CODEX ALIMENTARIUS COMMISSION

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Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6.2 **CX/RVDF 16/23/6**

April 2016

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-third Session

Houston, Texas, United States of America, 17 – 21 October 2016

PROPOSED DRAFT MRLS FOR IVERMECTIN (CATTLE FAT, KIDNEY, LIVER, MUSCLE), TEFLUBENZURON (SALMON FILLET, MUSCLE) AND ZILPATEROL HYDROCHLORIDE (CATTLE KIDNEY, LIVER, MUSCLE)

At Step 3

Governments and international organizations wishing to submit comments at Step 3 on the proposed draft Maximum Residues Limits for Veterinary Drugs arising from the 78th JECFA Meeting (see Annex 1) are invited to do so **no later than 1 September 2016** as follows: U.S. Codex Office, Food safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA (E-mail: CCRVDF-USSEC@fsis.usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (E-mail: Codex@fao.org).

BACKGROUND

1. The 81st Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was convened in Rome, Italy, from 17 to 26 November 2015 to evaluate residues of certain veterinary drugs in foods. The full report of the meeting is published in the WHO Technical Report Series (TRS 991)[1]. Toxicological monographs summarising the data that were considered by the Committee are published in *WHO Food Additives Series No.72*[2]; residue monographs summarising the data that were considered by the Committee are published in *FAO JECFA Monographs No. 18*[3].

2. Annex 1 to this document presents the recommendations of the 81st JECFA Meeting on numerical Maximum Residues Limits (MRLs) for the veterinary drugs: ivermectin, teflubenzuron and zilpaterol hydrochloride. Recommendations on other veterinary drugs i.e. diflubenzuron and sisapronil for which the 81st JECFA has not recommended MRLs as well as other considerations are provided in the document CX/RVDF 16/23/3 (Matters of Interest arising from FAO/WHO and from the 81st Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3. CCRVDF22 agreed to hold the proposed draft MRLs for ivermectin (cattle muscle) at Step 7[4], for consideration at its next session in the light of the 81st JECFA recommendations, which are presented in Annex 1 (Ref. REP15/RVDF paras 76-78 and Appendix V).

4. In view of the need to address the concerns of the European Union and Canada, CCRVDF22 also agreed to hold the proposed draft MRLs for lasalocid sodium (chicken, turkey, quail and pheasant tissues) at Step 4, for consideration at its next session in the light of the 81st JECFA recommendations (Ref. REP15/RVDF paras 79-84 and Appendix V). These MRLs and JECFA recommendations will be considered under Agenda Item 6.1.

[1] http://apps.who.int/iris/bitstream/10665/204670/1/9789240695504_eng.pdf?ua=1
[2] to be published on WHO website
[3] to be published on FAO website
[4] This MRL is presented in shaded font in Annex 1.

Annex 1

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS (MRLS) FOR VETERINARY DRUGS

(AT STEP 3)

IVERMECTIN (antiparasitic agent)

Acceptable Daily Intake (ADI): 0-10 µg/kg body weight on the basis of a no-observed-adverse-effect level (NOAEL) of 0.5 mg/kg body weight per day for neurological effects (mydriasis) and retardation of weight gain in a 14-week dog study, with application of an uncertainty factor of 50 (5 for interspecies differences based on pharmacokinetic studies in dogs and humans and 10 for intraspecies differences). The previous ADI of 0-1 µg/kg body weight was withdrawn. (81st JECFA, 2015)

Acute Reference dose (ARfD): 0.2 mg/kg body weight, based on a NOAEL of 1.5 mg/kg body weight, the highest dose tested in a safety, tolerability and pharmacokinetics study in healthy human subjects, with application of an uncertainty factor of 10 for intraspecies variability. (81st JECFA, 2015)

Estimated chronic dietary exposure (GECDE): The estimated daily intake (EDI) is 38 µg/person per day, based on a 60 kg individual, which represents 6% of the upper bound of the ADI.
The global estimate of chronic dietary exposure (GECDE) for the general population is 0.9 µg/kg body weight per day, which represents 9% of the upper bound of the ADI.
The GECDE for children is 1.5 µg/kg body weight per day, which represents 15% of the upper bound of the ADI.
The GECDE for infants is 1.3 µg/kg body weight per day, which represents 13% of the upper bound of the ADI. (81st JECFA, 2015)

Estimated Acute Dietary Exposure (GEADE): A combined analysis of all studies submitted showed that after 14 days, the maximum values of residues found at injection sites led to a Global Estimate of Acute Dose Exposure (GEADE) of 52 µg/kg bw for the general population and 87 µg/kg bw for children, corresponding, respectively, to 27% and 43% of the ARfD. (81st JECFA, 2015)

Residue Definition: Ivermectin B_{1a}.

Species	Tissue	MRLs(µg/kg) recommended by the 78th JECFA	Step	JECFA	MRLs (µg/kg) recommended by the 81st JECFA	Step	JECFA
Cattle	Fat				400	3	81
Cattle	Kidney				100	3	81
Cattle	Liver				800	3	81
Cattle	Muscle	4	7	78	30	3	81

In shaded font are the MRLs held at Step 4 by CCRVDF22.

TEFLUBENZURON (insectide)

Acceptable Daily Intake (ADI): 0-5 µg/kg body weight on the basis of a lower 95% confidence limit on the benchmark dose for a 10% response (BMDL10) of 0.54 mg/kg body weight per day for hepatocellular hypertrophy in male mice observed in a carcinogenicity study, with application of an uncertainty factor of 100 to account for interspecies and intraspecies variability. (81st JECFA, 2015)

Estimated chronic dietary exposure (GECDE): The EDI is 42.9 µg/person per day, on the basis of a 60 kg individual, which represents approximately 14% of the upper bound of the ADI.
The GECDE for the general population is 1.6 µg/kg body weight per day, which represents 31% of the upper bound of the ADI.
The GECDE for children is 2.1 µg/kg body weight per day, which represents 43% of the upper bound of the ADI.
The GECDE for infants is 0.9 µg/kg body weight per day, which represents 18% of the upper bound of the ADI. (81st JECFA, 2015)

Residue Definition: Teflubenzuron.

Species	Tissue	MRLs (µg/kg) recommended by the 81st JECFA	Step	JECFA
Salmon	Fillet[a]	400	3	81
Salmon	Muscle	400	3	81

[a] Muscle plus skin in natural proportion.

ZILPATEROL HYDROCHLORIDE (β2-adrenoceptor agonist)

Acceptable Daily Intake (ADI): 0-0.04 µg/kg body weight established at the seventy-eighth meeting (WHO TRS No. 988, 2014) and reaffirmed at the eighty-first meeting. (81st JECFA, 2015)

Acute Reference Dose (ARfD): 0.04 µg/kg body weight based on a lowest-observed-adverse-effect level (LOAEL) of 0.76 µg/kg body weight for acute pharmacological effects observed in a single-dose human study, with application of an uncertainty factor of 20, comprising a default uncertainty factor of 10 for human individual variability and an additional uncertainty factor of 2 to account for use of a LOAEL for a slight effect instead of a NOAEL. (81st JECFA, 2015)

Estimated Acute Dietary Exposure (GEADE): 1.9 µg/day for the general population, which represents approximately 80% of the ARfD.
The GEADE is 0.57 µg/day for children, which represents approximately 94% of the ARfD. (81st JECFA, 2015)

Residue Definition: Zilpaterol (free base) in muscle, liver and kidney.

Species	Tissue	MRLs (µg/kg) recommended by the 81st JECFA	Step	JECFA
Cattle	Kidney	3.3	3	81
Cattle	Liver	3.5	3	81
Cattle	Muscle	0.5	3	81