CODEX ALIMENTARIUS COMMISSION

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Food and Agriculture Organization of the United Nations

World Health Organization

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CL 2024/66-RVDF
July 2024

TO: Codex Contact Points
Contact Points of international organizations having observer status with Codex

FROM: Secretariat, Codex Alimentarius Commission,
Joint FAO/WHO Food Standards Programme

SUBJECT: **Request for comments/information on the priority list of veterinary drugs for evaluation or re-evaluation by JECFA**

DEADLINE: **30 September 2024**

BACKGROUND

Decisions of CCRVDF about the Priority List

Additional information on compounds evaluated by JECFA and JMPR

1. The 23rd Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF23, 2016) agreed[1] to add information on the registration of the compound as a pesticide and, where applicable, information on the evaluation of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) to the form requesting information on compounds for evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), attached to the Circular Letter (CL) soliciting proposals for inclusion in the Priority List.

Database on countries' needs for MRLs for veterinary drugs in foods

2. CCRVDF25 (2021) further agreed[2] to recommend that the database on countries' needs for MRLs for veterinary drugs in foods be made available as a reference document at every session of CCRVDF and should be available to the Codex Secretariat to accompany the distribution of the circular letter (CL) requesting comments on the priority list of veterinary drugs for evaluation by JECFA. CCRVDF therefore encouraged:

   (i) Codex member countries and observer organizations to submit relevant data/information to allow the evaluation of those compound/commodity combinations identified as high-priority needs and as feasible starting points for the establishment of relevant maximum residue limits (MRLs); and

   (ii) Codex member countries and observer organizations to submit relevant data/information to evaluate other compound/commodity combinations identified in the database on countries' needs for MRLs for veterinary drugs.

3. The United States of America (USA) and Costa Rica, as responsible for the maintenance of the database, have updated the database based on the decisions[3] made by CCRVDF26 (2022) and the 46th Session of the Codex Alimentarius Commission (CAC46, 2023) as follows:

   3.1 Updated ivermectin to reflect the updated MRLs for pigs and sheep adopted in 2023 and for goats adopted in 2023.

   3.2 Updated amoxicillin to reflect the new extrapolated MRLs for all other ruminants adopted in 2023.

   3.3 Updated oxytetracycline to reflect the new extrapolated MRLs for all other ruminants adopted in 2023.

   3.4 Updated cypermethrin and alpha-cypermethrin to reflect the new extrapolated MRLs for all other ruminants adopted in 2023.

1 REP17/RVDF23, para. 27
2 REP21/RVDF25, paras. 126-128
3 REP23/RVDF26, paras. 27, 28, 31, 34 and Appendices II, III
REP23/CAC46, paras. 45, 46 and Appendices IV, VI

New work on the Priority List

4. CCRVDF26 (2023) agreed[4] to forward the Priority List of Veterinary Drugs for Evaluation or Re-evaluation by JECFA to CAC46[5] for approval. CAC46 approved[6] the Priority List as submitted by CCRVDF26.

REQUEST FOR COMMENTS/INFORMATION

Part I. Veterinary drugs for inclusion in the Priority List for JECFA evaluation/re-evaluation

5. Paragraph 134, "Establishment of Priority List" of the *Risk Analysis Principles applied by CCRVDF* (CAC Procedural Manual), states that for a proposed veterinary drug to appear on the priority list of veterinary drugs for the establishment of an MRL, the proposed veterinary drug shall meet some or all the following criteria:

   (a) A Member has proposed the compound for evaluation (a template for information recommended for consideration in the priority list by CCRVDF has been completed and will be available to the Committee).

   (b) A Member has established good veterinary practices regarding the compound.

   (c) The compound can potentially cause public health and/or international trade problems.

   (d) The compound is available as a commercial product.

   (e) There is a commitment that a dossier will be made available.

6. Codex members and observers are invited to make proposals for veterinary drugs to be included on the priority list for subsequent recommendation to JECFA for evaluation or re-evaluation, including compounds listed in the database on countries' needs for MRLs for veterinary drugs in foods as appropriate, and to provide the data/information according to the template in Appendix I to this document.

Part II. Veterinary drugs for which data availability should be confirmed at CCRVDF27

Norfloxacin

7. CCRVDF26 agreed [7] to retain **norfloxacin** on the Priority List, subject to confirmation of data availability by CCRVDF27 (2024).

8. Codex members and observers wishing to support the evaluation of this compound are kindly invited to confirm the availability of relevant data/information for consideration at CCRVDF27, as indicated in REP23/RVDF26, Appendix IV, Part II, and to provide the data/information according to the template in Appendix I to this document.

Part III. Veterinary drugs for which additional data/information is necessary to complete the JECFA evaluation

Ethion, Flumethrin, and Fosfomycin

9. JECFA88 (2019) could not recommend MRLs for these compounds with the available data.

10. CCRVDF25 noted[8] the continuing JECFA evaluations for these compounds.

11. CCRVDF26 further noted the updates on **ethion**, **flumethrin**, and **fosfomycin**, which JECFA is considering.

12. Australia, as Chair of the Working Group on Priorities, reported that Argentina had indicated that data generation on ethion was delayed but expected to be completed by CCRVDF27. The other compounds were retained in Part III as some delegations were not present to provide an update. [9]

13. Codex members and observers who supported the evaluation of these compounds at CCRVDF sessions are kindly invited to update or reconfirm the availability of relevant data/information for consideration at CCRVDF27, as indicated in REP23/RVDF26, Appendix IV, Part III, and to provide the data/information according to the template in Appendix I to this document.

14. Other Codex members and observers wishing to support the evaluation of these compounds are kindly invited to confirm the availability of relevant data/information for consideration at CCRVDF27.

4 REP23/RVDF26, para. 144, Appendix IV (Parts I and V)
5 CAC reports and working documents are available online at: http://www.fao.org/fao-who-codexalimentarius/committees/cac/meetings/en/
6 REP23/CAC46, para. 44, Appendix V
7 REP23/RVDF26, para. 135, Appendix IV, Part II
8 REP21/RVDF25, para. 148, Appendix VI, Part III
9 REP23/RVDF26, para. 138

Part IV. Parallel review: Evaluation of a new compound

Selamectin

15. CCRVDF24 (2018) suggested that JECFA conduct a pilot parallel review on a new compound, including establishing an Acceptable Daily Intake (ADI) and recommending MRLs while the same compound is still under review by a national authority for registration.[10]

16. JECFA88 (2019) could not complete the evaluation of the new compound **selamectin** and, therefore, could not recommend MRLs for consideration by CCRVDF25.

17. CCRVDF25 (2021) addressed evaluating this compound by considering the findings of the pilot parallel review carried out by JECFA88, the parallel review of a new veterinary drug by JECFA and national regulatory agencies, and the priority list of veterinary drugs for evaluation or re-evaluation by JECFA. The Committee further noted the continuing parallel review of **selamectin** by JECFA.[11]

18. JECFA94 (2022) evaluated 4 veterinary drugs, including **selamectin**, but could not recommend MRLs for this compound due to a lack of established good veterinary practice (GVP).

19. At CCRVDF26 (2023), Australia, as Chair of the Working Group on Priorities, reported that the JECFA Secretariat provided an update on the parallel review of a new compound (selamectin) and referred to the information provided on this matter. The JECFA Secretariat had reiterated that specific MRLs could not be recommended without an established GVP for a product in at least one Member State. Therefore, full registration in a Member State, including GVP, was required to complete the residue assessment.

20. CCRVDF26 noted JECFA's update on the parallel review of selamectin and agreed to retain this veterinary drug in Part IV of the priority list.[12]

21. Codex members and observers wishing to support the completion of the evaluation of these compounds are kindly invited to confirm the availability of the required data/information for consideration at CCRVDF27, as indicated in REP23/RVDF26, Appendix IV, Part IV.

Part V. Extrapolation

22. CCRVDF agreed to recommend lufenuron, emamectin benzoate, and diflubenzuron to extrapolate MRLs to finfish.

23. Extrapolated MRLs for these compounds will be considered under Agenda Item 7.1.

24. Codex members and observers are invited to make proposals for veterinary drugs to be added to the priority list for extrapolation of MRLs, including compounds listed in the database on countries' needs for MRLs for veterinary drugs in foods as appropriate, and to provide the data/information according to the *Risk Analysis Principles applied by CCRVDF, Annex C, Approach for the Extrapolation of MRLs of Veterinary Drugs to One or More Species*. Annex C is attached in Appendix II for convenience.

Background documents for consultation

25. Please check the following documents to inform your replies to this Circular Letter.

- The Priority List as agreed at CCRVDF26[13][14]
- The Risk Analysis Principles applied by CCPR[15]
- Database on countries' needs for MRLs for veterinary drugs in foods[16]
- The Summary and Conclusions of JECFA88[17], JECFA94[18], and JECFA98[19]
- The full report of JECFA88[20], JECFA94[21], and JECFA98[22]
- Other relevant JECFA documents, such as toxicological/residue monographs, as available on the FAO and WHO websites[23]

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10 REP18/RVDF24, paras. 98-103
11 REP21/RVDF25, paras. 117-122, 129, 149, Appendix VI, Part IV
12 REP23/RVDF26, paras. 139-140, Appendix IV, Part IV
13 REP23/RVDF26, paras. 129-150, Appendix IV (Parts II, III and IV)
14 CCRVDF reports and working documents are available online at:
http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/en/?committee=CCRVDF
15 https://www.fao.org/fao-who-codexalimentarius/publications/en/
16 https://www.fao.org/fileadmin/user_upload/codexalimentarius/xls_upload/CCRVDF27DBcountryneedsMRLsVetDrugs_e.xlsx
17 https://www.fao.org/3/ca7030en/ca7030en.pdf ;
18 https://www.fao.org/3/cc0433en/cc0433en.pdf ;
19 https://openknowledge.fao.org/server/api/core/bitstreams/03c7c879-e048-4452-833a-28ae6a13fb3e/content
https://www.who.int/publications/m/item/ninety-eighth-meeting-joint-fao-who-expert-committee-on-food-additives-(jecfa)
20 https://www.who.int/publications/i/item/9789241210324
21 https://www.who.int/publications/i/item/9789240057586
22 https://www.who.int/publications/i/item/9789240095533
23 FAO: https://www.fao.org/food-safety/resources/publications/en/
WHO: https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)

REQUEST FOR COMMENTS

26. Codex member countries and observer organizations are invited to comment on the matters raised in Parts I, II, III, IV, and V, as requested in paragraphs 6, 8, 13, 14, 21, and 24, based on the information provided in the CL and documents listed in paragraph 25.

GUIDANCE ON THE PROVISION OF COMMENTS

27. Comments should be submitted through the Codex Contact Points of Codex members and observers using the OCS.

28. Contact Points of Codex members and observers may log in to the OCS and access the document open for comments by selecting “Enter” on the “My reviews” page.

29. Contact Points of Codex members and observers’ organizations are requested to provide proposed changes and relevant comments/justifications on a specific paragraph (under the categories: editorial, substantive, technical, and translation) and/or at the document level (general comments or summary comments). Additional guidance on the OCS comment categories and types can be found in the OCS Frequently Asked Questions (FAQs).

30. Other OCS resources, including the user manual and short guide, can be found at the following link: http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/.

31. For questions on the OCS, please contact Codex-OCS@fao.org.

APPENDIX I

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF
(To be completed by Codex members in relation to Parts I to IV of the Priority List)

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion
2. Veterinary drug names
3. Trade names
4. Chemical names and CAS registry number
5. Names and addresses of basic producers

PURPOSE, SCOPE, AND RATIONALE

6. Identification of the food safety issue (residue hazard)
7. Assessment against the criteria for inclusion on the priority list

RISK PROFILE ELEMENTS

8. Justification for use
9. Veterinary use pattern, including information on approved uses if available (*this should include product labels or other evidence of official use authorization*)
10. Commodities for which Codex MRLs are required

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

AVAILABLE INFORMATION[1]

12. Countries where the veterinary drugs are registered
13. National/Regional MRLs or any other applicable tolerances
14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available (*this should include a list of the data available with the full study titles and whether the compound is also registered as a pesticide and, as appropriate, has been evaluated or scheduled for evaluation or re-evaluation by JMPR*)

TIMETABLE

15. Date when data could be submitted to JECFA.

ADDITIONAL INFORMATION

16. Please provide additional information as appropriate by:
    - Including links under this section and/or
    - Sending attachments to the following addresses: CCRVDF-USSEC@usda.gov with a copy to codex@fao.org.

Note: Codex members interested in proposing MRLs for compounds listed in the database on countries' needs for MRLs for veterinary drugs can download the list of compounds/tissues from: https://www.fao.org/fileadmin/user_upload/codexalimentarius/xls_upload/CCRVDF27DBcountryneedsMRLsVetDrugs_e.xlsx

[1] When preparing a preliminary risk profile, Member(s) should consider the updated data requirement to enable evaluation of a veterinary drug to establish an ADI and MRLs published by JECFA.

APPENDIX II

ANNEX C: Approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species[1]

(For information when providing comments on Part V of the Priority List)

General criteria for extrapolation:

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

a) The reference and concerned species are related (see "A note on terminology").

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.

The M:T[2] (the marker 'M' to total residues of toxicological concern 'T') established for the reference species can be applied to the concerned species.

Specific criteria for extrapolation

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

a) Where identical Codex MRLs have been established in at least two related species based on JECFA recommendations or there is good reason to consider extrapolation from just one related species, these Codex MRLs can be extrapolated to other related species (e.g., extrapolate from cattle and sheep to all ruminants).

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

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

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

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

Explanatory note: *The fact that the M:T is 1 in all tissues/food commodities indicates that the marker residue includes all the compounds of concern. Assuming this would also be the case in the concerned species is reasonable.*

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

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

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

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1 As extracted from the Procedural Manual, Risk Analysis Principles applied by CCRVDF.

2 EHC 240 (1) defines the marker residue as: The parent drug, any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels. Where 'total residues of toxicological concern' are not defined, 'total residue' may be used where 'total residue' is defined CXA 5-1993 (2): the total residue of a drug in animal-derived food consists of the parent drug together with all the metabolites and drug-based products in the food after administration of the drug to food-producing animals. The amount of total residues is generally determined by a study using the radiolabeled drug and is expressed as the parent drug equivalent in mg/kg of the food.

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

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

A note on terminology
• 'Reference species' refers to a species in which Codex MRLs have been established based on a scientific evaluation by JECFA. • 'Concerned species' refers to a species for which extrapolation is being considered. • 'Related species' means species belonging to the same category of food-producing species of ruminant and non-ruminant mammals,[a] birds, or finfish.[b] • 'Unrelated species' refers to species belonging to different categories of food-producing species.

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

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

Special attention should be paid to harmonizing the terminology used for the edible tissues.

Reporting extrapolated MRLs

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

Note: Codex members interested in proposing MRLs for compounds listed in the database on countries' needs for MRLs for veterinary drugs can download the list of compounds/tissues from: https://www.fao.org/fileadmin/user_upload/codexalimentarius/xls_upload/CCRVDF27DBcountryneedsMRLsVetDrugs_e.xlsx