ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 25th SESSION OF CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOOD (CCRVDF25)

12 – 16 and 20 July 2021 Virtual Meeting

Substances/MRLs Submitted for Approval

AGENDA ITEM 6.1: MRLs for Ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) at Step 4

Objectives

This document offers an analysis of agenda items to support participation to the 25th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF25), taking place virtually in July 2021. The 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, in particular in **the Middle East and North Africa.**

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.

This analysis is prepared as part of the **Codex Initiative for the Middle East and North Africa**: ***MENA Codex Initiative***, implemented by PARERA and GFoRSS 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: Maximum residue limits for ivermectin (sheep, pigs and goats – fat, kidney, liver and muscle) at Step 4

Documents: CL 2020/17-RVDF and CX/RVDF 21/25/6

Background

The 24th session of CCRVDF requested that JECFA recommend MRLs for pigs, sheep and goats in muscle, liver, kidney and fat.

The proposed draft MRLs for Ivermectin are available for comment at Step 3 and will be discussed by CCRVDF25(2021) at Step 4.

Identification of the Substance

Ivermectin (CAS No. 70288-86-7) – is widely used as a broad-spectrum antiparasitic endectocide (endo and ecto) against nematode and arthropod parasites in food-producing animals.

n veterinary medicine, ivermectin is used in cattle, sheep, goats, pigs, horses, bison and reindeer. In human medicine, ivermectin is used to treat onchocerciasis, lymphatic filariasis, strongiloidiasis and scabies.

Summary of JECFA Assessments

JECFA, at their 81st meeting (2015), established an **ADI of 0–10 µg/kg** body weight on the basis of a no-observed-adverse-effect level (NOAEL) of 0.5 mg/kg body weight per day for neurological effects (mydriasis) and retardation of weight gain in a 14-week dog study, with application of an uncertainty factor of 50 (5 for interspecies differences based on pharmacokinetic studies in dogs and humans and 10 for intraspecies differences).

An ARfD of 0.2 mg/kg bw/day, based on a NOAEL of 1.5 mg/kg body weight, the highest acute dose tested in a safety, tolerability and pharmacokinetics study in healthy human subjects (n=12), with application of an uncertainty factor of 10 for intraspecies variability, was also established.

The previous ADI (1993) of 0–1 µg/kg body weight was withdrawn.

Ivermectin MRLs were recommended for **sheep, pigs and goat**s of

- 20 µg/kg for fat,
- 15 µg/kg for kidney,
- 15 µg/kg for liver and
- 10 µg/kg for muscle.

According to the report of the 88th JECFA existing MRLs for **sheep were confirmed for fat of 20 µg/kg** and **liver of 15 µg/kg**.

JECFA also recommended maintaining the existing **MRLs in pig fat (20 µg/kg)** and **pig liver (15 µg/kg)** tissues, and extending the MRLs for sheep muscle **to pig muscle (10 µg/kg)** and of 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.

No residue depletion data on ivermectin were available to calculate MRLs for goats. Based on the similarity of the residue distribution and depletion in different animal species, JECFA 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

The Global Estimate of Chronic Dietary Exposure (GECDE) for the general population was estimated at 0**.41 µg/kg bw per day** (4% of the ADI); based on estimated residues in cattle, sheep and pigs (muscle, liver, kidney and fat).

The GECDE for children was estimated at 0.59 µg/kg bw per day (5.9% of the ADI).

The Global Estimate of Acute Dietary Exposure (GEADE) for the general population was estimated at 87 µg/kg bw per day (43% of the ARfD), based on the consumption of cattle muscle. If based on the consumption of sheep muscle the value becomes 1.1 µg/kg bw (0.6% of the ARfD.

For Children, the GEADE was estimated at 82 µg/kg bw per day (41% of the ARfD), if based on the consumption of cattle muscle. The value reached was 1.1 µg/kg bw per day (0.5% of the ARfD), when based on the consumption of sheep muscle.

Previous JECFA Assessments, Other MRLs and Situation in Other Jurisdictions

At its 78th meeting, JECFA recommended a draft Ivermectin MRL of **4 µg/kg for cattle muscle** based on the value of **two times the LOQ of the analytical method** (LC-MS/MS).

CCRVDF22 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).

At the 81st JECFA meeting, the Committee recommended Ivermectin MRLs

for cattle tissues:

- 400 µg/kg for fat,
- 100 µg/kg for kidney,
- 800 µg/kg for liver, and
- 30 µg/kg for muscle.

The MRLs for cattle tissues are based on the upper limit of the one-sided 95% confidence interval over the 95th percentile of residue concentrations from depletion studies.

MRLs in other jurisdictions

EU (ppm): All mammalian food producing species → 0.10 (fat), 0.03 (kidney), 0.10 (liver), 0.03 (muscle).

Canada (ppm): Sheep → 0.12 (fat), 0.18 (kidney), 0.03 (liver), 0.01 (muscle); Pigs → 0.10 (fat), 0.15 (kidney), 0.015 (liver), 0.01 (muscle).

USA MRLs: Pigs → 0.02 (liver, muscle); Sheep → 0.03 (liver).

Position of Other Jurisdictions

There will likely be support for, at a minimum, moving the proposed MRLs to step 5, but not step 5/8.

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

Possible Path Forward and Recommendations

Considering the important margin of safety obtained with the recommended MRLs, and the limited opposition expressed in other discussions, the Committee may consider recommending adoption by the next Codex Alimentarius Commission at Step 5 (allowing for another round of comment and consideration by the Committee) or Step 5/8 (final adoption).

In discussing the approach followed to arrive at the derivation of these MRLs, the EWG discussed the need to ensure consistency of this approach with that followed for the development of other (already adopted) MRLs related to this substance in other tissues and in particular in Cattle tissues. This can be further examined by JECFA / CCRVDF, beyond the approval of the MRLs put forth at the current session of the CCRVDF.