CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 4 **CX/RVDF 15/22/4**

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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

MATTERS OF INTEREST ARISING FROM FAO/WHO AND FROM THE 78TH 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 78th and 79th) have been convened. These meeting addressed veterinary drug residues (JECFA 78th), and food additives and flavoring agents (JECFA 79th). The reports and detailed monographs from these meetings are available at the relevant FAO and WHO sites:

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

2. The 78th meeting of JECFA was convened in Geneva, Switzerland, from 5 to 14 November 2013 to evaluate residues of certain veterinary drugs in foods. The full report of the meeting is published in the WHO Technical Report Series (TRS 988)[1]. Toxicological monographs summarising the data that were considered by JECFA 78th are published in *WHO Food Additives Series No.69* [2]; residue monographs summarising the data that were considered by the Committee are published in *FAO JECFA Monographs No. 15*[3].

3. JECFA 78th recommended Maximum Residues Limits (MRLs) for the following veterinary drugs: derquantel, emamectin benzoate, ivermectin, lasalocid sodium and monepantel (see CX/RVDF 15/22/6).

4. Furthermore JECFA 78th evaluated other three veterinary drugs, as follows:

- Gentian violet - JECFA 78th concluded that it was inappropriate to set an ADI for gentian violet because it is genotoxic and carcinogenic. MRLs could not be recommended by the Committee, as it was not considered appropriate to establish an ADI. JECFA 78th also noted that there was limited information on residues.

  Note: Gentian violet is structurally related to malachite green. JECFA 78th evaluated malachite green in 2009 and concluded that the use of malachite green in food-producing animals could not be supported. because its major metabolite, leucomalachite green is carcinogenic and it could not be ruled out that this was by a genotoxic mode of action. Also for Gentian violet, which is metabolised to leucogentian violet, JECFA 78th concluded that it should be considered carcinogenic acting by a genotoxic mode of action.

- Recombinant bovine somatotropins - Based on a systematic review of the literature published since the last evaluation, JECFA reaffirmed its previous decision on ADIs “not specified” for somagrebove, sometribove, somavubove and somidobove, established at the fortieth meeting (WHO TRS No. 832, 1993). JECFA 78th reaffirmed its previous decision on MRLs “not specified” for somagrebove, sometribove, somavubove and somidobove, established at the fortieth meeting (WHO TRS No. 832, 1993).

- Zilpaterol hydrochloride - JECFA established an ADI of 0–0.04 µg/kg body weight on the basis of a LOAEL of 0.76 µg/kg body weight for tremor in humans. An uncertainty factor of 20 was applied, comprising a default uncertainty factor of 10 for human individual variability and an additional uncertainty factor of 2 to account for the use of a LOAEL for a slight effect instead of a NOAEL. JECFA 78th noted that the ADI is based on an acute effect. JECFA 78th also noted that the upper

[1] http://apps.who.int/iris/bitstream/10665/127845/1/9789241209885_eng.pdf?ua=1
[2] http://apps.who.int/iris/bitstream/10665/128550/1/9789241660693_eng.pdf?ua=1
[3] http://www.fao.org/3/a-i3745e.pdf

bound of the ADI provides a margin of safety of at least 1250 with respect to the NOAEL of 50 µg/kg body weight per day for the formation of leiomyomas in rats.

Only limited data were available for tissues other than muscle, and JECFA was unable to determine a suitable marker residue in other edible tissues. JECFA used the highest concentrations of total residues to estimate dietary exposure, because no median residue levels could be determined and no marker residue in liver and kidney was defined. The calculations indicated that the dietary exposure was higher than the ADI for the withdrawal times for which data were provided.JECFA 78th concluded that it was not possible to recommend MRLs for zilpaterol. The following data are needed to establish MRLs:

- results from studies investigating marker residue in liver and kidney;
- results from studies determining marker residue to total residue ratio in liver and kidney;
- results from depletion studies to enable the derivation of MRLs compatible with the ADI.

All such studies should use sufficiently sensitive validated analytical methods capable of measuring zilpaterol and its major metabolites in edible tissues of cattle.

After the publication of the report, the JECFA secretariat has provided further clarifications in response to a series of questions received from the Zilpaterol sponsor, concerning both the toxicological and the residue part of the evaluation.

Dietary exposure to veterinary drug residues

5. The FAO/WHO expert meeting on dietary exposure assessment methodologies for residues of veterinary drugs (November 2011) proposed new methods for acute and chronic dietary exposure estimates for veterinary drug residues and recommended that the new approaches should be piloted at the subsequent meeting of JECFA. The purpose of the pilot study was to explore the new calculations for dietary exposure assessment, compare them with estimates calculated using the model diet approach, identify the practical impact of using the new methods and make recommendations for dietary exposure assessment at future meetings. At JECFA 78th, dietary exposures were calculated for four veterinary drug residues (derquantel, emamectin benzoate, lasalocid, monepantel) using the model diet approach as well as the new methods for chronic and acute dietary exposure estimation. Overall the outcomes where very similar, but the new approach provides improved and more detailed exposure estimates, in particular for children and high consumers. In general, it was concluded that the new approach for dietary exposure assessment is preferable to the model diet approach, because it moves from a food basket to consumption amounts derived from surveys. For future meetings of JECFA, the new approach should continue to be used in parallel with the model diet approach until more experience has been obtained in the interpretation of the results with the new approach. JECFA also identified a number of areas for consideration to further improve the dietary exposure estimation methods.

Extrapolation of MRLs to minor species

6. CCRVDF21 addressed several comments and questions to JECFA concerning the extrapolation of MRLs to additional (minor) species, which were addressed by JECFA 78th. In addition, guidance was prepared on the criteria/assumptions used by JECFA for interspecies extrapolations, including minimum data required to support such extrapolations among physiologically related species and extrapolation to additional minor species. It was decided that JECFA will use the term *extension* when sufficient depletion data are available for the minor species to permit the derivation of MRLs for tissues of that species from the depletion curves. The term *extrapolation* will be used when insufficient depletion data are available in that species to derive MRLs for tissues from that species. A number of principles were established, to be applied by JECFA when considering the extrapolation of MRLs to additional species. In addition, a decision-tree was prepared to illustrate the process to be followed at future JECFA meetings.

MRLs for veterinary drug residues in honey

7. JECFA 78th responded to a question from CCRVDF21 regarding the establishment of MRLs for honey using monitoring data from national authorities, similar to the approaches for setting MRLs for spices used by JMPR. In addition, JECFA guidance for the establishment of MRLs in honey was prepared. Data on the depletion of residues in honey will be considered from statistically based field trials or other sources, such as statistically based national monitoring programmes. Three potential situations are envisaged and were discussed by JECFA: (i) the establishment of an MRL for honey for substances with an ADI, typically established by JECFA or JMPR, and/or a Codex MRL in a food-producing animal or food commodity; (ii) the establishment of an MRL for honey for substances for which an ADI has not previously been established by JECFA or JMPR; and (iii) the establishment of an MRL for honey for substances that are not approved for

use in food animals. A decision-tree for the establishment of MRLs for veterinary drug residues in honey was established for future use.

Scope of MRLs established by JECFA relating to fish and fish species

8. JECFA noted that some previous recommendations for MRLs have been for specific species of fish, such as salmon and trout, whereas others have been for "fish", which could be interpreted to include shellfish. To more accurately reflect the species for which MRL recommendations are made, JECFA recommended, consistent with the terminology used in the report of the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs, that the term "fish" should be used when an MRL recommendation applies to multiple species of finfish. For other "seafood", the term "mollusc" should be used for species such as clams, oysters and scallops, and the term "crustacean" should be used when MRLs are recommended for species such as shrimp, prawn and crayfish. When the recommendation of an MRL is for a specific species of fish or seafood, this will be reflected in the MRL recommendation. In this regard, JECFA considered that it may be appropriate to also identify some representative species of fish, such as salmon, and of seafood, such as shrimp (crustacean), as "major species" of fish and seafood. It was recommended that this matter should be further discussed at future JECFA meetings.

Requests for scientific advice

9. Both FAO and WHO continue to jointly prioritise the requests for scientific advice taking into consideration the criteria proposed by Codex as well as the requests for advice from Member Countries and the availability of resources. A list of all pending requests for scientific advice by JECFA will be posted on the respective FAO and WHO websites.

10. In scheduling the JECFA meetings and developing the agenda, the Joint Secretaries have to take into account the priorities requested by CCFA, CCCF and CCRVDF. Due to the increasing requests for scientific advice by JECFA not all requests can be addressed in the subsequent meeting. In prioritizing the work the JECFA Secretariat takes into account existing criteria, on-going Codex work and available resources.

11. To facilitate provision of extra-budgetary resources for scientific advice activities FAO and WHO established the Global Initiative for Food-related Scientific Advice (GIFSA). For additional information please contact Dr Vittorio Fattori, FAO Food Safety and Quality Unit (jecfa@fao.org) and Dr Angelika Tritscher, Department of Food Safety and Zoonoses, WHO (jecfa@who.int).

FAO/WHO Global Individual Food consumption data Tool (FAO/WHO GIFT)

12. Data on individual food consumption, taking into account gender and age dimensions, are needed in the development of food standards. Such data are available but extremely under-utilized, mainly because they are not easily accessible and not sufficiently standardized. FAO and WHO have put together an interdisciplinary team to build a pilot Global Individual Food consumption data Tool (FAO/WHO GIFT). The tool will be developed based on the needs of stakeholders in the field of nutrition and food safety. Ultimately, the objective is to collect, harmonize and disseminate – through a FAO hosted web-platform – individual food consumption data available all over the world at national and sub national level. This platform, intended for both experts and broader audience, is deemed to facilitate access to the micro-data and to compute food-based indicators allowing for comparison of data among different population groups and geographical areas. From the food safety perspective, these data will be used in risk assessments by supporting more accurate and refined dietary intake estimates of foods safety hazards.

Collection and collation of individual food consumption data in ASEAN countries through EU Codex trust fund

13. In Asia, individual consumption data have been made available in a harmonized format into the FAO/WHO Chronic Individual Food Consumption Database – Summary Statistics (CIFOCOss) for Australia/New-Zealand, China, Japan, Republic of Korea and Thailand . On the contrary in the 10 countries belonging to the Association of Southeast Asian Nations (ASEAN), data are sparse and heterogeneous. FAO and WHO decided to support the ASEAN countries in implementing a risk-based approach for food safety and nutrition, and to improve effective participation in Codex discussions. The Codex trust fund is elaborating a project to carry out individual food consumption surveys with technical assistance from FAO and WHO and other ASEAN countries which have undertaken a similar activity (twinning). Moreover, existing data in another ASEAN countries should be harmonized and input into the FAO/WHO Global Individual Food Consumption data Tool.

FAO/WHO activities on antimicrobial resistance (AMR)

14. The 67th Session of World Health Assembly (WHA) adopted a resolution on antimicrobial resistance (AMR) in May 2014 (EB134.R13). The resolution called for the development and implementation of a draft global action plan to combat antimicrobial resistance, including antibiotic resistance and to strengthen the existing FAO/OIE/WHO Tripartite collaboration as a mechanism for the implementation of the action plan and collaboration across sectors, including through the Codex Alimentarius. The Global Action Plan will be presented to the WHO Executive Board in January 2015 and be submitted for endorsement by the 68th WHA in May 2015. Further information is at http://www.who.int/drugresistance/amr_global_action_plan/en/

15. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) continued to assist WHO in its efforts to contain AMR from the food chain. The following activities have been undertaken during the past two years: (i) Development of training modules for Member States as well as provision of support to set up national programs on integrated surveillance of AMR to Brazil, Mexico and Chile; (ii) Updating the WHO list of Critically Important AMR for human medicine; (iii) Implement FAO/OIE/WHO tripartite activities on AMR; and (iv) Conducting country projects to conduct integrated surveillance of AMR and AMR usage in newly selected pilot sites (Bangladesh, Ghana, Lebanon, Peru and Uganda). More information can be found at : http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/agisar/en/

16. In recognizing the role of FAO in addressing the issue of AMR, the FAO Committee on Agriculture held in October 2014, recommended that work on AMR be incorporated into the FAO work programmes on food safety and sustainable production systems. Further consideration of this issue will be given by the FAO governing body in 2015.

Handbook on Risk Communication in food safety

17. FAO/WHO have finalized an handbook on Risk Communication in food safety which provides guidance on the good risk communication principles and practices and includes hands-on training materials (case-studies) for developing effective risk communication capacity across national agencies sharing responsibility in food safety. The handbook was pre-tested during regional training workshop in Budapest in June 2014 and will soon be available on line.

Response to specific requests from the 21st Session of CCRVDF on chlorpromazine, dimetridazole, ipronidazole, metronidazole and ronidazole

18. The JECFA Secretariat had agreed to provide advice on these compounds as to availability of toxicological data and possible implication on previous JECFA assessments.

Chlorpromazine

19. A targeted literature review was undertaken to assess whether data have become available since the last JECFA assessment in 1990 that would suggest an update of the previous JECFA evaluation. Although literature on chlorpromazine continues to be published in significant numbers, new toxicity data related to use in food producing animals are very limited.

20. The additional data retrieved do not address sufficiently the critical data gaps on the metabolism and toxicity of chlorpromazine previously identified by JECFA. The genotoxic profile is better characterized showing that it is a photomutagenic substance. Additional data considering endpoints related to reproduction and development verify embryo-toxicity as a hazard without providing a clear level of no effect.

21. As no additional metabolism and residue data have been identified, data on the fate and possible persistence (accumulation) of chlorpromazine residues in animal products remain insufficient and would not allow establishing maximum residue levels.

22. The available data are insufficient to establish the safety of residues of chlorpromazine for the human consumer. Considering the toxicological profile of the compound it is unlikely to modify the suggestion of the 38th JECFA that this drug should not be used in food producing animals.

Nitroimidazoles

23. The four antiprotozoal drugs dimetridazole, ipronidazole, metronidazole, and ronidazole were on the agenda of the 34th JECFA (1989). The Committee had initially intended to evaluate them as a group. However, this was not possible because the available data varied too much in amount and quality. The Committee was unable to establish MRLs and only in the case of ronidazole a Temporary ADI was established. Since no new data were made available for the 42nd meeting (1994) the tADI was not extended.

24. An extensive literature search was undertaken to investigate whether new published data had become available in the open literature since 1989/1994 which had filled certain critical knowledge gaps or could have the potential for modifying the basis of earlier risk assessments thereby justifying a re-evaluation by JECFA.

25. Although many publications have been identified, some of them are quite old and often contain limited information that also limits their usefulness in risk assessment. Metronidazole is carcinogenic in rodents via a genotoxic mechanism and has been classified as possibly carcinogenic to human (IARC 1987) or being reasonably anticipated to be a human carcinogen (13th Report on Carcinogens 2014).

26. Since the 34th JECFA meeting (1989) more detailed information is available on the toxicological mode of action. Overall it is unlikely that the available data fill all the specific information gaps identified by the JECFA. The great similarities of the group of 5-nitroimidazoles with regard to structure-related toxicological properties including underlying mechanism seem to be evident.

27. Nitroimidazoles (major examples: metronidazole, tinidazole, ornidazole) are considered by WHO as important antimicrobials in human medicine. In certain geographic regions, the class may be one of limited therapies for anaerobic infections including *C. difficile.*

Next JECFA meeting on Veterinary Drug Residues

28. The 81st meeting of JECFA is dedicated to the evaluation of veterinary drug residues in food, and will be held 17 to 26 November 2015. A call for data for to evaluations of ethoxyquin, sisapronil and to complete the evaluation of zilpaterol hydrochloride has been published[4], with a submission deadline of **15th March 2015.**

29. If at the 22nd session of CCRVDF availability of data for other compounds will be confirmed, additional veterinary drugs may be considered at JECFA 81st. The data for the additional compounds to be confirmed at CCRVDF22 will have to be submitted to FAO and WHO JECFA Secretariats not later than **15 May 2015**.

[4] http://www.who.int/entity/foodsafety/jecfa_81_call_for_data_final.pdf?ua=1
http://www.fao.org/fileadmin/user_upload/agns/pdf/JECFA_81_Call_for_data_FINAL.pdf