CODEX ALIMENTARIUS COMMISSION E

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CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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DISCUSSION PAPER ON EXTRAPOLATION OF MRLS TO ADDITIONAL SPECIES AND TISSUES

Report of the CCRVDF Electronic Working Group 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

Background:

1. At the 19th Session of the CCRVDF (Burlington, United States of America, 2010), the Committee agreed to consider the development of a risk analysis policy for extrapolation of MRLs to additional species and tissues. In this regard, the Committee agreed to establish an electronic working group, led by Canada and working in English only and open to all Codex members and observers, with the following tasks:

(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.

2. The committee noted the existence of basic principles for extrapolation of MRLs included in the EHC 240 as well as more than 10 years of experience of the European Union with the extrapolation of MRLs.

Issues:

3. The absence of MRLs for veterinary drugs in some food-producing animal species/tissues raises challenges for appropriate protection of human health, with regard to unsafe levels of veterinary drug residues likely to be found in the food commodities derived from these animals. The lack of MRLs hinders the control of veterinary drug residues in food commodities derived from these animals within the framework of national residue monitoring and surveillance programs.

4. The absence of internationally accepted MRLs in particular species/tissues may lead to the application of zero tolerance or arbitrary default in the international trade of such species/tissues. Such practice is generally not justified on food safety grounds, especially where a full toxicological assessment has been completed and MRLs for one or more species have been established.

5. These challenges have been identified at several sessions of the CCRVDF meetings by competent authorities as well as the veterinary pharmaceutical industry. The main reason for the inability to establish MRLs in some species is the lack of complete residue data package for those species, associated mainly with insufficient financial return or lack of patent protection for such investments.

6. To address these issues, extrapolation of the MRLs from a species in which a full residue data package has been evaluated to other species may be an option. A new approach, based on the concept of risk analysis which both associates- risk assessment and risk management, should be considered.

Items for Consideration and Discussion:

***Task I*: Collate and summarise all the available national and regional guidelines and documents and published literature pertinent to the extrapolation of MRLs:**

7. Members of the electronic working group (e-WG) on MRL extrapolation were requested to submit the currently available guidelines for MRL extrapolation within their jurisdiction. Based on the submitted information, the following guidelines on MRL extrapolation are available:

a. European Union (EU): EU has comprehensive guidelines in regards to MRL extrapolation. They include: (1) Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin, EMEA/CVMP/187/00, (2) Safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/SWP/66781/2005, (3) Note regarding CVMP guidelines on data requirements for veterinary medicinal products intended for minor uses or minor species, and (4) Technical guidance: Extrapolation of data from major species to minor species regarding the assessment of additives for use in animal nutrition, EFSA 2008 (The EFSA Journal, 803: 1-5). These guidelines provide information on extrapolation of MRLs between the same types of foodstuffs/matrices, i.e. typically from a major to a minor species. Such extrapolations are generally restricted between related species. However, when MRLs in more than one major food animal is available, extrapolation to all food producing animals are also possible. MRL extrapolation requires that the marker residue is present in the species in which the MRL is to be extrapolated, and the analytical method available is applicable to this species. Recently, EU has also passed a regulation (CR No 470/2009) that supports the extrapolation of MRLs between tissues. However, scientific guideline on such extrapolation is not yet available. It is important to note that this regulation emphasizes to take into account the adequacy of the safety factors already inherent in the establishment of MRLs so as not to compromise the drug availability and hence, the animal welfare.

b. JECFA - FAO/WHO EHC 240. The Chapter 8.5 of the FAO/WHO guidelines allows flexibility to extrapolate MRLs from one or more species to a physiologically-related species provided that the metabolic profile is comparable, the marker residue is present in the species for which the extension is considered, an analytical method is available, and there is an approved use. No detailed criteria are described, and the guideline recommends extrapolation to be considered on a case-by-case basis.

c. USA: Regulations (Code of Federal Regulations Title 21 Section 514.1) were previously published that allowed flexibility for the Center for Veterinary Medicine to extrapolate U.S. tolerances where scientifically appropriate from a major species to a minor species. The regulations have since been removed. Detailed scientific guidance is not available, but extrapolation of tolerances is considered on a case-by-case basis.

d. Canada: There is no policy in place in Canada regarding extrapolating MRLs from one animal species to another. However, there is a policy for extrapolating tolerances in honey for risk management purposes, called Working Residue Level (WRL) policy. These tolerances (WRL), though not an official standard, are derived based on a risk analysis approach, and guides the level of compliance and enforcement action commensurate with the level of risk to human health associated with the presence of certain veterinary drug residues in honey. WRLs are derived using the most conservative MRL value established in tissues (i.e. muscle MRL) of food producing animals, applying an additional factor (generally 10) to account for uncertainties, and adjusting for food consumption values. This approach, though scientifically debatable (especially on the residue kinetics and persistence in honey), has provided a practical way of managing drug residue risks without compromising human safety.

e. Other chemical or pesticide guidelines: Various scientific and regulatory authorities have explored the issue of extrapolating tolerance limits of other chemical entities (such as pesticides) between livestock species. The OECD has considered that results of chemical residue studies in cattle may be extrapolated to other mammalian species, while results in laying hens may be extrapolated to other

poultry species (OECD, 2007). JMPR has discussed the similar issue of extrapolation of residue data from major to minor crops.

<u>Task II</u>: 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

This section has been broken down into two parts based on the comments received:

IIa. Extrapolation of MRLs between species

8. The list of substances which were proposed by the e-WG members as priority for MRL extrapolation between species are detailed in Appendix Ia.

9. Prioritization of compounds for inter-species MRL extrapolation should be based on the following criteria. Drugs proposed for MRL extrapolation should meet some or all of the following criteria:

- 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.

10. Note that some of the compounds in Appendix Ia do not have JECFA-established MRLs in any species (amoxicillin, clopidol, lasalocid, oxibendazole, salinomycin). Issues surrounding extrapolation of MRLs for such compounds is discussed in further detail in Section IIIc, Point 6.

IIb. Extrapolation of MRLs between tissues of the same species

11. The list of substances which were proposed by the e-WG members as priority for MRL extrapolation to tissues within the same species are detailed in Appendix Ib.

12. The following rationale was provided by members on the need to extrapolate MRLs between tissues; some analytical methods (especially multi-residue methods) are developed in only one tissue or matrix (e.g, kidney or liver), and if MRLs are not set in that tissue it may pose a challenge for the national residue monitoring program. There is currently less agreement on the scientific validity of extrapolating MRLs from one tissue to another. This is particularly difficult for compounds in which the marker residue makes up a small proportion of the total residue, or the marker residue:total residue (MR/TR) ratio varies widely between tissues. The e-WG suggests that the CCRVDF approach JECFA to discuss scientifically valid mechanisms by which MRLs can be extrapolated between tissues of the same species.

<u>Task III</u>: 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:

This section has been divided into three parts:

IIIa. Current possibilities for MRL extrapolation between species within the JECFA (EHC 240) and EU guidelines

13. Current JECFA guidelines (EHC 240) provide flexibility of MRL extrapolation for the same tissue between related species (Table 1) provided that the following conditions are met:

- 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.

14. EU guidelines (EMA 2006) for MRL extrapolation are similar to the JECFA guidelines, though differences exist in the extent of species extrapolation (see Table 1).

Table 1. Comparison of EHC 240 and EU guidelines on possible MRL extrapolation between species

MRL extrapolation - EU Guidelines		**MRL extrapolation - EHC 240**	
Existing MRLs based on full data package:	*Extrapolation to:*	*Existing MRLs based on full data package:*	*Extrapolation to:*
Major ruminant (meat)	All ruminant (meat)	Ruminant (muscle, liver, kidney, fat)	All ruminants
Major ruminant milk	All ruminant milk	-	-
Major monogastric mammal	All monogastric mammals	Non-ruminant mammals (muscle, liver, kidney, fat)	All non-ruminant mammals
Chicken and eggs	Poultry and eggs	Chicken and eggs	Poultry and eggs
Salmonidae	All fin fish	-	-
Either a major ruminant or a major monogastric mammal	Horses	-	-
If identical MRLs in cattle (or sheep), pigs and chicken	All food producing animals (except fish)	-	-

IIIb. Current possibilities for MRL extrapolation between tissues or drug classes within the JECFA (EHC 240) and EU guidelines

15. Neither EHC 240 nor the EU guidelines specify whether extrapolation can be done from one food matrix (e.g., liver) to another (e.g., kidney); or whether MRL extrapolation could be done for different molecules within the related (same) class of compounds.

IIIc. Comments from the working group on specific approaches for extrapolation of MRLs

1. Extrapolation of an MRL between the same types of foodstuffs/matrices, in physiologically-related species:

16. This type of extrapolation is currently possible within the EHC 240 (on a case by case basis) for a limited number of physiologically-related species. This approach is also used extensively by the EU (Table 1). Such extrapolations of MRLs between physiologically-related species do not likely compromise food safety, due to the already conservative food consumption and acceptable daily intake allowances used by regulatory agencies. There is also significant empiric data to support this practice. Of the 44 compounds for which JECFA has established MRLs in more than one species, 32 / 44 compounds have the same MRLs for the same tissue matrices in all the species. A further 6 / 44 compounds have the same MRLs in all but one matrix between species (see Appendices 2a and 2b).

17. However, the guideline does not explicitly define how such criteria for interspecies extrapolation of MRLs are to be met. For example, a "comparable metabolic profile between species" for a given drug is not specified, and could be defined in a number of ways:

- Approach 1: The metabolite:total residue ratio for **each** major metabolite must be within a set percentage over a given time period for both species;
- Approach 2: The spectrum of metabolites produced by each species must be similar, although the relative quantities of such metabolites may differ.

18. Note that such approaches for verifying a "comparable metabolic profile between species" will necessitate qualification, and possibly quantification, of drug metabolites in both the original and extrapolated species. Such data is not likely to be available in most cases, as if it were available for both species the MRLs could be established using standard procedures (thus extrapolation of MRLs would not be required).

19. Further (updated) guidance from JECFA on the criteria/assumptions to be used for interspecies extrapolations, the minimum data required to support such extrapolation, and extrapolation to additional (unrelated) species may need to be sought.

- The CCRVDF may wish to ask JECFA for elaboration of the criteria described in EHC 240 (such as the precise definition of "metabolically comparable").
- Comments from JECFA should be sought regarding differences in the extent of interspecies MRL extrapolation between the EHC 240 and EU guidelines.
    - 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. Extrapolation of MRLs between fish and other aquaculture species is highly important to members of the working group. 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?
    - Unlike the EU guidelines, EHC 240 does not specify 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. Clarification from JECFA on the suitability of such an approach would be beneficial.
- JECFA may wish 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.
- 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.

2. Extrapolation between different types of foodstuffs/matrices of the same species:

20. There is an increasing demand and interest for such extrapolations (for example, multi-residue methods available often are only for one type of tissue), but there is very little experience in this approach. This type of extrapolation would require more sophisticated approaches based on pharmacokinetic models and validated correlations of marker residue: total residue (MR/TR) ratios between tissues. Such models have not been validated yet, and may need to be specific for each drug. If an approach to inter-tissue extrapolation is scientifically valid and feasible, such an approach would also be useful for extrapolation of MRLs for substances used under the cascade system (e.g., extra-label use of a substance in lactating animals, risk management of residues in specific commodity tissues where no MRL has been established).

21. However, working group members have expressed a number of concerns regarding inter-tissue extrapolation.

- Extrapolation of MRLs from a tissue with low marker residue concentration (such as muscle) to a tissue with higher, more slowly-depleting concentrations (such as liver or kidney) may result in a prohibitively long withdrawal period before residues in the slower-depleting tissue reach the extrapolated MRL.
- Unlike the history of MRL extrapolation between species, few drugs evaluated by JECFA have the *same* MRL for all tissues. Of the 90+ substances with JECFA-established MRLs in multiple tissues, only eight (colistin, erythromycin, nicarbazin, penicillin G, sulfadimidine, thiabendazole, trichlorfon, and tylosin) have the same MRL in muscle, liver, kidney and fat/skin. Some compounds have the same MRL in multiple tissues, but there is no apparent correlation between the MRLs of various tissue types.
- Exposure assessment scenarios may predict that extrapolating MRLs between tissues may produce only trivial differences in drug residue exposure compared to traditional approaches. However, such exposure assessments must be quantified.

22. Until such concerns have been addressed, more discussion and experience are required. To help provide the necessary data on which to base any future inter-tissue extrapolations (or demonstrate its

invalidity), sponsors and regulatory agencies could promote the establishment of MRLs in all major edible tissues when submitting/reviewing drug residue data packages. The working group may wish to recommend that JECFA evaluate the feasibility of such inter-tissue extrapolations.

3. Extrapolation of MRLs between therapeutically/chemically closely related compounds or members of the same class of compounds (group MRLs):

23. Such extrapolations have been done in the past in the case of natural penicillins, tetracyclines and sulfonamides (group MRLs). However, this is only appropriate if there is a common mechanism of toxicological/microbial concern for all compounds within the class, and all compounds are of comparable toxicity. As well, there is no general scientific approach on the criteria necessary to perform such extrapolations. 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. The CCRVDF may wish to seek further advice from JECFA on this issue.

4. Extrapolation of MRLs from terrestrial species to fish:

No such extrapolation has been performed by JECFA, however, such an extrapolation may be feasible in the following scenario:

- If the *parent* compound is the marker residue
- Similar *MRLs* have been established for muscle of more than one terrestrial species

24. In such cases the most conservative muscle MRL from a terrestrial species could be extrapolated to muscle of salmonidae, and consequently to all fin fish. The available studies comparing the metabolism of veterinary drugs in salmonidae and other animal species are rather rare. However, 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. Such an approach may be overly conservative, and lead to unnecessarily prolonged withdrawal periods for aquaculture drugs. The CCRVDF may wish to ask JECFA for the suitability of extrapolation of MRLs from terrestrial species to fish.

5. Extrapolation of MRLs to honey:

25. Currently there are no well-defined criteria for extrapolation of MRLs in honey due to complexity of drug residue kinetics in honey and differences in the treatment modalities. Advice should be sought from the CCRVDF working group on honey as to the feasibility of MRL extrapolation from foodstuffs of other species to honey. One approach which could be considered for extrapolation to honey is by using the most conservative MRL value established in tissues (i.e. muscle MRL) of food producing animals, applying an appropriate factor to account for uncertainties (MR/TR ratio, likely unsubstantial residue depletion other than some degradation in honey etc.) in extrapolation to honey, and adjusting for food consumption values that ensures that the overall exposure to residues from all sources is within the ADI.

26. The work of the CCRVDF Electronic Working Group on Honey is also relevant to aspects of this work on extrapolation of MRLs for veterinary drugs in honey. The chairs of both groups have discussed the potential for overlap here and agreed that both groups should address this topic in their respective papers prepared for the 20th session. The Committee is asked to consider the most appropriate forum to continue discussions on the extrapolation of MRLs to honey.

6. Acceptance of non-Codex MRLs versus MRL extrapolation

27. Mutual recognition by Codex members occurs for MRLs adopted in other recognized bodies when Codex does not have a standard in place. Many developed countries have responsibly set MRLs for veterinary drugs in species, which JECFA has not evaluated. Provided that the MRLs were set based on standards and practices equivalent (but not necessarily identical) to those applied by the JECFA, CCRVDF should be considering if these MRLs might be adopted for such species, even on a temporary basis, pending a more complete, independent assessment if necessary. Adoption of such non-Codex derived MRLs may alleviate the need for interspecies MRL extrapolation of many substances. However, differences in

environmental conditions (such as temperature/climate) or drug usage patterns between jurisdictions, as well as different consumption factors used in calculating MRLs, should be taken into account. Such differences could result in MRLs for a particular species that are appropriate for the original, but not subsequent, jurisdictions. The CCRVDF should consider if compounds without a JECFA-derived MRL in any species are eligible for MRL extrapolation to other species. If eligible, what priority should these compounds be given?

28. Numerous members stated that compounds without a JECFA-established MRL should be eligible for extrapolation based on regional/national MRLs, but are of lower priority than compounds with JECFA-established MRLs in at least one species. One member country considers that such compounds are not eligible for MRL extrapolation. The rationale was that ADI establishment and exposure assessment by JECFA are essential conditions for food safety evaluation. Members also noted that adoption of MRLs established by other regulatory agencies, not as an alternative to extrapolation but as temporary MRLs, should be considered so as to solve urgency cases in trade exchanges. These MRLs should remain as temporary until assessed by JECFA. The EWG considers that there is a diverse range of opinion on the issue of extrapolation of non-JECFA-derived MRLs, and further discussion will be required. However, such discussion need not delay implementation of other aspects of MRL extrapolation.

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

Scope

29. 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. Extrapolation of MRLs from one tissue to another in the same species may be more scientifically challenging. The objective of this policy is to provide guidance to (CCRVDF and) JECFA when considering extrapolation of MRLs for veterinary drug residues.

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.

Risk Analysis Policy

1. In order to extrapolate MRLs, JECFA should consider 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 on species in which the MRLs are to be extrapolated.
2. 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.
3. 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.
4. 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).
5. JECFA should consider that those drugs in which the parent compound is the marker residue are good candidates for MRL extrapolation.
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 tissues to honey may not be possible. 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. *(Note: There were some issues raised by the eWG members for MRL extrapolation to honey, and this should be further discussed at the upcoming CCRVDF meeting in collaboration with the working group on honey)*
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. *(Note: Some members have expressed concerns that this approach might lead to too conservative MRLs in fish, and needs further discussion at the upcoming CCRVDF meeting).*

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Appendix 1a. Substances proposed by the e-WG members as priority for MRL extrapolation between species:

Drug substance	**Extrapolation from (JECFA)**	**Extrapolation to****	**Requested by**	**Approved in:**
Abamectin	Cattle	All ruminants Horses	NZ	
Albendazole	Cattle Sheep	Goat	Thailand	
Amoxicillin*	Cattle tissues	Sheep tissues Swine tissues	USA	(Note: assessed by 75th JECFA)
Avilamycin	Chicken Turkey	All poultry	Thailand	
Ceftiofur	Cattle Pigs	All mammals	NZ	
Chortetracycline	Cattle Sheep Pig Poultry	Goat	Thailand	
Clenbuterol	Cattle Horse	Different species, tissues/matrices		
Clopidol*		Quail, rabbits		
Closantel	Cattle Sheep	Goat	Thailand	
Colistin	Chicken Turkey	All poultry	Thailand	
Cyhalothrin	Cattle Sheep Pig	Goat	Thailand	
Cypermethrin	Cattle Sheep	All mammals	NZ	
Deltamethrin	Cattle Sheep	All ruminants	NZ	
Doramectin	Cattle	All mammals	NZ	
Eprinomectin	Cattle	Deer	NZ	
Fenbendazole	Multiple ruminants	Sheep Deer	NZ	
Ivermectin	Cattle (liver, fat, milk) Sheep Pig	Bison, Deer, Elk, Horse		
Lasalocid*		Quail, Sheep, Rabbit, Turkey		
Levamisole	Cattle Sheep Pig Poultry	All mammals	NZ	
Lincomycin	Chicken	All poultry	Thailand	
Monensin	Cattle Sheep Goat Chicken Turkey Quail	Quail, Sheep, Rabbit, Turkey		
Moxidectin	Cattle	Bison, Deer, Elk, Horse		

Drug substance	Extrapolation from (JECFA)	Extrapolation to**	Requested by	Approved in:
	Sheep Deer			
Narasin	Cattle Pig Chicken	Quail, Sheep, Rabbit, Turkey		
Oxibendazole*		Sheep		
Oxytetracycline	Multiple species	Different species, tissues/matrices		
Ractopamine	Cattle Pig	Different species, tissues/matrices		
Salinomycin*		Quail, Sheep, Rabbit, Turkey		
Spectinomycin	Chicken	All poultry	Thailand	
Spiramycin	Chicken	All poultry	Thailand	
Streptomycin	Multiple species	Different species, tissues/matrices		
Sulfonamides (except sulfathiazole)	Cattle Sheep Pig Poultry	All mammals?		
Tetracycline	Multiple species	Different species, tissues/matrices		
Tilmicosin	Chicken Turkey	Rabbit All poultry species	?? Thailand	
Triclabendazole	Cattle Sheep	Goat	Thailand USA	
Tylosin	Cattle Pig Chicken	All food producing species	NZ	
Zilpaterol*		Different species, tissues/matrices		

*****denotes no JECFA-established MRL is available for these compounds

**MRLs should not be extrapolated to a species for which the compound is not approved. Therefore countries that request an extrapolation of MRLs to another species should provide evidence that the compound is indeed approved in that species.

Appendix 1b. Substances proposed by the e-WG members as priority for MRL extrapolation to tissues within the same species:

Drug substance	Extrapolation from:	Extrapolation to:	Request by:	Approved in:
Ivermectin	Cattle (liver, fat, milk)	Cattle muscle		

Appendix 2a: List of substances evaluated by JECFA with the same MRLs for the same tissues in multiple species

Compound (marker residue)	**Species for which MRLs are the same**	**Tissues (applicable to all species listed)**	**MRL (µg/kg)**
Albendazole (2-amino benzimidazole)	Cattle Sheep	Muscle Liver Kidney Fat Milk	100 5000 5000 100 100
Avilamycin (dichloroisoeverninic acid – DIA)	Pig Rabbit Chicken Turkey	Muscle Liver Kidney Fat/skin	200 300 200 200
Ceftiofur (desfuroylceftiofur)	Cattle Pig	Muscle Liver Kidney Fat	1000 2000 6000 2000
Chlortetracycline (tetracycline + chlortetracycline + oxytetracyline)	Cattle Sheep Pig Poultry	Muscle Liver Kidney Milk Eggs	200 600 1200 100 400
Clenbuterol (clenbuterol)	Cattle Horse	Muscle Liver Kidney Fat	0.2 0.6 0.6 0.2
Colistin (aka polymyxin) (colistin A + B)	Cattle Sheep Pigs Chicken Rabbit Goat Turkey	Muscle Liver Kidney Fat Milk Eggs	150 150 150 150 150 300
Cypermethrin (total cypermethrin residues)	Cattle Sheep	Muscle Liver Kidney Fat Milk	50 50 50 1000 100
Deltamethrin (deltamethrin)	Cattle Sheep Chicken Salmon (muscle only)	Muscle Liver Kidney Fat Milk Eggs	30 50 50 500 30 30
Dexamethasone (dexamethasone)	Cattle Pig Horse	Muscle Liver Kidney Milk	1 2 1 0.3
Diclazuril (diclazuril)	Sheep Poultry Rabbit	Muscle Liver Kidney Fat	500 3000 2000 1000
Dihydrostreptomycin (streptomycin + dihydrostreptomycin)	Cattle Sheep Pig Chicken	Muscle Liver Kidney Fat Milk	600 600 1000 600 200

Compound (marker residue)	Species for which MRLs are the same	Tissues (applicable to all species listed)	MRL (µg/kg)
Erthromycin (erythromycin)	Chicken Turkey	Muscle Liver Kidney Fat Eggs	100 100 100 100 50
Febantel (sum of metabolites expressed as oxfendazole sulfone)	Cattle Sheep Pig Horse Goat	Muscle Liver Kidney Fat Milk	100 500 100 100 100
Fenbendazole (sum of metabolites expressed as oxfendazole sulfone)	Cattle Sheep Pig Horse Goat	Muscle Liver Kidney Fat Milk	100 500 100 100 100
Flumequine (flumequine)	Cattle Sheep Pig Chicken Trout (muscle only) Shrimp (muscle only)	Muscle Liver Kidney Fat	500 500 3000 1000
Gentamicin (gentamicin)	Cattle Pig	Muscle Liver Kidney Fat Milk	100 2000 5000 100 200
Levamisole HCl (levamisole HCl)	Cattle Sheep Pig Poultry	Muscle Liver Kidney Fat	10 100 10 10
Monensin (monensin)	Cattle Sheep Goats	Muscle Liver Kidney Fat Milk	10 20 10 100 2
Monensin (monensin)	Chicken Turkey Quail	Muscle Liver Kidney Fat	10 10 10 100
Narasin (narasin A)	Cattle Pig Chicken	Muscle Liver Kidney Fat	15 50 15 50
Neomycin (neomycin)	Cattle Sheep Goat Pig Chicken Turkey Duck	Muscle Liver Kidney Fat Milk Eggs	500 500 10000 500 1500 500
Oxfendazole (sum of metabolites expressed as oxfendazole sulfone)	Cattle Sheep Pig Horse Goat	Muscle Liver Kidney Fat Milk	100 500 100 100 100

Compound (marker residue)	**Species for which MRLs are the same**	**Tissues (applicable to all species listed)**	**MRL (µg/kg)**
Oxytetracycline (tetracycline + chlortetracycline + oxytetracycline)	Cattle Sheep Pig Poultry Fish (muscle only) Prawns (muscle only)	Muscle Liver Kidney Milk Eggs	200 600 1200 100 400
Penicillin G (penicillin G)	Cattle Pig Chicken	Muscle Liver Kidney Milk	50 50 50 4
Phoxim (phoxim)	Sheep Goats Pigs	Muscle Liver Kidney Fat	50 50 50 400
Ractopamine (ractopamine)	Cattle Pigs	Muscle Liver Kidney Fat	10 40 90 10
Sarafloxacin (sarafloxacin)	Chicken Turkey	Muscle Liver Kidney Fat	10 80 80 20
Spectinomycin (spectinomycin)	Cattle Sheep Pig Chicken	Muscle Liver Kidney Fat Milk Eggs	500 2000 5000 2000 200 2000
Streptomycin (streptomycin)	Cattle Sheep Pig Chicken Turkey	Muscle Liver Kidney Fat Milk	600 600 1000 600 200
Sulfadimidine (sulfadimidine)	Cattle Sheep Pig Poultry	Muscle Liver Kidney Fat Milk	100 100 100 100 25
Tetracycline (tetracycline + chlortetracycline + oxytetracyline)	Cattle Sheep Pig Poultry	Muscle Liver Kidney Milk Eggs	200 600 1200 100 400
Thiabendazole (thiabendazole + metabolites)	Cattle Sheep Goat Pig	Muscle Liver Kidney Fat Milk	100 100 100 100 100
Tilmicosin (tilmicosin)	Cattle Sheep	Muscle Liver Kidney Fat	100 1000 300 100
Tylosin (A, B, C, D) (tylosin A)	Cattle Pig Chicken	Muscle Liver Kidney Fat Milk Eggs	100 100 100 100 100 300

Appendix 2b: List of substances evaluated by JECFA with different MRLs in the same tissues in multiple species

Compound (marker residue)	**Species for which MRLs are different**	**Tissues**	**MRL (µg/kg)**
Closantel (closantel)	Cattle Sheep	Muscle (cattle) Muscle (sheep) Liver (cattle) Liver (sheep) Kidney (cattle) Kidney (sheep) Fat (cattle) Fat (sheep)	1000 1500 1000 1500 3000 5000 3000 2000
Cyhalothrin (cyhalothrin)	Cattle Sheep Pig	Muscle (cattle, sheep, pig) Liver (cattle, pig) Liver (sheep) Kidney (cattle, sheep, pig) Fat (cattle, sheep, pig) Milk (cattle)	20 20 50 20 400 30
Danofloxacin (danofloxacin)	Cattle Pig Chicken	Muscle (cattle, chicken) Muscle (pig) Liver (cattle, chicken) Liver (pig) Kidney (cattle, chicken) Kidney (pig) Fat (cattle, pig, chicken)	200 100 400 50 400 200 100
Doramectin (doramectin)	Cattle Pig	Muscle (cattle) Muscle (pig) Liver (cattle, pig) Kidney (cattle, pig) Fat (cattle, pig) Milk (cattle)	10 5 100 30 150 15
Flubendazole (flubendazole)	Pig Poultry	Muscle (pig) Muscle (poultry) Liver (pig) Liver (poultry) Eggs (poultry)	10 200 10 500 400
Ivermectin (22, 23-dihydro-avermectin B1a)	Cattle Sheep Pig	Liver (cattle) Liver (sheep, pig) Fat (cattle) Fat (sheep, pig) Milk (cattle)	100 15 40 20 10
Lincomycin (lincomycin)	Pig Chicken Cattle (milk only)	Muscle (pig, chicken) Liver (pig, chicken) Kidney (pig) Kidney (chicken) Fat (pig, chicken) Milk (cattle)	200 500 1500 500 100 150
Monensin (monensin)	Cattle Sheep Goats Chicken Turkey Quail	Muscle (all species) Liver (ruminants) Liver (poultry) Kidney (all species) Fat (all species) Milk (cattle)	10 20 10 10 100 2
Moxidectin (moxidectin)	Cattle Sheep Deer	Muscle (cattle, deer) Muscle (sheep) Liver (cattle, sheep, deer) Kidney (cattle, sheep, deer) Fat (cattle, sheep, deer)	20 50 100 50 500

Compound (marker residue)	**Species for which MRLs are different**	**Tissues**	**MRL (µg/kg)**
Spiramycin (spiramycin + neospiramycin)	Cattle Pig Chicken	Muscle (cattle, pig, chicken) Liver (cattle, pig, chicken) Kidney (cattle, pig) Kidney (chicken) Fat (cattle, pig, chicken) Milk (cattle)	200 600 300 800 300 200
Tilmicosin (tilmicosin)	Cattle Sheep Pig Chicken Turkey	Muscle (cattle, sheep, pig, turkey) Muscle (chicken) Liver (cattle, sheep) Liver (pig) Liver (chicken) Liver (turkey) Kidney (cattle, sheep) Kidney (pig) Kidney (chicken) Kidney (turkey) Fat (cattle, sheep, pig) Fat (chicken, turkey)	100 150 1000 1500 2400 1400 300 1000 600 1200 100 250
Triclabendazole (keto-triclabendazole)	Cattle Sheep	Muscle (cattle) Muscle (sheep) Liver (cattle) Liver (sheep) Kidney (cattle) Kidney (sheep) Fat (cattle, sheep)	250 200 850 300 400 200 100