47th Joint Coordination Meeting of Arab and CCNE Codex Contact Points

Preparation For The 28th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF 28)

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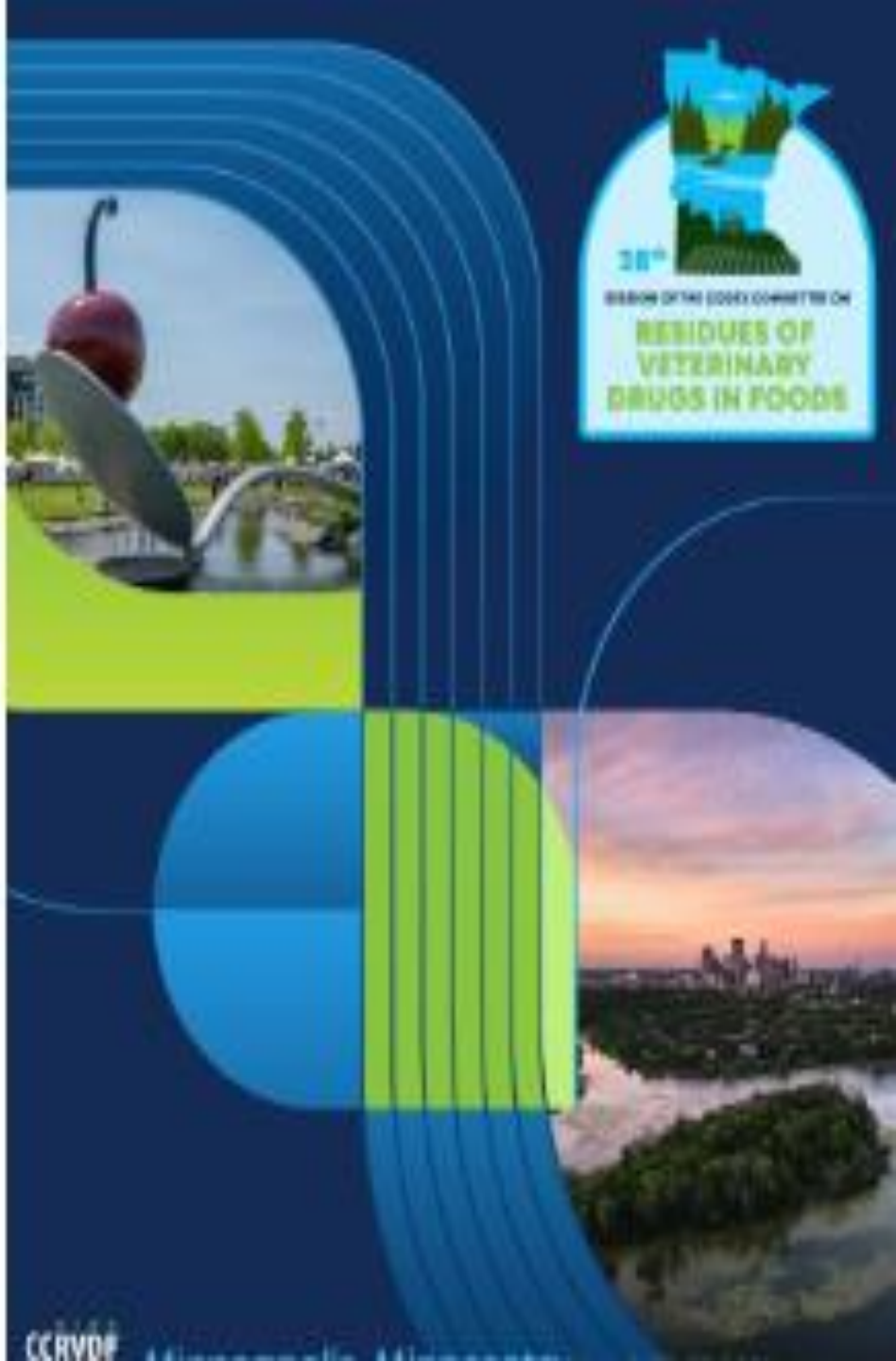
[March] [17], 2026

Agenda item 6

MRLS FOR FUMAGILLIN DICYCLOHEXYLAMINE (DCH) IN FISH (FILLET) AND HONEY (AT STEP 7) Comments in reply to CL 2026/10-RVDF



Background : Agenda Item 6

- The 27th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF27, 2024) considered the MRLs for fumagillin DCH

- Several member countries and organizations raised significant concerns about using DCH as a residue marker in honey. DCH is not a unique marker for fumagillin; it can originate from environmental and industrial sources, complicating regulatory compliance and potentially leading to misinterpretation of fumagillin use in food products. There were also concerns that if other fumagillin salts are used in the future, DCH would no longer be an appropriate marker. Additionally, the absence of comprehensive toxicology, metabolism, and residuedepletion data created uncertainty about the safety assessment, prompting some members to withhold support for the proposed MRLs until additional regional data and a review of JECFA monographs are available.

- Fumagillin is administered only as dicyclohexylamine (DCH) salt in veterinary medicine. As the fumagillin DCH salt dissociates into the two moieties, consumers would be exposed to residues of both. JECFA98 (2024) evaluated both fumagillin and DCH

Analysis : The purpose of this document

The purpose of this document to comment on the following proposed new work is MRLS FOR FUMAGILLIN DCH IN FINFISH (FILLET) AND HONE (For comments at Step 6).

Maximum residue limits (MRLs)

Species	Fillet (µg/kg)	Notes
Fish	10 (For the marker residue (MR) fumagillin)	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 determining DCH in fish fillets would need to be developed. (JECFA98, 2024)

Species	Honey (µg/kg)
-	20 (For the marker residue (MR) DCH)

Analysis : Technical issue under consideration

JECFA evaluation	98 (2024)
Acceptable daily intake	For fumagillin 0–0.003 mg/kg bw based on a no-observed-adverse-effect level (NOAEL) of 1.73 mg/kg bw per day for decreased body weight gain in a 13-week study in rats and for post-implantation loss, decreased fetal body weight, and associated morphological changes in a developmental toxicity study in rats at 4.32 mg/kg bw per day. A safety factor of 500 was used, which comprised 100 for interspecies and intraspecies differences and an additional factor of 5 for database uncertainty. For DCH 0–0.02 mg/kg bw based on a NOAEL of 10 mg/kg bw per day for haematological and clinical chemistry changes at 30 mg/kg bw per day in a 13-week toxicity study in rats. A safety factor of 500 was used, which comprised 100 for interspecies and intraspecies differences and an additional factor of 5 for database uncertainty.
Acute reference dose	For Fumagillin, an ARfD is unnecessary. For DCH, 0.7 mg/kg bw based on the NOAEL of 70 mg/kg bw per day for clinical signs and mortality after 4 days at 200 mg/kg bw per day in a 28-day toxicity study in rats. A safety factor of 100 was used to allow for interspecies and intraspecies differences.
Estimated chronic dietary exposure	Based on potential fumagillin residues in fish fillet and honey, the global estimates of chronic dietary exposure (GECDEs) are: • For adults and the elderly, 0.06 µg/kg bw per day. • For children and adolescents, 0.10 µg/kg bw per day. • For infants and toddlers, 0.11 µg/kg bw per day. (representing 2%, 3%, and 4%, respectively, of the upper bound of the ADI of 3 µg/kg bw)
Residue definition	The marker residue for fumagillin DCH in fish fillet is fumagillin. The marker residue for fumagillin DCH in honey is dicyclohexylamine (DCH).

Analysis : Annex II
concerne form submitted by Canada and the United States of American for maximum residue limits recommended by the 98th meeting of the joint FAO/WHO expert committee on food additives for fumagillin dicyclohexylamine in fish fillet and honey.
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- The United States and Canada have reviewed the report and the FAO monograph from the 98th JECFA meeting where the Committee established health-based guidance values (HBGVs) and maximum residue limits (MRLs) for fumagillin DCH. They note that:
  - Because the report provides only a summary of the toxicological studies, the details regarding the hazard assessment are not fully described. Nevertheless, based on the available information, we suggest that JECFA request comprehensive, high-quality dossiers to enable robust risk assessments and risk management recommendations. The approach used by JECFA in the Guidance for the safety evaluation of residues of veterinary drugs with incomplete data packages should be used in very limited situations as outlined in the guidance.
  - Although JECFA indicated that this Guidance was used when recommending HBGVs and MRLs for fumagillin DCH, the overall approach used for fumagillin DCH does not follow the practices used in current, modern risk assessments, including those outlined as harmonized procedures in VICH and OECD documents.
  - Specifically, for fumagillin DCH, there is a lack of several critical toxicology, metabolism, and residue chemistry studies that are generally recognized as needed for contemporary risk assessments. Additionally, the marker residue selected for fumagillin DCH in honey is not a unique marker; therefore, when monitoring honey, it will not be known if the source of DCH in honey is from use of fumagillin DCH as a veterinary drug or from other sources. This can cause trade disruptions for honey as noted by multiple delegations at CCRVDF27.
  - They recommend that JECFA provide a list of studies and data needed to conduct a robust risk assessment for fumagillin DCH that has less uncertainty. Below are our specific concerns based on the information available in the report and FAO monograph.

- Canada and the United States respectfully ask JECFA to reconsider their MRL recommendation for honey and to ask for additional studies to identify a suitable marker residue and MRL value that are consistent with GVP.

Analysis : Recommendations of the EWG

CCRVDF is invited to

Consider to forward MRLS for fumagillin dicyclohexylamine (dch) in fish (fillet) and honey to the Codex Alimentarius Commission (CAC49) for approval (at step 8).

Conclusion and recommendation

- The analysis highlighted that several Members raised scientific and regulatory concerns, particularly regarding the use of DCH as a marker residue in honey, as this compound is not specific to fumagillin and may also originate from other sources, which could complicate residue monitoring and enforcement. In addition, the limited availability of toxicological, metabolism and residue depletion data, was identifiedhave as a source of uncertainty in the risk assessment. These aspects may potential implications for compliance and international trade, especially for honey.
- At the same time, it is acknowledged that JECFA has established health-based guidance values (HBGVs) and proposed MRLs for fumagillin DCH, and that Codex decisions should continue to rely on sound scientific evaluation while facilitating international trade.

In light of the above considerations, it is recommended to:

- Acknowledge the scientific evaluation conducted by JECFA and the work undertaken by CCRVDF on the proposed MRLs for fumagillin DCH in fish (fillet) and honey.
- Encourage the generation and submission of additional scientific data, particularly on marker residue identification, toxicology, metabolism and residue depletion, to support a more robust risk assessment where necessary, considering the concerns raised by some Members regarding the selection of DCH as a marker residue and the limited availability of supporting data,
- Participate actively in the discussion at CCRVDF28 to ensure that the final decision appropriately balances consumer protection, scientific robustness and the potential trade implications for honey and fish products.

Agenda item 7.1

EXTRAPOLATION OF MAXIMUM RESIDUE LIMITS OF VETERINARY DRUGS IN FOODS TO ONE OR MORE SPECIES EXTRAPOLATION OF MRLs FOR CAMELIDS IN VARIOUS TISSUES: Albendazole, Ivermectin, and Oxytetracycline (At Step 4)

Background : Agenda Item 6

- The 27th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF27, 2024) established the Electronic Working Group (EWG) on Extrapolation to consider Codex Members' requests relating to the extrapolation of MRLs for veterinary drugs.
- There were two streams of work included in the Terms of Reference (ToR). The first workstream was to establish criteria to enable the extrapolation of established maximum residue limits (MRLs) to 'other edible offals'. The second workstream was to consider Codex Members' requests for extrapolation of established MRLs to additional species, in line with established criteria, which had been added to Part V of the Priority List.

The purpose of this document to providing comments on the proposed extrapolated MRLs and the following recommendations of the EWG

RECOMMENDATION 1: Extrapolating MRLs for albendazole to camelids. Extrapolation of the MRLs established for albendazole in the edible tissues and milk of cattle and sheep to camelids is not supported

RECOMMENDATION 2: Extrapolating MRLs for ivermectin to camelids is not supported.

RECOMMENDATION 3: Extrapolating MRLs for oxytetracycline to camelids is supported.

Proposed MRLs*:	Muscle	200 µg/kg
	Liver	600 µg/kg
	Kidney	1200 µg/kg
	Milk	100 µg/kg

Analysis : Technical issue under consideration

THE CRITERIA ESTABLISHED BY CCRVDF27 FOR EXTRAPOLATION TO CAMELIDS.

For camelids, extrapolation of MRLs 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.

• 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:

• identical MRLs have been established in at least one ruminant species and one non-ruminant mammalian species based on the recommendations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the M:T ratio used by JECFA was 1 in all tissues for the ruminant and nonruminant species, OR

• 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. The determination of whether the requested substances meet the criteria is in Appendix I.

Analysis : Technical issue under consideration

Albendazole: There is agreement amongst the EWG respondents that the proposed extrapolation of established albendazole MRLs to camelids does not meet the criteria established by CCRVDF. Therefore, extrapolation of albendazole to camelids is not recommended by the EWG

Ivermectin: There is agreement amongst the EWG respondents that the proposed extrapolation of established ivermectin MRLs to camelids does not meet the criteria established by CCRVDF. Therefore, extrapolation of ivermectin to camelids is not recommended by the EWG.

Oxytetracycline: For oxytetracycline, there was consensus amongst the respondents that this substance does meet the criteria and so can be extrapolated to camelids (tissues and milk), based upon the criteria established by CCRVDF. This is the report for the second workstream

Since the same criteria are also met for both **tetracycline and chlortetracycline** (and the marker residue is the sum of all three compounds), it is additionally recommended that the MRLs established for tetracycline and chlortetracycline are extrapolated to camelids (edible tissues and milk).

Recommendations

- The Committee may wish to support the advancement of the proposed MRLs for **oxytetracycline, tetracycline and chlortetracycline** through the Codex step procedure with a view to final adoption by the Codex Alimentarius Commission at Step 5/8.

- The Committee may also wish to note that the current extrapolation criteria established by CCRVDF do not allow the generation of MRLs for certain large or complex compounds, such as ivermectin and albendazole, despite their widespread use in camelids and their importance for animal health management in many countries of the Near East region.

- In this context, we may wish to support the inclusion of relevant veterinary drugs for camel species, particularly ivermectin and albendazole, in the CCRVDF priority list for JECFA evaluation, while encouraging the generation and submission of residue depletion and distribution data necessary to enable the establishment of Codex MRLs for camelid tissues.

- Strengthening regional collaboration and data generation efforts would also be important to support the work of JECFA and CCRVDF, particularly for veterinary drugs of significance to camel production systems in the Near East region.

Agenda item 8.2

ACTION LEVELS FOR RESIDUES OF NICARBAZIN AND LASALOCID IN CHICKEN EGGS DUE TO UNAVOIDABLE AND UNINTENTIONAL CARRYOVER IN FEED(For comments at Step 3)

Background : Agenda Item 8.2

- Codex Members and Observers are invited to provide comments on the action levels for residues of nicarbazin and lasalocid in chicken eggs as proposed in Appendix I to CX/RVDF 26/28/10.
- In providing comments on the proposed action levels, Codex Members and Observers are invited to take into account the data and information considered for the calculation of the action levels as presented in Appendix II to CX/RVDF 26/28/10.

The purpose of this document to providing comments

Table 1: Proposed Action Level for Nicarbazin in Chicken Egg.

Commodity	Proposed Action Level (mg/kg)
Egg	0.35
Marker residue - 4,4'-dinitrocarbanilide (DNC)	

Table 2: Proposed Action Level for Lasalocid in Chicken Egg.

Commodity	Proposed Action Level (mg/kg)
Egg	0.15
Marker residue - Lasalocid A	

Analysis : Technical issue under consideration

- Nicarbazin is a non-ionophoric coccidiostat that is administered in feed to broiler chickens for the prevention and control of coccidiosis caused by *Eimeria* spp. Nicarbazin is an equimolar mixture of 4,4’-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP). DNC is also known as N,N'-bis(4-nitrophenyl)urea and 1,3-Bis(4-nitrophenyl)urea. After oral ingestion, the complex dissociates into two major metabolites, DNC and HDP, with both components undergoing metabolism via different routes and at different rates
- Lasalocid sodium (referred to as lasalocid hereafter) is a monocarboxylic polyether ionophore obtained from fermentation of a strain of *Streptomyces*. It is used to control coccidiosis in chickens for fattening, chickens reared for laying, turkeys, and minor avian species (EFSA, 2017

Analysis : Technical issue under consideration

APPENDIX II for EStablishment of an action level for residues of lasalocid and Nicarbazin in chicken eggs due to unavoidable and unintentional carryover in feed (For information to support comments on the action levels proposed in Appendix I) and it includes :

- Nicarbazin **and Lasalocid presence in eggs due to unavoidable and unintentional lasalocid carry-over in animal feed**
- Risk Analysis Principles Applied by CCRVDF describes how CCRVDF is to derive action levels for residues of veterinary drugs in foods caused by unavoidable and unintentional carryover of veterinary drugs in animal feed.
- These procedures are applied to them in eggs as described :

Step 1. Animal dietary exposure assessment

Step 2. Estimates of anticipated residue levels in food of animal origin

Step 3. Action levels

Step 4. Human dietary exposure assessment

Recommendations

we appreciate the work done in the document and we do not object to the progress of the proposed action levels for residues of nicarbazin and lasalocid in chicken eggs to step 5/8 for adoption due to unavoidable and unintentional carryover in feed, without prejudice to the position that Egypt may take in the future in the Egyptian national legislation and food regulations it issues regarding this substance.

We would also like to note the possibility of calculate action level according to body weight 70 kg not 60 kg.


thank you
merci
gracias
danke
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teşekkür ederim
obrigado
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bedankt
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