CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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Agenda Item 8(a) **RVDF/22 CRD/31**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-second Session

San José, Costa Rica, 27 April – 1 May 2015

REPORT OF IN-SESSION WORKING GROUP ON DRAFT PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION BY JECFA

I. Introduction

The in-session working group (WG) was held on May 28, 2015 and chaired by Dr. Jason Lutze (Australia). Dr. Vittorio Fattori (FAO/JECFA Secretariat) and Dr. Angelika Tritscher (WHO/JECFA Secretariat) served as rapporteur. The Chair reminded the WG on the prioritization criteria, and the JECFA Secretariat emphasized the need for respecting the commitment to submit data in time.

II. Current Priority List

1. Amoxicillin: in reference to CRD 28 further clarification was requested on actual data availability. Korea has committed to provide method, residue, pharmacokinetic and monitoring data. The working group decided to recommend that amoxicillin be placed on the priority list.

2. Ampicillin: MRLs are requested only in fish. There is no current ADI established by JECFA. It was determined that data currently are lacking to establish ADI. It was therefore decided to include ampicillin in the priority list to confirm the availability of data at the 23rd Session of the CCRVDFR.

The WHO representative reminded the WG that amoxicillin and ampicillin are classified as critically important for human medicine and for veterinary medicine and therefore prudent use is recommended. While there may be a clear need for MRLs since there are approved uses, the Committee may want to consider reinforcing the prudent use of these antimicrobials.

3. Diflubenzuron: An ADI has been established by JMPR; pharmacokinetic, metabolism, residue depletion and method data are available. A delegation commented that the focus should perhaps be on fish groups rather than on all finfish as metabolism may differ across species. The working group recommend diflubenzuron for inclusion on the priority list.

4. Ivermectin: JECFA has previously established an ADI. The data available are for a review of the ADI and the MRLs for all edible tissues of cattle and include a depletion study with a new formulation. The JECFA Secretariat indicated that the original depletion studies with the original product would be potentially useful. The working group recommended that ivermectin be placed on the priority list.

5. Lufenuron: The request is for an MRL for fish. The sponsor confirmed that a complete data package will be available for June, 2016. Lufenuron is also on the JMPR agenda for toxicological evaluation in 2015. Several delegations noted the importance of this substance. The working group recommended that lufenuron should be included on the priority list.

6. Nitarsone: The JECFA Secretariat reminded the working group that the JECFA PTWI for inorganic arsenic had been withdrawn in 2011 because of health concerns. There is no industry sponsor and no source of data has been identified by the member state which nominated nitarsone. The working group decided that due to these considerations the nomination of nitarsone should not be supported and recommended that it should be removed from the priority list.

7. Teflubenzuron: the request is for MRLs for fish (salmon). An ADI was established by JMPR in 1994 but it was noted that an updated toxicological review may be required. Information (both toxicological and residue data) is available. It was confirmed that residue data will be provided for salmon. The working group decided to recommend that teflubenzuron should be included on the priority list.

8. Previously listed compounds: It was confirmed that JECFA has received a data package for the evaluation of Sisapronil. No data are currently available for Ethoxyquin, but the working group considered

that it should be retained on the priority list until the 23rd Session of CCRVDF, at which time the availability of data should be confirmed or Ethoxyquin should be then removed from the priority list.

9. Notifications for future nominations: It was noted that there were 3 substances identified by an eWG in 2012 – bacitracin, florfenicol, enrofloxacin. There may be a future request for the evaluation of florfenicol for the establishment of MRLs for swine tissues. It was noted that such a request should be made in response to the circular letter issued prior to the 23rd Session of CCRVDF.

III. General considerations for JECFA referred by the plenary to the WG

The working group discussed the issue of extension/extrapolation to multiple species of fish. Some draft text on the issue was provided by a delegation and, after some discussion, it was agreed that this text should be made available for further discussion in plenary. Several delegations commented on the issues related to extrapolation and the possible differences in metabolism in difference species of fish. The working group was also informed of work currently in progress by a VICH working group to classify fish into groups which were biologically equivalent. While the focus of this work relates to the establishment of withdrawal times, it may also be relevant to identifying species of fish which may be considered equivalent for the extension/extrapolation of MRLs.

The committee recommended that a concern form lodged by the EU (CRD13), and a concern form to be lodged by Canada (see CRD 27), be referred to JECFA for response

IV. Interactions between JECFA and the Priorities Working Group

The JECFA Secretariat briefly reviewed the process for scheduling the evaluation of a substance once it is on the priority list. Issues faced by the JECFA Secretariat include:

- Difficulties to obtain firm commitment for data submissions, with consequent impact on work of JECFA.
- Three different codex committees rely on JECFA (CCFA, CCCF and CCRVDF), so JECFA need the full cooperation of sponsoring member states and companies to provide data; when data don't arrive when promised, this disrupts timely evaluations.
- Time and resources are set aside and then data don't come, with a subsequent impact on efficiency.
- There is a need for a clear response, with no late submissions, and a need for more detailed information before a substance goes on the priority list.

The JECFA Secretariat will need to consider what may be accommodated in the upcoming meeting of JECFA in November 2015 and noted that an addendum to the call for data will go out next week.

V. The working group made the following recommendation to the Committee:

1. approve the substances recommended in the accompanying table for inclusion on the priority list (Appendix 1).

2. continue as a physical WG at the 23rd Session of the CCRVDF.

3. agree on the proposed amendment of the template for nominations in response to the CL (Appendix 2)

4. consider whether there should there be an annotation for MRLs for critically important antimicrobials.

Appendix 1

PRIORITY LIST OF VETERINARY DRUGS FOR EVALUATION OR RE-EVALUATION BY JECFA (PROPOSED)

Name of Compound	Question(s) to be answered	Data Availability / Timing	Proposed by	Comments	When will data package be available
PART A: Proposed for 2015 JECFA Meeting					
Amoxicillin	Request MRL establishment in fin fish muscle and skin in natural proportions	Nominator notes that relevant MRLs are established in a number on countries. Some data in public domain. IFAH members unable to provide data. Korea has method, residue, pharmacokinetic and monitoring data (nomination and CRD 28)	Republic of Korea	JECFA ADI of 0–0.7 µg/kg body weight on the basis of microbiological effects (2011). MRLs established in EU for all food producing species. Classified by WHO as critically important antimicrobial in human medicine (CIA). Prudent use in animal husbandry recommended. Classified by OIE as critically important antimicrobial in veterinary medicine (VCIA) with comments including: This class is very important in the treatment of many diseases in a broad range of animal species; Few economical alternatives are available.	Republic of Korea has data available, see CRD 28. Could be submitted for 81st JECFA
Ampicillin	Request ADI & MRL establishment in fin fish muscle and skin in natural proportions	Nominator notes that relevant MRLs are established in a number on countries. Availability of sponsor data not clear. Some data in public domain. IFAH members unable to provide data.	Republic of Korea	MRLs established in EU for all food producing species. Classified by WHO as critically important antimicrobial in human medicine (CIA). Prudent use in animal husbandry recommended. Classified by OIE as critically important antimicrobial in veterinary medicine (VCIA) with	No data to allow establishment of ADI. Leave on list, but not for 81st JECFA, to be reconsidered at 23rd CCRVDF.

Name of Compound	Question(s) to be answered	Data Availability / Timing	Proposed by	Comments	When will data package be available
		Korea has method, residue, pharmacokinetic and monitoring data (nomination and CRD 28)		comments including: This class is very important in the treatment of many diseases in a broad range of animal species; Few economical alternatives are available.	
Diflubenzuron	Request MRL establishment in fin fish (salmon) *muscle and skin in natural proportions*	Nominator notes pharmacokinetic, metabolism, residue depletion and method data available on request. Previous JMPR reports	Norway	ADI of 0-0.02 mg/kg body weight previously established by JMPR (1985). In 2001 JMPR confirmed the ADI established in 1985. MRL established in EU for Salmonidae. Norway notes CVMP is considering toxicological significance of metabolite 4-chloroaniline.	Data are available
Ivermectin	Request re-evaluation of the current JECFA ADI and re-evaluation of MRLs in all cattle tissues based on the revised ADI and other pertinent information	Toxicity in dogs, human tolerance and other use information in humans. Residue depletion study. Sponsor confirmed data availability	United States of America	JECFA ADI of 0–1 µg/kg body weight (1992). MRLs established by Codex and by many jurisdictions, including for all mammalian food producing species in EU. Cattle muscle MRL to be considered by 22nd CCRVDF.	Data are available Additional residue depletion and kinetic data available from Argentina
Lufenuron	Request ADI and MRL establishment in fin fish (salmon) *muscle and skin in natural proportions*		Norway and Chile	Fin fish MRL established in EU. Lufenuron on JMPR schedule for toxicology evaluation in 2015.	Data will be available by June 2016 Full data package (tox ad residue)
Nitarsone	Request ADI & MRL establishment in turkey edible commodities	Pharmacology, toxicology, metabolism, residue depletion, analytical methods. IFAH members unable to	Algeria	JECFA Provisional Tolerable Weekly Intake (PTWI) for inorganic arsenic withdrawn (2011).	**To be removed**

Name of Compound	Question(s) to be answered	Data Availability / Timing	Proposed by	Comments	When will data package be available
		provide data.			
Teflubenzuron	Request MRL establishment in fin fish (salmon) muscle and skin in natural proportions	Nominator notes data exists and that relevant MRLs are established in a number on countries.	Norway	ADI of 0-0.01 mg/kg body weight previously established by JMPR (1994). Proposed for periodic review by JMPR in 2016. MRL established in EU for Salmonidae.	Residue and tox data are available
Sisapronil (formally known as phenylpyrazole)	Request to establish ADI and recommend MRLs in cattle tissues (liver, kidney, muscle and fat)		USA	From RVDF21	Tox and residue have been submitted to JECFA Secretariat and will be considered by 81st JECFA; NOTE: currently no registration
Ethoxyquin (feed additive use)	Request to establish MRL in shrimp muscle		Philippines	From RVDF21 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)	No data submitted in response to call for data. Data availability to be confirmed at 23rd CCRVDF
Part B Concern Forms and other General Considerations for JECFA					
Species definitions for fish for use in MRL setting and extrapolation (using emamectin benzoate as example)	Referred from plenary				To be considered at 81st JECFA meeting

Name of Compound	Question(s) to be answered	Data Availability / Timing	Proposed by	Comments	When will data package be available
Lasalocid	Referred from plenary: Concern form lodged by EU (CRD 13) Concern form to be lodged by Canada on basis of CRD 27				To be considered at 81st JECFA meeting

Appendix 2

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion
2. Veterinary drug names
3. Trade names
4. Chemical names and CAS registry number
5. Names and addresses of basic producers

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)
7. Assessment against the criteria for the inclusion on the priority list

RISK PROFILE ELEMENTS

8. Justification for use
9. Veterinary use pattern, including information on approved uses if available. **[Explanatory note: This should include product labels or other evidence of official use authorisation.]**
10. Commodities for which Codex MRLs are required

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

AVAILABLE INFORMATION

12. Countries where the veterinary drugs are registered
13. National/Regional MRLs or any other applicable tolerances
14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available. **[Explanatory note: This should include a list of the data available with the full study titles**]

TIMETABLE

15. Date when data could be submitted to JECFA

Appendix 3

PROPOSED REQUEST TO JECFA ON DE-SPECIATION OF FISH MRLS

Request JECFA to provide an opinion for Emamectin Benzoate use in aquaculture finfish on whether:

- there is any specifically identified toxicological issue preventing CCRVDF progressing a generic finfish muscle/fillet MRL;
- JECFA used a standard dietary exposure modelling approach in elaborating the current MRLs and whether the extension of the MRLs to generic finfish would require a different dietary exposure modelling;
- there is any toxicological reason why any generic finfish MRLs should be stated in terms of a standardised fat content and if so, whether this is also a relevant consideration with respect to the large inherent variation that currently exists within single species and different genera, associated with different ages and sizes of fish or different production environments and practices;
- the current analytical methodology identified associated with the recommended MRLs is likely to be appropriate, with or without minor adaptation, to allow any residues of significant toxicological concern associated with possible uses in other species of commonly farmed finfish to be able to be monitored.
- there are any other relevant considerations for CCRVDF to consider, understanding that the setting of Good Veterinary Practice in the Use of Veterinary Drugs is a National Authority prerogative.

Furthermore, request JECFA to provide an opinion as to:

- what toxicological considerations may be appropriate for other drugs in considerations as to whether species specific or generic MRLs be considered for aquaculture fish
- if there are specific toxicological justifications for restricting certain MRLs to specified species, are there any narrower groupings of species at the Genera or the Phyla level where it is reasonable to assume a similar toxicological consideration is likely.