CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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CL 2020/17-RVDF
February 2020

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: **30 November 2020**

COMMENTS:

To:
CCRVDF Secretariat
U.S. Codex Office
Trade and Foreign Agricultural Affairs
US Department of Agriculture
E-mail: CCRVDF-USSEC@usda.gov

Copy to:
Codex Secretariat
Codex Alimentarius Commission
Joint FAO/WHO Food Standards Programme
E-mail: codex@fao.org

BACKGROUND

MRL at Step 7

1. The 24th Session of the Codex Committee on Residues of Veterinary Drugs in Foods[1] (CCRVDF24) (April 2018) agreed to advance a proposal that an MRL is "unnecessary" for flumethrin in honey to the 41st Session of the Codex Alimentarius Commission[2] (CAC41) (July 2018) for adoption at Step 5.[3] CAC41 adopted the MRL at Step 5 and advanced to Step 6 for comments and further consideration by CCRVDF25.[4]

2. Annex 1 presents the draft MRL for flumethrin (honey) for comments at Step 6 and consideration by CCRVDF25 at Step 7.

MRLs at Step 4

3. The 88th Session of the Joint FAO/WHO Expert Committee on Food Additives (JECFA88) (October 2019) was specifically convened to consider residues of veterinary drugs in food namely: to further elaborate principles for evaluating the safety of residues of veterinary drugs in food, establishing acceptable daily intakes (ADIs) and acute reference doses (ARfDs), and recommending 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 CCRVDF24. In total, eight veterinary drugs were evaluated by JECFA.

4. The report of the meeting will be published in the WHO Technical Report Series (TRS 1023)[5]. Toxicological monographs summarizing the data that were considered by JECFA88 in establishing ADIs will be published in WHO Food Additives Series No. 79[5]. Residue monographs summarizing the data that were considered by JECFA88 in recommending MRLs will be published in FAO JECFA Monographs No. 24[6]. The summary report[7] of JECFA88 is available on the FAO JECFA webpage for early consultation.

5. Annex 2 presents the recommendations of JECFA88 on MRLs for Diflubenzuron (salmon - muscle plus skin in natural proportion); Halquinol (in swine - muscle, skin plus fat, liver and kidney); Ivermectin (sheep, pigs and coats – fat, kidney, liver and muscle) for comments at Step 3 and consideration by CCRVDF25 at Step 4.

REQUEST FOR COMMENTS AND INFORMATION

6. Codex member countries and observer organizations are invited to provide comments on (i) MRLs for

[1] CCRVDF reports and working documents are available online at:
http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/en/?committee=CCRVDF
[2] CAC reports and working documents are available online at:
http://www.fao.org/fao-who-codexalimentarius/committees/cac/meetings/en/
[3] REP18/RVDF, paras. 65-73, Appendix IV.
[4] REP18/CAC, Appendix IV.
[5] WHO website: http://www.who.int/foodsafety/publications/jecfa-reports/en/
[6] FAO website: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/
[7] FAO website: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/summary-reports/en/

comments at Step 6 (paragraph 2) and (ii) MRLs for comments at Step 3 (paragraph 5) arising from the JECFA88 Evaluation.

7. Codex members and observers wishing to provide comments on these MRLs should send their proposals **by email**, in word file, to the above addresses and by the **deadline** indicated above.

ANNEX 1

DRAFT MRL FOR FLUMETHRIN (HONEY)[8]
(For comments at Step 6)

FLUMETHRIN (insecticide)

Acceptable Daily Intake (ADI)	0–0.004 mg/kg bw based on the NOAEL of 0.37 mg/kg bw per day for skin lesions in parental animals and reduced survival and body-weight gain in pups in a two-generation toxicity study in rats and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute Reference dose (ARfD)	0.005 mg/kg bw based on the NOAEL of 0.5 mg/kg bw for salivation in dams in a developmental toxicity study in rats and using a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated chronic dietary exposure (GECDE)	0.008 µg/kg bw per day (for the general population), which represents 0.2% of the upper bound of the ADI. 0.006 µg/kg bw per day (for children), which represents 0.2% of the upper bound of the ADI. Note: As flumethrin is also used as pesticide the overall dietary exposure was estimated. The assumptions and detailed results will be displayed in the JECFA85 report. Results below are only for use as veterinary drug.
Estimated Acute Dietary Exposure (GEADE)	0.1 µg/kg bw per day (for the general population), which represents 2.2% of the ARfD. 0.1 µg/kg bw per day (for children), which represents 2.2% of the ARfD.
Residue Definition	Flumethrin (trans-Z1 and trans Z2 diastereomers at a ratio of approximately 60:40).

Species	Tissue	MRLs (µg/kg)	Note	Step	JECFA
	Honey	Unnecessary	Residues resulting from the use of this substances as an insecticide in accordance with good practice for veterinary drug are unlikely to pose a hazard to human health.	6	85

[8] As extracted from REP18/RVDF, Appendix IV. See footnote 1 to download the report.

PROPOSED DRAFT MRLs FOR VETERINARY DRUGS[9]
(For comments at Step 3)

DIFLUBENZURON (insecticide)

Acceptable daily intake (ADI)	JECFA established an acceptable daily intake (ADI) of 0–0.02 mg/kg body weight (bw) – based on a no-observed-adverse-effect level (NOAEL) of 2 mg/kg bw per day for increased methaemoglobin and sulfhaemoglobin levels in a 2-year study of toxicity and carcinogenicity in rats; and increased methaemoglobin and sulfhaemoglobin levels, platelet counts and hepatic pigmentation in a 1-year study of toxicity in dogs – applying a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose (ARfD)	JECFA reiterated the conclusion of the 81st meeting *(1)* that it was not necessary to establish an acute reference dose (ARfD), in view of the low acute oral toxicity and the absence of developmental toxicity, and any other toxicological effects likely to be elicited by a single dose.
Estimated chronic dietary exposure (GECDE)	The GECDE for the general population is 0.84 µg/kg bw per day, which represents 4% of the upper bound of the ADI. The GECDE for children is 2.85 µg/kg bw per day, which represents 14% of the upper bound of the ADI.
Estimated acute dietary exposure (GEADE)	The acute dietary exposure was not estimated because JECFA concluded that it was not necessary to establish an ARfD.
Residue definition	JECFA reconfirmed diflubenzuron as the marker residue (MR) and the ratio of the MR to the total radioactive residue (TRR) of 0.9 established at its 81st meeting.
Maximum residue limits (MRLs)	JECFA recommended an MRL in salmon of 10 µg/kg in muscle plus skin in natural proportions.

Recommended MRL

Species	Tissue	MRLs (µg/kg) recommended by JECFA88	Step	JECFA
Salmon	Muscle plus skin in natural proportions	10	3	88

[9] As extracted from the Summary and Conclusion of JECFA88
http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/summary-reports/en/

HALQUINOL (broad-spectrum antimicrobial)

Acceptable daily intake (ADI)	JECFA established an ADI of 0–0.2 mg/kg bw, based on histopathological changes in the kidney, accompanied by increases in absolute and relative renal weight in a 1-year chronic toxicity study in rats, applying a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose (ARfD)	JECFA established an ARfD of 0.3 mg/kg bw, based on a NOAEL of 30 mg/kg bw for clinical signs in dams observed in a developmental toxicity study in mice, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated chronic dietary exposure (GECDE)	The GECDE for the general population is 5.9 µg/kg bw per day, which represents 3% of the upper bound of the ADI. The GECDE for children is 6.9 µg/kg bw per day, which represents 3.4% of the upper bound of the ADI.
Estimated acute dietary exposure (GEADE)	The GEADE was comparable for children and adults, being 2–224 µg/kg bw per day, which represents 0.5–75% of the ARfD.
Residue definition	The marker residue (MR) is the sum of 5-chloroquinolin-8-ol (5-CL), 5,7-dichloroquinolin-8-ol 5,7-DCL (5,7-DCL) and their glucuronide metabolites: 5-CLG (expressed as 5-CL equivalents) and 5,7-DCLG (expressed as 5,7-DCL equivalents).
Maximum residue limits (MRLs)	JECFA recommended MRLs in swine of 40 µg/kg for muscle, 350 µg/kg for skin plus fat, 500 µg/kg for liver and 9000 µg/kg for kidney.

Recommended MRLs

Species	Tissue	MRLs (µg/kg) recommended by JECFA88	Step	JECFA
Swine	Muscle	40	3	88
Swine	Skin plus fat	350	3	88
Swine	Liver	500	3	88
Swine	Kidney	9000	3	88

IVERMECTIN (broad-spectrum antiparasitic agent)

Acceptable daily intake (ADI)	The ADI of 0–10 µg/kg bw established by JECFA81 *(1)* remains unchanged.
Acute reference dose (ARfD)	The ARfD of 0.2 mg/kg bw established by JECFA81 remains unchanged.
Estimated chronic dietary exposure (GECDE)	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 (GEADE)	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_2B_{1a}, or 22,23-dihydroavermectin B_{1a}).
Maximum residue limits (MRLs)	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.

Recommended MRLs

Species	Tissue	MRLs (µg/kg) recommended by JECFA88	Step	JECFA
Sheep, pigs and goats	Fat	20	3	88
Sheep, pigs and goats	Kidney	15	3	88
Sheep, pigs and goats	Liver	15	3	88
Sheep, pigs and goats	Muscle	10	3	88