates estrogen levels in (prepubertal) children cannot be performed (physical/ psychological injury in healthy children).
- Epidemiological studies comparing adverse effects in matched populations of (healthy) children eating beef from hormone-treated and untreated animals would also be unethical.

→ **"Protect children from unnecessary clinical trials!"**

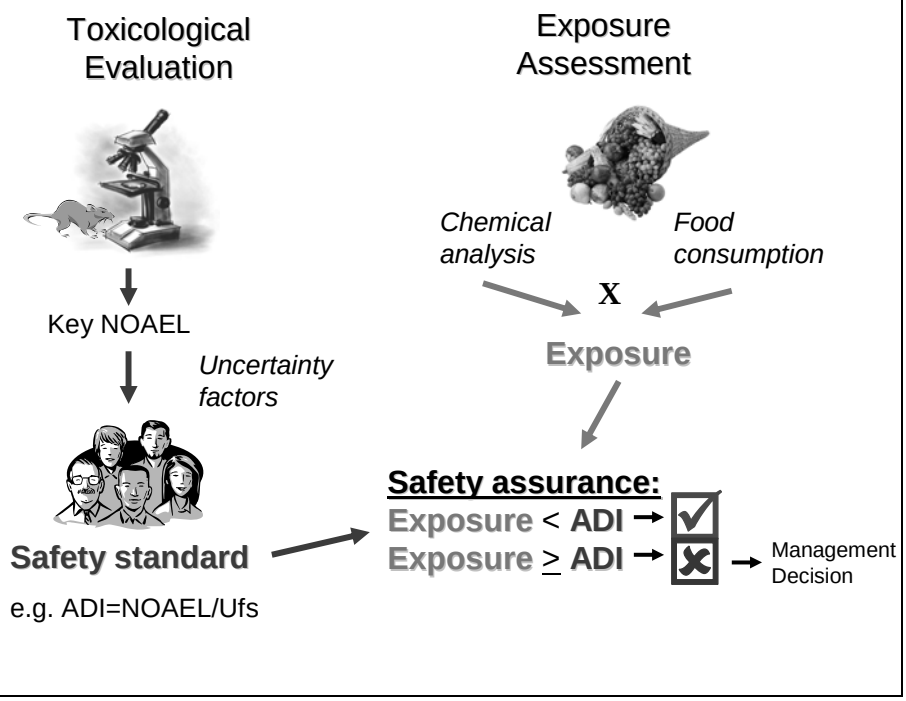
- Declaration of Helsinki
- Good Clinical Practice Guidelines
- EU Parliament Ruling ("Better Medicines for Children")

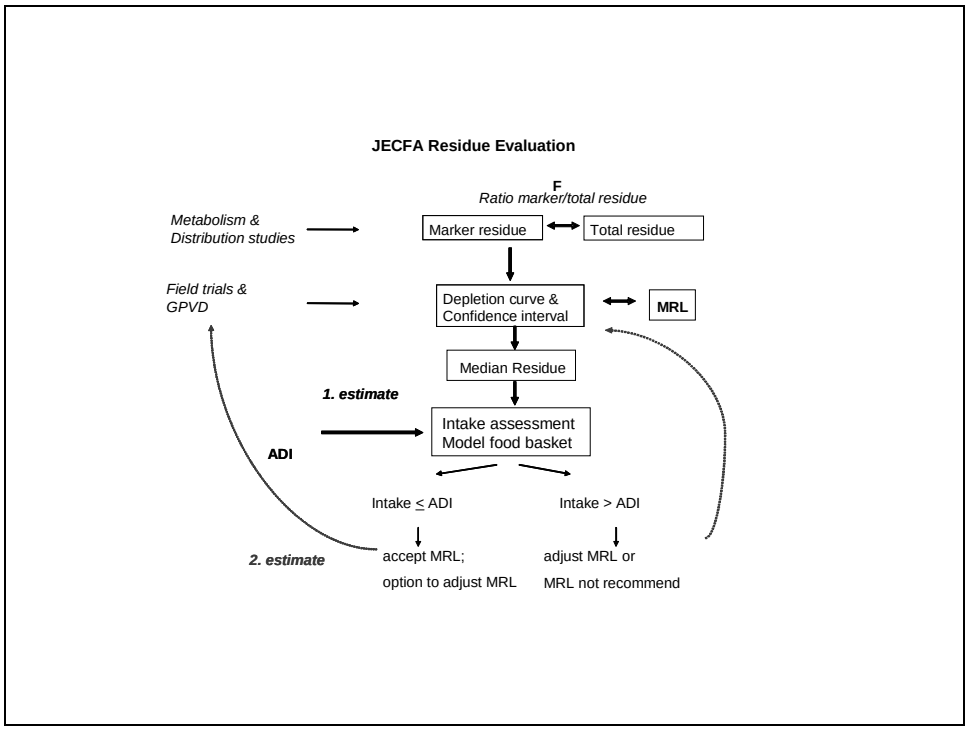
Attachment 2

Slides shown by Dr. Tritscher

International Food Safety Standards

- International food safety standards (Codex standards) are developed following the risk analysis paradigm
- They are based on independent international scientific risk assessments
- Codex Standards are an integral legal part in international food trade (WTO-SPS agreement)




JECFA Residue Evaluation
F
Ratio marker/total residue
Metabolism &
Distribution studies
Marker residue
Total residue
Field trials &
GPVD
Depletion curve &
Confidence interval
MRL
Median Residue
1. estimate
Intake assessment
Model food basket
ADI
Intake ≤ ADI
Intake > ADI
2. estimate
accept MRL;
option to adjust MRL
adjust MRL or
MRL not recommend