WHO Technical Report Series
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EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Fifty-eighth report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
Geneva

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations

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WHO Library Cataloguing-in-Publication Data

Joint FAO/WHO Expert Committee on Food Additives (2002 : Rome, Italy)
Evaluation of certain veterinary drug residues in food : fifty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives.

(WHO technical report series ; 911)

1.Food contamination 2.Drug residues — analysis 3.Drug residues — toxicity 4.Veterinary drugs — toxicity 5.Risk assessment 6.Maximum allowable concentration — standards 7.No-observed-adverse-effect level I.Title II.Series

ISBN 92 4 120911 9 **(NLM Classification: WA 712)**
ISSN 0512-3054

Typeset in France
Printed in Switzerland
2002/14725 — Communication in Science/Schuler — 7000

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1. Introduction

A meeting of the Joint FAO/WHO Expert Committee on Food Additives was held at Food and Agriculture Organization of the United Nations (FAO) Headquarters, Rome, from 21 to 27 February 2002. The meeting was opened by Mr Kraisid Tontisirin, Director, Food and Nutrition Division, FAO, on behalf of the Directors-General of FAO and the World Health Organization (WHO). Mr Tontisirin stressed the importance of the meeting of the Committee, which would address the following general issues. The *Conference on international food trade beyond 2000: Science-based decisions, harmonization, equivalence and mutual recognition*, held in October 1999 (*1*), recognized the necessity to 'update and to harmonize between [the Joint FAO/WHO Expert Committee on Food Additives] JECFA and [the Joint Meeting on Pesticide Residues] JMPR all the common principles of the toxicological evaluation of food chemicals (e.g., natural constituents, additives, contaminants, residues of pesticides and residues of veterinary drugs) and publish this information in a single consolidated document'. In response to this recommendation, FAO and WHO have initiated a joint project to update and consolidate the principles and methods for the risk assessment of chemicals in food, which was discussed at this meeting (section 2.2).

Mr Tontisirin noted that the Committee would be responding to a discussion paper on risk analysis (*2*) that was considered by the Codex Committee on Residues of Veterinary Drugs in Foods at its Thirteenth Session (*3*). He stressed that close cooperation between the Expert Committee and the Codex Committee was a fundamental requirement for general acceptance of the work of the Joint FAO/WHO Expert Committee on Food Additives. Such cooperation would require definition of areas of responsibility for each Committee, transparent rules and procedures, and effective communication. The comments provided by the Committee to the discussion paper (section 2.1) would be instrumental for improving the risk analysis of residues of veterinary drugs.

Thirteen meetings of the Committee had been held to consider veterinary drug residues in food (Annex 1, references *80*, *85*, *91*, *97*, *104*, *110*, *113*, *119*, *125*, *128*, *134*, *140* and *146*) in response to the recommendations of a Joint FAO/WHO Expert Consultation held in 1984 (*4*). The present meeting[1] was convened in response to a recommendation made at the fifty-

[1] As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives held in 1955 (FAO Nutrition Meeting Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956), there have been 57 previous meetings of the Joint FAO/WHO Expert Committee on Food Additives (Annex 1).

fourth meeting of the Committee that meetings on this subject should be held regularly (Annex 1, reference *146*). The Committee's purpose was to provide guidance to FAO and WHO Member States and to the Codex Alimentarius Commission on public health issues pertaining to residues of veterinary drugs in foods of animal origin. The specific tasks before the Committee were:

— to elaborate further 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 (see section 2); and

— to evaluate the safety of residues of certain veterinary drugs (see section 3 and Annex 2).

2. General considerations

2.1 Risk assessment principles

The Codex Committee on Residues of Veterinary Drugs in Foods, at its Thirteenth Session, considered a discussion paper on principles and methods for risk analysis (*2*). Annex I of that discussion paper relates to the policy for recommending MRLs for veterinary drug residues in food. The Codex Committee decided to forward the Annex to FAO and WHO, so that they could take it into consideration in a joint project to update and consolidate principles and methods of risk assessment, and also to the Joint FAO/WHO Expert Committee on Food Additives, so that it could review the Annex and relay its comments to the Codex Committee. The Expert Committee reviewed the Annex at its present meeting.

Many of the issues that are raised in the Annex have already been addressed by the Expert Committee, and its considerations are recorded in the reports of previous meetings. However, those considerations are not written in the context of risk analysis. In making decisions about risk management, therefore, the Codex Committee and other interested parties sometimes find it difficult to understand the risk assessment principles being used by the Expert Committee.

The procedures for risk assessment change with new scientific knowledge. In addition, there is increasing recognition that assessment procedures should be harmonized for various classes of chemicals and among scientific groups. Therefore, FAO and WHO have initiated a project to update principles and

methods for the assessment of chemicals in food (section 2.2). The aim of this long-term project will be to review the principles and procedures used by the Joint FAO/WHO Expert Committee on Food Additives and the Joint Meeting on Pesticide Residues and reaffirm those that remain valid in view of current scientific knowledge. It will also facilitate the incorporation of new scientific tools, approaches and knowledge into risk assessments of chemicals in food. Furthermore, it will attempt to harmonize, to the extent possible, risk assessment procedures for different classes of chemicals in food and the approaches used by FAO/WHO expert committees with those of other bodies assessing the risk of chemicals in food. This project will be instrumental in defining future policy for risk assessment of residues of veterinary drugs in foods and other chemicals that may be found in foods

The Expert Committee intends to provide a concise response to the issues raised in Annex I of the discussion paper of the Committee on Residues of Veterinary Drugs in Foods. Thus, a working paper addressing the list of questions in the Annex will be prepared by the Joint Secretariat with assistance from members of the FAO expert roster and the WHO expert panel. While it is likely that the Committee will be able to provide definitive information on current policy with regard to many of the issues that have been raised, the responses to some will depend on the conclusions of the project. As risk assessment is a dynamic process, these procedures are subject to constant change.

2.2 Project to update principles and methods for the risk assessment of chemicals in food

The Committee recognized the importance of this Project. It recommended that it consist of a wide-ranging review, based on existing guidance but no preconceptions. The Committee recommended that the Project:

— give clear guidance on risk assessment procedures;

— compile a list of all food-related risk assessment activities conducted by other organizations and review them to reduce duplication;

— harmonize, to the extent appropriate, its activities with similar activities of other organizations, in addition to JECFA and JMPR; and

— emphasize the need for appropriate quality assurance systems.

2.2.1 *Risk assessment practices*

The Committee suggested that use of the term 'safety' factor be reconsidered. The application of such factors in risk assessments should be distinguished from actions taken by risk managers, who may apply additional

factors on the basis of public or political concerns. The Committee agreed that careful consideration should be given to the issue of vulnerable groups, such as the young, the elderly and immunosensitive individuals. Guidance should also be developed on the incorporation of information on genetic polymorphisms into risk assessments. When probabilistic methods are used, advice about the proportion of the population to be protected might be required from risk managers. The activities of the International Programme on Chemical Safety (IPCS) should be reviewed in this respect, including the use of data-derived factors (*5*).

The Committee recommended that application of 'food factors' (the maximum intakes of various animal products) and other methods for assessing food consumption be re-evaluated. Examples of considerations relating to intake include (but are not limited to) harmonization of the ways in which dietary intake is measured by JECFA and by JMPR, guidance on an appropriate theoretical 'food basket', guidance on allocations of an ADI for compounds used both as a pesticide and a veterinary drug, and guidance on the appropriateness of statistical modeling for estimating exposure, particularly when the available data are limited. The Committee also recommended that the Project provide guidance on designing sampling plans for deriving intake data.

The Committee suggested that the establishment of an acute reference dose is appropriate for some veterinary drugs, such as slow-release, injectable formulated drugs or implants, and that the on-going work in this respect for pesticide residues by JMPR and other organizations is relevant to veterinary drugs.

The Committee recognized that it had a clear mandate from the Codex Committee on Residues of Veterinary Drugs in Foods to harmonize risk assessment and risk management practices associated with the development of MRLs, particularly with regard to the activities of the Expert Committee and JMPR. The Committee requested that the Project include re-evaluation and further development of risk assessment principles to provide guidance for these activities. It noted that some flexibility should be allowed in the choice of options for risk reduction, as patterns of use change. The Committee has already identified several cases in which appropriate guidance is needed: target tissues for residue control programmes and for food products in international trade, harmonization of MRLs for the same tissue in different food animals when the relative amounts of residues differ, harmonization and/or extrapolation of MRLs to minor food animal species from data for major food animal species, statistical and other computational approaches for recommending MRLs, and the use of factors to correct for low recovery with an analytical method when establishing MRLs.

The following general considerations were recommended:

— guidance on how and when quantitative risk assessment procedures should be used;

— alternative approaches to risk assessment, such as decision-trees and tiered approaches; and

— harmonization of approaches for carcinogens and non-carcinogens.

The Committee recognized the need to take into consideration other routes and sources of exposure and the possibility of combining the ADIs for compounds that act by a similar mechanism.

The Committee urged that guidance be given for quantifying uncertainty in risk parameters and exposure and for using modelling techniques, such as for identification of thresholds and of population dose–response relationships, in risk assessments.

2.2.2 *Other considerations*

The Committee suggested that additional guidance be provided for the submission of data, although caution should be exercised in deciding to add further toxicological testing requirements. The guidelines should represent a structured approach and be descriptive rather than prescriptive. Recognition of other international sources of guidance and harmonization with existing guidelines were encouraged. The Committee suggested that tiered approaches be considered in assessing the need for generation of toxicological data, and that use of decision-trees might be helpful.

The Committee recognized the limitations of current neurotoxicity testing strategies, particularly with regard to species differences, and suggested that the review being undertaken by JMPR and the approaches of other organizations to addressing the developmental neurotoxicity of pesticides be considered. The Committee urged that the range of observations in testing protocols for neurobehavioural assessment be expanded.

A tiered approach would allow inclusion of immunotoxicological end-points in traditional toxicity studies. Thus, special tests for immunotoxicity would be required only when there was some indication that such toxicity was present.

The Committee noted the importance of validating new toxicological models. Information used for the determination of toxicological end-points should be 'fit-for-purpose'. Guidance should be developed on what constitutes a validated toxicological test protocol or system.

The Committee recommended that the Project include a clear statement about the use of experimental animals. The goal should be to reduce, refine and, where possible, replace animal testing. Account should be taken of the fact that any alternative methods must be validated. Guidance should be provided on the validation and use of biomarkers and of use of the results of experiments in new sciences, such as proteomics, in risk assessments.

The Committee pointed out the need for better guidance in the design and interpretation of studies of kinetics, including toxicological evaluation of metabolites and isomers, and the important issues associated with sampling plans and analytical methods for the generation of data on residues. In order to address the needs of residue control programmes in developing countries, guidance should be given on alternatives to current analytical methods which are suitable for regulatory purposes. Guidance should also be given on relevant factors or protocols for evaluating method performance (including consideration of environmentally acceptable solvents and reagents), appropriate use of economical screening tests that may provide less definitive information than quantitative or confirmatory methods, and the role of uncertainty considerations in analytical methods. Harmonization in this area is an important consideration.

2.2.3 *Toxicological and microbiological end-points*

The Committee recommended that the IPCS 'mode-of-action framework' (*6*) and testing strategies for genotoxicity and carcinogenicity that are being developed, such as those by the International Life Sciences Institute, be considered. Recent advances in reproductive and developmental toxicity testing by national and international organizations are also relevant to the project.

The Committee suggested that the current decision-tree approach for evaluating the potential effects of veterinary drug residues on human intestinal microflora be reviewed. Furthermore, as the potential occurrence of antimicrobial resistance due to veterinary use of antimicrobial agents is an emerging concern, the Committee recommended that guidance be provided on testing protocols, laboratory methods, sampling design and post-marketing surveillance to assist in assessing the risk for antimicrobial resistance in human intestinal flora. The efforts of other groups working on these issues should be taken into account.

2.2.4 *Human data*

The Committee recommended that the Project consider providing more guidance on the use of human data, including observational studies of exposed individuals. The guidance should include the design and interpretation

of studies in humans, including clinical trials, epidemiological studies and post-approval monitoring.

3. Comments on residues of specific veterinary drugs

The Committee considered one antimicrobial agent, cefuroxime, for the first time. It reconsidered three anthelmintic agents, six antimicrobial agents, four insecticides, and one production aid. The recommendations on these substances and details of further information required are summarized in Annex 2.

3.1 Anthelmintic agents

3.1.1 *Doramectin*

Doramectin is a member of the avermectin class of compounds, which includes abamectin and ivermectin. It is a semisynthetic avermectin that has close structural similarity to abamectin and ivermectin. It is used as an endoparasitic agent in non-lactating cattle.

Doramectin was previously evaluated by the Committee at its forty-fifth meeting (Annex 1, reference *119*), when it established an ADI of 0–0.5 µg/kg bw on the basis of a NOEL of 0.1 mg/kg bw per day for mydriasis in a 3-month study in dogs treated by gavage, and using a safety factor of 200. An additional safety factor of 2 was applied because doramectin was not tested in CF-1 mice, which is the test animal most sensitive to the neurotoxic effects of this family of drugs. The 1997 JMPR concluded that the sensitivity to avermectins of CF-1 mice was due to a genetic variation that causes reduced expression of P-glycoprotein in the blood–brain barrier (*7*). The JMPR further concluded that the results of studies with CF-1 mice were not appropriate for establishing ADIs for avermectins.

P-glycoprotein was expressed in the brain and jejunum of all species studied. P-glycoprotein is a cell membrane protein that acts to remove a wide variety of lipophilic compounds from cells, including avermectins. In the capillary endothelium of the central nervous system, it serves as a functional component of the blood–brain barrier. In intestinal epithelium, P-glycoprotein can limit intestinal absorption of a range of compounds.

The Committee at its fiftieth meeting (Annex 1, reference *134*) accepted the conclusions of the JMPR and considered that it was no longer necessary to apply an additional safety factor of 2 for avermectins and milbemycins that had not been tested in CF-1 mice. Doramectin was re-evaluated by the

Committee at its present meeting in order to determine whether removal of the additional safety factor of 2 was appropriate. On the basis of the Committee's decision taken at its fiftieth meeting, the present Committee concluded that use of an additional safety factor of 2 in establishing the ADI for doramectin was no longer necessary.

Toxicological data

No new data were provided to the Committee. The literature was reviewed for published information on the toxicity of avermectins that was considered relevant to this evaluation. The Committee reviewed information on the mechanism of the toxicity of ivermectin in a subpopulation of collie dogs and observations of its toxicity in a subpopulation of Murray Grey cattle. The Committee also considered a published review of the relative sensitivities of mice, rats, rabbits, dogs and non-human primates to avermectins. The relative potencies of doramectin, ivermectin and abamectin were also considered. The Committee examined information about variants of the human gene that codes for P-glycoprotein and reviewed observations in humans in this respect.

The genetic basis for the sensitivity of collie dogs to the neurotoxic effects of ivermectin was studied in four males and three females previously identified as sensitive to ivermectin and in six which showed no marked sensitivity. Sensitive animals were identified as those which exhibited typical clinical signs of toxicity to the central nervous system after receiving ivermectin at an oral dose of 120 µg/kg bw. The levels of P-glycoprotein expression were similar in sensitive and insensitive test animals; however, a specific variant of the gene coding for P-glycoprotein was identified in the sensitive animals that caused production of a severely truncated, non-functional form of P-glycoprotein. The Committee noted that the sensitivity of CF-1 mice to the toxicity of avermectins has also been linked to a variant of the gene responsible for expression of P-glycoprotein. When the levels or functionality of P-glycoprotein are reduced, avermectin compounds may penetrate the blood–brain barrier and may be more extensively absorbed by the gastrointestinal tract.

Sensitivity to the toxicity of avermectin B_1 was observed in a herd of Murray Grey cattle in Australia in 1985. Eight of 312 cattle treated with ivermectin at a therapeutic dose of 120–200 µg/kg bw by injection showed symptoms of hypersensitivity. The average concentration of avermectin B_{1a} in brain tissue from the affected animals was 56 µg/kg, while that in brain tissue from a normal animal was 4 µg/kg. No adverse reactions occurred in 83 additional Murray Grey cattle from other areas of Australia, which were tested for sensitivity to avermectins by treating them with at least twice the normal therapeutic dose of avermectin B_1.

The Committee evaluated the relative potencies of doramectin, ivermectin and abamectin by comparing the NOELs reported for reproductive and developmental toxicity in rats and rabbits and in 90-day studies of toxicity in dogs treated orally. These were the only studies with which such a comparison could be made. On the basis of these data, the Committee concluded that the potencies of these compounds are similar.

Eleven variants of the human gene coding for P-glycoprotein were identified in a sample population of 461 white volunteers in Germany. One of the variants was correlated with decreased levels of P-glycoprotein expression in the duodenum. Volunteers with this variant gene showed enhanced bioavailability of an oral dose of digoxin, having a steady-state concentration that was 38% higher than that in volunteers without the variant gene. The difference was statistically significant. Whether this variant could result in enhanced bioavailability of orally administered avermectins is unknown. No studies of variations in the gene coding for P-glycoprotein in populations of other ethnic groups have been reported. The Committee noted that, although the effects resulting from variation in the human gene coding for P-glycoprotein are modest, the evidence to date does not exclude the possibility that a subpopulation of humans sensitive to the toxic effects of avermectins exists.

Ivermectin has been administered to several million human patients in Africa and Latin America since its introduction in 1987 as the main treatment for onchocerciasis at a recommended dose of 150 μg/kg bw administered once every 12 months. The adverse reactions that have been observed in treated patients have been described as allergic or inflammatory responses resulting from killing of microfilariae, referred to as the 'Mazotti reaction'. No signs of acute central nervous system toxicity have been reported. Ivermectin is now considered safe for use in pregnant women, on the basis of the finding of P-glycoprotein in human placentae and in human fetuses by week 28 of gestation and the absence of adverse effects to the fetus when pregnant women were inadvertently treated with ivermectin.

The pharmacokinetics of orally administered ivermectin was studied in 12 healthy male volunteers of unspecified race. A single dose at a therapeutic level of 12 mg (150–200 μg/kg bw) resulted in an average maximal plasma concentration of 46 ng/ml and an average time to maximum concentration in plasma of 3.6 h. No adverse clinical signs were reported.

An ADI for doramectin of 0–1 μg/kg of bw was established on the basis of a NOEL of 0.1 mg/kg bw per day for mydriasis in a 3-month study in dogs treated by gavage, with a safety factor of 100. The Committee noted that removal of the twofold safety factor resulted in an ADI that still provided an adequate margin of safety for all other toxicological end-points of doramectin.

The Committee also noted that the resulting ADI for dormectin is 150–200 times lower than the human therapeutic dose of the related compound ivermectin.

The Committee took special note of the available information on reduced expression of P-glycoprotein in humans, which results in increased bioavailability of substrates for this transporter. However, the effects on the bioavailability of avermectins and their ability to penetrate the blood–brain barrier are unknown. The Committee recommended that human populations continue to be monitored for possible genetic predisposition to sensitivity to avermectins.

An addendum to the toxicological monograph was prepared, summarizing the data that had become available since the previous evaluation.

3.1.2 *Ivermectin*

Ivermectin is widely used as a broad-spectrum drug against nematode and arthropod parasites in food-producing animals. In human medicine, it is used mainly for the treatment of onchocerciasis. Ivermectin was previously considered by the Committee at its thirty-sixth, fortieth, and fifty-fourth meetings (Annex 1, references *91, 104,* and *146*). At its fortieth meeting, the Committee established an ADI of 0–1 µg/kg bw and recommended MRLs of 100 µg/kg for liver and 40 µg/kg for fat as ivermectin B_{1a}. At its fifty-fourth meeting, the Committee evaluated data on residues in milk after topical application of the drug to dairy cows and recommended a temporary MRL of 10 µg/kg for whole milk, also expressed as ivermectin B_{1a}. The Committee noted that the limit of detection and limit of quantification of the assay had not been provided and requested that data for validation of the method be made available for evaluation in 2002. Additionally, the Committee requested the results of studies in which ivermectin was given by routes of administration other than topical. Information on the performance of the analytical method was provided to the Committee at its present meeting, with, although not requested, a new study of residues.

Residue data

A study of depletion of residues in milk that was conducted in compliance with GLP, in which eight lactating Holstein dairy cows received a single topical administration of pour-on ivermectin at a dose of 0.58 mg of active ingredient per kg bw. Milk samples were collected before treatment (day 0) and at approximately 12-h intervals on days 1–9 after treatment. A single morning sample was collected on day 10.

The concentrations of ivermectin increased after treatment, reaching a peak after 3–4 days, but declined during the final 5 days of the study. Although all

the milk samples collected from the treated animals contained detectable residues throughout the study, none of the samples collected on days 9 and 10 had concentrations that exceeded the temporary MRL of 10 µg/kg.

Analytical methods

Two analytical methods were submitted for evaluation. Both involved separation by high-performance liquid chromatography (HPLC) and detection of derivatized compounds (parent ivermectin, 22,23-dihydroavermectin B_{1a}, and the internal standard, avermectin B_{1a}) by fluorescence. Milk samples were prepared with addition of the internal standard, and ivermectin and the internal standard were extracted from the milk into an organic solvent system, derivatized and dissolved for isocratic HPLC separation with fluorescence detection.

In one method, linearity was demonstrated over a concentration range of 0.78–25 ng/ml ($r^2 > 0.9995$). The limit of detection was calculated to be 0.02 ng/ml (mean blank value plus three times the standard deviation), and the limit of quantification was identified as 0.78 ng/ml, reflecting the possibility of validation at this level. The accuracy and precision were 99% and $\leq$ 13.5%, respectively. The recovery was 88% at the limit of quantification, declining to 65% at a concentration of 25 ng/ml. The specificity of the method in the presence of other veterinary drugs was not described, and no data were provided to demonstrate the stability of the analyte on storage.

The Committee at its fifty-fourth meeting estimated a range of acceptable performance for a similar method of 5–50 µg/kg. Although a description of the analytical method was not submitted for the current evaluation, data supporting the calculated limit of detection of 0.1 ng/ml were provided. As the limit of quantification was set at 10 times the limit of detection, the limit of quantification for this assay was established at 1 ng/ml. The validating laboratory obtained a recovery of 87% and a precision of 3% at the limit of quantification.

The Committee concluded that the two methods could be recommended for routine monitoring of milk samples for ivermectin. It noted, however, that the internal standard used in both methods, ivermectin B_{1a}, is a component of an approved veterinary drug, and there was therefore potential for contamination of the milk with ivermectin B_{1a} before sampling.

The Committee recommended an MRL of 10 µg/kg for cows' milk, expressed as ivermectin B_{1a}.

3.1.3 *Tiabendazole (thiabendazole)*

Tiabendazole (thiabendazole) is a benzimidazole compound used both as a broad-spectrum anthelmintic in various animal species and for the control of parasitic infestations in humans. It was evaluated by the Committee at its fortieth meeting (Annex 1, reference *104*). An ADI of 0–100 µg/kg bw was established on the basis of reduced body-weight gain in a 2-year study in rats and reduced fetal weight in a study of developmental toxicity in rats, by applying a safety factor of 100 to the NOEL of 10 mg/kg bw per day. At its forty-eighth meeting (Annex 1, reference 128), the Committee reviewed the results of supplementary studies that allowed it to confirm its earlier evaluation. The NOELs in the 12-month study in dogs, the 2-year study of toxicity in rats and the two-generation study of reproductive toxicity in rats were all 10 mg/kg bw per day, identical to the NOEL that had served as the basis for the ADI. The Committee applied a safety factor of 100 and confirmed the ADI of 0–100 µg/kg bw established at its fortieth meeting.

As tiabendazole is also used as a fungicide in plant protection, its toxicity was evaluated by the 1970 and 1977 JMPR (*8*,*9*). At the 2000 JMPR (*10*), at which the residue and analytical aspects of tiabendazole were evaluated, the Meeting concluded that its toxicological profile included effects of concern that might indicate a need for an acute reference dose (acute RfD). The Meeting recommended that tiabendazole be considered further by the Joint FAO/WHO Expert Committee on Food Additives, which had conducted the most recent toxicological assessment of this chemical.

The Committee did not receive new data for establishing an acute RfD for tiabendazole. All the data considered had been evaluated and summarized previously by the Committee, at its fortieth and forty-eighth meetings. Those data were re-evaluated by the Committee at its present meeting, when it focused on aspects relevant for establishment of an acute RfD. In addition, the Committee consulted the literature for recently published information on the toxicity of tiabendazole and considered those relevant for this evaluation.

The studies of the acute toxicity of tiabendazole given orally, which gave LD_{50} values > 2000 mg/kg bw, did not provide any indication of effects. The only substance-specific clinical sign relevant for acute exposure in studies with single or repeated doses was emesis in dogs (NOEL, 40 mg/kg bw per day). The common side-effects reported in humans receiving therapeutic doses (≥ 25 mg/kg bw twice daily for 1–10 days) included anorexia, nausea, vomiting and dizziness. However, these effects were poorly described and did not allow identification of a NOEL. In a study in volunteers, in which controls were given a placebo, a dose of 125 mg of tiabendazole twice a day for 24 weeks (equivalent to 3.6 mg/kg bw per day for a 60-kg person) did not cause significant changes in subjective side-effects.

In the report of its fortieth meeting, the Committee noted renal injury in mice given tiabendazole for 1–7 days. The renal toxicity of tiabendazole in mice was investigated In a number of published studies, after single or repeated oral administration. Although renal toxicity was observed in the studies with repeated doses, these results were considered of limited value for establishing an acute RfD because of the high doses used (1200, 1800 or 2400 mg/kg bw per day in the diet) and their long duration (13–44 weeks). In the studies with single doses, mice received 0, 125, 250, 500, 1000 or 2000 mg/kg bw by gavage. Renal toxicity, mainly in the proximal tubules, was observed at doses of 250 mg/kg bw and higher and consisted of histopathological changes including mitochondrial swelling. The toxic effects were due to the parent compound and were most severe 2–3 days after dosing; after that time, tissue repair processes began. All the effects except tubule dilatation were either fully or partly reversed within 10 days of administration. These studies showed that tiabendazole is taken up by proximal tubule epithelial cells in the renal cortex and ultimately causes necrosis of those cells. The lowest dose of 125 mg/kg bw was the NOEL for acute renal toxicity in mice.

Haematotoxicity was observed in studies with repeated oral doses in rats and dogs, lasting 4 and 13 weeks in rats and 14 and 53 weeks in dogs. Analysis of blood samples from week 4 or 6 showed changes indicative of anaemia, which were occasionally seen early in studies rather than at the end. Related histopathological changes in the spleen and/or bone marrow were observed at the same and lower doses. As it cannot be excluded that histopathological changes indicative of anaemia could occur after one or a few doses, they were considered relevant for assessing acute exposure. The NOELs in rats and dogs were 9 and 10 mg/kg bw per day, respectively.

In a study with volunteers, 50 men received an oral dose of 125 mg of tiabendazole twice a day for 24 weeks (equivalent to 3.6 mg/kg bw per day for a 60-kg person), and 50 other men were given a placebo. Tiabendazole did not affect haematological parameters after 4, 12 or 24 weeks of treatment. However, owing to a number of shortcomings, no NOEL could be identified in this study. In particular, it was not possible to perform histopathological examinations, which in animals appeared to provide more sensitive indicators of haematotoxicity than the haematological parameters.

In a study of developmental toxicity in rabbits, changes related to hydrocephalus were observed after oral doses of tiabendazole of 120 mg/kg bw per day and higher (NOEL, 24 mg/kg bw per day). In another study with rabbits, no such effects were observed at oral doses of up to 600 mg/kg bw per day (NOEL, 150 mg/kg bw per day). In mice, teratogenic effects were observed after a single oral dose on day 9 of gestation, which consisted of