Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninety-eighth meeting (Safety evaluation of certain veterinary drug residues)
FAO headquarters, 20–29 February 2024

Summary and conclusions

Issued on 11 March 2024

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held at FAO headquarters in Rome, Italy, on 20–29 February 2024. The purpose of this meeting was to evaluate the safety of residues from veterinary drugs.

Dr A. Chicoine served as Chairperson and Professor (Emeritus) A. Boobis as Vice-Chairperson.

Dr Vittorio Fattori, FAO, and Mr Soren Madsen, WHO, served as joint secretaries.

The present meeting was the ninety-eighth in a series of similar meetings and the twenty-fifth JECFA meeting convened specifically to consider residues of veterinary drugs in food. The tasks before the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food; to establish acceptable daily intakes (ADIs) and acute reference doses (ARfDs); to recommend maximum residue limits (MRLs) for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs; to evaluate the safety of residues of certain veterinary drugs; and to respond to specific requests from the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).

The Committee evaluated the safety of two veterinary drugs, clopidol and fumagillin dicyclohexachloride. The Committee also completed the safety evaluation of imidacloprid started at its ninety-fourth meeting *(1)*. In the absence of complete information at that time to assess the direct impact of imidacloprid on representative human intestinal microbiota, neither an mARfD nor an mADI could be established. Therefore, JECFA at its ninety-fourth meeting was unable to establish an ARfD or an ADI for imidacloprid, and MRLs could not be recommended. At the present meeting, the Committee completed its assessment by evaluating microbiological data submitted by the sponsor.

Although ethoxyquin was initially included on the list of substances to be reviewed, it was not evaluated, as the sponsor did not submit any data.

The report of the meeting will be published in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances and recommendations. The report will summarize the main conclusions of the Committee in terms of acceptable daily intakes and other toxicological, dietary exposure and safety recommendations. Further discussions on Guidance for the Safety Evaluation of Residues of Veterinary Drugs with incomplete data packages are also summarized.

Annex 1 shows the results of toxicological evaluations of the veterinary drugs and the assessments of dietary exposure. Items of a general nature that contain information that the Committee would like to disseminate quickly are described in Annex 2. Future work and recommendations arising from the meeting are summarized in Annex 3. The participants are listed in Annex 4.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series. Residue monographs

summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monograph series.

Reference

1. Evaluation of certain veterinary drug residues in food. Ninet-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series, No. 1041). Geneva: World Health Organization; 2022 (https://www.fao.org/3/cc2118en/cc2118en.pdf).

More information on the work of JECFA is available at:

https://www.fao.org/food-safety/scientific-advice/jecfa/en/

and

https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/

Annex 1. Recommendations on the substances on the agenda

Clopidol (coccidiostat)

Acceptable daily intake	The Committee established an ADI for clopidol of 0–0.04 mg/kg bw based on a lowest-observed-adverse-effect level (LOAEL) of 40 mg/kg bw per day for decreased maternal and fetal body weight gain. An uncertainty factor of 1000 was applied, which comprises 100 for inter- and intra-species differences and additional factors of 2 to account for the use of a marginal LOAEL and 5 for database uncertainty.
Acute reference dose	The Committee concluded that it was unnecessary to establish an ARfD for clopidol.
Estimated dietary exposure	For clopidol included at 250 mg/kg in feed at 24 h withdrawal and the most conservative ratio of marker residues to total residues (MR:TR) considered of 0.5, the global estimate of acute dietary exposure (GECDE) for adults and the elderly, children and adolescents, and infants and toddlers were 32.9, 33.5 and 28.6 µg/kg bw per day, respectively (82%, 84% and 71%, respectively, of the upper bound of the ADI of 40 µg/kg bw).
Residue definition	The marker residue for clopidol in chicken liver, kidney, muscle and skin/fat is clopidol.
Maximum residue limits	The Committee recommended MRLs of 10 400 µg/kg (liver), 8800 µg/kg (kidney), 4100 µg/kg (muscle) and 2600 µg/kg (skin/fat) in chickens.

Fumagillin dicyclohexylamine (antimicrobial agent)

In veterinary medicine, fumagillin is administered only as the dicyclohexylamine (DCH) salt. As the fumagillin DCH salt dissociates into the two moieties, consumers would be exposed to residues of both. The Committee evaluated both fumagillin and DCH.

Acceptable daily intake	The Committee established an ADI of 0–0.003 mg/kg bw for fumagillin and an ADI of 0-0.02 mg/kg bw for DCH.
Acute reference dose	The Committee concluded that it was unnecessary to establish an ARfD for fumagillin. It established an ARfD of 0.7 mg/kg bw for DCH.
Estimated dietary exposure	For potential fumagillin residues in fish fillet and honey, the GECDE values for adults and the elderly, children and adolescents, and infants and toddlers were 0.06, 0.10 and 0.11 µg/kg bw per day, respectively, which represent 2%, 3% and 4% of the upper bound of the ADI of 3 µg/kg bw. There was insufficient information to estimate dietary exposure (chronic or acute) to DCH.
Residue definition	The marker residue for fumagillin DCH in fish fillet is fumagillin. The marker residue for fumagillin DCH in honey is DCH.
Maximum residue limits	The Committee recommended an MRL in fish fillet of 10 µg/kg for the marker residue fumagillin. The Committee recommended that residues of DCH (including any potential metabolites) be monitored when fumagillin DCH preparations are used in fish to ensure that the concentration is < 1000 µg/kg, a target level compatible with the upper bound of the ADI. The Committee noted that a suitable analytical method for the determination of DCH in fish fillet should be developed. The Committee recommended an MRL in honey of 20 µg/kg for the marker residue DCH.

Imidacloprid (neonicotinoid parasiticide)

Imidacloprid exerted very low or no measurable antibacterial activity against the representative bacterial strains of the human intestinal microbiome tested.

The Committee concluded that no mADI or mARfD was required.

Acceptable daily intake	The Committee established an ADI of 0–0.05 mg/kg bw, based on a NOAEL of 5.25 mg/kg bw per day for decreased body weight gain in the extended one-generation reproduction study, with application of a safety factor of 100 to allow for interspecies and intraspecies differences.

Acute reference dose	The Committee established an ARfD of 0.09 mg/kg bw based on a $BMDL_{05}$ of 9 mg/kg bw for acute neurobehavioural effects in rats and a safety factor of 100 to allow for interspecies and intraspecies differences.
Residue definition	The marker residue for imidacloprid in fin fish is the parent molecule, imidacloprid.
Dietary exposure	For Atlantic salmon only, the GECDE was 1.0, 2.7 and 0.9 µg/kg bw per day (2%, 5% and 2% of the upper bound of the ADI of 50 µg/kg bw) for adults and the elderly, children and adolescents, and toddlers and infants, respectively. For all fin fish, the GECDE was 1.8, 3.8 and 1.2 µg/kg bw per day (4%, 8% and 2% of the upper bound of the ADI of 50 µg/kg bw) for adults and the elderly, children and adolescents, and toddlers and infants, respectively. The GEADE, based on consumption of Atlantic salmon, was 7% of the ARfD for adults and children (6.2 and 6.6 µg/kg bw, respectively); the GEADE for all fin fish was 38% and 26% of the ARfD (34.1 and 23.8 µg/kg bw) for adults and children, respectively.
Maximum residue limits	The Committee recommended an MRL for Atlantic salmon and rainbow trout fillet (muscle with skin in natural proportions) and/or muscle of 600 µg/kg. It further recommended that the MRL be extrapolated to all fin fish.

Annex 2. General considerations

An edited version of this section will be included in the report of the ninety-eight meeting of JECFA. It is reproduced here so that the information can be disseminated quickly.

2.1 Matters of interest arising from previous sessions of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)

The Chairperson of CCRVDF, Ms Brandi Robinson, reported the results and activities of the CCRVDF at its twenty-sixth session (CCRVDF26), which was held in February 2023. She reported that the MRLs recommended by JECFA at its ninety-fourth meeting for nicarbazin in chicken tissues and for amoxicillin in sheep, goat and swine tissues had been advanced by CCRVDF and adopted by the Codex Alimentarius Commission at its the forty-sixth session (CAC46). She said that CCRVDF had extrapolated Codex MRLs for 10 compounds to apply to "all other ruminants" and had extrapolated MRLs for 2 compounds to finfish using the extrapolation approach described in "Risk analysis principles applied by CCRVDF". The extrapolated MRLs were advanced by CCRVDF26 and adopted by CAC46. The CCRVDF Chair also reported updates to the priority list and to the activities of the Joint CCRVDF/CCPR Electronic Working Group, which is harmonizing standards for compounds used as both pesticides and veterinary drugs and harmonizing food descriptors for both committees (CCRVDF and CCPR).

The CCRVDF Chair noted that CCRVDF continues to experience challenges in ensuring that compounds have robust dossiers for evaluation by JECFA. While many members are interested in having MRLs, many of the compounds in use for which they require MRLs are old, and the available information may not meet current standards. The CCRVDF Chair said that she would continue to encourage nomination of compounds for which there are robust dossiers and noted that Member States are working independently and cooperatively to ensure new data that could be evaluated by JECFA. She further noted that CCRVDF continues to seek innovative approaches to providing standards, such as a revision of the approach to allow extrapolation to additional species and tissues and preparation of a pilot review to shorten the time between national authorization and Codex MRLs. The CCRVDF Chair expressed her gratitude to JECFA for its advice and evaluations, which she said were critical to the work of CCRVDF.

2.2 Guidance for the Safety Evaluation of Residues of Veterinary Drugs with incomplete data packages

JECFA is sometimes asked to assess the risk of veterinary drug residues of compounds for which the data package is not comprehensive or is out of date. In such cases, generating a risk assessment that is of maximum utility for CCRVDF and other risk managers may require use of approaches different from those usually used by JECFA in assessing risk. JECFA first proposed development of guidance to address such situations at its sixty-sixth meeting, in 2006, and considered a first draft at its seventieth meeting, in 2008. Since then, the draft has been substantially revised and updated, including at the ninety-fourth meeting of JECFA, in 2022. At the current meeting, the Committee discussed the updated guidance and added relevant considerations for toxicological, microbiological and residue evaluation and for evaluating dietary exposure. The Committee adopted the guidance and welcomes comments from CCRVDF.

2.3 JECFA Toolbox for Veterinary Drug Residues Risk Assessment

The process used by JECFA for assessing risks resulting from veterinary drug residues in food is based on sound scientific principles and procedures. In order for stakeholders and new JECFA experts to understand this process, the FAO Agrifood Systems and Food Safety Division is developing a Toolbox for Veterinary Drug Residues Risk Assessment. The aim is to strengthen understanding of JECFA procedures by stakeholders interested in veterinary drug residues in food, such as regulatory agencies responsible for veterinary drug approval or food safety standards, the

pharmaceutical industry, producers in animal agriculture and veterinary associations. It is designed for use by potential JECFA experts in order to broaden the pool of experts available for the JECFA roster and to ensure greater geographical representation, particularly from regions with previously low representation in FAO and WHO expert bodies. The Toolbox is intended to increase understanding of the principles, modalities and technical requirements used by the Committee in assessing the risks of veterinary drug residues in food and in recommending MRLs. The Toolbox is also designed to expand understanding of the role of FAO experts on the Committee and their interaction with WHO experts in conducting full risk assessments during JECFA meetings and of critical information requirements. Additional sources of guidance listed in the Toolbox provide more detailed information about the specific steps in the risk assessment process.

The Toolbox is expected to be ready by the end of 2024 and will be publicly available on the FAO website.

Annex 3. Future work and recommendations

Recommendations relating to specific veterinary drugs, including ADIs and proposed MRLs, are given in section 3 of each monograph, which includes recommendations relating to future work by the JECFA Secretariat.

Guidance for the Safety Evaluation of Residues of Veterinary Drugs with incomplete data packages

The Committee adopted the guidance and welcomes comments from CCRVDF.

JECFA Toolbox for Veterinary Drug Residues Risk Assessment

The toolbox is expected to be available by the end of 2024 and will be publicly available on the FAO website.

Annex 4. List of participants

FAO members

Dr Alan Chicoine, Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Canada (*Chairperson*)

Mr Peter Cressey, Senior Scientist, Institute of Environmental Science and Research Limited, Christchurch Science Centre, Christchurch, New Zealand

Dr Holly Erdely, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Rockville (MD), United States of America (USA) (*FAO Rapporteur*)

Professor Susanne Rath, University of Campinas, Department of Analytical Chemistry, São Paulo, Brazil

Dr Rainer Reuss, Safe Work Australia, Canberra, Australia

WHO members

Professor (Emeritus) Alan R. Boobis, National Heart and Lung Institute, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland (United Kingdom) (*Vice-Chairperson*)

Professor Silvana Lima Górniak, School of Veterinary Medicine and Animal Sciences, University of São Paulo, São Paulo, Brazil

Professor Angelo Moretto, Department of Thoracic, Vascular and Public Health Sciences, University of Padua, Padua, Italy (*WHO Rapporteur*)

FAO experts

Dr Anke Finnah, German Federal Office of Consumer Protection and Food Safety, Berlin, Germany

Mr Samuel Fletcher, Veterinary Medicines Directorate, Addlestone, Surrey, United Kingdom of Great Britain and Northern Ireland (United Kingdom)

Dr Amy-Lynn Hall, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Rockville (MD), USA

Professor Lingli Huang, College of Veterinary Medicine, Huazhong Agricultural University, Wuhan City, China

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WHO experts

Dr Mayumi Ishizuka, Laboratory of Toxicology, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

Dr Silvia A. Piñeiro, Rockville (MD), USA

Secretariat

Dr Vittorio Fattori, Agrifood Systems and Food Safety Division, FAO, Rome, Italy (*FAO JECFA Secretary*)

Mr Soren Madsen, Department of Nutrition and Food Safety, WHO (*WHO JECFA Secretary*)

Dr Markus Lipp, Agrifood Systems and Food Safety Division, FAO (*FAO Secretariat*)

Dr Keya Mukherjee, Agrifood Systems and Food Safety Division, FAO, Rome, Italy (*FAO Secretariat*)

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Ms Elisabeth Heseltine, France (*WHO editor*)

Ms Ngai Yin Ho, Department of Nutrition and Food Safety, WHO (*WHO Consultant*)