

CODEX ALIMENTARIUS COMMISSION



Food and Agriculture
Organization of the
United Nations



World Health
Organization

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CL 2022/71-RVDF
October 2022

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

DEADLINE: 5 January 2023

BACKGROUND

MRL at Step 7

1. The 25th Session of the Codex Committee on Residues of Veterinary Drugs in Foods¹ (CCRVD25) (2021) agreed to advance proposed maximum residue limits (MRLs) for ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) to the 44th Session of the Codex Alimentarius Commission² (CAC44) (2021) for adoption³ at Step 5. CAC44 adopted⁴ the MRLs at Step 5 and advanced them to Step 6 for comments and further consideration by CCRVD26 at Step 7. Annex 1 presents the proposed aforesaid MRLs.
2. In submitting comments on these MRLs, Codex members and observers are invited to consider the discussion held at CCRVD26³ and the recommendations of JECFA94 in relation to ivermectin as indicated in Annex 2 of this circular letter (CL).

MRLs at Step 4

3. The 94th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA94, 2022) considered residues of veterinary drugs in food. JECFA further elaborated principles for evaluating the safety of residues of veterinary drugs in food, established acceptable daily intakes (ADIs) and acute reference doses (ARfDs), and recommended 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). JECFA94 also responded to specific requests from CCRVD. In total, four veterinary drugs were evaluated by JECFA.⁵
4. The report of the meeting is published in the WHO Technical Report Series (TRS 1041). Toxicological monographs summarizing the data considered by JECFA94 in establishing ADIs will be published in WHO Food Additives Series No. 85. Residue monographs summarizing the data that considered by JECFA94 in recommending MRLs will be published in FAO JECFA Monographs No. 28. The summary report⁶ of JECFA94 is available on the FAO and WHO webpages for consultation. The full report⁷ of JECFA94 is available on the WHO webpage for consultation.
5. Annex 2 presents the recommendations of JECFA94 on MRLs for Ivermectin (pigs, sheep and goats) and Nicarbazin (chicken) for comments at Step 3 and consideration by CCRVD26 at Step 4.

REQUEST FOR COMMENTS

6. Codex member countries and observer organizations are invited to provide comments on (i) MRLs for comments at Step 6 (paragraph 2) and (ii) MRLs for comments at Step 3 (paragraph 6) arising from the JECFA94 Evaluation.

¹ CCRVD reports and working documents are available online at:

<http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/en/?committee=CCRVD>

² CAC reports and working documents are available online at:

<http://www.fao.org/fao-who-codexalimentarius/committees/cac/meetings/en/>

³ REP21/RVD25, paras. 51-59, Appendix II.

⁴ REP21/CAC44, para. 62, Appendix IV.

⁵ JECFA documents e.g., reports, monographs, etc., are available on the FAO and WHO websites as follows:

- FAO: <https://www.fao.org/food-safety/resources/publications/en/>
- WHO website: [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa))

⁶ <https://www.fao.org/3/cc0433en/cc0433en.pdf>

[https://www.who.int/publications/m/item/ninety-fourth-meeting-joint-fao-who-expert-committee-of-food-additives-\(jecfa\)](https://www.who.int/publications/m/item/ninety-fourth-meeting-joint-fao-who-expert-committee-of-food-additives-(jecfa))

⁷ <https://www.who.int/publications/i/item/9789240057586>

GUIDANCE ON THE PROVISION OF COMMENTS

7. Comments should be submitted through the Codex Contact Points of Codex members and observers using the OCS.
8. Contact Points of Codex members and observers may login to the OCS and access the document open for comments by selecting “Enter” in the “My reviews” page, available after login to the system.
9. 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 \(FAQs\)](#).
10. 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/>.
11. For questions on the OCS, please contact Codex-OCS@fao.org.

ANNEX 1

MRLs FOR IVERMECTIN⁸
(SHEEP, PIGS AND GOATS – FAT, KIDNEY, LIVER AND MUSCLE)
(For comments at Step 6)

IVERMECTIN (broad-spectrum antiparasitic agent) – See also Annex 2

For information

Acceptable daily intake	The ADI of 0–10 µg/kg bw established by JECFA81 (1) remains unchanged.
Acute reference dose	The ARfD of 0.2 mg/kg bw established by JECFA81 remains unchanged.
Estimated chronic dietary exposure	JECFA established a GECDE for the general population of 0.41 µg/kg bw per day, which represents 4% of the upper bound of the ADI. JECFA established a GECDE for children of 0.59 µg/kg bw per day, which represents 5.9% of the upper bound of the ADI.
Estimated acute dietary exposure	JECFA established a GEADE for the general population of 87 µg/kg bw per day, which represents 43% of the ARfD, from consumption of cattle muscle, and of 1.1 µg/kg bw, which represents 0.6% of the ARfD, from consumption of sheep muscle. JECFA established a GEADE for children of 82 µg/kg bw per day, which represents 41% of the ARfD, from consumption of cattle muscle and of 1.0 µg/kg bw, which represents 0.5% of the ARfD, from consumption of sheep muscle.
Residue definition	The marker residue (MR) in sheep, pigs and goats is Ivermectin B _{1a} (H ₂ B _{1a} , or 22,23-dihydroivermectin B _{1a}).
Maximum residue limits	JECFA established MRLs for sheep, pigs and goats of 20 µg/kg for fat, 15 µg/kg for kidney, 15 µg/kg for liver and 10 µg/kg for muscle.

For comments

Recommended MRLs

Species	Tissue	MRLs (µg/kg) recommended by JECFA88	Step	JECFA
Sheep, pigs and goats	Fat	20	5	88
Sheep, pigs and goats	Kidney	15	5	88
Sheep, pigs and goats	Liver	15	5	88
Sheep, pigs and goats	Muscle	10	5	88

⁸ As extracted from REP21/RVDF25, Appendix IV. See footnote 1 in CL 2022/71-RVDF to download the report.

MRLs FOR VETERINARY DRUGS⁹
(For comments at Step 3)

IVERMECTIN (broad-spectrum antiparasitic agent) (see also Annex 1)

For information

Acceptable daily intake	JECFA established an ADI of 0–10 µg/kg body weight at the eighty-first meeting.
Acute reference dose	JECFA established an ARfD of 200 µg/kg body weight at the eighty-first meeting.
Residue definition	The marker residue in sheep, pigs and goats is ivermectin B _{1a} (H ₂ B _{1a} , or 22,23-dihydroavermectin B _{1a}).
Estimated chronic dietary exposure	<p>The GECDE for adults and the elderly is 0.72 µg/kg bw per day, which represents 7.2% of the upper bound of the ADI of 10 µg/kg bw.</p> <p>The GECDE for children and adolescents is 0.93 µg/kg bw per day, which represents 9.3% of the upper bound of the ADI of 10 µg/kg bw.</p> <p>The GECDE for infants and toddlers is 0.48 µg/kg bw per day, which represents 4.8% of the upper bound of the ADI of 10 µg/kg bw.</p>
Estimated acute dietary exposure	<p>The GEADE for cattle muscle, applicable to children and the general population, is 69 µg/kg bw, which represents 35% of the ARfD of 200 µg/kg bw.</p> <p>The GEADE for sheep muscle, applicable to children and the general population, is 73 µg/kg bw, which represents 37% of the ARfD of 200 µg/kg bw.</p> <p>The GEADE for pig muscle, applicable to children and the general population, is 30 µg/kg bw, which represents 15% of the ARfD of 200 µg/kg bw.</p>

For comments

Recommended maximum residue limits (MRLs)

Species	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Fat (µg/kg)
Pigs	15	30	20	50
Sheep and goats	30	60	20	100

⁹ As extracted from the Summary and Conclusion of JECFA94. See footnotes 5, 6 and 7 in CL 2022/71-RVDF to download the reports.

NICARBAZIN (coccidiostat)For information

Toxicological effects	The NOAEL was 60 mg/kg bw per day (equivalent to 42.5 mg/kg bw per day of DNC) due to prominent liver lobulation, observed in a study of developmental toxicity in the rabbit.
Uncertainty factor	When considering nicarbazin it is DNC that is the toxic component, and its absorption alone or in a mixture with HDP is substantially less (< 5%) than when formed from ingested nicarbazin. As DNC is the residue of concern and there is no nicarbazin in products from treated animals, JECFA concluded that despite limitations in the database, a reduction in the default safety factor of 100 used to account for interspecies and intraspecies variability, would be justified. JECFA was unable to quantify just how much of a reduction would be appropriate, but concluded that 50 could certainly be supported, and would still result in a conservative evaluation.
Toxicological ADI	The tADI for nicarbazin was established at 0–0.9 mg/kg bw (DNC).
Microbiological effects	Nicarbazin and/or its metabolites show no antimicrobial activity towards representative bacteria of the human intestinal microbiota.
Microbiological ADI	JECFA concluded that it was not necessary to establish an mADI for nicarbazin.
Acceptable daily intake	The ADI for nicarbazin was established at 0–0.9mg/kg bw based on toxicological effects.
Acute reference dose	JECFA concluded that it was not necessary to establish an ARfD for nicarbazin.
Residue definition	The marker residue in chickens is DNC.
Estimated dietary exposure	<p>Based on incurred DNC residues in chicken muscle, offal, and skin with fat, at 24 hours withdrawal time and 125 mg/kg feed:</p> <p>The global estimate of chronic dietary exposure (GECDE) for adults and the elderly is 120 µg/kg body weight (bw) per day, which represents 13% of the upper bound of the ADI of 900 µg/kg bw.</p> <p>The GECDE for children and adolescents is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw.</p> <p>The GECDE for infants and toddlers is 210 µg/kg bw per day, which represents 23% of the upper bound of the ADI of 900 µg/kg bw.</p> <p>Based on incurred DNC residues in chicken muscle, offal, and skin with fat, at zero days withdrawal time and 50 mg/kg feed:</p> <p>The GECDE for adults and the elderly is 95 µg/kg bw per day, which represents 11% of the upper bound of the ADI of 900 µg/kg bw.</p> <p>The GECDE for children and adolescents is 120 µg/kg bw per day, which represents 14% of the upper bound of the ADI of 900 µg/kg bw.</p> <p>The GECDE for infants and toddlers is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw.</p>

For comments**Recommended maximum residue limits (MRLs)**

Species	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Skin with fat (µg/kg)
Chicken	4000	15 000	8000	4000