CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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RISK ANALYSIS POLICY ON EXTRAPOLATION OF MRL'S OF VETERINARY DRUGS TO ADDITIONAL SPECIES AND TISSUES

(replies to CL 2012/11-RVDF, Part B, Points 7 & 8)

Comments of the JECFA Secretariat

RESPONSE TO REQUEST[1] FOR COMMENTS REGARDING THE PROPOSED RISK ANALYSIS POLICY ON EXTRAPOLATION OF MRLS OF VETERINARY DRUGS TO ADDITIONAL SPECIES AND TISSUES (REP12/RVDF APPENDIX XI)

The following comments are provided by the JECFA Secretariat, 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.*

Title

The proposed *Risk Analysis Policy on Extrapolation of MRLs of Veterinary Drugs to Additional Species and Tissues* (REP12/RVDF Appendix XI) provides a good overview of the issue and offers some sound, scientifically based proposals. However, it should be noted that the 66th JECFA has concluded that "extrapolation may not be the appropriate term, but rather extension of the MRL." In the comments that follow, the terms "extrapolation" and "extrapolated" could be replaced by the "extension" and "extended", respectively.

"Scope"

JECFA agrees with the need to have clear guidance to be followed when considering the feasibility of the extrapolation (or extension – see comment under "title") of MRLs for veterinary drug residues previously recommended for a major species to a minor species. As noted in the proposed statement of scope, there typically are gaps in data in the information provided for assessment of the drug residues in the minor species, so a transparent risk analysis approach incorporating both risk assessment and risk management principles is a key element to ensuring that the process provides the intended protection to consumers. However, "a lack of metabolism" data is not consistent with the minimum data requirements for extrapolation of MRLs recommended in EHC 240. Without sufficient comparative metabolism data, it is not apparent how JECFA could determine that the same marker residue, metabolic pathway, marker-to-total residue relationship and depletion profiles may be common to the two species and recommend extrapolation of the MRLs using the criteria in EHC 240. We therefore recommend limiting the statement in the scope to "a lack of complete residue depletion data".

General Aspects

i) "Generally, comprehensive data packages for veterinary drugs are available for at least one (or more) species of animals that are farmed in large numbers (i.e. "major" species)."

Comment: The 52nd JECFA has defined major species as cattle, sheep, pigs and chickens and the terms "major species" and "minor species" have been used consistently in JECFA reports. While this list of

[1] Paragraph 157 of REP12/RVDF
[2] Paragraph 157 of REP12/RVDF

”major species” may require some additions since it was originally stated by JECFA in 2000, we believe it is preferable to clearly state which species are designated as “major”, so that all other food animals not included in that group become “minor species”. The designations “farmed in large numbers” and “farmed in small numbers” are subjective and may vary by country or region.

ii) “While considering extrapolation of MRLs between species, focus should be on criteria that are likely to be least variable. Avoiding, or minimising the weightage of, factors that will likely have higher variation will ensure that food safety is not compromised.”

Comment: The meaning of this statement is ambiguous and it could be interpreted in different ways. It would be useful for the CCRVDF to provide clarification to JECFA on which criteria and factors are meant in the statement for further consideration by JECFA.

iii) “Precaution is an inherent element of risk analysis. Sources and degree of uncertainty and variability should be explicitly considered in the risk analysis process. Where there is sufficient scientific evidence to allow JECFA to proceed to extrapolate MRLs, the assumptions used for risk analysis should reflect the degree of uncertainty and the characteristics of the potential hazard.”

Comment: The considerations used in deciding whether or not an MRL established for a major species can be extrapolated or to a minor species are typically stated when JECFA performs such an evaluation and makes a recommendation to CCRVDF. Gaps in available data which create uncertainties are clearly stated and the balance of evidence which allows or prevents an extrapolation of the MRLs is provided in the risk assessment and associated risk management recommendation provided by JECFA. These key decision points are typically provided in the JECFA Meeting Report (WHO Technical Report Series) in the section “Maximum Residue Limits” when there are MRL recommendations or in “Summary” and “Recommendations” when an evaluation by JECFA does not lead to MRL recommendations.

iv) “MRL extrapolation should be based on the principles of risk assessment. Due consideration should be given to - 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., minor species tissues are consumed less frequently and in smaller quantity) and the adequacy of the safety factors already inherent in the establishment of MRLs.”

Comment: The basic assumption in the daily intake calculation is that each day a typical consumer will eat all items from a food basket containing specified quantities of edible tissues, milk and eggs, irrespective of the species from which the food is derived, and that each of these items will contain residues at the median concentration associated with the MRL (estimated dietary intake, or EDI) or at the MRL concentration (theoretical maximum daily intake, or TMDI). The intake estimates are not currently done individually for each species, unless MRLs have only been recommended for a single species. The form of dietary estimate (EDI or TMDI) used relates to the quantity and quality of residue depletion data available for evaluation. The assumption that meat from minor species is consumed less frequently than meat from a major species is therefore not relevant in these models. The only factors used in the intake estimates are those used to adjust concentrations of marker residue to total residues (when all residues are considered of toxic concern and are therefore assumed to have the same toxicity as the parent drug and/or metabolites represented by the marker residue) and factors for bioavailability of residues in the food. We do not therefore feel that this would be a useful consideration in most situations, based on the requests for extrapolation of MRLs which have been referred to date by JECFA.

v) “While extrapolating MRLs, relevant data should be considered from different parts of the world and should include consideration of different consumption patterns, however such a consideration should not preclude extrapolation of MRLs.”

Comment: The relevant data on different consumption patterns in different parts of the world have not previously been available. However, the new proposed exposure assessment methodology will allow for more differentiated exposure assessment, provided the relevant data are made available.

vi) “The list of priority drugs and species and tissues for extrapolation should be made available by CCRVDF and kept up to date for priority setting.”

Comment: The maintenance of such a list would facilitate planning and scheduling of work by the JECFA Secretariat and might provide some opportunities to consolidate work on some substances identified for evaluation.

Proposed Risk Assessment Policy for JECFA

i) Para. 2. In order to extrapolate MRLs, it should be considered that the marker residue in target tissues of the new (extrapolated) species is present in concentrations high enough that can be monitored by the available analytical method. This means that limited pharmacokinetic and/or residue depletion data may be required in species in which the MRLs are to be extrapolated.

Comment: The marker residue should be appropriate for monitoring of residues in the species to which the MRLs are extrapolated. However, this should be considered in light of another recommendation made in EHC 240, which is that the metabolic profile is comparable, thus ensuring that the marker residue is not only present, but is representative of the residues found in the species to which the MRLs are to be extrapolated. In theory, there could be a situation in which the marker residue identified in the major species is not the appropriate marker residue for that species. The availability of comparative metabolism data ensures that the marker residue selected is appropriate for all species included in the MRL recommendations. We agree that for most situations involving an extrapolation, some limited pharmacokinetic and/or residue data are desirable. However, if a full set of residue depletion data are available for the minor species, the MRLs will be derived using that data, not by extrapolation.

ii) Para. 3. JECFA should consider that those drugs in which the parent compound is the marker residue are good candidates for MRL extrapolation.

Comment: This is not necessarily the case. Designation of parent compound as the marker residue does not imply that there is no requirement for factors relating the marker residue to the total residue. There are a number of substances for which MRLs have been recommended by JECFA where the marker residue is formed by a chemical reaction of parent compound and metabolites to a common compound or where the marker residue is a sum of several compounds, such as the parent compound and a major metabolite. It might be more productive to consider as good candidates for extrapolation those drugs where only the marker residue is of toxicological concern, so that there is no requirement for factors to adjust from marker to total residues in any species which has received the drug. Those compounds for which there are no detectable residues in any (or all) tissues could also be considered as excellent candidates for MRL extrapolation. For such compounds, MRLs have typically been recommended by JECFA at a concentration twice the limit of quantitation (LOQ) of the residue control method of analysis.

iii) Para. 4. There should be sufficient information to determine that a unique metabolite(s) of toxicological concern is unlikely to occur in species in which MRLs are going to be extrapolated. In the absence of species-specific metabolism data, information from a theoretical metabolic reaction pathway that the drug (and/or drug class of which the parent compound is a member) could undergo may be considered.

Comment: This is indeed a concern, but one which can be addressed in most situations by conducting an in vitro comparative metabolism experiment using tissues from the relevant species. In the absence of such a study, a consideration of potential metabolic reaction pathways could be considered, particularly when information on the behaviour of other structurally similar drugs is available. This again demonstrates the need for consideration of extrapolation requests to JECFA on a case-by-case basis

RESPONSE TO REQUEST FOR COMMENT[3] ON THE CCRVDF DISCUSSION PAPER ON THE POLICY FOR THE ESTABLISHMENT OF MRLS OR OTHER LIMITS FOR HONEY (CX/RVDF 12/20/14)

The following comments are provided by the JECFA Secretariat, assisted by the electronic working group, in response to the request for JECFA advice[4] on the CCRVDF *Discussion paper on the policy for the establishment of MRLs or other limits for honey* (CX/RVDF 12/20/14).

The criteria for placement of a drug on the CCRVDF priority list for JECFA evaluation, as stated in the Codex Alimentarius Commission Procedural Manual, 21st edition, include “a Member has established good veterinary practices with regard to the compound” and “the compound has the potential to cause public health and/or international trade problems”. This means that data on residues resulting from the approved use are required if MRLs are to be established which are consistent with the GVP use of the drug, which is the current mandate of JECFA.

The discussion paper prepared for the 70th Meeting of JECFA describes the various issues related to the establishment of MRLs for honey and some particular problems associated with the evaluation of residues for the establishment of MRLs. Extensive variability can be observed in the concentrations of the residue found in samples collected from different areas of the same hive or from different hives. For large scale

[3] Paragraph 146 of REP12/RVDF
[4] Paragraph 146 of REP12/RVDF

production, where products from various sources are blended in bulk, samples from multiple hives at multiple locations and times may be required to derive a representative picture for the typical bulk product in international trade. In addition, any reduction in residue concentration is typically a result of dilution or chemical degradation of the parent drug from sources such as moisture, heat and light exposure, rather than from metabolic processes. Furthermore, since the depletion pathway is different in honey than the typical metabolic pathways in animals treated with drugs, the marker residue designated for tissues, milk and/or eggs may not be appropriate for honey.

Honey is not generally sold internationally in small quantities collected from a single hive or producer, but as a bulk commodity which contains honey from multiple sources. Thus, MRLs established within the Codex Alimentarius system must reflect residue concentrations expected to be found in bulk honey from multiple producers with hives treated under GVP. If practices followed by JECFA in recommending MRLs for veterinary drugs used in honey production are to be consistent with those followed for recommending MRLs for edible tissues, milk and eggs from food-producing animals treated with veterinary drugs, the following information is required:

- evidence of an approved use in a Codex member state;
- an existing ADI or the availability of toxicological data to establish an ADI;
- data to establish a marker residue in honey;
- evidence of a validated analytical method for the determination of residues in honey;
- data on the nature of residues in honey, typical concentrations found and the stability of these residues; and
- data about frequency of use (prevalence of disease in bees).

A dietary consumption factor of 50g per person per day is recommended in the CCRVDF working paper, consistent with the recommendation of the 70th JECFA. It also notes that the evaluation of drugs in honey differs from the evaluation of drugs used in other species of food-producing animals, as there are no pharmacokinetic depletion data or metabolic pathways to consider and that reduction of residues in honey is from dilution and/or environmental factors. In addition, use of veterinary drugs in honey production is usually considered as a minor use in a minor species and therefore a policy on risk assessment requires some flexibility. Three potential situations are envisaged:

- the establishment of an MRL for honey for substances with established ADI and/or MRL (preferably recommended by JECFA) in a food-producing animal or food commodity;
- the establishment of an MRL for honey for substances generally regarded as safe, such as food components or additives; or
- the establishment of an MRL for honey for substances which are not approved for use in food animals or are new drugs.

The manner in which each of these situations may be assessed and the data requirements for such assessments differs, based on the information that is already available from prior evaluations of the safety of the substance.

i) Substances with an established ADI and/or MRL (preferably by JECFA) in a food producing animal or food commodity

The main groups of substances that typically leave residues in edible bee products are antibiotics and persistent lipophilic acaricides. Of the products known to be used for treatment of bee diseases, most, but not all, have a national registration and a JECFA or JMPR evaluation with an ADI and/or MRL (or the equivalent in national legislation) for either a food-producing animal or other food commodity, and usually the active ingredients are substances with a long history of use.

The MRLs recommended by JECFA must be practical and must protect consumer health while ensuring that the veterinary product can be used effectively. It is proposed in the draft policy that the data requirement would be limited to residue depletion studies in honey, which could be used to establish MRLs in honey and by national authorities to also establish withdrawal periods following treatment. While available information suggests that the parent drug is expected to be the marker residue in honey in most situations, this should be confirmed before residue studies are conducted. Residue studies using the marker residue compound in honey may then be used to provide data for the recommendation of MRLs consistent with GVP which are therefore practical for monitoring residues in products in international trade. MRLs derived using other

approaches, such as extrapolation from MRLs previously established for tissues, with safety factors, may result in MRLs for honey that are not consistent with the approved GVP use in member states.

Further details of the factors to consider in developing MRLs relating to the use of veterinary drugs for bees, are available in the report of the 70th session of JECFA.

ii) The establishment of an MRL for honey for substances generally regarded as safe, such as food components or additives

Several substances are unlikely to raise public health concerns, because any use in food-producing animals, especially the use in bees, is generally regarded as safe. Examples of such substances include formic acid, lactic acid, oxalic acid, thymol and menthol. In the case of a substance that has clear documentation to support the designation as "generally regarded as safe" by national regulatory authorities and not requiring a MRL, a similar designation can be made. It would require a proviso that equivalence can be demonstrated

in honey and that the ADI is sufficient so that no MRL would be required and the ADI is not exceeded. In the case of a new substance not previously considered for registration by national authorities, substances would have to be evaluated as new animal drugs or pesticides and subject to a full food safety risk assessment.

This issue was discussed at the 70th session of JECFA and outlined in the report.

iii) The establishment of an MRL for honey for substances which are not approved for use in food animals or are new drugs

In the situation where a substance is not approved for use in food-producing animals (e.g. chloramphenicol or nitrofurans), no exception for honey would be applied.

This issue was discussed at the 70th session of JECFA and outlined in the report.