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

Risk Assessment Report

Flufenoxuron (Fourth edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

June 2021

ABSTRACT

The FSCJ conducted a risk assessment of flufenoxuron (CAS No. 101463-69-8), a benzophenylurea insecticide, based on submitted documents. For this fourth edition, additional test results were submitted by the Ministry of Health, Labour and Welfare, including fate in animals (goats and chickens), residue in crops (including onions and Chinese chives) and residue in livestock products (cattle and chickens).

The data used in the assessment include fate in animals (including rats, dogs and goats), fate in plants (including Chinese cabbage i.e. napa cabbage, and tomatoes), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of flufenoxuron were observed in body weight (suppressed weight gain) and blood (including anemia). No neurotoxicity, effect on fertility, teratogenicity or biologically significant genotoxicity was observed.

Based on these results, flufenoxuron (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products, livestock products and fishery products.

No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values across these studies were compared, of which the lowest value was a NOAEL of 3.7 mg/kg bw per day in a one-year chronic toxicity study in dogs. The FSCJ specified an acceptable daily intake (ADI) of 0.037 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

Regarding potential adverse effects of a single oral administration of flufenoxuron, a lowest-observed-adverse-effect level (LOAEL) of 3,000 mg/kg bw was obtained from an acute toxicity study in rats. It was considered unnecessary to specify an acute reference dose (ARfD), since the LOAEL was above the cut-off level of 500 mg/kg bw.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 50, 500, 5 000, 10 000, 50 000 ppm M: 0, 3.3, 32.9, 336, 657, 3 500 F: 0, 4.0, 39.3, 386, 800, 4 070	M: 32.9 F: 4.0	M: 336 F: 39.3	M: Decreased plasma TG and MCV levels, etc. F: Increased mean red blood cell diameters, etc.
	28-day subacute neurotoxicity study	0, 1 000, 5 000, 20 000 ppm M: 0, 88.3, 435, 1 770 F: 0, 94.9, 475, 1 930	M: 88.3 F: 1 930	M: 435 F: -	M: Low body weight, suppressed body weight gain (No subacute neurotoxicity)
	Two-year chronic toxicity study	0, 1, 5, 50, 500, 5 000, 50 000 ppm M: 0, 0.044, 0.226, 2.21, 22.0, 233, 2 470 F: 0, 0.055, 0.279, 2.82, 28.3, 301, 3 210	M: 22.0 F: 28.3	M: 233 F: 301	M/F: Suppressed body weight gain, etc.
	Two-year carcinogenicity study	0, 500, 5 000, 50 000 ppm M: 0, 21.6, 218, 2 290 F: 0, 25.9, 276, 2 900	M: 21.6 F: 25.9	M: 218 F: 276	M/F: Suppressed body weight gain, etc. (No carcinogenicity is observed.)
	Two-generation reproductive toxicity study	0, 50, 190, 710, 10 000 ppm PM: 0, 3.8, 14.3, 53.6, 772 PF: 0, 4.3, 16.0, 61.0, 907 F_1M: 0, 4.2, 16.1, 62.5, 865 F_1F: 0, 4.8, 18.6, 69.2, 956	Parent and offspring: PM: 3.8 PF: 4.3 F_1M: 4.2 F_1F: 4.8	Parent and offspring: PM: 14.3 PF: 16.0 F_1M: 16.1 F_1F: 18.6	Parent: Suppressed body weight gain, increased relative kidney weights, etc. Offspring: Reduced weaning weight, increased relative weights of the liver (No effect on fertility is observed.)
	Developmental toxicity study	0, 10, 100, 1 000	Dams: 1 000 Fetuses: 1 000	Dams: - Fetuses: -	Dams: No toxicity Fetuses: No toxicity (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 50, 500, 5 000, 10 000, 50 000 ppm	M: 10.2 F: 11.4	M: 102 F: 127	M/F: Increased plasma bilirubin, increased

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
		M: 0, 10.2, 102, 1 060, 2 100, 10 900 F: 0, 11.4, 127, 1 260, 2 460, 13 000			relative weights of the liver
	Two-year carcinogenicity study (the 1st study)	0, 500, 5 000, 50 000 ppm M: 0, 56.0, 559, 7 360 F: 0, 73.2, 739, 7 780	M: 56.0 F: 73.2	M: 559 F: 739	M/F: Suppressed body weight gain, etc.
	Two-year carcinogenicity study (the 2nd study)	0, 100, 1 000, 10 000 ppm M: 0, 15.3, 152, 1 590 F: 0, 17.4, 187, 1 890	M: 1 590 F: 187	M: - F: 1 890	F: Suppressed body weight gain, extramedullary hematopoiesis (No carcinogenicity is observed)
Rabbit	Developmental toxicity study	0, 10, 100, 1 000	Dams: 1 000 Fetuses: 1 000	Dams: - Fetuses: -	Dams: No toxicity Fetuses: No toxicity (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 500, 5 000, 50 000 ppm M: 0, 18.9, 164, 1 930 F: 0, 21.1, 180, 2 040	M: - F: -	M: 18.9 F: 21.1	M/F: Increased sulfhemoglobin and methemoglobin, increased trend in femoral bone marrow hyperplasia, etc.
	One-year chronic toxicity study	0, 10, 100, 500, 50 000 ppm M: 0, 0.4, 3.9, 19, 2 100 F: 0, 0.4, 3.7, 19, 1 880	M: 3.9 F: 3.7	M: 19 F: 19	M: Increased MCV, methemoglobin, and sulfhemoglobin, etc. F: Increased white blood cells, etc.
ADI			NOAEL: 3.7 SF: 100 ADI: 0.037		
The critical study for setting ADI			One-year chronic toxicity study in dogs		

ADI, Acceptable daily intake; MCV, Mean corpuscular volume; NOAEL, No-observed-adverse-effect level; SF, Safety factor; TG, Triglyceride
-: NOAEL or LOAEL could not be specified.
[1)] The adverse effect observed at LOAEL

Table 2. *Potential adverse effects of a single oral administration of flufenoxuron*

Species	Study	Dose (mg/kg bw or mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw) [1)]
Rat	Acute toxicity study	M/F: 3 000	M/F: - M: Abnormal gait, piloerection, etc. F: Lacrimation, abnormal posture, etc.
Mouse	Acute toxicity study	M/F: 5 000	M/F: - M/F: Piloerection
ARfD			Considered unnecessary to specify. (Above the cut-off level of 500 mg/kg bw)

ARfD; Acute reference dose
-: NOAEL could not be observed.
[1)] The adverse effect observed at LOAEL