codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 9 **CX/RVDF 01/9-Add. 1**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Thirteenth Session
Charleston, South Carolina, USA, 4-7 December 2001

COMMENTS ON THE DISCUSSION PAPER ON RISK ANALYSIS PRINCIPLES AND METHODOLOGIES IN THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

UNITED STATES

1. The United States would like to commend the French delegation for drafting and revising the Discussion Paper.

2. Regarding paragraph 7, neither the Codex Alimentarius Commission nor the Joint FAO/WHO Expert Committee on Food Additives (JECFA) use a risk/benefit analysis as part of their procedures. Both consider the risk to public health but neither evaluate and determine the benefit of a drug's or its metabolites' benefit to the food animal or the public. See also paragraph 53.

3. Regarding paragraph 16, the toxic effects noted in the laboratory animals are assumed to be representative of toxic effects likely to occur in humans. A comparison of the metabolic profiles in laboratory animals and the target food animal does not demonstrate the toxic effects in people. The comparative metabolism data contrasts differences in metabolic profiles between the laboratory animal and food animal species.

4. Regarding paragraph 22, no relative value is assigned to the parent drug or metabolite attributing toxicological cause. However, in the absence of other information, parent drug is considered to present the greatest toxicological burden. The parent drug is expected to metabolize through predictable pathways each time the drug is administered. Therefore, studying each metabolite individually usually adds no knowledge to a human food safety decision over studying the administration of the parent drug. This comment also pertains to paragraph 17 in Annex 1 where the same point is repeated.

5. Regarding paragraph 24, it is more appropriate to indicate that in dose-response assessments, JECFA estimates the dose that has no adverse health effect on humans rather than a dose that is risk-free (independent of mathematical extrapolation to determine a "virtually safe" dose as indicated).

6. Regarding paragraph 37, the bulleted reasons provided are not always applicable and as such should not be used in recommending MRLs. For example, many drugs are in common use and could be present in a majority of foods derived from treated animals. Further, some animals such as veal calves and roaster pigs are slaughtered at young ages, sometimes not long after they would be expected to be treated with veterinary medicinal products. This comment also pertains to paragraph 37 in Annex 1.

7. Regarding paragraph 44, some clarification is suggested. The second indent should indicate that JECFA has harmonized MRLs of a specific veterinary medicine for tissues of different animal species (e.g. muscle, tissue of cattle, pigs or sheep) for 31 veterinary medicines rather than providing identical MRLs for 31 veterinary medicines for all animal species.

8. Regarding paragraph 54, we concur on developing guidelines to assist the JECFA and facilitate coherence in their evaluations. The November 2001 FAO/WHO planning meeting will be a start to this effort.

9. Regarding paragraph 55, we concur that the CCRDVF should develop guidance for its risk management responsibilities.

10. Regarding paragraph 60, we concur that this information from the JECFA meetings would be helpful for CCRVDF risk management deliberations.

11. Regarding paragraph 65, we concur that this is an important need that the CCRVDF should address as soon as possible.

12. Regarding Annex 1, the FAO and WHO have initiated a formal review of their food safety evaluation procedures. It would seem appropriate to put any recommendations into abeyance until such time as the completed effort puts forth its new procedures for the appropriate expert bodies. Alternatively, the CCRVDF should determine the appropriate mechanism for communicating its comments to the JECFA.

CONSUMERS INTERNATIONAL

13. Consumers International commends France for this superb paper. We believe that the document will significantly advance the quality, consistency, scientific integrity, and transparency of decision-making in CCRVDF and JECFA. It provides a clear explanation of how risk analysis should work for veterinary drugs in Codex, how it actually does work, what the weaknesses are with the current approach, and how it should be improved. We applaud the progress towards developing a risk assessment policy as outlined in Annex I. It is a very impressive first step in the dialogue that will need to take place within CCRVDF and between CCRVDF and JECFA. In our view it should be a model for other committees to follow as they elaborate the use of risk analysis principles and methodologies in their respective committees. Overall we support the recommendations to CCRVDF given in Annex II. We recommend that the entire document be sent to CCPR and CCFAC once it is finalized or at another appropriate point in the process.

Discussion Paper

14. In paragraph 21, there is a typo in the last sentence in the word “example”

15. In paragraph 26, the word “genetic” should be deleted twice in the first sentence of the second main bullet point in paragraph 26, so that the sentence reads “The second factor is designed to take account of the variability of the consumers susceptible to eat these drug residues, which is much wider than the variability of the laboratory animals used in the toxicological study.” This would be in alignment with paragraph 23 of Annex I, which correctly describes the intraspecies variability factor as intended to take into account genetic variability, age, sex, health status, and other differences amongst consumers. Genetic variability is not the only type of variability which this factor addresses.

16. In paragraph 31, it is stated that if it is not possible to determine a “no observed effect level”, or NOEL, (also sometimes called a “no observed adverse effect level”, or NOAEL) then it is not possible to establish an ADI. However, Consumers International notes that in some countries and contexts, a “lowest observed effect level”, or LOEL (sometimes called a “lowest observed adverse effect level”, or LOAEL) is used to derive the ADI, with an additional factor of 10 to account for the possible difference between the LOEL and the NOEL.

17. On Hazard Characterization, the standard 100-fold safety factor approach and the basis for it is explained but there is not much critical evaluation of this approach provided, except in paragraphs 31 and 32, which

note that it may not be possible to determine a NOEL in all cases, and that using a standard safety factor does not consider the slope of the dose-response curve. And, paragraph 24 does suggest that JECFA address the issue of using mathematical models to determine a "virtually safe" dose. We support this suggestion, since such an approach generally makes better use of the available data. We also agree that the determination of the appropriate level of risk (e.g., 1 in 1 million) would be one for risk managers (CCRVDF) to make.

18. However, we think the document should also acknowledge that a number of experts are questioning whether a factor of 10 is not sufficient to account for intra-species variability. This conclusion is supported by at least two lines of evidence. First, there are identifiable sub-populations of many types (the very young, the very old, pregnant women, those with illnesses, those with unique metabolic conditions, etc.) who can in some cases be shown to be more than 10-fold more sensitive than the average healthy adult, just based on empirical human data on responses to side effects of (human) drugs, etc. Second, as Dr. Fred vom Saal has pointed out based on his experiments with bisphenol-A in mice, sensitivity to (estrogenic) effects of bisphenol A varies by more than 1000-X among different strains of mice used in tests trying to establish experimental models for the effects. In one species (mice) over 1000-X differences have been observed in a single response (one effect of one chemical). This issue should also be addressed in section 2.2.4 of Annex I.

19. In paragraph 37, bullet one, it is stated that, "by definition," veterinary medicinal products are intended to cure ill animals and thus only some animals require a veterinary therapy. However, the definition of veterinary drug is given in the Codex Alimentarius Commission Procedural Manual (11th edition) as "any substance applied or administered to any food producing animal ... whether used for therapeutic, prophylactic, or diagnostic purposes or for modification of physiological functions or behavior." Thus, veterinary drugs may be used for therapeutic as well as non-therapeutic purposes. When considering drugs that have non-therapeutic purposes as well as those used for therapeutic purposes, it would not uncommon for a large group of animals to be given drugs, or even several drugs at one time. The bullet should therefore be modified to read, "veterinary medicinal products are often used for the purpose of curing ill animals and thus only some animals require a veterinary therapy." This same comment applies to the first bullet of paragraph 36 in Annex I.

20. We agree, as stated in paragraph 45, that CCRVDF should assume greater responsibility in its role as risk manager, for example, when considering JECFA-proposed MRLs that have been based in part on choices made by JECFA.

21. In paragraph 49 there is a typo in the first sentence in the word "first". It also states that the first three components of risk evaluation, the first stage of risk management, corresponds to work currently done by CCRVDF with the help of member states during the first step of the Codex MRL establishment. The first three components include identification of a food safety problem, establishment of a risk profile, and ranking of the hazard for risk assessment and management priority. While it could be considered that a food safety problem is identified and prioritization of the hazard for risk assessment does occur at that stage, Consumers International does not agree that a risk profile is established in the work currently done by CCRVDF during the first step of establishing a Codex MRL. By way of illustration, the Codex Committee on Food Hygiene (CCFH) is discussing a risk profile on antimicrobial resistant bacteria in food (CX/FH 01/12) at its thirty-fourth session in October 2001. This 11-page document includes a description of the situation, the values expected to be placed at risk, potential consequences, consumer perceptions and perspectives on the risks, distribution of benefits and risks, risk management options, recommendations, and includes a list of references.

22. We do agree, however, that it would be useful to review the criteria for establishing priority substances. We note that CCPR has recently revised the criteria it uses to establish priorities for compounds to be evaluated by JMPR, which better integrate public health considerations into the prioritization process. For example, new safer versions of agricultural chemicals may be given higher priority, as would compounds where hazard or exposure information indicate a possible concern to health. We believe that it would be useful for CCRVDF to review the procedures now used in CCPR with an eye towards harmonization. Such a review is important so that priority setting does not rely too heavily on the commercial/economic priorities of manufacturers rather than on health considerations. Such a review might go beyond Recommendation no. 2 in Annex 2 by explicitly integrating public health considerations into the criteria.

23. In paragraph 51, it is suggested that a discussion be started between CCRVDF and FAO and WHO to consider ways to improve the conduct and management of JECFA meetings by FAO and WHO. Consumers International fully supports this suggestion. We understand that some meetings have already planned that might address this suggestion.

24. In paragraphs 55 and 56, it is stated that CCRVDF seldom considers various possible management options. In the view of Consumers International, CCRVDF needs to consider an array of possible management options, and may need to direct JECFA in this regard, as JECFA currently suggests only one MRL for each substance and each food.

25. Paragraph 60 suggests that it would be useful if JECFA could better inform CCRVDF by clearly indicating in the assessment reports of each substance the choices made during the risk assessment process that relate to risk management, and the scientific uncertainties and the degree of confidence in the data provided and how they were taken into account in risk assessment. We fully support this suggestion. Furthermore, we suggest that consideration be given to JECFA providing a qualitative description (e.g., low, medium, high) of the confidence it has in the critical study used to determine the ADI, the database generally, and the ADI, along with a short explanation for the ratings chosen. For example, the confidence in the database might be given a "low" rating if there were significant data gaps, (e.g., lack of an adequate reproduction study), or inadequate sensitive endpoints studied in existing studies. The confidence in the critical study and the database generally would lead to the confidence in the resulting ADI. A high confidence in the ADI would indicate a high probability that the ADI would not change should additional data become available.

26. We fully agree with paragraph 61 that improvement is needed in the timeliness of JECFA reports.

27. We fully agree with the suggestion in paragraph 62 for improving the role of CCRVDF in communication on risk management.

28. In paragraph 63, it is stated that the priority of the Committee is to limit as far as possible the presence of drug residues in foods of animal origin so that the resulting risk to public health can be considered as negligible. This is essentially an "ALARA", or "as low as reasonably achievable" approach. Consumers International supports an approach that seeks to minimize exposures of consumers in order to protect public health. We also recognize that the separation of risk assessment and risk management responsibilities between JECFA and CCRVDF needs to be more clearly delineated.

29. As concluded in paragraph 65, Consumers International agrees that it is essential that CCRVDF rapidly increase its involvement in risk management. And, perhaps most importantly, we agree that CCRVDF needs to establish a risk assessment policy.

Annex I

30. Consumers International welcomes the information requested from JECFA regarding acute toxic effects, including a strategy to assess the safety of residues of substances likely to cause acute toxicity (paragraph 16) and the need for acute NOELs and acute RfDs (paragraph 34).

31. In paragraph 26, to address some of the new science regarding the adequacy of safety/uncertainty factors as described above in our comment concerning the Hazard Characterization section of the main body of the document, we recommend that a second bullet be added which states that "the adequacy of the factors applied to the NOEL to address inter species (animal to human) and intraspecies (among humans) variability"

32. In paragraph 67, the term "limited" should be deleted in bullet 5 since this is a value judgment.

Annex II

33. As noted above, we generally agree with the recommendations to CCRVDF in Annex II, but have the following comments:

34. While we support Recommendation 2 for an alternative option for inclusion of substances in the priority list, we believe that the criteria recently revised by CCPR should be reviewed to see if more specific criteria can be developed to better integrate public health concerns into the priority setting process.

35. We strongly agree with recommendation no. 3, that JECFA reports be made available 2 months prior to the CCRVDF meetings. It is essential for risk managers to have the risk assessment prior to making decisions.

36. We support recommendation no. 4, that CCRVDF, in light of the work carried out by CCGP, give further thought on other types of information which might be considered by risk managers. This should be considered both for the international level as well as for the national level. This is relevant to the Statements of Principle Concerning the Role of Science in the Codex Decision-Making Process and the Extent to which Other Factors are taken into Account.

EUROPEAN COMMUNITY

37. The paper on risk analysis and scientific methodology to be developed and implemented in the work of CCRVDF can serve as an excellent basis for future discussions in the Committee and interaction with JECFA. It has, however, to be underlined that the basis of the work undertaken to establish maximum residue limits is the intended use of the substance in veterinary medicine/as feed additive and the documentation requirements. Unless the scientific requirements are fixed and a consistent evaluation method is applied in the risk analysis, any risk management procedures will become arbitrary and variable, which should be avoided as far as possible. As JECFA is a separate and independent Committee, the possibilities for CCRVDF to request or impose any risk assessment methodologies have to be further clarified.

38. The European Community has since a number of years a developed science based risk assessment methodology for evaluation of dossiers for establishment of maximum residue limits and supports the basic principles of risk analysis. Furthermore, the detailed documentation requirements including advice to applicants/sponsors have recently been updated (EUDRALEX Rules Governing Medicinal Products in the European Union Volume 8) and guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin has been put in place.

Discussion Paper

39. Paragraphs 25 – 30. The procedure for determining a toxicological ADI is described but the procedure to establish a microbiological ADI should also be outlined.

40. Paragraph 31. It is stated that maximum residue limits can be set for a substance even if it is not possible to establish an ADI. This is in principle not accepted in the European Union. Only for those substances for which it is not necessary to establish quantitative maximum residue limits, i.e. for substances included in Annex II of Council Regulation No 2377/90, this may be acceptable under certain circumstances.

41. Paragraph 39. The standardised daily food intake is discussed and figures for the intakes given. In the European Union these figures apply to mammals. For poultry the figure for fat is 90 g and for kidney 10 g. As regards fish the estimated intake is 300g muscle and skin in natural proportions.

Annex I

42. Paragraph 4. JECFA is requested to take into consideration the procedure followed by JMPR in the establishment of maximum residue limits for pesticides. This should preferably be a reciprocal communication. For substances used both as veterinary drugs and as pesticides, the aim should be a mutual harmonisation of the risk evaluation performed by these expert groups.

43. Paragraph 8. The radio-labeled studies should not be required to be performed in all tissues, but in those tissues which are deemed to be the target tissues. The definition of muscle tissue should be harmonised between CCRVDF and CCPR (muscle vs. meat).

44. Paragraph 9 - 1st bullet point. The feasibility of providing general guidance on how to deal with metabolites will be difficult if not impossible, as this will be highly substance dependent, and such data are only important for the choice of marker residue, in cases where the substance is a prodrug or the metabolites have pharmacological activity. It is suggested to modify this point along those lines.

45. Paragraph 9 - 2nd bullet point. Such guidance has been put in place in the European Community (Note for Guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin adopted by the Committee for Veterinary Medicinal Products under the European Agency for Evaluation of Medicinal Products EMEA/CVMP/187/00-FINAL). In most cases, extrapolation cannot be performed without a minimum set of data.

46. Paragraph 15. Good Laboratory Practice does not assure that the protocols are suitable with respect to endpoints and exposure. It only assures that the trials are carried out to certain standards and which are possible to control retrospectively.

47. Paragraph 16. In the framework of VICH (Veterinary International Conference on Harmonisation), the requirements for assessing the safety of veterinary medicinal products are progressing and it would seem important to take the development of VICH guidelines into consideration. The 3rd bullet point. Immunotoxicity studies are required by European legislation for applications for establishment of MRLs. The second bullet point is not in line with any risk analysis approach, as lack of certain data can only be justified on a case by case basis. The 5th bullet point should also address pharmacological effects.

48. Paragraph 26. A third bullet point may be introduced referring to ADIs already established by e.g. CCPR or by regional bodies with relevant legislation in place.

49. Paragraph 37 should be modified as follows: Assess the potential overestimate (rest of paragraph unmodified). Replace infants by relevant sensitive groups of the population.

50. Paragraph 54. The criterion should not be that the method is easily implemented, but that it is suitable for the purpose of residue control.

51. Paragraph 58. It should be pointed out that the establishment of MRLs should also consider the necessity to account for future new species, new tissues and other uses for the substance (such as in plant protection).

52. Paragraph 60. The food commodity honey should be included.

53. Paragraph 67. Last bullet point. This point should be deleted, as this is an impossible task. The eating habits world-wide differ too much to make such distinctions.

54. Paragraph 71. The issue of the withdrawal period can not be explicitly linked to the analytical method for control. It is in the vast majority of cases possible to improve the sensitivity of the analytical control methods. A set of criteria for proposals not to specify numerical MRLs have to be developed and agreed by CCRVDF.