APPENDIX II

MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS IN FOODS

FLUMETHRIN (HONEY)

(For adoption at Step 8)

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).

Recommended MRL

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.	**8**	85

DIFLUBENZURON
(SALMON - MUSCLE PLUS SKIN IN NATURAL PROPORTION)
(For adoption at Step 5/8)

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	**5/8**	88

HALQUINOL
(SWINE - MUSCLE, SKIN PLUS FAT, LIVER AND KIDNEY)
(For adoption at Step 5/8)

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	**5/8**	88
Swine	Skin plus fat	350	**5/8**	88
Swine	Liver	500	**5/8**	88
Swine	Kidney	9000	**5/8**	88

IVERMECTIN
(SHEEP, PIGS AND GOATS – FAT, KIDNEY, LIVER AND MUSCLE)
(For adoption at Step 5)

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	**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

ZILPATEROL HYDROCHLORIDE
(CATTLE FAT, KIDNEY, LIVER, MUSCLE)
(At Step 4)
(for advice by CCEXEC and CAC
REP21/RVDF, paragraph XX)

ZILPATEROL HYDROCHLORIDE (β2-adrenoceptor agonist)

Acceptable daily intake (ADI)	ADI is 0-0.04 µg/kg body weight established at JECFA78 (WHO TRS No. 988, 2014) and reaffirmed at JECFA81 (2015) and JECFA85 (2017).
Acute reference dose (ARfD)	ARfD is 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 (JECFA81).
Estimated acute dietary exposure (GEADE)	GEADE is 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 (JECFA81).
Residue Definition	Zilpaterol (free base) in muscle, liver and kidney.

Recommended MRLs

Species	**Tissue**	**MRLs (µg/kg)**	**Step**	**JECFA**
Cattle	Kidney	3.3	**4**	81, 85
Cattle	Liver	3.5	**4**	81, 85
Cattle	Muscle	0.5	**4**	81, 85

APPENDIX III

AMENDMENT TO PROCEDURAL MANUAL:
RISK ANALYSIS PRINCIPLES APPLIED BY THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
(For adoption)

Part A

ANNEX C : APPROACH FOR THE EXTRAPOLATION OF MAXIMUM RESIDUE LIMITS OF VETERINARY DRUGS TO ONE OR MORE SPECIES

General criteria for extrapolation:

1. Extrapolation should take place only between the same tissues/food commodities in the reference and concerned species (e.g. muscle to muscle, fat to fat etc.).

2. Extrapolation of reference species MRLs to a concerned species on a one to one basis should be considered only if **all** of the following are satisfied:

   (i) the reference and concerned species are related (see "A note on terminology" below),
   (ii) the marker residue in the reference species is the parent compound only, or is the same as the total residues of toxicological concern, or the Codex MRL status in the reference species is 'unnecessary' and there is an expectation that the active substance will be used under the same conditions (i.e. by the same administration routes and at similar doses) in both species.
   (iii) the M:T[1] (the marker 'M' to total residues of toxicological concern 'T') established for the reference species can be applied to the concerned species.

Specific criteria for extrapolation

3. In order to ensure that the third of the above-mentioned three general criteria is satisfied, the following specific criteria are proposed.

   (i) Where identical Codex MRLs have been established in at least two related species on the basis of JECFA recommendations **or there is good reason to consider extrapolation from just one related species**, these Codex MRLs can be extrapolated to other related species (e.g. extrapolate from cattle and sheep to all ruminants).

   Explanatory note: *The existence of identical MRLs in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species.*

   (ii) Where identical M:T values have been used in JECFA calculations for two related species but the MRLs recommended (by JECFA) differ, the most conservative set of Codex MRLs (i.e. the MRLs from the species associated with the lowest consumer exposure estimate) can be extrapolated to other related species (e.g. where different MRL values have been established for cattle and sheep and extrapolation is considered to goats, the lowest set of MRLs should be used for extrapolation).

   Explanatory note: *The fact that JECFA considered it appropriate to use identical M:T values in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species.*

   (iii) Where the M:T established by JECFA is 1 ~~**or approaching 1**~~ in all tissues in a single reference species, the same Codex MRLs can be extrapolated to related species.

   Explanatory note: *The fact that the M:T is 1 in all tissues/food commodities indicates that the marker residue includes all the compounds of concern.*~~*substance is not metabolised to any significant degree.*~~ *It is considered reasonable to assume that this would also be the case in the concerned species.*

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[1] EHC 240 (1) defines the marker residue as: The parent drug, or any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels. Where 'total residues of toxicological concern' are not defined, 'total residue' may be used where 'Total residue' is defined CAC/MISC 5-1993 (2): the total residue of a drug in animal derived food consists of the parent drug together with all the metabolites and drug based products in the food after administration of the drug to food producing animals. The amount of total residues is generally determined by means of a study using the radiolabelled drug, and is expressed as the parent drug equivalent in mg/kg of the food'.

Finally, while the above criteria can be used in all cases, the following additional criteria are proposed for fish, milk and eggs (i.e. extrapolation for fish, milk and eggs may be based on the above criteria OR based on the additional criteria below):

(iv) For fish, where the MRL in muscle/fillet recommended by JECFA was established based on the LoQ (e.g., twice the LoQ), the Codex MRL can be extrapolated to all bony fish.

Explanatory note: *The fact that the MRL in muscle/fillet is below the LoQ indicates that residues in muscle/fillet are not measurable and so do not make a significant contribution to the intake calculation. Even if there are differences in metabolism between fish species, the possibility that they will be so dramatic as to result in a level of residues in muscle/fillet sufficiently high to significantly impact on overall consumer exposure is considered unrealistic.*

(v) For milk and eggs, where the M:T established by JECFA is 1 (in milk or eggs of a reference species), the milk/egg Codex MRL of the reference species can be extrapolated to milk of other ruminants and eggs of other domesticated poultry species, respectively, even if the M:T is not 1 in tissues.

Explanatory note: *For milk and eggs, there may be a concern that the fat content differs between related species. However, if the M:T is 1 in the reference species this indicates that the M:T is not significantly influenced by the fat content.*

A note on terminology

- 'Reference species' is used to refer to a species in which Codex MRLs have been established based on a scientific evaluation by JECFA
- 'Concerned species' is used to refer to a species for which extrapolation is being considered
- 'Related species' means species belonging to the same category of food producing species of ruminant and non-ruminant mammals*, birds or **fin** fish** ~~**(Osteichthyes)**~~
- 'Unrelated species' is used to refer to species belonging to different categories of food producing species

* The category of non-ruminant food producing mammals is considered to include pigs, horses and rabbits

** Three distinct classes of fish are usually identified: (i) jawless fish (Agnatha), (ii) cartilaginous fish (Chondrichytes) and (iii) ~~**bony**~~ **fin**fish ~~**(Osteichthyes)**~~. To date, MRL data have been provided only for ~~**bony**~~ **fin**fish, and it is these that are predominantly farmed and eaten. Consequently, it is proposed that MRL extrapolations in fish should be limited to this class.

***** Special attention should be paid to harmonizing the terminology used for the edible tissues.**

Reporting extrapolated MRLs

4. Where CCRVDF agrees to extrapolate MRLs, it should be clear that these MRLs were established by extrapolation rather than on the basis of a substance/species specific JECFA assessment. An appropriate symbol should be included next the relevant values reported in the MRL database. Moreover, extrapolated MRLs should be reconsidered in case the reference MRLs are modified or new data/information on the active substance in question becomes available.

Part B

Amendment to paragraph 30 of the *Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Food*

(Consequential amendment for adoption)

(Amendments are shown in **bold/underlined** font).

A footnote in paragraph 30 of the Risk Analysis Principles – 2nd bullet point: **Approach for the extrapolation of MRLs of veterinary drugs to one or more species is presented in Annex C to these principles**

APPENDIX IV

AMENDMENT TO THE *GLOSSARY OF TERMS AND DEFINITIONS*
***(RESIDUES OF VETERINARY DRUGS IN FOODS*)**
(CXA 5 -1993)
(For adoption)

Edible offal : Those parts of an animal, apart from the skeletal muscle and attached skin, that are considered fit for human consumption

APPENDIX V

PRINCIPLES AND APPROACH TO THE PARALLEL REVIEW OF A NEW VETERINARY DRUG BY JECFA AND REGULATORY AGENCIES[1]

(For information and use by CCRVDF)

Principles

The following principles, as is the case during any scientific review by JECFA, should be observed:

1. **Transparency**. Nominating member country and drug sponsor should identify if a veterinary drug is intended for a parallel process and be open about dossier submission timeframes.
2. **Confidentiality**. Much of the data submitted to JECFA or national regulator(s) is confidential and there is a good precedent to respect the confidentiality of the data.
3. **Independence**. The national authorization process and JECFA process are two separate independent processes and subject to their own independent decisions and therefore are not contingent on one another.

Process

The proposed phases of the process are:

Phase 1: Identification of a candidate

A product is identified by a drug sponsor and during bilateral discussions with a member country(ies), the product is identified as a candidate. The current Priority List nomination requirements of a veterinary drug would also apply to a JECFA parallel review process. The Risk Analysis Principles Applied by the CCRVDF lists criteria required for a veterinary drug to appear on the Priority List. A proposed veterinary drug shall meet some or all of the following criteria:

- "A Member has proposed the compound for evaluation (a template for information recommended for consideration in the priority list by Codex Committee on Residues of Veterinary Drugs in Foods has been completed and be available to the Committee);
- "A Member has established good veterinary practices with regard to the compound;
- "The compound has the potential to cause public health and/or international trade problems;
- "The compound is available as a commercial product; and
- "There is a commitment that a dossier will be made available."

Phase 2: Submission

A product is submitted (or is expected to be submitted) to a national regulatory authority, most likely in one of the larger markets (in practice, most veterinary products are first submitted for review in the U.S. or in Europe). At the following CCRVDF meeting, the product would be submitted (by the Codex Member who received the product application or is expected to receive the application by a certain date) for inclusion on the priority list at CCRVDF (Step 1).

Phase 3: Assessment

JECFA and the national assessor follow their normal processes of assessing the product. (Step 2).

Phase 4: Consideration by CCRVDF

Draft ADI and MRLs proposed by JECFA and circulated for comment (Step 3).

The remainder of the uniform procedures for the elaboration of Codex standards and related texts would be followed, consistent with the current process.

[1] The discussion paper on the parallel review of a new veterinary drug by JECFA and regulatory agencies can be downloaded from the Codex website (CX/RVDF 21/25/10): http://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=25

APPENDIX VI

PRIORITY LIST OF VETERINARY DRUGS
(Parts I and V for approval by CAC44, Part II for action by CCRVDF26 and Part III and IV for follow-up by JECFA)

Name of Compound	Question(s) to be answered	Registration status	Proposed by	Comments	When will data package be available
PART I: Veterinary drugs for inclusion in the Priority List for JECFA evaluation / re-evaluation					
Imidacloprid	Request for MRL for fin fish in muscle and skin in natural proportions.	Nominator notes that relevant MRLs are established in the EU.	Norway	ADI set by JMPR at 0-0.06 mg/kg bw (2001), ARfD 0.4 mg/kg bw (2002).	Residue and toxicological data available July 2021.
Ivermectin	Request for re-evaluation of MRLs for sheep, goat ad pig tissues.	MRLs are established in many countries.	EU	ADI set by JECFA at 0-10 µg/kg bw (2015), ARfD 0.2 mg/kg bw (2015).	Residue data on sheep are available.
Nicarbazin	Request re-evaluation of MRLs for chicken tissues	Nominator notes that relevant MRLs are established in many countries.	Argentina/Malaysia	ADI set by JECFA at 0-0.4 mg/kg bw (1998).	Residue data available July 2021.

Part II. Veterinary drugs for which data availability should be confirmed at the next CCRVDF				
Name of Compound	**Question(s) to be answered**	**Proposed by**	**Comments**	**When will data package be available**
Amoxicillin	Request for MRLs for chicken tissues.	Chile	ADI set by JECFA at 0-0.07 µg/kg bw (2011), ARfD 0.005 mg/kg bw (2017). Classified by WHO as a CIA and by the OIE as VCIA.	Residue data expected available July 2024.
Ethoxyquin (feed additive use)	Request to establish MRL in shrimp muscle.	Philippines/India	Carried over from CCRVDF21 (2013). ADI 0-0.005 mg/kg bw (2005 JMPR). The ADI and the ARfD are applicable to ethoxyquin and its metabolites/degradation products methylethoxyquin (MEQ), dihydroethoxyquin (DHEQ), dehydrimethylethoxyquin (DHMEQ) ARfD 0.5 mg/kg bw (2005 JMPR).	India advised data are being generated.
Norfloxacin	Request to establish MRLs for cattle, camelids, equines, goats, poultry, sheep and swine tissues.	Peru	Norfloxacin is classified by WHO as a CIA and by the OIE as a veterinary CIA.	Peru to advise at next CRVDF if data are available.

Part III. Veterinary drugs for which additional data / information is necessary to complete the JECFA evaluation				
Name of Compound	**Information required by JECFA**		**Comments**	**When will data package be available**
Ethion	Additional data/scientific argument to enable MR and MR:TRR to be determined, analytical method.	Argentina (Costa Rica, Uruguay)	From JECFA85, ADI 0-0.002 mg/kg bw, ARfD 0.02 mg/kg bw for general population and 0.002 mg/kg bw for women of child-bearing age.	Metabolism studies to identify compounds of concern, validation of an analytical method and a radiolabel study to enable MR and MR:TRR to be determined are expected to be completed in 2024.
Flumethrin	Additional data/scientific argument to enable MR and MR:TRR to be determined, residue depletion data, identity of metabolite in milk and toxicological profile.	EU	ADI set by JECFA at 0-0.004 mg/kg bw (2017), ARfD 0.005 mg/kg bw (2017).	Additional data not expected to be available for 3-4 years.
Fosfomycin	Additional data/scientific argument to enable a mADI to be set, additional data/scientific argument to enable MR and MR:TRR to be determined, analytical method.	Argentina/Paraguay		

Part IV. Parallel review – Evaluation of a new compound				
Name of Compound	**Information required by JECFA**		**Comments**	**When will data package be available**
Selamectin	Additional data/scientific argument to enable MR and MR:TRR to be determined, analytical method, information on GVP, stability of radiolabel in tissues.	Canada/US	Sponsor intends to submit: •Characterization of the residues in tissues in order to establish an MR:TRR. •An MR depletion study under conditions of use, conducted in a laboratory. •Information on an analytical method suitable for monitoring purposes. •Information on the proposed withdrawal period. •Confirmation of the stability of the radiolabel in tissues. •Revised chronic toxicology study report (rat).	Available.
Part V Compounds for which CCRDVF will consider extrapolation of Codex MRLs to additional species				
Name of compound	**Extrapolation**			
~~Amoxicillin~~	~~Ruminants~~			
~~Benzyl penicillin~~	~~Ruminants~~			
~~Tetracyclines~~	~~Ruminants~~			
~~Cyhalothrin~~	~~Ruminants~~			
~~Cypermethrin~~	~~Ruminants~~			
~~Deltamethrin~~	~~Ruminants~~			
~~Moxidectin~~	~~Ruminants~~			
~~Spectinomycin~~	~~Ruminants~~			
~~Levamisole~~	~~Ruminants~~			
~~Tilmicosin~~	~~Ruminants~~			
~~Deltamethrin~~	~~Fish~~			
~~Flumequine~~	~~Fish~~			
~~Teflubenzuron~~	~~Fish~~			
Ivermectin	**Goat and sheep milk**			