CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6 **CX/RVDF 13/21/6**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-first Session

Minneapolis, Minnesota, United States of America, 26 – 30 August 2013

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

(N10-2012)

(Report of the CCRVDF Electronic Working Group on Risk Management Recommendations for Residues of Veterinary Drugs for which no ADI and/or MRLs has been Recommended by JECFA due to Specific Human Health Concerns)

Governments and international organizations wishing to submit comments on the proposed draft Risk Management Recommendations (*see* Annex 1) are invited to do so **no later than 30 June 2013** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA; E-mail: CCRVDF-USSEC@fsis.usda.gov , with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy; E-mail: Codex@fao.org).

Please note that only comments submitted by the above deadline will be compiled, translated and made well in advance to the 21st CCRVDF.

Format for submitting comments: In order to facilitate the compilation of comments and prepare a more useful comments document, Members and Observers, which are not yet doing so, are requested to provide their comments in the format outlined in Annex 2 to this document.

Background

1. In the context of the discussions on risk management recommendations for veterinary drugs for which no ADI and/or MRL has been recommended by JECFA due to specific human health concerns, the last (20th) Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) which met in San Juan, Puerto Rico from 7 to 11 May 2012, agreed to establish an electronic Working Group, led by the European Union, open to all Members and Observers and working in English only:

- To develop further risk management recommendations for **carbadox, the two nitrofurans (furazolidone and nitrofural), chlorpromazine, stilbenes, olaquindox and the four nitroimidazoles (dimetridazole, ipronidazole, metronidazole and ronidazole)** for circulation for comments at Step 3 and consideration by the next Session, pending approval of the new work by the Commission;[1] [2]
- To review the JECFA assessments when developing the risk management recommendations for the above-mentioned veterinary drugs, and if it determines that additional data were available, a request could be made through the CCRDFV to JECFA to evaluate these data.[3]

2. The 35th session of Codex Alimentarius Commission approved the new work.

Considerations

3. For each substance listed in the terms of reference, the eWG elaborated a short description of the substance, a summary of the JECFA conclusions[4] and recommendations for appropriate risk management measures. The outcome of this work is presented in the Annex.

[1] REP12/RVDF – para 137
[2] REP12/CAC – Appendix VI
[3] REP12/RVDF – para 138

4. When formulating the risk management recommendations, the eWG took as a starting point the wording agreed by the 20th session of CCRVDF[5] for chloramphenicol and malachite green and circulated for comments at Step 3 in CL 2012/23-RVDF:

> *"In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of substance xxx or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of substance XXX in food. This can be accomplished by not using substance xxx in food producing animals."*

5. A majority of the eWG participants supported this wording as a risk management recommendation for all substances under discussion in the eWG. They considered that clear, crisp and scientifically sound recommendation effectively managing the health risks posed by these substances would benefit all Codex members. The following justifications were given to support this view:

a) The specific human health concerns identified by JECFA relate in most cases to genotoxicity and carcinogenicity. Substances that are both genotoxic and carcinogenic should not be considered acceptable for use as veterinary drugs. This is because for such substances no threshold dose can be established below which no adverse effects are expected to occur, and some degree of risk may exist at any level of exposure. This principle is confirmed in the joint FAO/WHO publication *Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food*[6]. It is therefore scientifically justified and logic to recommend that these substances should not get into the food chain because health risks cannot not be ruled out even at very low concentrations.

b) More solid risk management language "*Substance XXX should not be used in food producing animals*", would be more justified and clearly preferable. However, in the spirit of compromise the language agreed at the 20th session of CCRVDF "*This can be accomplished by not using substance XXX in food producing animals*" is considered sufficient to manage the health risks posed by the substances under discussion in the eWG.

c) Clear advice to governments is particularly important given that meat and seafood are widely traded, and governments rarely test incoming products for residues. Thus, controls on drug use in the country of origin are essential to ensure effective protection of consumers from toxic drug residues in meats and seafood. Such controls protect both domestic consumers and consumers living in importing countries. In these cases, it is essential to provide national authorities with clear, crisp language restricting the use of all drugs under discussion in the eWG.

d) Some of the substances that are genotoxic are metabolized to metabolites that are also genotoxic. When a substance has not been allocated an ADI or MRLs, a proper marker residue is usually not established. Metabolites might be depleted more slowly in the animals than the parent drug. Therefore monitoring of residues of toxic substances does not always give a real picture of the substance as metabolites often have a slower depletion than the parent compound. This makes it even more necessary to recommend that such substances should not be used in food producing animals as knowledge on residue metabolites as well as analytical methods often are missing.

e) The same risk management recommendation should also apply to metronidazole although this substance was not evaluated by JECFA. This is because it belongs to the group of nitroimidazoles (dimetridazole, ipronidazole, metronidazole and ronidazole) which have the same mechanism of action, i.e. the action is due to a partial reduction of the nitro group. They all have mutagenic properties *in vitro* and some of them also *in vivo*. They cause tumours in rats and neoplastic changes in the lung. Furthermore, the International Agency for Research on Cancer (IARC) found metronidazole to be carcinogenic in animals[7].

f) For some of the substances under discussion in the eWG, JECFA identified a risk to human health but could not complete the assessment due to incomplete or insufficient data. This situation is anticipated in the Codex Procedural Manual in the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* which recommends that in such cases "the Codex Alimentarius Commission should not proceed to elaborate a standard but should consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence." The proposed risk management recommendation is supported by the available scientific evidence and it is thus in line with the Codex working principles for risk analysis.

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

[5] REP12/RVDF – para 135

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

[7] http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-110.pdf

6. A minority of the eWG participants was of the view that the risk management language agreed at the 20th session of CCRVDF was not appropriate. In their view, the proposed risk management recommendations needed to be tailored to the available scientific data that in consequence drove the outcome of the JECFA evaluations, in order to achieve clear, crisp and scientifically sound recommendations to effectively manage the health risks posed by these substances to the benefit of all Codex members. These members therefore suggested that the specific situation for each substance should be reflected with appropriately tailored wording, and, where necessary, tailored risk management recommendations. In their view, not using a substance in food-producing animals was only one possible risk management measure, and a text to that effect would allow Codex members to choose one or several appropriate risk management measures for their countries' situations. These members emphasised that:

a) For a number of substances under discussion in the eWG, while JECFA identified potential toxicity and potential human health concerns, JECFA clearly indicated that the reason no ADI and/or MRL was recommended was because additional data had been identified as necessary for the risk assessment and had not been provided. In two cases JECFA was sufficiently sure of the evaluation to recommend a temporary ADI for residues of the drug, while requesting specific additional data. In these cases JECFA withdrew the temporary ADI because the requested data were not made available. JECFA did not withdraw the temporary ADIs because they were in error, or even unsafe, but rather because information was not made available to provide a daily dietary exposure that was based on data, rather than reasonable scientific assumptions and projections. In these cases, the circumstances are clearly different from those cases (such as chloramphenicol or malachite green) where sufficient data were provided, and JECFA determined that an ADI was not appropriate, and MRLs could not be recommended due to specific human health concerns.

b) CCRVDF, as a risk management body, should carefully consider the risk management recommendations that are appropriate when the risk assessment could not be completed because of inadequate data – but still recognize the potential risks to the human consumer that were identified by the JECFA evaluation.

c) It is important to recognize that a pharmaceutical company is unlikely to provide data for JECFA evaluation of a new veterinary drug, if the risk management response to a JECFA conclusion that the data are inadequate for risk assessment (and therefore an ADI cannot be established and MRLs cannot be recommended), is the same as when JECFA concludes that, based on a complete evaluation, there are specific human health concerns that prevent establishing an ADI or recommending MRLs. Yet the risk management body must recognize that more is known about the potential risks, even following an evaluation of inadequate data, than when no evaluation has been made. Accordingly, while it may be appropriate to recommend that competent authorities prevent residues of a drug for which the data were inadequate, but potential human health concerns were identified, this recommendation should be provided in appropriate context. In such circumstances, the competent authority shoulders a higher burden to consider the risks and benefits of the use of the veterinary drug, and to consider a broader range of potential risk management options.

d) Neither Codex nor the WTO/SPS Agreement suggest that foods containing residues of veterinary drugs which have not been evaluated for international standards cannot, or should not, be used in international trade. Rather, these bodies point to the responsibility of national authorities to review available information and take steps to protect the human consumer.

e) National authorities seeking to develop their own risk management strategies have an opportunity to take advantage of the scientific expertise in JECFA, and the risk management expertise in Codex, for the substances under discussion in the eWG, with the exception of metronidazole, which was not evaluated by JECFA because no data was available.

f) The appropriate roles of JECFA as the pre-eminent risk assessment body for Codex, of Codex to make appropriate risk management recommendations to ensure protection of consumers while being no more trade restrictive than necessary, and of national authorities as end of line risk managers that need to implement the Codex recommendations in their specific legislative environment should be respected. The *Working Principles for Risk Analysis for Food Safety for Application by Governments* **(**CAC/GL 62-2007) attempts to offer national authorities a balanced perspective for risk management. Pointing out the primary objective of protecting the health of the consumer (paragraph 30), the guideline goes on to emphasize the importance of examination of the full range of risk management options, as well as recommending that when faced with risk management options that are equally protective of public health, the selected options should be no more trade restrictive than necessary (paragraph 38).

Recommendations

7. In the Annex two options are given for the recommended risk management measures for each substance for CCRVDF to consider. Option A reflects the majority view of the eWG and option B reflects the minority view.

8. The eWG did not identify additional data on any of the substances under consideration and therefore no recommendations are made for further JECFA evaluations.

Annex 1

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR RESIDUES OF VETERINARY DRUGS FOR WHICH NO ADI AND/OR MRLS HAS BEEN RECOMMENDED BY JECFA DUE TO SPECIFIC HUMAN HEALTH CONCERNS

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR CARBADOX

N10-2012(c)

(At Step 3 of the Procedure)

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 recommended withdrawal of the MRLs recommended by the 36th JECFA.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of carbadox or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of carbadox in food. This can be accomplished by not using carbadox in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, no safe level of residues of carbadox or its associated metabolites in food has been established that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of carbadox in food. Ways in which competent authorities may choose to prevent residues may include preventing the use of carbadox in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR FURAZOLIDONE

N10-2012(d)

(At Step 3 of the Procedure)

Furazolidone belongs to the nitrofurans. These 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

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.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of furazolidone or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of furazolidone in food. This can be accomplished by not using furazolidone in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, no safe level of residues of furazolidone or its associated metabolites in food has been established that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of furazolidone in food. Ways in which competent authorities may choose to prevent residues may include preventing the use of furazolidone in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR NITROFURAL

N10-2012(e)

(At Step 3 of the Procedure)

Nitrofural belongs to the nitrofurans. These 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

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 measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of nitrofural or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of nitrofural in food. This can be accomplished by not using nitrofural in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of nitrofural or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of nitrofural in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of nitrofural in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR CHLORPROMAZINE

N10-2012(f)

(At Step 3 of the Procedure)

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 measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of chlorpromazine or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of chlorpromazine in food. This can be accomplished by not using chlorpromazine in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of chlorpromazine or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of chlorpromazine in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of chlorpromazine in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR STILBENES

N10-2012(g)

(At Step 3 of the Procedure)

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

JECFA/IARC evaluation

5th (1960) JECFA

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

Since the WHO International Agency for Research on Cancer (IARC) in their monographs program follows comparable principles and procedures regarding transparency, convening of independent international expert groups and evaluating the scientific evidence, it is recommended on an exceptional basis to use the latest IARC evaluation of DES, being the model compound for stilbenes, as a basis for risk management recommendations rather than requesting a JECFA evaluation.

IARC has recently completed an updated evaluation of the archetypical stilbene, diethylstilbestrol (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2012, Volume 100A, WHO Press). In its assessment, IARC determined that there is sufficient evidence in humans for the carcinogenicity of DES. This determination was based on substantial evidence indicating that exposure to DES is associated with cancer in women who were exposed to DES *in utero*, as well as women who exposed to DES while pregnant. Large, recent cohort studies indicate that DES causes cancer of the breast in women who were exposed while pregnant. DES also causes clear cell adenoma in the vagina and cervix of women who were exposed *in utero*. In addition, positive associations were observed between exposure to DES and cancer of the endometrium, and between *in utero* exposure to DES and squamous cell carcinoma of the cervix and cancer of the testis. There is sufficient evidence in experimental animals for the carcinogenicity of DES. DES exposure resulted in increased incidences of ovarian, endometrial and cervical tumours, as well as mammary adenocarcinomas in female mice. In male rasH2 and XPa/p53 mice DES exposure increased the incidence of osteosarcomas and Leydig cell tumors, respectively. Based on the above findings, the final determination by IARC is that DES is carcinogenic to humans (Group 1).

Recommended risk management measures

Option A

In view of the available scientific information, there is no safe level of residues of stilbenes or their metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of stilbenes in food. This can be accomplished by not using stilbenes in food producing animals.

Option B

In view of the available scientific information no safe level of residues of stilbenes or their associated metabolites in food has been established that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of stilbenes in food. Ways in which competent authorities may choose to prevent residues may include preventing the use of stilbenes in food producing animals or ensuring that use does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR OLAQUINDOX

N10-2012(h)

(At Step 3 of the Procedure)

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.

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.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of olaquindox or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of olaquindox in food. This can be accomplished by not using olaquindox in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of olaquindox or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of olaquindox in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of olaquindox in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR DIMETRIDAZOLE

N10-2012(i)

(At Step 3 of the Procedure)

Dimetridazole belongs to the nitroimidazoles which are active against protozoal parasites and anaerobic bacteria. In veterinary medicine, dimetridazole is used for the prevention of histomoniasis in turkeys.

JECFA evaluation

34th (1989) JECFA

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.

JEFCA considered dimetridazole 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.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of dimetridazole or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of dimetridazole in food. This can be accomplished by not using dimetridazole in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of dimetridazole or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of dimetridazole in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of dimetridazole in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR IPRONIDAZOLE

N10-2012(j)

(At Step 3 of the Procedure)

Ipronidazole belongs to the nitroimidazoles which are active against protozoal parasites and anaerobic bacteria.

JECFA evaluation

34th (1989) JECFA

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.

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.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of ipronidazole or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of ipronidazole in food. This can be accomplished by not using ipronidazole in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of ipronidazole or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of ipronidazole in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of ipronidazole in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR METRONIDAZOLE

N10-2012(k)

(At Step 3 of the Procedure)

Metronidazole belongs to the nitroimidazoles which are active against protozoal parasites and anaerobic bacteria.

JECFA evaluation

34th (1989) JECFA

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.

Recommended risk management measures

Option A

In view of the JECFA conclusions on the available scientific information concerning nitroimidazoles, there is no safe level of residues of metronidazole or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of metronidazole in food. This can be accomplished by not using metronidazole in food producing animals.

Option B

In absence of a JECFA evaluation, no specific risk management measures can be recommended for metronidazole.

PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR RONIDAZOLE

N10-2012(l)

(At Step 3 of the Procedure)

Ronidazole belongs to the nitroimidazoles which are active against protozoal parasites and anaerobic bacteria.

JECFA evaluation

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

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 measures

Option A

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of ronidazole or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of ronidazole in food. This can be accomplished by not using ronidazole in food producing animals.

Option B

In view of the JECFA conclusions on the available scientific information, there are insufficient data to establish a safe level of residues of ronidazole or its associated metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of ronidazole in food until data are available for a comprehensive risk assessment that identifies a safe level of residues of the drug for the consumer. Ways in which competent authorities may choose to prevent residues may include limiting the use of ronidazole in food producing animals or ensuring that use of the drug does not result in residues of toxicological concern.

Annex 2

GENERAL GUIDANCE FOR THE PROVISION OF COMMENTS

In order to facilitate the compilation and prepare a more useful comments' document, Members and Observers, which are not yet doing so, are requested to provide their comments under the following headings:

(i) General Comments

(ii) Specific Comments

Specific comments should include a reference to the relevant section and/or paragraph of the document that the comments refer to.

When changes are proposed to specific paragraphs, Members and Observers are requested to provide their proposal for amendments accompanied by the related rationale. New texts should be presented in **underlined/bold font** and deletion in ~~strikethrough font~~.

In order to facilitate the work of the Secretariats to compile comments, Members and Observers are requested to refrain from using colour font/shading as documents are printed in black and white and from using track change mode, which might be lost when comments are copied / pasted into a consolidated document.

In order to reduce the translation work and save paper, Members and Observers are requested not to reproduce the complete document but only those parts of the texts for which any change and/or amendments is proposed.

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