CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - Fax: (+39) 06 5705 4593 - E-mail: codex@fao.org - www.codexalimentarius.org

**CX 4/60** **CL 2012/23-RVDF**
**August 2012**

**TO:** Codex Contact Points
Interested International Organisations

**FROM:** Secretariat, Joint FAO/WHO Food Standards Programme,
Codex Alimentarius Commission
Viale delle Terme di Caracalla
00153 Rome, Italy

**SUBJECT**: **Request for comments on:**

**Part A: Comments at Step 6 on the draft Maximum Residue Levels (MRLs) for Monepantel (sheep tissues)**

**Part B: Comments at Step 3 on the proposed draft Risk Management Recommendations for Chloramphenicol and Malachite green (N10-2012)**

**DEADLINE:** **30 May 2013**

**COMMENTS:**

**To:**

U.S. Codex Office,
Food Safety and Inspection Service
US Department of Agriculture Secretariat
Room 4861, South Building,
14th Independence Avenue, S.W.,
Washington DC 20250, USA
E-mail: CCRVDF-USSEC@fsis.usda.gov

**Copies to:**

Secretariat
Codex Alimentarius Commission
Joint FAO/WHO Food Standards Programme
Viale delle Terme di Caracalla
00153 Rome, Italy
E-mail: codex@fao.org

## PART A: COMMENTS AT STEP 6 ON THE DRAFT MAXIMUM RESIDUE LEVELS (MRLs) FOR MONEPANTEL (SHEEP TISSUES)

### BACKGROUND

1. The Twentieth Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) agreed to forward the proposed draft MRLs for monepantel in sheep tissues to the 35th Session of the Commission for adoption at Step 5 and to request JECFA to evaluate the safety of the proposed higher MRLs in light of the information provided by the Committee (*see* REP12/RVDF para. 65 and App. V).

2. The 35th Session of the Codex Alimentarius Commission (July 2012) adopted the above draft MRLs at Step 5 and advanced them to Step 6 (REP12/CAC, para. 122 and Appendix IV). They will be considered by the 21st CCRVDF (United States of America, 26-30 August 2013).

### REQUEST FOR COMMENTS

3. Comments are hereby requested at Step 6 on the draft MRLs for monepantel (sheep tissues) as presented in Appendix V of REP12/RVDF. The document is available at the following address: ftp://ftp.fao.org/codex/reports/reports_2012/REP12_RVe.pdf.

4. Governments and international organizations wishing to provide comments should do so in sending their comments **by e-mail** to the above addresses before **30 May 2013**.

## PART B: COMMENTS AT STEP 3 ON THE PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR CHLORAMPHENICOL AND MALACHITE GREEN

### BACKGROUND

5. The 20th CCRVDF agreed to forward a proposal on the development of risk management recommendations for veterinary drugs for which no ADI and/or MRL has been recommended by JECFA due to specific human health concerns to the 35th Session of the Commission for approval as new work. The new work would consider the following veterinary drugs: carbadox, chloramphenicol, chlorpromazine, malachite green, nitrofurans, nitroimidazoles, olaquindox and stilbenes (diethylstilbestrol). [1]

6. The Committee further agreed, when the new work is approved by the Commission, to circulate the risk management recommendations for chloramphenicol and malachite green, prepared during the Session, for comments at Step 3 and consideration by its 21st Session (REP12/RVDF, paras 134-138 and Appendix X).

7. The 35th Session of the Codex Alimentarius Commission (July 2012) approved the elaboration of new work as proposed by the 20th CCRVDF (REP12/CAC, para. 138 and Appendix VI).

### REQUEST FOR COMMENTS

8. Comments are hereby requested at Step 3 on the proposed draft Risk Management Recommendations for Chloramphenicol and Malachite green as, presented in Appendices I and II to this Circular Letter.

9. Governments and international organizations wishing to provide comments should do so in sending their comments **by e-mail** to the above addresses before **30 May 2013**.

[1] The 20th CCRVDF established an electronic Working Group to develop risk management recommendations for the other veterinary drugs, i.e. carbadox, the two nitrofurans, chlorpromazine, stilbenes, olaquindox and the four nitroimidazoles, for circulation for comments at Step 3 and consideration by the next Session

**Appendix I**

**PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR CHLORAMPHENICOL**

**N10-2012(a)**

(at Step 3)

Chloramphenicol is a broad-spectrum antibiotic with historical veterinary uses in many 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.

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.

**Recommended risk management measures**

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

**Appendix II**

**PROPOSED DRAFT RISK MANAGEMENT RECOMMENDATIONS FOR MALACHITE GREEN**

**N10-2012(b)**

(at Step 3)

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 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.

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.

**Recommended risk management measures**

In view of the JECFA conclusions on the available scientific information, the competent authorities should prevent residues of malachite green in food. This can be accomplished by not using malachite green in food producing animals.