CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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RISK MANAGEMENT RECOMMENDATIONS FOR THE VETERINARY DRUGS FOR WHICH NO ADI AND/OR MRL HAS BEEN RECOMMENDED BY JECFA DUE TO SPECIFIC HUMAN HEALTH CONCERNS

(Report of the Electronic Working Group, led by the European Union, with the assistance of Argentina, Australia, Brazil, Canada, China, Denmark, Finland, France, Germany, Japan, Mexico, the Netherlands, Norway, Serbia, Sweden, Thailand, United Kingdom, United States of America, JECFA Secretariat, Consumer International, IACFO, IFAH)

Background

1. At the last (19th) Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), which met in Burlington, USA, 30th August- 3rd September 2010, the Committee agreed to establish an electronic working group, led by the European Union and working in English only and open to all Codex members and observers, with the following terms of reference:

> (i) To develop risk management recommendations for the following veterinary drugs for which no ADI and/or MRL has been recommended by JECFA due to specific human health concerns: carbadox, chloramphenicol, chlorpromazine, malachite green, nitrofurans, nitroimidazoles, olaquindox, stilbenes (diethylstilbestrol);
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> (ii) The risk management recommendations should be based on an evaluation of the information available through the JECFA reports and monographs and through dialogue with the JECFA secretariats; and
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> (iii) The risk management recommendations should incorporate the decisions of the 18th Session of CCRVDF that chloramphenicol and malachite green should not be used in food producing animals.

Recommendations/considerations

2. For each substance listed in the terms of reference, the eWG elaborated a short description of the substance, a summary of the JECFA conclusions[1] and recommendations to CCRVDF for appropriate risk management measures. The outcome of this work is presented in the Annex.

3. The specific human health concerns identified by JECFA relate in most cases to genotoxicity and carcinogenicity. In developing risk management recommendations, the eWG considered the principle that substances that are both genotoxic and carcinogenic would in general not be considered acceptable for use as veterinary drugs. This is because for such substances there may not be a threshold dose below which no adverse effects are expected to occur, and some degree of risk may exist at any level of exposure. This principle was recently confirmed in the joint FAO/WHO publication *Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food*[2].

[1] Full JECFA reports and monographs are available at http://www.who.int/foodsafety/chem/jecfa/publications/en/index.html

[2] http://www.who.int/ipcs/food/principles/en/index.html

4. In view of the above principle, some members of the eWG supported a risk management recommendation that a substance should not be used in food producing animals when the health concerns identified by JECFA were based on genotoxicity and carcinogenicity or when other significant health risks were identified by JECFA. In their view, this was a clear and logical recommendation for substances which should not get into the food chain because health risks could not be ruled out even at very low concentrations.

5. Some members of the eWG were of the view that a recommendation not to use a substance in food producing animals may be too restrictive, create trade barriers and rule out other effective options for risk management. For example, a long withdrawal period could sufficiently mitigate health risks allowing the use of a genotoxic and carcinogenic drug without endangering public health. Other members of the eWG argued that a long withdrawal period is not an effective risk management measure for substances for which there is no threshold below which no health effects occur.

6. Some members of the eWG opposed creating a "negative list" of veterinary drugs. In their view, the decision on whether a substance that is both genotoxic and carcinogenic should, in general, be considered acceptable for use as a veterinary drug is most appropriately made as a risk management decision by the nation or region. It was not an appropriate risk management starting point for the CCRVDF as this body does not have before it all of the information that would allow a nation/region to balance the hazard, exposures, and benefits of the proposed use. Other members of the eWG did not agree with this argument because in their view all relevant information should be made available for the CCRVDF and in any case metabolism and residues of compounds with potential genotoxic and carcinogenic properties is an aspect that is independent of a geographic region.

7. Some members of the eWG suggested that when ADIs or MRLs cannot be set because of genotoxicity and carcinogenicity of a substance, there could be alternative approaches for setting limits for the substance in food. For example, in the case of genotoxic and carcinogenic contaminants, JECFA is using a concept called "margin of exposure" (MOE) described in the EHC 240. Other members of the eWG emphasised that the MOE concept was developed for inadvertent food contaminants, and not for substances that are intentionally added to foods.

8. Finally, some members were of the view that some of the substances did not meet the criteria of those drugs for which JECFA could not establish an ADI or recommend MRLs due to specific human health concerns. In the case of nitroimidazoles and olaquindox, while JECFA could not establish an ADI, it indicated that there were data upon which an acceptable concentration of residues of these substances in edible tissues could be established. In the case of stilbenes, JECFA did not carry out a risk assessment.

9. The diverging views of the eWG are reflected in the Annex, which gives alternative risk management recommendations for CCRVDF to consider, namely options A and B.

10. Residues of some of the substances under discussion may occur even if their use is not authorised in the target animals. This may be for example due to environmental contamination or the occurrence of a natural metabolite in the animal. Modern laboratory methods are capable of finding such residues at ever lower levels which could lead to trade disputes. Therefore, if CCRVDF chooses to go along with a recommendation that a substance should not be used in food producing animals, then, as a next step, CCRVDF may wish to consider if there is a need to recommend certain low levels of residues for the substance which would be considered as limits for taking regulatory actions in imports and exports of food with a clear understanding that they are not a result of a deliberate use of these substances. In setting such levels, the performance of analytical methods should be taken into account. It would also have to be ascertained that these levels would not be harmful for the health of consumers.

ANNEX

Risk management recommendations for substances for which JECFA could not establish ADI/MRL due to specific health concerns

CARBADOX

Carbadox is a quinoxaline antibiotic used as a feed additive for pigs to promote growth and as an antibacterial drug for the prevention of dysentery in pigs.

JECFA evaluation

36th (1990) and 60th (2003) JECFA

Carbadox was originally evaluated by the 36th JECFA which evaluated toxicological and residue data. Carbadox was found to be genotoxic and carcinogenic; the metabolite desoxycarbadox was found to be carcinogenic, while the metabolites methyl carbazate and quinoxaline 2-carboxylic acid (QCA) were not. Hydrazine, a likely metabolite of carbadox, was shown to have genotoxic and carcinogenic potential. Because of the genotoxic and carcinogenic nature of carbadox and some of its metabolites, JECFA could not establish an ADI.

On the basis of data from studies on the toxicity of QCA and on the metabolism and depletion of carbadox, and the nature of the compounds released from the bound residues, JECFA concluded that residues resulting from the use of carbadox in pigs were acceptable, provided that residues of QCA were below 0.03 mg/kg in pig liver and 0.005 mg/kg in pig muscle. Below those concentrations of QCA carcinogenic residues were not detectable. Therefore, JECFA recommended MRLs of 0.03 mg/kg in liver and 0.005 mg/kg in muscle of pigs measured as QCA.

The 60th JECFA confirmed the conclusion of the 36th JECFA that both carbadox and its metabolites should be regarded as carcinogens that act by a genotoxic mechanism and therefore it would be inappropriate to establish an ADI. After reviewing new toxicology and residue studies, the 60th JECFA concluded that carcinogenic residues, in particular desoxycarbadox, are present in edible tissues with a relatively long persistence, which was a new finding. The new studies showed that desoxycarbadox is still present in liver when the concentrations of QCA have reached the MRL recommended by the 36th JECFA. The 60th JECFA could not determine the amounts of residues of carbadox and its metabolites in food that represented an acceptable risk to consumers and therefore withdrew the MRLs recommended by the 36th JECFA.

Recommended risk management measures

Option A

In view of the health risks identified by JECFA, CCRVDF recommends that carbadox should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of carbadox. JEFCA considered carbadox to present a health related hazard because of (a) carcinogenicity with the evidence of a genotoxic mechanism and (b) residues of carcinogenic concern were evident 15 days after treatment. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; based on the available information, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

Competent authorities, in making a decision in the management of risk concerning the use of carbadox as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or

- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

CHLORAMPHENICOL

Chloramphenicol is a broad-spectrum antibiotic with historical veterinary uses in all major food-producing animals and with current uses in companion animals.

JECFA evaluation

12th (1968), 32nd (1987), 42nd (1994) and 62nd (2004) JECFA

Chloramphenicol was first evaluated by the 12th JECFA that considered published reports of toxicities, including blood dyscrasias, aplastic anemia, liver damage, optic neuritis and grey syndrome in the newborn infant, and concluded that there were no acceptable concentrations of residues in food.

The 32nd JECFA was not able to establish an ADI because it was not possible to give an assurance that residues in foods of animal origin would be safe for human consumption, since it was concluded that human exposure to chloramohenicol could cause aplastic anaemia.

The 42nd JECFA evaluated additional genotoxicity data, epidemiological data related to aplastic anemia, and re-evaluated the previously submitted toxicology data summarized in the monograph of the 32nd meeting. Chloramphenicol was found to be genotoxic in a number of *in vivo* and *in vitro* studies, and no adequate cancer studies were available. JECFA concluded that systemic exposures on the same order as that resulting from ophthalmic treatment would be unlikely to result in aplastic anemia, but was unable to quantify that systemic exposure. The 42nd JECFA was unable to establish an ADI for chloramphenicol because information was needed to assess carcinogenicity and reproductive toxicity and because of positive genotoxicity. No MRLs could be recommended in the absence of an ADI.

The 62nd JECFA reconsidered chloramphenicol found at low concentrations in animal products, with specific emphasis on the possiblity of low level contamination resulting from environmental contamination. The evaluation was based on published literature, and re-assessment of the data evaluated by the 32nd meeting. No adequate studies were available to fully assess potential reproductive toxicity although chloramphenicol was shown to be embryotoxic and fetotoxic in a number of laboratory animal species. JECFA reaffirmed the finding of evidence of genotoxicity, and the lack of a definitive cancer study, while noting that the International Agency for Research on Cancer (IARC) classified chloramphenicol as “probably carcinogenic in humans”. Of further concern was the finding from epidemiological studies of aplastic anemia following treatment with chloramphenicol.

JECFA concluded that it would be prudent to assume that chloramphenicol could cause some effects, such as cancer, through a genotoxic mechanism for which there is no identifiable threshold dose. The apparent idiosyncratic nature of the aplastic anemia and evidence of leukemia in some survivors of the aplastic anemia was also noted. JECFA was unable to quantify the risk of aplastic anemia in humans following the ophthalmic use of chloramphenicol.

JECFA concluded that it was not appropriate to establish an ADI for chloramphenicol because it was unable to establish a threshold for carcinogenicity given the evidence of a possible genotoxic mechanism. In addition, epidemiological studies in humans showed that it was not possible to establish any dose–response relationship or threshold dose for the induction of a potentially fatal aplastic anemia. In light of these findings, JECFA considered it not appropriate to establish an ADI, and consequently could not recommend MRLs for chloramphenicol.

Recommended risk management measures

Option A

In view of the health risks identified by JECFA, CCRVDF reconfirms the recommendation of its 18th session that chloramphenicol should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of chloramphenicol. JEFCA considered chloramphenicol to be a health related hazard because of (a) carcinogenicity with the evidence of a genotoxic mechanism and (b) epidemiological studies in humans showed that it is not possible to establish any dose-relationship or threshold dose for the induction of a potentially fatal aplastic anemia. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; based on the available information, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

Competent authorities, in making a decision in the management of risk concerning the use of chloramphenicol as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

CHLORPROMAZINE

In veterinary medicine, chlorpromazine has been used as a tranquilliser and antiemetic agent.

JECFA evaluation

38th (1991) JECFA

Chlorpromazine was evaluated by the 38th JECFA who noted a lack of short-term, long-term and carcinogenicity studies available for the drug. Limited genotoxicity information suggested that chlorpromazine may be genotoxic and some reactive metabolic intermediates were found to be capable of binding to DNA. Published literature raised concern by JECFA for behavioural effects on the pups of mothers treated during foetal development.

In view of the lack of relevant toxicological data, the long-term persistence of chlorpromazine in humans, the spectrum of additional effects of the drug, and the probability that even small doses can cause behavioural change, JECFA was unable to establish an ADI. Furthermore, JECFA suggested that chlorpromazine should not be used in food producing animals.

Recommended risk management measure

Option A

In view of the health risks identified by JECFA, and the JECFA suggestion that chlorpromazine should not be used in food producing animals, CCRVDF recommends that chlorpromazine should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of chlorpromazine. JEFCA considered chlorpromazine to be a health related hazard because of (a) potential behavioral effects in offspring following exposure during fetal development and (b) insufficient information to evaluate short term or long term toxicity, genotoxicity, or carcinogenicity. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; specific toxicological effects of public health concern were identified and there were significant endpoints of toxicity for which available data were inadequate.

Competent authorities, in making a decision in the management of risk concerning the use of chlorpromazine as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

MALACHITE GREEN

Malachite green is an *N*-methylated triphenylmethane used as an industrial dye. It has been used in the past as an antifungal and antiprotozoal agent in aquaculture.

JECFA evaluation

70th (2008) JECFA

Malachite green was put on the agenda of the 70th JECFA at the request of the 17th CCRVDF which requested JECFA to consider a literature review and advise if this substance could be supported for use in food-producing animals (as the available data were probably not sufficient to derive an ADI and MRLs). The evaluation was based on a comprehensive review of the published literature and two risk assessments provided by national authorities.

Neither malachite green nor leucomalachite green were found to be genotoxic in traditional assays. Leucomalachite green was found to induce cII mutations in the liver cells of female Big Blue B6C3F1 transgenic mice. Both malachite green and leucomalachite green were found to cause DNA adduct formation. JECFA concluded that leucomalachite green caused cancer in female mice by a genotoxic mechanism and that malachite green is readily converted to leucomalachite green, primarily by gastrointestinal microflora.

The 70th JECFA further considered the potential exposure to the sum of leucomalachite green and malachite green and established a margin of exposure (MOE) of between 900 to 10,000 for exposure to residues of carcinogenic potential in fish treated with malachite green and (genotoxic) carcinogenicity. JECFA further noted that it agreed with the 64th JECFA that MOEs of less than 10,000 for genotoxic and carcinogenic contaminants indicate a health concern.

JECFA considered it inappropriate to establish an ADI for malachite green and and in response to the specific question from CCRVDF did not support the use of malachite green for food-producing animals, due to genotoxic and carcinogenic properties of its main metabolite leucomalachite green. Consequently, JECFA did not recommend MRLs for malachite green and leucomalachite green.

Recommended risk management measures

Option A

In view of the health risks identified by JECFA, and the JECFA recommendation that malachite green should not be used in food-producing animals, CCRVDF reconfirms the recommendation of its 18th session that malachite green should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of malachite green. JEFCA considered malachite green to be a health related hazard because of (a) carcinogenicity with the evidence of a genotoxic mechanism and (b) an inadequate margin of exposure to assure protection of public health based on the use of malachite green in market size fish. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; based on the available information, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

Competent authorities, in making a decision in the management of risk concerning the use of malachite green as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

NITROFURANS

Nitrofurans are antimicrobial substances which have been used in the past therapeutically and prophylactically in a number of food producing species including pigs, poultry and cattle.

JECFA evaluation

40th (1992) JECFA

The 40th JECFA evaluated two nitrofurans: furazolidone and nitrofural.

Furazolidone:

Furazolidone was evaluated based on data from pharmacodynamic, pharmacokinetic, metabolic, acute and short term toxicity, carcinogenicity, genotoxicity, reproductive and teratogenicity studies as well as studies on endocrine function and clinical studies in humans.

JECFA concluded that furazolidone was a genotoxic carcinogen. Neither embryotoxicity nor teratogenicity was observed.

Because of the rapid metabolism of furazolidone, the genotoxicity of metabolites was also considered. While many postulated metabolites were negative for genotoxicity, there was insufficient information on the presence of the metabolites in edible tissues and on the release of and toxicological characterization of compounds from bound residues. JECFA concluded that because of the genotoxic and carcinogenic nature of furazolidone, and the deficient data available on metabolites, it was unable to establish an ADI. JECFA requested detailed information on the nature, quantity and toxicity of the metabolites of furazolidone, including the bound residues, prior to further consideration of the compound. For these reasons, MRLs were not recommended.

Nitrofural:

Nitrofural (Nitrofurazone) was evaluated based on acute and short term toxicity, teratogenicity, genotoxicity, and carcinogenicity studies.

Nitrofural was not teratogenic but it was fetotoxic at maternally toxic doses. Adequate studies on reproductive performance were not available, but it was noted that there was testicular degeneration in rats without a no-observable-effect-level (NOEL) in the two-year study, and that no point of departure was established for degenerative changes in joints of rats.

Nitrofural was genotoxic *in vitro*, but not *in vivo*, and it was found to be tumorigenic, but not carcinogenic, in rats and mice. JECFA concluded that nitrofural may be a secondary carcinogen, producing effects in endocrine-responsive organs by a mechanism that remains to be elucidated.

JECFA concluded that it could not establish an ADI for nitrofural because no-effect levels had not been established for the tumorigenic effects. Prior to re-evaluation, JECFA requested further data from long-term rat studies, with particular concern for effects on joint articular cartilage and testicular degeneration, data supporting an endocrine-based mode of action for tumor formation in rodents, and additional information on the identity, quantity, and biological characteristics of nitrofural metabolites. For these reasons, the lack of information on the quantity and nature of the total residues of nitrofural, and because the residue data were insufficient to identify a marker residue, no MRLs could be recommended.

Recommended risk management measure

Option A

JECFA evaluated only furazolidone and nitrofural but it is reasonable and justified to assume that the health risks identified by JECFA for these substances apply to all nitrofurans. Therefore, CCRVDF recommends that nitrofurans should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of furazolidone and nitrofural. JEFCA considered furazolidone and nitrofural to be health related hazards because of (a) carcinogenicity with the evidence of a genotoxic mechanism for furazolidone, (b) tumorigenicity by an undetermined mechanism affecting endocrine responsive organs for nitrofural, (c) inadequate information to establish characterize a NOAEL for reproductive and joint articular effects for nitrofural, and (d) inadequate information on the identity, quantity, and biological characteristics of nitrofural metabolites. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs for the evaluated nitrofurans; based on the available information, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

Competent authorities, in making a decision in the management of risk concerning the use of nitrofurans as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

NITROIMIDAZOLES

Nitroimidazoles are active against protozoal parasites and anaerobic bacteria. In veterinary medicine, the most important indication is the prevention of histomoniasis in turkeys with dimetridazole.

JECFA evaluation

34th (1989) and 42nd (1994) JECFA

Initially, the 34th JECFA intended to deal with the four nitroimidazole compounds (dimetridazole, metronidazole, ronidazole, and ipronidazole) as a group. This was because of their many similarities, including certain common toxicological properties, notably their ability to induce mutations in bacterial test systems and increase tumour yields in laboratory animals. However, this was not possible owing to the variation in the quantity and quality of the data available. Therefore, the compounds were evaluated individually.

Dimetridazole:

Dimetridazole was evaluated by the 34th JECFA based on acute, chronic, teratogenic, multigeneration reproductive, carcinogenic, and genetic toxicity studies.

No evidence was found of teratogenicity or effects on reproductivity. Dimetridazole was mutagenic in bacterial test systems but not in mammalian systems. Dimetridazole was tumorigenic in rats by an unidentified mechanism, with a NOEL of 4 mg/kg bw per day. JECFA could not establish an ADI because a carcinogenicity study in a second species was not available.

Prior to further evaluation, JECFA requested a long-term study in mice, studies investigating the mechanism of action for tumorigenesis, total residue studies for dimetridazole in poultry and swine with an appropriate radiolabel, and metabolism studies in poultry and swine that characterize the metabolism of total/bound residues.

Ipronidazole:

Ipronidazole was evaluated by the 34th JECFA based on pharmacokinetic, genotoxicity, embryotoxicity, teratogenicity, and short and long-term toxicity studies.

Ipronidazole showed mutagenic properties in bacterial test systems. Because of the inadequate design of studies in mammalian test systems, JECFA could not properly evaluate the genotoxic potential of ipronidazole. There was no evidence of embryotoxicity or teratogenicity but degenerative changes in testes were observed. Ipronidazole was found to be tumorigenic. JECFA was unable to establish an ADI because the rat carcinogenicity study was inadequate to determine a no-effect-level for ipronidazole.

Prior to further evaluation, JECFA requested adequate *in vitro* and *in vivo* genotoxicity data, a carcinogenicity study in rats to access the effect on the mammary gland and other tissue, studies on the mechanism of action for the tumor incidence, adequate total residue depletion studies in swine and turkeys, an *in vivo* metabolism study with ring-labelled ipronidazole in the rat, and metabolism studies in swine and turkeys to characterize the total residues.

Metronidazole:

Metronidazole was not evaluated toxicologically by the 34th JECFA because the relevant data were not made available to JECFA. Neither were studies available on the depletion of residues of metronidazole in food-producing animals. Prior to further evaluation, JECFA requested comprehensive information on toxicology, studies of the total residue depletion and metabolism in food producing animals, and analytical procedures to measure and identify residues.

Ronidazole:

The 34th JECFA evaluated ronidazole based on acute toxicity, subchronic toxicity, long-term toxicity, multigeneration reproductive toxicity, teratogenicity, genotoxicity, and carcinogenicity studies.

Ronidazole was genotoxic *in vitro* but not *in vivo*, and was carcinogenic in rats and tumorigenic in mice. No evidence was found of teratogenicity or adverse effects on reproduction. A range of postulated and/or identified metabolites were found not to be genotoxic in the Ames test. The 34th JECFA established a temporary ADI with a safety factor that reflected the results of genotoxicity studies in mammalian systems, lack of genotoxicity for metabolites, and the NOELs in the cancer studies. However, MRLs could not be established for ronidazole due to a failure to establish a relative toxicological potency for the bound residues and an inability to establish a marker to total residue relationship. Ronidazole was re-evaluated by the 42nd JECFA. As no new data were available for the evaluation, the temporary ADI was not extended.

Recommended risk management measure

Option A

Concerns regarding genotoxicity and carcinogenicity of nitroimidazoles remain unresolved in the absence of the requested toxicological data. Due to these concerns, many countries have banned the use of nitroimidazoles in food producing animals as a precautionary measure. The main argument against such measure is that there are no suitable alternative chemical treatments available for the control of histomoniasis in turkeys, a disease that can cause substantial losses in turkey production. However, the experience gained in countries that do not allow the use of nitroimidazoles demonstrates that histomoniasis in turkeys can be controlled by alternative means, e.g. improved biosecurity. This allows strong risk management fully eliminating the risks caused by the potential genotoxicity and carcinogenicity of nitroimidazoles. Therefore, CCRVDF recommends that nitroimidazoles should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of dimitridazole. JEFCA considered dimitridazole to be a health related hazard because (a) while it was non-genotoxic, dimitridazole was tumorigenic in rodents and the mode of action for tumorigenesis could not be identified, and (b) information on carcinogenicity or tumorigenicity in a non-rodent mammalian bioassay was not available. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; due to limitations of the available data, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

JECFA evaluated the safety of residues of ipronidazole. JEFCA considered ipronidazole to be a health related hazard because of (a) inadequate data to evaluate the potential for genotoxicity, (b) tumorigenicity in rodents while the mode of action for tumorigenesis could not be identified and (c) a NOAEL could not be established for chronic toxicity based on the cancer bioassay. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; specific toxicological effects of public health concern were identified and there were significant endpoints of toxicity for which available data were inadequate.

Metronidazole was not evaluated toxicologically by the JECFA.

The 34th JECFA evaluated the safety of residues of ronidazole. JEFCA noted possible concern for public health because (a) while it was non-genotoxic, ronidazole was tumorigenic in rodents, (b) individual animal data were not available for the carcinogenicity study reports and (c) the mode of action for tumorigenesis could not be identified. JECFA originally concluded that it could establish a temporary ADI of 0-0.025 mg/kg bw pending information to address the data gaps. Information to address these data gaps has not been provided since ronidazole was last evaluated and the temporary ADI was not extended by the 42nd JECFA.

Competent authorities, in making a decision in the management of risk concerning the use of nitroimidazoles as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or

- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

OLAQUINDOX

Olaquindox is a quinoxaline antibiotic used as a feed additive for pigs to promote growth.

JECFA evaluation

36th (1990) and 42nd (1994) JECFA

The 36th JECFA evaluated olaquindox based on acute and subacute, reproductive, and developmental toxicity, mutagenicity, and carcinogenicity studies.

Olaquindox was not found to have developmental effects below the maternally toxic dose, while reductions in fertility rate and litter size were seen in multigeneration studies. Olaquindox was genotoxic in both *in vitro* and *in vivo assays*, and was found to be tumorigenic, but not carcinogenic, in mice with a clear NOEL for tumors. There was no increase in tumors seen in rats. Because of doubts over the mechanism of the benign tumor production in rats, and the positive genotoxicity results, JECFA was unable to establish an ADI.

In the meantime, the 36th JECFA concluded that residues resulting from the use of olaquindox in food producing animals under conditions of Good Practice in the Use of Veterinary Drugs (GPVD) were temporarily acceptable. JECFA determined that, before MRLs could be established, it would need the results of a tissue depletion study designed to characterize the nature and availability of residues of olaquindox and to identify a suitable marker compound. Prior to further evaluation of olaquindox, JECFA also requested data to assess the genotoxic potential of olaquindox on germ-line cells, data to evaluate the effect of olaquindox on adrenal function, sperm morphology, and fertility in rats to allow NOELs to be set for those end points, and information on the binding of olaquindox or its metabolites to structural proteins or enzymes or proteins involved in DNA synthesis or repair.

Olaquindox was again evaluated by the 42nd JECFA based of additional residue studies. Olaquindox was found to be extensively metabolized, with the production of a large number of metabolites in food producing animals that were subsequently found to be also present in rodent tissues. Consequently, JECFA considered that the general toxicity of metabolites had been tested. The 42nd JECFA concluded that, because of the genotoxic potential of the parent compound and the absence of specific toxicity studies on metabolites, it was unable to allocate an ADI. However, it noted that the parent drug was absent in muscle at the proposed withdrawal time and that the toxicity of metabolites could be partially evaluated based on available data. Therefore, JECFA extended the temporary acceptance of residue resulting from the use of olaquindox in pigs in accordance with GPVD. JECFA further concluded that a residue concentration in muscle of 4 µg/kg of the metabolite 3-methylquinoxaline-2-carboxylic acid (MQCA) is consistent with the use of olaquindox in pigs in accordance with GPVD. JECFA requested review by 1996 of the results of studies to determine residues in liver and kidney of pigs with MQCA being used as the marker residue.

Recommended risk management measure

Option A

The potential genotoxicity and carcinogenicity of olaquindox cannot be ruled out because the necessary toxicological data for their evaluation has not been made available although there was ample time to produce such data since the first JECFA evaluation in 1990. A number of countries have banned the use of olaquindox without adverse effects in their pig production which proves that the use of olaquindox in pigs is not necessary. This allows strong risk management fully eliminating the risks caused by the potential genotoxicity and carcinogenicity of olaquindox. Therefore, CCRVDF recommends that olaquindox should not be used in food producing animals.

Option B

JECFA evaluated the safety of residues of olaquindox. JEFCA considered olaquindox to be a health related hazard because it was found to be (a) genotoxic, (b) a potential germ cell mutagen and (c) tumorigenic while the mode of action for tumorigenesis could not be identified. JECFA concluded that it was not appropriate to establish an ADI or recommend MRLs; based on the available information, a concentration in food could not be established below which an exposure may be expected to be deemed safe.

Competent authorities, in making a decision in the management of risk concerning the use of olaquindox as a veterinary drug in food producing animals, can consider:

- Basing the risk management conclusion on results of the existing JECFA risk assessment(s); or
- Basing the risk management conclusion on risk assessments conducted by other government/competent authorities; or
- Basing the risk management conclusion on approaches to determine an acceptable level of risk and residue concentrations that result in consumers not exceeding that level of risk (such as an acceptable margin of exposure or extrapolation of the dose response curve to a specified risk level); or
- Basing the risk management conclusion on development of scientific data to address the concerns identified in the JECFA risk assessment; or
- Basing the risk management conclusion on establishment of conditions of use that limit exposure of the consumer to residues of concern (such as limiting use to a very early life stage or establishing a long withdrawal time).

STILBENES

Stilbenes are synthetic sexual steroids that were used in the past as a growth promoter in cattle.

JECFA evaluation

5th (1960) JECFA

The 5th JECFA noted that diethylstilbestrol has carcinogenic properties. However, the information regarding carcinogenicity was not evaluated, a risk assessment was not performed, and a conclusion regarding the safety of diethylstilbestrol or stilbenes in food was not provided.

Recommended risk management measure

Option A

The genotoxic and carcinogenic properties of stilbenes (not only diethylstilbestrol but also others like dienestrol and hexestrol) are well recognised internationally, e.g. diethylstilbestrol is classified by IARC as a known human carcinogen. For this reason, their use in food producing animals is banned in most if not all countries. It is important that this widely accepted policy is recognised and confirmed by Codex Alimentarius. Therefore, CCRVDF recommends that stilbenes should not be used in food producing animals.

Option B

A well conducted risk assessment by JECFA is the appropriate starting point for risk management by CCRVDF. JECFA has not provided such a risk assessment for stilebenes. Accordingly, CCRVDF should not make any recommendation for risk management for stilbenes.