Date: January 27, 2021

FREEDOM OF INFORMATION SUMMARY

Import Tolerance

VMF 006-294

hexaflumuron

salmonids

0.5 parts per million (ppm) in muscle with adhering skin

Petitioner:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

VMF 006-294

B. Petitioner

Zoetis Inc.
333 Portage Street
Kalamazoo, MI 49007

C. Drug Established Name

Hexaflumuron

D. Pharmacological Category

Antiparasitic

E. Species/Class

Salmonids

F. Import Tolerances for Drug Residues in Edible Tissues

0.5 ppm hexaflumuron in muscle with adhering skin

II. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

After reviewing information both submitted by the sponsor (literature, data, etc.) and available in the public domain, the Agency determined:

- hexaflumuron is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
- hexaflumuron is not used to treat gastroenteritis or other bacterial diseases in humans,
- hexaflumuron (or a similar class representative) is not under development to treat bacterial diseases in humans, and
- hexaflumuron is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to develop or submit for review, microbial food safety (antimicrobial resistance) information for the requested hexaflumuron import tolerance in salmonids.

B. Toxicology

1. Toxicology Studies

   Toxicology studies considered in the determination of the acceptable daily intake (ADI) for total residue of hexaflumuron are listed in Table B.1 below:

Table B.1. Summary of Toxicology Studies (test article: hexaflumuron, also referred to as XRD 473)

Study Title; Study Number; Doses Tested	**NOEL/NOAEL (mg/kg body weight (bw)/day)* (NOEL/NOAEL basis)**
13 weeks dietary toxicity study of XRD 473 in mice; DET 907 0, 5, 25 and 250 mg/kg bw/day	**5** (increased plasma transaminase activities and enlarged hepatocytes in males observed at the next higher dose)
13-weeks toxicity study of XRD 473 in rats; DET 759 0, 25, 125, 750 and 1500 mg/kg bw/day	**25** (splenic hemosiderin deposition found at the next higher dose)
52-week dietary toxicity study of XRD 473 in rats; DET 1037 0, 5, 75, and 500 mg/kg bw/day	**75** (body weight increases at the next higher dose)
52-week oral toxicity study with XRD 473 in dogs; RCC 048240 0, 0.5, 2, 5, and 25 mg/kg bw/day	**0.5** (induction of methemoglobinemia along with hemosiderin deposits in the Kupffer cells in liver at the next higher dose)
XDE-473 oral gavage teratology study in Sprague-Dawley rats; DR-0210-2650-009 0, 25, 125, and 1000 mg/kg bw/day	**1000** (fetal and maternal) (no fetal and maternal effects up to the highest dose)
Effect of XRD 473 on pregnancy of the rabbit; DWC 482/87309 0 and 1000 mg/kg bw/day	not determined
XRD 473 potential tumorigenic effects in prolonged dietary administration (80 weeks) to mice; B86-0385 0, 5, 25, and 125 mg/kg bw/day	**5 (systemic)** (change in spleen weight and the hematological finding) **25 (reproductive)** (increased pup death and reduced pup and litter weight in the high-dose group of the F0 generation)
80-week oral (feeding) toxicity study in the mice (tumorigenic effects); GHE-T-182 0, 2, 5, and 25 mg/kg bw/day	**5** (lung adenomatosis in males noted at the highest dose) Not carcinogenic
XRD-104-week dietary combined chronic toxicity/ carcinogenicity study in rats; GHE-T-211 0, 5, 75, and 500 mg/kg bw/day	**75** (non-neoplastic lesion in the liver and kidney at the highest dose) not carcinogenic

*NOEL = no-observed-effect level, NOAEL = no-observed-adverse-effect level

The following genotoxicity studies also were considered, and it was concluded that hexaflumuron was not genotoxic:

- Bacterial Reverse Mutation Test (Ames Test)
  Study Number VRE0012
- *In Vitro* Mammalian Chromosome Aberration Test
  Study Number 15138-0-444
- Mammalian Erythrocyte Micronucleus Test
  Study Number DR-0210-2650-003
- *In Vitro* Mammalian Cell Gene Mutation Test using HPRT
  Study Number 15138-0-435DR

2. Determination of Toxicological NOEL/NOAEL for Chronic Exposure

   Based on the available toxicology studies, the NOEL/NOAEL of 0.5 mg/kg bw/day for the induction of methemoglobinemia along with hemosiderin deposits in the Kupffer cells in liver from the 52-week oral toxicity study in dogs (Study Number RCC 048240) was selected to be the most appropriate for the determination of the toxicological ADI for total residue of hexaflumuron.

3. Acceptable Daily Intake (ADI)

   The toxicological ADI for total residue of hexaflumuron is calculated using the following formula based on the NOEL/NOAEL of 0.5 mg/kg bw/day from the 53-week oral toxicity study in dogs. A safety factor of 100 was applied to account for a 10-fold factor for animal to human variability and a 10-fold factor for human to human variability in sensitivity to the toxicity.

$$\text{Toxicological ADI} = \frac{\text{NOEL/NOAEL}}{\text{Safety Factor}} = \frac{0.5 \text{ mg/kg bw/day}}{100}$$
$$= 0.005 \text{ mg/kg bw/day} = 5 \text{ µg/kg bw/day}$$

   The toxicological ADI for total residue of hexaflumuron is 5 µg/kg bw/day. Hexaflumuron is not an antimicrobial drug and is not known to possess antibacterial activity or be involved in selection of resistance to antimicrobial drugs among bacteria. Therefore, there is no need to consider establishing a microbiological ADI. Because a microbiological ADI is not needed, the toxicological ADI is the final ADI.

4. Safe Concentration for Total Residues in Edible Tissues

   The calculation of the tissue safe concentration is based on recommendations in the "General Principles for Evaluating the Human Food Safety of New Animal Drugs used in Food-Producing Animals" (FDA/CVM Guidance for Industry #3, June 2018). The daily consumption value of the edible tissue of fish (muscle with adhering skin) is 300 g. The safe concentration for total residues of hexaflumuron in the edible tissue of salmonids (muscle with adhering skin) is calculated using the following formula:

$$\text{Safe Concentration} = \frac{\text{ADI} \times \text{Human Body Weight}}{\text{Food Consumption Value}}$$

$$\text{Safe Concentration (muscle with adhering skin)} = \frac{5\ \mu g/kg\ bw/day \times 60\ kg}{300\ g/day} = 1\ \mu g/g = 1\ ppm$$

Therefore, the safe concentration for total residues of hexaflumuron is 1 ppm in muscle with adhering skin in salmonids.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Study

      Title: Hexaflumuron: Metabolism in Marine Fish. (Study Number VRE0010)

      Conclusions: The study conducted in Atlantic salmon demonstrated that the major component of total residues in fillet was parent hexaflumuron. The data showed that total residues were below the safe concentration of 1 ppm at all sampling times.

   b. Comparative Metabolism Studies

      Title: Absorption, distribution, excretion and metabolism of ^{14}C-labeled XRD 473 after single oral administration via feed admixture to dogs. (Study Number 072415)

      Title: Absorption, distribution, excretion and metabolism of XRD 473 after single oral administration to rats. (Study Number 050668)

      Conclusion: The major metabolite of hexaflumuron in fish is parent hexaflumuron, which also is present in the dog and the rat.

2. Target Tissue and Marker Residue

   The target tissue is muscle with adhering skin. The marker residue is parent drug, hexaflumuron.

3. Import Tolerance

   An import tolerance of 0.5 ppm is established for hexaflumuron in the muscle with adhering skin of salmonids.

4. Withdrawal Period

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

D. Analytical Method for Residues

1. Description of the Analytical Method

   The LC-MS/MS analytical procedure described in FDA Laboratory Information Bulletin (LIB) 4637 can be used to analyze for residues of hexaflumuron.

2. Availability of the Analytical Method

   To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

III. AGENCY CONCLUSIONS

The Center for Veterinary Medicine assigns an import tolerance of 0.5 ppm for hexaflumuron in salmonids. The data submitted in support of establishment of an import tolerance for hexaflumuron in salmonids satisfy the requirements of section 512(a)(6) of the Federal Food, Drug, and Cosmetic Act.