ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 26th SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CCRVDF26)

13 to 17 February 2023

Portland, Oregon, United States of America

Agenda item 6.1: MRLs for Ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) at Step 7

Agenda item 6.2: MRLs for ivermectin (sheep, pigs and goats) and Nicarbazin (chicken) at Step 4

Objective

This document offers a review and analysis of the agenda items planned for discussion at the 26th session of the **Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)**, scheduled to take place face to face from 13 to 17 February 2023. This document is intended for possible use by the Codex communities of practice, promoted by GFoRSS and PARERA, as part of their contribution to enhancing awareness and supporting effective participation in international food standard setting meetings (Codex meetings) by representatives from members and observers.

The analysis provided in this document offers a factual review of agenda items, their background and a discussion of some considerations. This analysis is indicative in nature and does not represent an official position of the organizations mentioned above (PARERA and GFoRSS), their membership or their management. It provides a synthesis and analysis of the work currently under discussion by the CCRVDF, which may be useful for delegations from Arab countries to prepare their positions considering the needs and specificity of the region and the potential impact of the proposed food standards. This analysis is prepared as part of the **Codex Initiative for the Arab Region: Arab Codex Initiative**, implemented by PARERA and GFoRSS, hosted and coordinated by the Arab Industrial Development, Standardization and Mining Organization (AIDSMO) and funded by the US Codex Office, US Department of Agriculture.

**It is important to note that experts – members of the Expert Working Group (EWG) – do not represent the organizations and / or jurisdictions to which they are affiliated. The selection and participation in the EWG proceedings is based on each expert's own credentials and experience which should not be misconstrued as the country's / delegation's / organization's position to which they belong.*

Agenda item 6.1: MRLs for Ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) at Step 7

Documents

CL 2022/71-RVDF and CX/RVDF 23/26/6

Background

Ivermectin is an antiparasitic veterinary drug for which Codex standards have been established for a number of food producing animals. In response to a request from CCRVDF24 (2018),

Ivermectin was previously evaluated by the Committee at its 36th, 40th, 54th, 58th, 75th, 78th, 81st, 88th and 94th meetings.

At the 78th JECFA meeting (2013), the committee had conducted an evaluation of the data summarized in earlier residue monographs and had recommended a draft Ivermectin MRL of 4 µg/kg for cattle muscle based on twice the Limit of Quantification (2 × LOQ) of the analytical method (LC-MS/MS).

CCRVDF22 (2015) noted that this MRL is ≥2.5-fold lower than similar MRLs in other countries for cattle muscle and did not reflect current Good Veterinary Practice (GVP).

JECFA81 (2015) re-evaluated the ADI and the MRLs of ivermectin in all cattle tissues at the request of the CCRVDF22. JECFA81 established an Acceptable Daily Intake (**ADI**) **of 0–10 µg/kg bw and** Acute reference dose **(ARfD) of 0.2 mg/kg.** The previous ADI of 0–1 µg/kg bw (JECFA41, 1992) was withdrawn.

JECFA81 recommended the following revised MRLs in cattle tissues: 400 µg/kg for fat, 100 µg/kg for kidney, 800 µg/kg for liver and 30 µg/kg for muscle based on the upper limit of the one-sided 95% confidence interval over the 95th percentile of residue concentrations from depletion studies.

CCRVDF24 agreed to the new proposals for Ivermectin (MRLs for sheep and pigs) and request evaluation by JECFA.

JECFA88 (2019) proposed MRLs for fat, kidney, liver and muscle for sheep, pigs, and goats*:* 20 µg/kg for fat, 15 µg/kg for kidney, 15 µg/kg for liver and 10 µg/kg for muscle.

CCRVDF25 (2021) discussed these MRLs at Step 4. The EU provided a concern form on the basis that the proposed MRLs used a small fraction of the available Acceptable Daily Intake (ADI), were considerably lower than the MRLs established in the EU, and based on longer withdrawal periods; consequently, there was concern that animal products containing residues resulting from registered uses following Good Veterinary Practices (GVP) in the EU may exceed the proposed MRLs, while still being safe for the human consumer.

No data was provided to support the concern; however, data was promised to allow the JECFA to evaluate residues resulting from GVP according to registered use in the EU, and to consider re-evaluation of the proposed MRLs.

The CCRVDF25 agreed to advance proposed maximum residue limits (MRLs) for ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) to the 44th Session of the Codex Alimentarius Commission (CAC44) for adoption at Step 5.

CAC44 (2021) adopted the MRLs at Step 5 and advanced them to Step 6 for comments and further consideration by CCRVDF26 at Step 7.

During the CCRVDF26, the Committee will discuss and consider the proposed draft MRLs for Ivermectin for pigs, sheep and goats in muscle, liver, kidney and fat at Step 7.

MRLs in other jurisdictions

- The European Union MRLs 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): 30 ppb for sheep liver and 20 ppb for pig liver and muscle

Analysis

JECFA has evaluated Ivermectin several times, and this compound was on the agenda of JECFA88.

JECFA88 (2019) re-evaluated the ADI and recommended MRLs for pigs, sheep and goats in muscle, liver, kidney and fat as requested by CCRVDF24.

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.
- Data supporting residues following GVP were only provided by two members.

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).

JECFA considers that it would be within the remit of Risk Management (i.e. CCRVDF) to change the MRLs to accommodate more GVPs**.** As noted in the EU Concern Form, the recommended MRLs include a substantial margin of safety.

Proposed MRLs

JECFA 88 recommended the following **MRLs in sheep, pig and goats**

Species	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Fat (µg/kg)
Sheep, Pigs and goats	10	15	15	20

- **MRLs for sheep tissues**: JECFA88 confirmed the existing MRLs for fat of 20 µg/kg and liver of 15 µg/kg and recommended 15 µg/kg for kidney and 10 µg/kg for muscle.
- **MRLs for pig tissues:** JECFA88 confirmed the existing MRLs in pig fat (20 µg/kg) and pig liver (15 µg/kg) tissues, and extended MRLs for sheep muscle to pig muscle (10 µg/kg) and sheep kidney to pig kidney (15 µg/kg), considering the limited residue data in pigs and similarity of the overall tissue distribution and residue depletion in both species.
- **MRLs for goats**: No residue depletion data on ivermectin was available to calculate MRLs for goats. Based on the similarity of the residue distribution and depletion in different animal species, the Committee recommended extrapolation of the MRLs for sheep and pig tissues to goat tissues (10 µg/kg for muscle, 15 µg/kg for liver, 15 µg/kg for kidney and 20 µg/kg for fat).

Estimation of Exposure

- Estimated chronic dietary exposure: The Committee established a **GECDE** for:
  - **The general population:** 0.41 µg/kg bw per day, which represents **4%** of the upper bound of the ADI.
  - **Children:** 0.59 µg/kg bw per day, which represents **5.9%** of the upper bound of the ADI.
- Estimated acute dietary exposure: The Committee established a **GEADE** for:

- **The general population** of 87 µg/kg bw per day, which represents **43%** of the ARfD, from consumption of **cattle muscle** and of 1.1 µg/kg bw, which represents **0.6%** of the ARfD, from consumption of **sheep muscle**.
- **Children** of 82 µg/kg bw per day, which represents **41%** of the ARfD, from consumption of **cattle muscle** and of 1.0 µg/kg bw, which represents **0.5%** of the ARfD, from consumption of **sheep muscle**.

General comments on the proposed MRLs

- Saudi Arabia, Egypt, Costa Rica, Cuba, Kenya, Panama, support the MRLs for Ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) proposed by JECFA88 and supports advancing to the next step.
- Considering the new evaluation from JECFA94, Chile proposes suspending this MRL project for Ivermectin in the 4 matrices (fat, kidney, liver and muscle) in sheep, pigs and goats.
- Brazil suggests the discontinuation of the procedures at step 6 for this drug, considering that the MRLs recommended for Ivermectin at step 6 are the result of an older assessment by JECFA and are more restrictive when compared to existing GVPs.
- The UK does not support the proposed draft Codex MRLs for sheep, goats and pigs and considers that they are unnecessarily low, and that their adoption will imply the need to revise the withdrawal periods.
- In addition to the review of the proposed MRLs for sheep, pigs and goats (fat, kidney, liver and muscle), requests were made for the inclusion of ivermectin MRLs for goats and sheep milk. However, noting that there was no data available, it was proposed that consideration could be given to extrapolate MRLs for ivermectin in goat and sheep milk from the existing MRLs for cattle milk.
- A delegation noted the particular need for MRLs for camels, and asked that this be considered a priority and for CCRVDF to provide for the extrapolation of MRLs for this species.

General conclusion and recommendations

MRLs proposed by JECFA88, for sheep, pigs and goats incorporate a substantial safety margin and are considerably lower than those established in the EU and other jurisdictions which would pose a difficulty in regards to established Good Practice in the use of Veterinary Drugs (GPVD).

Considering the new evaluation from JECFA94, Arab delegations may suggest suspending work on this agenda item as it was based on an outdated JECFA evaluation (JECFA88).

Agenda item 6.2: MRLs for ivermectin (sheep, pigs and goats) and Nicarbazin (chicken) at Step 4

Documents

CL 2022/71-RVDF and CX/RVDF 23/26/6

Background

CCRVDF25 (2021) agreed to include imidacloprid, ivermectin and nicarbazin on the priority list and to forward the priority list of veterinary drugs as amended to CAC44 for approval. CAC44 (2021) approved the priority list of veterinary drugs for evaluation or re-evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

During the CCRVDF26, the Committee will consider the proposed draft MRLs for Ivermectin for pigs, sheep and goats and Nicarbazin (chicken) at Step 4 **arising from the JECFA94 Evaluation.**

IVERMECTIN (broad-spectrum antiparasitic agent)

JECFA is requested by CCRVDF25 (2021) to conduct a re-evaluation of the MRLs for pig, sheep and goat tissues taking into account the additional data and established Good Veterinary Practice (GVP) from the EU which had not been provided to JECFA88 and may support higher MRLs.

JECFA94 (2022) considered residues of veterinary drugs in food. JECFA further elaborated principles for evaluating the safety of residues of veterinary drugs in food, established acceptable daily intakes (ADIs) and acute reference doses (ARfDs), and recommended MRLs for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs (GVP). JECFA94 also responded to specific requests from CCRVDF25.

Nicarbazin (coccidiostat)

Nicarbazin has previously been evaluated by JECFA and an ADI has been set (1998). It has been over 20 years since the toxicology was last evaluated. As JECFA now considers whether an ARfD needs to be established and the toxicology may need to be considered.

JECFA94 evaluated nicarbazin at the request of the 25th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) with a view to recommending maximum residue limits (MRLs) for edible chicken tissues.

Analysis

Ivermectin

- Dietary exposure to ivermectin may occur only through its use as a veterinary drug. There is no registered use for ivermectin as a pesticide. When used as a veterinary drug, dietary exposure was estimated based on the potential occurrence of ivermectin residues in cattle, sheep, pig and goat tissues.
- **At the 94th JECFA meeting (2022),** The committee considered data submitted by three sponsors that included information on residue depletion studies in pigs (one study utilizing radiolabelled ivermectin and two using non-radiolabelled ivermectin), sheep (one study employing radiolabelled ivermectin and two studies using non-radiolabelled ivermectin), and goats (one study using nonradiolabelled ivermectin). In addition, the Committee reviewed metabolism studies in pigs (one study) and sheep (one study). No metabolism studies were available to the Committee for ivermectin in goats.
- JECFA94 assessment: the committee received a report of findings for residues of ivermectin in pigs, goat and lambs from one competent national authority for residues control. Samples of liver and muscle were collected between 2015 and 2021 and analyzed using LC-MS/MS or HPLC-FLD, for which the LOQ was2 µg/kg.
- JECFA had previously evaluated milk residue data and recommended an MRL of 10 µg/kg for milk in cattle There are no MRLs for ivermectin residues in milk from other species.
- The ADI previously established by the Committee at the 81st meeting was 0–10 µg/kg bw.
- The ARfD previously established by the Committee at the 81st was 200 µg/kg bw.

Nicarbazin

- Dietary exposure to nicarbazin may occur only through its use as a veterinary drug. There is no registered use for nicarbazin as a pesticide. When used as a veterinary drug, dietary exposure was estimated based on the potential occurrence of DNC residues in chicken tissues.
- A toxicological re-evaluation was undertaken to establish health-based guidance values due to the time that had elapsed since its last review.
- JECFA reviewed radiolabelled and non-radiolabelled studies on the pharmacokinetics, metabolism and residue depletion of nicarbazin in chickens. Th e analytical method used to analyse tissue samples was assessed
- The sponsor provided unpublished proprietary studies as well as data from studies in the published literature to support the assessment.
- JECFA94 established a ADI for nicarbazin (as DNC) of 0–0.9 mg/kg bw based on toxicological effects and concluded that it was not necessary to establish an ARfD for nicarbazin (or DNC) in view of their low acute oral

toxicity, the absence of developmental toxicity or of any other toxicological effects that would be likely to be elicited by a single dose.

Proposed MRLs for Ivermectin

Species	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Fat (µg/kg)
Pigs	15	30	20	50
Sheep and goats	30	60	20	100

Estimation of Exposure

- Estimated chronic:
  - The GECDE for adults and the elderly is 0.72 µg/kg bw per day, which represents 7.2% of the upper bound of the ADI of 10 µg/kg bw.
  - The GECDE for children and adolescents is 0.93 µg/kg bw per day, which represents 9.3% of the upper bound of the ADI of 10 µg/kg bw.
  - The GECDE for infants and toddlers is 0.48 µg/kg bw per day, which represents 4.8% of the upper bound of the ADI of 10 µg/kg bw.
- Estimated acute:
  - The GEADE for cattle muscle, applicable to children dietary exposure and the general population, is 69 µg/kg bw, which represents 35% of the ARfD of 200 µg/kg bw.
  - The GEADE for sheep muscle, applicable to children and the general population, is 73 µg/kg bw, which represents 37% of the ARfD of 200 µg/kg bw.
  - The GEADE for pig muscle, applicable to children and the general population, is 30 µg/kg bw, which represents 15% of the ARfD of 200 µg/kg bw.

Proposed MRLs for Nicarbazin

Species	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Skin with Fat (µg/kg)
Chicken	4000	15 000	8000	4000

Estimation of Exposure

- Estimated dietary exposure:

  Based on incurred DNC[1] residues in chicken muscle, offal, and skin with fat, at 24 hours withdrawal time and 125 mg/kg feed:
  - The GECDE for adults and the elderly is 120 µg/kg body weight (bw) per day, which represents 13% of the upper bound of the ADI of 900 µg/kg bw.
  - The GECDE for children and adolescents is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw.
  - The GECDE for infants and toddlers is 210 µg/kg bw per day, which represents 23% of the upper bound of the ADI of 900 µg/kg bw.

[1] The marker residue in chickens is DNC

Based on incurred DNC residues in chicken muscle, offal, and skin with fat, at zero days withdrawal time and 50 mg/kg feed:

- The GECDE for adults and the elderly is 95 µg/kg bw per day, which represents 11% of the upper bound of the ADI of 900 µg/kg bw.
- The GECDE for children and adolescents is 120 µg/kg bw per day, which represents 14% of the upper bound of the ADI of 900 µg/kg bw.
- The GECDE for infants and toddlers is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw.

General comments on the proposed MRLs

Saudi Arabia, Brazil, Chile, Costa Rica, Cuba and Panama support advancing the proposed draft MRL for the veterinary drugs Ivermectin and Nicarbazin to the next steps.

Other consideration for Arab region

- Camel tissues and milk are widely used in Arab countries therefore Arab delegations may request CCRVDF to establish MRLs for ivermectin for camel tissues.
- Arab delegations would have to submit all information and GVPs in order to consider Arab region conditions during the JECFA assessment process.
- Arab countries should develop more studies related to residues of vet drugs used for camels that could support the establishment of standards for this species.

General conclusion and recommendations

Considering the new evaluation from JECFA94, taking into account the additional data and established Good Veterinary Practice (GVP), Arab delegations may support the adoption of MRLs for Ivermectin and Nicarbazin proposed by JECFA94 at step 5/8. The application of these MRLs seems to be more achievable.

In general terms, Ivermectin is very much used in the Arab region for camels, cattle, sheep and goats, so it is highly recommended at the Arab/regional level ensure:

- Monitoring programs be devoted to this substance in the Arab region.
- Existing monitoring data for vet drugs residue in the Arab region is assembled and reviewed.