CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - Fax: (+39) 06 5705 4593 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 3 **CX/RVDF 16/23/3**

June 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

MATTERS OF INTEREST ARISING FROM FAO/WHO AND FROM THE 81ST MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

Information from the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

1. Since the last session of the CCRVDF, two JECFA meetings (i.e. JECFA 80th and 81st) have been convened. These meetings addressed food additives and contaminants (JECFA 80th), and veterinary drug residues (JECFA 81st). The reports and detailed monographs from these meetings are available at the relevant FAO and WHO sites:

- FAO: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/
- WHO: www.who.int/foodsafety/publications/jecfa/en/

2. JECFA 81st was held 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 997)[1]. Toxicological monographs summarising the data that were considered by JECFA 81st are published in *WHO Food Additives Series No.72*[2]; residue monographs summarising the data that were considered by JECFA 81st are published in *FAO JECFA Monographs No. 18*[3].

3. JECFA 81st recommended Maximum Residues Limits (MRLs) for the following veterinary drugs: ivermectin, teflubenzuron and zilpaterol hydrochloride (see CX/RVDF 16/23/6).

4. Furthermore JECFA 81st evaluated other three veterinary drugs, as follows:

Diflubenzuron - In the absence of adequate information on exposure to 4-chloroaniline (PCA), a genotoxic and carcinogenic metabolite and/or degradate of diflubenzuron, JECFA was unable to establish an ADI for diflubenzuron because it was not possible to assure itself that there would be an adequate margin of safety from its use as a veterinary drug. JECFA also noted that in the absence of adequate information on exposure to PCA it was also not possible to calculate a margin of exposure for PCA.

Consequently, JECFA was unable to recommend MRLs for diflubenzuron and identified the additional information that would assist in the further evaluation of the compound

- A comparative metabolism study of diflubenzuron in humans and rats (e.g. in hepatocytes)
- Information on PCA exposure associated with the consumption of treated fish
- Information on the amount of PCA (if present) as an impurity in the product formulation
- Information on the amount of PCA generated during food processing.
- A method suitable for monitoring diflubenzuron residues in fish muscle and fillet (muscle plus skin in natural proportions)

Finally, JECFA recommended that JMPR consider the re-evaluation of diflubenzuron at a future meeting and that the WHO Pesticide Evaluation Scheme (WHOPES) and the WHO *Guidelines for Drinking-water Quality* (GDWQ) Chemical Working Group reconsider their recommendations for the use of diflubenzuron as a vector control agent in drinking-water.

[1] http://apps.who.int/iris/bitstream/10665/204670/1/9789240695504_eng.pdf?ua=1
[2] http://apps.who.int/iris/bitstream/10665/205797/1/9789241660723_eng.pdf
[3] http://www.fao.org/documents/card/en/c/1cc884f7-c40c-4a9d-a8ec-48533c709656/

Lasalocid sodium - Following consideration of the issues raised in the two concern forms from CCRVDF22, the ADI established and MRLs recommended by JECFA 78th (WHO TRS No. 988, 2014) remain unchanged. The detailed JECFA responses to the concern forms are provided in in the WHO Technical Report Series (TRS 997)[4] and in *FAO JECFA Monographs No. 18*[5].

Sisapronil - JECFA concluded that an ADI could not be established because JECFA had no basis upon which to determine an uncertainty factor that would allow to appropriately compensate for the lack of a long-term toxicity study. Consequently, JECFA could not recommend MRLs and identified the additional information that would assist in the further evaluation of the compound

- Data to address long-term toxicity relevant to humans (e.g. 1-year dog study)
- Comparative pharmacokinetic studies and an explanation of interspecies differences in the pharmacokinetic profiles

General Considerations by JECFA 81st

Chronic dietary exposure assessment

5. During its previous meetings, JECFA agreed to develop an approach to assess more accurately the chronic dietary exposure to veterinary drug residues (i.e. GECDE). JECFA 81st decided to continue using this approach in parallel with the EDI model in order to gain experience and to continue improving the methodology. Moreover, JECFA 81st identified two additional important issues concerned with the methodologies applied by JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) to estimate chronic dietary exposures that merit general consideration.

- Approach for dietary exposure assessment of compounds used for multiple purposes (i.e. veterinary drugs and pesticides)
- Dietary exposure assessment for less-than-lifetime exposure

6. The Joint FAO/WHO Secretariats of JECFA and JMPR have established a Working Group of experts to address these issues and a call for expression of interest for national institutions to contribute was launch[6].

MRLs for generic fish species

7. The following two questions were forwarded to JECFA 81st by CCRVDF 22.

a) To provide an assessment on whether on the basis of data from one or more fish species, it is possible to establish an MRL for finfish, crustaceans or molluscs in general, or for multiple similar groups.

b) For emamectin benzoate, to provide an assessment as to whether there are any identified toxicological, dietary exposure modelling, or analytical methodology issues preventing extrapolation of the proposed MRLs to a general finfish MRLs or a more appropriate sub-grouping.

8. In response to the first question, JECFA concluded that in order to properly address the issue of extrapolation of MRLs to fish species, JECFA requires (in addition to the information identified by JECFA 78th) further information on adequate groupings of fish species so that representative species can be identified from which MRLs may be extrapolated to other similar species. JECFA 81st noted that several principles for grouping of fish species may be applied – for example, based on criteria such as a common aquaculture environment (salinity and temperature), phylogeny or common physiology (high lipid or low lipid) and common behaviour (demersal or not, type of diets). JECFA 81st further noted that it would be critical to develop clear boundaries around each group and define the inclusion and exclusion criteria for each group. JECFA is aware of work on this issue being conducted by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and will review the applicability of the guidance that results from that activity.

9. In response to the second question, JECFA concluded that in order to consider a request to extrapolate the MRLs recommended for salmon and trout to additional fish species, JECFA81st would require information on such approved uses, data to demonstrate pharmacokinetic and depletion behaviour of emamectin in a non-salmonid species and information to demonstrate that the method validated for the analysis of the high lipid content tissue of salmon and trout is applicable to non-salmonid species, preferably a species with low lipid content.

[4] http://apps.who.int/iris/bitstream/10665/204670/1/9789240695504_eng.pdf?ua=1
[5] http://www.fao.org/documents/card/en/c/1cc884f7-c40c-4a9d-a8ec-48533c709656/
[6] http://www.who.int/entity/foodsafety/RequestForExpressionOfInterest.pdf

10. The detailed JECFA responses are provided in in the WHO Technical Report Series (TRS 997)[7].

11. CCRVDF **is invited to consider** the need for guidance raised by JECFA concerning adequate groupings of fish species so that representative species can be identified from which MRLs may be extrapolated to other similar species.

Acute reference dose (ARfD) for veterinary drugs

12. The safety of veterinary drug residues in human food is typically assessed based on results from studies in laboratory animals. Human data, when available, and results from *in vitro* and *in-silico* studies are also considered in this safety assessment. The ADI provides a human health-based guidance value (HBGV) for chronic or long-term exposures to residues in food, and is most often established from a point of departure (POD, e.g. no-observed-adverse-effect level (NOAEL)) identified from repeated-dose exposure study (ies) in experimental animals. In some instances, there is a potential for veterinary drug residues to cause adverse acute effects in humans following only a single meal**.** Following a recommendation of JECFA 75th , a working group to elaborate guidance on the establishment of ARfDs for veterinary drugs was formed. This guidance is posted on the WHO website for public comments, prior to its full implementation by JECFA.

Processing of food containing residues of veterinary drugs

13. During the evaluation of diflubenzuron by JECFA 81st, the possibility of its thermal degradation to 4-chloroaniline (PCA), a metabolite of substantial toxicological concern, was discussed. As this reaction can occur at temperatures achievable during home cooking (>100 °C), the possibility for the degradation of diflubenzuron to PCA has to be taken into account in the risk assessment of the residues of diflubenzuron. In the evaluation of residues of pesticides by JMPR, the effect of processing, including cooking in the home, on the amount and nature of the residues ingested by consumers is routinely considered. JECFA therefore considered whether this should also be undertaken routinely in its assessment of residues of veterinary drugs.

14. JECFA noted that whereas for many pesticides, residue levels may be reduced or eliminated prior to cooking (e.g. residues in skin would be removed by peeling), this would rarely, if ever, be the situation for residues of veterinary drugs. In addition, the variation in cooking conditions and temperatures of food containing residues of veterinary drugs is appreciably greater than that for food containing pesticide residues, as would the impact on bioavailability of non-extractable residues. Also, more foods containing pesticide residues are eaten raw (without cooking) than are foods containing residues of veterinary drugs. These factors would make the task of routinely assessing the effects of processing of foods on residues of veterinary drugs much more complex and onerous than when assessing pesticide residues. Reflecting this, such information is not routinely requested by regulatory authorities (e.g. European Medicines Agency, United States Food and Drug Administration) involved in the assessment of veterinary drugs for use in food-producing animals.

15. JECFA therefore concluded that it would not routinely assess, or seek to address, the effects of processing foods on residues of veterinary drugs. However, if there is evidence, or some other reason to suspect, that processing of foods containing residues of specific veterinary drugs could have toxicological implications, such as for diflubenzuron, the effect of processing should be taken into consideration in the assessment of that compound.

Coordination of the agendas of JECFA and JMPR

16. JMPR evaluates residues of pesticides in food, whereas JECFA (veterinary drug residues) evaluates residues of veterinary drugs in food. In general, although there are many assessment principles in common – and these are being harmonized to the extent possible – the groups tend to operate largely independently. There are some substances that are used both as pesticides and as veterinary drugs – for example, teflubenzuron at the present meeting. Because of differences in their residue profiles and exposures when used, respectively, as a pesticide and a veterinary drug, both JMPR and JECFA will be asked to assess such compounds for both their toxicology and their residues. In general, different experts are involved in the assessment of the compounds by JECFA and JMPR, and hence it is quite possible that there will be some differences in the interpretation of data and the conclusions reached. It is also possible that there are different sponsors for the substance when used as a pesticide and when used as a veterinary drug, which could lead to differences in the data made available to the respective experts. Indeed, this might even happen when the sponsor is the same, but different departments are responsible for pesticide and veterinary use. In the event that this leads to different outcomes or recommendations – for example, the ADI established – this would lead to confusion among those relying on such assessments. As such, JECFA 81st recommended that where dual use substances are to be evaluated by both JMPR and JECFA, CCPR and CCRVDF coordinate the prioritization of such substances for evaluation by the respective experts.

[7] http://apps.who.int/iris/bitstream/10665/204670/1/9789240695504_eng.pdf?ua=1

Update and revision of Principles and methods for the risk assessment of chemicals in food (EHC 240)

17. The JECFA discussed whether processing data should be sought for all residues of veterinary drugs. It was agreed that this would not be practical, but that the issue should be dealt with on a case-by-case basis, where there was some reason for possible concern. Some minor amendment of EHC 240 might be necessary to reflect this.

18. JECFA 81st agreed to adopt the practice of JMPR to consider identifying an overall NOAEL for studies in dogs of 90 days' and 12 months' duration (see paragraph 16 above). EHC 240 should be updated to reflect this procedure, now in use by both JMPR and JECFA (veterinary drugs).

Update on JECFA databases

19. The FAO JECFA databases (one for food additives, one for flavouring agents and one for residues of veterinary drugs) were developed in early 2000 and were based on outdated underlying software. The FAO Secretariat has therefore carried out a project to modernize these three databases.

20. Although the major features and output do not differ significantly, the project aimed to develop an online platform that allows the Secretariat to manage the process from adding records to or updating records in the database to publishing the adopted JECFA evaluations. The new databases do also allow for improved interconnectivity with other databases, such as the Codex database of adopted MRLs of residues of veterinary drugs and the WHO summaries of JECFA evaluations.

21. The new databases are available on the FAO JECFA web site - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/

Guidance for the evaluation of veterinary drug residues in food by JECFA

22. The FAO/WHO JECFA Secretariat has revised the guidance documents for JECFA monographers and reviewers evaluating residues of veterinary drugs. While these guidance documents are intended primarily for JECFA Experts who prepare residue and toxicological monographs for JECFA, they will also be useful to manufacturers who submit dossiers to JECFA and other parties interested in understanding the process followed in the evaluation of residues of veterinary drugs in food by JECFA.

23. The revised FAO JECFA guidance is divided in three modules that are available on the FAO web site[8].

Global Food Consumption Databases and ongoing activities to support countries to generate and to use data for risk analysis purposes

24. Reliable information on food consumption, collected at individual level, is needed to estimate dietary exposure to chemicals and biological agents in the general population and in vulnerable population groups. To address the issue of insufficient access to such data, FAO and WHO have continued the work on the two following tools (initiated in 2014), to develop global food consumption databases.

- CIFOCOss (FAO/WHO Chronic Individual Food Consumption Data summary statistics) has been further implemented with data from additional countries and available summary statistics are now published at http://www.who.int/foodsafety/databases/en/
- FAO/WHO GIFT (FAO/WHO Global Individual Food consumption data Tool) is the name given to the comprehensive database collating micronutrient data for the production of indicators in the field of nutrition, dietary exposure and environmental impact. The pilot version is under development based on four datasets. The food categorization system is the one developed by the European Food Safety Authority (EFSA), which was implemented for use at global level. More information is available at http://www.fao.org/food/nutrition-assessment/foodconsumptiondatabase/en/

25. As part of the ongoing efforts to build national capacity and to populate these databases, a study to improve and harmonize food consumption data in ASEAN countries will be conducted over 2 years starting in May 2016. The project, funded by the EU through the Codex Trust Fund, and technically supported by FAO and WHO, will consist of: i) conducting individual food consumption survey in Lao PDR and ii) harmonizing existing data from individual food consumption data in other ASEAN countries in a consistent format. This harmonization activity will consist of:

- Training national teams to perform preliminary categorizing based on the classification of foods using the global categorization system (FoodEx2) developed by the European Food Safety Authority (EFSA)

[8] Module I: http://www.fao.org/3/a-bl002e.pdf
Module II: http://www.fao.org/3/a-bl003e.pdf
Module III: http://www.fao.org/3/a-bl004e.pdf

- The preparation of data in the format needed (variable types, standard codifications, etc.).
- The ultimate aim is to improve the assessment of nutrient intake and dietary exposure to chemical and biological agents in food (supporting national and international Codex standard-setting).

FAO/WHO activities on antimicrobial resistance (AMR)

FAO

26. To support the implementation of the FAO Resolution on AMR and contribute appropriately to the AMR Global Action Plan, FAO has developed a plan of action which defines its role and approach to supporting the food and agriculture sectors on the issue of AMR. This revolves around the four pillars of: (i) Awareness; (ii) Evidence; (iii) Governance; and (iv) Practices; and focuses on a cross cutting approach to ensure involvement of the relevant food and agriculture entities as well as the legislative and standard setting bodies. It places particular emphasis on an integrated and multidisciplinary approach along the food chain. There is limited information on antimicrobial resistance, antimicrobial use and the impact of AMR in the food and agriculture sectors, particularly in low and middle income countries. In this context FAO is already supporting a number of countries in Africa and Asia in their efforts to consider food and agriculture in the development of national action plans on AMR and ensure that these sectors are appropriately represented in both the development and implementation of such plans. More information on the FAO work on AMR is available at http://www.fao.org/antimicrobial-resistance/en/, and in addition, some of the AMR-related work areas with particular relevance for food safety are highlighted the paper that was discussed at the last session of CAC (CX/CAC 16/39/12).

WHO

27. Since the adoption of the WHO Global Action Plan (GAP) on AMR in 2015, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) is playing an active role in the implementation of GAP and in 2015 developed a five-year strategic framework to support the GAP. Five thematic working groups were established to operationalize this framework with the ultimate aim to minimize the public health impact of AMR associated with the use of antimicrobials in the food chain. Work is also underway to update the WHO list of Critically Important Antimicrobials (CIA) for Human Medicine, which was developed to provide a tool to support the elaboration of risk management strategies related to antimicrobial use in food production animals, in order to preserve the efficacy of last resort antibiotics for human medicine.