



JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Eighty-eighth meeting (Residues of veterinary drugs)
Rome, Italy, 22–31 October 2019

SUMMARY AND CONCLUSIONS

Issued on 14 November 2019

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, on 22–31 October 2019. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Dr Stefan Scheid served as Chairperson, and Professor (Emeritus) Alan R. Boobis served as Vice-Chairperson.

Mr Soren Madsen, World Health Organization (WHO), and Dr Vittorio Fattori, Food and Agriculture Organization of the United Nations (FAO), served as Joint Secretaries.

The present meeting was the 88th in a series of similar meetings and the 24th JECFA meeting specifically convened 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, establishing acceptable daily intakes (ADIs) and acute reference doses (ARfDs), and recommending 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 (GVP); 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). In total, eight veterinary drugs were evaluated by the Committee.

The report of the meeting will be published in the WHO Technical Report Series (No 1023). Its presentation will be similar to that of previous reports; namely, general considerations, comments on specific substances and recommendations. The report will include an annex (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs, dietary exposure and MRLs.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included 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 No. 79. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monographs No. 24.

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More information on the work of JECFA is available at:

<http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/>

and

<https://www.who.int/foodsafety/en/>

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Annex 1: Recommendations on the substances on the agenda

Diflubenzuron (insecticide)

Acceptable daily intake	The Committee 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	The Committee 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	The global estimate of chronic dietary exposure (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	Acute dietary exposure was not estimated because the Committee concluded that it was not necessary to establish an ARfD.
Residue definition	The Committee 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	The Committee recommended a maximum residue limit (MRL) in salmon of 10 µg/kg in muscle plus skin in natural proportions.

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Ethion (acaricide)

Acceptable daily intake	The ADI of 0–0.002 mg/kg bw established by the Committee at the 85th meeting (2) remains unchanged.
Acute reference dose	The ARfD of 0.02 mg/kg bw established by the Committee at the 85th meeting remains unchanged.
Estimated dietary exposure	No dietary exposure assessment could be conducted.

Maximum residue limits The committee concluded that it would not be possible to recommend MRLs with the available data.

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Flumethrin (type II pyrethroid insecticide)

Acceptable daily intake The ADI of 0–0.004 mg/kg bw established by the Committee at the 85th meeting (2) remains unchanged.

Acute reference dose The ARfD of 0.005 mg/kg bw established by the Committee at the 85th meeting remains unchanged.

Estimated dietary exposure No dietary exposure assessment was conducted because no MRLs were recommended.

Maximum residue limits The committee concluded that it would not be possible to recommend MRLs with the available data.

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Fosfomycin (broad-spectrum antimicrobial)

Acceptable daily intake In the absence of a NOAEL and information required to determine an overall microbiological ADI (mADI), the Committee was unable to establish an ADI for fosfomycin.

Acute reference dose The Committee established an ARfD of 0.08 mg/kg bw based on microbiological effects (specifically, disruption of the intestinal colonization barrier).

Estimated dietary exposure No dietary exposure assessment could be conducted.

Maximum residue limits The Committee concluded that no MRLs can be recommended with the available data.

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Halquinol (broad-spectrum antimicrobial)

Acceptable daily intake The Committee 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 The Committee 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	<p>The GECDE for the general population is 5.9 µg/kg bw per day, which represents 3% of the upper bound of the ADI.</p> <p>The GECDE for children is 6.9 µg/kg bw per day, which represents 3.4% of the upper bound of the ADI.</p>
Estimated acute dietary exposure	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 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	The Committee 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

	Muscle	Skin plus fat	Liver	Kidney
Species	(µg/kg)	(µg/kg)	(µg/kg)	(µg/kg)
Swine	40	350	500	9000

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Ivermectin (broad-spectrum antiparasitic agent)

Acceptable daily intake	The ADI of 0–10 µg/kg bw established by the Committee at the 81st meeting (1) remains unchanged.
Acute reference dose	The ARfD of 0.2 mg/kg bw established by the Committee at the 81st meeting remains unchanged.
Estimated chronic dietary exposure	<p>The Committee 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.</p> <p>The Committee established a GECDE for children of 0.59 µg/kg bw per day, which represents 5.9% of the upper bound of the ADI.</p>
Estimated acute dietary exposure	<p>The Committee 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.</p> <p>The Committee 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.</p>

Residue definition	The MR in sheep, pigs and goats is ivermectin B _{1a} (H ₂ B _{1a} , or 22,23-dihydroivermectin B _{1a}).
Maximum residue limits	The Committee 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	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Sheep, pigs and goats	20	15	15	10

Selamectin (broad-spectrum antiparasitic agent)

Acceptable daily intake	The Committee established an ADI of 0–0.01 mg/kg bw, based on a NOAEL of 1 mg/kg bw per day for a reduction in serum cholesterol and triglycerides, alterations in haematology parameters, and increased liver and uterus/cervix weights in females at 5 mg/kg bw per day in a 1-year study in rats, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee established an ARfD of 0.4 mg/kg bw, based on a NOAEL of 40 mg/kg bw per day for malformations observed in developmental toxicity studies in rats at 60 mg/kg bw per day, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated dietary exposure	No dietary exposure assessment was conducted because an MRL could not be recommended.
Maximum residue limits	The Committee concluded that no MRLs can be recommended with the available data.

Sisapronil (ectoparasiticide)

No additional data were submitted. As a result, the ADI and MRLs remain unestablished.

Annex 2: General considerations

An edited version of this section will be included in the report of the 88th meeting of JECFA. It is reproduced here so that the information can be disseminated quickly.

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

The 24th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) (3):

- noted the advancement of the maximum residue limits (MRLs) for amoxicillin and ampicillin for finfish, lufenuron for salmon and trout, and monepantel for cattle to final standards by the 42nd Session of the Codex Alimentarius Commission (CAC) (4);
- continued the advancement of flumethrin in honey, with an MRL not deemed necessary;
- agreed with the risk management recommendation for gentian violet (this standard was also finalized by the CAC); and
- noted the lack of consensus for the advancement of the MRLs for zilpaterol hydrochloride (HCl), and decided to hold the proposed MRLs for zilpaterol HCl at Step 4 (5) for further discussion.

Comments on the parallel review process

The 24th Session of CCRVDF (3) suggested that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) conduct a pilot parallel review, including establishing an acceptable daily intake (ADI) and recommending MRLs while the same compound is still under review by a national authority for registration.

The JECFA Secretariat therefore evaluated selamectin at the current meeting to pilot this process. Based on the experience with this evaluation, the Committee emphasized the need to maintain maximum transparency and scientific rigour, and concluded that:

- the process and requirements should be essentially the same as those for a compound that has already received registration in a Member State, including providing a complete dossier to make it possible to establish health-based guidance values (HBGVs) and recommend MRLs;
- even if a finalized good practice in the use of veterinary drugs (GVP) is not available for a product that has not yet been formally approved or registered, a proposed dosing regimen(s) and withdrawal period(s) should be provided; and
- additional discussion on this process would be welcome (noting that CCRVDF has agreed to develop a discussion paper to examine the advantages and disadvantages).

Report on JECFA/JMPR Residue Definition Working Group

Previous working groups of JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have recommended that JECFA and JMPR pursue harmonization of their residue definitions, to facilitate exposure assessment of dual-use compounds (i.e. those used both as a veterinary drug and as a pesticide) and harmonization of enforcement strategies. A joint

working group of JECFA and JMPR experts, in conjunction with an Organisation for Economic Co-operation and Development (OECD) working group, met in Geneva in 2018. The Committee agreed with the conclusions and recommendations of the joint working group, and supports further work on this subject.

General considerations about the use of scientific literature in risk assessment

The Committee considered that the ideal source for data used in a scientific risk assessment is from studies conducted and presented to internationally agreed guidelines; conducted in accordance with the principles of good laboratory practice (GLP), if applicable; and ideally containing individual data. It acknowledged that it considers all relevant evidence (e.g. published scientific literature peer-reviewed publications and theses) in support of a risk assessment. The Committee summarized what information published reports should contain for a toxicological evaluation and a residue evaluation, and noted that it will not be able to use reports that are missing critical information.

Toxicological profiling of compounds and less-than-lifetime dietary exposure assessment

Following the recommendations and previous work done by JECFA and JMPR, an electronic working group comprising experts from JMPR and JECFA was formed to finalize the approach to the toxicological profiling of compounds and less-than-lifetime dietary exposure assessment. The working group recommended that:

- exposure experts participating in JECFA and JMPR should routinely provide dietary exposure estimates for a range of subpopulations;
- experts participating in JECFA and JMPR should systematically compare the ADI or theoretical daily intake (TDI) with the various exposure estimates, and document the risk characterization; and
- because risk characterization is a key component of the risk assessment process, JECFA and JMPR Secretariats should allocate sufficient time for risk characterization before the adoption of the report.

The 2019 JMPR piloted this approach, and the outcome will be included in Chapter 4 of the report of that meeting.

The present Committee reiterated its view that the toxicological profile of a compound should be the basis for identifying potential at-risk subpopulations (e.g. temporary high consumers and specific life stages) for comparison of exposure estimates with the upper bound of the ADI. However, the Committee accepted that there is currently no general acceptance of how this should be done. Therefore, for the time being, JECFA accepts the recommendation of the joint JECFA/JMPR electronic working group and will calculate exposure estimates for all potentially relevant subpopulations. At the present meeting, the Committee concluded that there were no less-than-lifetime concerns for diflubenzuron and halquinol, the only compounds on the current agenda for which both safety and residue evaluations were completed.

Combined exposure to multiple chemicals

The EuroMix project, 2015–2019k¹ is funded by the European Commission to develop approaches and methods for the risk assessment of combined exposures to multiple chemicals. In April 2019 it was complemented by a joint FAO/WHO expert consultation that

¹ See www.euromixproject.eu and <https://cordis.europa.eu/project/rcn/193181/factsheet/en>.

aimed to develop an internationally applicable approach for the risk assessment of combined exposure to multiple chemicals (6).

The participants of the FAO/WHO expert consultation agreed to restrict recommendations to substances that are not DNA reactive mutagens, which they suggested should instead be addressed by the WHO working group on Guidance for the Evaluation of Genotoxicity of Chemical Substances in Food. Participants then developed an approach for the risk assessment of combined exposure to multiple chemicals in food. They recommended that the approach should be piloted at forthcoming meetings of JECFA and JMPR, and that after its application for 2–3 years, it should be evaluated and revised as necessary, including the pragmatic cut-off point.

The present Committee agreed to pilot the approach based on chronic exposure for compounds being evaluated at the meeting, but concluded that 2–3 years would be insufficient to judge the utility of the approach. Moreover, estimating combined exposure at an international level would be challenging with respect to both the availability of suitable data and the application of the methodology (e.g. where distributions for consumption are available from some countries but not others).

At the present meeting, neither of the compounds that were on the agenda for which safety and residue evaluations were completed (diflubenzuron and halquinol) belonged to an established assessment group for the combined exposure to multiple chemicals. For neither of the compounds did the estimated dietary exposure from veterinary use exceed 10% of the upper bound of the ADI in any population or subpopulation.

Microbiological effects as part of the safety evaluation of veterinary drug residues in food

JECFA assesses chronic risk of residues in food of veterinary drugs for food-producing animals by determining an ADI, based on toxicological or pharmacological effects. In the case of veterinary drugs with antibacterial activity, effects on the human intestinal microbiota are also assessed, to determine a microbiological ADI (mADI).

The Committee follows International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline (GL) 36 (7), which provides a step-by-step approach to determine whether drug residues with antimicrobial activity reaching the human colon remain microbiologically active, and whether an mADI determination is necessary. Two end-points of concern for human health are considered in this assessment: disruption of the colonization of the human intestinal microbiome, and increases in the population(s) of resistant bacteria in the human intestinal microbiome.

The Committee noted at the present meeting that although sponsors typically provide adequate data on disruption of the colonization barrier, they often do not provide data to address the antimicrobial resistance end-point of concern. Without such information, the Committee may not be able to complete its assessment, resulting in the inability to establish an ADI for the compound, as was the case with fosfomycin at the present meeting. The Committee therefore emphasizes the need for sponsors submitting a data package for evaluation by JECFA to take into account the potential for veterinary drugs at residue levels in food to select for the development of resistance in the microbiota in the gastrointestinal tract. Suitable in vivo and in vitro test systems and methods for determining no-observed-adverse-effect concentrations (NOAECs) and NOAELs for the end-point of antimicrobial resistance are provided in the VICH GL36 guideline.

Annex 3: Future work and recommendations

Ethion

Information essential in the evaluation of the compound

The Committee reiterated that the following information, identified at the 85th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), would be needed to complete the assessment:

- A metabolism study, using radiolabelled ethion in cattle, that identifies the metabolites and measures the depletion of total residues. Suitable marker residue(s) (MRs) should be identified, and their relative distribution in edible tissues and the ratio of marker to total residues should be determined. A way to address this would be to provide a study conducted in line with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline (GL) 46 (8).
- Depending on the outcome of the metabolism and MR determination, if the MR is different to parent ethion, a non-radiolabelled residues study, in line with good practice in the use of veterinary drugs (GVP).
- A comparison between metabolites in cattle and metabolites in laboratory species, to ensure that all residues of toxicological concern produced in cattle are covered by the available toxicology studies.
- Analytical method(s) that can measure suitable MRs in all edible tissues, validated in accordance with established guidance (9), if it is found to be necessary to change the proposed MR.

Flumethrin

Data required to complete the assessment

The following data will be required to determine suitable MRLs:

- Data to confirm the metabolites formed in cattle after treatment with flumethrin.
- Data to confirm the MR, and to determine the ratio of MR to total radioactive residue (MR:TRR) at suitable timepoints.
- Data to identify the unidentified metabolite in milk and determine whether this metabolite is formed in laboratory species, and then, if not, to determine its toxicological profile.
- Residue depletion data from studies conducted according to GVP, using the dosing regimen leading to the highest and most persistent residues, in both edible tissues and milk.

Fosfomicin*Data required to complete the assessment*

The following data will be required to complete the assessment:

- Information on the selection for and emergence of resistance in the microbiota in the gastrointestinal tract.
- Results from non-radiolabelled studies in both target species, using the highest intended dose and duration of treatment, as well as the administration route leading to the highest residue concentrations in edible tissues derived from treated animals.
- Full study reports, including individual sample residue concentrations.
- Full validation data according to the requirements published in CAC/GL71-2009 (9) for the liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method, to allow for assessment of the usability of LC-MS/MS in routine residue control.

Selamectin*Further information required to complete the residue assessment*

The following data will be needed to complete the residue assessment:

- Characterization of the residues in tissues in order to establish an MR:TRR.
- An MR depletion study under conditions of use.
- Information on an analytical method suitable for monitoring purposes.
- Information on the proposed withdrawal period.
- Confirmation of the stability of the radiolabel in tissues.

Annex 4: List of participants

Eighty-eighth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Rome, Italy, 22–31 October 2019

World Health Organization (WHO) members

Professor (Emeritus) Alan R. Boobis, National Heart and Lung Institute, Imperial College London, London, United Kingdom (*Co-Chair*)

Dr Carl E. Cerniglia, Director, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, United States of America

Mr G.J. (Johan) Schefferlie, Medicines Evaluation Board, Veterinary Medicinal Products Unit, Utrecht, The Netherlands (*WHO Rapporteur*)

Food and Agriculture Organization of the United Nations (FAO) members

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

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

Dr Pascal Sanders, ANSES [French Agency for Food, Environmental and Occupational Health & Safety] – Laboratoire de Fougères, Fougères, France

Dr Stefan Scheid, BVL – Federal Office of Consumer Protection and Food Safety, Department of Veterinary Medicines, Berlin, Germany (*Chair*)

FAO experts

Professor Benjamin U. Ebeshi, Department of Pharmaceutical & Medicinal Chemistry, Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria

Dr Holly Erdely, Residue Chemistry Team, Division of Human Food Safety, FDA Center for Veterinary Medicine, Rockville, United States of America

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

Mr Samuel Fletcher, United Kingdom Veterinary Medicines Directorate, Surrey, United Kingdom

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

Dr Rainer Reuss, Safe Work Australia, Canberra, Australia

WHO expert

Professor Silvana Lima Górnaiak, Department of Pathology, School of Veterinary Medicine and Animal Sciences, University of São Paulo

WHO temporary adviser

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

Secretariat

Ms Gracia Brisco, Food Standards Officer, Joint FAO/WHO Food Standard Programme, Food and Agriculture Organization of the United Nations, Rome, Italy (*Codex Secretariat*)

Dr Hilary Cadman, Cadman Editing Services, Bellingen, Australia (*WHO technical editor*)

Dr Vittorio Fattori, Food Safety and Quality Unit, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations (*FAO Secretariat*)

Dr Kevin Greenlees, Senior Advisor for Science and Policy, Center for Veterinary Medicine, US Food and Drug Administration, Maryland, United States of America (*Chair of Codex Committee on Residues of Veterinary Drugs in Foods*)

Dr Markus Lipp, Senior Food Safety Officer, Scientific Advice and FAO JECFA Secretary, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Secretariat*)

Mr Soren Madsen, WHO JMPR and JECFA Secretariat, Department of Food Safety and Zoonoses (FOS), World Health Organization, Switzerland (*WHO Secretariat*)

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