CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 8 **CX/RVDF 10/19/8**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOOD

Nineteenth Session

Burlington, Vermont, United States of America 30 August - 3 September 2010

FACTORS TAKEN INTO ACCOUNT IN CONNECTION WITH ESTABLISHING THE ADI AND THE CURRENT PROCESS OF RECOMMENDING MRLs.

(Discussion paper drafted by France, with the assistance of Australia, Brazil, Canada, European Union, Sweden, Switzerland, United States of America, IFAH)

Governments and international organizations wishing to submit comments on this document are invited to do so **no later than 31 July 2010** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA (Telefax: +1 202 720 3157 ; or ***preferably*** E-mail: CRVDF-USSEC@fsis.usda.gov),with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org, ***preferably***).

Format for submitting comments: In order to facilitate the compilation of comments and prepare more useful comments' document, Members and Observers, which are not yet doing so, are requested to provide their comments under the following headings: (i) General comments; and (ii) Specific comments. Specific comments should include a reference to the relevant section and/or paragraph of the document that the comments refer to. In order to facilitate the work of the Secretariats to compile comments, Members and Observers are requested to refrain from using colour font/shading as documents are printed in black and white and from using track change mode, which might be lost when comments are copied / pasted into a consolidated document. In order to reduce the translation work and save paper, Members and Observers are requested not to reproduce the complete document but only those parts of the texts for which any change and/or amendments is proposed.

Background:

1. At its last (18th) session (Natal, Brazil – 11-15 May 2009), the Committee considered several issues relevant for setting MRLs (Use of the Estimated Daily Intake (EDI); Utilization of full ADI; Use of Regional Consumption Factors; Additional comments of the United States of America in CX/RVDF 09/18/9 Add. 1 – pp. 5-6) and "*endorsed the recommendation that the CCRVDF review all the factors taken into account in connection with establishing the ADI and the current process of recommending MRLs. It agreed to establish electronic working groups, led by France, open to all interested members and observers and working in English only*". The working group would collect comments from Members and Observers and prepare a discussion paper for further discussion at its 19th Session.

2. The Committee also agreed to establish a physical working group, which would meet immediately before its next session, under the chairmanship of France, to consider the report of the electronic working group and comments submitted in order to facilitate the discussion in the Plenary. (ALINORM 09/32/31 – para. 149)

3. Other topics considered during the last (18th) session as the improving communication between JECFA and the Committee on general subjects (ALINORM 09/32/31 – para. 144), Starter cultures, Appending risk management recommendations to MRLs, Old drug policy, Threshold of toxicological concern, Residues at injection sites and harmonization of withdrawal periods' calculation (ALINORM 09/32/31 – para. 152 to 157) were not reviewed by the electronic working group. Therefore, only topics that fall within the terms of reference of the electronic working group have been given serious consideration in this discussion paper.

4. It was noted that active and constructive participation of interested members and observers was critical for the consideration of this topic." (ALINORM 09/32/31 – para. 148)

5. The French delegation is grateful to acknowledge the inputs received from Australia, Brazil, Canada, European Union, Sweden, Switzerland, United States of America, International Federation of animal health (IFAH), as they all have been of great importance for putting together this discussion paper.

6. The electronic working group also considered of the JECFA on-going work on "*A Risk-Based Decision Tree Approach for the Safety Evaluation of Residues of Veterinary Drugs*", still at the drafting stage.

7. The electronic working group also noted the recommendation by the 18th session of the CCRVDF to request FAO/WHO to convene an Expert consultation on dietary exposure assessment as it relates to veterinary drug residues in food, subject to the availability of adequate funding (ALINORM 09/32/31 – para. 150).

Items identified for consideration:

8. Discussions have been ongoing for years on possible changes in the elaboration of MRLVD. In relation to previous Codex recommendations for the harmonisation with the approach for setting MRLs for pesticides residues and the objectives of the Update project launched by FAO and WHO in 2002, need of harmonization emerged a couple of years ago in relation to the establishment of MRLs for dual use substances. To what extent (dual substances or all substances) the assessment approaches between JECFA and JMPR should be harmonized, the goals of such a harmonization and the possible impacts should be discussed.

9. The 18th session of the Committee agreed on the topics to consider (ALINORM 09/32/31 – para. 148). The electronic working group considered the use of regional food consumption data, the EDI approach, the "one meat plus egg plus milk" approach, the utilisation of the full ADI, the decision tree paper prepared by JECFA when relevant, the interpretation of the MRL definition and all the issues arising from these topics.

10. The topics considered by the electronic working group are discussed separately; however, before taking any decision on the methodology, the Committee should gain a clear understanding of what they entail for food safety: it will be important to discuss the combined effect of proposed changes and not to consider each only in isolation, as they directly impact the level of protection of consumer's health afforded by the Codex process of establishing MRLs. There may be a need to take into account that some of the concepts are not compatible with one another.

A- Estimated Daily Intake (EDI) approach

11. During its last session, the CCRVDF agreed with the assessment of the in-session working group that the EDI approach was an improvement relative to the current evaluation of the risk from chronic exposure only and could be successfully used if adequate data packages were made available; however the EDI approach did not cover the risk arising from acute and sub-acute exposure.

12. The JECFA acknowledged that the use of the EDI was currently applicable only to the evaluation of chronic toxicity of, and chronic exposure to, residues as reflected by the ADI. The JECFA indicated that it would use the older TMDI approach when the data did not allow for the use of the EDI approach and that the EDI should not be applied when there was concern for acute toxicity or acute exposure.

13. A member pointed out that the process of establishing MRLs is very sensitive to variability and extreme values in the data, which in turn are to a considerable degree dependent on the design and quality of the residue study performed and therefore argued that the applicability of the EDI approach even for chronic effects would need to be restricted to cases of adequate design and quality of the residue studies and alternative approaches need to be investigated to overcome this issue.

14. Another member noted that while the EDI approach does not currently directly address risks from acute exposures, neither does the more traditional TMDI approach: Both approaches used food consumption values based on chronic consumption only. Another pointed out that the use of the TMDI provided additional protection for the consumer as it was designed to ensure that residue intake would always remain below the ADI on any given day.

15. The Committee also supported further work by JECFA on acute and sub-acute exposure assessment, as part of the on-going development of the "decision-tree" paper.

16. To date, JECFA has not circulated any new version of its draft. However, in order to take on board the EDI approach and move forward the current discussion, the Committee may settle for a provisional conclusion viz. the EDI approach, once finalized by JECFA, may generally lead to higher MRLVDs.

Recommendation:

17. The current draft decision tree does not address the issue of the EDI; therefore, the Committee may wish to defer discussions until after the final JECFA document becomes available. In order to address this specific issue, the Committee may wish to request JECFA to:

- Consider and recommend approaches regarding acute risk and acute exposure;
- Clearly define the criteria that need to be met in order to allow the use of the EDI (i.e. experimental design, quality of data, statistical methodology used to produce the median values …).

B- Utilization of the full ADI:

18. A member pointed out an important part of this issue rests with how a portion of the MRLVD definition is currently being interpreted. In its view, the phrase "*the MRLVD may be reduced to be consistent with good practices in the use of veterinary drugs*" may imply a requirement for establishing an MRLVD based on the indications and conditions of use at the time of the evaluation and no regard for the potential for new and changing uses of the veterinary drug or for specific conditions existing in and perhaps limited to developing countries.

19. It also noted that it was important that the residue data submitted in support of an MRLVD be the result of studies conducted in compliance with good practice in the use of veterinary drugs (GVP); that a total residue approach should be used, where the concentration of all residues of toxicological concern in each edible tissue was determined based upon the upper bound of the ADI and the fraction of the total diet represented by that edible tissue: The sum of the individual MRLVDs would be required not to exceed the upper bound of the ADI (The MRLVD would then represent the concentration of residues determined by analysis of the marker residue in a specific tissue that reflects the concentration of total residue in that tissue).

20. Some members and observers indicated that Good Veterinary Practices (GVP) in determining withdrawal period, though theoretically sound, have practical limitations. Agricultural practices may vary from country to country, and from region to region within a country; how information on GVP is used in the process of recommending MRLs may be in need of clarification. Furthermore, proposing MRLs based on GVP may create practical difficulties in certain circumstances (e.g. MRLs may need to be readjusted with change in formulations or animal husbandry, or proposals for new indications). As a result, it may challenge international harmonization of MRLs which may impact international trade.

21. In order to overcome these difficulties, a member recalled that, currently, the GVP were only used in certain situations, where recommended MRLVDs would lead to impractical withdrawal periods in particular case of animal production with short lifespan (e.g. poultry).

22. Another member noted that, in general, the plant-protection-products-approach (i.e. GAP-derived MRLs) might offer an alternative procedure to the usual derivation of MRLVD (based on toxicology), if residue data used result from studies performed under GVP.

23. Reviewing the full ADI issue from a toxicological perspective, most of the members, which have sent written comments, agreed in principle with this approach, although they recognized that it was not applicable in all cases. For example, for a dual-use substance (such as pesticides/biocides with use as Veterinary Drug), the full ADI should be interpreted as the part of the ADI allocated for veterinary use. Similarly, in some cases, the possible impact of possible future extension of uses (e.g. development of MRLs for other food commodities, milk, and possible future dual-use applications) on previously established MRLs should be considered.

Recommendations:

24. The Committee may wish to conclude that in a process resulting in MRLVDs that do not exceed the ADI, the use of the full ADI should be recommended. However, the Committee may wish to discuss practical aspects and possible impact (dual use, possible extension of use to more food commodities).

25. The Committee may also wish to seek clarification from JECFA on how GVP are used in the process of developing MRLs.

C - Food basket content

C1- Regional Food consumption data

26. The Bilthoven workshop reviewed the MRLs methodologies used for both pesticides and Veterinary drugs. As mentioned in the Bilthoven workshop report: "*The theoretical food basket approach leads, in combination with the MRL, to over conservative estimates of the long-term exposure to veterinary drugs of "average eaters" and highly conservative estimates for the "preferential eaters". Although the JECFA food basket is very conservative when compared to the GEMS/Food regional diets used by JMPR to assess the long-term exposure, these values are lower than those in the GEMS/Food database on the highest 97.5th percentiles of consumption used by JMPR to assess the short-term exposure*." The method for dietary exposure was assessed and a proposal was made '*to make chronic intake estimates more realistic*". The recommendation was to use the EDI approach and not to use regional consumption data in developing MRLs.

27. One can argue that the current standard food basket used for elaborating MRLs overestimates the long-term exposure to residues of veterinary drugs of the "average consumer". A member pointed out that this statement would require a detailed review of using different regional consumption factors.

28. For instance, in the EU, the EFSA (European Food Safety Agency) PRIMO model is used for pesticide residue exposure assessment. A comparison of its output with the JECFA food basket reveals that the latter does not overestimate the intake for an EFSA "adult large portion" for muscle, liver, kidney and fat and eggs. The milk intake is marginally lower with the EFSA PRIMO model for both adults and children.

29. Using regional consumption factors will require that adequate national data be available. Reviewing available in FAOSTAT[1] and GEMS/Food Regional Diets shows that the current data may be insufficient. There are very limited data for fish; detailed data for kidney and liver are not available. For fat, the value is simply derived as a percentage of meat (20% for mammals, 10 % for poultry meat).

30. These data also show differences in regional consumption patterns. A methodology would have to be agreed upon before regional consumption data could be used for MRLVD calculation. If the JECFA procedure is aligned on the JMPR's, this would lead to important changes in the current methodology for establishing MRLVD. For instance, JMPR performs two estimations: one for children (with a body weight of 15 kg), one for the general population (with a body weight of 60 kg with the exception of certain regions were 55 kg is used).

31. One may note that the current JECFA approach already takes into account special population groups, such as children, that have a higher consumption of milk compared to the general population. It may also be argued that the current approach does have considerable advantages: it is simple to understand and easy to apply; it provides a harmonized approach for estimating exposure. Some members argued that the use of regional consumption data would adversely affect Codex's goal of harmonization, as the consumption of animal products is strongly influenced by the geography and socio-economic status.

32. An observer pointed out that, while the current approach did not take account of regional and cultural dietary differences, communities and diets were increasingly "globalised" and would continue to change over time. Any move away from the existing harmonized approach would need to take account of the changing nature of diets. This might be regarded as a further reason to keep the current approach: Regional data may still be used by member countries for domestic purposes.

[1] www.fao.org/docrep/005/AC911E/ac911e05.htm

C2 – 'One Meat, plus milk, plus egg' approach

33. One member proposed recommending MRLs using an exposure calculation that recognizes a "more realistic daily consumption" of meats, respecting that eggs and milk are separate commodities. It argued that it was reasonable to presume that, on any given day, the consumer of a meal derived from muscle would not regularly also have a meal from kidney, and so forth; therefore it was appropriate to calculate daily cumulative exposure (preferably using the EDI approach) based only on one meat plus milk plus eggs (where applicable), with MRLs assigned accordingly. However, another member pointed out that, assuming that a person consumed, on any day, a meal derived from kidney alone, it was very unlikely that the person would consume only 50 g of it. As a result, if the Committee agrees to follow this new approach, adjusting consumption factors to better reflect the real diets would be required.

34. A member noted that, for control of residues, it was important to establish MRLs for several tissues, since the distribution of different substances varied, i.e. when residues could not be found in muscle, they might be present at high concentrations in liver, fat or kidney. Another argued that, at the end of the recommended withdrawal period, there should be no residue level higher than the MRL, or the ADI, in all tissues Usually, residues in fat and muscle (except at injections-site) would deplete down under the MRL, earlier than in liver or kidney. Therefore, if MRLs are only set for muscle, established withdrawal periods would be too short to ensure adequate depletion from higher levels in other tissues.

35. This approach should be considered in conjunction with the discussion on the use of regional food consumption data. However, the electronic working group has not been able to collect sufficient information on the specifics of the implementation of this proposal, as the comments received from members and observers do not allow a complete description to be presented at this stage; it has identified several outstanding questions to be answered before further consideration of this proposal:

- Would this approach lead to the establishment of MRLs for all four tissues (as currently) or to the establishment of an MRL for only one tissue?
- Then, what would the consequences for residue control be if an MRL were only established for one tissue?
- If an MRL were established for only one tissue, would it always be the same tissue (for example, muscle)?
- Can the proposed approach be interpreted as a change (simplification) in the food basket?
- Would MRLs still be established for milk and eggs?
- Would the proposed approach allow the ADI to be used several times or would the ADI be split between the various food commodities (as currently)?
- Would the proposed approach no longer take account of the tissue distribution, and if so, what would the consequences be for residue control and consumer safety?

Recommendations:

36. The Committee may wish to recommend not changing the current food basket approach as the use of regional consumption factors would make the process developing MRLs significantly more complex and less transparent and may have a negative impact on the establishment of harmonized MRLs.

37. As an alternative, the Committee may wish to postpone decision on the use of regional consumption factors pending the outcome of the expert consultation on dietary exposure assessment related to veterinary drugs.

38. The Committee may wish to keep the "one meat plus milk plus egg" approach under review and request comments in order to provide more details on its implementation and investigate how it may represent a simplification of the MRL setting procedure

Overview of the possible changes in the methodology of elaboration of MRLVD

39. The purpose of Codex Alimentarius is to protect consumer health and to ensure fair practices in the food trade. The approach taken up to now has been successful in protecting public health and has ensured successful harmonization at international level.

40. Some delegations have questioned the impact on food trade and expressed concerns that current practices may have lead to setting an MRL too low (where a higher level would have still adequately protected the health of the consumer). Some members consider that any change in the methodology should be carefully assessed as it is stated that the approach taken to date has been successful in protecting public health and has ensured successful international harmonization.

41. The discussion should achieve a sustainable and efficient process of setting MRLs that protects the health of the consumer and, at the same time, supports appropriate use of veterinary medicines required to ensure the health of food producing animals. Any recommended change should be constrained by Codex dual objectives of protecting the consumer health and ensuring fair trade practices are achieved.

Recommendation:

42. The Committee may wish to have a general discussion in order to clarify the goals, the extent and the potential impact of the harmonization process between JECFA and JMPR.

43. The Committee may wish to make recommendations based on available information taking into account the review of the topics discussed in previous section of the discussion paper. These recommendations concern the use of full ADI where possible (see B above), the use of the current food basket versus the use of regional consumption (see C1 above).

44. The Committee may also wish to postpone consideration on some other topics which still need clarification as the EDI approach (see A above), the ‘one meat, one milk, one egg’ approach (see C2 above).

45. Any recommendation will have to be done taking consideration of the combined impact of approaches. The completed “decision tree” approach prepared by JECFA is awaited.