This is provisional English translation of an excerpt from the original full report.

# Risk Assessment Report

# Flumioxazin (Second Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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## ABSTRACT

The FSCJ conducted a risk assessment of an N-phenyl phthalimide herbicide, flumioxazin (CAS No. 103361-09-7), based on results from various documents. In the revision of the second edition, the additional results of the following studies were submitted by the Ministry of Health, Labour and Welfare: residues in crops (domestic: garden peas, overseas: coffee beans); developmental toxicity study (rats, inhalation exposure); fetus anemia induction study; and others.

The test results used in the assessment includes the data on plant metabolism (mandarin oranges, soybeans, etc.), residues in crops, livestock metabolism(goats and chickens), fate in animals (rats and rabbits), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), acute neurotoxicity (rats), subacute neurotoxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity and others.

The major adverse effects of flumioxazin were observed in blood (anemia, etc.) and liver (hepatocyte hypertrophy, weight increase, etc.). Neurotoxicity, immunotoxicity, carcinogenicity, and biologically significant genotoxicity were not observed.

In a two-generation reproductive toxicity study, the decline of copulation index, delivery index, and viability index on day 4 was observed.

In a developmental toxicity study, cardiovascular malformation including ventricular septal defect (VSD) and skeleton malformation such as scapular curvature were observed in fetuses of rats.

Based on the results from various studies, flumioxazin (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 1.8 mg/kg bw per day in a combined two-year chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.018 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The NOAEL and lowest-adverse-effect-level (LOAEL) values were compared for potential adverse effects of a single oral administration of flumioxazine, of which the lowest value was the NOAEL of 3 mg/kg bw per day in a developmental toxicity study (oral administration) in rats. The identified findings include fetal ventricular septal defect (VSD) at doses that do not cause adverse effects in dams. Accordingly, the FSCJ specified an acute reference dose (ARfD) of 0.03 mg /kg bw by applying a safety factor of 100 to this NOAEL for pregnant or potentially pregnant women.

For the general population, the lowest NOAEL for possible adverse effects from a single oral administration was 1,000 mg/kg bw per day, above the cut-off value (500 mb/kg bw), in the developmental toxicity study in rabbits. Accordingly, the FSCJ determined that specifying an ARfD is unnecessary.

**Table 1.** *Levels relevant to toxicological evaluation of flumioxazin*

| Species | Study | Dose (mg/kg bw per day) | NOAEL (mg/kg bw per day) [1)] |
|---|---|---|---|
| Rat | 90-day subacute toxicity study (the 1st study) | 0, 30, 300, 1 000, 3 000 ppm<br>M: 0, 1.9, 19.3, 65.0, 196<br>F: 0, 2.2, 22.4, 72.9, 218 | M: 19.3<br>F: 2.2<br><br>M: Decrease of Hb, MCV, MCH, MCHC, etc.<br>F: Decrease of MCV and MCH |
| | 90-day subacute toxicity study (the 2nd study) | 0, 30, 300, 1 000, 3 000 ppm<br>M: 0, 2.3, 21, 70, 244<br>F: 0, 2.2, 22, 72, 230 | M: 21<br>F: 22<br><br>M/F: Decrease of MCV, etc. |
| | Two-year combined chronic toxicity/ carcinogenicity study | 0, 50, 500, 1 000 ppm<br>M: 0, 1.8, 18.0, 36.5<br>F: 0, 2.2, 21.8, 43.6 | M: 1.8<br>F: 2.2<br><br>M/F: Extramedullary hematopoiesis in the spleen, etc.<br>(No carcinogenicity is observed.) |
| | 90-day subacute neurotoxicity study | 0, 500, 1 500, 4 500 ppm<br>M: 0, 37, 110, 323<br>F: 0, 41, 124, 358 | M: -<br>F: 41<br><br>M: Decrease of MCV and MCH<br>F: Decrease of Hb, Ht, etc.<br>(No subacute neurotoxicity is observed.) |
| | Two-generation reproductive toxicity study | M: 0, 37, 110, 323<br>F: 0, 41, 124, 358<br>PM: 0, 3.2, 6.3,12.7, 18.9<br>PF: 0, 3.8, 7.6, 15.1, 22.7<br>$F_1$M: 0, 3.7, 7.5, 15.0, 22.4<br>$F_1$F: 0, 4.3, 8.5, 17.2, 25.6 | Parent<br>PM: 6.3<br>PF: 15.1<br>$F_1$M: 7.5<br>$F_1$ F: 17.2<br><br>Offspring<br>PM: 6.3<br>PF: 7.6<br>$F_1$M: 7.5<br>$F_1$F: 8.5<br><br>Fertility<br>PM: 12.7<br>PF: 15.1<br>$F_1$M: 15.0<br>$F_1$F: 17.2<br><br>Parent<br>M: Decrease of absolute and relative weight of epididymis<br>F: Suppressed body weight gain, etc. |

| Species | Study | Dose (mg/kg bw per day) | NOAEL (mg/kg bw per day) [1)] |
|---|---|---|---|
| | | | Offspring: Low body weight, etc.<br><br>Fertility<br>M: Decrease of copulation index<br>F: Decrease of delivery index |
| | Developmental toxicity study | 0, 1, 3, 10, 30 | Dams: 30<br>Fetuses: 3<br><br>Dams: No toxicity<br>Fetuses: Ventricular Septal Defect (VSD), etc. |
| Mouse | 28-day subacute toxicity study | 0, 1 000, 3 000, 10 000 ppm<br>M: 0, 152, 420, 1 370<br>F: 0, 165, 482, 1 700 | M: 420<br>F: 165<br>M/F: Increase of absolute and relative weight of liver |
| | 18-month carcinogenicity study | 0, 300, 3 000, 7 000 ppm<br>M: 0, 31.1, 315, 754<br>F: 0, 36.6, 346, 859 | M: 31.1<br>F: 36.6<br>M/F: Hepatocyte hypertrophy, etc.<br><br>(No carcinogenicity is observed.) |
| Rabbit | Developmental toxicity study | 0, 300, 1 000, 3 000 | Dams: 1 000<br>Fetuses: 3 000<br><br>Dams: Decreased body weight/suppressed body weight gain and decreased food consumption<br>Fetuses: No toxicity<br><br>(No teratogenicity is observed.) |
| Dog | 90-day subacute toxicity study | 0, 10, 100, 1 000 | M/F: 100<br>M/F: Increase of ALP, T. Chol, PL, etc. |
| | One-year chronic toxicity study | 0, 10, 100, 1 000 | M/F: 10<br>M/F: Increase of ALP, etc. |
| ADI (cRfD) | | | NOAEL: 1.8<br>SF: 100<br>ADI: 0.018 |
| The critical study for setting ADI (cRfD) | | | Two-year combined chronic toxicity/carcinogenicity study (rat) |

NOAEL: No-observed-adverse-effect level, SF: Safety factor, ADI: Acceptable daily intake, UF: Uncertainty, cRfD: Chronic reference dose, Hb: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, ALP: Alkaline Phosphatase, PL: Phospholipids (PL), T. Chol: Total Cholesterol

[1)] The adverse effect observed at LOAEL

-: NOAEL could not be specified.

**Table 2-1.** *Potential adverse effects of a single oral administration of flumioxazin* (*General population*)

| Species | Study | Dose (mg/kg bw or mg/kg bw per day) | Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day) [1)] |
|---|---|---|---|
| Mouse | General pharmacological study (General condition) | 0, 1 500, 5 000 | M/F: 1 500<br><br>M/F: Decrease in locomotor activities |
| | General pharmacological study (Momentum in locomotive activities) | M: 0, 1 500, 5 000 | M: 1 500<br><br>M: Decreased momentum in locomotor activities |
| Rabbit | Developmental toxicity study | 0, 300, 1 000, 3 000 | Dames: 1 000<br><br>Dames: Decreased body weight and decreased food consumption |
| ARfD | | | Not required<br>[Above cut-off level (500 mg/kg bw)] |

ARfD: Acute reference dose

[1)] The adverse effect observed at LOAEL

**Table 2-2.** *Potential adverse effects of a single oral administration of flumioxazin* (*Pregnant or potentially pregnant women*)

| Species | Study | Dose (mg/kg bw or mg/kg bw per day) | Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day) [1)] |
|---|---|---|---|
| Rat | Developmental toxicity study (Oral administration) | 0, 1, 3, 10, 30 | Fetus: 3<br><br>Fetus: Ventricular septal defect (VSD), etc. |
| | Developmental toxicity study (Critical period of pregnancy examination) | 0, 400 | Fetus: -<br><br>Fetus: Death of embryo/fetus, low body weight and ventricular septal defect (VSD) |
| | Developmental toxicity study (Pathological examination) | 0, 1 000 | Fetus: -<br><br>Fetus: Death of embryo |
| | Developmental toxicity study (Expression mechanism examination) | 0, 400 | Fetus: -<br><br>Fetus:Death of embryo/fetus |
| | Developmental toxicity study (Fetus anemia-induced examination) | 0, 15, 30, 60 | Fetus: -<br><br>Fetus: Ventricular septal defect (VSD) |
| ARfD | | | NOAEL: 3<br>SF: 100<br>ARfD: 0.03 |
| The critical study for setting ARfD | | | Developmental toxicity study (rat) |

ARfD: Acute reference dose, NOAEL: No-observed-adverse-effect level, SF: Safety factor
[1)] The adverse effect observed at LOAEL.
-: NOAEL could not be specified.