ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 26th SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CCRVDF26)

13 to 17 February 2023

Portland, Oregon, United States of America

Agenda item 7.1: Extrapolated MRLs for different combinations of compounds / commodities at Step 4

Agenda Item 7.2: Extrapolation of MRLs for residues of veterinary drugs in edible tissues.

Objective

This document offers a review and analysis of the agenda items planned for discussion at the 26th session of the **Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)**, scheduled to take place face to face from 13 to 17 February 2023. This document is intended for possible use by the Codex communities of practice, promoted by GFoRSS and PARERA, as part of their contribution to enhancing awareness and supporting effective participation in international food standard setting meetings (Codex meetings) by representatives from members and observers.

The analysis provided in this document offers a factual review of select agenda items, their background, and a discussion of some considerations. This analysis is indicative in nature and does not represent an official position of the organizations mentioned above (PARERA and GFoRSS), their membership, or their management. It provides a synthesis and analysis of the work currently under discussion by the CCFA, which may be useful for delegations from Codex delegations, part of the GFoRSS Network Community, to prepare their positions considering the needs and specificity of the region and the potential impact of the proposed food standards.

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**It is important to note that experts – members of Expert Working Groups – do not represent the organizations and / or jurisdictions to which they are affiliated. The selection and participation in Expert Working Group proceedings is based on each expert's own credentials and experience, which should not be misconstrued as the country's / delegation's / organization's position to which they belong.*

Agenda item 7.1: Extrapolated MRLs for different combinations of compounds/commodities at Step 4

Agenda Item 7.2: Extrapolation of MRLs for residues of veterinary drugs in edible tissues.

Documents

CX/RVDF 23/26/7; CX/RVDF 23/26/7-Add.1 (CL 2022/75-RVDF); CX/RVDF 23/26/8

Background

In order to make the MRLs of veterinary drug residues more available and to overcome the lack of scientific data needed to carry out the risk assessment work done by JECFA, the CCRVDF has considered the adoption of the MRL extrapolation approach in several sessions of the Committee, especially with regard to the limits/challenges/principles of the methodology, with the objective to establish practical modalities for its application to different animal species.

At its 24th Session, CCRVDF decided to extend the development of the MRL extrapolation approach to all animal species (beyond aquatic species) and to carry out a pilot study on the extrapolation of some compounds for which there are already adopted Codex MRLs, considering the list of compounds in the MRL database required for countries. For this purpose, it was agreed to: (i) modify the Risk Analysis Principles applied by the CCRVDF to provide more autonomy to risk managers to propose extrapolation of MRLs to one or more species, in contrast to the adopted policy that MRLs can be recommended only when the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has determined that it is scientifically justifiable and uncertainties have been clearly defined, and (ii) identify 10 compounds on the list of Codex MRLs to drive extrapolation.

Thus, an Electronic Working Group (EWG) was established, chaired by the European Union (EU) and co-chaired by Costa Rica with the mandate to: i) Develop a working paper exploring pragmatic approaches on how the CCRVDF, in its role as risk manager, could extrapolate MRLs to one or more species; ii) Prepare and compare these approaches with the revised Option C for aquatic species[1]; iii) Conduct a pilot study on the extrapolation of MRLs identified in Part D of the Priority List[2].

At the 25th Session of the CCRVDF, the EWG presented its discussion paper to the Committee, which included: (i) the EWG's proposed extrapolation approach; (ii) the comparison of the proposed approach and the revised Option C for aquatic species; and (iii) the pilot study on the extrapolation of MRLs identified in Part D of the priority list following the proposed approach[3].

Considering the discussions of the previous meetings, the CCRVDF forwarded the approach for extrapolation of the established MRLs[4] to the Codex Commission for adoption, which approved its adoption at its forty-fourth session (CAC, 2021) and its inclusion as Annex C of the Risk Analysis Principles applied by the CCRVDF[5].

The committee requested Codex Secretariat to issue the proposed extrapolated MRLs for comments through a circular letter (CL 2021/98-RVDF) done in December 2021.

The Committee established an electronic working group (EWG), chaired by the European Union (EU) and co-chaired by Costa Rica, with the following terms of references (i) To continue discussions on extrapolated MRLs taking into account the comments submitted in response to CL 2021/98-RVDF, and to prepare revised proposals for consideration by the Twenty-sixth Session of the CCRVDF[6]; (ii) To consider the extrapolation of MRLs for Ivermectin in milk from goats and sheep[7]; (iii) To develop an adapted approach to the extrapolation of MRLs for veterinary drug residues in offal tissues[8].

1 RVDF24/CRD34 (Report of the in-session working group on the discussion paper on MRLs for fish species groups) and revised Option C
2 REP18/RVDF Appendix VI - Part D
3 CX/RVDF 21/25/8, June 2020
4 REP21/RVDF25, par. 105(i), Annexe III
5 REP21/CAC44, Appendix II
6 REP21/RVDF25, par. 105(iv)
7 REP21/RVDF25, par. 150(iii)
8 REP21/RVDF25, par. 150(vi)

During the CCRVDF26, the Committee will consider the EWG's proposals related to the revision of MRLs for the veterinary drugs under consideration, the opinion on the possibility of extrapolating MRLs for Ivermectin for goat and sheep milk and the proposed approach to extrapolation of MRLs for residues of veterinary drugs in edible tissue

Analysis

29 countries, 3 observer organizations and FAO participated in the work of the EWG. A discussion paper containing an analysis of the comments received, an analysis of the extrapolation of MRLs for ivermectin in goat and sheep milk and a proposal for a possible approach to the extrapolation of MRLs for residues of veterinary drugs in edible tissues was prepared by the EWG and forwarded to the Codex Secretariat on 30 November 2022[9].

The primary comment received was from Kenya which did not support extrapolation of the MRL for kidney for Tilmicosin as different M:Ts were used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for cattle and sheep kidney. The EWG maintained the proposal of MRL considering that the MRLs recommended by JECFA for cattle and sheep kidney were identical. Therefore, in line with the agreed approach on extrapolation, the MRL can be extrapolated despite the fact that the M:Ts are not identical in cattle and sheep.

For deltamethrin, the EWG considered the criteria met for extrapolating the bovine and sheep MRLs for muscle, fat, liver, and kidney to all ruminants. However, the EWG was unsure whether the extrapolation criteria had been met for milk knowing that JECFA did not report an M:T value for this commodity. The EWG decided to seek advice from JECFA on whether the appropriate M:T value for residues of deltamethrin in bovine milk is 1 before establishing MRL for sheep and bovine milk.

Proposed MRLs under the application of the approach extrapolation of maximum residue limits for veterinary drugs to one or more species

The EWG presented the outcome of their investigation and recommendations on the pilot study on the application of the Approach of Extrapolation of Maximum Residue Limits for Veterinary Drugs to one or more species.

The methodology was applied to 10 veterinary drugs whose MRLs were extrapolated to all ruminant species. However, only two veterinary products were considered for fish species and MRLs were proposed for finfish.

The opinions and recommendations concerning the veterinary drugs considered, as well as the related rationale, are presented in Table 1

Table 1: Proposed MRL for vet drugs considered by the EWG under the application of MRL extrapolation approach

Vet Drug	Rationale	Recommended MRL
Amoxicillin	✓ Product evaluated by JECFA (WHO SRT 969 (10)) and a microbiological ADI is established. ✓ The microbiologically active residue is the initial substance ✓ The M:T ratio is 1 in all food products and there are already identical MRLs for 2 ruminant species.	**Extrapolation to ruminants** **Muscle 50 µg/kg** **Fat* 50 µg/kg** **Liver 50 µg/kg** **Kidney 50 µg/kg** **Milk 4 µg/kg** ** Fat/skin for pigs*

[9] CX/RVDF 23/26/7, décembre 2022

Benzylpenicillin	✓ Product evaluated by JECFA (WHO SRT 799 (10)). ✓ The marker residue is the initial compound ✓ The M:T ratio is 1 in all food products.	***Extrapolation to ruminants*** ***Muscle 50 µg/kg*** ***Liver 50 µg/kg*** ***Kidney 50 µg/kg*** ***Milk 4 µg/kg***
Tétracyclines	✓ Product evaluated by JECFA (WHO SRT 888(10)) ✓ The microbiologically active residue is the initial substance ✓ M:T ratio of 1 in all tissues, milk and eggs. ✓ Identical MRLs already exist for 2 related ruminant species.	***Extrapolation to ruminants*** ***Muscle 200 µg/kg*** ***Liver 600 µg/kg*** ***Kidney 1200 µg/kg*** ***Milk 100 µg/kg***
Cyhalothrine	✓ Product evaluated by JECFA (WHO SRT 900(10)) ✓ The microbiologically active residue is the initial substance ✓ The M:T ratios established for cattle and sheep are identical, ✓ The M:T ratio for cattle milk being 1, the MRL can be extrapolated to other ruminant milk.	***Extrapolation to ruminants*** ***Muscle 20 µg/kg*** ***Fat 400 µg/kg*** ***Liver 20 µg/kg*** ***Kidney 20 µg/kg*** ***Milk 30 µg/kg*** **The MRL of 20 µg/kg in liver applies to all ruminants except sheep. The MRL in liver for sheep is 50 µg/kg.*
Cyperméthrine	✓ Product evaluated by JECFA (WHO SRT 911 and FAO FNP 41/16) ✓ The microbiologically active residue is the initial substance ✓ For tissues, the M:T ratios established for cattle and sheep are identical ✓ identical MRLs already exist for 2 ruminant species. ✓ For cattle milk the M:T ratio is 0.95 and an MRL has been established only in milk of one ruminant species.	***Extrapolation to ruminants*** ***Muscle 50 µg/kg*** ***Fat 1 000 µg/kg*** ***Liver 50 µg/kg*** ***Kidney 50 µg/kg***
Deltaméthrine	✓ Product evaluated by JECFA (WHO SRT 893 and 918) ✓ The microbiologically active residue is the initial substance ✓ For muscle, the M:T ratio is not indicated, but equivalent values were applied for all species. ✓ The MRLs in cattle and sheep are identical. ✓ For milk, no M:T ratio is indicated for bovine milk.	***Extrapolation to ruminants*** ***Muscle 30 µg/kg*** ***Fat 500 µg/kg*** ***Liver 50 µg/kg*** ***Kidney 50 µg/kg*** *For milk: The EWG agreed that the CCRVDF should seek advice from JECFA to determine if the correct M:T ratio in cattle milk is 1 before extrapolating the MRL in cattle milk to all ruminants.*

Moxidectine	✓ Product evaluated by JECFA (WHO SRT 888) ✓ The microbiologically active residue is the initial substance ✓ M:T ratios are the same for all three species ✓ Identical MRLs were initially established for cattle, sheep and deer, ✓ The MRL in muscle for sheep was increased after a new residue study in sheep while the M:T ratio remained the same.)	***Extrapolation to ruminants*** ***Muscle* 20 µg/kg*** ***Fat 500 µg/kg*** ***Liver 100 µg/kg*** ***Kidney 50 µg/kg*** **The MRL of 20 µg/kg in muscle applies to all ruminants except sheep. The MRL in muscle for sheep is 50 µg/kg.*
Spectinomycine	✓ Product evaluated by JECFA (WHO SRT 888) ✓ The microbiologically active residue is the initial substance ✓ M:T ratios are identical for all species ✓ Identical MRLs already exist for 2 related ruminant species. ✓ For milk, the M:T ratio is 1.	***Extrapolation to ruminants*** ***Muscle 500 µg/kg*** ***Fat 2 000 µg/kg*** ***Liver 2 000 µg/kg*** ***Kidney 5 000 µg/kg*** ***Milk 200 µg/kg***
Levamisole	✓ Product evaluated by JECFA (WHO SRT 851) ✓ The microbiologically active residue is the initial substance ✓ M:T ratios are identical for all species ✓ Identical MRLs already exist for 2 related ruminant species.	***Extrapolation to ruminants*** ***Muscle 10 µg/kg*** ***Fat 10 µg/kg*** ***Liver 100 µg/kg*** ***Kidney 10 µg/kg***
Tilmicosine	✓ Product evaluated by JECFA (WHO SRT 876) ✓ The microbiologically active residue is the initial substance ✓ Although the M:T ratio is different in cattle and sheep kidney, the recommended MRLs for these two species are identical.	***Extrapolation to ruminants*** ***Muscle 100 µg/kg*** ***Fat 100 µg/kg*** ***Liver 1000 µg/kg*** ***Kidney* 300 µg/kg*** **Kenya presented their reserve for the proposed MRL for kidney, as different M:T ratios were used*
Deltamethrine	✓ Product evaluated by JECFA (WHO RST 893) ✓ The microbiologically active residue is the initial substance ✓ No M:T ratio was established for salmon muscle. However, the concentrations of marker residue and total residues were very low in muscle (of all species), with an MRL established on the basis of two times the LOQ.	***Extrapolation to finfish*** ***Muscle 30 µg/kg***
Flumequine	✓ Product evaluated by JECFA (WHO SRT 900(10)) ✓ Microbiologically active residue is the initial substance ✓ M:T ratio for trout is likely to be 1 (suggesting no sensitive metabolism in fish) ✓ Identical MRLs have been established for several unrelated species.	***Extrapolation to finfish*** ***Muscle 500 µg/kg***

Extrapolation of bovine milk MRL for ivermectin to goat and sheep milk

The EWG were not able to apply extrapolation of the bovine milk MRL for ivermectin to goat and sheep milk as the extrapolation approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species does not allow the extrapolation for this compound/commodity.

Vet Drug	Rationale	Recommended MRL
Ivermectine	✓ ***The MRL in milk has been established for only 1 species*** ✓ ***The M:T ratio is not equal to 1*** ✓ ***Doubts were expressed as to whether ivermectin B1a could be considered identical to the parent compound.***	***The extrapolation of MRLs to goat and sheep milk is not possible.***

Extrapolation of MRLs for residues of veterinary drugs in edible tissues

The EWG was unable to develop a suitable approach to extrapolate MRLs for veterinary drug residues in edible offal tissue; a pragmatic approach was considered by the EWG to extrapolate the lowest MRL established for liver or kidney to all offal tissues. However, this approach was discarded due to the lack of experience and data regarding the establishment of MRLs in offal tissues other than liver and kidney and the persistence of related concerns including:

- The extrapolation of an MRL in one type of edible offal tissue to another does not consider the additional source of dietary exposure from the consumption of edible offal tissue with the newly extrapolated MRL;
- There is no evidence that the M:T ratio determined in liver or kidney is applicable to other edible organ meats;
- There is no evidence that the elimination (e.g., kinetics, binding, etc.) of a marker residue in kidney or liver is similar to its elimination in other edible offal tissues.

Considering the concerns identified, the EWG considered that further discussions at the CCRVDF26 level would be helpful on how to generate MRLs in edible offal tissues other than kidney and liver.

General conclusion and recommendations

Considering the arguments supported by the EWG regarding the MRLs recommended as a result of the application of the extrapolation approach and the limited opposition expressed by delegations in response to the related Circular Letter, the Committee may wish to consider recommending the adoption of the proposed MRLs at the next Codex Alimentarius Commission at Step 5/8 (final adoption).

Regarding the discussion on the approach to be followed for the derivation of MRLs for edible tissues, the Expert Working Group (EWG) expressed the need for further discussion and work on the establishment of a consistent approach for the establishment of MRLs for edible tissues. This may be further considered by JECFA/CCRVDF, given the limitations and concerns identified by the EWG.

Given the importance of establishing maximum residue limits for veterinary drugs, especially for SWP countries for which Codex is considered as the reference for food standards, it would be appropriate to support the adoption of the proposed standards developed by the extrapolation approach at step 5/8.