CODEX ALIMENTARIUS COMMISSION

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Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 7 **CX/RVDF 21/25/8**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

25th Session
(Virtual)
12-16 and 20 July 2021

DISCUSSION PAPER ON EXTRAPOLATION OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS TO ONE OR MORE SPECIES

(Prepared by the Electronic Working Group
chaired by the European Union and co-chaired by Costa Rica)

Codex members and observers wishing to submit comments on the proposed approach for the extrapolation of MRLs for veterinary drugs to one or more species and on the proposals for extrapolation of MRLs for veterinary drugs for compounds identified in Part D of the Priority List of Veterinary Drugs[1]
should do so as instructed in CL 2020/42-RVDF available on the
Codex webpage/Circular Letters[2] or CCRVDF/Related Circular Letters[3]

INTRODUCTION

1. In the context of the discussion on maximum residue limits (MRLs) for groups of fish species, the 24th session of the Codex Committee on Residues of Veterinary Drugs (CCRVDF24, 2018) observed that the desirability of extrapolating MRLs was not limited to fish species, but also other animals, noting the extensive list of compounds in the database[4] on countries' needs for MRLs, which might benefit from extrapolation and increased availability of Codex MRLs for veterinary drugs for trade. It was proposed that further consideration be given to developing a policy for extrapolation of MRLs for all species as opposed to only aquatic species and that a pilot be undertaken on extrapolation of some compounds for which there were already existing (adopted) Codex MRLs. In view of this observation, CCRVDF24:

   (i) agreed to amend the *Risk analysis principles applied by CCRVDF* to provide for more autonomy to risk managers to propose extrapolation of MRLs to one or more species as opposed to the current policy that such MRLs could only be recommended where the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had identified that it is scientifically justifiable and the uncertainties have been clearly defined, and
   (ii) identified 10 compounds from the list of Codex MRLs to pilot extrapolation

2. The 41st Session of the Codex Alimentarius Commission (CAC41, 2018) approved the amendment of Section 3.4, paragraph 30 of the *Risk Analysis Principles applied by CCRVDF* as proposed by CCRVDF24. The Commission further approved the Priority List of Veterinary Drugs Part A (compounds for evaluation / re-evaluation by JECFA) and Part D (compounds for which CCRVDF will consider extrapolation of MRLs to additional species).[5]

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1 REP18/RVDF, Appendix VI.
Working documents, including CRDs, INFO documents and the report of the CCRVDF24 session, are available on: http://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=24

2 http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/

3 http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF

4 See Agenda Item 10, CX/RVDF 20/25/11. Working documents for CCRVDF25 are available at: http://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=25

5 REP18/RVDF, paras. 83, 84, 109, 115 and Appendix VI-Part D
REP18/CAC, paras. 14-15 and Appendices II and VI.
CAC reports can be downloaded from: http://www.fao.org/fao-who-codexalimentarius/committees/cac/meetings/en/

3. CAC41 further noted the clarification from the JECFA Secretariat that the proposed amendment would not modify the intent of the work or the safety evaluation for residues of veterinary drugs in foods, but serve instead to clarify how CCRVDF could approach its proposed work to develop extrapolation of MRLs as a risk-management decision and from the Codex Secretariat that, until such an amendment as proposed was made by CCRVDF, MRLs for minor species already requested by developing countries would not be available.

4. An Electronic Working Group (EWG) chaired by the European Union (EU) and co-chaired by Costa Rica was established[6] to:

   - Prepare a discussion paper to explore pragmatic ways on how CCRVDF in its role as risk manager could extrapolate MRLs to one or more species;
   - Prepare and contrast such approaches with the revised Option C for aquatic species[7];
   - Conduct a pilot on extrapolation of MRLs identified in Part D of the Priority List[8].

PARTICIPATION AND METHODOLOGY

5. The EWG registered 35 Member countries, 1 Member Organization and FAO to participate in this work. The List of Participants is presented in Appendix IV.

6. The EWG Chairs circulated the first draft document to the EWG members on 2nd October 2018 in English and in Spanish. In line with the terms of reference (TOR) of the EWG, the document contained a proposed approach for CCRVDF for extrapolation, a comparison of the proposed approach with the revised Option C for aquatic species and a proposal on how the proposed approach could be applied in the pilot on extrapolation of MRLs identified in Part D of the Priority list. Sixteen EWG members provided comments on this draft.

7. On the basis of these comments, the EWG Chairs prepared a second draft document and circulated it to the EWG members on the 7th December 2019. Fourteen EWG members sent their comments on this draft.

8. The EWG Chairs finalized the discussion paper and submitted it to the Codex Secretariat for consideration by Codex members and observers.

SUMMARY OF DISCUSSION

9. In their comments on the first draft document, the main comment of a number EWG members was about the uncertainty that exists with regard to the similarity of metabolism between reference and concerned species, even when these are related species, and suggested the need for evidence to support similarity of metabolism on a case-by-case basis. While acknowledging that the availability of such evidence would certainly provide additional assurance, the EWG Chairs noted that the relevant data is not routinely available. They further reminded that the idea behind extrapolation at CCRVDF is precisely to address those situations where species specific data are not available and to provide a pragmatic, risk management approach based on general principles.

10. The EWG Chairs tested the proposed approach using those substances for which Codex MRLs already exist in related species (based on JECFA recommendations). By comparing results of a consumer intake calculation performed using MRLs that would have been established on the basis of extrapolation with results of the consumer intake calculation performed using established MRLs, the EWG Chairs were able to use real data to consider the possible impact of extrapolation on consumer safety. The conclusion of this evaluation was that in the vast majority of cases (23 out of 24 identified cases), extrapolating MRLs based on the originally proposed rules would not be expected to result in a safety concern. However, in a small number of cases exceedance of the ADI could occur. The EWG Chairs therefore accepted that some additional provisions were required in order to guard against this possibility. Such provisions were introduced in the second draft document resulting in a far more conservative approach than originally proposed. In addition, a number of other modifications were introduced to address the comments raised.

11. In their responses, the EWG members signaled their overall agreement with the proposed approach on extrapolation as presented in the second draft document although a number of specific points for consideration were raised. The EWG Chairs responded to the specific points and did some further fine-tuning of the document on the basis of the EWG members additional comments.

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6 REP18/RVDF, para. 84; REP18/CAC para. 15

7 RVDF24/CRD34 (Report of the in-session Working group on groups of fish species) and Revised Option C

8 REP18/RVDF, Appendix VI-Part D

CONCLUSIONS

12. The EWG completed its task as per its TOR. The outcome is presented in the discussion paper attached in Appendix I. For convenience, the revised Option C for aquatic species and Part D of the Priority List for Veterinary Drugs as agreed by CCRVDF24 and approved by CAC41 are presented in Appendices II and III respectively to inform comments on Sections II and IV of Appendix I.

13. The proposal for MRL extrapolations put forward in the discussion paper aims to provide a pragmatic approach for the establishment of MRLs in food producing species for which residue data are not available. The approach builds upon positive evaluations performed by JECFA for the reference species, and lays down criteria (described in Section II of the discussion paper) which, when satisfied, support the conclusion that metabolism in the reference and concerned species is sufficiently similar to allow the reference species MRLs to be applied to the concerned species while maintaining protection of the consumer. The use of this approach would enhance (human and animal) public health by enabling use of certain veterinary drugs in animal species for which the absence of MRLs currently precludes use.

RECOMMENDATIONS

14. Codex members and observers are invited to consider:

    (i) the proposed approach on extrapolation as presented in Section II of the discussion paper;

    (ii) the comparison of the proposed approach with the revised Option C for aquatic species as presented in Section III of the discussion paper; and

    (iii) the pilot on extrapolation of MRLs identified in the priority list Part D using the proposed approach as presented in Section IV of the discussion paper.

APPENDIX I

Discussion Paper

Extrapolation of maximum residue limits for veterinary drugs to one or more species
- See CL 2020/42-RVDF as per Sections II and IV -

I. Introduction

1. The approach on extrapolation proposed in this document relies on there being confidence that metabolism in the concerned species will be similar to that in the reference species, i.e. that major metabolic pathways are comparable and major metabolites are produced in comparable proportions. As a rule, this can be considered to be the case when the reference and concerned species are related species (see 'A note on terminology'). The proposal aims to provide a pragmatic approach based on general principles that can be applied in order to allow establishment of maximum residue limits (MRLs) in species related to those for which MRLs already exist and which were established on the basis of the recommendations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The proposal is specifically aimed at those situations where species-specific data for the concerned species are not available.

2. In terms of selecting a marker residue[9] (i.e. the residue used for monitoring purposes), if there is confidence that metabolism is similar in the reference and concerned species, then the marker residue selected for the reference species should also be appropriate for use in the concerned species. However, confidence in the choice of the marker residue will be greatest in those cases where the marker residue is the parent compound only (as no metabolism is required to produce the marker residue).

3. There can be less confidence when considering possible extrapolations between unrelated species and in cases where a metabolite is included in the marker residue. Therefore, such cases are not considered in this document but could be considered in the future following agreement on the principles to be applied in the most straight forward cases.

A note on terminology

- 'Reference species' is used to refer to a species in which MRLs have been established based on a scientific evaluation by JECFA
- 'Concerned species' is used to refer to a species for which extrapolation is being considered
- 'Related species' means species belonging to the same category of food producing species of ruminant and non-ruminant mammals*, birds or bony fish** (Osteichthyes)
- 'Unrelated species' is used to refer to species belonging to different categories of food producing species

* The category of non-ruminant food producing mammals is considered to include pigs, horses and rabbits

** Three distinct classes of fish are usually identified: (i) jawless fish (Agnatha), (ii) cartilaginous fish (Chondrichytes) and (iii) bony fish (Osteichthyes). To date, MRL data have been provided only for bony fish, and it is these that are predominantly farmed and eaten. Consequently, it is proposed that MRL extrapolations in fish should be limited to this class.

4. When considering possibilities for extrapolation of MRLs, it is important to recognize that the establishment of MRLs represents only part of the process of ensuring consumer safety. Equally important is the establishment of a withdrawal period/withholding time that ensures that the MRLs are respected (this remains a competence of national/regional authorities).

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9 The EHC 240 (1) defines the marker residue as: The parent drug, or any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels. 'Total residue' is defined in CXA 5-1993 (2) as the total residue of a drug in animal derived food consists of the parent drug together with all the metabolites and drug based products in the food after administration of the drug to food producing animals. The amount of total residues is generally determined by means of a study using the radiolabelled drug, and is expressed as the parent drug equivalent in mg/kg of the food'.

5. It is acknowledged that differences may occur in the time taken for residues to deplete in reference and concerned species. However, as long as the pattern of residues in the two species is similar (implying similar ratios of marker to total residues in the two species) at the time at which residues deplete to the MRL (in all tissues[10] and food commodities[2]), these differences are not expected to impact on the safety of extrapolated MRLs. This is because if the pattern of residues is similar and the MRLs are respected, then the consumer will be exposed to the same quantity of residue regardless of whether it is a tissue/food commodity from the reference or concerned species that is ingested (provided that the same quantity of food is consumed from each species). What may differ is the time taken for residues to deplete to the level of the MRLs in the two species, and it is therefore critical that the withdrawal periods applied are sufficient to ensure compliance with the MRLs.

6. Where there are substantial differences in the relative proportions of the marker residue and other residues in the reference and concerned species, the appropriateness of extrapolated MRLs becomes more questionable. Such differences would be reflected by differences in the ratio of marker to total residues (M:T). If the M:T is lower in the concerned than in the reference species and the same MRLs are applied in both species, then, at the time-point at which residues deplete to the MRL, total residue concentrations will be higher in tissues/food commodities from the concerned species than in those from the reference species and, in principle, could possibly lead to consumer exposure exceeding the acceptable daily intake (ADI). Therefore, extrapolation of MRLs should take place where it can be assumed that the M:T used in the intake calculation undertaken for the reference species can also be safely applied to the concerned species.

7. Using the criteria detailed below (under point II. 'Proposed approach'), extrapolation would be possible for many already existing substances. However, it is likely that the possibility of extrapolating MRLs for new substances following future JECFA recommendations will be limited as, for new substances, specific criteria (refer to points II [i] and II [ii] for details) will rarely be satisfied since information for two species would generally be needed.

II. Proposed approach

General criteria for extrapolation

1. Extrapolation should take place only between the same tissues/food commodities in the reference and concerned species (e.g. muscle to muscle, fat to fat etc.).

2. Extrapolation of reference species MRLs to a concerned species on a one to one basis should be considered only if **all** of the following are satisfied:

    1. the reference and concerned species are related.

    2. the marker residue in the reference species is the parent compound only or the MRL status in the reference species is 'unnecessary' and there is an expectation that the active substance will be used under the same conditions (i.e. by the same administration routes and at similar doses) in both species.

    3. the M:T established for the reference species can be applied to the concerned species.

Specific criteria for extrapolation

3. In order to ensure that the third of the above-mentioned three general criteria is satisfied, the following specific criteria are proposed.

    (i) Where identical MRLs have been established in at least two related species on the basis of JECFA recommendations, these MRLs can be extrapolated to other related species (e.g. extrapolate from cattle and sheep to all ruminants).

    Explanatory note: *The existence of identical MRLs in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species*.

    (ii) Where identical M:T values have been used in JECFA calculations for two related species but the MRLs recommended (by JECFA) differ, the most conservative set of MRLs (i.e. the MRLs from the species associated with the lowest consumer exposure estimate) can be extrapolated to other related species (e.g. where different MRL values have been established for cattle and sheep and extrapolation is considered to goats, the lowest set of MRLs should be used for extrapolation).

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10 In the context of this document the term 'tissues' is used to refer to muscle, fat, fat and skin, kidney and liver while the term 'food commodity' is used to refer to milk, eggs or honey.

Explanatory note: *The fact that JECFA considered it appropriate to use identical M:T values in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species.*

(iii) Where the M:T established by JECFA is 1 in all tissues in a single reference species, the same MRLs can be extrapolated to related species.

Explanatory note: *The fact that the M:T is 1 in all tissues/food commodities) indicates that the substance is not metabolized to any significant degree. It is considered reasonable to assume that this would also be the case in the concerned species.*

Finally, while the above criteria can be used in all cases, the following additional criteria are proposed for fish, milk and eggs (i.e. extrapolation for fish, milk and eggs may be based on the above criteria OR based on the additional criteria below):

(iv) For fish, where the MRL in muscle/fillet recommended by JECFA was established based on the limit of quantification (LoQ) (e.g., twice the LoQ), the MRL can be extrapolated to all bony fish.

Explanatory note: *The fact that the MRL in muscle/fillet is below the LoQ indicates that residues in muscle/fillet are not measurable and so do not make a significant contribution to the intake calculation. Even if there are differences in metabolism between fish species, the possibility that they will be so dramatic as to result in a level of residues in muscle/fillet sufficiently high to significantly impact on overall consumer exposure is considered unrealistic.*

(v) For milk and eggs, where the M:T established by JECFA is 1 (in milk or eggs of a reference species), the milk/egg MRL of the reference species can be extrapolated to milk of other ruminants and eggs of other domesticated poultry species, respectively, even if the M:T is not 1 in tissues.

Explanatory note: *For milk and eggs, there may be a concern that the fat content differs between related species. However, if the M:T is 1 in the reference species this indicates that the M:T is not significantly influenced by the fat content.*

Reporting extrapolated MRLs

4. Where CCRVDF agrees to extrapolate MRLs, it should be clear that these MRLs were established by extrapolation rather than on the basis of a substance/species specific JECFA assessment. An appropriate symbol should be included next the relevant values reported in the Codex MRL database. Moreover, extrapolated MRLs should be reconsidered in case the reference MRLs are modified or new data/information on the active substance in question becomes available.

Table summarizing proposed MRL extrapolations

From reference species	To concerned species
Tissues of a ruminant (e.g. cattle, sheep, goats)	Tissues of all ruminants if the marker residue is the parent only* and one of the following apply: (i) identical MRLs already exist in 2 ruminant species (ii) identical M:Ts exist in 2 ruminant species (iii) MRLs have been established in only 1 ruminant species but the M:T = 1 in all tissues.
Milk of a ruminant (e.g. cattle, goats)	Milk of all ruminants if the marker residue is the parent only* and one of the following apply: (i) identical MRLs already exist in milk of 2 ruminant species (ii) identical M:Ts exist in milk of 2 ruminant species (iii) a milk MRL has been established in only 1 ruminant species and the M:T = 1 in milk.

From reference species	To concerned species
Tissues of a non-ruminant mammal (e.g. pigs)	Tissues of all non-ruminant mammals if the marker residue is the parent only* and one of the following apply: (i) Identical MRLs already exist in 2 non-ruminant mammal species. (ii) Identical M:Ts exist in 2 non-ruminant mammal species. (iii) MRLs have been established in only 1 non-ruminant species but the M:T = 1 in all tissues.
Tissues of a bird (e.g. chickens)	Tissues of all birds if the marker residue is the parent only* and one of the following apply: (i) Identical MRLs already exist in 2 bird species. (ii) Identical M:Ts exist in 2 bird species. (iii) MRLs have been established in only 1 species but the M:T = 1 in all tissues.
Eggs from a bird (e.g. chickens)	Eggs from all birds if the marker residue is the parent only* and one of the following apply: (i) Identical MRLs already exist in eggs of 2 bird species. (ii) Identical M:Ts exist in eggs of 2 bird species. (iii) MRLs have been established in only 1 bird species but the M:T = 1 in eggs.
Muscle/fillet of a bony fish (e.g. salmon)	Muscle/fillet of all bony fish if the marker residue is the parent only* and one of the following apply: (i) Identical MRLs already exist in muscle/fillet of 2 bony fish species. (ii) Identical M:Ts exist in muscle/fillet of 2 bony fish species. (iii) MRLs have been established in only 1 fish species but the M:T = 1 in the reference species. (iv) The MRL in the reference species was established based on twice the LoQ.

*The requirement that the marker residue is the parent only does not apply in cases where the MRL classification is 'unnecessary' as there is no marker residue in these cases.

III. Comparison with the revised Option C for aquatic species as presented at CCRVDF24

1. This paper and proposal on extrapolation of MRLs was initiated by a discussion considering extrapolation of MRLs for (groups of) fish species. CCRVDF24 noted the work of the electronic working group (EWG) that had been considering the feasibility of establishing MRLs for (groups of) fish species(3) and received a presentation arising from an in-session meeting of the working group(4). This followed on from previous discussion both at CCRVDF(5) and JECFA(6) on the topic of extrapolation of MRLs. While these reports acknowledge that JECFA can extrapolate its MRL recommendations, a number of factors limit opportunities for this, perhaps most notably the fact that JECFA rules require that there is an authorized use of a substance in the relevant species in order for it to be able to recommend MRLs. JECFA noted that it has guidance on the minimum requirements for extrapolation, which is presented in Environmental Health Criteria (EHC) 240(1), and which include data on metabolism in the concerned species, a common marker residue and the availability of an analytical method suitable for application to foods derived from the concerned species.

2. The proposal that came out of the CCRVDF working group exercise, referred to as the 'revised Option C'(7), was that extrapolation could be considered where the original (or reference) MRL was established in an aquatic species, based on an MRL evaluation by JECFA in line with standard practices (i.e. including existence of an established use in the reference species in line with good veterinary practices (GVP)). This MRL could then be extrapolated to one or more orders of aquatic species, based on the categories identified in Guidelines GL57(8) of the harmonization of technical requirements for registration of veterinary medicinal products (VICH), and from there possibly to fin fish. Extrapolation could be undertaken without a new JECFA evaluation and would not require the existence of an established use in line with GVP in the species to which the MRLs are extrapolated.

3. The CCRVDF did not reach a conclusion on the appropriateness of the revised Option C proposal but noted that interest in extrapolating MRLs was also relevant for species other than fish. It was therefore agreed that an EWG should work to prepare a broader discussion paper on extrapolation (which has resulted in the current paper)(9).

4. The proposal made in this paper is similar to the 'revised Option C' in that it requires that the reference species MRLs are supported by a full JECFA evaluation in line with standard practices (i.e. including existence of an established use according to GVP in the reference species) and in that it allows for extrapolation without a new JECFA evaluation and without an established use according to GVP in the concerned species.

5. The proposal made in this paper goes beyond the 'revised Option C' in that it allows for extrapolation from one or more bony fish species directly to all bony fish under certain conditions (refer to point II [iv] above for details) and it does not require an intermediate step in which MRLs are first extrapolated to orders of fish based on the groupings presented in VICH GL57. As pointed out in the discussions at CCRVDF 24, VICH GL57 was developed as a basis for establishing withdrawal periods and not MRLs. A premise for establishing a common withdrawal period for an order of fish in line with VICH GL57 is, of course, that a common MRL applies to all members of the group. The fact that the VICH guideline raises the possibility that identical withdrawal periods may not be appropriate for all orders of fish acknowledges the fact that the rate of residue depletion may vary (even if an identical MRL exists for all fish species). This is consistent with the current document, which also emphasizes that adequate withdrawal periods need to be established to ensure compliance with extrapolated MRLs. Finally, it should be noted that the confirmatory data recommended by VICH GL57 would still be expected in order to establish a withdrawal period applicable to an order, and this represents a further level of security.

IV. A pilot on extrapolation of MRLs identified in the priority list Part D (Appendix VI of REP18/RVDF(9))

1. This pilot is limited to the extrapolation of MRLs identified in Part D of the Priority List established by CCRVDF24. However, it should be noted that the proposed approach may allow some further extrapolations. For example, where MRLs have been established for tissues of non-ruminant mammals, these could be extrapolated to tissues of other non-ruminant mammal species) where relevant criteria are met (refer to point II for details).

1. Amoxicillin – proposed extrapolation to ruminants					
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pig (µg/kg)	Finfish
	Muscle	50	50	50	50**
	Fat*	50	50	50	-
	Liver	50	50	50	-
	Kidney	50	50	50	-
	Milk	4	4	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes				
Is the marker residue the parent compound?	Yes				
What are the M:Ts	The JECFA report (WHO TRS 969(10)) establishes a microbiological ADI and indicates that the only microbiologically active residue is the parent substance. The M:T in all tissues and milk is therefore considered to be 1 in all species				
Can the MRLs be extrapolated to ruminants?	Yes, as the M:T is 1 in all commodities and, in addition, identical MRLs already exist in 2 ruminant species				
If so, what MRLs are proposed?	Muscle	50 µg/kg			
	Fat*	50 µg/kg			
	Liver	50 µg/kg			
	Kidney	50 µg/kg			
	Milk	4 µg/kg			

* Fat/skin for pigs
** This value applies to finfish fillet

2. Benzylpenicillin – proposed extrapolation to ruminants				
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pig (µg/kg)
	Muscle	50	50	50
	Fat	-	-	-
	Liver	50	50	50
	Kidney	50	50	50
	Milk	4	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes			
Is the marker residue the parent compound?	Yes			
What are the M:Ts	The JECFA report (WHO TRS 799(10)) uses a M:T of 1 in all tissues and milk of all species			
Can the MRLs be extrapolated to ruminants?	Yes, as the M:T is 1 in all commodities and, in addition, identical MRLs already exist in 2 ruminant species			
If so, what MRLs are proposed?	Muscle	50 µg/kg		
	Fat	-		
	Liver	50 µg/kg		
	Kidney	50 µg/kg		
	Milk	4 µg/kg		

3. Tetracyclines – proposed extrapolation to ruminants							
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pigs (µg/kg)	Poultry (µg/kg)	Fish* (µg/kg)	Giant prawn* (µg/kg)
	Muscle	200	200	200	200	200	200
	Fat	-	-	-	-	-	-
	Liver	600	600	600	600	-	-
	Kidney	1200	1200	1200	1200	-	-
	Milk	100	100	-	-	-	-
	Eggs	-	-	-	400	-	
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes						
Is the marker residue the parent compound?	Yes						
What are the M:Ts	The JECFA report (WHO TRS 888(10) uses a M:T of 1 in all tissues, milk and eggs						
Can the MRLs be extrapolated to ruminants?	Yes, as the M:T is 1 in all tissues, milk and eggs and, in addition, identical MRLs already exist in 2 related ruminant species						
If so, what MRLs are proposed?	Muscle	200 µg/kg					
	Fat	-					
	Liver	600 µg/kg					
	Kidney	1200 µg/kg					
	Milk	100 µg/kg					

* Applies only to oxytetracycline

4. Cyhalothrin – proposed extrapolation to ruminants				
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pigs (µg/kg)
	Muscle	20	20	20
	Fat	400	400	400
	Liver	20	50	20
	Kidney	20	20	20
	Milk	30	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes			
Is the marker residue the parent compound?	Yes			
What are the M:Ts	The JECFA report (WHO TRS 900(10) uses the same M:T values in all species (1 in muscle, fat and milk, 0.06 in liver and 0.2 in kidney)			
Can the MRLs be extrapolated to ruminants?	Yes, as the M:Ts established for cattle and sheep are identical, the more conservative set of MRLs (cattle) can be extrapolated to other ruminants. As the M:T for cattle milk is 1, the MRL can be extrapolated to milk of other ruminants			
If so, what MRLs are proposed?	Muscle	20 µg/kg		
	Fat	400 µg/kg		
	Liver	20 µg/kg		
	Kidney	20 µg/kg		
	Milk	30 µg/kg		

5. Cypermethrin – proposed extrapolation to ruminants			
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)
	Muscle	50	50
	Fat	1000	1000
	Liver	50	50
	Kidney	50	50
	Milk	100	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes		
Is the marker residue the parent compound?	Yes		
What are the M:Ts	The JECFA reports use the following values: 0.3 in muscle, 0.8 in fat, 0.1 in liver, 0.05 in kidney (WHO TRS 911(10) and 1 in milk (TRS 925(10) The same values appear to have been used for cattle and sheep		
Can the MRLs be extrapolated to ruminants?	Yes, as the M:Ts established for cattle and sheep are identical and, in addition, identical MRLs already exist in 2 ruminant species. As the M:T for cattle milk is 1, the MRL can be extrapolated to milk of other ruminants		
If so, what MRLs are proposed?	Muscle	50 µg/kg	
	Fat	1000 µg/kg	
	Liver	50 µg/kg	
	Kidney	50 µg/kg	
	Milk	100 µg/kg	

6. Deltamethrin – proposed extrapolation to ruminants					
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Chicken (µg/kg)	Salmon (µg/kg)
	Muscle	30	30	30	30
	Fat	500	500	500	-
	Liver	50	50	50	-
	Kidney	50	50	50	-
	Milk	30	-	-	-
	Eggs	-	-	30	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes				
Is the marker residue the parent compound?	Yes				
What are the M:Ts	The JECFA reports (WHO TRS 893 and 918(10) use the following values: 0.6 in fat, 0.04 in liver, 0.03 in kidney and 1 in milk M:T for muscle not reported but equivalent values were applied in all species				
Can the MRLs be extrapolated to ruminants?	Yes, the MRLs for cattle and sheep tissues are identical and so can be extrapolated. While the MRL for milk has only been established in one species, the M:T used for milk was 1 and consequently the MRL can be extrapolated to milk of other ruminants				
If so, what MRLs are proposed?	Muscle	30 µg/kg			
	Fat	500 µg/kg			
	Liver	50 µg/kg			
	Kidney	50 µg/kg			
	Milk	30 µg/kg			

7. Moxidectin – proposed extrapolation to ruminants				
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Deer (µg/kg)
	Muscle	20	50	20
	Fat	500	500	500
	Liver	100	100	100
	Kidney	50	50	50
	Milk	-	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes			
Is the marker residue the parent compound?	Yes			
What are the M:Ts	The JECFA report (WHO TRS 888(10) uses the following values: 0.75 for fat, 0.4 for muscle, 0.4 for liver and kidney for all three species			
Can the MRLs be extrapolated to ruminants?	Yes, as the M:Ts are the same in all three species (identical MRLs were originally established for cattle, sheep and deer [TRS 864(10)] but the muscle MRL for sheep was subsequently raised following a new residue study in sheep with the M:T remaining unchanged)			
If so, what MRLs are proposed?	Muscle	20 µg/kg		
	Fat	500 µg/kg		
	Liver	100 µg/kg		
	Kidney	50 µg/kg		
	Milk	-		

8. Spectinomycin – proposed extrapolation to ruminants					
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pig (µg/kg)	Chicken (µg/kg)
	Muscle	500	500	500	500
	Fat	2000	2000	2000	2000
	Liver	2000	2000	2000	2000
	Kidney	5000	5000	5000	5000
	Milk	200	-	-	--
	Eggs	-	-	-	2000
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes				
Is the marker residue the parent compound?	Yes				
What are the M:Ts	The JECFA report (WHO TRS 888(10)) uses the following values: 0.25 for liver and 1 for all other tissues, milk and eggs in all species				
Can the MRLs be extrapolated to ruminants?	Yes, as the M:Ts are the same in all species and, in addition, identical MRLs already exist in 2 related ruminant species				
If so, what MRLs are proposed?	Muscle	500 µg/kg			
	Fat	2000 µg/kg			
	Liver	2000 µg/kg			
	Kidney	5000 µg/kg			
	Milk	200 µg/kg			

9. Levamisole – proposed extrapolation to ruminants					
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pig (µg/kg)	Poultry (µg/kg)
	Muscle	10	10	10	10
	Fat	10	10	10	10
	Liver	100	100	100	100
	Kidney	10	10	10	10
	Milk	-	-	-	-
	Eggs	-	-	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes				
Is the marker residue the parent compound?	Yes				
What are the M:Ts?	The JECFA report (WHO TRS 851(10) uses the following values: 0.024 for all tissues				
Can the MRLs be extrapolated to ruminants?	Yes, as the M:Ts are the same in all species and, in addition, identical MRLs already exist in 2 related ruminant species				
If so, what MRLs are proposed?	Muscle	10 µg/kg			
	Fat	10 µg/kg			
	Liver	100 µg/kg			
	Kidney	10 µg/kg			
	Milk	-			

10. Tilmicosin – proposed extrapolation to ruminants						
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pigs (µg/kg)	Chicken* (µg/kg)	Turkey* (µg/kg)
	Muscle	100	100**	100	150	100
	Fat	100	100	100	250	250
	Liver	1000	1000	1500	2400	1400
	Kidney	300	300	1000	300	1200
	Milk	-	-	-	-	-
	Eggs	-	-	-	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes					
Is the marker residue the parent compound?	Yes					
What are the M:Ts?	The JECFA report (WHO TRS 876(10) uses the following values: 0.05 for cattle and sheep liver, 0.10 for sheep kidney, 0.25 for cattle kidney, 0.10 for cattle and sheep muscle and fat, 0.50 for pig liver and kidney, 0.10 for pig muscle and fat					
Can the MRLs be extrapolated to ruminants?	Yes, although there is a difference in the M:T for cattle and sheep kidney, the MRLs recommended for these 2 species were identical					
If so, what MRLs are proposed?	Muscle	100 µg/kg				
	Fat	100 µg/kg				
	Liver	1000 µg/kg				
	Kidney	300 µg/kg				
	Milk	-				

* The value for fat applies to skin/fat

** Value not shown in database, but it was in the recommendation from JECFA

11. Deltamethrin – proposed extrapolation to bony fish					
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Chicken (µg/kg)	Salmon (µg/kg)
	Muscle	30	30	30	30
	Fat	500	500	500	-
	Liver	50	50	50	-
	Kidney	50	50	50	-
	Milk	30	-	-	-
	Eggs	-	-	30	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes				
Is the marker residue the parent compound?	Yes				
What are the M:Ts?	The JECFA report (WHO TRS 893(10) indicates that a M:T in muscle of salmon was not established. However, the concentrations of the marker residue and total residues were very low in muscle (of all species), with the MRL established based on twice the LoQ (From TRS 918(10): 0.04 for liver, 0.03 for kidney and 0.60 for fat)				
Can the MRLs be extrapolated to bony fish?	Yes, as residues in muscle of all species evaluated including salmon were very low (<LoQ) and do not make a significant addition to consumer exposure (Note that it was considered appropriate to extend the MRL for mammalian muscle to *Salmonidae* without metabolism data in this family)				
If so, what MRLs are proposed?	Muscle	30 µg/kg			

12. Flumequine – proposed extrapolation to bony fish						
Which species have MRLs been established in?		Cattle (µg/kg)	Sheep (µg/kg)	Pigs (µg/kg)	Chicken (µg/kg)	Trout (µg/kg)
	Muscle	500	500	500	500	500
	Fat	1000	1000	1000	1000	-
	Liver	500	500	500	500	-
	Kidney	3000	3000	3000	3000	-
	Milk	-	-	-	-	-
	Eggs	-	-	-	-	-
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes					
Is the marker residue the parent compound?	Yes					
What are the M:Ts?	The JECFA report (WHO TRS 900(10) uses the following values: Cattle: muscle, kidney and fat: 0.79, liver: 0.17 Sheep: muscle, kidney and fat: 0.4, liver: 0.06 Pigs: muscle, kidney and fat: 0.59, liver:0.07 Chickens: 0.82 in all tissues Trout: no measurable residues of flumequine metabolites, so most probably M:T = 1					
Can the MRLs be extrapolated to bony fish?	Yes, as the M:T in trout is most probably 1 (suggesting no significant metabolism in fish) and, in addition, identical MRLs have been established in multiple unrelated species.					
If so, what MRLs are proposed?	Muscle	500 µg/kg				

13. Teflubenzuron – proposed extrapolation to bony fish		
Which species have MRLs been established in?		Salmon (µg/kg)
	Muscle	400
	Fillet*	400
Were the MRLs established on the basis of a full evaluation undertaken by JECFA?	Yes	
Is the marker residue the parent compound?	Yes	
What are the M:Ts?	The JECFA report (WHO TRS 997(10) uses 0.8 for both muscle and fillet	
Can the MRLs be extrapolated to bony fish?	No, as the M:T is not 1 (i.e. there is metabolism) and as the MRLs are not based on the LoQ (indicating that residues make a significant contribution to the overall consumer intake)	

* Muscle and skin in natural proportions

V. Conclusion

1. The proposal for MRL extrapolations put forward in the present document aims to provide a pragmatic approach for the establishment of MRLs in food producing species for which residue data are not available. The approach builds upon positive evaluations performed by JECFA for the reference species, and lays down criteria (described in section II of this document) which, when satisfied, support the conclusion that metabolism in the reference and concerned species is sufficiently similar to allow the reference species MRLs to be applied to the concerned species while maintaining protection of the consumer. The use of this approach would enhance (human and animal) public health by enabling use of certain veterinary drugs in animal species for which the absence of MRLs currently precludes use.

VI. References

1. Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria 240 (2009). Available at: https://www.who.int/foodsafety/publications/chemical-food/en/
2. Glossary of Terms and Definitions (Residues of Veterinary Drugs in Foods). CXA 5-1993. Available at: http://www.fao.org/fao-who-codexalimentarius/codex-texts/miscellaneous/en/
3. Discussion paper on MRLs for groups of fish species (2018) - CX/RVDF 18/24/7. Available as Item 7 on the CCRVDF24 webpage: http://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=24
4. Report of the in-session working group on MRLs for groups of fish species (2018) — CRD34. Available as Item 7 on the CCRVDF24 webpage: http://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=24
5. Report of CCRVDF20 (2012) — REP12/RVDF. Available on the CCRVDF webpage: http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/en/?committee=CCRVDF
6. Evaluation of certain veterinary drug residues in food (2014) — WHO TRS 988. Available at: https://www.who.int/foodsafety/publications/jecfa-reports/en/
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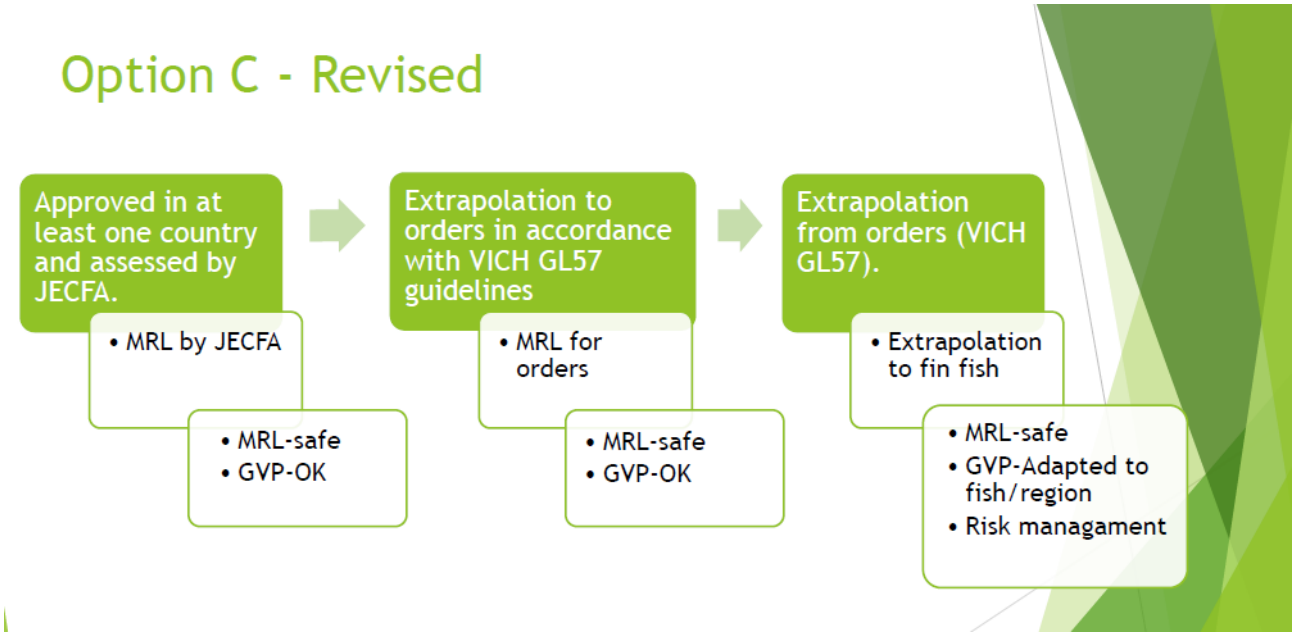
8. VICH GL57. Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species. Available at: https://www.vichsec.org/en/guidelines/pharmaceuticals/pharma-safety/metabolism-and-residue-kinetics.html
9. Report CCRVDF24 (2018) - REP18/RVDF. Available on the CCRVDF webpage: http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/en/?committee=CCRVDF
10. WHO TRS reports. Available from https://www.who.int/foodsafety/publications/jecfa-reports/en/

APPENDIX II

REVISED OPTION C
FOR AQUATIC SPECIES
(As considered at CCRVDF24)
- For information -



APPENDIX III

PRIORITY LIST OF VETERINARY DRUGS
- For information -

Part D. Compounds for which CCRVDF will consider extrapolation of Codex MRLs to additional species	
Amoxicillin	Ruminants
Benzylpenicilin	Ruminants
Tetracyclines	Ruminants
Cyhalothrin	Ruminants
Cypermethrin	Ruminants
Deltamethrin	Ruminants
Moxidectin	Ruminants
Spectinomycin	Ruminants
Levamisole	Ruminants
Tilmicosin	Ruminants
Deltamethrin	Fish
Flumequine	Fish
Teflubenzuron	Fish

APPENDIX IV

LIST OF PARTICIPANTS

Chair **European Union** Risto Holma European Commission	**Vice-Chair** **Costa Rica** Heilyn Fernández / José Solano Servicio Nacional de Salud Animal (SENASA)

MEMBER COUNTRY / ORGANIZATION[11]	**ORGANIZATION[1]**
1. Argentina	1. FAO
2. Australia	
3. Belgium	
4. Brazil	
5. Chile	
6. Costa Rica	
7. Croatia	
8. Ecuador	
9. Egypt	
10. El Salvador	
11. European Union	
12. Finland	
13. France	
14. Germany	
15. Honduras	
16. Hungary	
17. India	
18. Iran	
19. Ireland	
20. Jamaica	
21. Japan	
22. Kazakhstan	
23. North Macedonia	
24. Mexico	
25. New Zealand	
26. Nigeria	
27. Norway	
28. Panama	
29. Peru	
30. Republic of Korea	
31. The Netherlands	
32. Thailand	
33. Uganda	
34. United Kingdom	
35. United States of America	
36. Uruguay	

11 Please contact the focal point of the Member Country or Observer Organization for the details of the delegates. The list of Codex contact points for members and observers are available from the Codex website at: http://www.fao.org/fao-who-codexalimentarius/about-codex/members/en/ http://www.fao.org/fao-who-codexalimentarius/about-codex/observers/observers/obs-list/en/