CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 7 **CX/RVDF 23/26/7-Add.1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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Portland, Oregon, United States of America

EXTRAPOLATION OF MRLS FOR VETERINARY DRUGS IN FOODS TO ONE OR MORE SPECIES

Comments in reply to CL 2022/76-RVDF

submitted by
Brazil, Chile, European Union (EU), Kenya, Mauritius, Peru, Philippines, Uganda, United States of America (USA) and the International Commission for Uniform Methods of Sugar Analysis (ICUMSA)

Background

1. This document compiles comments received through the Codex Online Commenting System (OCS) in response to circular letter CL 2022/76-RVDF[1] issued in December 2022. Under the OCS, comments are compiled in the following order: general comments are listed first, followed by comments on specific sections. For this CL, comments comprise general and specific comments.

Explanatory notes on the annexes

2. Comments submitted through the OCS are hereby annexed and presented in tabulated format.

[1] http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/
http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF

Annex

GENERAL AND SPECIFIC COMMENTS

COMMENT	MEMBER/OBSERVER
PART I: REQUEST FOR COMMENTS ON PROPOSED MRLs EXTRAPOLATED IN ACCORDANCE WITH THE APPROACH FOR THE EXTRAPOLATION OF MRLs FOR VETERINARZ DRUGS TO ONE OR MORE SPECIES based on the information provided in the table and in CX/RVDF 23/26/7, paragraphs 8-16 Brazil congratulates the EWG on its work and supports the proposed extrapolations as presented, as they are based on the criteria agreed by CCRVDF and MRLs are needed in various commodities to facilitate international trade and protect human food safety. **PART II: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR IVERMECTIN FROM BOVINE MILK TO GOAT AND SHEEP MILK based on the information provided in CX/RVDF 26/23/7, paragraph 17** Brazil supports the criteria agreed by CCRVDF for the extrapolation, and considering that, in the case of ivermectin, these criteria have not been met, namely, MRL for milk has only been established in 1 species and the M:T is not 1, we agree that, in this specific case, the extrapolation should not be performed. **PART III: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR RESIDUES OF VETERINARY DRUGS FOR EDIBLE OFFAL based on the information provided in CX/RVDF 26/23/7, paragraphs 18-20** Brazil acknowledges the fact there was no data demonstrating that the M:T value determined in the liver or kidney is applicable to other edible offal tissues, and there was no data demonstrating that the disposition of a marker residue in kidney or liver is similar to that in other offal tissues. Thus, we agree that, if the disposition of the marker residue is different in the extrapolated tissue than in kidney or liver, the concentration of the marker residue could exceed the extrapolated MRL even when good veterinary practices (GVPs) are followed and extrapolating the kidney or liver MRL to other edible offal tissues might create trade barriers even when established GVPs are followed. these parameters it (Option A). Extrapolation to all offals using a conservative approach, while waiting for sufficient data for grouping according to the aforementioned parameters, might result in unnecessarily conservative MRLs Considering the limitations mentioned above and the lack of data for the establishment of MRLs for offal tissues other than liver and kidney, Brazil agrees that MRLs for edible offal tissues other than kidney and liver should not be determined by extrapolation procedures. Brazil agrees that, regarding the dietary exposure assessment, the MRLs established for the commodities in the standard food basket are sufficiently conservative to provide a margin of safety that addresses uncertainty related to exposure via other commodities, ensuring consumer safety. So, if commodities other than those considered in the standard food basket are ingested, this would mean that less of the standard food basket commodities are ingested. In this regard, there would be no need to consider ingestion of offal tissues other than liver and kidney as adding to the overall consumer exposure to residues. In view of the above, other edible offal other than kidney or liver would not be important from the perspective of dietary exposure and, for the majority of offals, there would be no need to establish an MRL, unless metabolism studies show that the disposition of the marker residue or metabolites are high in this tissue, raising toxicological concerns. Brazil considers that, unless specific toxicological concerns are raised, CCRVDF and JECFA should continue establishing MRLs only for kidney and liver and this issue should be approached from the perspective of risk management in countries where offal is consumed. Lastly, Brazil reiterates that, even if a suitable approach for the extrapolation of MRLs for residues of veterinary drugs for offal tissues could not be generated at this time, this should not prevent (or delay) the other extrapolated MRLs listed in this document to progress to the subsequent Step of the Procedure. Advancing this issue of extrapolation is of utmost importance for CCRVDF, so that we can increase the number of MRLs for veterinary drugs approved by Codex.	**Brazil**

COMMENT	MEMBER/OBSERVER
PART IV: REQUEST FOR COMMENTS ON WHETHER THE APPROPRIATE M:T VALUE FOR RESIDUES OF DELTAMETHRIN IN BOVINE MILK IS 1 Considering that, for the reasons noted by the EWG, namely: 1. residues in cattle milk were below the LOQ , indicating that they do not make a significant contribution to the intake calculation; 2. residues other than the parent compound will have reduced toxicity compared to that of the parent; Brazil agrees that, even if the fat composition of milk varies across species and even without a statement from JECFA specifying the M:T in milk, establishing the same MRL in milk of ruminants as currently exists for cattle would not represent a consumer safety concern. Therefore, even though this would not be following the rules specified in the defined Approach, additional criteria could be adopted to allow for the extrapolation. However, from a more conservative perspective and considering that the existent data from JECFA dates back to 1999 and 2003, Brazil supports the recommendation that CCRVDF should seek advice from JECFA on whether the appropriate M:T value in bovine milk is, 1 before extrapolating the bovine milk MRL to all ruminants.	
PART I: **1. Amoxicillin – extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Amoxicillin for extrapolation to ruminants **2. Benzylpenicillin – extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Benzylpenicillin for extrapolation to ruminants **3. Tetracyclines - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Tetracyclines for extrapolation to ruminants **4. Cyhalothrin - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Cyhalothrin for extrapolation to ruminants **5. Cypermethrin - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Cypermethrin for extrapolation to ruminants **6. Deltamethrin - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Deltamethrin for extrapolation to ruminants **7. Moxidectin - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Moxidectin for extrapolation to ruminants **8. Spectinomycin - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Spectinomycin for extrapolation to ruminants **9. Levamisole - extrapolation to ruminants** Chile agrees with the proposed extrapolated MRLs for Levamisole for extrapolation to ruminants **10. Tilmicosin - extrapolation to ruminants**	**Chile**

COMMENT	MEMBER/OBSERVER
Chile agrees with the proposed extrapolated MRLs for Tilmicosin -inextrapolation to ruminants **11. Deltamethrin - extrapolation to finfish** Chile agrees with the proposed extrapolated MRLs for Deltamethrin for extrapolation to finfish **12. Flumequine - extrapolation to finfish** Chile agrees with the proposed extrapolated MRLs for Flumequine for extrapolation to finfish **PART II: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF BOVINE MILK MRLs FOR IVERMECTIN TO GOAT AND SHEEP MILK based on the information provided in CX/RVDF 26/23/7, paragraph 17** Chile has no comments on this point and takes note of the recommendations in the document **PART III: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR RESIDUES OF VETERINARY DRUGS FOR OFFAL TISSUES based on the information provided in CX/RVDF 26/23/7, paragraphs 18-20** Chile agrees with studying new forms of extrapolation in these new matrices. **PART IV: REQUEST FOR COMMENTS ON WHETHER THE APPROPRIATE M:T VALUE FOR RESIDUES OF DELTAMETHRIN IN BOVINE MILK IS 1** Based on the prioritization of JECFA work and the already-agreed-upon approach to this exercise, Chile is of the opinion that it is best to use specific data to evaluate this substance and develop a proposed MRL for milk.	
The European Union (EU) would like to thank Codex members for the continuous support to the work on extrapolation. The EU has the following comments on the questions raised in CL 2022/76-RVDF: **PART I: REQUEST FOR COMMENTS ON PROPOSED MRLs EXTRAPOLATED IN ACCORDANCE WITH THE APPROACH FOR THE EXTRAPOLATION OF MRLs FOR ~~VETERINARZ~~ VETERINARY DRUGS TO ONE OR MORE SPECIES based on the information provided in the table and in CX/RVDF 23/26/7, paragraphs 8-16** a. The EU agrees that the proposed extrapolated MRLs in Appendix I CX/RVDF 23/26/7 comply with the agreed approach on extrapolation. The EU notes that existing Codex MRLs for tetracyclines, deltamethrin, spectinomycin and tilmicosin and the proposed extrapolated MRLs for these substances in ruminant tissues are in some cases higher than the corresponding EU MRLs and represent a safety concern as the ADI will be exceeded in an assessment using the TDMI approached used by the EU. Therefore, the EU would like to express its reservation for the following extrapolated MRLs: • MRLs for tetracyclines in ruminant muscle, liver and kidney • MRLs for deltamethrin in ruminant muscle, fat, liver, kidney and milk • MRLs for spectinomycin in ruminant muscle, fat and liver • MRLs for tilmicosin in ruminant muscle and fat **PART II: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR IVERMECTIN FROM BOVINE MILK TO GOAT AND SHEEP MILK based on the information provided in CX/RVDF 26/23/7, paragraph 17** b. The EU notes that the agreed approach on extrapolation does not allow extrapolation of bovine milk MRL for ivermectin to goat and sheep milk.	**EU**

COMMENT	MEMBER/OBSERVER
PART III: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR RESIDUES OF VETERINARY DRUGS FOR EDIBLE OFFAL based on the information provided in CX/RVDF 26/23/7, paragraphs 18-20 c. The EU remains open to consider pragmatic approaches to extrapolate MRLs for residues of veterinary drugs for offal tissues other than liver and kidney while acknowledging that there may not be data available confirming the validity of such approaches. **PART IV: REQUEST FOR COMMENTS ON WHETHER THE APPROPRIATE M:T VALUE FOR RESIDUES OF DELTAMETHRIN IN BOVINE MILK IS 1** d. The EU supports consulting JECFA on whether the appropriate M:T value for residues of deltamethrin in bovine milk is 1. **3. Tetracyclines - extrapolation to ruminants** The EU would like to express its reservation for the MRLs for tetracyclines in ruminant muscle, liver and kidney **6. Deltamethrin - extrapolation to ruminants** the EU would like to express its reservation for the MRLs for deltamethrin in ruminant muscle, fat, liver, kidney and milk **8. Spectinomycin -extrapolation to ruminants** The EU would like to express its reservation for the MRLs for spectinomycin in ruminant muscle, fat and liver **10. Tilmicosin extrapolation to ruminants** EU would like to express its reservation for the MRLs for tilmicosin in ruminant muscle and fat.	
Kenya commends the chairs of the EWG for the good work undertaken in developing the discussion paper on extrapolation of MRL. Kenya supports the proposal by the EWG, that further discussions should be held during CCRVDF26 on how to generate MRLs in edible offal tissues other than kidney and liver. Further, Kenya recommends that JECFA to submit datasets for elaboration of MRLs in smooth muscles and that further extrapolation of the established MRLs should be done in smooth muscles. Justification: It is noted that the EWG was not able to develop a suitable approach for the extrapolation of MRLs for residues of veterinary drugs in offal tissues. Most offal tissues are smooth muscles which are quite different from skeletal muscles for which MRLs have already been determined. Extrapolation could work if corresponding tissues are used across species. Guidance may be provided by JECFA on how to address the concerns raised about the proposed approach.	**Kenya**
The extrapolated MRLs for the 12 different drugs in the various animal species be advanced to Step 5. The extrapolation was done in line with the rules set out in the Approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species that was adopted by CAC44. The compounds are commonly used in the African region for the treatment of common diseases in the animals. The availability of MRLs for the compounds will facilitate trade and provide a reference to assure protection of consumer health	**Mauritius**
Peru does not have comments on the extrapolation of MRLs for the drugs cited in CX/RVDF 23/26/7. In the case of deltamethrin in fish, Peru recommends that the information that the European Medicines Agency (EMA) and the relevant authorities in the United States of America rely on to establish limits for residues in fish be evaluated, as they set a lower MRL than what is proposed in the Circular Letter.	**Peru**
The Philippines would like to thank the Electronic Working Group (EWG) as chaired by the European Union and co-chaired by Costa Rica for the discussion document on the following:	**Philippines**

COMMENT	MEMBER/OBSERVER
• proposed extrapolated MRLs for veterinary drugs to one or more species in accordance with the approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species • extrapolation of bovine milk MRL for ivermectin to goat and sheep milk and • extrapolation of MRLs of veterinary drugs for edible offal Rationale: With the adoption of codex texts on the "Risk Analysis Principles Applied by CCRVDF: Approach for the Extrapolation of MRLs for veterinary drugs to one or more species in CAC 44", in which the agreed principle approach is consistent with the three aspects of the extrapolation criteria: the grouping of species; authorized use and GVP established in the species to which extrapolation is proposed; and consideration for the need for analytical methods for monitoring purposes, we support the advancement of the discussion document to Step 4 on the above-mentioned topics. This would allow member countries to provide comments and further input upon discussion in the general session.	
PART I: REQUEST FOR COMMENTS ON PROPOSED MRLs EXTRAPOLATED IN ACCORDANCE WITH THE APPROACH FOR THE EXTRAPOLATION OF MRLs FOR VETERINARZ DRUGS TO ONE OR MORE SPECIES based on the information provided in the table and in CX/RVDF 23/26/7, paragraphs 8-16 Uganda supports the proposed extrapolated MRLs for different drugs/compounds in the different animal species, and therefore proposes advancement of these MRLs (for the 12 compounds) to Step 5. The extrapolation was done in line with the rules spelt out in the Approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species that was adopted by CAC44. **PART II: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR IVERMECTIN FROM BOVINE MILK TO GOAT AND SHEEP MILK based on the information provided in CX/RVDF 26/23/7, paragraph 17** The "Approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species" does not allow the extrapolation of bovine milk MRL for Ivermectin to goat and sheep milk. According to information in the report of the electronic working group (EWG), bovine milk MRL didn't meet the "specific criteria for extrapolation" to goats and sheep as indicated because of the following: MRL for milk has only been established in 1 species and the M:T is not 1. Also some uncertainty was also expressed with regards to whether Ivermectin B1a can be considered to be the same as the parent compound. Given the above background, Uganda recommends that CCRVDF26 may request the industry and developed countries to generate data packages and information required for evaluation of Ivermectin in goat and sheep milk by JECFA. **PART III: REQUEST FOR COMMENTS ON THE EXTRAPOLATION OF MRLs FOR RESIDUES OF VETERINARY DRUGS FOR EDIBLE OFFAL based on the information provided in CX/RVDF 26/23/7, paragraphs 18-20** The EWG was not able to develop a suitable approach for the extrapolation of MRLs for residues of veterinary drugs in offal tissues. The specific concerns that were raised on the suggested pragmatic approach to extrapolate the lowest MRL established in liver or kidney to all offal tissues are all technically acceptable. Therefore, a proposal by the EWG, that further discussions should be held during CCRVDF26 on how to generate MRLs in edible offal tissues other than kidney and liver is supported by Uganda. Secondly Uganda recommends that more guidance may be provided by JECFA on how to address the concerns raised about the proposed approach. **PART IV: REQUEST FOR COMMENTS ON WHETHER THE APPROPRIATE M:T VALUE FOR RESIDUES OF DELTAMETHRIN IN BOVINE MILK IS 1**	**Uganda**

COMMENT	MEMBER/OBSERVER
Uganda is in support of the M:T value for residues of Deltamethrin in bovine milk being 1 and also in support of the proposal to seek advice from JECFA on the same	
The United States thanks the European Union and Costa Rica for providing leadership on this topic, including extrapolation of MRLs to edible offal tissues other than kidney and liver (i.e., other edible offal). The United States considers this an important topic because it underscores the diversity of foods consumed by Codex members. In cases where there are no data enabling JECFA to recommend MRLs for veterinary drug residues in other edible offal tissues and CCRVDF has included MRLs for a veterinary drug in other edible offal tissues on the Priority List, the United States proposes a possible procedure for extrapolating existing MRLs for residues of veterinary drugs to other edible offal tissues. The report of the electronic working group (EWG) for Extrapolation of Maximum Residue Limits of Veterinary Drugs to One or More Species initially proposed extrapolating the lowest MRL established in liver or kidney to all other edible offal tissues. The United States has expressed the view and continues to think that this approach, alone, would result in establishing MRLs without the benefit of a science based assessment of consumer safety (i.e., a dietary exposure assessment). The usual types of dietary exposure assessment models (i.e., TMDI, EDI, GECDE, GEADE) rely on residue data and consumption data to estimate the dietary exposure to total residues of the compound. The United States recognizes that residue data (marker residue (MR) and total residue (TR) data) likely are not available for other edible offal tissues. This represents a challenge for conducting a dietary exposure assessment to account for residue exposure from other edible offal tissues. However, the United States notes that the FAO/WHO Chronic Individual Food Consumption – summary statistics (CIFOCOss) database contains consumption data for other edible offal tissues. The United States proposes that CCRVDF ask JECFA to conduct a margin of exposure (MOE) assessment that accounts for the dietary exposure resulting from the established MRLs and the would be extrapolated MRL for other edible offal tissues. Then, based on the outcome of the MOE assessment, CCRVDF can make a risk management decision on whether MRLs should be extrapolated to other edible offal tissues in the absence of residue data. A possible approach is outlined below. 1. CCRVDF proposes an MRL value for other edible offal tissues that is the lower of the established liver or kidney MRLs. 2. CCRVDF asks JECFA to conduct an MOE assessment that accounts for the dietary exposure resulting from the established MRLs and the proposed extrapolated MRL for other edible offal tissues. a. For the dietary exposure resulting from the edible tissues with established MRLs, CCRVDF would ask JECFA to estimate this value as they would normally, relying on the available residue data (e.g., marker residue data and MR:TR ratio) and consumption data. b. For the dietary exposure resulting from other edible offal tissues, CCRVDF would ask JECFA to estimate this value using the proposed extrapolated MRL value and the available consumption data. It is important to note that this value would only represent an exposure value for the marker residue, not total residues. c. CCRVDF would then ask JECFA to generate an MOE value that is ratio between the Health Based Guidance Value (HBGV) and sum of the two values in 2a and 2b. 3. CCRVDF then makes a risk management decision based on the MOE value. Specifically, CCRVDF would decide whether the MOE is sufficiently large to reasonably to conclude that the total residue exposure from the tissues with established MRLs and other edible offal tissues will not exceed the HBGV despite not knowing the MR:TR in other edible offal tissues. 4. If CCRVDF determines that the MOE is sufficiently large, then CCRVDF can extrapolate the lower of the liver or kidney MRLs to other edible offal tissues.	**USA**

COMMENT	MEMBER/OBSERVER
The benefit of the proposed approach is that it produces a standard that incorporates two fundamental features of Codex MRLs, namely, an assessment of consumer safety by JECFA (i.e., the MOE assessment) and a risk management decision made by CCRVDF. Nevertheless, the United States acknowledges that the proposed approach is not without any flaws. Although the approach would allow extrapolation of MRLs in the absence of residue data, it does not provide assurance that the extrapolated MRLs are compatible with the established GVPs for a given compound. That is, there is a possibility that the marker residue value in the other edible offal tissues could exceed the extrapolated MRLs value even when GVPs are followed. Therefore, the United States proposes that, as part of the risk management process, CCRVDF determine, on a case by case basis, whether the need for these extrapolated MRLs outweighs the risk of inadvertently creating barriers to trade. Moreover, risk management within CCRVDF includes monitoring and review of decisions taken. The United States considers this aspect of risk management to be particularly important when considering extrapolating MRLs to other edible offal tissues without residue data. Therefore, the United States also suggests that CCRVDF consider that extrapolating MRLs to other edible offal tissues likely will require some form of post action monitoring to ensure that the extrapolated MRLs do not inadvertently cause barriers to trade. Member countries could be encouraged to discuss suspected problems caused by the extrapolated MRLs within CCRVDF. Finally, the United States notes that the proposed approach should not replace the current methodologies for generated MRLs in the standard tissues (muscle, liver, kidney, fat (skin with fat) and milk). Moreover, it should not be used for other edible offal tissues where data are available to generate MRLs under the standard approach.	
PART I: REQUEST FOR COMMENTS ON PROPOSED MRLs EXTRAPOLATED IN ACCORDANCE WITH THE APPROACH FOR THE EXTRAPOLATION OF MRLs FOR VETERINARZ DRUGS TO ONE OR MORE SPECIES based on the information provided in the table and in CX/RVDF 23/26/7, paragraphs 8-16 Typo - VETERINARZ should be VETERINARY There is no asterisk next to the MRL value for muscle. This is required in order for the note at the bottom of the page to make sense. A correct use of the asterisk is shown on the page for Cyhalothrin	**ICUMSA**