CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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CL 2024/65-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 on maximum residue limits for veterinary drugs in foods**

DEADLINE: **30 September 2024**

BACKGROUND

MRLs at Step 4

1. The 98th Meeting of the Joint FAO/WHO Expert Meeting of Food Additives (JECFA98, 2024) was part of a series of similar meetings convened to assess food additives, contaminants, and veterinary drugs, and the 25th JECFA Meeting convened specifically to consider residues of veterinary drugs in food. The tasks before the Committee were to elaborate further principles for evaluating the safety of residues of veterinary drugs in food, to establish acceptable daily intakes (ADIs) and acute reference doses (ARfDs), to recommend maximum residue limits (MRLs) for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs (GVP); to evaluate the safety of residues of certain veterinary drugs; and to respond to specific requests from the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).[1]
2. JECFA98 evaluated the safety of two veterinary drugs, clopidol and fumagillin dicyclohexylamine.
3. JECFA also completed the safety evaluation of imidacloprid started at JECFA94 (2022)[2]. In the absence of complete information at that time to assess the direct impact of imidacloprid on representative human intestinal microbiota, neither a microbiological ARfD (mARfD) nor a microbiological ADI (mADI) could be established. Therefore, JECFA94 could not establish an ARfD or an ADI for imidacloprid, and MRLs could not be recommended at that time. At the present meeting, JECFA completed its assessment by evaluating microbiological data submitted by the sponsor.
4. Although ethoxyquin was initially included on the list of compounds to be reviewed, it was not evaluated, as the sponsor did not submit any data.
5. The meeting report is published in the WHO Technical Report Series (TRS 1055). Toxicological monographs summarizing the data considered by JECFA98 in establishing ADIs will be published in the WHO Food Additives Series No. 89. Residue monographs summarizing the data considered by JECFA98 in recommending MRLs will be published in FAO JECFA Monographs No. 33. The summary report[3] of JECFA98 is available on the FAO and WHO webpages for consultation. The full report[4] of JECFA98 is available on the WHO webpage for consultation.
6. The Annex to this CL presents the recommendations of JECFA98 on MRLs for:
   - Clopidol
   - Fumagillin dicyclohexylamine
   - Imidacloprid

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1 JECFA documents, e.g., reports, monographs, etc., are available on the FAO and WHO websites as follows:
- FAO: https://www.fao.org/food-safety/scientific-advice/jecfa/en/
  https://www.fao.org/food-safety/resources/publications/en/
- WHO website: https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)

2 https://www.fao.org/3/cc2118en/cc2118en.pdf

3 https://openknowledge.fao.org/server/api/core/bitstreams/03c7c879-e048-4452-833a-28ae6a13fb3e/content

4 https://www.who.int/publications/i/item/9789240095533

REQUEST FOR COMMENTS

7. Codex member countries and observer organizations are invited to provide comments on MRLs for comments at Step 3 arising from the JECFA98 Evaluation.

GUIDANCE ON THE PROVISION OF COMMENTS

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

9. Contact Points of Codex members and observers may log in to the OCS and access the document open for comments by selecting “Enter” in the “My reviews” page, which is available after logging in to the system.

10. 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).

11. 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/.

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

ANNEX

MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS IN FOODS[5]
(For comments at Step 3)

CLOPIDOL (coccidiostat)

For information

JECFA evaluation	98 (2024)
Acceptable daily intake	JECFA98 established an ADI for clopidol of 0–0.04 mg/kg bw based on a lowest-observed-adverse-effect level (LOAEL) of 40 mg/kg bw per day for decreased maternal body weight gain and fetal body weight in a developmental toxicity study in rats. An uncertainty factor of 1000 was applied, comprising 100 for interspecies and intraspecies differences, additional factors of 2 to account for using a marginal LOAEL, and 5 for database uncertainty.
Acute reference dose	JECFA98 concluded that, in view of the low acute oral toxicity of clopidol and the absence of developmental toxicity or any other toxicological effects likely to be elicited by a single dose, it was unnecessary to establish an ARfD for clopidol.
Estimated chronic dietary exposure	For clopidol included at 250 mg/kg in feed at 24-hour withdrawal and the most conservative ratio of marker residues to total residues (MR:TR) considered of 0.5, the global estimates of chronic dietary exposure (GECDEs) are: • For adults and the elderly, 32.9 µg/kg bw per day. • For children and adolescents, 33.5 µg/kg bw per day. • For infants and toddlers, 28.6 µg/kg bw per day. (representing 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.

For comments

Recommended MRLs

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

[5] As extracted from the report of JECFA98. See footnotes 1, 2, 3, and 4 in CL 2024/65-RVDF to download the reports.

FUMAGILLIN DICYCLOHEXYLAMINE (DCH) (mycotoxin)

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.

For information

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, it is unnecessary to establish an ARfD. 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).

For comments

Recommended MRLs

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)

For information

JECFA evaluation	94 (2022), 98 (2024)
Acceptable daily intake	0–0.05 mg/kg bw, based on a no-observed-adverse-effect level (NOAEL) of 5.25 mg/kg bw per day for decreased body weight gain in an extended one-generation reproductive toxicity study in rats, with the application of a safety factor of 100 to allow for interspecies and intraspecies differences. (JECFA98).
Acute reference dose	0.09 mg/kg bw based on a benchmark dose lower bound for a 5% response ($BMDL_{05}$) of 9 mg/kg bw for acute neurobehavioural effects in rats and a safety factor of 100 to allow for interspecies and intraspecies differences. (JECFA98)
Estimated chronic dietary exposure	For Atlantic salmon only, the global estimates of chronic dietary exposure (GECDEs) are: • For adults and the elderly, 1.0 µg/kg bw per day. • For children and adolescents, 2.7 µg/kg bw per day. • For infants and toddlers, 0.9 µg/kg bw per day. (representing 2%, 5%, and 2%, respectively, of the upper bound of the ADI of 50 µg/kg bw) For all fin fish, the GECDEs are: • For adults and the elderly, 1.8 µg/kg bw per day. • For children and adolescents, 3.8 µg/kg bw per day. • For infants and toddlers, 1.2 µg/kg bw per day. (representing 4%, 8%, and 2%, respectively, of the upper bound of the ADI of 50 µg/kg bw) The global estimate of acute dietary exposure (GEADE), based on consumption of Atlantic salmon, was 7% of the ARfD for adults and children (6.2 and 6.6 µg/kg bw, respectively); the GEADE for all fin fish was 38% and 26% of the ARfD (34.1 and 23.8 µg/kg bw) for adults and children, respectively. (JECFA98)
Residue definition	The marker residue (MR) for imidacloprid in fin fish is the parent molecule, imidacloprid. (JECFA98)

For comments

Recommended MRLs

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).