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

Risk Assessment Report

Flazasulfuron

(Pesticides)

Food Safety Commission of Japan (FSCJ)
December 2020

ABSTRACT

FSCJ conducted the risk assessment of sulfonylurea herbicide, flazasulfuron (CAS No. 104040-78-0), based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (grapes and sugarcane), subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction (rats), developmental toxicity (rats and rabbits), genotoxicity, and immunotoxicity (mice).

Major adverse effects of flazasulfuron observed are inflammatory cell infiltration in the liver (dogs) and increased weight of the liver, chronic nephropathy (rats), and atrophy/degeneration of the skeletal muscle (dogs). Flazasulfuron showed no neurotoxicity, carcinogenicity, effects on reproduction, genotoxicity and immunotoxicity.
Although ventricular septum defect was observed in a developmental toxicity study in rats, it was considered not such a serious finding[1]. While, teratogenicity was not observed in rabbits.

FSCJ identified flazasulfuron (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 1.31 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.013 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of flazasulfuron was NOAEL of 50 mg/kg bw/day obtained in acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.5 mg/kg bw by applying a safety factor of 100 to the NOAEL.

[1] Although the ventricular septal defect (VSD) was only developmental toxicity of flazasulfuron observed by different toxicity studies in rats, occurrence and seriousness of the VSD in the data used in this assessment as well as that reported in literatures are inconsistent. Hence, FSCJ considered it not such a serious finding.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)]	
			FSCJ	Reference (Summary reports)
Rat	90-day subacute toxicity study	0, 40, 200, 1 000, 5 000 ppm M: 0, 2.31, 11.7, 57.1, 287 F: 0, 2.53, 12.8, 61.5, 309	M: 11.7 F: 61.5 M/F: Suppressed body weight	M: 11.7 F: 61.5 M/F: Suppressed body weight
	90-day subacute neurotoxicity study	0, 300, 3 000, 10 0000 ppm M: 0, 19, 190, 649 F: 0, 22, 229, 732	M: 19 F: 229 M/F: Suppressed body weight (No subacute neurotoxicity)	M: 19 F: 229 M/F: Suppressed body weight (No subacute neurotoxicity)
	Combined two-year chronic toxicity/carcinogenicity study	M: 0, 40, 400, 2 000 ppm F: 0, 40, 400, 4 000 ppm M: 0, 1.31, 13.3, 70.1 F: 0, 1.60, 16.5, 173	M: 1.31 F: 136.5 M: Chronic nephropathy F: Suppressed body weight (No carcinogenicity)	M: 1.313 F: 1.601 M: Chronic nephropathy F: Hepatocellular foci (eosinophilic) (No carcinogenicity)
	Two-generation reproductive activity study	0, 200, 2 000, 10 000 ppm PM: 0, 13.7, 135, 675 PF: 0, 15.7, 155, 760 F_1M: 0, 14.6, 148, 761 F_2F: 0, 16.3, 165, 842	Parent: PM: 13.7 PF: 155 F_1M: 14.6 F_1F: 165 Offspring: PM: 135 PF: 155 F_1M: 148 F_1F: 165 Parent: M: Nephropathy F: Suppressed body weight Offspring: Low body weight (No effects on reproductive activity)	Parent: PM: 13.7 PF: 15.7 F_1M: 14.6 F_2F: 16.3 Offspring: PM: 134.8 PF: 155.0 F_1M: 147.8 F_2F: 164.9 Reproductive activity PM: 674.6 PF: 760.2 F_1M: 760.5 F_2F: 841.5 Parent: Nephropathy Offspring: Low body weight (No effects on reproductive activity)

	Developmental toxicity study (the 1st study)	0, 100, 300, 1 000	Dams/Fetuses: 100 Dams: Suppressed body weight Fetuses: Ventricular septal defect	Dams/Fetuses: 100 Dams: Suppressed body weight Fetuses: Ventricular septal defect
	Developmental toxicity study (the 2nd study)	0, 100, 300, 1 000	Dams: 300 Fetuses: 300 Dams: Suppressed body weight Fetuses: Low body weight	Dams: 100 Fetuses: 300 Dams: Increased relative weight of the liver Fetuses: Low body weight (No teratogenicity)
Mouse	6-week subacute toxicity study	0, 200, 1 000, 5 000, 10 000 ppm M: 0, 34, 181, 884, 1 750 F: 0, 43, 212, 1 030, 2 040	M: 181 F: 2 040 M: Increased Chol F: No toxicity was observed	
	18-month carcinogenicity study	0, 500, 3 500, 7 000 ppm M: 0, 70.4, 498, 987 F: 0, 88.5, 596, 1 170	M: 70.4 F: 88.5 M/F: Increase in absolute and relative weight of the liver, centrilobular hypertrophy of hepatocytes (No carcinogenicity)	M: 70.4 F: 88.5 M/F: Increase in absolute and relative organ weight of the liver (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 50, 150, 450	Dams: 150 Fetuses: 450 Dams: Feeding disruption, miscarriage Fetuses: No toxicity was observed (No teratogenicity)	Dams: 150 Fetuses: 450 Dams: Miscarriage Fetuses: No toxicity was observed (No teratogenicity)
Dog	90-day subacute toxicity study	M: 0, 2, 10, 50, 250 F: 0, 2, 10, 50, 100	M: 2 F: 10 M/F: Brown pigmentation in the liver	M: 2 F: 10 M/F: liver lesion
	One-year chronic toxicity study	M: 0, 0.4, 2.0, 10.0, 50.0 F: 0, 2.0, 10.0, 50.0	M/F: 2.0 M/F: Inflammatory cell infiltration in the liver	M/F: 2.0 M/F: Inflammatory cell infiltration in the liver

ADI (cRfD)	NOAEL: 1.31 SF: 100 ADI: 0.013	NOAEL: 1.313 SF: 100 ADI: 0.013
The critical study for setting ADI (cRfD)	Combined two-year chronic toxicity/carcinogenicity study in rats	Combined two-year chronic toxicity/carcinogenicity study in rats

ADI: Acceptable daily Intake, cRfD: Chronic reference dose, UF: Uncertainty factor, NOAEL: No-observed-adverse-effect level, NOEL: No Observed Effect Level, SF: Safety factor, –: NOAEL could not be specified.
/: No description
[1)] The adverse effect observed at LOAEL
[2)] Summary reports use NOEL.

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

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day)[1)]
Rat	Acute neurotoxicity study	M/F: 0, 50, 1 000, 2 000	M: 50 F: 1 000 M: Decreased locomotor activity
	Developmental toxicity study (the 1st study)	0, 100, 300, 1 000	Dams: 300 Fetuses: 100 Dams: Suppressed body weight, decreased feed intake Fetuses: Ventricular septal defect
	Developmental toxicity study (the 2nd study)	0, 100, 300, 1 000	Dams: 300 Dams: Suppressed body weight, decreased feed intake
Mouse	Acute toxicity study	M/F: 2 500, 5 000	M: 2 500 F: - M/F: Body weight loss
ARfD			NOAEL: 50 SF: 100 ARfD: 0.5
The critical study for setting ARfD			Acute neurotoxicity study in rats

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