Date: October 21, 2022

# FREEDOM OF INFORMATION SUMMARY

## Import Tolerance

VMF 006-441

imidacloprid

salmonids

0.6 parts per million (ppm) imidacloprid in muscle with adhering skin

Petitioner:

Benchmark Animal Health Ltd

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# I. GENERAL INFORMATION

## A. File Number

VMF 006-441

## B. Petitioner

Benchmark Animal Health Ltd
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Edinburgh Technopole
Milton Bridge near Penicuik
Midlothian, EH26 0GB
United Kingdom

## C. Drug Established Name

imidacloprid

## D. Pharmacological Category

Antiparasitic

## E. Species/Class

Salmonids

## F. Import Tolerances for Drug Residues in Edible Tissues

0.6 ppm imidacloprid in muscle with adhering skin

# II. HUMAN FOOD SAFETY

## A. Antimicrobial Resistance

The Agency evaluated the need to address the impact of the use of imidacloprid on antimicrobial resistance among bacteria of public health concern in or on imidacloprid-treated salmonids. After reviewing information both submitted by the sponsor (literature, data, etc.) and available in the public domain, the Agency determined:

1) Imidacloprid 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;
2) Imidacloprid is not used to treat gastroenteritis or other bacterial diseases in humans;
3) Imidacloprid (or a similar class representative) is not under development to treat bacterial diseases in humans; and
4) Imidacloprid is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined that a microbial food safety assessment was not required for this use of imidacloprid in salmon.

## B. Toxicology

1. Toxicology Studies

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

**Table 1. Summary of Toxicology Studies (test article: imidacloprid)**

| **Study Type; Study Number or Study Reference; Tested Doses** | **NOEL/NOAEL or LOEL/LOAEL* (mg/kg body weight (bw)/day) (NOEL/NOAEL or LOEL/LOAEL basis)** |
|---|---|
| 98-day oral (dietary) toxicity study in rats; JMPR, 2001***<br><br>0, 11, 57, 410 mg/kg bw/day | NOEL/NOAEL: **11**<br><br>(Decreased body weight gain at higher doses) |
| 13-week oral (dietary) toxicity study in dogs; JMPR, 2001<br><br>0, 200, 600 or 1800/1200 ppm | NOEL/NOAEL: **7.5** (200 ppm)<br><br>(Reduced food consumption at higher doses) |
| 12-month oral (dietary) toxicity study in rats; ANT 0022<br><br>0, 5.6, 16.3, 55.9 mg/kg bw/day | LOEL/LOAEL: **5.6**<br><br>(Increased concentration of creatine (F**), decreased calcium (M**, F), decreased sodium (M), increased hemoglobin distribution width (M), increased mean platelet volume (M); decreased hemoglobin (F) and pack cell volume (F) in plasma at the lowest dose level) |
| 52-week oral (dietary) toxicity study in dogs, JMPR, 2001<br><br>0, 6.1, 15, and 41/72 mg/kg bw/day | NOEL/NOAEL: **15**<br><br>(Food intake reduction, increased plasma cholesterol concentration, increased P450 activity, slightly increased liver weight at the next higher dose level) |
| Oral (gavage) prenatal developmental toxicity study in the rat; ANT 0018<br><br>0, 5, 15, 50 mg/kg bw/day | NOEL/NOAEL: **15** (maternal)<br><br>(Decreased food consumption (F) and decreased body weight (F) at the highest dose)<br><br>LOEL/LOAEL: **5** (fetal)<br>(Increased minor fetal abnormalities, incomplete ossification of the frontal skull region and increased incidence of one or more wavy ribs in fetus at the lowest dose) |

| **Study Type; Study Number or Study Reference; Tested Doses** | **NOEL/NOAEL or LOEL/LOAEL* (mg/kg body weight (bw)/day) (NOEL/NOAEL or LOEL/LOAEL basis)** |
|---|---|
| Oral (gavage) prenatal developmental toxicity study in rabbits, JMPR, 2001<br><br>0, 8, 24, and 72 mg/kg bw/day | NOEL/NOAEL: **8** (maternal)<br>(Decreased food intake and body weight gain at higher doses)<br><br>NOEL/NOAEL: **24** (fetal)<br><br>(Reduced body weight of the fetuses, increased incidences of fetuses with retarded ossification at the highest dose) |
| Oral (dietary) extended one-generation reproductive toxicity study in rats; 8382174<br><br>0, 100, 300, 1000 ppm, corresponding test article intake dosage varying markedly from 4.7 to 16.6 mg/kg bw/day for the low dose, from 14.2 to 48.6 mg/kg bw/day for the mid dose, and from 48.1 to 134.4 mg/kg bw/day for the high dose respectively due to growth, pregnancy, and lactation. | LOEL/LOAEL: **4.7** (systematic)<br><br>(Hepatocyte hypertrophy (F), hyperplasia of the mammary gland (F), increased serum thyroid stimulating hormone (TSH) (M) at the lowest dose group of the F0 generation and hepatocyte hypertrophy at the lowest dose group of the F1 generation)<br><br>NOEL/NOAEL: **8** (reproductive)<br><br>(Decreased implantation sites at the medium dose group in the F0 generation)<br><br>NOEL/NOAEL: **120** (developmental neurotoxicity)<br>(No neurotoxic effect up to the highest dose)<br><br>NOEL/NOAEL or LOEL/LOAEL: not determined (developmental immunotoxicity)<br><br>(Reduction of T-cell dependent antibody response in females at all doses levels in a non-linear pattern) |
| 24-month oral (dietary) carcinogenicity study in the mice, JMPR, 2001<br><br>0, 20, 66, 210, and 410 mg/kg bw/day | NOEL/NOAEL: **66**<br><br>(Reduced body weight gains and more mineralization of the thalamus)<br><br>No carcinogenic effect |
| 24-month oral (dietary) carcinogenicity study in rats, JMPR, 2001<br><br>0, 5.7, 17, 51 mg/kg bw/day | NOEL/NOAEL: **5.7**<br><br>(Increased body weight gains and increased low-grade periacinal hepatic-cell hypertrophy in males and increased mineralization of the thalamus in brain in males at the next higher dose)<br><br>No carcinogenic effect |

* NOEL/NOAEL: no-observed-effect level/no-observed-adverse-effect level
LOEL/LOAEL: lowest-observed-effect level/lowest-observed-adverse-effect level
** M: male; F: female
*** JMPR 2001: The toxicological evaluation of imidacloprid was carried out at the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2001[1]

It was concluded that imidacloprid is not genotoxic based on the following studies along with genotoxicity studies assessed in the JMPR 2001:

- Bacterial Reverse Mutation Assay (Ames)
  Study Number: 8387334
- *In Vitro* Micronucleus Assay
  Study Number: 8387335
- Rat Bone Marrow Mammalian Erythrocyte Micronucleus Assay
  Study Number: ANT0025

2. Toxicological Point of Departure for the ADI Determination

The point of departure of 5 mg/kg bw/day was selected for the ADI determination, considering the LOEL/LOAEL for effects on clinical chemistry and hematology at 5.6 mg/kg bw/day in the one year toxicity study in rats, the LOEL/LOAEL for increased incidences of fetal abnormalities at 5 mg/kg bw/day in the developmental toxicity study, and the LOEL/LOAEL for the systemic effects on liver, mammary gland, and TSH in parental animals and the systemic effects on liver in F1 animals at 4.7 mg/kg bw/day in the extended one generation reproductive toxicity study.

3. Acceptable Daily Intake (ADI)

The toxicological ADI for total residue of imidacloprid is determined based on the LOEL/LOAEL of approximately 5 mg/kg bw/day from the one-year toxicity study in rats, developmental toxicity study in rats, and extended one generation reproductive toxicity study in rats. A safety factor of 1000 is applied to account for a 10-fold factor for animal to human variability, a 10-fold factor for human-to-human variability in sensitivity to the toxicity, and a 10-fold factor for extrapolation from LOEL/LOAEL to NOEL/NOAEL and the non-linear treatment-related immunosuppressive effects noted in the extended one generation reproductive toxicity study. The toxicological ADI for total residue of imidacloprid is calculated as follows:

$$\text{Toxicological ADI} = \frac{\text{Point of Departure}}{\text{Safety Factor}} = \frac{5 \text{ mg/kg bw/day}}{1000}$$
$$= 0.005 \text{ mg/kg bw/day} = 5 \text{ µg/kg bw/day}$$

The toxicological ADI for total residue of imidacloprid is 5 µg/kg bw/day.

[1] Pesticide residues in food 2001: toxicological evaluations for imidacloprid/Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group (2001, Geneva, Switzerland), World Health Organization, WHO/PCS/02.1, 2002

Imidacloprid is not an antimicrobial drug. Because bacteria do not have nicotinic acetylcholine receptors for which imidacloprid mainly acts on, imidacloprid is not expected to have effects against bacteria. Therefore, there is no need to establish a microbiological ADI, and 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 our 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, May 2022). The daily consumption value of the edible tissue of fish (muscle with adhering skin) is 300 g. The safe concentration of total residues of imidacloprid in the edible tissue of salmonids (muscle with adhering skin) is calculated using the following formula:

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

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 imidacloprid 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:** The Metabolism of [$^{14}$C] IV-38 in Atlantic Salmon (*Salmo salar* L.) (Study No. 224444, Report No. 36620)

**Conclusions:** The study conducted in Atlantic salmon demonstrated that the major component of total residues in fillet (≥90%) was parent IV-38 (imidacloprid). Total residues were below the 1 ppm safe concentration at all sampling timepoints.

b. Comparative Metabolism Study

The need for a comparative metabolism study was waived because parent imidacloprid represented over 90% of total radiolabeled residues.

2. Target Tissue and Marker Residue

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

3. Import Tolerance

   An import tolerance of 0.6 ppm is established for residue of imidacloprid 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 procedures for imidacloprid in trout fillet (AP.229128.03) and in salmon fillet (AP.225406B.03) can be used to analyze residues of imidacloprid in salmonids. These procedures are research methods that were not evaluated in an FDA method transfer trial.

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 0.6 ppm for imidacloprid in salmonids. The data submitted in support of establishment of an import tolerance for imidacloprid in salmonids satisfy the requirements of section 512(a)(6) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 510, Subpart C.