CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 9(a) **CX/RVDF 12/20/11**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twentieth Session

San Juan, Puerto Rico, 7-11 May 2012

DRAFT PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION BY JECFA

Replies of Canada, Chile, Costa Rica to CL 2010/50-RVDF

CANADA

Administrative information

1. Member(s) submitting the request for inclusion:

Canada

2. Veterinary drug names:

Gentian Violet (CAS #: 548-62-9)

3. Trade names:

Co-op Pinkeye spray (Interprovincial Co-op Ltd), **Cristisol** (Dominion Veteirnary Laboratories Ltd.), **Pinkeye guard** (Dominion Veteirnary Laboratories Ltd.), **Pinkeye spray** (Citadel Animal Health), **Wound and Pinkeye spray** (Bimeda-MTC Animal Health Inc.)

4. Chemical names:

Hexamethyl pararosaniline chloride

5. Names and addresses of basic producers:

There are several companies that produce the active drug substance

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)

Gentian violet (GV), also called crystal violet, is a triphenyl methane dye closely related to malachite green. It has antibacterial, antifungal and antiparasitic properties, and was used in the past both in human and veterinary medicine including aquaculture. It is mainly used through topical application. Many member countries (e.g., Australia, USA) have withdrawn the registration of gentian violet for use in food animals either as a veterinary drug or as a feed additive. Studies conducted by the United States National Toxicology Program have identified it to be potentially carcinogenic in rodents. Other studies have shown it to be potentially mutagenic. However, gentian violet containing products are still used in some member countries (e.g., topical preparations in Canada). Although its use in aquaculture in developing countries is not well documented, fish products imported to the USA, EU or Canada have occasionally tested positive for gentian violet or its metabolite, leucogentian violet. This has led to issuance of import advisory from different regulators, including compliance and enforcement action, and likely trade inconvenience.

JECFA has recently evaluated a related compound, malachite green. However, considering the potential carcinogenic potential, JECFA could not establish an ADI or MRLs for either malachite green or leucomalachite green, and has recommended that malachite green should not be used in food producing animals. Within this context, and considering the demonstrated carcinogenic effect of gentian violet in the

rodent model, the 19th session of the CCRVDF agreed to include it in the priority list if there is a commitment to provide a data package. Canada agreed to prepare a data package for JECFA's assessment, mainly based on review of published literature. This request to include gentian violet in the priority list is made as Canada has compiled the published literature and can submit the dossier for JECFA's assessment.

7. Assessment against the criteria for the inclusion on the priority list

This compound meets the criteria for inclusion in the priority list for the following reasons:

- A member (Canada) is proposing the compound for evaluation
- The compound is approved for topical use in at least in one of the member countries (e.g., Canada). However, Canada has not recently reevaluated whether the current scientific evidence supports its continual use in food producing animals. Other countries which have reassessed the compound in recent years have considered it not be safe for use in food producing animals and have revoked its registration.
- The compound has potential to cause public health and/or trade concerns. It is shown to be carcinogenic, potentially with genotoxic mechanisms, and many countries have issued advisories regarding zero tolerance or low level minimum required performance limits (e.g., 0.5 ppb in EU and Canada) for the residues of this chemical in foods.
- This is available as a commercial product in many countries.
- Canada has made a commitment that it will provide a dossier based on published literature review and compilation of studies submitted by member countries.

8. Justification for use

In countries where it is used, its use has been grandfathered often without assessment of scientific data that would be required for the approval of a new compound for use in food producing animals. In veterinary medicine it is mainly used for topical use, and currently there are often safer alternatives available. This compound is not used in Canadian aquaculture. Whether there is a justification for its continual use food animal production, including aquaculture, needs to be assessed. However, being a cheap compound, there might be some financial incentive for its use in some developing countries.

9. Veterinary use pattern

In Canada, the drug is used for topical use for treatment of skin infections and pink eye (keratitis).

10. Commodities for which Codex MRLs are required

Gentian violet has approval for topical use in cattle, swine, sheep, goats and horses. However, the question for JECFA should be whether an ADI for this compound could be established, and whether its continual use in food producing animals would be safe from human health perspective. MRL establishment would be secondary to the assessment that an ADI can be established for this compound.

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

As a comprehensive literature review is conducted, and all cited references will be included in the dossier, it can be assessed as a regular JECFA submission. However, as the compound is also found in the environment as a contaminant from multiple industrial and laboratory uses, a multi-pronged approach might have to be undertaken for its assessment.

12. Specific request to risk assessors

JECFA is requested to assess whether the current scientific evidence can support continual use of this product in food producing animals, and if so, whether JECFA can establish ADI and MRLs for gentian violet in a number of food producing animals. The literature that will be submitted to JECFA also indicates that the compound and its metabolites are also found in the environment, and JECFA's assessment might have to take that into account as well. As the dossier does not have the all standard typical toxicological studies required as per the current guidelines, JECFA might have to use a number of alternative approaches (e.g., BMDL, MOE etc.) for the safety assessment of gentian violet.

A*vailable information*[1]

13. Countries where the veterinary drugs is registered

Canada

14. National/Regional MRLs or any other applicable tolerances

Not-available

15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

A brief review of available data is attached with this request.

Timetable

16. Date when data could be submitted to JECFA

The data package is ready, and could be submitted at any time when requested.

CHILE

Administrative information

1. Member(s) submitting the request for inclusion

Chile

2. Veterinary drug names

   a) Flumequine

   b) Emamectin Benzoate

   c) Oxolinic Acid

3. Trade names

   a) Flumequine

   - Flumepren 10 %
   - Flox-Feed 80 %
   - Flumepren 80 %

   b) Emamectin Benzoate

   - Slice 0,2%
   - Calbiofarm
   - Quinafish

   c) Oxolinic Acid

   - Bandrol 80 %
   - Litoflox 80 %

4. Chemical names

   a) Flumequine

   7-fluoro-12-methyl-4-oxo-1-azatricyclo [7.3.1.05,13] trideca-2,5,7,9(13)-tetraene-3-carboxylic acid

   $C_{14}H_{12}FNO_3$

   b) Emamectin Benzoate

   A mixture of natural avermectin dimethylamino-4'-deoxy 4' avermectin B1a and B1b

[1] When preparing a preliminary risk profile, Member(s) should take into account the updated data requirement, to enable evaluation of a veterinary drug for the establishment of an ADI and MRLs, published by JECFA.

$C_{56}H_{81}NO_{15}$ (Emamectin Benzoate B1a + $C_{55}H_{79}NO_{15}$ Emamectin Benzoate B1b)

c) Oxolinic Acid

5-Ethyl- 8-oxo- 5,8-dihydro [1,3] dioxolo [4,5-g]quinoline-7-carboxylic acid

$C_{13}H_{11}NO_5$

5. Names and addresses of basic producers

a) Flumequine

- Centrovet Ltda., Av. Cerrillos 602, Cerrillos, Santiago de Chile
- Veterquímica S.A., Camino a Lonquén 10.387, Maipú, Santiago de Chile.

b) Emamectin Benzoate

- Centrovet Ltda., Av. Cerrillos 602, Cerrillos, Santiago de Chile
- Laboratorios Recalcine S.A.
- Schering Plough Ltda./Intervet Chile Ltda., Mariano Sánchez Fontecilla 310, piso 7, Las Condes, Santiago.Av. Pedro de Valdivia 295, Providencia, Santiago de Chile.

c) Oxolinic Acid

- Veterquímica S.A., Camino a Lonquén 10.387, Maipú, Santiago de Chile
- Centrovet Ltda., Av. Cerrillos 602, Cerrillos, Santiago de Chile

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)

Besides having the need to have pharmaceutical products for the treatment of illnesses in salmon aquaculture production, there is a need to protect consumer health; avoiding residues present in food products for human consumption.

Residues or pharmaceutical products in salmon and trout meat can cause changes in consumer's intestinal flora, as well as the development of resistance to microorganism, and allergy induction in sensitive individuals.

7. Assessment against the criteria for the inclusion on the priority list

The antibiotics and anti-parasites stated are essential for trout and salmonidae national production, as they are part of a key therapeutic tool to control bacteria and parasite infections, to this date there are no other therapeutic or preventative alternatives to control them successfully. Its clinical efficiency and a good and ample range of therapeutic tools on hand, along with the best practices and therapeutic rotation, to lessen its environmental impact and help to avoid or diminish bacteria and parasite resistance.

The stated veterinary drugs are available as a commercial product duly registered for their use on the stated species, and they are also the choice products for the treatment of two of the major illnesses present in Chilean salmon aquaculture production, Salmon Rickettsial Syndrome and Caligiasis.

Therefore, for public health protection, it is required to set an acceptable maximum residue level in salmon and trout meat that won’t produce foreseeable impacts in consumers.

Risk profile elements

8. Justification for use

a) Flumequine

Due to its wide spectrum action, quick absorption, bactericidal action mechanism, intracellular penetration capacity, besides other characteristics, it is the choice product against the clinical signs of disease caused by both gram negative and gram positive bacteria. Due to its lipophilic nature, it has an ample tissue distribution, penetrating cell membranes, causing it to be the choice to fight against intra cellular replicating organisms like rickettsias. This drug is especially recommended in aquaculture to control several bacterial infections like,

- Salmon Rickettsial Syndrome (SRS), caused by *Piscirickettsia salmonis*, where the vaccine development hasn't shown full effectiveness yet.
- Furunculosis in salmonidae farming, caused by atypical *Aeromonas salmonicida* infections.
- Several illnesses in fresh water [species] caused by bacteria of the Flavobacterium genus, like *Flavobacterium columnare* and *Flavobacterium psychrophilum*, where vaccine availability and effectiveness is limited or doesn't exist.
- Vibriosis in fin fish and crustaceans caused by *Vibrio anguillarum* and other related species.

It is also used in salmonidae species occasionally to treat edwardsiellosis caused by *Edwardsiella tarda* and Pasteurellosis caused by *Pasteurella piscicida*.

b) Emamectin Benzoate

This is the anti-parasite drug choice to control all parasitic stages and development phases of sea lice, a species represented in Chile by *Caligus rogercresseyi*.

Caligidosis is a highly prevalent parasitic disease in Chile and worldwide. It has serious health and production wise consequences, both directly and indirectly for salmon and trout species.

c) Oxolinic Acid

Oxolinic Acid represents an important alternative in the aquaculture veterinary drugs rotation. It is usually prescribed to treat several bacterial infections like bacterial hemorrhagic septicemia (caused by different Aeromonas and Pseudomonas species), Furunculosis (caused by atypical *Aeromonas salmonicida*), and in general to control fresh water diseases caused by flavobacterium.

All these diseases are present and widely distributed in the nation.

9. Veterinary use pattern

a) Flumequine

Oral: 10-30 mg/Kg w/day10-15 days in feed

b) Emamectin Benzoate

Oral: 50 µg/Kg p v/day for 7 days in feed

c) Oxolinic Acid

Oral: 10-30 mg/Kg w/day for10-15 days in feed.

10. Commodities for which Codex MRLs are required

a) Flumequine

b) Emamectin Benzoate

c) Oxolinic Acid

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

12. Specific request to risk assessors

Establish MRLs for proposed drugs, because they are duly registered drugs and widely used to treat diseases in domestic aquaculture, some of them already have MRLs for these products in different destination countries, including Chile.

Available information [1]

13. Countries where the veterinary drug is registered

Just to mention a few:

Flumequine: European Union

Emamectin Benzoate: European Union

Oxolinic Acid: European Union

14. National/Regional MRLs or any other applicable tolerances

Pharmaceutical Product	Chile	European Union	Japan
Oxolinic Acid	100 μg/ Kg	100 μg/ Kg	50 μg/ Kg
Flumequine	600 μg/ Kg	600 μg/ Kg	500 μg/ Kg
Emamectin Benzoate	100 μg/ Kg	100 μg/ Kg	100 μg/ Kg

15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

Timetable

16. Date when data could be submitted to JECFA

COSTA RICA

Costa Rica appreciates the opportunity to express its comments to CL 2010/50-RVDF, Request for Comments / Information on Priority List of Veterinary Drugs Requiring Evaluation or Reevaluation

Due to current regulations it is very difficult for us to help contribute veterinary drugs to be included in such a list of Veterinary Drugs Requiring Evaluation or Reevaluation.

Justification:

Due to current parameters and all documents we have to submit to become part of the Priority List requiring evaluation by JECFA, it is impossible for us to contribute scientific data, despite the fact that many of the drugs that have not been evaluated by JECFA are registered in our countries and they have been used for a long time.