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ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 27th SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERENARY DRUGS IN FOOD (CCRVDF27)

Prepared to Support the Participation Codex Communities of Practice Supported by GFoRSS*

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Disclaimer and Disclosure of Interest

It is important to note that the proposed analysis and associated conclusions and recommendations are stemming from the work of independent food regulatory experts. The analysis and associated recommendations or positions are presented as mere suggestions and should not be considered as a direction or final recommendation to the competent authority empowered to develop and endorse Codex positions

Disclosure of Interest: *Experts involved in the development of this analysis contribute to various food safety and nutrition regulatory capacity building initiatives funded by other Governments, aid agencies, industry and international organizations.*

OBJECTIVES

This document offers an analysis of agenda items to support participation in the **27th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF27)**, taking place in Omaha, Nebraska, United States of America, from **21 to 25 October 2024**.

The document is intended for possible use by the Codex communities of practice promoted by the Global Food Regulatory Science Society (GFoRSS), as part of their contribution to enhancing awareness and supporting effective participation in international standard setting meetings (Codex meetings), by representatives from member countries and observers.

This document will offer an analysis of select key agenda items to support the development of positions at the national and regional level. This analysis is indicative in nature and does not represent an official position of the organization, its membership or its management.

The analysis provided in this document offers a factual review of key agenda items of CCRVDF27, pertaining to:

A. **Agenda Item 6: MRLs for veterinary drugs in foods arising from JECFA98 (2024).**
B. **Agenda Item 7.1: Extrapolated MRLs for different combinations of compounds/commodities at Step 4.**
C. **Agenda Item 7.2: Other matters related to the extrapolation of MRLs for veterinary drugs in foods to one or more species.**
D. **Agenda Item 8: Criteria and procedures for the establishment of action levels for veterinary drugs in food of animal origin resulting from unavoidable and unintentional veterinary drug carry-over in nontarget animal feed.**

This analysis is indicative in nature and does not represent an official position of the organization, its membership or its management.

A. Agenda item 6: MRLs for veterinary drugs in foods arising from JECFA98 (2024)

Document Number: CL 2024/65-RVDF and CX/RVDF 24/27/6

Status in Codex Process: Step 3

Background

JECFA (Joint FAO/WHO Expert Committee on Food Additives) plays a crucial role in protecting public health and supporting international trade by offering globally recognized guidelines and scientific opinions. The expert committee has achieved several significant advancements in assessing risks related notably to veterinary drug residues. Key accomplishments include establishing international standards for Maximum Residue Limits (MRLs), developing risk assessment methodologies for various chemicals, and providing science-based recommendations to ensure global food safety.

At its 98th meeting (2024), JECFA evaluated the safety of two veterinary drugs, **clopidol and fumagillin dicyclohexylamine,** and also completed the safety evaluation of **imidacloprid** started at JECFA94 (2022), for which previous data were insufficient to establish ARfD or ADI. Although ethoxyquin was on the review list, it was not evaluated due to a lack of data from the sponsor.

The meeting report is published in the WHO Technical Report Series (TRS 1055). Toxicological monographs summarizing the data considered by JECFA98 in establishing ADIs are published in the WHO Food Additives Series No. 89. Residue monographs summarizing the data considered by JECFA98 in recommending MRLs are published in FAO JECFA Monographs No. 33. The summary report of JECFA98 is available on the FAO and WHO webpages for consultation.

At the 27th session of CCRVDF (2024), the committee will discuss the recommendations of JECFA98 on MRLs for:

- **Clopidol (coccidiostat)**

Specie	Tissue	MRLs (µg/kg) recommended by JECFA98	For consideration by CCRVDF27 at Step
Chicken	Kidney	8800	4
Chicken	Liver	10400	4
Chicken	Muscle	4100	4
Chicken	Skin/Fat	2600	4

- **Fumagillin dicyclohexylamine (DCH) (mycotoxin)**

Species	Tissue	MRLs (µg/kg) recommended by JECFA98	For consideration by CCRVDF27 at Step	Notes
Fish	Fillet	10 (For the marker residue (MR) fumagillin)	4	Residues of DCH (including any potential metabolites) should be monitored when fumagillin DCH preparations are used in fish to ensure that the concentration is < 1000 µg/kg, a target level compatible with the upper bound of the ADI. A suitable analytical method for the determination of DCH in fish fillets would need to be developed (JECFA98, 2024)
-	Honey	20 (For the marker residue (MR) DCH)	4	

❖ **Imidacloprid (neonicotinoid parasiticide)**

Species	Tissue	MRLs (µg/kg) recommended by JECFA98	For consideration by CCRVDF27 at Step	Notes
Atlantic salmon and rainbow trout	Fillet (muscle with skin in natural proportions) and/or muscle	600	4	The MRL should be extrapolated to all fin fish (JECFA98, 2024).

Analysis

❖ **Clopidol**

It is a veterinary drug primarily used as a coccidiostat in poultry and other food-producing animals. It is used to prevent and control coccidiosis, a parasitic disease that can significantly impact animal health and productivity. Studies have demonstrated that clopidol effectively reduces the severity of coccidiosis and improves overall growth performance in infected animals.

Clopidol has not previously been evaluated by JECFA. The Committee evaluated clopidol at the request of the CCRVDF at its twenty-sixth session in order to establish relevant health-based guidance values and to recommend MRLs for residues in chicken liver, kidney, muscle and skin/fat.

The Committee (JECFA) reviewed data provided by the sponsor and conducted a literature review across various databases, including AGRIS, CAB Abstracts, and PubMed, identifying 17 potentially relevant articles on clopidol and its toxicity. Additional toxicological summaries were found in reviews by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Health Council of the Netherlands. To assess the impact of clopidol residues on the human intestinal microbiome, a comprehensive search using terms related to microbiota and antimicrobial resistance was conducted but yielded no relevant references regarding clopidol's effects on the human microbiome. The main reference toxicological value established by JECFA are presented billow:

Key Points

1. Classification: Clopidol is a coccidiostat used primarily in veterinary medicine to prevent and control coccidiosis in poultry and other food-producing animals.
2. Mechanism of Action: It works by inhibiting the growth and reproduction of coccidia, parasites that can cause severe intestinal disease in affected animals.
3. Efficacy: Clopidol has been shown to improve animal health, growth performance, and overall productivity in livestock by effectively managing coccidiosis.
4. Safety Evaluations: JECFA has established acceptable daily intakes (ADIs) and maximum residue limits (MRLs) for clopidol to ensure the safety of animal products for human consumption (table 1).
5. Toxicological Profile: Studies indicate that clopidol has a favorable safety profile when used according to recommended guidelines, but there may be concerns regarding potential residues in food.
6. Regulatory Compliance: The use of clopidol must align with good veterinary practices to minimize the risk of residues and ensure effective disease management.

Table 1 : Summary of JECFA assessment for Clopidol

Acceptable daily intake	0–0.04 mg/kg bw based on (LOAEL) of 40 mg/kg bw per day for decreased maternal and fetal body weight gain
Acute reference dose	Assumed unnecessary
Estimated dietary exposure	The global estimate of acute dietary exposure (GECDE) is 0.5, for adults and were 32.9, 33.5 and 28.6 µg/kg bw per day, respectively for the elderly, children and adolescents, and infants and toddlers (82%, 84% and 71%, respectively, of the upper bound of the ADI of 40 µg/kg bw).
Residue definition	The marker residue for clopidol in chicken liver, kidney, muscle and skin/fat is clopidol.
Maximum residue limits	10 400 µg/kg (liver), 8800 µg/kg (kidney), 4100 µg/kg (muscle) and 2600 µg/kg (skin/fat) in chickens.

❖ **Fumagillin dicyclohexylamine**

Fumagillin dicyclohexylamine is a veterinary drug primarily used to treat and prevent diseases caused by microsporidia in food-producing animals. It acts as an antimicrobial agent, effectively controlling infections caused by specific parasites.

It's used as a veterinary drug in feed for fish and honeybees or as an immersion bath treatment for fish, in human medicine for the treatment of certain infectious diseases and some forms of cancer. Fumagillin DCH is not currently registered for use as a pesticide. Fumagillin DCH has not previously been evaluated by the Committee.

The Committee evaluated fumagillin DCH at the present meeting at the request of the CCRVDF at its Twenty-sixth Session with a view to establishing relevant health-based guidance values and recommending MRLs for fish and for honey.

In veterinary medicine, fumagillin is administered only as the DCH salt. However, because the fumagillin DCH salt dissociates into the two moieties and consumers would be exposed to the residues of both, the Committee evaluated both fumagillin and DCH.

The Committee reviewed data submitted by the sponsor and conducted a search of scientific literature in publicly accessible databases, including Web of Science, PubMed, and Scopus. This process identified a total of 33 relevant papers on fumagillin and 13 on dicyclohexylamine.

To evaluate the impact of residues on the human intestinal microbiome, the Committee performed a comprehensive search in a library catalogue covering 228 databases, including PubMed and Scopus. However, this search did not yield any literature relevant to the effects of fumagillin residues on the human intestinal microbiome.

Key Points

1. Mechanism of Action: Fumagillin inhibits the growth of microsporidia, which are intracellular parasites that can affect the health and productivity of affected animals.
2. Usage: Commonly used in the treatment of Nosema disease in bees and for certain parasitic infections in fish. Its application helps to maintain animal health and improve production efficiency.
3. Safety and Efficacy: JECFA has evaluated fumagillin, establishing safety profiles, including acceptable daily intakes (ADIs) and maximum residue limits (MRLs) to ensure consumer safety (table 2).
4. The Committee noted that a suitable analytical method for the determination of DCH in fish fillet should be developed.

Table 2 : Summary of JECFA assessment for Fumagillin dicyclohexylamine

Acceptable daily intake	0–0.003 mg/kg bw for fumagillin and an ADI of 0-0.02 mg/kg bw for DCH.
Acute reference dose	0.7 mg/kg bw for DCH.
Estimated dietary exposure	The GECDE values for adults and the elderly, children and adolescents, and infants and toddlers were 0.06, 0.10 and 0.11 µg/kg bw per day, respectively, which represent 2%, 3% and 4% of the upper bound of the ADI of 3 µg/kg bw. There was insufficient information to estimate dietary exposure (chronic or acute) to DCH.
Residue definition	The marker residue for fumagillin DCH in fish fillet is fumagillin. The marker residue for fumagillin DCH in honey is DCH.
Maximum residue limits	In honey: 20 µg/kg for the marker residue DCH In fish fillet: 10 µg/kg for the marker residue fumagillin

❖ **Imidacloprid (neonicotinoid parasiticide)**

Imidacloprid is a broad-spectrum insecticide belonging to the neonicotinoid class, widely used in agriculture and veterinary medicine. It acts as an insect neurotoxin, targeting the nervous systems of pests.

Imidacloprid was first evaluated by JMPR in 2002, establishing an acceptable daily intake (ADI) of 0–0.06 mg/kg body weight and an acute reference dose (ARfD) of 0.4 mg/kg body weight. During its twenty-fifth meeting, CCRVDF requested JECFA to evaluate imidacloprid for use in all finfish and recommend maximum residue limits (MRLs) for muscle and fillet. At its ninety-fourth meeting, JECFA derived a toxicological ADI (tADI) of 0–0.05 mg/kg body weight and a toxicological ARfD (tARfD) of 0.09 mg/kg body weight. However, due to incomplete information on the impact of imidacloprid on the human intestinal microbiota, the Committee could not establish an mARfD or a microbiological ADI (mADI), nor recommend MRLs. The current meeting included imidacloprid on the agenda to complete its assessment, particularly regarding microbiological data submitted by the sponsor.

Key Points

1. **Mechanism of Action**: Imidacloprid is a neonicotinoid parasiticide in the chloronicotinyl nitroguanidine chemical family. It works by binding to nicotinic acetylcholine receptors in the nervous system of insects, leading to paralysis and death. Its specificity for insect receptors makes it effective against a wide range of pests.
2. **Uses**: It is commonly used in crop protection, as well as in veterinary medicine. It is also employed in termite control and as a flea treatment in dogs and cats. It is used to control sea lice on farmed fish and to control sucking insects, chewing insects (including termites), soil insects and fleas on pets. Imidacloprid may be applied to structures, crops and soil and can be used as seed treatment.
3. **Safety Evaluations**: JECFA has evaluated imidacloprid, focusing on its safety profile and potential residues in food (table 3). However, at previous meetings, the Committee noted insufficient data to establish acceptable daily intakes (ADIs) and maximum residue limits (MRLs).
4. **Toxicology**: While imidacloprid is effective against pests, concerns about its potential effects on non-target organisms, including bees and other beneficial insects, have been raised. Studies on its toxicological effects in mammals, including any impacts on the human microbiome, have also been conducted.
5. **Regulatory Considerations**: The use of imidacloprid must adhere to good agricultural and veterinary practices to minimize risks of residues in food products. Continuous monitoring and research are essential to ensure its safe use.
6. **Environmental Impact**: The persistence of imidacloprid in the environment and its potential to contaminate soil and water have raised ecological concerns. Research continues to assess its long-term effects on ecosystems.

Table 3 : Summary of JECFA assessment for Imidacloprid

Acceptable daily intake	0–0.05 mg/kg bw, based on a NOAEL of 5.25 mg/kg bw per day for decreased body weight gain
Acute reference dose	0.09 mg/kg bw based on a BMDL05 of 9 mg/kg bw for acute neurobehavioural effects in rats
Estimated dietary exposure	The GEADE, based on consumption of Atlantic salmon, was 7% of the ARfD for adults and children; the GEADE for all fin fish was 38% and 26% of the ARfD for adults and children, respectively.
Residue definition	The parent molecule, imidacloprid
Maximum residue limits	The Committee recommended an MRL for Atlantic salmon and rainbow trout fillet (muscle with skin in natural proportions) and/or muscle of 600 µg/kg. It further recommended that the MRL be extrapolated to all fin fish.

Conclusion and Recommendations

Given the importance of establishing maximum residue limits for veterinary drugs, especially for developing countries, for which Codex is considered as the reference for food standards, it would be recommended to support the adoption of the standards as proposed by JECFA.

These guidelines, which include acceptable daily intakes (ADIs) and maximum residue limits (MRLs), provide a scientifically based framework for assessing the safety of veterinary drug residues in food products.

The adoption of JECFA's recommendations for compounds like clopidol, fumagillin dicyclohexylamine and imidacloprid, is essential for ensuring food safety and protecting public health. Moreover, all criteria for extrapolation are met in the case of imidacloprid, therefore extrapolation might be considered also for all fin fish.

By aligning their regulatory standards with the international best practices, member countries can facilitate trade and safeguard both animal and human health. However, national adoption of these limits may need to consider local uses and regulatory measures, agricultural practices, and specific public health concerns, requiring a thorough review and possible adaptation of JECFA's recommendations to suit the national context.

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

C. Agenda Item 7.2: Other matters related to the extrapolation of MRLs for veterinary drugs in foods to one or more species.

Document Number: CX/RVDF 24/27/7 and CX/RVDF 24/27/7-Add.1

Status in Codex Process: Agenda Item 7.1 at Step 4

Background

To enhance the availability of Maximum Residue Limits (MRLs) for veterinary drug residues and address the shortage of scientific data necessary for JECFA's risk assessment, the CCRVDF has discussed the adoption of the **MRL extrapolation approach** in several committee sessions. This focus has included examining the methodology's limits, challenges, and principles, with the aim of establishing practical guidelines for its application across various animal species.

At its 24th Session (2018), 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) identified 10 compounds on the list of Codex MRLs to drive extrapolation.

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 (2021), it was agreed to rules for extrapolating maximum residue limits (MRLs) of veterinary drugs to one or more species REP21/RVDF25, para. 105, Appendix III. The 44th Session of the Codex Alimentarius Commission (CAC44, 2021) adopted 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.

The Committee re-established the 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, and to prepare revised proposals for consideration by the Twenty-sixth Session of the CCRVDF[3]; (ii) To consider the extrapolation of MRLs for Ivermectin in milk from goats and sheep[4]; (iii) To develop an adapted approach to the extrapolation of MRLs for veterinary drug residues in offal tissues[5].

At the 26th session of CCRVDF (2023), the committee used the agreed rules to extrapolate MRLs for several substances which were adopted by CAC46 (2023) REP23/CAC46, para. 36(iii), Appendix II and included in CX/MRL 2-2023 – Maximum Residue Limits and Risk Management Recommendations for Residues of Veterinary Drugs in Foods.

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 on 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.

The committee agreed to establish an electronic working group (EWG) chaired by the European Union (EU) and co-chaired by Costa Rica to work 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.

At the 27th session of CCRVDF (2024), the committee will discuss the following EWG's recommendations based on the EWG's discussion and comments submitted by Codex members and observers in reply to CL 2024/67-RVDF.

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 REP21/RVDF25, par. 105(iv)
4 REP21/RVDF25, par. 150(iii)
5 REP21/RVDF25, par. 150(vi)

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

- Criterion 2b of the Approach for the extrapolation of MRLs of veterinary drugs to one or more species should be amended to:

"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.

- The MRL of 1350 µg/kg established for lufenuron in salmon and trout fillets can be extrapolated to finfish.
- With agreement on R1, the MRL of 100 µg/kg established for emamectin benzoate in muscle and fillet of salmon and trout can be extrapolated to finfish.
- Extrapolation of the MRL established for ***diflubenzuron in the muscle of salmon is not supported.***

Recommendation 2: Development of a possible approach for extrapolation of MRLs 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 nonruminant 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

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

"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."

- Extrapolation of the cattle milk MRL for deltamethrin to the milk of other ruminants is not recommended currently.
- Extrapolation of the cattle milk MRL for ivermectin to the milk of other ruminants is not recommended.
- Except for Recommendation R1 above, the current criteria for extrapolating between milk of different species are not enhanced.

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

- ❖ Fundamental questions remain on which it would be useful to have input from CCRVDF:

1. determine if further work would be needed in this regard and if so
2. guide any future EWG on the task it is charged with.

- ❖ The following question is put forward for consideration:
- ▪ ***Question:*** 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?
- ▪ **Considerations:** 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"?
- ❖ To address the issues identified by the EWG, CCRVDF is invited to provide further guidance regarding Recommendation 4 to allow additional work in an EWG if appropriate.

Analysis

Participation and methodology

- ❖ Thirty Codex members and two Observers registered to participate in the EWG.
- ❖ An introductory document was prepared which 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 were done:
  - ▪ *In the first consultation with EWG (documents shared on 27 February 2024), comments were received from Canada, France, USA and Italy.*
  - ▪ *In the second consultation with EWG (document shared on 28 June 2024), comments were received from Canada, USA, Italy and EU.*
- ❖ *The EWG used the extrapolation rules as presented in Annex C to the Risk Analysis Principles applied by CCRVDF as its starting point.*
- ❖ The EWG didn't recommend substance-specific extrapolations as part of the current work assuming il 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.
- ❖ A final document was prepared including a summary of the work undertaken, comments received and conclusions/recommendations.
- ❖ A CL 2024/67-RVDF was sent to CODEX members and observers to collect their comments and observation.

Summary of Discussion and Commentary of EWG Members

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

- ❖ **Lufenuron**

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

Proposed MRL: Fillet -Muscle plus skin in natural proportions- 1350 µg/kg

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.

The arguments supported by the EWG for this decision are:

- JECFA concerns need not prevent CCRVDF from extrapolating, as the MRL represents a safe value;
- Identical MRLs have been established in 2 species (***Salmon and Trout***) based on JECFA recommendations; the marker residue is the parent compound;
- M: T is considered to be 1 according JECFA report (WHO TRS 1008);
- MRL is established based on a full evaluation undertaken by JECFA.

Withdrawal periods need to be in place that take account of local conditions where the substance will be used.

❖ **Emamectin benzoate**

The EWG agreed that MRL extrapolation to finfish can be recommended **if the proposed modification of Criterion 2b is accepted by CCRVDF**.

Proposed MRL: Fillet -Muscle plus skin in natural proportions- 100 µg/kg

The reasons that prevented JECFA from extrapolating to other fish species were:

- 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.

The arguments supported by the EWG for this decision are:

- JECFA concerns need not prevent CCRVDF from extrapolating, as the MRL represents a safe value;
- Identical MRLs have been established in 2 species (***Salmon and Trout***) based on JECFA recommendations.
- MRL is established based on a full evaluation undertaken by JECFA
- M:T of 0.9 in muscle and fillet of salmon was established by JECFA (WHO TRS 988)
- The marker residue is not the parent compound (emamectin benzoate consists of 90% emamectin B1a benzoate and 10% emamectin B1b benzoate). However, **the EWG considers that the present 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.**

Withdrawal periods need to be in place to account for local conditions where the substance will be used.

❖ **Diflubenzuron**

The EWG agreed that MRL extrapolation is not possible as the criteria are not met, the MRL established for Salmon is not applicable for finfish

The arguments supported by the EWG for this decision are:

- MRL has been established in a single species,
- M:T is not 1,
- MRL is not based on the LOQ of the analytical method.

Commentary of members

Canada

Raises a comment regarding drug substances that consist of a mixture of homologous compounds.

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.

France

Supports the extrapolation proposals for fish species,

Italy

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;

Generally, in accordance with EU Regulation (EC) No 470/2009), MRLs for salmonids can be extended to other finfish due to similar metabolism. However, when a specific metabolite is involved, extrapolation should only occur if there is evidence that the metabolite is not significantly produced in other species.

USA

Suggests that CCRVDF consider adding a sub-point to criterion 2b as proposed by the EWG recommendation which would allow CCRVDF to extrapolate the emamectin MRLs in fillet and muscle from salmon and trout to fillet and muscle from all finfish.

Supports the extrapolation proposals for fish species for lufenuron ***but suggested that CCRVDF confirm with JECFA that the inability to extrapolate was not due to a specific consumer health reason.***

Agrees that the criteria have not been met to extrapolate the MRL for diflubenzuron in muscle plus skin in natural proportions from salmon to muscle plus skin in natural proportions from all finfish.

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

- The approach proposed by the EWG is built generally on the approach already accepted by CCRVDF for extrapolation based on three criteria:

  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. *If identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species (pigs, horses or rabbits).*

     The presence of identical MRLs in both ruminants and non-ruminant mammals should give more confidence indicating minimal variation in metabolism across mammalian species.
  3. *Extrapolation of an MRL for milk should also be considered in those cases where the M:T in milk = 1:*

     It should provide sufficient assurance that additional testing for residues in camelid milk is unnecessary.

- EWG highlighted that camelids are not explicitly included in the current CCRVDF rules allow for extrapolation rules.
  - The rules are established within groups of related species (ruminants, non-ruminant mammals, birds, finfish).
  - Camelids are classified as "pseudo-ruminants" due to differences in their gastrointestinal systems compared to true ruminants, leading to greater uncertainty when extrapolating MRLs from ruminants or monogastric mammals to camelids.

  Camelids have a three-chambered stomach, different from true ruminants' four chambers, leading to greater uncertainty when extrapolating MRLs from either ruminants or monogastric mammals.

- EWG established a list of active substances (22 molecules) for whish MRL extrapolations could be considered on the basis of the proposed extrapolation principles and mentioned species for which MRLs already exist and established MRLs.

Commentary of members

Canada

Supports the proposed approach for MRL extrapolation to camelids but highlights the limited availability of analytical methods for detecting veterinary drug residues in camelids. This raises concerns about the lack of suitable regulatory methods to support the proposed MRLs. Specifically, the low MRLs for dexamethasone and clenbuterol may not be reliably detected by methods validated in other species, which may not perform similarly in camelids.

Italy

Recognizes the need for MRLs to enhance international trade and food security, thus supporting the extrapolation of MRLs for pharmacologically active substances to camelids via the proposed approaches.

Extrapolation recommendations for individual substances for camelid treatment should be requested by member countries based on need. The import of camel meat and milk is regulated by EU rules, with the European Commission responsible for MRLs on behalf of all Member States, as it is a harmonized matter.

USA

Building on the criteria proposed by the Chair and Co-Chair, the United States proposes additional criteria to further reduce uncertainty associated with extrapolation:

They proposed also that CCRVDF first establish extrapolation criteria for camelids. Once these criteria are agreed upon, member countries can nominate compounds for extrapolation to be included in Part V of the Priority List.

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.

- **Deltamethrin**

Consideration was pointed out by the EWG supporting the decision to not recommend at this time the extrapolation of cattle milk MRL to the milk of other ruminants:

- Variations in fat composition of ruminant milk and volumes across ruminant species may affect residue concentrations, creating significant uncertainty about the levels of toxicologically relevant residues in their milk.
- Knowing that MRL for deltamethrin in the milk of animals other than marine mammals, set for pesticide use at 50 µg/kg, is already applicable, establishing a different MRL by extrapolating the existing cattle milk MRL of 30 µg/kg would create additional conflicting Codex MRLs;
- The Joint CCPR/CCRVDF EWG is discussing harmonizing milk MRLs for deltamethrin, so consulting this group is recommended before establishing additional MRLs by extrapolation.

- **Ivermectin**

Consideration was pointed out by the EWG supporting the decision to not recommend the extrapolation of cattle milk MRL to the milk of other ruminants:

- Since ivermectin consists of homologous compounds and the marker residue is just one homologue, Criterion 2b is technically not met.
- Due to the large milk discard required for ivermectin compliance, variations in milk fat content, and potential differences in the M:T ratio across ruminant species, the EWG does not recommend extrapolating the cattle milk MRL to another ruminant's milk.

Some commentary of members during the discussions

Italy

Italy urges caution, highlighting concerns about promoting off-label use due to potential milk discard and uncertainties around varying fat content in different ruminant species' milk. It suggests that revising MRLs for cattle, particularly for ivermectin, may be a suitable solution.

USA

Concerns were expressed about extrapolating deltamethrin MRLs to milk, noting that established criteria are not met and that deltamethrin's lipophilicity leads to variable M:T ratios across ruminant species. Although JECFA extended tissue MRLs from cattle to sheep, it did not do so for milk, indicating potential issues with such extrapolation. Therefore, the USA does not support extending the cattle milk MRL to other ruminants.

The USA points out also that the criteria for milk extrapolation are not met for ivermectin, which, like deltamethrin, is fat-soluble, and its M:T ratio has not been confirmed to be 1. Additionally, JECFA has established different M:T values for cattle and sheep tissues, indicating that the M:T ratio in milk may also vary.

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.

Considering the limited data and guidance on the subject, the EWG raised several questions and considerations based on the following points:

- 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.
- There is uncertainty about the need for MRLs in non-standard offal since these tissues are already consumed without safety concerns.
- The current approach assumes a "worst case" scenario, so exposure from non-standard offal is unlikely to exceed that from standard foods.
- The key question is whether establishing MRLs is only for facilitating trade and residue control, and if an additional exposure calculation is required.
- An example of the extrapolation approach was circulated to the EWG, focusing on the possible extrapolation of the ivermectin MRL for pig fat to non-standard pig offal.

Some commentary of members

Canada

Supports the proposed approach for MRL extrapolation to camelids but highlights the limited availability of analytical methods for detecting veterinary drug residues in camelids. This raises concerns about the lack of suitable regulatory methods to support the proposed MRLs. Specifically, the low MRLs for dexamethasone and clenbuterol may not be reliably detected by methods validated in other species, which may not perform similarly in camelids.

Republic of Korea

Assumed that the types and quantities of offal consumed differ by country, with the liver and kidneys playing distinct roles in metabolism compared to other edible by-products. Thus, to assess the feasibility of extrapolation, it is essential to perform a data-driven review, which should include evaluations of consumer exposure to residues in offal tissues beyond just the liver and kidneys.

USA

It believes that if an MRL is to be extrapolated to other offal, a residue dietary intake evaluation is necessary, similar to that for typical meat tissues. Existing dietary exposure assessments can be seen as worst-case estimates, but they do not directly establish the safety of specific residue concentrations in other tissues. The U.S. also emphasizes that the discussion at CCRVDF26 regarding MRLs for other offal being solely a trade issue reflects only some delegations' views and not a consensus.

The United States believes that MRLs for veterinary drugs with consistent values across all meat-type tissues and the same M:T ratio may not need further consumer exposure assessments, as consuming other offal tissues wouldn't increase exposure.

For extrapolated MRLs, the U.S. recommends starting with the highest existing MRL from typical tissues. If intake evaluations exceed the Codex Health-Based Guidance Value (HBGV), the next highest MRL can be considered.

Data on tissue distribution is essential to support proposed extrapolated MRLs, including information from related compounds and species for assessing compatibility with Good Veterinary Practices (GVPs). The U.S. agrees that MRLs classified as "unnecessary" or "not specified" in standard tissues could be similarly applied to other offal without further evaluation, pending more discussion on these terms.

Conclusion and Recommendations

In light of the arguments presented by the Electronic Working Group (EWG) regarding the extrapolation approach for lufenuron, emamectin benzoate, and diflubenzuron in finfish, delegations may consider supporting the adoption of the EWG's general recommendation and the proposed MRLs for lufenuron and emamectin benzoate at the next Codex Alimentarius Commission session at Step 5/8 (final adoption).

Regarding the establishment of MRLs for camelids, the EWG proposed new criteria, highlighting the need for additional studies to address key questions, particularly concerning occurrence data, depletion studies, and the limited availability of analytical methods for detecting veterinary drug residues in camelids. Once these extrapolation criteria are finalized, member countries could nominate compounds for inclusion in Part V of the Priority List.

To address the absence of MRLs for camel products, it is recommended that interested countries (Arab and African countries, etc.) adopt the proposed extrapolation criteria and advocate for the inclusion of MRLs for camels in the CCRVDF priority lists. Additionally, it is important to encourage molecule developers to generate data supporting the establishment of MRLs for camelid tissues alongside other species.

Furthermore, during discussions on deriving MRLs for edible tissues, the EWG emphasized the necessity for further dialogue and efforts to create a consistent approach. This topic may be revisited by JECFA/CCRVDF, considering the limitations and concerns identified by the EWG. So, it is advised to support the continuation of work on developing an extrapolation approach for MRLs in edible offal tissues. It is crucial to highlight during the meeting that the consumption of edible tissues is significant in several regions in the world. Establishing MRLs for veterinary drugs in these tissues is vital to mitigate health risks associated with drug residues. Countries should also encourage the generation of data on the occurrence of these residues which is essential for informed decision-making regarding MRLs.

D. Agenda item 8: Criteria and procedures for the establishment of action levels for veterinary drugs in food of animal origin resulting from unavoidable and unintentional veterinary drug carry-over in nontarget animal feed.

Document Number: CX/RVDF 24/27/8

Status in Codex Process: NA

Background

An Electronic Working Group (EWG) chaired by Australia and co-chaired by Canada was re-established to further develop the criteria and procedures for establishing action levels based on discussions at **CCRVDF26 (2023)**. The terms of reference (ToR) of the EWG were mainly to update the criteria and procedures for establishing action levels of veterinary drug residues in food products from non-target animals linked to the unintended and unavoidable veterinary drug carry-over in non-target animal feed. Moreover, the EWG worked on expanding the pilot study estimating action levels for unavoidable and unintentional carry-over in chicken eggs to include nicarbazin and lasalocid.

Outcomes related to the criteria and procedures for establishing action levels were presented in a discussion paper attached in Appendix I of the working document, while the pilot studies were presented in details in Appendix II.

Among the received comments, the United States of America proposed an alternative management approach to deal with residues resulting from unavoidable and unintentional carry-over instead of setting action levels, and which was presented in Appendix III of the working document.

CCRVDF27 is invited to consider the recommendations below:

- The proposed approach to establishing action levels as presented in **Appendix I** (for comments).
- Pilot studies using nicarbazin and lasalocid residues in chicken eggs to illustrate the proposed approach (**Appendix II**).
- The alternative approach submitted by the United States of America as presented in **Appendix III** (for comments).

Should Codex members support the approach proposed by the EWG in Appendix I, consider whether the action levels proposed for nicarbazin and lasalocid in eggs in Appendix II (as shown in the following table), could be submitted for adoption by CAC47.

Proposed action level for nicarbazin in chicken egg

Commodity	Proposed action level (mg/kg)	Notes
Egg	0.220	Marker residue - 4,4'-dinitrocarbanilide (DNC)

Proposed action level for lasalocid in chicken egg

Commodity	Proposed action level (mg/kg)	Notes
Egg	0.1	Marker residue – Lasalocid A

Analysis of Discussion paper and pilot studies presented in Appendices I & II

Key considerations

- According to Appendix I, Action level is defined as the maximum concentration of residue resulting from unintended and unavoidable carry-over in a feed of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) in a non-target animal that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.
- Several keywords can be highlighted out of this definition, particularly the unintended and the unavoidable aspects that should be fulfilled in the considered residue/food couple. The definitions precise clearly that in order for these aspects to be considered, all required mitigation procedures should be performed (e.g., flushing, sequencing, or physical clean-out). This aspect is mentioned at several other places in the text, emphasizing the fact that the best practice should be followed (e.g., Code of Practice on Good Animal Feeding (CXC 54-2004), Good Manufacturing Practices (GMP) and Hazard Analysis and Critical Control Point (HACCP)) to minimize the unavoidable and unintended veterinary drug carry-over in non-target animal feed.
- Action levels should be based on the 'As Low as Reasonably Achievable' concept, while ensuring that all mitigation measures were applied to minimize the veterinary drug carry-over.
- Action levels should be developed only to cover situations where low-level residues of an approved/registered
- veterinary drug used according to good veterinary practices are consistently detected by a competent authority in edible commodities from non-target animals and investigations confirm the source to be unintended and unavoidable carry-over.
- Action levels should be derived only for veterinary drugs authorized for use in a target class of animals, and that have adopted (or JECFA recommended) maximum residue limits (MRLs).
- Analytical methods should be available for the veterinary drug residue in the edible commodity for which action levels are proposed.

Proposed procedure

The proposed procedure follows 4 steps:

Step 1. Assess animal dietary exposure assessment.

Step 2. Estimate anticipated residue levels in food commodities of animal origin.

Step 3. Set Action levels.

Step 4. Evaluate human dietary exposure assessment.

CCRVDF will be responsible for covering steps 1 to 3, while JECFA will be asked to perform step 4.

The first 3 steps will rely on data such as residue transfer and residue monitoring data from peer-reviewed scientific literature and/or data provided by regulatory authorities. Mainly, data should demonstrate that unavoidable and unintended carry-over occurs even when mitigation steps are followed, and that is responsible for the occurrence of residues in edible commodities from non-target animals.

In **step 1**, a default hypothetical carry-over of 1% can be applied to the highest authorized dose of the veterinary drug in feed for the target class of animals in situations where unintended and unavoidable carry-over has been demonstrated, and suitable data is not available, or from the maximum observed concentration of unavoidable and unintended veterinary drug carry-over in non-target feed determined in feed mills operating under routine good manufacturing conditions.

In **step 2**, the potential transfer of a veterinary drug from feed to food can be estimated by calculating a transfer factor (TFs) based on suitable feeding studies on non-target animals fed feed containing the veterinary drug at levels close to the unavoidable and unintentional carry-over levels.

$$TF = \frac{\text{residue level in food of animal origin (milk, eggs or tissues) (fresh weight), expressed in mg/kg}}{\text{level in total feed ration (dry weight), expressed in mg/kg}}$$

Then, the **Anticipated residue level** will be calculated as:

Anticipated residue level = TF × veterinary drug carry-over level in animals total feed ration (dry weight)

Action levels can be then estimated in **step 3**, based on the anticipated residue levels in food of animal origin from animals exposed under practical conditions.

In **step 4**, an estimate of consumer dietary exposure from residues present at action levels in food of animal origin (eggs, milk, meat, edible offal) from non-target animals, will be calculated following approaches for both chronic exposure (based on the ADI) and acute exposure (based on the ARfD, when established).

Pilot studies

Two pilot studies were presented in support of the proposed approach, with all the previous steps detailed and all calculations explained. Nicarbazin and Lasalocid were targeted in chicken eggs. The target animals are chicken (broilers), where non-target animals are Laying hens. The reason for the carry-over was proved as unavoidable and unintentional, since feed for chickens and laying hens is often prepared at the same feed mill. Data came from surveys or residue monitoring data in poultry eggs and feeding studies on non-targeted animals.

Following the proposed procedure, the proposed action level for Nicarbazin was 0.22 mg/kg, which was found to be concordant with the EU and New-Zealand regulation (0.3 mg/kg).

For Lasalocid, the proposed action level was 0.1 mg/kg, positioning between the Australia MRL (0.05 mg/kg) and the EU MRL (0.15 mg/kg).

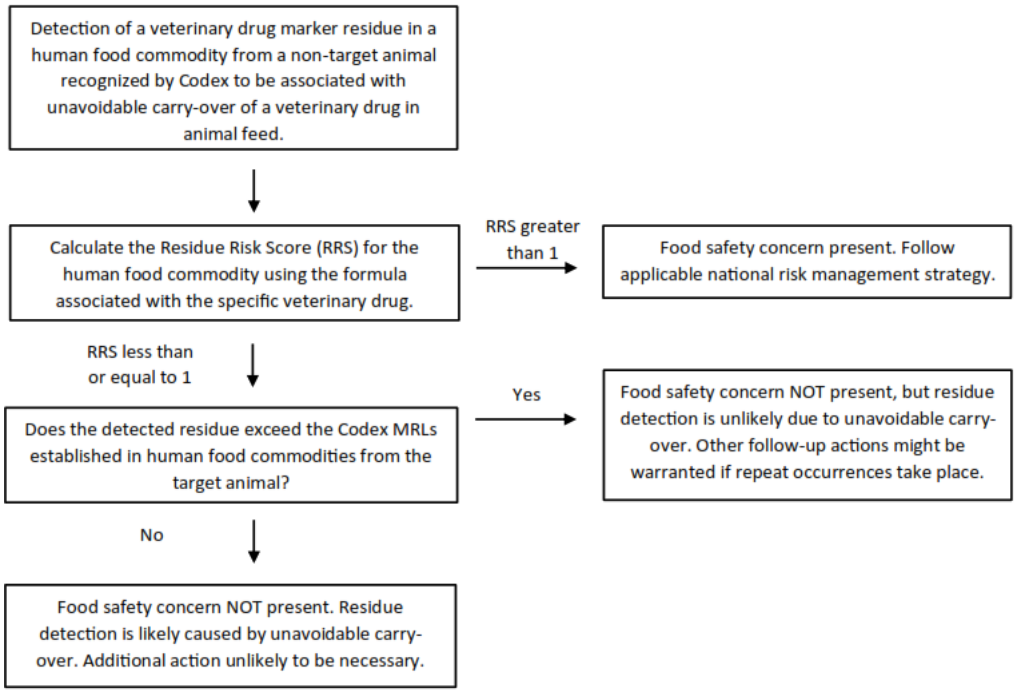
Analysis of proposal of the USA in Appendix III

Upon reviewing the proposed approach outlined in Appendices I and II, it becomes evident that a significant amount of data is necessary to successfully implement the procedure. This includes, but is not limited to, data on residue transfer and monitoring in food and feed, as well as feeding studies for non-target species, among other essential information..

To overcome this limiting challenge of data availability, the United States of America proposes a procedure based a Risk Management Decision Tool (RMDT) for the potential use by competent authorities. This approach does not require estimates of the carry-over amount and the associated residue concentrations in the food commodity and avoids potentially establishing a residue level that is incompatible with amounts detected in human food commodities caused by unavoidable carry-over in animal feed.

The proposed RMDT is outlined in the following figure.

When unavoidable carry-over of the veterinary drug in the animal feed is the suspected by the competent authority, a Residue Risk Score (RRS) is calculated, placing the detected residue value into the context of the established health-based guidance value (HBGV) for the veterinary drug. All details to the calculation of the RRS are provided in the appendix with a hypothetical example on Nicarbazin in chicken eggs.



Conclusion and Recommendations

The development of systematic, data-driven methodologies to address the longstanding issue of unintended veterinary drug carryover, including pilot studies and their outcomes, is highly commendable. However, it may be worth considering a more straightforward and practical risk management approach. This would help overcome challenges related to data availability, avoid barriers to trade by setting very low action levels and make the solution more accessible to countries with varying levels of development.