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 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 6 **CX/RVDF 21/25/6(REV)**

April 2021

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

25th Session
(Virtual)
12-16 and 20 July 2021

COMMENTS AT STEP 3 IN REPLY TO CL 2020/17-RVDF ON MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS IN FOODS FOR CONSIDERATION AT STEP 4 BY CCRVDF25

MRLs for diflubenzuron (salmon - muscle plus skin in natural proportion); halquinol (in swine - muscle, skin plus fat, liver and kidney); and ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle)

Comments received from Argentina, Brazil, Chile, Costa Rica, Cuba, Ecuador, El Salvador, European Union, Panama, Peru, Uganda, United Kingdom

PART I: COMMENTS ON MRLs

MEMBERS

Argentina

Maximum Residue Limits (MRLs) at Step 4 – Annex 2

- MRLs for Diflubenzuron in salmon: Argentina has no comments or objection to the MRLs proposed in the final report of the 88th meeting of JECFA88 (Evaluation of veterinary drug residues) and to advance it for further consideration by CCRVDF25 at Step 4.
- MRLs for Halquinol in swine: Argentina has no comments or objection to the MRLs proposed in the final report of the 88th meeting of JECFA88 (Evaluation of veterinary drug residues) and to advance it for further consideration by CCRVDF25 at Step 4.
- MRLs for Ivermectin in sheep, pigs and goats: Although MRLs were recommended for all matrices in the requested species, Argentina offers the following comments:
  - The MRL recommendations were not made based on the new ADI established for the substance.
  - We understand that the current evaluation was based on the 65-day withhold period. The evaluation is based on the premise that the 65-day withhold period is acceptable; based on the data stemming from the depletion trials, exposure (GECDE and GEADE) is calculated at day 65 to verify its consistency with the ADI and ARfD. Analysis of these calculations reveals that the GECDE and GEADE values only reach a very low percentage of the upper ADI limit (4% in adults and 5.9% in children). For the ARfD, it would only be 1.1% with sheep muscle in adults, with similar values for children. However, it is understood that the ARfD values should not be added among species, like with ADI evaluations.
  - Argentina deems it appropriate to request that the requested MRLs not be adjusted for the 65-day withhold period, rather that a system for calculating MRLs with greater use of ADIs and ARfDs be applied. Although this calculation would not include milk consumption, this molecule is not for agricultural use, such that a larger proportion of the ADI and ARfD values may be used. This would allow for more adequate withhold periods for current production practices. It would, thus, be appropriate for the JECFA to re-evaluate the MRLs recommended at the 88th meeting, bearing in mind the new ADI values established for this molecule.
  - It would also be appropriate to carry out an extrapolation based on the MRLs adopted for cattle and verify their consistency with ADIs and ARfDs, using the extrapolation criteria in document CX/RVDF 20/25/8: Discussion paper on MRL extrapolation for veterinary drugs to one or more species.

Brazil

Brazil congratulates JECFA for its work and supports the recommendations of the 88th Session of the Joint FAO/WHO Expert Committee on Food Additives on MRLs for the veterinary drugs diflubenzuron, halquinol and ivermectin, as presented in Annex 2, for consideration by CCRVDF25 at Step 4.

Chile

Chile supports advancing the proposed draft MRLs for the following compounds.

- Diflubenzuron in the matrix for muscle plus skin in salmon.
- Halquinol in the 4 matrices (muscle, skin plus fat, liver and kidney) in swine.
- Ivermectin in the 4 matrices (fat, kidney, liver and muscle) in sheep, pigs and goats.

Rationale: It is important for Codex to move forward with the analysis and establishment of MRLs for active ingredients that are regularly used in animals, and for which Codex has not yet established an MRL or which is being re-evaluated.

Costa Rica

Costa Rica would like to thank JECFA and CCRVDF for the work they have done and for the opportunity to submit comments. Costa Rica would like to express its support for the MRLs for the drugs proposed at the different steps (flumethrin, Diflubenzuron in salmon, Halquinol in swine, and Ivermectin in sheep, pigs, and goats).

Cuba

We have no contradictions to the MRL ranges established for ivermectin in pigs, sheep and goats in the various exposed tissues (fat, kidney, liver and muscles).

It does not refer to the fact that it should not be used in goats that produce milk for human consumption.

It only refers to sheep, pigs and goats. It does not refer to cattle. Would it be kept for this species what has already been approved by Codex?

Ecuador

Ecuador thanks JECFA for its work at the 88th Session of the Joint FAO/WHO Expert Committee on Food Additives on the numeric values of the maximum residue limits for the substances indicated in the document, and we state the following in response:

Diflubenzuron (salmon muscle plus skin in natural proportions)

No comment on the presented proposal.

Halquinol (muscle, skin plus fat, liver and kidney of swine)

Ecuador supports the MRLs recommended by JECFA regarding Halquinol, for muscle, skin plus fat, liver and kidney tissue, given that they would be very useful and of interest to our country for the purpose of safe food production, therefore we support advancing the document through accelerated steps.

Ivermectin (fat, kidney, liver and muscle of sheep, pigs and goats)

Ecuador supports the MRLs recommended by JECFA regarding this active ingredient, for fat, kidney, liver and muscle tissue, and supports advancing the document to the next step.

El Salvador

Regarding the proposed draft MRLs for Halquinol at Step 3:

In consideration of the results of JECFA88, which was held to respond to the specific requests submitted by CCRVDF24, and the information available in CL 2020/17-RVDF, we agree for the proposed MRLs to continue, in accordance with the internal procedure of the Codex Alimentarius.

Regarding the proposed draft MRLs for Ivermectin at Step 3:

After examining the results of the re-evaluation of Ivermectin MRLs in pigs, sheep and goats, we support the proposed MRLs for fat, kidney, liver and muscle tissues, taking into consideration that the MRLs established in the 20th session of the CAC for Liver and Fat for Pigs and Sheep are maintained.

European Union

Diflubenzuron

The EU supports the proposed draft MRL for diflubenzuron in salmon because it does not raise any consumer safety concerns. This proposed draft MRL is the same as the EU MRL.

Halquinol

The EU notes that halquinol is an antimicrobial agent, which is indicated for use in pigs and poultry as a growth promoter and for controlling diarrhea. The EU emphasises that the use of antimicrobial agents, including halquinol, is not authorised in the EU for growth promotion and recalls that the use of antimicrobials for growth promotion does not correspond to a prudent use of antimicrobials, which is necessary to fight antimicrobial resistance. The EU therefore wishes to voice its strong concerns as to the establishment of MRLs for halquinol. Halquinol is not authorised as a veterinary medicinal product nor as a feed additive in the EU, therefore no MRLs are established for halquinol in the EU.

Panama

Panama appreciates the work presented by JECFA and agrees with the advancement of the proposed draft MRLs recommended at the 88th meeting of the Joint FAO / WHO Expert Committee on Food Additives on MRLs for Veterinary Drugs: Diflubenzuron (salmon - muscle and skin in natural proportions), Halquinol (pork - muscle, skin and fat, liver and kidney), Ivermectin (sheep, pigs and goats - fat, kidney, liver and muscle), to step 4.

We support JECFA research, which is based on science and would contribute to the health authorities of countries like ours, as a health tool, to supervise and control the presence of drug residues in food, maintaining international trade and the safety of foods of animal origin.

Peru

Diflubenzuron is used as a treatment for sea lice (Lepeophtheirus salmonis1 and Caligus rogercresseyi) and is added to salmon feed, in accordance with the European Medicines Agency (EMA), at a dose of 3 mg/kg live weight/day for 14 consecutive days.

In Peru, the farmed species of salmonids is rainbow trout (Oncorhynchus mykiss), which is known to be vulnerable to sea lice. This external parasite is present in marine environments and affects trout in farming systems using farming cages in the open sea, which is a system that is not currently used in this country. The last EMA report, EMA/CVMP/115336/20183, published in July 2020, establishes a maximum residue limit equal to that in the proposed draft submitted to this committee. Report conclusions show that for exposures to the metabolite 4-chloroaniline, derived from diflubenzuron, a 100-fold reduction in the MRL for diflubenzuron will further reduce the potential for consumer exposure to diflubenzuron and its metabolite 4-chloroaniline in commercially available fish.

To this end, we consider the proposal to be in line with current considerations and that these established values be taken into consideration in the Prohibited Substances and Residues in Aquaculture Products Control Program and for importing salmon products for human consumption.

In regard to halquinol and ivermectin, the European Union has indicated no MRLs for halquinol, but it has for ivermectin: 100 µg/kg for fat, 100 µg/kg for liver, and 30 µg/kg for kidneys for all species of mammals intended for food production.

The United States of America (USA) also does not indicate MRLs for halquinol, but it does for ivermectin: 30 ppb for sheep liver and 20 ppb for pork liver and muscle.

The recommended MRLs from JECFA88 are similar to the MRLs from the USA, however more information should be gathered to provide a basis for the MRLs to indicate the proposal's feasibility.

Uganda

Uganda is in agreement with the MRLs arising from the JECFA88 Evaluation

Uganda appreciates the work done, this will help the industry.

United Kingdom

Diflubenzuron (insecticide)

The proposed MRL for salmon is the same as already approved in the UK. The recommendation is supported.

Halquinol (broad-spectrum antimicrobial)

There are no MRLs established for halquinol in the UK for any species and therefore cannot be used in food-producing species. The risk assessment conducted by JECFA is supported and the risk for the consumers can be mitigated with the proposed MRLs, ensuring consumer safety. However, halquinol is an antimicrobial substance used as a growth promoter. According to UK legislation, antibiotics, other than coccidiostats or histomonostats, shall not be authorised for this purpose. Therefore, acceptance of the proposed MRLs for halquinol would be in contradiction to UK legislation. Whereas the UK has no objection of a scientific nature, the adoption of the proposed MRLs for halquinol might not be possible according to the current UK legislative framework for the use of growth promoters.

Ivermectin (broad-spectrum antiparasitic agent)

The UK does not support the proposed draft Codex MRLs for sheep, goats and pigs.

The MRL values proposed by JECFA are substantially lower than the UK MRLs. The UK considers that they are unnecessarily low, and that their adoption will imply the need to revise the withdrawal periods in sheep, pigs and goats of products containing ivermectin. Adoption of these MRLs in the UK would most probably lead to unnecessarily high withdrawal periods in these species, which are not justified from a consumer safety point of view.

OBSERVERS

Health for Animals

Comments from HealthforAnimals on JECFA88 MRLs for Halquinol (in swine-muscle, skin plus fat, liver and kidney) at Step 3 for consideration by CCRVDF25 at Step 4.

1. Background

HealthforAnimals wishes to thank the 88th JECFA for its scientific review of halquinol and completely supports the conclusion found by JECFA88. In concurring with JECFA's findings, HealthforAnimals notes that halquinol is important because of its use as a therapeutic nonmedically important antimicrobial available for swine.

In support of this conclusion, HealthforAnimals offers the following comments:

- The Acceptable daily intake (ADI) recommended by JECFA of 0–0.2 mg/kg bw is appropriate and consistent with the data. We concur with the estimated chronic dietary exposure and toxicological rationale.
- The marker residue, assigned as the sum of 5-chloroquinolin-8-ol (5-CL), 5,7-dichloroquinolin-8-ol 5,7-DCL (5,7-DCL) and their glucuronide metabolites: 5-CLG (expressed as 5-CL equivalents) and 5,7-DCLG (expressed as 5,7-DCL equivalents) is metabolically relevant and measurable.
- The Committee recommended Maximum Residue Limits (MRLs) in swine of 40 µg/kg for muscle, 350 µg/kg for skin plus fat, 500 µg/kg for liver and 9000 µg/kg for kidney. These are appropriate and we concur with the recommendation.

2. HealthforAnimals Proposal

- HealthforAnimals encourages CCRVDF to accept JECFA's recommendation and support the advancement for consideration at the next Codex Alimentarius Commission at Step 5/8.

HealthforAnimals thanks the 25th CCRVDF for its consideration of these comments and proposal.

INFOFISH

As IVERMECTIN (Broad Spectrum anti-parasitic agent) has been used in some Fin Fishes (Indian and Chinese Carp and Catfishes etc) to prevent ectoparasite. Recommended MRLs should also be fixed for these species like sheep, pigs and goats.

PART II: CONCERN FORMS

European Union

Ivermectin

The EU notes that the proposed draft MRLs for ivermectin incorporate a substantial safety margin. For this reason, they are considerably lower than those established in the EU and, while not representing a consumer safety concern, would pose a difficulty in relation to established Good Practice in the use of Veterinary Drugs (GPVD).

In view of the substantial margin of safety, the EU proposes that CCRVDF requests JECFA to review its recommendation with a view to setting MRLs that are compatible with established GPVD. A concern form with further details is attached.

CONCERN FORM

Submitted by: The European Union

Date: 30 November 2020

Veterinary drug: Ivermectin

Commodity (species and tissues): Sheep, pig and goat tissues

MRL (µg/kg):

Species	Fat	Kidney	Liver	Muscle
Sheep, pigs and goats	20 µg/kg	15 µg/kg	15 µg/kg	10 µg/kg

Present Step: Step 3

Description of the concern:

It is an established principle that one of the factors to be considered when setting MRLs is Good Practice in the use of Veterinary Drugs (GPVD), defined in the Codex Alimentarius Commission Procedural Manual as "the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions".

JECFA calculated chronic dietary exposure based on estimated residues in cattle, sheep and pigs to be below 6% of the ADI (the reported Global Estimate of Chronic Dietary Esposure values for the general population and for children are 4% and 5.9% of the upper bound of the ADI, respectively). The available data did not allow JECFA to estimate acute dietary exposure on the basis of residues in pigs or goats but, based on data relating to residues in injection site muscle in sheep, acute dietary exposure was estimated to be below 1% of the ARfD (the reported Global Estimate of Acute Dietary Exposure is 0.6% and 0.5% for adults and children, respectively).

From the above, it is clear that the recommended MRLs incorporate a substantial safety margin relative to the ADI and ARfD.

The recommended MRLs are considerably lower than those established in the EU and would pose a difficulty in relation to established GPVD. Indeed, TRS 1023 indicates that for sheep and pigs the recommended MRLs relate to withdrawal periods of 65 and 35 days, respectively. This is considerably longer than established withdrawal periods for many ivermectin-containing products for sheep and pigs authorised in the EU.

In view of the substantial margin of safety between the estimated dietary exposure estimate and the ADI and ARfD, it would seem appropriate to request JECFA to review its recommendation with a view to setting MRLs that are compatible with established GPVD.

Summary of the supporting documentation that will be submitted to JECFA (e.g. toxicology, residue, microbiology, dietary exposure assessment): Examples of product information for authorised products.

JECFA's reply to the Concern Form from the European Union on the MRLs for Ivermectin

1. In response to the Concern Form submitted by the EU regarding the Ivermectin MRLs recommended by JECFA 88 for sheep, pig and goat tissues, JECFA would like to offer the following considerations.
2. As noted in the TRS 1023, JECFA has evaluated Ivermectin several times, and this compound was on the agenda of JECFA 88 at the request of the 24th session of CCRVDF to recommend MRLs for pigs, sheep and goats in muscle, liver, kidney and fat.
3. JECFA considered data submitted by one Member State that included information on two formulations of ivermectin (one formulation containing ivermectin, and another formulation of ivermectin with levamisole), both approved for use in sheep. No residue depletion data were received for pigs or goats, and no additional pharmacokinetic and residue depletion data for ivermectin in the target species were received. Information on GVPs was submitted only by one Member State. To complement the very limited data received in response to the call for data, JECFA conducted a comprehensive review of accessible literature databases.
4. JECFA recommended the MRLs for ivermectin in sheep tissues based on the available residue depletion study, and the GVPs that were submitted in response to the call for data; as for standard JECFA practices, the MRLs recommended are compatible with the GVPs. JECFA extrapolated the MRLs for sheep to goats, and re-confirmed the MRLs in liver and fat (pig and sheep) that were previously recommended (JECFA 36).
5. As also noted in the EU Concern Form, the recommended MRLs include a substantial margin of safety. JECFA considers that it would be within the remit of Risk Management (i.e. CCRVDF) to change the MRLs to accommodate more GVPs. JECFA further notes that, going through JECFA for this would much delay the process for amending MRLs that could otherwise be readily expedited by CCRVDF. It is also worth noting that, at this stage, it has not been decided when the next JECFA meeting dedicated to residue of veterinary drugs will be scheduled.
6. Finally, the FAO/WHO JECFA Secretariat would like to take this opportunity to remind all CCRVDF Members of the importance of submitting all relevant data/information in response to the call, in order to feed into the JECFA evaluation and ensure an effective and timely process.