CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME
CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
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Canada Comments
Highlights from the Chair of the Electronic Working Group on

EXTRAPOLATION OF MRLS TO ADDITIONAL SPECIES AND TISSUES

Report of the CCRVDF Electronic Working Group (eWG) on Extrapolation of MRLs for Veterinary Drugs to Additional Species and Tissues, prepared by Canada with the assistance of Argentina, Australia, Brazil, European Union, Germany, Ireland, Japan, Mexico, The Netherlands, New Zealand, Norway, South Africa, Sweden, Thailand, United Kingdom, United States of America, JECFA Secretariat and IFAH

The tasks of the eWG were:
(i) Collate and summarise all the available national and regional guidelines and documents and published literature pertinent to the extrapolation of MRLs;

(ii) Prepare a list of substances with existing MRLs in a number of species/food matrices for which extrapolation is considered necessary and make a proposal for prioritization;

(iii) Prepare recommendations for the CCRVDF to request JECFA to consider whether EHC 240 provides sufficient guidance for JECFA to develop a scientific framework for extrapolating MRLs between species and tissues, or whether additional scientific considerations are required; and

(iv) Propose potential risk analysis policy for use by CCRVDF when considering extrapolating MRLs.

Summary of work:
Task II:

Proposed criteria for prioritization of compounds for inter-species MRL extrapolation (meet all or some) are:

- Compounds for which an MRL has been established in one or more species by JECFA;
- Compounds that are frequently used in food animal production, or used in the production of food animal commodities often traded internationally;
- Compounds for which a specific request for extrapolation has been made by a member country to the CCRVDF;
- If use of the compound in a species currently without an MRL is necessary to improve animal welfare or minimize the development of infectious organism resistance. .

Task III: **Prepare recommendations for the CCRVDF to request JECFA to consider whether EHC 240 provides sufficient guidance for JECFA to develop a scientific framework for extrapolating MRLs between species and tissues, or whether additional scientific considerations are required**

Criteria used in EHC 240 for MRL extrapolation between tissues

- A full set of residue data is available for the original/major species
- The metabolic profile is comparable
- The marker residue is present in the species in which MRLs are to be extrapolated, and could be monitored by a validated analytical method
- There is an approved use in the species in which the MRLs are to be extrapolated.

Questions CCRVDF may consider asking JECFA:

1. EHC 240 does not define "what comparable metabolic profile between species" means. JECFA may consider elaboration of the criteria described in EHC 240 (such as the precise definition of "metabolically comparable".
2. 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.
3. 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 EU 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?
    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.
4. 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 may 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 may also wish to consider the use of in vitro metabolic models for certain compounds.
5. 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.
6. 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.
7. Whether extrapolation of MRLs from terrestrial species to fish could be considered.
8. 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 ratio, likely unsubstantial residue depletion other than some degradation in honey etc.) in extrapolation, and adjusting for food consumption values.
    a. The work of the CCRVDF Electronic Working Group on Honey needs to be aligned for this activity.

9. Whether non-Codex MRLs (from member countries) could be used as supporting data for MRL extrapolation.

10. 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.

Task IV: Proposed risk analysis policy for use by CCRVDF when considering extrapolating MRLs:

Scope

The objective of this policy is to provide suggested guidance to (CCRVDF and) JECFA when considering extrapolation of MRLs for veterinary drug residues. Extrapolation of the MRLs from a species in which a full residue data package has been evaluated to other species is scientifically feasible. A new approach based on the concept of risk analysis (incorporating both risk assessment and risk management) for extrapolating MRLs from one species to another should be considered. This approach should recognize that extrapolation of MRLs is required due to a lack of metabolism or residue depletion data in some species. However, a detailed risk assessment may determine that extrapolated MRLs, if derived from adequate initial data, does not represent any additional risks to public health.

General Aspects

- 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).
- Extrapolation of MRLs is generally required for species which are farmed in small numbers for which a full data package to establish JECFA MRLs by normal procedures is not available.
- 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.
- 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.
- 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.
- 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.
- 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.

Proposed Risk Assessment Policy for JECFA

1. 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.
2. JECFA should consider that those drugs in which the parent compound is the marker residue are good candidates for MRL extrapolation.

3. 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.

4. JECFA should take into account that physiologically-related food producing species (ruminants to ruminants, monogastric to monogastric), generally exhibit similar patterns of metabolism and residues. Therefore extrapolation of MRLs between related tissue matrices of similar species is justified (e.g., cattle liver to sheep liver). If the metabolic profile of a particular compound is known to be different between such species, information regarding the ratio of MR/TR should be sought. Such ratios can then be used to make appropriate modifications to the extrapolated MRL.

5. Where identical or only slightly different, MRLs have been established for the same tissue matrices in three different animal classes (e.g., ruminant, monogastric and avian) based on separate and complete residue data packages, these MRLs could possibly be extrapolated to all food-producing animals (except fish and honey).

6. Substances for which no or limited metabolism occurs (e.g. sulfonamides, penicillins and tetracyclines), or the metabolites have little or no pharmacologic/toxicologic activity compared to the parent compound, are also likely to be good candidates for group MRLs. However, this may need consideration that the toxicity/antimicrobial activities of chemicals within that class are comparable.

7. JECFA should consider alternative ways for extrapolating MRLs to honey since simple extrapolation of MRLs from animal tissues to honey may not be scientifically justifiable. For example, this could be addressed by using the most conservative MRL, applying an appropriate correction factor to account for the uncertainty (e.g., lack of data on MR/TR ratio, residue depletion/degradation in honey compared to in animal tissues etc.), and considering the differences in consumption factors of honey and the tissue from which MRL is to be extrapolated.

8. JECFA should consider alternative ways for extrapolating MRLs to fish. Metabolism in fish is likely to be slower than in warm-blooded animals and the parent compound is the most common marker residue identified in fish. As a result, the MR/TR ratio is likely to be higher in fish (MR being the parent compound), and the muscle MRL extrapolated from warm-blooded animal to fish is likely to be conservative. However, consideration should be given to that the MRLs established in such manner are not overly conservative.