

Date: April 5, 2016

FREEDOM OF INFORMATION SUMMARY

IMPORT TOLERANCE

I. GENERAL INFORMATION

- A. Established Name:** azamethiphos
- B. Food-Animal Species:** salmonids
- C. Tolerances/tissues:** 0.02 ppm azamethiphos in salmonids muscle/skin
- D. File Number:** VMF 005-969
- E. Petitioner:** FVG Ltd., 22 Carsegate Rd.,
Inverness, Scotland, IV3 8EX

II. HUMAN FOOD SAFETY

A. Toxicology:

Toxicity tests determining the human food safety of azamethiphos are summarized below:

1. Summary of Toxicology Studies:

Study Type	Description
Sub-Chronic Oral Toxicity Study in Non-Rodents:	Toxicity Study in Beagle Dogs; Additional Group (Dietary administration for 13 weeks followed by 4 weeks observation)
Chronic Oral Toxicity Study in Non-Rodents:	12-Month Chronic Dietary Toxicity Study in Beagle Dogs
Chronic Oral Toxicity Study in Rodents:	Lifetime Oral (dietary administration) Oncogenicity and Toxicity Study in the Rat with an Interim Kill after 52 Weeks and a 4-Week Treatment-free Period
Oral Carcinogenicity Study in Mouse:	Lifetime Oral (dietary administration) Oncogenicity Study in the Mouse
Oral Developmental Toxicity Study in Rodents:	A Teratology (Segment II) Study in Rats
Oral Developmental Toxicity Study in Non-Rodents	A Teratology (Segment II) Study in Rabbits
Two-Generation Oral Reproductive Toxicity Study in Rats:	Two-Generation Dietary Reproduction Study with CGA-18809 in Rats

Genetic Toxicology Studies:

- Bacterial Reverse Mutation Assay (Ames Test): Two *Salmonella*/Mammalian Microsome Mutagenicity tests
- Gene Mutation Test: K5178 YK+/-mouse lymphoma mutagenicity test
- Gene Mutation Test: Dominant lethal mouse study
- Structural chromosomal aberration test: Nucleus anomaly test in somatic interphase nuclei
- Structural chromosomal aberration test: Sister chromatid exchange study
- Two Intravenous Host-Mediated *Salmonella* mutagenicity tests: Gene Mutation Test: Assay with *S. Typhimurium*, U.S. EPA Guidelines No. 84-2
- *Saccharomyces Cerevisiae* D7/Mammalian Microsome Mutagenicity Test: U.S. EPA Guidelines No. 84-2
- BALB/3T3 Cell Transformation Assay
- Tests for Other Genotoxic Effects Autoradiographic DNA Repair Test on Rat Hepatocytes, EPA Guidelines No. 84-4
- Tests for Other Genotoxic Effects Autoradiographic DNA Repair Test on Human Fibroblasts, EPA Guidelines No. 84-4

Non-Pivotal Studies

- 4-Week Oral Dose Range Finding Study
- 90-Day Toxicity Study in Rats

2. Determination of No Observed Effect Level (NOEL) for chronic exposure:

The inhibition of the cholinesterase activity is the most sensitive toxicological endpoint for azamethiphos toxicity. Based on the available toxicology studies, the NOEL/NOAEL of 0.1 mg/kg bw/day from the two-generation reproductive study in rats was considered to be the most appropriate NOEL/NOAEL for the determination of the toxicological ADI from this endpoint for chronic exposure of human consumers to total residues of azamethiphos.

3. Acceptable Daily Intake (ADI):

Because of the lack of antibacterial activity for azamethiphos, a microbiological ADI was not needed. Therefore, the toxicological ADI was set as the final ADI. The toxicological ADI for total residues of azamethiphos is calculated using the following formula based on the NOEL/NOAEL of 0.1 mg/kg bw/day from the two-generation reproductive study in rats and a safety factor of 100. A safety factor of 100 was applied to the NOEL/NOAEL in calculating the ADI to account for possible animal-to-human variability and human-to-human variability in response to azamethiphos.

$$\begin{aligned} \text{Toxicological ADI} &= \frac{\text{NOEL/NOAEL}}{\text{Safety Factor}} = \frac{0.1 \text{ mg/kg bw/day}}{100} \\ &= 0.001 \text{ mg/kg bw/day} = 1 \text{ } \mu\text{g/kg bw/day} \end{aligned}$$

4. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

The calculation of the tissue safe concentrations is based on the General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals (FDA/CVM, revised July 2006). The daily consumption value of the edible tissue of fish (muscle and skin in natural proportion) is approximated as 300 g. The safe concentration of total azamethiphos residues (ppm) in the edible tissue of fish (muscle with adhering skin in natural proportion) is calculated as the following:

$$\begin{aligned} \text{Safe Concentration} &= \frac{\text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}} \\ &= \frac{1 \text{ } \mu\text{g/kg bw/day} \times 60 \text{ kg}}{300 \text{ g/day}} = 0.2 \text{ } \mu\text{g/g} = 0.2 \text{ ppm} \end{aligned}$$

Therefore, the safe concentration for total azamethiphos is 0.2 ppm for fish muscle with adhering skin in natural proportions.

B. Summary of Residue Chemistry Studies:

1. Total Residue and Metabolism Study:

The Fate of ¹⁴C-labeled Azamethiphos ([2-¹⁴C]Pyridyl CGA 18809) in an Atlantic Salmon/Sea Water System

Total residues were less than the safe concentration at all sampling timepoints (0, 3, 12, 24, 48, 96, 168 hours after treatment). At zero withdrawal, total residues in muscle and skin were 0.02 ppm and 0.117 ppm azamethiphos equivalents, respectively. Total residues in muscle and skin were too low for characterization of the metabolites. The major metabolite in bile was the glucuronic acid conjugate of 2-amino-3-hydroxy-5-chloro-pyridine, which also was found in the rat during the comparative metabolism study.

2. Comparative Metabolism Studies:**The Absorption, Distribution and Excretion of [2-¹⁴C] Pyridyl CGA-18 809 in the Rat****The Metabolite Profiles in Urine and Feces of Rats After Oral and Intravenous Administration of [2-¹⁴C] Pyridyl CGA 18 809**

Azamethiphos, sulfuric acid and glucuronic acid conjugates of 2-amino-3-hydroxy-5-chloro-pyridine were found in urine.

3. Target Tissue and Marker Residue Assignment:

The target tissue is muscle with adhering skin. The marker residue is parent drug, azamethiphos, because that is the compound measured by the analytical method.

4. Tolerance Assignment:

An import tolerance of 0.02 ppm is assigned for azamethiphos in salmonids.

5. Withdrawal Period:

A withdrawal period is not assigned in establishing an import tolerance.

6. Microbial Food Safety:

Azamethiphos is not considered to be an antimicrobial product and therefore a microbiological safety assessment was not needed.

C. Analytical Method for Residues:

A validated HPLC method for measuring the azamethiphos in salmon edible tissue was provided. The method is available from the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

D. Conclusions:

The Center for Veterinary Medicine concludes that we have the appropriate information for us to assign an import tolerance for azamethiphos in salmonids. We assign an import tolerance of 0.02 ppm azamethiphos in muscle/skin of salmonids.

III. AGENCY CONCLUSIONS

These data support the establishment of an import tolerance of 0.02 ppm azamethiphos in muscle/skin of salmonids as provided under Sec. 512(a)(6) of the Food, Drug, and Cosmetic Act.