



**Food and Agriculture Organization
of the United Nations**



**World Health
Organization**

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-second meeting
Rome, 4–12 February 2004**

SUMMARY AND CONCLUSIONS

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 4 to 12 February 2004. The purpose of the meeting was to evaluate certain residues of veterinary drugs in food.

Dr D. Arnold, Berlin, Germany served as Chairman, Dr J.G. McLean, Camberwell, Victoria, Australia, served as Vice-Chairman.

Dr M. Lützow, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, International Programme on Chemical Safety, World Health Organization, served as Joint Secretaries.

The present meeting was the sixty-second in a series of similar meetings and was the sixteenth meeting of JECFA convened to deal with 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 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.

The report of the meeting will appear 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 containing a detailed table (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs 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.53*. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in *FAO Food and Nutrition Paper Series No. 41/16*.

More information on the work of JECFA is available at

www.fao.org/es/esn/jecfa/index_en.stm

www.who.int/pcs/jecfa/jecfa.htm

The issuance of this document does not constitute formal publication. The document may, however, be freely reviewed, abstracted, reproduced, or translated, in whole or in part, but not for sale or use in conjunction with commercial purposes.

Annex 1**Recommendations on compounds on the agenda****Antimicrobial agents****Cefuroxime**

Acceptable daily intake: The temporary ADI established at the fifty-eighth meeting of the Committee (WHO TRS 911, 2002) was withdrawn.

Residues: The temporary MRL for cattle milk was withdrawn.

Chloramphenicol

Acceptable daily intake: The Committee concluded that it is not appropriate to establish an ADI for chloramphenicol.

Residues: The Committee concluded that

There was no evidence supporting the hypothesis that chloramphenicol is synthesized naturally in detectable amounts in soil. Although this possibility is highly unlikely, data generated with modern analytical methods would be required to confirm this;

There was evidence that low concentrations of chloramphenicol found in food monitoring programs in the year 2002 could not originate from residues of chloramphenicol persisting in the environment after historical veterinary uses of the drug in food producing animals. However, due to the high variability of the half life of chloramphenicol under different environmental conditions, such a mechanism might occasionally cause low level contamination in food;

Valid analytical methods are available to monitor low levels of chloramphenicol in foods. However confirmatory methods require sophisticated and expensive equipment.

Flumequine

Acceptable daily intake: The Committee re-established an ADI of 0–30 µg/kg bw.

Residue definition: Flumequine

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	1000	3000	500	500
Black tiger shrimp (<i>P. monodon</i>)	-	-	-	500 ^a
Chicken	1000	3000	500	500
Pigs	1000	3000	500	500
Sheep	1000	3000	500	500
Trout	-	-	-	500 ^b

^a The MRL is temporary; the following information is requested by 2006: (1) A detailed description of a regulatory method, including its performance characteristics and validation data; (2) Information on the approved dose for treatment of black tiger shrimp and the results of residue studies conducted at the recommended dose.

^b Muscle including normal proportions of skin.

Lincomycin

Acceptable daily intake: 0-30 µg/kg bw (established at the fifty-fourth meeting of the Committee (WHO TRS 900, 2001))

Residues: The MRLs that were recommended by the fifty-fourth (WHO TRS 900, 2001) and fifty eighth (WHO TRS 911, 2002) meeting of the Committee were not reconsidered and maintained. MRL for cattle tissues were considered but not recommended by the sixty-second meeting.

Pirlimycin

Acceptable daily intake: The Committee established an ADI of 0–8 µg/kg bw

Residue definition: Pirlimycin

Recommended maximum residue limits (MRLs)^a

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Milk (µg/kg)	Muscle (µg/kg)
Cattle	100	400	1000	100	100

^a For the Maximum Residue Limits for pirlimycin, the Committee noted that the analytical method submitted by the sponsor had been validated suitably, however, the mass spectrometry interface was not commercially available anymore and therefore the method would not comply with all Codex requirements for a Regulatory Analytical Method. Since the Committee received information that verification of this method using different equipment was on the way, it recommends that CCRVDF only proposes the MRL for adoption by the Codex Alimentarius Commission if this work has been completed and made available to the WG Methods of Analysis and Sampling in the CCRVDF.

Insecticides**Cyhalothrin**

Acceptable daily intake: The Committee established a permanent ADI of 0 – 5 µg/kg bw

Residues definition: Cyhalothrin

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Milk (µg/kg)	Muscle (µg/kg)
Cattle	400	20	20	30	20
Pigs	400	20	20	-	20
Sheep	400	20	50	-	20

Cypermethrin and alpha-cypermethrin

Acceptable daily intake: The Committee established a common ADI of 0–20 µg/kg bw for both cypermethrin and alpha-cypermethrin

Residue definition: Total of cypermethrin residues (resulting from the use of cypermethrin or alpha-cypermethrin as veterinary drugs)

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Milk (µg/kg)	Muscle (µg/kg)
Cattle	1000	50	50	100	50
Sheep	1000	50	50	100	50

Doramectin

Acceptable daily intake: 0-1µg/kg bw (established at the fifty-eighth meeting, WHO TRS 911, 2002)

Residue definition: Doramectin

Recommended maximum residue limit (MRL)

Species	Milk (µg/kg)
Cattle	15 ^a

^a The committee noted that (1) on the basis of a 15 µg/kg MRL for doramectin in whole milk in cattle, the milk discard times would be approximately 240 hours based on the studies using the pour-on treatment. Milk discard times would be approximately 480 hours following treatment using the injection formulated dose; (2) in milk containing 4 per cent milk fat, the residues in milk fat would be equivalent to 375 µg/kg (15 µg/kg ÷ 0.04 = 375µg/kg) This is higher than the 150 µg/kg MRL in fat tissue; (3) the discard time necessary to accommodate the recommended MRL in milk is unlikely to be consistent with good veterinary practice.

Phoxim

Acceptable daily intake: 0 - 4 µg/kg bw (established at the fifty-second meeting (WHO TRS 893, 2000))

Residues: The MRLs for sheep, pigs and goats that were recommended by the fifty eighth (WHO TRS 911, 2002) meeting of the Committee were not reconsidered and maintained.
The temporary MRLs for cattle that were recommended by the fifty-second (WHO TRS 893, 2000) and fifty-eighth (WHO TRS 911, 2002) meeting of the Committee were withdrawn.

Production aids**Melengestrol acetate**

Acceptable daily intake: 0-0.03 µg/kg bw (established at the fifty-fourth meeting of the Committee (WHO TRS 900, 2001))

Residues definition: Melengestrol acetate

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Liver (µg/kg)
Cattle	8	5

Ractopamine

Acceptable daily intake: 0–1 µg/kg bw

Residues definition: Ractopamine

Recommended maximum residue limits (MRLs)

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	10	90	40	10
Pigs	10	90	40	10

Annex 2

General consideration items

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

Response to CCRVDF on Draft Risk Assessment Policy

At its 60th meeting the Committee had provided answers to CCRVDF on some specific questions regarding its risk assessment principles (<ftp://ftp.fao.org/es/esn/jecfa/ccrvdf60.pdf>). On the request of FAO and WHO, the Committee at the present meeting reviewed Annex I of the *Discussion Paper on Risk Analysis Principles and Methodologies in the Codex Committee on Residue of Veterinary Drugs in Food* (CX/RVDF 01/9 ftp://ftp.fao.org/codex/ccrvdf13/rv01_09e.pdf).

Although the Committee recognised the value of a risk assessment policy, it was concerned that the current draft document to CCRVDF was not adequate due to serious flaws in structure and content.

At the present meeting the Committee agreed that Annex I of the above mentioned draft discussion paper in its current form requires substantial revision, which should consider the following issues:

- A risk assessment policy should provide a general policy framework for the work of risk assessors and not describe the details of the four steps of the risk assessment process.
- The roles and responsibilities of risk assessors and risk managers need to be clearly defined, recognizing the independence and transparency of the risk assessment process.
- The development of risk assessment guidelines is an inherent part of the corresponding scientific work which needs to be accomplished by risk assessors.
- The Expert Committee is an independent scientific body that provides advice not only to Codex but also directly to FAO and WHO and to member countries. The risk assessment policy needs to recognize these related but independent roles of the Committee.
- The Committee noted that similar activities are on-going in other Codex Committees (e.g. CCFAC, CCFH, CCPR) and therefore strongly recommends that every effort should be made to harmonise these activities.

The Committee recommended that a risk assessment policy (principles and processes) should include at least the following elements:

- Objectives of a risk assessment
- Responsibilities of risk manager and risk assessor in the process of problem formulation
- Need and mechanisms for effective dialogue between risk manager and risk assessor
- Core principles to conduct a risk assessment (e.g. scientific soundness, transparency, etc)
- Inputs to the risk assessment (e.g. sources of data, confidentiality etc)
- Outputs of the risk assessment (form and detail, including request for different risk management options and their consequences)
- Level of protection to be provided by the risk assessment

The Committee welcomed the opportunity to comment on the current document; the Joint Secretariat is asked to continue the discussion with CCRVDF and to consider the possibility of consulting members of JECFA before the next meeting of the Committee in a written procedure. A close co-ordination with other ongoing activities is also desirable.

Conclusions On Specific Toxicological Endpoints

In an effort to improve consistency and transparency, the Committee recommended that a series of standard statements be developed that allow for clear and consistent conclusions on specific toxicological endpoints, in particular on genotoxic and carcinogenic potentials, as well as on reproductive toxicity. The

Committee noted that JMPR has developed a set of statements with defined circumstances which should be used as a basis and adapted and/or expanded as appropriate.

The Committee recommended that a small working group, including experts from other JECFA and JMPR panels, should elaborate a set of phrases for conclusions on genotoxic and carcinogenic potentials for discussion at the next meeting, taking into consideration existing efforts. The working group should address standard reporting for other toxicological endpoints as well.

Statistical methods for the estimation of MRLs

On several previous meetings the Committee has discussed that it was desirable to use statistical methods when deriving Maximum Residue Limits for Veterinary Drugs (MRLs) whenever a suitable data base was available. A statistical approach was followed on several occasions where the data met the necessary criteria.

This statistical approach included:

- Linear regression analysis of data describing the terminal depletion of a suitable marker residue in edible tissues following the (last) administration of the drug under approved conditions of use;
- Subsequent use of the results of the regression analysis for the estimation of upper limits of the 95% (alternatively 99%) confidence interval for the upper one-sided tolerance limit on the 95th (alternatively 99th) percentile of the population sampled;
- Iterative calculation of such statistical limits as a function of time over the whole phase of terminal elimination of the marker residue;
- The statistical method includes a mechanism for the derivation of Maximum Residue Limits for Veterinary Drugs from a set of data.

Since the necessary calculations are complex and should be performed reproducibly and in a fully transparent manner, the Secretariat has supported the development of a tool which is based on spreadsheets and which facilitates the application of the necessary statistical tests to kinetic residue depletion data and the calculation of the above mentioned statistical tolerance limits. The currently available test version supports the estimation of suitable MRLs for edible tissues. The workbook uses only basic EXCEL instructions. Intentionally no use of sophisticated programming has been made in order to allow the user to control every individual calculation and fully understand the procedure.

The Committee welcomed the initiative of the Secretariat and recommended that the Secretariat continues with the necessary steps:

- to further improve the current applications and the documentation of the tool;
- to extend the applicability of the tool to include estimation of MRLs for milk;
- to publish the tool and invite all interested parties to comment on it;
- to test and validate the tool.

Lipid Soluble Residues of Veterinary Drugs with MRLs in Milk

At this meeting of the Committee, consideration was given to the potential public health impact of lipid soluble residues of veterinary drugs in milk where milk fat may be used for production of processed dairy products. Examples of classes of particular compounds include, but are not necessarily limited to, the macrocyclic lactones and pyrethroids.

The Committee has routinely tried to harmonize its recommendations on MRLs where possible with the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the Codex Committee on Pesticide Residues (CCPR), particularly in those situations where a substance may be used as a pesticide or as a veterinary drug. For a substance such as the cypermethrins, for example, JMPR recommends MRLs in animal milk based on milk fat content. In this regard, reporting a MRL of a lipid soluble compound in cattle milk on a milk fat basis would be consistent with JMPR procedures. Further, this would permit consideration for a single MRL for a substance regardless of its origin either as a veterinary drug or as a pesticide.

At previous meetings of the Committee where MRLs for these classes of compounds have been considered, the Committee has limited its MRL recommendations to fresh milk rather than including recommendations as MRLs in milk fat where large concentration factors occur. This is consistent with the definition of an MRL in raw, unprocessed products. However, the definition does take into account other relevant risks as well as food technological aspects. An example of the effect of reporting an MRL on a

milk fat basis is demonstrated by a situation with an MRL of 1 mg/kg in whole milk. If fresh milk contains four percent milk fat, the MRL value in milk fat would be 25mg/kg ($1 \text{ mg/kg} \div 0.04 = 25\text{mg/kg}$), assuming all residue partitions into the milk fat.

In those situations where milk or milk fat may be used in producing commodities such as butter and cheese, milk fat may be a very high percentage of the finished product and result in very high amounts of residues. These highly elevated amounts of residues in the finished, processed product may cause public health concerns, if resulting in amounts of residues that may exhibit an effect in humans. Such a determination would have to be considered on a case by case basis.

Recognizing the potential public health consequences identified by this matter, the Committee requests early consideration by the Codex Committee on Residues of Veterinary Drugs (CCRVDF) as risk managers on how JECFA should proceed in the future where MRLs of lipid soluble residues in milk originating from the use of veterinary drugs are identified. It should be noted that if CCRVDF indicates to the Committee to proceed in this manner, it would require JECFA to reconsider those MRLs where lipid soluble residues with MRLs in whole milk have been recommended.

Analytical Terminology for Codex Use

The Committee considered a document on proposed revised definitions of analytical terminology contained in the Codex Procedural Manual prepared by the Codex Committee on Methods of Analysis and Sampling, CCMAS (CL 2003/43-MAS). It noted that the Committee report, FAO Food & Nutrition Paper 41/14 contains a section on *Requirements for Validation of Analytical Methods*. The CCMAS document generally references Codex definitions and provides guidance on the experimental data required in response to the definitions. Several proposed revised definitions, however, are of analytical terms also defined in the FAO Food & Nutrition Paper 41/14. The Committee was also aware that the Codex Committee on Residues of Veterinary Drugs in Foods is reviewing requirements for analytical methods, for residues of veterinary drugs in foods. The Committee agreed in principle that definitions of analytical terminology used in JECFA documents should be harmonized with definitions used in the Codex Procedural Manual and in Codex Volume 3.

Since work is in progress in the Codex Committees and final definitions have not been approved by the Codex Alimentarius Commission, the 62nd JECFA Committee agreed that this matter should be considered at the next meeting of the Committee. It recommended that an expert should be assigned to review and report on the status at that Meeting.

Annex 3**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Rome, 4-12 February 2004****Members**

- Dr D. Arnold, Consultant, Berlin, Germany (*Chairman*)
- Prof A.R. Boobis, Section on Clinical Pharmacology, Division of Medicine, Faculty of Medicine, Imperial College, London, England
- Dr R. Ellis, Division of Human Food Safety, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, USA
- Dr A. Fernández Suárez, INTA-ITA- Instituto Nacional de Tecnología Agropecuaria Centro de Agroalimentos, Buenos Aires, Argentina
- Dr K. Greenlees, Division of Human Food Safety, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, USA
- Dr L.D.B. Kinabo, Faculty of Veterinary Medicine, Sokoine University of Agriculture, Morogoro, Chuo Kikua, United Republic of Tanzania
- Dr J. MacNeil, Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon Laboratory, Saskatoon, Saskatchewan, Canada
- Prof J.G. McLean, Professor Emeritus, Camberwell, Victoria, Australia (*Vice-Chairman*)
- Prof Eric S. Mitema, Dept. of Public Health, Pharmacology and Toxicology, Faculty of Veterinary Medicine, College of Agriculture and Veterinary Sciences, University of Nairobi, Kabete, Kenya
- Dr G. Moulin, Agence Française de Sécurité Sanitaire des Aliments, Fougères, France
- Prof João Palermo-Neto, Department of Pathology, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil
- Dr J.L. Rojas Martínez, Ministerio de Agricultura y Ganadería, Laboratorio Nacional de Servicios Veterinarios, Barreal de Heredia, Heredia, Costa Rica
- Dr S. Soback, Head, National Residue Control Laboratory and Department Food Hygiene, Kimron Veterinary Institute, Beit Dagan, Israel

Secretariat

- Dr C.E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, AR, USA (*WHO Temporary Adviser*)
- Dr P. Chamberlain, Department of Toxicology, Covance Laboratories, Vienna, VA, USA (*WHO Temporary Adviser*)
- Dr L.G. Friedlander, Physiologist, Division of Human Food Safety, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Rockville, MD, USA (*FAO Consultant*)
- Dr Zegeye Hailemariam, Food Safety and Beverage, Hygiene and Environmental Health Department Quality Control, Federal Ministry of Health, Addis Ababa, Ethiopia (*FAO Consultant*)
- Dr Jacek Lewicki, Division of Pharmacology and Toxicology, Department of Preclinical Sciences, Faculty of Veterinary Medicine, Warsaw Agricultural University, Warsaw, Poland (*FAO Consultant*)
- Dr M. Lützwow, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, Rome, Italy (*FAO Joint Secretary*)
- Dr Heidi Mattock, St Jean d'Ardières, France (*Editor*)

- Dr Yasuo Ohno, Division of Pharmacology, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)
- Dr Sujittra Phongvivat, D.V.M., Food and Nutrition Division, Food and Agriculture Organization of the UN, Rome, Italy, (*FAO Visiting Scientist*)
- Mrs Ir Marja E.J. Pronk, Center for Substances and Integrated Risk Assessment, National Institute for Public Health and the Environment, Bilthoven, The Netherlands (*WHO Temporary Adviser*)
- Dr Fernando Ramos, Laboratório de Bromatologia, Nutrição e Hidrologia, Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal (*FAO Consultant*)
- Dr P.T. Reeves, National Registration Authority for Agricultural and Veterinary Chemicals, Kingston, ACT, Australia (*FAO Consultant*)
- Mr D. Renshaw, Food Standards Agency, London, England (*WHO Temporary Adviser*)
- Prof L. Ritter, Canadian Network of Toxicology Centres, Department of Environmental Biology University of Guelph, Ontario, Canada (*WHO Temporary Adviser*)
- Dr Gladwin Roberts, Therapeutic Goods Administration, Commonwealth Department of Health and Ageing, Woden, Australia (*WHO Temporary Adviser*)
- Prof G.E. Swan, Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria, Pretoria, South Africa (*FAO Consultant*)
- Dr Angelika Tritscher, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (*WHO Joint Secretary*)
- Prof F.R. Ungemach, Institute of Pharmacology, Faculty of Veterinary Medicine, University of Leipzig, Leipzig, Germany (*WHO Temporary Adviser*)
- Dr Janenuj Wongtavatchai, Department of Medicine, Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand (*WHO Temporary Adviser*)