



Food and Agriculture
Organization of
the United Nations



JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Seventy-eighth meeting (Residues of veterinary drugs)
Geneva, 5–14 November 2013

SUMMARY AND CONCLUSIONS

Issued 22 November 2013

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 5 to 14 November 2013. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Professor A. Boobis, Imperial College London, London, England, United Kingdom, served as Chairman, and Dr P. Sanders, ANSES-Laboratoire de Fougères, Fougères, France, served as Vice-Chairman.

Mr S.J. Crossley, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, Department of Food Safety and Zoonoses, World Health Organization, served as Joint Secretaries.

The present meeting was the seventy-eighth in a series of similar meetings and was the twentieth meeting of JECFA 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, for establishing acceptable daily intakes (ADIs) and for 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 concerns raised by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). In total, eight veterinary drugs were considered by the Committee.

The report of the meeting will be printed 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 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. The participants are listed in Annex 3.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 69. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monographs No. 15.

More information on the work of JECFA is available at:

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

and

<http://www.who.int/foodsafety/chem/jecfa/en/index.html>

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Annex 1

Recommendations on the substances on the agenda

Derquantel (anthelmintic agent)

Acceptable daily intake: The Committee maintained the ADI of 0–0.3 µg/kg body weight established at its seventy-fifth meeting (WHO TRS No. 969, 2011).

Estimated dietary exposure: There were insufficient data to calculate an estimated daily intake (EDI), and the theoretical maximum daily intake (TMDI) approach was used. Using the model diet and the marker residue to total residue ratio approach with the MRLs recommended, the estimated dietary exposure is 6.8 µg/person, which represents approximately 38% of the upper bound of the ADI.

Residue definition: Derquantel

Recommended maximum residue limits (MRLs)

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---------|----------------|-------------------|------------------|-------------------|
| Sheep | 7.0 | 0.4 | 0.8 | 0.3 |

Emamectin benzoate (antiparasitic agent)

Acceptable daily intake: The Committee confirmed the ADI of 0–0.0005 mg/kg body weight established by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2011, based on an overall no-observed-adverse-effect level (NOAEL) of 0.25 mg/kg body weight per day for neurotoxicity from 14- and 53-week studies in dogs, supported by an overall NOAEL of 0.25 mg/kg body weight per day from 1- and 2-year studies in rats. An

uncertainty factor of 500 was applied to the NOAEL, which includes an additional uncertainty factor of 5 to account for the steep dose–response curve and irreversible histopathological effects in neural tissues at the lowest-observed-adverse-effect level (LOAEL) in dogs, as used by JMPR and confirmed by the current Committee.

Estimated dietary exposure: The EDI is 11 µg/person per day, which represents approximately 37% of the upper bound of the ADI.

Residue definition: Emamectin B1a

Recommended maximum residue limits (MRLs)

| Species | Muscle (µg/kg) | Fillet ^a (µg/kg) |
|---------|-------------------|--------------------------------|
| Salmon | 100 | 100 |
| Trout | 100 | 100 |

^a Muscle plus skin in natural proportion.

The Committee extended the MRLs for muscle and fillet in salmon to trout.

Gentian violet (antibacterial, antifungal and anthelmintic agent)

Acceptable daily intake: The Committee concluded that it is inappropriate to set an ADI for gentian violet because it is genotoxic and carcinogenic.

Maximum residue limits: MRLs could not be recommended by the Committee, as it was not considered appropriate to establish an ADI. The Committee also noted that there was limited information on residues.

Ivermectin (antiparasitic agent)

Acceptable daily intake: The Committee established an ADI of 0–1 µg/kg body weight at its fortieth meeting (WHO TRS No. 832, 1993).

Estimated dietary exposure: The fortieth meeting of the Committee (WHO TRS No. 832, 1993) included an estimate of the potential intake from muscle. No further assessment of dietary exposure was undertaken at the current meeting.

Residue definition: Ivermectin B1a

Recommended maximum residue limits (MRLs)

| Species | Muscle (µg/kg) |
|---------|-------------------|
| Cattle | 4 |

Lasalocid sodium (antiparasitic agent)

Acceptable daily intake: The Committee established an ADI of 0–5 µg/kg body weight on the basis of a NOAEL of 0.5 mg/kg body weight per day from a developmental toxicity study in rabbits and a multigeneration reproductive toxicity study in rats, with application of an uncertainty factor of 100 for interspecies and intraspecies variability.

Estimated dietary exposure: An EDI of 52 µg/person per day was calculated, which represents approximately 17% of the upper bound of the ADI.

Residue definition: Lasalocid A

Recommended maximum residue limits (MRLs)

| Species | Skin + fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|----------|-----------------------|-------------------|------------------|-------------------|
| Chicken | 600 | 1200 | 600 | 400 |
| Turkey | 600 | 1200 | 600 | 400 |
| Quail | 600 | 1200 | 600 | 400 |
| Pheasant | 600 | 1200 | 600 | 400 |

The Committee extended the MRLs in chicken to turkey and quail and extrapolated the MRLs in chicken to pheasant. No information was available for duck, including on approved uses. As the compound is not registered for use in laying hens, according to the sponsor, it is not appropriate to recommend MRLs for eggs.

Monepantel (anthelmintic)

Acceptable daily intake: An ADI of 0–20 µg/kg body weight was established by the Committee at its seventy-fifth meeting (WHO TRS No. 969, 2012).

Estimated dietary exposure: Using the model diet and marker residue to total residue ratios of 1.00 for muscle and 0.66 for fat, liver and kidney, and applying a correction factor of 0.94 to account for the mass difference between monepantel sulfone (the marker residue) and monepantel, the EDI is 446 µg/person per day, which represents approximately 37% of the upper bound of the ADI.

Residue definition: Monepantel sulfone, expressed as monepantel

Recommended maximum residue limits (MRLs)

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---------|----------------|-------------------|------------------|-------------------|
| Sheep | 13 000 | 1700 | 7000 | 500 |

These MRLs are consistent with the shortest withdrawal time assigned in Member States with an approved use of monepantel.

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Recombinant bovine somatotropins (growth hormones)

Acceptable daily intake: Based on a systematic review of the literature published since the last evaluation, the Committee reaffirmed its previous decision on ADIs “not specified” for somagrebove, sometribove, somavubove and somidobove, established at the fortieth meeting (WHO TRS No. 832, 1993).

Maximum residue limits: The Committee reaffirmed its previous decision on MRLs “not specified” for somagrebove, sometribove, somavubove and somidobove, established at the fortieth meeting (WHO TRS No. 832, 1993).

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Zilpaterol hydrochloride (β_2 -adrenoceptor agonist)

Acceptable daily intake: The Committee 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. The Committee noted that the ADI is based on an acute effect. The Committee also noted that the upper 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.

Residue definition: Zilpaterol (in muscle). The Committee was unable to determine a suitable marker residue in other edible tissues.

Maximum residue limits: The Committee 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.

Annex 2

General considerations

An expanded version of this section will be included in the report of the seventy-eighth meeting of JECFA. It is reproduced here so that the information can be disseminated quickly. This draft will be subject to extensive editing.

A risk-based decision-tree approach for the safety evaluation of residues of veterinary drugs

The present Committee followed the recommendation from the seventy-fifth meeting to review the proposed decision-tree approach for the safety evaluation of residues of veterinary drugs and agreed to the establishment of electronic working groups to address the following aspects and to prepare reports for consideration at the next JECFA meeting:

- Preliminary risk assessment, as envisaged in the decision-tree, would be most readily accomplished by Member States when considering suggesting compounds for evaluation by JECFA. The Committee recommended that an electronic working group should be established to develop guidance on what would comprise a preliminary risk assessment, taking into account the risk analysis principles applied by CCRVDF.
- There are a number of issues that would need to be addressed in applying the threshold of toxicological concern (TTC) approach to residues of veterinary drugs. In particular, some pharmacologically active compounds are very potent, and it is possible that the current TTC values, based primarily on toxicological end-points, would not be applicable. The Committee recommended that an electronic working group should be established to perform a feasibility exercise on the application of the TTC approach to residues of veterinary drugs and, if appropriate, to make specific recommendations for developing such an application.
- The Committee confirmed the importance of developing guidance for the acute risk assessment of residues of veterinary drugs. It was recommended that an electronic working group should be established to develop guidance for establishing acute reference doses (ARfDs) for residues of veterinary drugs, addressing situations in which it would be necessary to establish an ARfD and how this would be done. Consideration should also be given to compounds for which the ADI is based on an acute effect (e.g. pharmacological effects, antimicrobial effects). The working group should include an expert from JMPR who is experienced in the establishment of ARfDs.

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Dietary exposure to veterinary drug residues

An expert meeting on dietary exposure assessment methodologies for residues of veterinary drugs that was held in 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 the current meeting, dietary exposures were calculated for four veterinary drug residues using the model diet approach as well as the new methods for chronic and acute dietary exposure estimation. 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 the Committee, 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.

A number of areas were identified that should be investigated to further improve dietary exposure methodology for residues of veterinary drugs, and the Committee recommended that a working group should be set up to discuss these issues.

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Antimicrobial resistance: update on activities relevant to JECFA

Dr Awa Aidara-Kane from the Department of Food Safety and Zoonoses presented an overview of ongoing activities within WHO, addressing the issue of antimicrobial resistance related to the veterinary use of antimicrobial agents in food animal production and its impact on the therapeutic use of these drugs in human medicine. Dr Carl E. Cerniglia described the complex interactions of the mechanisms involved in the emergence and spread of antimicrobial resistance. His overview focused on the use of antimicrobial agents in food animals and what is currently known about the potential for antimicrobial resistance development.

The Committee will continue to monitor developments in this area and apply those relevant to its work, as appropriate.

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Review of the need to update *Principles and methods for the risk assessment of chemicals in food* (EHC 240)

JECFA, like other expert groups advising WHO and FAO, has codified the general principles by which it evaluates residues of veterinary drugs for their possible risk to consumers from dietary exposure. These were published in reports of the JECFA meetings as they were developed. WHO sought to consolidate these evolving principles and to harmonize, to the extent possible, the approaches used by the various expert groups (JECFA, JMPR, etc.). This culminated in the publication, in 2009, of EHC 240: *Principles and methods for the risk assessment of chemicals in food*. Even at the time of publication, it was recognized that regular updating would be necessary, and it was envisaged that this could be done by providing updates online.

The present Committee agreed that a review of EHC 240 should be a standing item on its agenda from its next meeting, and that any sections or chapters requiring updating would be identified. In such cases, the Committee would make specific recommendations on how this might be achieved.

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Feedback from JMPR on ongoing work on general criteria for interpretation of toxicological data

The Committee was informed that JMPR is developing guidance on the interpretation of minor and adaptive changes observed in studies in experimental animals. This work started with publication of “Guidance on the interpretation of hepatocellular hypertrophy” in 2006. JMPR is extending this guidance to cover a variety of additional end-points. This guidance will also have relevance to JECFA, and it will form a discussion document for eventual inclusion as a section of EHC 240: *Principles and methods for the risk assessment of chemicals in food*.

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Extrapolation of MRLs to minor species

The Twenty-first Session of CCRVDF addressed several comments and questions to JECFA concerning the extrapolation of MRLs to additional (minor) species, which were addressed by the present Committee. 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 meetings of the Committee.

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MRLs for veterinary drug residues in honey

The Committee responded to a question from the Twenty-first Session of CCRVDF 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 the Committee: 1) 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; 2) the establishment of an MRL for honey for substances for which an ADI has not previously been established by JECFA or JMPR; and 3) 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 prepared.

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

The Committee 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, the Committee 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, the Committee 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 a future meeting of the Committee.

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JECFA analytical method validation requirements

Current JECFA guidelines for the validation of analytical methods were adopted at the fifty-second meeting of the Committee in 1999 and subsequently published as Annex 3 of Food & Nutrition Paper 41/14. The present Committee noted that a new Codex guideline, *Guidelines for the design and implementation of national regulatory food safety assurance programme associated with the use of veterinary drugs in food producing animals* (CAC/GL 71-2009), includes detailed updated information on criteria for the selection and validation of analytical methods suitable for use in regulatory programmes for the control of veterinary drug residues in foods. The Committee agreed that the method selection and validation criteria contained in CAC/GL 71-2009 and subsequent revisions to these guidelines will be applied when assessing the suitability of methods proposed to JECFA as regulatory methods to support recommended MRLs. The Committee also agreed that in view of developments in method validation criteria that have occurred since the adoption of the current JECFA method validation requirements in 1999, the criteria for validation of methods used in the pharmacokinetic, metabolism and depletion studies submitted to the Committee should be reviewed and updated at a future meeting of the Committee.

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Annex 3

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

Geneva, Switzerland, 5–14 November 2013

Members

Professor A. Anadón, Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain (*Joint Rapporteur*)

Dr S. Barlow, Toxicologist, Brighton, East Sussex, England, United Kingdom

Dr J.O. Boison, Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon, Saskatchewan, Canada

Professor A.R. Boobis, Centre for Pharmacology & Therapeutics, Department of Experimental Medicine, Division of Medicine, Faculty of Medicine, Imperial College London, London, England, United Kingdom (*Chairman*)

Dr L.G. Friedlander, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA (*Joint Rapporteur*)

Professor S.H. Jeong, Department of Applied Biotoxicology, Hoseo University, Hoseo Toxicology Research Centre, Asan City, Chungnam, Republic of Korea

Professor J. Palermo-Neto, Department of Pathology, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil

Professor Emeritus L. Ritter, University of Guelph, Guelph, Ontario, Canada

Dr P. Sanders, National Reference Laboratory for Veterinary Drug Residues and Antimicrobial Resistance, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES), Fougères, France (*Vice-Chairman*)

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa

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Ms A. Bruno, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy (*Codex Secretariat*)

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Mr S.J. Crossley, Provision of Scientific Advice, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Joint Secretary*)

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Dr N. Jarrett, European Medicines Agency, London, England, United Kingdom (*WHO Expert*)

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- Mr J. Kim, Risk Assessment and Management, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland (*WHO Secretariat*)
- Professor B. Le Bizec, Laboratoire d'Étude des Résidus et des contaminants dans les aliments (LABERCA), École Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes Atlantique (ONIRIS), Nantes, France (*FAO Expert*)
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