Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Seventy-fifth meeting (Residues of veterinary drugs)
Rome, 8–17 November 2011

REVISED Annex 1

SUMMARY AND CONCLUSIONS

Issued 31 January 2012

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 8 to 17 November 2011. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Professor A. Boobis, Imperial College London, London, England, served as Chairman, and Dr D. Arnold, Berlin, Germany, served as Vice-Chairman.

Dr A. Wennberg, Nutrition and Consumer Protection Division, 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-fifth in a series of similar meetings and was the nineteenth meeting of JECFA 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 and for establishing acceptable daily intakes (ADIs) and recommend maximum residue limits (MRLs) for certain drugs when they are administered to food-producing animals in accordance with good practice in the use of veterinary drugs. 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. 66. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monographs No. 12.

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

Annex 1

Recommendations on the substances on the agenda

Amoxicillin (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–0.7 µg/kg body weight on the basis of microbiological effects.

Estimated dietary exposure: The Committee did not calculate an estimated daily intake (EDI) for amoxicillin owing to the small number of quantifiable residue data points. Using the model diet of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat and 1.5 litre of milk with the MRLs recommended, the theoretical maximum daily intake (TMDI) is 31 µg/person, which represents 74% of the upper bound of the ADI.

Residue definition: Amoxicillin

Recommended maximum residue limits (MRLs)

Species	Fat[a] (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)	Milk (µg/kg)
Cattle	50	50	50	50	4
Sheep	50	50	50	50	4
Pigs	50	50	50	50	

[a] Includes skin plus fat in pigs.

Apramycin (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–30 µg/kg body weight on the basis of microbiological effects.

Estimated dietary exposure: Using the limits of quantification (LOQs) of the analytical methods as calculated by the Committee as residue levels for muscle, fat and liver, together with the proposed MRL for

kidney, the theoretical intake in the worst-case scenario would be around 1400 µg/day and would not exceed the upper bound of the ADI.

Residue definition: Apramycin

Recommended maximum residue limits (MRLs)

Species	Kidney (µg/kg)
Cattle	5000[a]
Chickens	5000[a]

[a] The MRLs are temporary. Because of data limitations, the Committee was unable to recommend MRLs in tissues and species other than cattle kidney and chicken kidney. The sponsor is requested to provide improved analytical methods with better performance and lower LOQs and residue depletion studies with appropriate sampling points close to the zero withdrawal periods for all tissues and species. The validated analytical methods and residue depletion studies are requested by the end of 2014.

Derquantel (anthelminthic)

Acceptable daily intake: The Committee established an ADI of 0–0.3 µg/kg body weight on the basis of a lowest-observed-adverse-effect level (LOAEL) of 0.1 mg/kg body weight per day for acute clinical observations in dogs, consistent with antagonistic activity on the nicotinic acetylcholine receptors. A safety factor of 300 was applied to the LOAEL.

Estimated dietary exposure: As the ADI was based on an acute effect, the Committee did not calculate an EDI. Using the model diet of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat and 1.5 litre of milk with the MRLs recommended, the TMDI is 8.04 µg/person, which represents 45% 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	0.7	0.2	2.0	0.2

The Committee was not able to recommend an MRL for sheep milk, as no residue data were provided.

Ivermectin (anthelminthic)

No data on ivermectin were submitted following a public request for data.

The Committee established an ADI of 0–1 µg/kg body weight at its 40th meeting (WHO TRS No. 832, 1993). The Committee concluded at the current meeting that there was a need to evaluate the toxicological information on ivermectin with a view to identifying a critical effect other than in the CF-1 mouse for the establishment of an ADI. Information that would be of value in future toxicological evaluation of ivermectin includes reports on the effects of ivermectin when used as a therapeutic agent in humans and information from in vitro and/or in vivo studies evaluating the critical effects upon which recent ADIs for other avermectins have been established.

MRLs were proposed at the 58th meeting (WHO TRS No. 911, 2002). Before it could re-evaluate the residue depletion of ivermectin and propose updated MRLs, the Committee would need a submission indicating the animals and products for which MRLs are requested, marker residue depletion studies in support of proposed withdrawal times and/or in support of applications for MRLs, and pharmacokinetics and metabolism studies in food-producing animals that might enable interspecies extrapolations. A complete up-to-date list of approved products on the market together with documentation of approved uses, including withdrawal times and all relevant parts of proprietary studies directly or indirectly supporting the approved uses, and an expert report summarizing the above content of the submission and additional relevant published data are also requested. Suitably validated analytical methods should be provided for regulatory control based on contemporary analytical techniques for any future re-evaluation of ivermectin.

Monensin (antimicrobial agent and production aid)

Acceptable daily intake: The Committee established an ADI of 0–10 µg/kg body weight at its 70th meeting (WHO TRS No. 954, 2009).

Estimated dietary exposure: Using the revised MRL, the exposure estimate (TMDI) from the 70th meeting of the Committee was recalculated, resulting in a value of 481 µg/person, which represents 80% of the upper bound of the ADI.

Residue definition: Monensin A

Recommended maximum residue limits (MRLs)

Species	Liver (µg/kg)
Cattle	100

The Committee was unable to revise the current MRLs for goats and sheep, as no additional residue data were provided.

Monepantel (anthelminthic)

Acceptable daily intake: The Committee established an ADI of 0–20 µg/kg body weight on the basis of a NOAEL of 1.8 mg/kg body weight per day, considering liver effects in mice, and a safety factor of 100, with rounding to one significant figure.

Estimated dietary exposure: Using the model diet and a ratio of marker residue to total residue of 100% for muscle and 66% for fat, liver and kidney, and applying a correction factor of 0.94 to account for the mass difference between the marker residue and monepantel, the EDI is 201 µg/person, which represents 17% of the upper bound of the ADI.

Residue definition: Monepantel sulfone

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Sheep	5500	700	3000	300

The Committee was unable to propose an MRL for sheep milk, as no data were provided.

Narasin (antimicrobial agent and production aid)

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 and a safety factor of 100 at its 70th meeting (WHO TRS No. 954, 2009).

Residue definition: Narasin A

Recommended maximum residue limits (MRLs)

The Committee recommended full MRLs, as a validated analytical method for residue control purposes is available and was evaluated as satisfactory for the purpose.

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	50	15	50	15

Triclabendazole (anthelminthic)

The Committee concluded that the available database on the residues of triclabendazole in goat was too limited to allow a scientifically justifiable extrapolation of MRLs for cattle and sheep tissues to this species of animal.

Annex 2

General considerations

An edited version of this section will be included in the report of the seventieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information can be disseminated quickly. This draft will be subject to extensive editing.

Comments on documents under elaboration for the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)

The Committee reviewed the draft report of the *Electronic Working Group on the Revision of the Risk Analysis Principles Applied by the CCRVDF and Risk Assessment Policy for the Setting of MRLVDs* (no date), especially as it relates to the work of JECFA. The Committee commented on some of the proposed revisions, for the JECFA Secretariat to bring into the discussion at the upcoming Twentieth Session of CCRVDF (May 2012).

Regarding the draft *Report of the Electronic Working Group to Develop Risk Management Options for Veterinary Drugs for which No ADI and/or MRL has been Recommended by JECFA due to Specific Human Health Concerns* (8 July 2011), the Committee emphasized that any requests for further assessments on such compounds to JECFA needed to be accompanied by a clear description of the specific request from CCRVDF and formulation of the risk management needs.

Regarding the draft report of the *CCRVDF Electronic Working Group on Extrapolation of MRLs for Veterinary Drugs to Additional Species and Tissues* (17 October 2011), the Committee provided comments on proposed risk analysis policy aspects, for the JECFA Secretariat to bring into the discussion at the upcoming Twentieth Session of CCRVDF (May 2012).

Information on registration/approval status of veterinary drugs

Nationally approved good practices in the use of veterinary drugs make an important contribution to the risk profile of a drug. For JECFA, it is important that all related information relevant for the risk assessment is available to the Committee when it evaluates substances with a view to recommending MRLs. In the past, information on registration/approval status of veterinary drugs and on approved conditions of use was not always available to the Committee in time, leading to unnecessary difficulties in its discussions. The Committee therefore requests:

- that CCRVDF provide the Secretariat with information on registration/approval status and the use pattern of veterinary drugs whenever it requests an evaluation by JECFA;
- that the JECFA Secretariat always include a request for submission of such information by the sponsors of the data into future calls for data. The Secretariat should also verify that such information is contained in the data submission of sponsors before it makes work assignments to the experts of the Committee.

Extrapolation of MRLs

The Committee recognized the importance of using good science when extrapolating between food animal species to support the development of MRLs in additional food animal species and commodities. In addition, the Committee recognized the ongoing CCRVDF electronic working group that is collecting and evaluating information and developing recommendations on a risk analysis policy for use by CCRVDF when extrapolating MRLs.

The Committee agrees that it is important to develop minimum criteria for information upon which to base extrapolation between food animal species and commodities. In view of the foregoing, the Committee recommended that the Secretariat establish an electronic working group to continue work commenced at the current meeting and to develop proposed minimum criteria for consideration at the next JECFA meeting for veterinary drugs.

Dietary exposure assessment methodologies

Explanation
At its seventieth meeting, following discussion of the decision-tree approach as well as consideration of the output of the workshop on MRLs in pesticides and veterinary drugs, held in Bilthoven in 2005, the Committee identified that further work was required on approaches for exposure assessments for veterinary drug residues, in particular for chronic and acute exposures.

At its Eighteenth and Nineteenth Sessions, CCRVDF responded with a request to FAO and WHO to convene an expert consultation on exposure assessment methodologies for residues of veterinary drugs in foods. CCRVDF requested that FAO and WHO address the following: review of the current model diet (so-called market basket approach) applied by JECFA; possible simplification of the current model diet; possible development of several model diets to reflect regional differences in consumption patterns; and development of approaches for acute and subchronic dietary exposure assessment.

To help address this need for updated methodology, FAO and WHO issued a call for data on consumption of foods of animal origin in 2010. In response, food consumption data from 47 countries were submitted, and a submission from an interested party was also received. To provide an opportunity for stakeholders and interested parties to present their views, FAO and WHO held an open stakeholder meeting in Rome on 7 November 2011. The stakeholder meeting was attended by members of an expert meeting convened to review and update the principles and methodology to assess dietary exposure to residues of veterinary drugs in food, held from 7 to 11 November 2011, as well as participants at the seventy-fifth meeting of JECFA.

The experts on exposure assessment prepared a draft report outlining their proposed new approaches for acute and chronic [1] dietary exposure assessment for veterinary drug residues, taking the key findings, concerns and recommendations of the stakeholders into consideration. Discussions and exchanges were organized between participants at both the meeting on dietary exposure assessment methodologies and the seventy-fifth JECFA. Examples to compare the current model with proposed models were collaboratively developed.

[1] Includes subchronic for the purposes of this exercise.

JECFA considerations for acute dietary exposure estimates

Acute dietary exposure estimates should cover a time period of food consumption over a single meal or one day and are intended to be used for comparison with acute reference dose (ARfD) values in a risk assessment process. The present Committee emphasized that, depending on the health end-points for acute risk, acute exposure should be estimated for both the general population and children.

JECFA considerations for chronic dietary exposure assessments

Chronic dietary exposure estimates cover food consumption over the long term and are intended to be used for comparison with a health-based guidance value based on chronic toxicity, such as an ADI, in a risk assessment process. At its seventieth meeting, the Committee confirmed the use of the median residue level from depletion studies, with a correction for marker residue to total residue, instead of the MRL for long-term dietary exposure estimates, when supported by the available data.

Main outputs of the expert meeting on dietary exposure assessment methodologies

Models were proposed to estimate both acute and chronic exposure to residues of veterinary drugs in food. The Committee noted that, compared with the current model, the proposed models use more detailed consumption data. The exploration of new approaches to the assessment of dietary exposure to veterinary drug residues is part of the ongoing process of ensuring that evaluations undertaken by the Committee incorporate available data as well as recent advances in methodology and scientific knowledge. When finalized, the proposed models should be considered as tools for potential use in the assessment of dietary exposure to residues of veterinary drugs.

The report of the expert meeting will include the proposed new models for assessing acute and chronic dietary exposure to residues of veterinary drugs, the data on food consumption received and evaluated for use in the models and a summary of the input and views expressed at the stakeholder meeting.

Further steps

Comments on the draft report of the expert meeting will be solicited from participants of the seventy-fifth meeting of the Committee soon after the meeting. Following consideration of these comments, a revised draft report will be prepared for public comments. The final report will be presented to CCRVDF at its Twentieth Session (May 2012) for discussion and comments. The dietary exposure models will then be discussed at a future meeting of the Committee, and other worked examples will be performed based on the proposed models to gain more experience.

Decision-tree approach to the evaluation of residues of veterinary drugs

The Committee gave further consideration to the proposal for a hypothesis-driven decision-tree approach for the safety evaluation of residues of veterinary drugs discussed at its seventieth meeting, following up on the recommendations from the discussion at that meeting. The JECFA Secretariat informed the Committee that the expert meeting on dietary exposure assessment methodologies conducted in parallel to this meeting was convened to address the recommendation to develop methods for acute and chronic exposure assessment. The other recommendations remain to be addressed.

In discussing the recommendations of the seventieth meeting, the Committee recommended that the JECFA Secretariat establish an electronic working group to elaborate principles to establish acute reference doses for residues in veterinary drugs, taking the guidance developed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) into account as well as ongoing efforts by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). A draft guidance document will be prepared for discussion at the next meeting.

In discussing the application of a threshold of toxicological concern (TTC) approach to veterinary drugs, the Committee agreed that this is a valid approach and relevant for veterinary drugs in some circumstances; however, it requires additional specific consideration for veterinary drugs with respect to their possible pharmacological and microbiological effects. The Committee recommended that the JECFA Secretariat establish an electronic working group to develop the scope of work for application of the TTC approach to veterinary drugs and to develop a project plan to address this work.

The Committee also noted that a step for providing a preliminary risk assessment, covered under the problem formulation step in the decision-tree, is mentioned in the risk analysis policy as applied by CCRVDF. However, it seems that this step is currently not being implemented, and the Committee recommends that CCRVDF, when updating its risk analysis policy, develop guidance on how to implement this step in the future.

Guidance for JECFA experts

At its present meeting, the WHO group identified a number of inconsistencies in style or convention in its working documents, in addition to those identified at recent previous meetings, reflecting the fact that the present guidance to experts was prepared some time ago. It was agreed that the guidance to experts for the preparation of working documents should be updated and include clear advice on those issues identified at recent meetings.

It was further agreed that the guidance to FAO experts for the preparation of meeting documents should be consolidated and updated.

The Committee requests the JECFA Secretariat to undertake this work. The importance of interaction when updating the WHO and FAO guidance was emphasized, as there are several issues requiring common agreement.

Annex 3

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

Rome, Italy, 8–17 November 2011

Members

Professor A. Anadón, Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Dr D. Arnold, Consultant, Berlin, Germany *(Vice-Chairman)*

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

Dr R. Ellis, Consultant, Myrtle Beach, SC, United States of America (USA) *(Joint Rapporteur)*

Dr A. Fernández Suárez, Ciencias Veterinarias, Universidad del Salvador, Buenos Aires, Argentina

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Dr K.J. Greenlees, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(Joint Rapporteur)*

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

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa[1]

Secretariat

Dr J. Boison, Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon, Saskatchewan, Canada *(FAO Expert)*

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

Dr C.E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, AR, USA *(WHO Temporary Adviser)*

[1] Dr Swan was invited but unable to attend the meeting.

Dr P.L. Chamberlain, Office of the Chief/Office of the Chief Scientist/Office of Counterterrorism and Emerging Threats, Food and Drug Administration, Department of Health and Human Services, Silver Spring, MD, USA *(WHO Temporary Adviser)*

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