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 ITEMS 5, 6.1

MRLs for Flumethrin in Honey and Diflubenzuron in Salmon

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Agenda Item 5	Maximum residue limit for flumethrin (honey) at Step 7
Agenda Item 6.1	Maximum residue limits for diflubenzuron (salmon - muscle plus skin in natural proportion) at Step 4

**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.*

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.

Agenda Item 5: Maximum residue limit for flumethrin (honey) at Step 7

Documents: REP18/RVDF-App. IV and CX/RVDF 21/25/5

Background

A proposed draft MRL for Flumethrin in honey was recommended by JECFA85 (2017). This MRL was based on **twice the limit of quantification** of the most reliable analytical method used in the residue studies.

At CCRVDF24 (2018), some members raised concerns that the method used as a basis for the development of the MRL was deemed expensive and not readily available in developing countries. It was noted that some trade problems may occur due to the lack of laboratory capacity to measure such low levels.

The JECFA Secretariat noted that when Flumethrin was used according to Good Veterinary Practice, the amount of residue that could be expected in honey is at or below the limit of quantification of current methods and that there was little risk that residues would move from the wax to the honey due to Flumethrin's highly lipophilic properties.

The CCRVDF24 (2018) agreed to forward a proposal to the Codex Alimentarius Commission (CAC) that an MRL was 'unnecessary' for adoption at Step 5 (allowing for another round of comment and consideration by the Committee). CAC41 (2018) adopted the CCRVDF proposal at Step 5. The draft MRL was circulated for comment at Step 6 and will be considered by CCRVDF25 (2021) at Step 7.

Summary of the Scientific Evaluation of Flumethrin

Chemical Name: (RS)-cyano-4-fluoro-3-phenoxybenzyl 3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate.

CAS number:69770-45-2

JECFA number: 85

JECFA Evaluation year: 2017

Functional Class: Veterinary Drug - **pyrethroid (type II) insecticide**

Flumethrin is registered in several countries for the **diagnosis and control in honeybee colonies of varroatosis** (also known as varroosis), a disease caused by parasitic mites. Previous approved uses include the external treatment against parasitic insects and ticks on cattle, sheep, goats, horses, and dogs.

Although a synthetic pyrethroid, pyrethroids were developed from natural pyrethrum extracts (Chrysanthemum flowers).

Highlights of the Chronic Toxicity Assessment

ADI: 0–0.004 mg/ kg bw

Health Based Guidance Values (HBGV) based on skin lesions in parental animals and reduced survival and body-weight gain in pups in a two-generation toxicity study in rats. NOAEL from the 2-generation study was **0.37 mg/kg bw/day** (standard 100-fold UF).

Inflammatory ulcerative skin changes were consistently noted in short term toxicity studies. *Flumethrin is not considered to be genotoxic or carcinogenic.*

Highlights of the Acute Toxicity Assessment

ARfD: 0.005 mg/kg bw based on the rat developmental toxicity study.

The NOAEL for maternal toxicity was 0.5 mg/kg bw per day based on clinical signs at 1.0 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 1.0 mg/kg bw per day based on reduced placental weight, reduced fetal weights and an increase in the incidence of skeletal variations at 2.0 mg/kg bw per day. There was no evidence of teratogenicity. 100-fold UF used to set ARfD.

Typically, pyrethroid (type II) insecticides are neurotoxic (CNS), especially in humans. They interact with voltage-gated sodium channels in neurons, resulting in depolarization caused by the prolonged influx of sodium ions during excitation. The extended depolarization is what leads to repetitive nerve activity that can result in hyperexcitation and death. Type II pyrethroids also cause paresthesia, which is characterized by transient burning/tingling/itching sensation of the exposed skin. Although not described in the JECFA evaluation, this may be the basis for the skin lesions.

Intake: The global estimate of chronic dietary exposure (GECDE) is 0.008 µg/kg bw per day (general population) and 0.006 µg/kg bw per day (children).

The global estimate of acute dietary exposure (GEADE): 0.1 µg/kg bw per day (general population) and 0.1 µg/kg bw per day (children).

It is important to note that the Highest estimated dietary intakes would account for only 2% of the ARfD : very low contribution to the overall intake, leading to an excellent margin of safety.

Comments on the proposed MRL

The proposed MRL for honey is set at 6 µg/kg (6ppb), which is twice the limit of quantification of the most reliable analytical method (liquid chromatography coupled with tandem mass spectrometry; LC–MS/MS) used in the residue studies.

Of the studies reviewed by JECFA, **no quantifiable residues were found in honey** after treatment with the flumethrin products.

Conclusion

This MRLs appears to be both adequate for health protection and from the stand point of achievability and would benefit to move for Adoption at Step 8.

Recommendations of the Expert Working Group

There appears to be very limited data available documenting the occurrence of residues of veterinary substances and pesticides in honey. Honey being an importance food commodity consumed in the region, it is highly recommended that dedicated monitoring programs be devoted to this commodity.

Agenda Item 6.1: Maximum residue limits for diflubenzuron (salmon - muscle plus skin in natural proportion) at Step 4

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

The proposed draft MRL for diflubenzuron in salmon (**10 ug/kg**) is available for comment at Step 3 and will be discussed by CCRVDF25 (2021) at Step 4.

Background

Name: Diflubenzuron; 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl) urea

CAS number: 35367-38-5

Veterinary Drug – insecticide: Diflubenzuron is **intended for use in Atlantic salmon** for the treatment of **sea lice** (Lepeophtheirus salmonis) infestations, with an intended oral dosage (feed) of 3-6 mg diflubenzuron/kg bw/day during 14 consecutive days. Diflubenzuron specifically inhibits the formation of chitin (exoskeleton of sea lice). MRLs for diflubenzuron from its pesticide use have been set in a wide range of commodities including cereals (e.g. rice, wheat and barley), fruits (e.g. pome fruits, citrus fruits and stone fruits), animal products (e.g. meats, eggs, milks and offal), tree nuts, vegetables (e.g. mushrooms and peppers) and some fodder. MRLs range from 0.01 mg/kg in rice to 20 mg/kg in dried chilli and tea.

Previous CCRVDF Discussions

At the 22nd Session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF), concerns were raised about the metabolism of diflubenzuron and the possible formation of the **genotoxic metabolite, 4-chloroaniline (p-chloroaniline or PCA)**.

Following discussions, the Committee noted that an **ADI of 0-0.02 mg/kg body weight had previously been established by JMPR for diflubenzuron** and requested JECFA to recommend MRLs for diflubenzuron in salmon muscle and skin in natural proportion.

Summary of JECFA Discussions

2015 – 81st JECFA: In the absence of adequate information on exposure to 4-chloroaniline (PCA), a genotoxic and carcinogenic metabolite and/or degradate of diflubenzuron, and on whether diflubenzuron can be metabolized to PCA in humans, the Committee was unable to establish an ADI for diflubenzuron because it was not possible to assure itself that there would be an adequate margin of safety from its use as a veterinary drug.

2019 – 88th JECFA: Diflubenzuron was again considered, including the available toxicological data on metabolites/degradates, specifically PCA. JECFA concluded that 4-chloroaniline (PCA) is clastogenic in vitro and in vivo, and mutagenic in vitro; **however, it is not mutagenic in vivo**. It was considered that the genotoxicity of 4-chloroaniline was due to a mechanism secondary to reactive oxygen production rather than a direct reaction of 4-chloroaniline with DNA, and **that the effect would exhibit a threshold.** JECFA also concluded that the carcinogenicity of 4-chloroaniline would exhibit a threshold.

Based on the NOAEL of 2 mg/kg bw per day for increased methaemoglobin and sulfhaemoglobin levels in a 2-year study of toxicity and carcinogenicity in rats, and for increased methaemoglobin and sulfhaemoglobin levels, platelet counts and hepatic pigmentation in a 1-year study of toxicity in dogs, **JECFA established an ADI of 0–0.02 mg/kg bw/ day for diflubenzuron (100-fold UF).**

The JECFA ADI of **0–0.02 mg/kg bw/ day for diflubenzuron** is the same value as previously established by the US EPA. PCA was assessed by comparing estimated exposure with the Cramer Class III TTC (threshold of toxicological concern) value of 1.5 µg/kg bw per day. Based on the LOAEL dose that is associated with splenic tumours from a chronic rat study, the TTC Class III value is 8600-fold lower. Estimated dietary exposure to PCA from the use of diflubenzuron in salmon is only 1% of the TTC Class III value of 1.5 ug/kg bw/day.

Estimation of Exposure: The global estimate of chronic dietary exposure (GECDE) for the general population was estimated to be **0.84 µg/kg bw per day (4% of ADI)**

The global estimate of chronic dietary exposure (GECDE) for children was estimated to be 2**.85 µg/kg bw per day** (**14% of ADI**).

Although an MRL for diflubenzuron of **590 ug/kg in salmon** would be possible based on the ADI, JECFA concluded that this may result in unacceptable PCA residues and therefore recommended **an MRL for diflubenzuron of 10 ug/kg,** based on considerations of analytical LOQs (1-10 ug/kg) (LC-MS/MS and UHPLC-HRMS methods reviewed) and available monitoring data which demonstrated the majority of results for diflubenzuron in salmon are <2 ug/kg (in 641 samples analyzed between 2010–2017, 98.6% had no detectable residues).

Possible Recommended Path Forward

Considering the conservative approach followed to lead to the proposed MRL, there will likely be support for advancing this MRL to at least step 5.

Situation in Other Jurisdictions and Considerations

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

Previously, the EU MRL for diflubenzuron in salmon was set at 1000 ug/kg, but the opinion re. the safety of diflubenzuron was re-assessed by the Committee for Medicinal Products for Veterinary Use (**CVMP**) in 2018 following a request by the EU commission that the European Medicines Agency (EMA) consider the genotoxic potential of 4-chloroaniline. The updated EC MRL of 10 ug/kg was published in 2019.

United States / US EPA: As part of its re-registration decision for diflubenzuron, the US Environmental Protection Agency (EPA) also considered possible exposure to **4-chlorophenylurea (CPU)**, a chemical that is structurally related to N,N-dimethyl-CPU, a compound producing tumors of the kidney and liver in male rats. The EPA has assumed PCA and CPU as probable human carcinogens. Applicable cancer risk estimates were reported to be in the range of **1-3 x 10^{-6}** which EPA considered as negligible. Neither the CVMP or JECFA considered CPU.

There are some differences between the assessments conducted by EFSA and by JECFA. Namely JECFA, at the 88th meeting, considered PCA not to be mutagenic in vivo, whereas EFSA concluded that the weight of evidence suggests that 4-chloroaniline is an in vivo genotoxic agent. The CVMP in its 2018 re-assessment used BMDLs from the EFSA evaluation to estimate doses associated with **a negligible cancer risk for PCA (1 x 10^{6})** and used the TTC value for chemicals with structural alerts for genotoxicity (0.15 ug/person/day or 0.0025 ug/kg bw/day). The MRL for diflubenzuron in salmon **of 10 ug/kg recommended by CVMP was set based on ensuring 4-chloroaniline in edible salmon tissues are associated with a cancer risk of less than 1 in 10^{6}.**

Additional considerations

Diflubenzuron has been registered as a pesticide since the 1970's, with numerous MRLs in food crops (majority <3 mg/kg).

It may be worthy for Codex (through a request from CCRVDF) to recommend that a review covers the crop MRLs, taking into consideration the recent decision to set the MRL for diflubenzuron in salmon **on the basis of analytical LOQs and available monitoring data**.

Salmon is not a fish species that is farmed in the region. Other species such Tilapia are more commonly found in fish farms. It may be useful to study the applicability or the necessity of adaptation of the established MRLs to the fish species farmed in the region.

Similar to what was noted for honey, there is little data available documenting the level of occurrence of residues in farmed fish in the MENA region. Investment in the development of such monitoring data would be warranted.