CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 3 **CX/RVDF 13/21/3 - Add. 2**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-first Session

Minneapolis, Minnesota, United States of America, 26 – 30 August 2013

MATTERS ARISING FROM FAO/WHO AND FROM THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

RESPONSE TO THE QUESTIONS RAISED BY THE 20TH MEETING OF THE CCRVDF TO THE JOINT EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA) IN RELATION TO MRL EXTRAPOLATION

INTRODUCTION

1. The 20th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), meeting in San Juan, Puerto Rico (7-11 May, 2012) considered a working paper on the extrapolation of maximum residue limits (MRLs) to additional species and tissues (CX/RVDF 12/20/15). Following discussion, the CCRVDF posed a series of questions to JECFA to better determine whether EHC 240 provides sufficient guidance for JECFA to develop a scientific framework for extrapolating MRLs between species and tissues. The JECFA Secretariat responded that an electronic working group of JECFA would be convened "to develop minimum criteria for information upon which to base extrapolation between food animals and commodities".

PROCEDURE FOR PREPARATION OF THIS DOCUMENT

2. The JECFA Secretariat engaged a consultant to prepare a draft working paper to review the background and describe current JECFA practices regarding extrapolation of MRLs from major to minor species by JECFA, to review available guidance from other sources and to prepare responses to each of the questions forwarded from the 20th Session of the CCRDVF. The working paper was then circulated to an electronic working group of JECFA residue experts for comment and discussion. The nine questions[1] forwarded to JECFA by the 20th Session of the CCRVDF are listed below, with the responses to each question as agreed by the electronic working group.

3. The JECFA Secretariat has also provided comments, assisted by the electronic working group, in response to the request[2] for JECFA advice on the proposed *Risk Analysis Policy on Extrapolation of MRLs of Veterinary Drugs to Additional Species and Tissues* and in response to the request for JECFA advice[3] on the CCRVDF *Discussion paper on the policy for the establishment of MRLs or other limits for honey* (CX/RVDF 12/20/14).

4. Further detailed guidance on extrapolation will be developed by the 78th session of JECFA in November 2013, including minimum criteria for information upon which to base extrapolation between food animals and commodities.

RESPONSE TO THE NINE "PARAGRAPH 156 QUESTIONS"

Question i: EHC 240 does not define "what comparable metabolic profile between species" means. JECFA may wish to consider elaboration of the criteria described in EHC 240 (such as the precise definition of "metabolically comparable")

5. A "comparable metabolic profile between species" implies that the same major metabolites are present in both species and that they are present in similar proportions. When comparing metabolic profiles qualitatively, the same major compounds should appear in the metabolic profile. This may include both parent compound (if available) and one or more metabolites, including bound residues. Quantitatively, the

[1] Paragraph 156 of REP12/RVDF
[2] Paragraph 157 of REP12/RVDF
[3] Paragraph 146 of REP12/RVDF

compounds should be present in similar proportions, within reasonable limits reflecting measurement uncertainty and biological variability. JECFA has not to this point established precise numerical limits for quantitative comparison of metabolic profiles. This is still subject to interpretation on a case-by-case basis, based on the data provided.

Question ii: Guidance on the criteria/assumptions to be used for interspecies extrapolations, including minimum data required to support such extrapolation among physiological related species, and extrapolation to additional (unrelated) species.

6. When requested to consider the extrapolation of MRLs to another species, JECFA must address certain issues related to the approved usage of the drug, toxicology of the drug residues and the dietary intake calculations, based on the MRLs, which are used to ensure consumer safety. Issues considered by JECFA include:

- JECFA bases MRL recommendations on the authorized use of drugs (GVP). Without an existing approved use for a drug in a minor species in a member state and provision of a label or equivalent information documenting the approved use, JECFA does not recommend MRLs for the drug in the minor species.
- JECFA will consider a request for extrapolation of MRLs from a major species, which the 52nd JECFA defined as being cattle, sheep, pigs and chickens, when full MRLS have been recommended for one or more major species. JECFA does not generally consider extrapolation of MRLs from a major species to a minor species when only temporary MRLS are recommended for the major species.
- There should not be any metabolites or bound residues of unknown toxicity in the minor species that are not present in the major species. Comparative metabolism in the minor and major species may be shown through available scientific literature sources, through a limited experiment with a minimum number of test animals or through in vitro methods, as described in VICH guidance.
- When the marker residue is the only residue of toxicological concern, it is not necessary to consider total residues in the dietary intake estimates, thus eliminating one of the issues that must be addressed when considering extrapolation of MRLs. However, when the total residue is considered of toxicological concern, then the ratio between marker and total residues (M/T ratio) must be considered.
- If the conditions of use are the same or equivalent in the two species, then similar depletion profiles may be deduced from limited pharmacokinetic, metabolism and/or depletion data. If there are differences in pharmacokinetics observed in the two species and very limited data from depletion experiments or if the conditions of use differ significantly in the two species, the available data may be considered insufficient to warrant extrapolation, requiring submission of additional data to provide a basis for the recommendation of MRLs for the minor species.
- If data from a full residue study in the minor species are provided, MRLs will be derived using that data, which may result in extension of the MRLs already established for a major species to the minor species. This process does not involve extrapolation.
- The relative amounts of the food basket items used in the intake calculation are currently considered suitable to represent the majority of consumers and should, in fact, provide an inflated estimate of the food consumed on a daily basis by most typical consumers. JECFA is considering alternatives to the present dietary intake calculations, but currently applies the same food basket to foods from all species, using the MRLs for each food basket item which yield the highest intake estimate.
- Analytical methodology should be available for the monitoring of drug residues in the minor species. Preferably, there should be a method that has been validated for food basket items from the minor species, although there may be situations where JECFA experts are satisfied that a method validated for the food basket items from a major species should be applicable to the same items from the minor species.

7. The quantity and quality of data available to JECFA when reviewing a request for extrapolation of MRLs from a major to a minor species are quite variable, usually requiring considerable discussion and the application of expert judgement on a case-by-case basis as to whether the data available from all sources are sufficient to support the extrapolation. Thus, it is important that all available information pertaining to the approved use and residues associated with that use in a minor species should be provided to JECFA.

Question iii: Possibility of extending extrapolation by JECFA similar to that allowed under the current EU guidelines.

a) EHC 240 does not allow for the extrapolation of MRLs from muscle of salmonidae to other fin fish, but this is allowable based on European Union guidelines. JECFA should consider extrapolation of MRLs between fish species. If the data required to support such MRL extrapolation is not available, what further work may be required?

JECFA must first receive information to confirm that there is an existing approval in a member state for use of the drug in the species of fish for which extrapolation of MRLs is requested, including a label or a statement of the approved conditions of use (GVP). The conditions of approved use (GVP) may differ depending on species of fish and region. However, the water temperature at which a product is used for treatment of fish and at which residue studies have been conducted are major considerations in the recommendation of MRLs for fish. This may result in different MRLs being recommended for different species, based on the GVP established for the use of the drug in one or more fish species in a member state or member states.

b) Whether MRLs can be extrapolated to all food-producing species when the established MRLs in three different "classes" of major species (ruminant, pigs, and chickens) are similar.

JECFA must be provided with evidence of an approved use of the drug (GVP) in a member state for any food-producing species for which extrapolation of MRLs is requested. Since the data available for review differ for each compound and species nominated for extrapolation, review on a case-by-case basis is therefore currently considered more appropriate by JECFA than a blanket policy which would be applied in all cases.

Question iv: whether it would be possible for JECFA to consider metabolism and pharmacokinetic data of non-food animals (such as laboratory animals or humans), in addition to the data provided for major food producing species. This might provide further evidence of a common route of metabolism within all mammals for a given compound, and could be used to justify extrapolating MRLs for that compound to all mammalian species. JECFA might also wish to consider the use of in vitro metabolic models for certain compounds.

JECFA typically includes any metabolic and pharmacokinetic data available for laboratory animals and humans in the evaluation of a drug. Requirements for a toxicological evaluation by JECFA specifically include acute and chronic toxicity experiments conducted in laboratory animals. Data generated using in vitro experiments have also been a source of information on comparative metabolism in the review of a number of compounds by JECFA. The preponderance of information, including metabolism and pharmacokinetic studies in laboratory animals and data from use in humans, has been used to recommend MRLs in one or more species for some compounds, particularly those with a long history of use in both veterinary and human medicine.

Question v: it is understood that MRL extrapolation would be based on the principles of risk assessment. Whether the risk associated with uncertainties in extrapolation of MRLs to a new species could sufficiently be addressed by the likely lower exposure to residues from tissues of extrapolated species (e.g. tissues of certain species are consumed less frequently and in smaller quantity) and the adequacy of the safety factors already inherent in the establishment of MRLs.

JECFA has consistently taken a conservative approach to the estimate of chronic exposure based on food intake, using consumption factors adopted by the 34th Meeting of the Committee and confirmed following a review of data provided by member governments of the Codex Alimentarius to the 40th Meeting of JECFA. A draft version of the Report of the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs, issued in response to a request to the FAO and WHO from the 18th and 19th Meetings of the CCRVDF, was considered at the 75th Meeting of JECFA. It was decided that the dietary exposure models proposed in the Report of the Expert Meeting would be further considered at future meetings of JECFA, along with worked examples using the new models.

A primary concern is that the consumption factors used for exposure estimates should reflect the food consumption by what are termed "high level" consumers, typically those who fall in the 97.5th percentile for consumption of the food. In addition, the Expert Meeting observed that currently there are "insufficient data from different world regions to support a regional diet approach". When different MRLs are recommended for different species, JECFA currently takes a conservative approach and bases the intake calculations on residues associated with the highest potential residue consumption associated with an MRL recommended for any tissue, irrespective of species. At this time, it is perhaps premature to state how risk assessment principles might be applied to extrapolation of MRLs using the new dietary models. However, the issue

raised is part of the on-going considerations and will be addressed in any changes in approaches to estimates of dietary exposure which may be adopted in the future by JECFA.

CCRVDF Question vi: Whether extrapolation could consider group MRLs for therapeutically/chemically related compounds. More sophisticated approaches might need to be developed (e.g. predictive approaches using structure activity relationships or in silico tools to predict ADME properties) for its routine use.

In the past, JECFA has considered and recommended group MRLs for therapeutically/chemically related compounds where appropriate. For example, the related compounds, febantel, fenbendazole and oxfendazole, which produce common metabolites, have a group MRL and share a common marker residue. The 58th JECFA recommended common MRLs for residues of streptomycin and dihydrostreptomycin, and also group MRLs for chlortetracycline, oxytetracycline and tetracycline residues. In each of these cases, there was an assignment of a group ADI. JECFA will continue to consider and recommend group ADIs and MRLs for chemicals which are therapeutically/chemically related, with a similar toxicological profile, and to harmonize MRL recommendations across species where the data indicate such action is appropriate.

JECFA also continues to assess developing approaches, such as the use of in silico and in vitro approaches for investigation of adsorption, metabolism, excretion and distribution (ADME) and to use data from such studies, when available. For example, data from in silico studies were included in the toxicological evaluation of derquantel by the 75th JECFA. However, caution must be taken in interpretation as in vitro studies may provide very different metabolic profiles from in vivo experiments, as the experimental conditions differ and this could have marked influences in the observed metabolism.

CCRVDF Question vii: Whether extrapolation of MRLs from terrestrial species to fish could be considered.

JECFA has recommended MRLs in fish without receipt of any metabolism data other than for terrestrial species, but usually based on the availability of residue depletion data. These situations therefore are more in the nature of an extension of MRLs to include the fish species, rather than extrapolation. JECFA will consider the extension or extrapolation of MRLs from terrestrial species to fish when suitable data are available to support such recommendations, such as a common level for allergic response to a residue or the availability of sufficient residue data in a species of fish. Such an extrapolation or extension of MRLs is considered on a case-by-case basis, requiring first evidence of an approved use of the drug for one or more species of fish in a member state, with some information on the nature of the residues found in a representative species of fish for which use was approved.

CCRVDF Question viii: Whether extrapolation of MRLs to honey would be feasible by using the most conservative MRL from terrestrial animal tissues and applying an appropriate factor to account for uncertainties (MR/TR ratio2:1, likely unsubstantial residue depletion other than some degradation in honey etc.) in extrapolation and adjusting for food consumption values.

It is stated in EHC 240 that “It is not appropriate to consider honey as a candidate for extension of MRLs from one species to another because of the difficulty in extrapolating from mammals, birds or fish to bees, as the treatment modalities are not comparable.” Procedures for the establishment of MRLs for the use of veterinary drugs in the production of honey were discussed at the 70th JECFA, which made a number of recommendations concerning potential approaches to the establishment of such MRLs. Issues to be considered include whether the marker residue identified for monitoring residues of a drug used in treatment of animals is also appropriate for monitoring residues in honey and the nature of residues found in honey. While typically there is no metabolic pathway in honey, there may be degradation or dilution of residues.

JECFA bases MRL recommendations on residue data produced under GVP conditions of use in one or more member states. A critical consideration in the establishment of MRLs for honey is that the MRL must be consistent with good bee-keeping practice, i.e. the MRL should be high enough to avoid non-compliant residues from use of the substance according to the label instructions under field conditions (GVP use), but not so high as to permit use of the drug without following the withdrawal period required under the GVP approved conditions of use. The establishment of MRLs for honey by some form of extrapolation from MRLs previously established for tissues, milk or eggs, in the absence of residue depletion data for honey, poses the risk that MRLs may be established which are not consistent with the approved GVP usage and therefore are not practical.

It may therefore be prudent to await the outcome of a review by a future JECFA of a request to establish an MRL for a veterinary drug used in honey, at which time the practical application of the principles discussed by the 70th JECFA and the CCRVDF working group can be evaluated.

CCRVDF Question ix: whether JECFA could evaluate the feasibility of inter-tissue extrapolations within the same species. However, due to limited experience in this area, it might be scientifically challenging.

There is currently no scientific basis on which extrapolation of MRLs between different tissues from a species appears warranted in the absence of data which demonstrate the relative concentrations of the residue in the various tissues. Therefore, there are very limited situations in which inter-tissue extrapolation within the same species may be contemplated, such as where there is a common threshold for allergic response or an acute reference dose. The most obvious example where common MRLs are recommended by JECFA for different tissues from the same species is when there are no detectable residues of a drug in two or more tissues. In such situations, JECFA has based MRL recommendations on the limit of quantitation (LOQ) of the analytical method (2xLOQ), provided that the method is considered to have a sufficiently low LOQ to ensure that any residues present were indeed at very low concentrations. The same MRL then may be assigned to multiple tissues. While there have been some publications in peer-reviewed scientific journals exploring approaches to model the distribution of residues in various tissues or fluids based on limited data, these models have not yet been validated to the point where they could be routinely applied by regulatory authorities (or JECFA) for the extrapolation of MRLs to various tissues within the same species.