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CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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Agenda Item 7 **CX/RVDF 24/27/7**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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Omaha, Nebraska, United States of America

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 Recommendations 1-4, as described in Appendix I should do so as instructed in CL 2024/67-RVDF available on the Codex webpage/Circular Letters[1] or CCRVDF/Related Circular Letters[2]

INTRODUCTION

1. The 25th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF25, 2021) agreed to rules for extrapolating maximum residue limits (MRLs) of veterinary drugs to one or more species.[3] The 44th Session of the Codex Alimentarius Commission (CAC44, 2021) adopted[4] the rules as proposed by CCRVDF 25 and included them in the Procedural Manual, Risk Analysis Principles applied by CCRVDF, Annex C—Approach *for the Extrapolation of Maximum Residue Limits of Veterinary Drugs to One or More Species*[5].

2. CCRVDF26 (2023) used these rules to extrapolate[6] MRLs for several substances which were adopted[7] by CAC46 (2023) and included in CX/MRL 2-2023 – *Maximum Residue Limits and Risk Management Recommendations for Residues of Veterinary Drugs in Foods*[8].

TERMS OF REFERENCE

3. CCRVDF26 further agreed to establish an electronic working group (EWG) chaired by the European Union (EU) and co-chaired by Costa Rica to further work on the extrapolation of MRLs. The EWG was charged with working on the following topics:

- Continue to evaluate the extrapolation of MRLs for different combinations of compounds/commodities, particularly for considering the extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish.
- Summarize available information on the distribution of compounds in different edible offal tissues with a view to evaluating the possibility of extrapolating MRLs to edible offal tissues other than liver and kidney.
- Examine opportunities to enhance the current criteria's potential for extrapolation across species where justified, such as between ruminants and camels and between milk of different species.

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1 http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/
2 http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF
3 REP21/RVDF25, para. 105, Appendix III
4 REP21/CAC44, para. 36(ii), Appendix II
5 https://openknowledge.fao.org/items/dfc93e42-67f3-4de9-9dad-b33fb1600b32
6 REP23/RVDF26, para. 34, Appendix III
7 REP23/CAC46, para. 36(iii), Appendix II
8 https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-standards/en/?committee=CCRVDF

PARTICIPATION AND METHODOLOGY

4. Thirty Codex Members and two Observers registered to participate in the EWG. The list of participants is attached in Appendix III.

5. The EWG Chairs circulated the first message to the participants on 27th February 2024 in English and Spanish. An introductory document explained the Chair's understanding of the work to be undertaken and outlined specific tasks to be addressed. Two rounds of comments from EWG members followed, followed by a summary of the work undertaken and conclusions/recommendations, which are provided below. The detailed documents and comments circulated within the EWG are available in Appendix II for information.

SUMMARY OF DISCUSSION

6. The EWG worked on the following four tasks:

- **Task 1.** Extrapolation of MRLs for lufenuron, emamectin benzoate and diflubenzuron in finfish.
- **Task 2.** Development of a possible approach for extrapolation of MRLs to camelids.
- **Task 3.** Consideration of opportunities to enhance the current criteria's potential for extrapolation between the milk of different species, with a particular focus on deltamethrin and ivermectin.
- **Task 4.** The development of a possible approach for extrapolating MRLs to edible offal tissues other than the liver and kidney, considering available information on the distribution of compounds in edible offal tissues.

Task 1. Extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish

7. To determine the appropriateness of extrapolating MRLs for lufenuron, emamectin benzoate, and diflubenzuron, the EWG used the extrapolation rules as presented in Annex C to the Risk Analysis Principles applied by CCRVDF as its starting point.

<u>Lufenuron</u>

8. The EWG agreed that the extrapolation criteria are met for lufenuron and that extrapolation to finfish can be recommended.

<u>Emamectin benzoate</u>

9. The EWG noted that Criterion 2b of the established extrapolation rules states that the marker residue in the reference species should be the parent compound only or the total residues of toxicological concern.

10. However, certain veterinary drugs, including emamectin (and ivermectin), are made up of homologous compounds, and the marker residue is just one of the homologues. Strictly speaking, as the marker residue is only part of the parent compound, Criterion 2b is not met. The EWG agreed that the intention of Criterion 2b was not to exclude the possibility of extrapolation for substances that are made up of homologous compounds and that the criterion should be amended to allow for the possibility of extrapolation in cases where the marker residue is a homolog that constitutes a major part of the parent substance. Specific wording is proposed (see recommendations/conclusions below).

11. With the proposed amendment to Criterion 2b, the EWG agreed that extrapolation of the MRL for emamectin benzoate to finfish could be recommended.

<u>Diflubenzuron</u>

12. The EWG agreed that the extrapolation criteria are not met for diflubenzuron. In particular, the MRL has been established in only one species, the established ratio of marker to total residues (M:T) is not 1, and the MRL is not based on the LOQ of the analytical method. Consequently, extrapolation of the MRL to finfish is not recommended.

Task 2. Development of a possible approach for extrapolation of MRLs to camelids.

13. The EWG considered that its task was to develop an approach for extrapolating MRLs to camelids but not to recommend substance-specific extrapolations as part of the current work. Substance-specific recommendations can follow if the criteria are agreed upon and if member countries nominate relevant compounds for extrapolation for inclusion in Part V of the Priority List

14. The approach proposed for extrapolating MRLs to camelids builds on the approach already accepted by CCRVDF. It suggests that extrapolation to camelids should be allowed where, based on existing MRLs established following JECFA evaluations, there is clear evidence of cross-species conservation of metabolism.

15. CCRVDF's existing rules on extrapolation focus on extrapolation within groups of related species, as it is within these groups that metabolism will be most similar. The existing rules identify four groups of related species: ruminants, non-ruminant mammals, birds, and finfish. Three species are identified within the non-ruminant mammal group: pigs, horses, and rabbits. Camels and other camelids are not explicitly mentioned in the existing rules and are not considered covered by the existing rules.

16. Like ruminants, camelids regurgitate, rechew, and reswallow their food. However, the gastrointestinal system of camelids differs from that of ruminants, with camelids having a three-chambered stomach as opposed to the four-chambered stomach of true ruminants. Camelids are therefore classified as "pseudo-ruminants."

17. As camels are neither true ruminant nor monogastric mammals, extrapolation of MRLs from either ruminants or monogastric mammals to camels would be associated with a greater degree of uncertainty than the already accepted extrapolation within the group of ruminants or group of non-ruminant mammals (i.e., pigs, horses, and rabbits). However, if the MRL conclusions already reached for different groups of species (ruminants, non-ruminant mammals, and avian species) indicate that metabolism is similar across groups, then this evidence of conserved metabolism across species provides the assurance necessary to allow extrapolation to camelids.

18. The EWG considered that sufficient evidence of cross-species conservation of metabolism can be deemed to have been demonstrated if either (a) identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species based on JECFA recommendations and the M:T ratio used by JECFA was 1 in all tissues for the ruminant and non-ruminant species, OR (b) identical MRLs have been established in at least one ruminant species, one non-ruminant mammalian species, and one avian species based on JECFA recommendations, and JECFA used the same M:T ratio for each tissue type for all three species.

Task 3. Consideration of opportunities to enhance the current criteria's potential for extrapolation between the milk of different species, with a particular focus on deltamethrin and ivermectin.

19. CCRVDF26 considered the possibility of extrapolating MRLs in milk for deltamethrin and ivermectin. Milk MRLs were previously established in a single species (cattle) based on a JECFA evaluation for both substances. In line with the established criteria, extrapolation to milk of other ruminants is possible if the ratio of marker to total residues (M:T) = 1. Since the M:T ≠ 1 for either substance, extrapolation to the milk of other ruminants was not accepted at CCRVDF 26.

20. As CCRVDF26 concluded that the established extrapolation criteria for deltamethrin and ivermectin are not met, the EWG considered that its task was to evaluate whether there might be a justification for extrapolation even though the established criteria are not met, and based on this experience, consider whether amendments to the established extrapolation criteria should be recommended.

<u>Deltamethrin</u>

21. It was noted that identical tissue MRLs have been established across a range of species (cattle, sheep, and chickens), indicating conservation of metabolism across species; that JECFA reports indicate that residue levels in cattle milk are low (below the LOQ of 15 µg/l), that they did not contribute significantly to consumer intake of residues and that residues other than the parent compound will have reduced toxicity compared to that of the parent compound; and that based on existing MRLs, total dietary exposure to residues of deltamethrin resulting from the use of the substance in veterinary medicines and pesticides uses up only 68% of the ADI (25% from pesticide use and 43% from veterinary drug use). Therefore, it was suggested that an adequate margin of safety might be available to compensate for uncertainties in consumer exposure if the cattle milk MRL was extrapolated to the milk of other ruminants.

22. Conversely, it was recognized that the fat composition of ruminant milk varies across species and that deltamethrin residues in milk are distributed predominantly in milk fat. It was also noted that the ratio of marker to total residues in milk is not 1 and we cannot be sure it will not vary across milk of ruminants containing different fat content to that of cattle milk. Differences in milk fluid volumes are a further factor that may impact the concentration of residues in the milk of different ruminant species. Together, these factors result in considerable uncertainty with regard to the proportion of residues of toxicological concern that will be present in milk of different ruminant species.

23. It was also pointed out that a Codex MRL for deltamethrin in the milk of animals other than marine mammals, established for pesticide use (50 µg/kg), is already applicable and that establishing a different MRL by extrapolating the existing cattle milk MRL (30 µg/kg) would create additional divergent Codex MRLs.

24. Furthermore, the Joint CCPR/CCRVDF Electronic Working Group is currently discussing the harmonization of milk MRLs for deltamethrin, and consultation with this Joint EWG would be appropriate before any additional milk MRLs are established by extrapolation.

25. Considering all the above considerations, the EWG concluded that extrapolating the cattle milk MRL to the milk of other ruminants is not appropriate at this time.

Ivermectin

26. The existing cattle milk MRL of 10 µg/kg was derived from the unused portion of the ADI when it was set at 0 – 1 µg/kg bw per person (JECFA 54 – TRS 900). JECFA subsequently revised the ADI to 0 – 10 bw per person (JECFA 81 – TRS 997).

27. Consumer exposure to residues resulting from ingesting tissues and milk is estimated to equate to only 9% of the current ADI for ivermectin

28. The EWG noted that JECFA has indicated that compliance with the existing cattle milk MRL requires the discard of a substantial amount of milk – up to 11 milkings would need to be discarded (JECFA 54 – TRS 900). Ivermectin is highly lipophilic, and for species producing milk with greater fat content than cattle, it can be considered that an even greater number of milk discards may be needed to achieve compliance with the MRL.

29. It was further noted that JECFA established different M:T values for cattle and sheep tissues, raising the possibility that the M:T in milk may also vary between species.

30. Given the high level of milk discard required to comply with the MRL, it is unlikely that companies would develop ivermectin products aimed specifically at lactating ruminants. Any use of ivermectin in milk-producing ruminants would, therefore, be off-label. There was uncertainty about encouraging such off-label use, particularly as compliance with the extrapolated MRL would only be ensured if national/regional rules regarding off-label use are strict enough to ensure substantial milk discard.

31. It was also noted that since the current MRLs use up a relatively small proportion of the ADI for ivermectin, a revision of the current cattle milk MRL might allow the establishment of a value that is more practical for use in lactating animals, requiring less milk to be discarded. Such a value would be more appropriate for extrapolation.

32. The EWG noted that, in previous discussions relating to extrapolating the milk MRL for ivermectin, some uncertainty was expressed regarding whether ivermectin B1a could be considered the same as the parent compound. Criterion 2b of the established extrapolation rules states that the marker residue in the reference species should be the parent compound only or the total residues of toxicological concern. However, certain veterinary drugs, including ivermectin (and emamectin), are made up of homologous compounds, and the marker residue is just one of the homologues. Strictly speaking, as the marker residue is only part of the parent compound, Criterion 2b is not met.

33. The EWG agreed that the intention of Criterion 2b was not to exclude the possibility of extrapolation for substances that are made up of homologous compounds and that the criterion should be amended to allow for the possibility of extrapolation in cases where the marker residue is a homolog that constitutes a major part of the parent substance. Specific wording is proposed (see below).

34. Considering the substantial milk discard that would be required to ensure compliance with an extrapolated MRL for ivermectin in milk of ruminants other than cattle, considering the uncertainties linked to the fact that the fat content of milk of different ruminant species varies considerably, and considering that the M:T may vary in milk of different ruminant species (as it does in their tissues), the EWG does not recommend extrapolation of the cattle milk MRL to milk of other ruminants.

Task 4. Development of a possible approach for extrapolating MRLs to edible offal tissues other than the liver and kidney, considering available information on the distribution of compounds in edible offal tissues.

35. There was uncertainty about some fundamental issues connected with this work. Most notably, it was noted that globally, non-standard offal tissues are already regularly consumed, and there does not appear to be a general concern over consumer safety associated with the associated exposure to residues. It was considered that this is largely because the existing approach to setting MRLs and calculating dietary exposure can be regarded as the "worst case", and consequently, the level of exposure to residues that result from diets including non-standard offal is not expected to exceed that experienced by consumers ingesting the standard food basket that JECFA has used to estimate consumer exposure to residues.

36. If residue levels in non-standard offal tissues are already considered safe, what is the purpose of establishing MRLs in these tissues? Is it purely to provide a value for use by residue control authorities and facilitate trade? If so, and if residues present in non-standard offal tissues are already considered safe, would CCRVDF need to undertake an exposure calculation using MRLs extrapolated to non-standard offal tissues?

37. It was noted that, at CCRVDF26, at least one member argued that the need for MRLs in other offal tissues focuses on facilitating trade rather than ensuring consumer safety (as it is already assumed that the residues do not represent a consumer safety concern). On the other hand, within the EWG, it was argued that the current exercise is aimed at establishing the safety of **specific** residue concentrations in offal, and for this, a dietary intake evaluation would be needed.

38. Regarding the starting MRLs that should be used for extrapolation, it was suggested that the highest MRL could be used as a starting point, as this would minimize the chance of non-compliant residue findings in cases where veterinary drugs have been used according to established GVP. If a dietary intake calculation (assuming one is required) indicates that the health-based guidance value (usually the Acceptable Daily Intake (ADI)) is exceeded, the next highest value could be considered.

39. It was noted that data on the distribution of residues to non-standard offal tissues are limited and that a variety of data types should be considered to support the validity of extrapolated MRLs. These could include data from unrelated species (including laboratory species), data for related compounds, and physicochemical data. It was noted that, given the large number of potential non-standard offal tissues, it cannot be expected that we will ever have supporting data from all relevant tissues. Some agreement would be needed on the number of tissues in relation to which supporting data would be required.

40. It was suggested that, in the first instance, it might be helpful to select a small number of substances to focus on. This would make the task of gathering relevant residue distribution data more manageable. If successful, the task could be extended to include additional substances. Over time, CCRVDF would build up a collection of tissue distribution information.

41. A member of the EWG put forward a possible approach for checking whether a proposed extrapolation to non-standard offal tissues could be considered reasonable from a consumer safety perspective. The approach focuses on determining (i) an appropriate M:T ratio for use in estimating possible dietary intake and (ii) possible consumption values for non-standard offal tissues, also for use in estimating possible dietary intake.

42. The M:T ratio to use would be the average established for standard tissues, to which an uncertainty factor would be applied. The uncertainty factor would be based on the variability between the M:T ratios for standard tissues.

43. A range of consumption values would be used for non-standard offal tissues, allowing for the possibility that the consumption of non-standard offal tissues replaces the consumption of one, two, three, or all four standard tissues in the TMDI food basket.

44. An example of the above approach was circulated to the EWG, focusing on the possible extrapolation of the ivermectin MRL for pig fat to non-standard pig offal.

45. The detailed approach is provided in Appendix II.

46. The EWG considered that, for substances with an MRL classification of “unnecessary” or “not specified” in standard tissues, there would be a strong case for extrapolating the same classification to non-standard offal tissues with no further consideration, as CCRVDF has already concluded that, for these substances, residues in the diet do not represent a consumer safety concern. However, there was uncertainty about the significance of the different terms used (i.e., “unnecessary” versus “not specified”), and clarification on these would be appropriate.

CONCLUSIONS/RECOMMENDATIONS

47. CCRVDF is invited to consider the EWG's conclusions/recommendations, which are presented in Appendix I, based on comments submitted by Codex Members and Observers in reply to CL 2024/67-RVDF and the data/information provided in this working paper.

APPENDIX I

RECOMMENDATIONS FOR COMMENTS AND CONSIDERATION BY CCRVDF27 REGARDING EXTRAPOLATION OF MRLs TO ONE OR MORE SPECIES (For comments)

RECOMMENDATION 1: Extrapolating MRLs for lufenuron, emamectin benzoate, and diflubenzuron to finfish.

1.1 Criterion 2b of the Approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species should be amended to[9]:

2b) The marker residue in the reference species is the parent compound only or is the same as the total residues of toxicological concern, or the Codex 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.

i. *In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as the parent if it is a homolog that is a major component of the active substance.*

1.2 The MRL of 1350 µg/kg established for lufenuron in salmon and trout fillets can be extrapolated to finfish.

1.3 With agreement on Recommendation 1.1, the MRL of 100 µg/kg established for emamectin benzoate in muscle and fillet of salmon and trout can be extrapolated to finfish.

1.4 Extrapolation of the MRL established for diflubenzuron in the muscle of salmon is not supported.

9 The same recommendation is made in the EWG recommendations concerning opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin Proposed EWG recommendation for ivermectin

1. LUFENURON	Existing MRLs		
		Salmon (µg/kg)	Trout(µg/kg)
Commodity	Fillet*	1350	1350
Were the MRLs established based on a full evaluation undertaken by JECFA?	Yes (JECFA 85, 2017 – WHO TRS 1008 (2018))		
Is the marker residue the parent compound?	Yes		
What are the M:Ts	The JECFA report (WHO TRS 1008) establishes a M:T of 1.0 in all tissues and milk. M:T is therefore considered to be 1		
Can the MRLs be extrapolated to finfish?	In principle, yes, as identical MRLs have been established in 2 species based on JECFA recommendations. It is noted that JECFA commented that it could not extrapolate to other fish species. The reasons that prevented JECFA from extrapolating to other fish species were: • Lufenuron is lipophilic, and its concentration is higher in fatty tissues. The fat content in fish depends on species and growing conditions. • The decrease of residues is dependent on time after administration and the increase in body weight, both dependent on water temperature. • No depletion data were provided for species other than salmonids. These concerns need not prevent CCRVDF from extrapolating, as the MRL represents a safe value. However, they emphasize that, as for any vet drug for use in fish, withdrawal periods need to be in place that take account of local conditions where the substance will be used.		
Proposed MRL:	Fillet*	1350 µg/kg	

* Muscle plus skin in natural proportions

2. EMAMECTIN BENZOATE	Existing MRLs		
		Salmon (µg/kg)	Trout (µg/kg)
Commodity	Muscle	100	100
	Fillet*	100	100
Were the MRLs established based on a full evaluation undertaken by JECFA?	Yes (JECFA 78, 2013 – WHO TRS 988 (2014))		
Is the marker residue the parent compound?	Strictly speaking, no. The marker residue is emamectin B1a benzoate, which is the major component of the parent compound (emamectin benzoate consists of 90% emamectin B1a benzoate and 10% emamectin B1b benzoate). The EWG considers that extrapolation Criterion 2b should be modified so that it does not exclude the possibility of extrapolation where the marker residue is one of the homologous compounds that make up the parent substance.		
What are the M:Ts	The JECFA report (WHO TRS 988) establishes a M:T of 0.9 in muscle and fillet of salmon.		
Can the MRLs be extrapolated to finfish?	If the proposed modification of Criterion 2b is accepted, extrapolation can be recommended (identical MRLs have been established in 2 species based on JECFA recommendations). It is noted that JECFA commented that: • Emamectin B1a residues decrease in muscle with different half-lives as a function of water temperature. • Strict control of treatment conditions, rate of feed ingestion, and a residue monitoring programme are recommended for this compound because of its wide range of terminal half-lives reported in several studies and the variation in feed intake according to local living conditions of fish These concerns need not prevent CCRVDF from extrapolating, as the MRL represents a safe value. However, they emphasize that, as for any vet drug for use in fish, withdrawal periods need to be in place to account for local conditions where the substance will be used.		
Proposed MRL:	Fillet*	100 µg/kg	

* Muscle plus skin in natural proportions

3. DIFLUBENZURON	Existing MRLs	
		Salmon (µg/kg)
Commodity	Muscle*	10
Were the MRLs established based on a full evaluation undertaken by JECFA?	Yes (JECFA 81, 2015 – TRS 997; JECFA 88, 2019 – WHO TRS 1023)	
Is the marker residue the parent compound?	Yes	
What are the M:Ts	The JECFA report (WHO TRS 1023) establishes a M:T of 0.9 in salmon fillet.	
Can the MRLs be extrapolated to finfish?	No, as an MRL has been established in a single species, the M:T is not 1, and the MRL is not based on the LOQ of the analytical method.	
Proposed MRL:	Not applicable	

* Muscle plus skin in natural proportions

RECOMMENDATION 2: Development of a possible approach for extrapolation of MRLs to camelids:

2.1 CCRVDF previously agreed that the existing rules as presented in the Procedural Manual, *Risk Analysis Principles applied by CCRVDF*, Annex C – *Approach for the Extrapolation of Maximum Residue Limits of Veterinary Drugs to One or More Species,* do not apply to camelids. A separate set of rules is now recommended, specifically for extrapolation to camelids:

Extrapolation of MRLs to camelids can be supported where the following criteria are satisfied:

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

2) The marker residue is the parent compound.

a. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as the parent if it is a homolog that is a major component of the active substance.

3) For meat tissues, extrapolation of reference species MRLs to camelids on a one-to-one basis should be considered if either:

a. identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species based on JECFA recommendations, and the M:T ratio used by JECFA was 1 in all tissues for the ruminant and non-ruminant species, OR

b. Based on JECFA recommendations, identical MRLs have been established in at least one ruminant, non-ruminant mammalian, and avian species. JECFA used the same M:T ratio for each tissue type for all three species.

4) Where conditions 2 and 3 are satisfied, extrapolation of an MRL for milk should also be considered in those cases where the M:T ratio used by JECFA was 1 in milk.

RECOMMENDATION 3: Opportunities to enhance the current criteria's potential for extrapolation between the milk of different species, with a particular focus on deltamethrin and ivermectin. Proposed EWG recommendation for ivermectin:

3.1 Criterion 2b of the Approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species should be amended to[10]:

2b) The marker residue in the reference species is the parent compound only or is the same as the total residues of toxicological concern, or the Codex 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.

i. *In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as the parent if it is a homolog that is a major component of the active substance.*

3.2 Extrapolation of the cattle milk MRL for deltamethrin to the milk of other ruminants is not recommended currently.

3.3 Extrapolation of the cattle milk MRL for ivermectin to the milk of other ruminants is not recommended.

3.4 Except for Recommendation 3.1 above, the current criteria for extrapolating between milk of different species are not enhanced.

[10] The same recommendation is made in the EWG recommendations on extrapolation of MRLs for lufenuron, emamectin benzoate and diflubenzuron to finfish

RECOMMENDATION 4: Development of a possible approach for extrapolation of MRLs to edible offal tissues other than liver and kidney

4.1 Some fundamental questions remain (see paragraphs 35-46 of CX/RVDF 24/27/7) on which it would be useful to have input from CCRVDF to:

4.1.1 determine if further work would be needed in this regard and if so

4.1.2 guide any future EWG on the task it is charged with.

4.2 In particular, the following question per paragraph 46 of CX/RVDF 24/27/7, is put forward for consideration:

Question	Considerations
For substances with an MRL classification of "unnecessary" or "not specified" in standard tissues, could the same classification be extrapolated to non-standard offal tissues without further consideration?	CCRVDF has already concluded that, for these substances, residues in the diet do not represent a consumer safety concern. What is the difference between the terms "unnecessary" and "not specified"?

4.3 Based on the issues raised in paragraphs 35-46 and any other matters that Codex Members and Observers may identify, CCRVDF is invited to provide further guidance regarding Recommendation 4 to allow additional work in an EWG if appropriate.

APPENDIX II

ORIGINAL LANGUAGE ONLY

Appendix to the report from the electronic working group on extrapolation of maximum residue limits for veterinary drugs to one or more

EWG EXCHANGES

(For information)

First consultation with EWG - documents shared on 27 February 2024

Annex I: Extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish, using the established extrapolation rules

CCRVDF26 charged this EWG with continuing to work on extrapolation of MRLs, including considering extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish. Based on the extrapolation rules agreed at CCRVDF 25 (and subsequently integrated into the Procedural Manual) and considering the analysis presented in the table below, it is proposed that the EWG should recommend extrapolation for these substances as follows:

- Lufenuron: Extrapolation of the existing fillet MRL (1350 µg/kg) to finfish
- Emamectin benzoate: Extrapolation of the existing muscle and fillet MRL (100 µg/kg) to finfish
- Diflubenzuron: Extrapolation is not recommended

Annex II – Development of a possible approach for extrapolation of MRLs to camelids.

Background

A conference room document (CRD10) on the subject of extrapolation of MRLs to camelids was submitted at CCRVDF26 by Jordan, Morocco, AIDMSO and IUFoST. Following a discussion of the topic at the physical meeting of the extrapolation EWG, CCRVDF agreed that the extrapolation EWG should consider approaches to extrapolate MRLs for certain veterinary drugs to camelids.

Introduction

The approach proposed in this document builds on the approach already accepted by CCRVDF for extrapolation, i.e. it proposes that extrapolation to camelids should be allowed where, based on existing MRLs established following JECFA evaluations, there is clear evidence of cross-species conservation of metabolism.

CCRVDF's existing rules on extrapolation focus on extrapolation within groups of related species, as it is within these groups that metabolism will be most similar. Four groups of related species are identified in the existing rules: ruminants, non-ruminant mammals, birds and fin fish. Within the non-ruminant mammals group, three species are identified: pigs, horses and rabbits. Camels and other camelids are not specifically mentioned in the existing rules and are not considered to be covered by the existing rules.

Like ruminants, camelids regurgitate, rechew and reswallow their food. However, the gastrointestinal system of camelids differs from that of ruminants, with camelids having a three-chambered stomach as opposed to the four-chambered stomach of true ruminants. Camelids are therefore classified as "pseudo-ruminants".

As camels are neither true ruminant nor monogastric mammals, extrapolation of MRLs from either ruminants or monogastric mammals to camels would be associated with a greater degree of uncertainty than the already accepted extrapolation within the group of ruminants or within group of non-ruminant mammals (ie pigs, horses and rabbits). However, if the MRL conclusions already reached for both ruminants and non-ruminant mammals indicate that metabolism is similar across these two groups, then this evidence of conserved metabolism across mammalian species is considered to provide the assurance necessary to allow extrapolation to camelids.

Proposed approach

(i) 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).

(ii) Extrapolation of reference species MRLs to camelids on a one to one basis should be considered if identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species (pigs, horses or rabbits).

Explanatory note: the existence of identical MRLs in ruminants and non-ruminant mammals provides grounds upon which to base the assumption that metabolism does not vary significantly between mammalian species

(iii) Where condition (ii) is satisfied, extrapolation of an MRL for milk should also be considered in those cases where the M:T in milk = 1

Explanatory note: as condition (ii) provides assurance of similar metabolism between ruminant and non-ruminant mammals, additional reassurance relating specifically to residues in milk of camelids is not necessary. For consistency with the established rules on extrapolation of a milk MRL from a single ruminant species to milk of other ruminants, the M:T in milk should be 1.

MRL extrapolations that can be considered on the basis of the above principles

See table overleaf

Table 1. Substances for MRLs could be extrapolated to camelids. Identical MRLs have been established in at least one ruminant and at least one non-ruminant mammalian species following JECFA evaluations and extrapolation of identical MRLs to camelids could therefore be proposed (note that in some cases it would not be possible to extrapolate the milk MRL):

	Species for which MRLs already exist			Established MRLs (µg/kg)				
Substance	Ruminant species	Non-ruminant species	Other species*	Muscle	Fat	Liver	Kidney	Milk (Ruminants)
Amoxicillin	Cattle, sheep	Pig	Finfish (muscle)	50	50	50	50	4
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 969) establishes a microbiological ADI and indicates that the only microbiologically active residue is the parent substance. The M:T in and milk (as well as in tissues) is therefore considered to be 1 in all species							
(Procaine) Benzylpenicillin	Cattle	Pig	Chicken	50	-	50	50	4
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 799) uses a M:T of 1 in milk (as well as in tissues) of all species							
Ceftiofur	Cattle	Pig	-	1000	2000	2000	6000	100
	Comment on milk MRL: The milk MRL **can be** extrapolated as the summary of evaluation (available by clicking on the "Search JECFA" link on the relevant page of the Veterinary Drugs Database) states that MRLs are expressed as the marker residue, desfuroylceftiofur, which accounts for all active residues and only these are used in calculating a theoretical daily exposure. The M:T can therefore be considered to be 1 in milk							
Clenbuterol	Cattle	Horse		0.2	0.2	0.6	0.6	0.05
	Comment on milk MRL: The milk MRL **can be** extrapolated as the summary of evaluation (available by clicking on the "Search JECFA" link on the relevant page of the Veterinary Drugs Database) states that parent drug is the marker residue and accounts for 100% of residues in milk. The M:T can therefore be considered to be 1 in milk							
Chlortetracycline/ Oxytetracycline/ Tetracycline	Cattle, sheep	Pig	Poultry	200	-	600	1200	100
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 888) uses a M:T of 1 in milk (as well as in tissues and eggs)							
Colistin	Cattle, sheep, goat	Pig, rabbit	Chicken, turkey	150	150	150	200	50
	Comment on milk MRL: The milk MRL **cannot be** extrapolated as the JECFA evaluation (WHO TRS 939) uses a M:T of 0.8 in milk. As the M:T is not 1 in milk, the milk MRL cannot be extrapolated							
Cyhalothrin	Cattle, sheep	Pig	-	20	400	20	20	30
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 900) uses a M:T of 1 in milk (as well as in tissues)							
Dexamethasone	Cattle	Pig, horse	-	1	-	2	1	0.3
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 851) indicates that although dexamethasone undergoes extensive metabolism, the metabolites did not exhibit any biological activity. Consequently, the marker residue (dexamethasone) can be considered to be represent total residues of toxicological concern (i.e, M:T can be considered to be 1).							
Diclazuril	Sheep	Rabbit	Poultry	500	1000	3000	2000	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
	Cattle, sheep	Pig	Chicken	600	600	600	1000	200

	Species for which MRLs already exist			Established MRLs (µg/kg)				
Dihydrostreptomycin/ Streptomycin	Comment on milk MRL: The milk MRL **can be** extrapolated. The JECFA evaluation (TRS 855) indicates that "the ratio of the marker to total residues is uncertain, although it was predicted that there is little metabolism of either drug and the ratio may be close to unity". A M:T of 1 was used in the JECFA exposure calculation.							
Febantel/ Fenbendazole/ Oxfendazole	Cattle, sheep, goat	Pig, horse	-	100	100	500	100	100
	Comment on milk MRL: The milk MRL **can be** extrapolated. The JECFA report (TRS 815) indicates that the metabolites present as the major residues in edible tissues are oxfendazole, fenbendazole and oxfendazole sulfone. The Marker residue was established as the sum of these three residues and consumer exposure was calculated using a M:T of 1.							
Flumequine	Cattle, sheep	Pig	Chicken, trout (muscle)	500	1000	500	3000	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
Gentamicin	Cattle	Pig	-	100	100	2000	5000	200
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA evaluation (TRS 888) uses a M:T of 1 in the consumer intake.							
Levamisole	Cattle, sheep	Pig	Poultry	10	10	100	10	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
Narasin	Cattle	Pig	Chicken	15	50	50	15	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
Neomycin	Cattle, sheep, goat	Pig	Chicken, duck, turkey	500	500	500	10000	1500
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA evaluation (TRS 918) indicates that that the parent drug, neomycin, represents all the residues present (i.e, M:T can be considered to be 1).							
Phoxim	Sheep, goat	Pig	-	50	400	50	50	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
Ractopamine	Cattle	Pig	-	10	10	40	90	-
	Comment on milk MRL: No extrapolation as there is no MRL to extrapolate from							
Spectinomycin	Cattle, sheep	Pig	Chicken	500	2000	2000	5000	200
	Comment on milk MRL: The milk MRL **can be** extrapolated as the JECFA report (WHO TRS 888) indicates that the parent drug is the only microbiologically active residue in milk, indicating that the M:T is 1 in milk							
Spiramycin	Cattle	Pig	Chicken	200	300	600	300	200
	Comment on milk MRL: The milk MRL **can be** extrapolated. The marker residue in cattle is the sum of the concentrations of spiramycin and neospiramycin. The JECFA report (TRS 879) indicates that these two residues account for 100% of the total residues in milk, ie, the M:T in milk is 1							
Thiabendazole	Cattle, sheep, goat	Pig	-	100	100	100	100	100
	Comment on milk MRL: The milk MRL **can be** extrapolated. The marker residue is the sum of thiabendazole and 5-hydroxythiabendazole. The JECFA report (TRS 832) indicates that total residues can be approximated to the sum of thiabendazole and 5-hydroxythiabendazole, which is used as the M:T							

	Species for which MRLs already exist			Established MRLs (µg/kg)				
Tylosin	Cattle	Pig	Chicken	100	100	100	100	100
	Comment on milk MRL: The milk MRL **can be** extrapolated. The JECFA report (TRS 954) indicates that the marker residue is tylosin A, which represents approximately 100% of the microbiologically active residues (except in honey). The M:T can therefore be considered to be 1							

* the existence of identical MRLs in species other than ruminants and non-ruminant mammals provides further reassurance that metabolism is conserved across species

Tasks for members of the electronic working group:

1. comment on the proposed approach laid out above.
2. comment on whether, if the approach can be agreed, the extrapolations above should immediately be recommended, or whether extrapolation recommendations for individual substances should only take place following requests from member countries, based on the need for these substances for treatment of camelids.

Annex III: Consideration of opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin.

Background

CCRVDF26 considered the possibility of extrapolating MRLs in milk for deltamethrin and ivermectin For both substances, milk MRLs had previously been established in a single species (cattle) on the basis of a JECFA evaluation. In line with the agreed criteria, extrapolation to milk of other ruminants is possible in such cases if the ration of marker to total residues (M:T) = 1. As, in the case of both deltamethrin and ivermectin the M:T ≠ 1, extrapolation to milk of other ruminants was not accepted.

CCRVDF charged the extrapolation EWG with considering other approaches for extrapolation of MRLs in milk across species.

As the existing extrapolation rules were only agreed at CCRVDF 25, we consider that it is too soon to already seek to revise these default extrapolation criteria. We propose that, instead, in those cases where CCRVDF considers that it is appropriate (as in the cases of deltamethrin and ivermectin), the EWG should consider whether there are particular factors that would justify extrapolation despite the fact that the default criteria are not met. In time, we may find that the experience gained through these case by case considerations provides a basis for a more general set of factors to take into account when considering substances that do not quite satisfy the default criteria.

Considerations relating to deltamethrin:

In the run up to CCRVDF 26, the EWG agreed that the criteria for extrapolation were not met for milk because a milk MRL was established in only one ruminant species and the M:T ≠ 1 (see CX/RVDF 23/26/7).

A M:T for milk does not seem to have been formally established for deltamethrin. JECFA52 (WHO TRS 893) reported only that parent deltamethrin was 42 to 55% of the total residue in milk fat. JECFA60 (WHO TRS 918) did not report a M:T value for milk either. JECFA52 further reported that most of the deltamethrin residues in milk are distributed predominantly in milk fat.

JECFA52 reported that residues other than the parent compound will have reduced toxicity compared to that of the parent.

JECFA52 reported that residues in cattle milk were <LOQ (15µg/L) and the MRL was therefore established at twice this level. JECFA did not include residues in milk in its intake calculation, indicating that residues in cattle milk were considered too low to make a significant contribution to the dietary intake and can, in fact, be ignored.

The fact that identical tissue MRLs have been established across a range of species (cattle, sheep and chickens) is a strong indicator that metabolism is conserved across species.

While the fat composition of milk of different ruminants could affect residue disposition, possibly resulting in increased levels of residues in milk of species producing milk with a high fat content, given that residues in cattle milk are <LOQ, it can be expected that even in high fat content milk, residues will make only a very limited contribution to the overall dietary intake of residues.

JECFA60 reports that the total amount of the ADI used up by residue intake resulting from pesticide use (25% of the ADI) and veterinary drug use (43%) will be 68%. This leaves a more than adequate margin of safety to cover uncertainties relating to the possibility that high fat content milk may contain residues at a slightly greater level than seen in cattle milk. Furthermore, MRLs for deltamethrin have already been established in cattle (tissues and milk), sheep (tissues), chicken (tissues and eggs) and salmon (muscle), so the likelihood of needing to use this remaining portion of the ADI to establish MRLs in the future is extremely low.

Furthermore, as for any veterinary drug, a withdrawal period should be established that ensures compliance with the MRL. If products are used off-label, national/regional rules with regard to off-label use should be in place to ensure that an appropriate safety margin is built into the withdrawal period applied. In this way, even if, at any given time point, the level of residues in milk of some ruminants other than cattle slightly exceeds that seen in cattle milk, the MRL will not be exceeded and consumer exposure to these residues will remain at a safe level (i.e. below the MRL).

Proposed EWG recommendation for deltamethrin:

The MRL of 30 µg/kg established for cattle milk can be extrapolated to milk of ruminants other than cattle.

Considerations relating to ivermectin:

In the run up to CCRVDF 26, the EWG agreed that the criteria for extrapolation were not met for milk because a milk MRL was established in only one ruminant species and the M:T ≠ 1 (see CX/RVDF 23/26/7). Some uncertainty was also expressed with regards to whether ivermectin B1a can be considered to be the same as the parent compound.

JECFA recommended a temporary MRL of 10 µg/kg for ivermectin in cattle milk at its 54th meeting (TRS 900). A milk residue study using 2 cattle breeds was provided. The MRL was derived from the unused portion of the ADI (21 µg out of 60 µg / person was left available for use in recommending a milk MRL – i.e. approximately 35% of the ADI). A concentration of 10 µg/kg of ivermectin B1a in milk would result in the intake of an additional 15 µg based on a daily intake of 1.5 kg milk. JECFA acknowledged that this MRL would mean that milk from up to 11 milkings would need to be discarded (note that this comment related to the topical route of administration used in the study).

At its 58th meeting (TRS 911) JECFA considered a further topical administration residue study in lactating cattle. Milk samples were collected at approximately 12 hour intervals on days 1 to 9 after treatment and a single morning sample was collected on day 10. Concentrations of ivermectin B1a in milk reached a peak after 3-4 days and declined over the final 5 days. All milk samples collected from treated animals contained detectable residues. None of the samples collected on days 9 and 10 had concentrations that exceeded 10 µg/kg. Based on the JECFA 58 assessment the temporary milk MRL was made a full MRL.

The JECFA evaluations establish a safe level of residues in milk but highlight that residues below this level will only be achieved following discard of a very considerable amount of milk.

From a safety perspective, there is no reason why an MRL of 10 µg/kg would be less safe for milk of ruminants other than cattle compared to cattle milk. However, ivermectin is highly lipophilic and, for species producing milk with a greater fat content than that of cattle, a greater number of milk discards may be needed in order to achieve the MRL.

It is noteworthy that JECFA 88 (TRS 1023) reported that there are currently no approvals for the application of ivermectin formulations to lactating dairy cattle. This is not unexpected in light of the high level of milk discard necessary to achieve the MRL. In line with this, it seems highly unlikely that companies would develop ivermectin products aimed specifically at lactating ruminants other than cattle. Consequently, if Codex agrees to extrapolate the MRL for ivermectin to milk of ruminants other than cattle, it is likely that any use in these species will be off-label and consequently compliance with the MRL will only be ensured if national/regional rules with regard to off-label use are strict enough to ensure substantial milk discard.

In relation to the point, raised in the first paragraph, that there was uncertainty with regard to whether ivermectin B1a can be considered the same as the parent compound, ivermectin consists of two homologous compounds – ivermectin B1a and ivermectin B1b in an 80 to 20 ratio. So although ivermectin is not exclusively made up of ivermectin B1a, it is predominantly made up of ivermectin B1a. Furthermore, JECFA 54 (TRS 900) reported that, in milk, the contribution of residues of ivermectin B1b to the concentration of total residues was insignificant and typically below the LOD (1 µg/kg). Therefore, the fact that ivermectin B1a is not the entire parent compound is not considered to represent an obstacle to the extrapolation of the MRL.

Finally, JECFA 81 (TRS 997) revised the ADI for ivermectin: the ADI of 0 – 1 µg/kg was revised to 0 – 10 µg/kg, so while the tissue and milk MRLs previously accounted for approximately 90% of the ADI, with this revision they can be considered to account for only 9% of the ADI.

Proposed EWG recommendation for ivermectin

The existing milk MRL of 10 µg/kg represents a safe value for milk of all ruminants and would provide a safe reference point for trade purposes. However, because of the large amount of milk that needs to be discarded in order to achieve this MRL, it is highly unlikely that extrapolation would succeed in encouraging companies to develop ivermectin products specifically for use in lactating ruminants. In reflecting on the possibility of extrapolation, EWG members are encouraged to consider whether the provisions relating to off-label use in their countries are strict enough to ensure that the amount of milk discarded would be sufficient to ensure compliance with the extrapolated MRL.

Consideration could also be given to recommending that, in view of the fact that the ADI was increased as a result of the JECFA 81 evaluation, JECFA could be requested to reconsider the cattle milk MRL with a view to establishing an MRL that does not require substantial milk discard.

Before proposing an overall EWG recommendation it would seem appropriate to review comments from EWG members in relation to the above.

Comments received from EWG members.

Canada's Comments on CCRVDF EWG - Extrapolation of MRLs for Veterinary Drugs

Canada thanks the chair and the co-chair for their work on leading this project and allowing Canada the opportunity to participate in the electronic working group for Extrapolation of MRLs for Veterinary Drugs.

Please see our comments below.

Annex I: Extrapolation of MRLs for lufenuron, emamectin benzoate and diflubenzuron in finfish using the established extrapolation rules.

Canada would like to raise a comment regarding drug substances that consist of a mixture of homologous compounds. In accordance with the criteria for extrapolating MRLs outlined in the discussion paper, the marker residue is required to be the parent compound only (with the exception of cases where the MRL classification is listed as "unnecessary"). However, for drug substances containing homologous compounds (i.e. emamectin benzoate), regardless of the homolog selected, the marker residue would not represent the entire parent compound. This would prevent such drug substances from meeting the general criteria for extrapolation. This point was also raised in Annex III for the extrapolation of ivermectin in milk, which was met with uncertainty amongst the EWG. Canada proposes that the general criteria for extrapolation be amended to include drug substances that consist of homologous compounds, where the marker residue is the homolog that accounts for the greatest proportion of the parent substance.

Annex II: Development of a possible approach for extrapolation of MRLs to camelids.

Canada has no objection to the proposed approach for the extrapolation of MRLs to camelids. However, Canada notes that there are very few analytical residue methods for veterinary drug residues in camelids published in the literature. As such, there is concern that there may be no suitable regulatory analytical methods available to support the proposed MRLs. In particular, the MRLs for dexamethasone and clenbuterol are quite low and it should not be assumed that methods validated in another species will have similar performance in camelids.

Annex III: Consideration of opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin.

Nil comments at this time.

Comments from France

France supports the extrapolation proposals for fish species, camelids milk, and deltametrine in milk. We note that the current MRL value for ivermectin in cattle milk is very low, which may hinder the establishment of a withdrawal period at the national level. In that respect, France would welcome more consideration on this proposal and would be open to requesting JECFA to reconsider this milk MRL taking into account the ADI established by JECFA 81.

Italian comment on WK 3242/2024

CCRVDF - eWG Request for comments on Extrapolation of maximum residue limits of veterinary drugs to one or more species

Annex I

In examining the extrapolations covered by Annex I, relating to finfish, it is noted that the maximum residual limits (MRLs), proposed for lufenurone and emamectin benzoate, are in line with the approach for extrapolation, from one or more species to another or more species, of the MRLs of pharmacologically active substances, based on Regulation (EC) n.470/2009, which establishes community procedures for the determination of residue limits of pharmacologically active substances in foods of animal origin, as well as based on Regulation (EU) 2017/880 which establishes rules on the application of a maximum residue limit set for a pharmacologically active substance in a specific food product to another food product obtained from the same species and of a maximum residue limit set for a pharmacologically active substance in one or more species to other species.

As regards diflubenzuron, reference is made to Commission Implementing Regulation (EU) 2019/1881 which amends Regulation (EU) no. 37/2010 in order to classify the substance diflubenzuron with regards to its maximum residue limit. Below is an extract from the EMA CVMP assessment report (EMA/CVMP/115336/2018) which led to the reclassification and which indicates the orientation that we want to support for the extrapolation of RMLs to finfish.

“In line with Article 5 of Regulation (EC) No 470/2009, the CVMP is required to consider the possibility of extrapolating its recommendation on maximum residual limits in one species to other food producing species and commodities. Based on the similarity of metabolism between salmon and other fin fish an MRL recommended in salmonidae can usually be extrapolated to other finfish. However, in this case, where a metabolite is the main concern, it is not recommended to extrapolate without evidence that this metabolite is not formed in any relevant amount in every species concerned”.

Annex II

We recognize the need for MRLs in various products to facilitate international trade and protect food security and, therefore, we support the extrapolation of MRLs for pharmacologically active substances to camelids according to the three proposed approaches. In addition, it is proposed to consider art.115 paragraph 1 letter a) and b) of Regulation (EU) 2019/6, in reference to waiting times for medicines used in conditions not foreseen by the terms of the marketing authorization on the market in animal species intended for food production, of which, for convenience, the extract is reported below.

“Waiting time for medicines used in conditions not foreseen by the terms of the authorisation

to the placing on the market in animal species intended for food production

1. For the purposes of Articles 113 and 114, unless a medicinal product used has a withdrawal period foreseen in the summary of product characteristics for the animal species concerned, the veterinarian shall set a withdrawal period according to the following criteria:

(a) for meat and offal of mammals intended for food production, poultry and farmed feathered game, the withdrawal period must not be less than:

(i) the longest withdrawal period foreseen in the summary of product characteristics for meat and offal,

multiplied by the factor 1.5;

ii) 28 days if the medicinal product is not authorized for food-producing animals;

iii) one day, if the medicinal product has a zero withdrawal period and the product is used in a family

different taxonomic compared to the authorized target species;

(b) for milk from animals producing milk for human consumption, the withdrawal period must not be less than:

i) the longest waiting time for milk among those foreseen in the summary of product characteristics for each animal species, multiplied by the factor 1.5;

ii) 7 days if the medicinal product is not authorized for animals producing milk for human consumption;

iii) one day, if the medicine has a zero waiting time".

Extrapolation recommendations for individual substances should be made at the request of member countries, based on need for the treatment of camelids.

Imports of camel meat and milk are currently regulated by EU rules and therefore also for any aspects of the MRLs the European Commission is responsible on behalf of all Member States (MS). Since it is, in fact, a harmonized matter at EU level, it cannot be left to the choices of individual Member States.

In fact, European legislation establishes the list of countries and factories authorized to ship to the EU and the required health certifications.

In this case, camel milk can come from the United Arab Emirates and camelid meat from a series of countries listed in Regulation (EU) 2021/404. In the last 4 years there have been no imports of such products through Italian PCFs.

In the case of imports, consignments would be subject to monitoring or, if necessary, suspicion checks in accordance with the relevant EU rules. If residues are found, Regulation (EU) 470/2018 would apply.

Annex III

Specifically regarding the possibility of extrapolating the MRLs for deltamethrin and ivermectin between milk of different species, it is believed that the revision of the criteria requires caution and specific in-depth analysis, taking into account on the one hand the real possibility of "incentivising" off-label use, due to the large quantity of milk that must be discarded and on the other hand, the possibility that highly lipophilic pharmacologically active substances, such as those in question, may be more present as residues in milk with a higher fat content than that of bovines, as in this case that of ruminants other than cattle, especially if the waiting times are not respected. On the other hand, a revision of the MRLs in cattle would be a solution to consider.

Comments from The United States of America on Annex I, Annex II, and Annex III from the Electronic Working Group (EWG) on Extrapolation

The United States appreciates the efforts of the European Union and Costa Rica on the topic of extrapolation. We offer the following comments for consideration by the EWG on the Annex documents provided to the group.

Existing Criteria

The United States thinks that a minor addition might be needed to the existing extrapolation criterion 2b, which requires the marker residue to be the parent compound. The United States recalls the reason for this requirement was to ensure that metabolism, which may differ qualitatively between species, does not have to occur in order for the marker residue to be present. As we have now seen with compounds like ivermectin and emamectin, there are cases where the marker residue is the major component of the parent compound but not truly parent in a strict sense. Because the existing criteria do not allow for major components to be considered the same as parent, compounds like ivermectin and emamectin are procedurally excluded from extrapolation even though the original intent has been met. Therefore, the United States suggests that CCRVDF consider adding a sub-point to criterion 2b as follows:

2b) The marker residue in the reference species is the parent compound only or is the same as the total residues of toxicological concern, or the Codex 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.

i. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as parent if it is a homolog that is a major component of the active substance.

Annex I: Extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish

Lufenuron

The United States agrees that the criteria have been met to extrapolate the lufenuron MRLs in fillet from salmon and trout to fillet from all finfish.

It is worth noting that the report from the 85th Meeting of JECFA specifically stated that the Committee could not extrapolate to all finfish. Before extrapolating the existing MRLs, the United States suggests that CCRVDF confirm with JECFA that the inability to extrapolate was not due to a specific consumer health reason.

Emamectin benzoate

The criteria have not been met to extrapolate the emamectin MRLs in fillet and muscle from salmon and trout to fillet and muscle from all finfish because the marker residue is not truly parent compound. Nevertheless, as noted by the Chair and co-Chair, the marker residue is the major component of the parent compound. The United States suggests that CCRVDF add an additional sub-point to the existing criteria to account for compounds like emamectin where the marker residue is one of the major homologous compounds that comprise the parent compound (see comment above on existing criteria). This type of addition would allow CCRVDF to extrapolate the emamectin MRLs in fillet and muscle from salmon and trout to fillet and muscle from all finfish.

Diflubenzuron

The United States agrees that the criteria have not been met to extrapolate the MRL in muscle plus skin in natural proportions from salmon to muscle plus skin in natural proportions from all finfish.

Annex II: Development of a possible approach for extrapolation of MRLs to camelids

Proposed Extrapolation Criteria

The United States suggests strengthening the proposed extrapolation criteria by applying some of the principles found in the existing extrapolation criteria for related species and by considering the thorough examination of information on camelid species presented at CCRVDF26 by Jordan, Morocco, the Arab Industrial Development, Standardization and Mining Organization (AIDSMO) and the International Union of Food Science and Technology (IUFoST).[1]

The established extrapolation criteria for related species requires that the marker residue be the parent compound. The United States recalls the reason for having this criterion was to ensure that metabolism, which may differ qualitatively between species, does not have to occur in order for the marker residue to be present. Because camelid species are not considered to be related to other species in CCRVDF's current extrapolation criteria, the United States thinks that the marker residue being the parent compound is even more important.

The United States also recalls that one of the conclusions about camelids presented at CCRVDF26 was that metabolism of drugs in camelids is notably different compared to other domestic animals.[2] Because of this notable difference, the United States thinks that extrapolation criteria for camelids should provide a high level of certainty that metabolism is conserved across multiple groups of species. To achieve this, the United States suggest requiring that identical MRLs be established in at least one ruminant species, one non-ruminant species, and one avian species on the basis of JECFA recommendations, and that the marker to total (M:T) ratio used by JECFA was 1 in all tissues for all three unrelated species. If JECFA recommended identical MRLs in three unrelated species and determined that the M:T ratio is 1 in all tissues for those species, then it is reasonable to conclude that the same would be true for camelid species.

Therefore, building on the criteria proposed by the Chair and Co-Chair, the United States proposes the following criteria for extrapolation of existing MRLs to camelid species.

5) 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.*).

6) The marker residue is the parent compound.

    a. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as parent if it is a homolog that is a major component of the active substance.

7) For meat tissues, extrapolation of reference species MRLs to camelids on a one-to-one basis should be considered if identical MRLs have been established in at least one ruminant species, one non-ruminant species, and one avian species on the basis of JECFA recommendations, and the M:T ratio used by JECFA was 1 in all tissues for all unrelated species.

8) Where condition (ii) and (iii) are satisfied, extrapolation of an MRL for milk also should be considered in those cases where M:T ratio used by JECFA was 1 in milk.

Considering Compounds for MRL Extrapolation to Camelids

The United States suggests that CCRVDF first work towards establishing extrapolation criteria for camelid species. After extrapolation criteria are developed and agreed upon, member countries can then nominate compounds for extrapolation and inclusion in Part V of the Priority List. This approach would allow the extrapolation of MRLs to camelid species to be based on member countries' needs and would be consistent with how the current extrapolation criteria for related species were developed and applied.

[1] RVDF26/CRD10

[2] RVDF26/CRD10, paras. 10 and 11

Annex III: Consideration of opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin

Deltamethrin

At the Physical Working Group on the Extrapolation of MRLs to One of More Species held prior to CCRVDF26, the JECFA Secretariat confirmed that the M:T ratio for deltamethrin in cow's milk is not equal to 1.[3] Therefore, the MRL for deltamethrin in cow's milk does not meet the procedural requirements for extrapolation because there is only one MRL established in milk and the M:T ratio in milk is not 1. The existing extrapolation criteria explain that, in cases like deltamethrin where only one milk MRL has been established and the M:T is not equal to 1, there is a concern that the fat content of milk differs among related species (*i.e.*, ruminants). That the fat content of milk differs among ruminants is even more of a concern for fat-soluble compounds like deltamethrin because the fat content can greatly influence the deposition of deltamethrin and deltamethrin metabolites in the milk. Therefore, because JECFA determined that the M:T ratio in cow's milk is not 1 for deltamethrin residues, CCRVDF lacks the confidence that the milk M:T ratio will not differ among ruminants because of the varying fat content among ruminants and fat solubility of deltamethrin and its metabolites. Moreover, the 52nd Meeting of JECFA extended the cattle MRLs to sheep for tissues, but specifically did not do so for milk[4], suggesting that it is not scientifically advisable to extrapolate the MRL for cow's milk to all other ruminants. Therefore, the United States does not support CCRVDF extrapolating the single MRL in cow's milk to milk of all other ruminants because the procedural requirements have not been met and the available scientific information does not provide confidence that the M:T ratio in cow's milk can be assumed to be the same for all other ruminants.

Ivermectin

Regarding whether the marker residue, ivermectin B_{1a}, can be considered to be the same as the parent compound, the United States suggests that CCRVDF add an additional sub-point to the existing criteria to account for compounds like ivermectin where the marker residue is one of the major homologous compounds that comprise the parent compound (see comment above on existing criteria).

As discussed previously[5], it remains unclear if JECFA determined that the M:T ratio for ivermectin in cow's milk is equal to 1, as the report from the 54th Meeting of JECFA does not discuss an M:T ratio. Therefore, the MRL for ivermectin in cow's milk does not meet the procedural requirements for extrapolation. Similar to deltamethrin, because ivermectin is a fat-soluble compound, the differential fat content among ruminants can greatly influence the deposition of ivermectin and ivermectin metabolites in the milk. In the absence of JECFA determining that the M:T ratio for ivermectin in cow's milk is equal to 1, the United States is unsure if the M:T ratio for ivermectin in milk can be assumed to the same among ruminants. The uncertainty about the M:T ratio in milk is further augmented by the fact that JECFA reported different M:T ratios in muscle, liver, kidney and fat for cattle and sheep (Table 1). Because the M:T ratios differ between cattle and sheep for muscle, liver, kidney and fat, it seems likely that the M:T ratio in milk also would differ among ruminant species.

Table1. Marker to total (M:T) ratios reported by 81st and 94th meeting of JECFA for ivermectin in cattle and sheep[6,7]

Tissue	Cattle M:T	Sheep M:T
Muscle	0.67	0.54
Liver	0.37	0.56
Kidney	0.54	0.08
Fat	0.18	0.25

[3] RVDF26/CRD03
[4] JECFA52 Report, WHO TRS 893
[5] CX/RVDF 23/26/7
[6] JECFA81 Report, WHO TRS 997
[7] JECFA94 Report, WHO TRS 1041

The United States thinks that CCRVDF does not have enough information at this time to recommend extrapolating the MRL for ivermectin in cow's milk to the milk from all other ruminants. The United States suggests that CCRVDF ask the JECFA Secretariat (as done for deltamethrin at CCRVDF26) if JECFA determined that the M:T ratio for ivermectin in cow's milk is equal to 1.

With respect to whether JECFA should reevaluate the existing ivermectin MRL for cow's milk, the United States thinks that recommending reevaluation of an existing MRL in a reference species should be addressed through the established procedures to prioritize work (*i.e.*, the nomination to the Priority List).

Comments from The United States on Extrapolating MRLs to Offal Tissues Other than Liver and Kidney

The United States would like to offer our thoughts on how CCRVDF might progress the important work on extrapolating MRLs to offal tissues other than liver and kidney (*i.e.*, other offal). In general, the United States views the work on other offal extrapolation as being comprised of two parts:

- Collecting tissue distribution information on veterinary drug compounds or related compounds to reasonably conclude that the other offal tissues can comply with the extrapolated MRL value when Good Veterinary Practices (GVPs) are followed.
- Evaluating the risk management decision to extrapolate an existing MRL to other offal tissues from a consumer safety perspective.

Collecting tissue distribution information on veterinary drug compounds or related compounds

The 26th Session of CCRVDF (2023) tasked the EWG with summarizing the available information on the distribution of compounds in different edible offal tissues with a view towards evaluating the possibility of extrapolating MRLs to edible offal tissues other than liver and kidney. In hindsight, the United States wonders whether CCRVDF should first identify two to three compounds on which to focus. This would concentrate the efforts to gather tissue distribution information on specific compounds (or related compounds), rather than any compound of potential interest. If CCRVDF finds success with the two to three compounds, then additional compounds can be assigned to the EWG at successive CCRVDF sessions. Thus, over time, CCRVDF would build a collection of tissue distribution information on compounds relevant to residues of veterinary drugs in foods which would enable more compounds to be considered for other offal extrapolation.

Evaluating the risk management decision to extrapolate an existing MRL to other offal tissues from a consumer safety perspective

Previous discussions focused on extrapolating an existing MRL value to other edible offal tissues for a particular compound and species.[8] However, members were hesitant to apply this approach because residue data and consumption data for other edible offal tissues are sparce or non-existent, which prevents CCRVDF from fully understanding the risk associated with a decision to extrapolate.

The ratio between the marker residue and total residues in the other offal tissues (M:T ratio) and data on how much other offal is consumed would allow CCRVDF to evaluate the outcome of extrapolating one of the existing meat-tissue MRLs (*i.e.*, muscle, liver, kidney, fat) to other offal tissues from a consumer safety perspective. The United States proposes a process by which CCRVDF could estimate the M:T ratio and consumption values for other offal, followed by a risk management evaluation that considers the dietary consumption of residues if one of the existing meat-tissue MRLs is extrapolated to other offal. With this approach, CCRVDF would use the existing JECFA risk assessments as a tool to evaluate the risk management decision to extrapolate.

Estimating the ratio between the marker residue and total residues for other offal

Because residue data are sparce to non-existent for other offal tissues, an M:T ratio for these tissues cannot be established by traditional approaches. However, CCRVDF does have access to the M:T ratios established by JECFA in the four meat tissues that JECFA typically evaluates (*i.e.*, muscle, liver, kidney, and fat (skin/fat)). From these existing M:T ratios, an understanding of how M:T ratios for a compound vary between meat tissues in a species can be gained. This can allow CCRVDF to make an informed risk management decision about estimating a possible M:T ratio for other offal tissues in a specific species for a specific compound. The United States proposes the following approach to estimate the M:T ratio for other offal based on the existing JECFA risk assessment.

1. For a specific compound and species (*e.g.*, ivermectin in pigs) with at least three Codex MRLs in meat tissues (*i.e.*, muscle, liver, kidney, and fat (skin/fat)) established on the basis of JECFA-recommended MRLs, obtain the M:T ratios used in the JECFA risk assessment(s) that served as the basis for the current MRLs.

[8] CX/RVDF23/26/7, para. 18

2. Determine the magnitude of difference between the maximum M:T ratio and minimum M:T ratio in the meat tissues used by JECFA. For example, the 94th meeting of JECFA determined the M:T ratios for ivermectin in pig muscle, liver, kidney and fat to be 0.44, 0.25, 0.50 and 0.20, respectively. Thus, the magnitude of difference between the highest and lowest M:T value for ivermectin in pigs is a 2.5-fold difference (0.5 ÷ 0.2 = 2.5).
3. Use the value determined in #2 as an uncertainty factor to account for the uncertainty associated with extrapolating existing M:T ratio information from the four typical meat tissues to other offal tissues.
4. Estimate an M:T ratio in other offal tissues by applying the uncertainty factor to the average M:T ratio used by JECFA in the typical meat tissues. The average M:T ratio is used because it is a measure of the central tendency of the known M:T ratio information. It is then adjusted by the uncertainty factor which is a measure of the known magnitude by which M:T ratios can differ.

$$Other\ offal\ M{:}T = \frac{Average\ M{:}T\ used\ by\ JECFA\ in\ meat\ tissues}{Uncertainty\ Factor}$$

Using ivermectin in pigs as an example, the M:T ratio for other offal would be estimated to be 0.14.

$$Other\ offal\ M{:}T = \frac{(0.44 + 0.25 + 0.50 + 0.2) \div 4}{2.5} = 0.14$$

For cases in which JECFA used the same M:T ratio for all meat tissues, the uncertainty factor would be calculated to be 1, meaning that the estimated M:T ratio for other offal would be the same as that used for the other meat tissues.

Estimating other offal consumption

The other piece of missing information that prevents derivation of MRLs in other offal tissues by traditional approaches is consumption data.

At CCRVDF26, the JECFA Secretariat advised that CCRVDF might use the Theoretical Maximum Daily Intake (TMDI) model as an initial risk management tool when making risk management decisions about residues of veterinary drugs in food.[9] The TMDI model conservatively assumes that a typical person consumes 0.5 kg of meat, 0.1 kg of eggs, 1.5 kg of milk, and 0.05 kg of honey daily for a lifetime, with the 0.5 kg of meat being comprised of 0.3 kg muscle, 0.1 kg liver, 0.05 kg kidney, and 0.05 kg fat (skin with fat). These quantities of foods historically have been referred to as the "food basket."

Previous discussion within the extrapolation EWG included the concept that, if a person consumes other offal tissues, the consumption of the other meat tissues in the food basket would decrease.[10] Indeed, this is a reasonable assumption because it is unlikely that a person consumes the current 0.5 kg of meat plus an additional amount of other edible offal daily for a lifetime.

However, because there is not a robust global estimate of other edible offal consumption[11], it is unknown by how much the consumption of the other meat tissues in the food basket would decrease. To circumvent this challenge, the United States proposes that CCRVDF consider different dietary scenarios in which other offal replaces one, two, three, or all four meats in the TMDI food basket. This yields 15 possible dietary scenarios for meat consumption (Table 1).

[9] REP23/RVDF26, para. 95
[10] CX/RVDF23/26/7, para. 19
[11] RVDF26/CRD03

Table 1. Possible Dietary Scenarios Used to Estimate Dietary Consumption of Other Offal

Meat Tissue	Diet 1	Diet 2	Diet 3	Diet 4	Diet 5	Diet 6	Diet 7	Diet 8	Diet 9	Diet 10	Diet 11	Diet 12	Diet 13	Diet 14	Diet 15
Muscle (kg)	0.3	0.3	0.3	0	0.3	0.3	0.3	0	0	0	0.3	0	0	0	0
Liver (kg)	0.1	0.1	0	0.1	0.1	0	0	0.1	0.1	0	0	0.1	0	0	0
Kidney (kg)	0.05	0	0.05	0.05	0	0.05	0	0.05	0	0.05	0	0	0.05	0	0
Fat (Skin/Fat) (kg)	0	0.05	0.05	0.05	0	0	0.05	0	0.05	0.05	0	0	0	0.05	0
Other Offal (kg)	0.05	0.05	0.1	0.3	0.1	0.15	0.15	0.35	0.35	0.4	0.2	0.4	0.45	0.45	0.5
Total (kg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

The underlying assumption in this approach is that, if an individual consumes other offal, it is reasonable to assume that other offal likely will replace between one and four of the other meat commodities in the food basket. By considering replacement of one (Diets 1 through 4), two (Diets 5 through 10), three (Diets 11 through 14), or four of the meat commodities (Diet 15) in the food basket, CCRVDF can estimate the possible consumption of other offal across a range of values and, by doing so, estimate a range of dietary residue consumption from other edible offal that might occur without knowing an exact consumption value for other offal.

Risk Management Decision Evaluation

Using the previously described approach to estimate an M:T ratio for other offal and the possible consumption scenarios for other offal, CCRVDF can evaluate the risk management decision to extrapolate an existing MRL to other offal by considering the dietary consumption of residues using the TMDI approach. The TMDI evaluation would be conducted under the 15 dietary scenarios presented in Table 1 and would consist of the following:

- Consumption of residues associated with the current Codex MRLs, using the JECFA-determined M:T ratios and the food basket consumption values for muscle, liver, kidney and fat (skin/fat).
- Consumption of residues associated with extrapolating one of the existing meat-tissue MRLs to other offal, using the estimated M:T ratio and the estimated consumption values for other offal (Table 1).
- Consumption of residues from non-meat edible commodities (*i.e.*, milk, eggs, and honey) estimated previously by JECFA.

If the TMDI from all 15 dietary scenarios does not exceed the ADI, CCRVDF could make the risk management decision to extrapolate an existing MRL to other edible offal tissues. In this way, the proposed TMDI evaluation can serve as an initial screening tool for CCRVDF. If an exceedance of the ADI occurs, then CCRVDF can consider the next steps on a case-by-case basis. For example, CCRVDF could seek specific scientific advice from JECFA.

Pilot Exercise

The United States undertook a pilot exercise for terrestrial species in which we performed the proposed approach on 139 unique pairs of compounds and species for which we could readily find the M:T ratios used by JECFA. Of the 139 compound-species combinations that were tested, 93 passed this initial screening for extrapolating one of the existing meat-tissue MRLs to other offal tissues. Thus, this initial screening approach would give CCRVDF the confidence, from a consumer safety perspective, to extrapolate an existing MRL to other edible offal in more than a majority of cases for terrestrial species.

As an example, we present the results from evaluating the extrapolation of the fat MRL to other offal for ivermectin in pigs (Table 2). In this case, CCRVDF could select the fat MRL to be the most appropriate MRL to test for extrapolation to other offal tissues because ivermectin is lipophilic and fat had the highest MRL. However, the selection of which MRL to extrapolate to other offal depends on the specific veterinary drug and the available information. As seen in Table 2, consumption of residues from extrapolating the fat MRL to other offal is estimated to range between 9.54% (dietary scenario 1) and 32.48% (dietary scenario 15) of the ADI, indicating that, for ivermectin in pigs, extrapolating the fat MRL to other offal is acceptable from a consumer safety perspective.

Table 2. Theoretical maximum daily intake evaluation of extrapolating the fat MRL to other edible offal for ivermectin in pigs.

IVERMECTIN			Theoretical Maximum Daily Intake (TMDI)						Acceptable Daily Intake (µg/kg bw): 10			
Species: Pig			Residue Definition: Ivermectin B_{1a}									
			Dietary Scenario 1		Dietary Scenario 2		Dietary Scenario 3		Dietary Scenario 4		Dietary Scenario 5	
Tissue	MRL[1] (µg/kg)	M:T [2]	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)
Muscle	15	0.44	0.30	10.23	0.30	10.23	0.30	10.23	0.00	0.00	0.30	10.23
Liver	30	0.25	0.10	12.00	0.10	12.00	0.00	0.00	0.10	12.00	0.10	12.00
Kidney	20	0.50	0.05	2.00	0.00	0.00	0.05	2.00	0.05	2.00	0.00	0.00
Fat	50	0.20	0.00	0.00	0.05	12.50	0.05	12.50	0.05	12.50	0.00	0.00
Offal	50	0.14	0.05	17.99	0.05	17.99	0.10	35.97	0.30	107.91	0.10	35.97
Meat dietary exposure (µg/day)			42.21		52.71		60.70		134.41		58.20	
Non-meat dietary exposure (µg/day) [3]			15.00		15.00		15.00		15.00		15.00	
Total dietary exposure (µg/day)			57.21		67.71		75.70		149.41		73.20	
Acceptable Daily Intake (µg/day)			600.00		600.00		600.00		600.00		600.00	
Acceptable Daily Intake Utilization (%)			**9.54**		**11.29**		**12.62**		**24.90**		**12.20**	
			Dietary Scenario 6		Dietary Scenario 7		Dietary Scenario 8		Dietary Scenario 9		Dietary Scenario 10	
Tissue	MRL[1] (µg/kg)	M:T [2]	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)
Muscle	15	0.44	0.30	10.23	0.30	10.23	0.00	0.00	0.00	0.00	0.00	0.00
Liver	30	0.25	0.00	0.00	0.00	0.00	0.10	12.00	0.10	12.00	0.00	0.00
Kidney	20	0.50	0.05	2.00	0.00	0.00	0.05	2.00	0.00	0.00	0.05	2.00
Fat	50	0.20	0.00	0.00	0.05	12.50	0.00	0.00	0.05	12.50	0.05	12.50
Offal	50	0.14	0.15	53.96	0.15	53.96	0.35	125.90	0.35	125.90	0.40	143.88
Meat dietary exposure (µg/day)			66.18		76.68		139.90		150.40		158.38	
Non-meat dietary exposure (µg/day) [3]			15.00		15.00		15.00		15.00		15.00	
Total dietary exposure (µg/day)			81.18		91.68		154.90		165.40		173.38	
Acceptable Daily Intake (µg/day)			600.00		600.00		600.00		600.00		600.00	
Acceptable Daily Intake Utilization (%)			**13.53**		**15.28**		**25.82**		**27.57**		**28.90**	
			Dietary Scenario 11		Dietary Scenario 12		Dietary Scenario 13		Dietary Scenario 14		Dietary Scenario 15	
Tissue	MRL[1] (µg/kg)	M:T [2]	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)	Tissue Consumption (kg)	TMDI (µg)
Muscle	15	0.44	0.30	10.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Liver	30	0.25	0.00	0.00	0.10	12.00	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	20	0.50	0.00	0.00	0.00	0.00	0.05	2.00	0.00	0.00	0.00	0.00
Fat	50	0.20	0.00	0.00	0.00	0.00	0.00	0.00	0.05	12.50	0.00	0.00
Offal	50	0.14	0.20	71.94	0.40	143.88	0.45	161.87	0.45	161.87	0.50	179.86
Meat dietary exposure (µg/day)			82.17		155.88		163.87		174.37		179.86	
Non-meat dietary exposure (µg/day) [3]			15.00		15.00		15.00		15.00		15.00	
Total dietary exposure (µg/day)			97.17		170.88		178.87		189.37		194.86	
Acceptable Daily Intake (µg/day)			600.00		600.00		600.00		600.00		600.00	
Acceptable Daily Intake Utilization (%)			**16.19**		**28.48**		**29.81**		**31.56**		**32.48**	

[1] The MRL values for muscle, liver, kidney and fat were adopted previously based on JECFA recommendations. The MRL

value for other offal is extrapolated from fat.

[2] The M:T values for muscle, liver, kidney and fat were used by JECFA. The M:T value for other offal is estimated using an average M:T value of 0.35 and an uncertainty factor of 2.5.

[3] The dietary exposure value for non-meat commodities was determined by JECFA.

Second consultation with EWG - Responses to EWG extrapolation comments – document shared on 28 June 2024

Comments were received from Canada, USA and Italy (Canada makes no comments on Annex III). A summary of the comments received on each of the annexes is provided below along with responses from the chair. The USA also provided comments on extrapolating MRLs to offal tissues other than liver and kidney. In the last part of this document the EU provides some comments on this topic.

Annex I - Extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish

Summary of comments received from	Response from chair
Canada No comments on specific MRL recommendations but proposes to amend the general criteria for extrapolation to allow extrapolation where the MR is a homologue that makes up the greatest proportion of the parent substance	Thank you for the comment. We note that a similar comment was made by USA. The EU supports the proposed amendment to the relevant criterion in the extrapolation rules.
USA For lufenuron: the USA agrees that the relevant criteria are met but, noting that JECFA could not extrapolate to all finfish, suggests checking with JECFA that this was not due to a specific consumer health concern.	Thank you for the comments. In relation to lufenuron and the suggestion that CCRVDF should consult JECFA to confirm that there was not a specific consumer health concern that prevented JECFA from extrapolating its recommendation, we take the opportunity to highlight that the report of JECFA's 85th meeting (TRS 1008) provides the following explanation for its decision not to extrapolate: • *Lufenuron is lipophilic and its concentration is higher in fatty tissues, and the fat content in fish depends on species and growing conditions.* • *The decrease of residues is dependent on time after administration and on the increase in bodyweight, both of which are dependent on water temperature.* • *No depletion data were provided for species other than salmonids.* The combination of these points could be said to represent a "specific consumer health reason". The points indicate that there is uncertainty about the quantity (but not the nature) of residues that will occur fish of different species. However, as indicated in the initial extrapolation proposal for lufenuron, these concerns need not prevent extrapolation, but they do emphasize the need to have appropriate withdrawal periods in place. In view of the fact that the JECFA report already explains the decision not to extrapolate, we would like to ask the USA to confirm that it considers that a further consultation with JECFA is necessary.
For emamectin benzoate: the USA makes a comment similar to that made by Canada and proposes updated wording for the extrapolation criteria.	Thank you for the proposed amendment to the relevant criterion in the extrapolation rules, which we support.
For diflubenzuron: the USA agrees that the criteria for extrapolation are not met	Thank you for the statement, which supports the initial proposal.
Italy Italy comments that the recommendations are in line with the EU approach for extrapolation	Thank you for the additional information

Overall conclusions on Annex I:

1. Some further comment on the need to consult JECFA in relation to the proposed extrapolation for lufenuron is requested from USA before a decision can be taken on whether to already propose extrapolation.

2. The EWG will recommend modification of criterion 2b of the Approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species as in line with the comments made by Canada and USA. Specifically, the following text can be recommended for addition as a subpoint to the criterion:

   ii. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as parent if it is a homolog that is a major component of the active substance.

   With agreement on the addition of this subpoint, extrapolation of the MRL of 100µg/kg to fillet of finfish can be recommended for emamectin benzoate.

3. The EWG will recommend that no MRL extrapolation to finfish is made for diflubenzuron.

Annex II - Development of a possible approach for extrapolation of MRLs to camelids

Summary of comments received from	Response to comments
Canada The comments are supportive of the proposed approach in principle but express concern that there may be no suitable analytical methods for control of residues in tissues and milk of camelids. This concern is amplified where extrapolated MRLs are low.	Thank you for the comments. The need for analytical methods was discussed in the development of the accepted criteria for extrapolation and the following points were made at that time: • Analytical methods reviewed by JECFA are often methods submitted by sponsors and optimized for the measurement of an individual marker residue. In practice residue monitoring programmes do not use these methods as, instead, they employ multi-residue methods capable of detecting marker residues of a number of substances in a single run. So, while the existence of a validated method reviewed by JECFA does demonstrate that the marker residue can be measured under certain conditions, these will not be the conditions used for residue monitoring purposes. • If it has been demonstrated that a substance can be adequately measured in one species, it is very unlikely that the method could not be adapted to measure the same substance in a related species. • Determining whether existing analytical methods are adequately validated is a scientific task and so would push the extrapolation process at least partly into the realms of risk assessment. In the end CCRVDF decided not to require the availability of an analytical method developed for detection of residues in the species to which extrapolation is being considered. While it is acknowledged that, in the current case, we are considering extrapolation between less closely related species than was considered in the development of the original extrapolation rules, we propose that the same principle can nevertheless be applied.
USA The USA proposes three significant modifications of the proposal, as outlined below. In relation to the question of whether, if an approach can be agreed, the EWG should already make substance-specific recommendations to CCRVDF or whether such recommendations should only be made if member countries request extrapolation, the USA considers that the EWG should focus its efforts on establishing the criteria for extrapolation and that substance specific recommendations should only be made once the criteria are in place and member countries have nominated compounds for extrapolation for inclusion in Part V of the Priority List.	Thank you for the comments. Implementation of the proposals from the USA would further reduce uncertainty associated with extrapolation to camelids. However, we wonder if requiring that all three additional criteria are demonstrated for each substance would represent an overly cautious approach and so unnecessarily restrict opportunities for extrapolation. We support the view that recommendations for substance specific extrapolation should only be made once the relevant criteria are in place and substances have been included in Part V of the Priority List.
1. The marker residue should be the parent compound (as is this case for extrapolation between related species)	As pointed out by the USA, this is a requirement of the established extrapolation criteria for related species and means that metabolism does not have to occur in order for the marker residue to be present. We agree that there is a strong case for also applying this criterion for extrapolation to camelids.
2. The M:T used by JECFA was 1 in all tissues for all three unrelated species (ie ruminant, non-ruminant and avian species).	We note that in the established extrapolation criteria for related species, this is one of three possible justifications for concluding that the M:T established for the reference species can be applied to the concerned species. The two other possible justifications are that identical MRLs have been established in at least two species or that different MRLs have been established in two species but the same M:T was used by JECFA.

Summary of comments received from	Response to comments
	The combination of proposed modification 1 and 2 amounts to a requirement that no metabolism of the compound should take place (or that, where metabolism does take place, the only metabolite of toxicological/microbiological interest is the parent). As far as we can establish based on a review of the substances for which Codex MRLs are in place, of those substances for which MRLs have been established for at least one ruminant, one non-ruminant and one avian species, and for which the M:T=1 in the ruminant and non-ruminant species, it is also the case that the M:T=1 in the avian species (relevant substances are amoxicillin, benzylpenicillin, tetracyclines, diclazuril, dihydrostreptomycin/streptomycin, neomycin and tylosin). This would seem to suggest that the added value of requiring that the M:T has been demonstrated to be 1 in the avian species as well as in the mammalian species is questionable. We would therefore like to suggest that extrapolation should be allowed if the marker residue is the parent compound and the M:T=1 in both a ruminant and a non-ruminant species (without the need for this to have been demonstrated to also be the case for an avian species)
3. Identical MRLs should exist in at least one ruminant species, one non-ruminant species **and one avian species** on the basis of JECFA recommendations.	Addition of a requirement for the existence of identical MRLs in a third unrelated species (ie an avian species) would provide a very considerable degree of additional confidence that metabolism is conserved across species. If a requirement for identical MRLs in a third unrelated species is incorporated into the criteria, we would like to suggest that, with this additional evidence of conserved metabolism, it would not be necessary to require that the M:T = 1.
	Overall, we consider that there is a case for incorporating additional confidence into the proposal but we think it would be sufficient to require EITHER that the marker residue is the parent substance and M:T = 1 in both a ruminant and a non-ruminant mammalian species (without the requirement for this to also have been demonstrated in an avian species) OR that the marker residue is the parent substance and identical MRLs exist in at least one ruminant species, one non-ruminant species and one avian species (without the requirement for the M:T=1).
Italy The proposed approach is supported. Italy considers that recommendations for substance specific extrapolations should only be made following requests from member countries, based on the need for treatment of camelids. Information is also provided on the withdrawal periods that apply in the EU when veterinary medicines are used outside the terms of the marketing authorisation. Finally, Italy provides information relating to the import of camelid meat and milk into the EU.	Thank you for the comments and support. The comment that recommendations for substance specific extrapolations should only be made following requests from member countries is consistent with a comment made by USA. We agree with the comment. The information on withdrawal periods that apply in the EU when veterinary medicines are used outside the terms of the marketing authorisation is noted. While this information may be of interest to Codex member countries, as Codex does not establish withdrawal periods, it is considered to have been provided for information only. Similarly, the information relevant to the import of camelid meat and milk into the EU is considered to have been provided for information only.

Overall conclusions on Annex II:

1. A concern was expressed relating to the possible lack of analytical methods for monitoring of residues in camelid tissues and milk. While parallel concerns were raised during the development of the existing rules on extrapolation, the existence of validated methods was not made a condition of extrapolation. We propose to follow the same principle in this case.

2. Additional criteria were proposed in order to further reduce uncertainty associated with extrapolation. We propose to modify these additional criteria, resulting in the extrapolation criteria set out below:

    9) 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.*).

    10) The marker residue is the parent compound.

        a. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as parent if it is a homolog that is a major component of the active substance.

    11) For meat tissues, extrapolation of reference species MRLs to camelids on a one-to-one basis should be considered if either:

        a. identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species on the basis of JECFA recommendations, and the M:T ratio used by JECFA was 1 in all tissues for the ruminant and non-ruminant species, OR

        b. identical MRLs have been established in at least one ruminant species, one non-ruminant mammalian species and one avian species.

    12) Where condition 2 and 3 are satisfied, extrapolation of an MRL for milk also should be considered in those cases where M:T ratio used by JECFA was 1 in milk.

3. The EWG will not recommend substance-specific extrapolations as part of the current work. Substance specific recommendations should only be made once the criteria are in place and member countries have nominated compounds for extrapolation for inclusion in Part V of the Priority List.

Annex III - Consideration of opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin

Summary of comments received from	Response to comments
USA **Regarding deltamethrin**, the USA notes that the established criteria for extrapolation to milk are not met, that deltamethrin is a lipophilic substance and that the M:T≠1. There is therefore a concern that the M:T may in milk may vary depending on the ruminant species from which the milk is produced (which would impact on consumer exposure to residues). The USA further notes that, while JECFA extended tissue MRLs from cattle to sheep, it did not do the same for the milk MRL, suggesting that it may not be advisable to extrapolate to milk. Overall, the USA does not support extrapolation of the existing cattle milk MRL to milk of other ruminant species.	Thank you for the comments. We agree that the established criteria for extrapolation are not met. Indeed, this was acknowledged by CCRVDF 26. Our interpretation of the charge given to this EWG is that we should consider whether there would be justification for recommending extrapolation despite the fact that the established criteria are not met and, ultimately, we should consider whether the established criteria should be modified. Based on this, we don't consider the fact that the established criteria are not met to be, on its own, a barrier to the EWG recommending extrapolation. We acknowledge that deltamethrin is a lipophilic substance and that, therefore, the quantity of residues present in milk will differ depending on the species from which the milk is taken (and the fat content of that milk). We further acknowledge that, since the M:T≠1, we cannot rule out the possibility that the M:T will be influenced by the fat content of the milk. In line with the concerns expressed, we note that the fat content of cow's milk is relatively low (approximately 3.5 to 5.5% depending on the breed) compared to that of certain other ruminant's milk. Sheep's milk has a particularly high fat content (sometimes reported to be >13%*). JECFA52 reports that, in milk, most deltamethrin residues were found in fat and that, in a total residues study, the maximum level of residues in whole (cow's) milk was 5.7µg/kg. This suggests that, even in milk with 5 times the fat content of cow's milk, the intake of residues from milk would amount to less than 45µg (from 1.5 litres of milk). JECFA's residues intake estimate for deltamethrin was 250µg/person, which corresponds to approximately 42% of the ADI. If we add another 45µg as a generous estimate of additional residue intake that could be associated with drinking 1.5 litres sheep's milk, the consumer intake of residues of veterinary drugs would still correspond to less than 50% of the ADI. When intake of pesticides residues is also considered (reported by JECFA60 as corresponding to 25% of the ADI), a significant portion of the ADI remains 'unused'. We therefore consider that the uncertainties associated with the fact that the fat content of milk varies across ruminant species and the fact that the M:T≠1 are adequately compensated for by a combination of the facts that (i) residues in (cow's) milk have been shown to be very low and (ii) estimates of consumer intake of deltamethrin residues from both veterinary drugs and pesticides leave a substantial portion of the ADI unused.
In relation to ivermectin and the question of whether ivermectin B1a can be considered to be the same as the parent compound, the USA refers to its comments above on homologous compounds that comprise the parent compound.	We support the comment and the proposed amendment to the extrapolation criteria, as reported in the discussion relating to Annex I, above.
The USA notes that the established criteria for extrapolation to milk are not met and that, like deltamethrin, ivermectin is fat soluble and that the M:T has not been confirmed to be 1. It is further noted that JECFA has established different M:T values in tissues of cattle and sheep, which suggests that the M:T in milk may also vary.	We support the concerns raised. We consider that the situation for ivermectin is different to that for deltamethrin as, for ivermectin, JECFA (TRS 900) has reported that residues are present in cow's milk at significant levels and that, in order to allow residues in cow's milk to deplete to below the MRL, significant milk discard would be needed.

Summary of comments received from	Response to comments
It is concluded that there is not currently enough information to recommend extrapolation and it is suggested that the JECFA secretariat should be asked should be asked whether JECFA determined the M:T for ivermectin in cow's milk to be 1.	
With regard to the suggestion that JECFA could be asked to reevaluate the existing ivermectin for cow's milk, the USA considers that this would be a matter to be addressed through established procedures (ie nomination to the Priority List).	We support the suggestion.
Italy Italy emphasises the need for caution. It expresses particular concern over the possibility of encouraging use outside the terms of the marketing authorisation, which a need to discard significant quantities of milk might do, and over the uncertainties associated with the varying fat content of milk of different ruminant species. Italy notes that a revision of the MRLs in cattle might be an appropriate solution (presumably this relates particularly to ivermectin).	Thank you for the comments; we note the concerns raised. As noted in our response to the USA comments, we consider that the risks associated with extrapolation of the deltamethrin milk MRL are adequately addressed while those associated with extrapolation of the ivermectin milk MRL are not.

*Arrichiello et al (2022) Comparison of nutritional value of different ruminant milks in human nutrition. https://doi.org/10.3892/ijfn.2022.28

Overall conclusions on Annex II:

1. The USA is asked to consider the further arguments relating to deltamethrin and indicate whether it remains of the view that extrapolation should not be recommended.
2. The EWG will not recommend extrapolation of the ivermectin MRL.
3. The EWG notes that the, with the revision of the ADI for ivermectin by JECFA 81, consumer exposure to residues of ivermectin accounts for less than 10% of the ADI. There may therefore be scope for a re-evaluation of the milk MRL in order to reduce the level of milk that would need to be discarded in order to achieve compliance with the MRL. A revised milk MRL for cattle may facilitate extrapolation to milk of ruminants other than cattle. However, a request for re-evaluation of the existing milk MRL should proceed according to established procedures (nomination to the priority list).

Response to US comments on extrapolating MRLs to offal tissues other than liver and kidney

The EU would like to thank the USA for its proposal. The proposal provides a way of undertaking a consumer exposure estimate in the absence of actual data in other offal tissues.

The EU has also been considering how MRLs might be extrapolated to offal tissues other than liver and kidney (hereafter referred to as 'other offal tissues') and in thinking about this we have been grappling with a number of issues that, we feel, would benefit from discussion within the group.

1. Is a consumer exposure assessment of residues in other offal tissues required?

Codex has been establishing MRLs for veterinary drugs for several decades and, in that time, the only offal tissues for which MRLs have been established are liver and kidney. Yet, across the world, other offal tissues are regularly consumed. Within CCRVDF, individual member states have occasionally raised concerns in relation to the potential for specific substances to result in residues in particular other offal tissues. However, we are not aware that CCRVDF has expressed a general concern that residues in other offal tissues might present a risk to consumer health. Some might argue that this is because existing dietary exposure calculations should be accepted as worst case estimates of consumer exposure. In line with this, it is notable that, in the discussion that took place at CCRVDF26, the point was made that the desire to establish MRLs for other offal tissues is not focused on the potential for adverse health effects but rather on the need for MRLs in order to facilitate trade as, in the absence of MRLs, some importing jurisdictions may take a zero tolerance approach and reject consignments of other offal found to contain any such residues.

2. Should extrapolated MRLs be based on the lowest or highest existing MRLs?

A large number of tissues come under the heading of "other offal" and it can be expected that, in reality, residue concentrations will vary from one other offal tissue to another. Consequently, even if tissue specific data were available, it might not always be possible to select a single MRL value that would reflect residue concentrations across these various tissues. The exception to this is for substances for which Codex has established MRL classifications of "unnecessary" or "not specified", which are addressed in question 4.

For substances for which numerical MRLs have been established, consideration needs to be given to which (if any) of the existing MRLs should be used as a basis for extrapolation:

- A conservative approach would be to select the lowest existing MRL for extrapolation to other offal tissues. However, this approach would maximise the chances of non-compliant residue findings in cases where veterinary drugs have been used according to established GVP.
- Considering the highest existing MRL as the basis for extrapolation to other offal tissues would minimise the chance of inappropriate non-compliant residue findings.

3. Would a data-based check on proposed extrapolated MRLs be needed?

Even by selecting the highest existing MRL, there is always a possibility that residues in one or other offal tissue might exceed this level. Availability of data on distribution of residues to other offal tissues is limited. So, what level of data would be appropriate to support a proposed extrapolation?

a. Should some data on distribution to other offal tissues be required in order to allow extrapolation?

b. Would data relating to three other offal tissues be sufficient to support a general extrapolation to other offal?

c. Could distribution data in laboratory or other unrelated species be accepted as support for extrapolation?

4. Is there agreement that, for substances with an MRL classification of "unnecessary" or "not specified" in standard tissues, the same MRL classification could be extrapolated to other offal tissues with no further consideration?

For these substances Codex has already concluded that residues in the diet do not represent a consumer safety concern.

While some progress has been made in outlining issues for consideration, further discussion is necessary in order to address these.

Additional comments received from EWG members

Comments from The United States of America on the Second Request for Comments within the Electronic Working Group (EWG) on Extrapolation

The United States appreciates the continued discussion on extrapolation led by the Chair and co-Chair. Below are our comments on the requested topics.

Annex I: Extrapolation of MRLs for lufenuron, emamectin benzoate, and diflubenzuron in finfish

Lufenuron

The United States appreciates the consideration and additional explanation for lufenuron. We agree that, based on the explanation provided in the report from JECFA85, the reason that JECFA "could not extrapolate the MRL" to other finfish was not due to a specific consumer health reason. Rather, as noted by the Chair and co-Chair, it seemed to be due to lack of residue data to ensure that compliance with the MRL could be achieved under GVPs. As ability to comply with the MRLs is not a consideration in the extrapolation criteria in the Procedure Manual, the United States agrees that the criteria have been met to extrapolate the lufenuron MRLs in fillet from salmon and trout to fillet from all finfish, and that no additional clarification is needed from JECFA.

Overall Draft Conclusions on Annex I

The United States agrees with the draft conclusions presented for Annex I

Annex II: Development of a possible approach for extrapolation of MRLs to camelids

Overall Draft Conclusions on Annex II

The United States agrees with the draft conclusions presented as #1 and #3. With regards to draft conclusion #2, the United States appreciates the consideration provided by the Chair and co-Chair. The United States proposes one addition to the revised extrapolation criteria for camelids provided by the Chair and co-Chair.

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) The marker residue is the parent compound.
    a. In cases where the active substance is a combination of homologous compounds, the marker residue can be considered the same as parent if it is a homolog that is a major component of the active substance.
3) For meat tissues, extrapolation of reference species MRLs to camelids on a one-to-one basis should be considered if either:
    a. identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species on the basis of JECFA recommendations, and the M:T ratio used by JECFA was 1 in all tissues for the ruminant and non-ruminant species, OR
    b. identical MRLs have been established in at least one ruminant species, one non-ruminant mammalian species and one avian species on the basis of JECFA recommendations, and JECFA used the same M:T ratio for each tissue type for all three species.
4) Where condition 2 and 3 are satisfied, extrapolation of an MRL for milk also should be considered in those cases where M:T ratio used by JECFA was 1 in milk.

The United States provides this addition to the extrapolation criteria because identical MRLs does not necessarily mean that metabolism is similar between unrelated species. Adding the requirement for the M:T ratio to be the same in each tissue type provides confidence that metabolism is well-conserved across unrelated species, which is one of the key assumptions associated with extrapolating between species.

Annex III: Consideration of opportunities to enhance the current criteria's potential for extrapolation between milk of different species, with a particular focus on deltamethrin and ivermectin

Draft Conclusion #1

The United States appreciates the additional information provided by the Chair and co-Chair with regards to the maximum total residue concentration of deltamethrin that has been reported in cow's milk and the influence that differential fat content might have on residues in milk from other ruminants. The United States is unsure about the worst-case estimate provided because, although it considers differential fat content, it does not account for the reduction in milk fluid volume that would be in place for smaller dairy ruminants, which would impact residue concentrations and thus dietary exposure. Nevertheless, the United States continues to think that the cow's milk MRL for deltamethrin does not meet the established extrapolation criteria found in the Procedural Manual.

The United States also thinks that extrapolation of the deltamethrin cow's milk MRL (30 µg/kg) to the milk of all ruminants is not needed because there is a Codex MRL for deltamethrin in the milk from mammals other than marine mammals established for pesticide use (50 µg/kg), which would include ruminants. Moreover, if CCRVDF were to extrapolate the existing MRL in cow's milk established for veterinary use (30 µg/kg) to all other ruminants, it would create additional divergent Codex MRL values, which the United States thinks should be avoided when possible.

The United States notes that discussion of harmonizing the milk MRLs for deltamethrin is ongoing within in the Joint Electronic Working Group between CCRVDF and CCPR, and it might be prudent to await the outcome of those discussions before CCRVDF makes a unilateral decision that might impact another Codex Committee (*i.e.*, CCPR).

For these reasons, the United States does not support extrapolating the existing MRL in cow's milk established for veterinary use (30 µg/kg) to the milk of all ruminants.

Draft Conclusion #2

The United States agrees with draft conclusions #2.

Draft Conclusion #3

The United States agrees that re-evaluation of the existing milk MRL for ivermectin should be done according to established procedures (*i.e.*, nomination to the Priority List).

The United States seeks clarification on the statement that, "A revised milk MRL for cattle may facilitate extrapolation to milk of ruminants other than cattle" before including it as conclusion from the EWG. The United States seeks clarification because, even if a new MRL is recommended by JECFA, the current risk assessment information indicates that the milk MRL for ivermectin does not meet the established extrapolation criteria in the Procedure Manual. If a re-evaluation of ivermectin is added to the Priority List, perhaps CCRVDF could ask JECFA to consider whether the existing or a newly recommended milk MRL could be extended or extrapolated to the milk of all ruminants.

Extrapolating MRLs to offal tissues other than liver and kidney

The United States appreciates the additional discussion that the Chair and co-Chair have provided on other offal. We provide our thoughts on the questions that were asked.

Is a consumer exposure assessment of residues in other offal tissues required?

The United States thinks that, if an existing MRL is to be extrapolated to other offal, an evaluation of residue dietary intake that is comparable to that performed for the typical meat tissues is needed.

The United States agrees with the statement that the existing dietary exposure assessments for the typical tissues can be accepted as a worst-case estimate of consumer exposure. However, it is important to note that it is a worst-case exposure scenario from the perspective of exposure when the associated product is used in accordance with GVPs and residue concentrations in the typical tissues conform to their MRLs. That is, when the veterinary drug product is used in accordance with GVPs, and residue concentrations in the typical tissues conform to their MRLs, it is reasonable to conclude that if an individual consumes other offal from these same animals, then it is safe to do so. Although related, this principle of dietary residue exposure is different from what CCRVDF is seeking to do, which is to determine an MRL value to establish the safety of other offal tissue. In other words, that the existing dietary exposure assessments for the typical tissues are worst-case estimates of consumer exposure does not necessarily establish the safety of a specific residue concentration in another tissue (*i.e.*, extrapolated MRL value). To establish the safety of a specific residue concentration, a dietary residue intake evaluation of some kind is needed.

The United States acknowledges the referenced discussion at CCRVDF26, in which it was stated that establishing MRLs in other offal tissues is only a trade issue. The United States would like to point out that the referenced discussion represented only some delegations' point of view and was not a conclusion of CCRVDF26.

One group of MRLs that might not require further consumer exposure consideration are those veterinary drug compounds for which the MRLs are the same for all meat-type tissues in a species and for which JECFA used the same M:T ratio for all meat-type tissues in that species. In these scenarios, the available risk assessment information would indicate that the M:T ratio can be assumed to be constant throughout meat-type tissues. Therefore, the dietary exposure from consuming other offal tissue instead of one of the typical meat tissues would not increase because neither the residue concentration (*i.e.*, MRL value) nor the M:T ratio is changing for other offal tissues.

Should extrapolated MRLs be based on the lowest or highest existing MRL?

For other offal in a specific species, the United States thinks that CCRVDF should consider the highest MRL in the typical tissues as the candidate value to start. Then, if an evaluation of residue dietary intake indicates that the Codex Health-Based Guidance Value (HBGV) is exceeded, the next highest MRL value can be considered.

Would a data-based check on proposed extrapolated MRLs be needed?

The United States thinks that information to support the tissue distribution pattern will help enable CCRVDF to extrapolate an existing MRL to other offal tissues. This is information would allow CCRVDF to reasonably conclude that the extrapolated MRL is compatible with GVPs. The United States thinks that this information **should not be** limited to the veterinary drug compound in question and the target animal species. Information on tissue distribution from related compounds and other animal species can be used to determine a reasonably expected distribution pattern for the veterinary drug compound in the target animal species. In addition, physicochemical characteristics of the veterinary drug compound can help understand the possible distribution pattern. For example, fat soluble compounds typically accumulate in high-lipid tissues, so it might be that CCRVDF determines that, for these compounds, the MRL assigned to fat is not expected to cause compliance issues if extrapolated to other offal tissues.

Is there agreement that, for substances, with an MRL classification of "unnecessary" or "not specified" in standard tissues, the same MRL classification could be extrapolated to other offal tissues with no further consideration?

In principle, the United States thinks that this could be done and looks forward to additional discussion on this approach. It might be helpful to understand whether there are any differences between the two terms.

Comments from Republic of Korea

The Republic of Korea appreciates the efforts of the electronic working group towards reaching a consensus on extrapolation. Here are the opinions of the Republic of Korea regarding the extrapolation of offal tissues. The types and amounts of offal tissues consumed vary by country, and there are differences in the roles of the liver and kidneys compared to other edible by-products in the metabolic process. Therefore, to determine the feasibility of extrapolation, it is necessary to conduct a data-based review, including consumer exposure assessments for residues in offal tissues other than the liver and kidneys.

APPENDIX III

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