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

Risk Assessment Report

Fluxametamide

(Pesticides)

Food Safety Commission of Japan (FSCJ)
December 2017

ABSTRACT

FSCJ conducted a risk assessment of fluxametamide (CAS No. 928783-29-3), an isoxazoline insecticide, based on results from various studies.

The data used in the assessment include the fate in animals (rats), fate in plants (strawberries, egg plants and others), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) genotoxicity.

Major adverse effects of fluxametamide are alveolar macrophage accumulation, vacuolated epithelial cells in the small intestine, and hepatocellular vacuolation. Fluxametamide showed no neurotoxicity, reproductive toxicity, teratogenicity or genotoxicity.

Thyroid follicular cell adenomas were observed in male rats in a two-year combined chronic toxicity/carcinogenicity study and increase in the incidence of hepatocellular adenomas was observed in male mice in an 18-month carcinogenicity study. However, a genotoxic mechanism was unlikely to be involved in the tumor induction, and it was thus considered possible to establish a threshold dose in the assessment.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 0.85 mg/kg bw/day in the two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable (ADI) of 0.0085 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

FSCJ considered it unnecessary to specify an acute reference dose (ARfD), since it is unlikely that fluxametamide exerts toxic effects after a single oral dose administration.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	NOAEL[1)]
Rat	90-day subacute toxicity study	0, 200, 2 000, 20 000 ppm M: 0, 14, 140, 1 430 F: 0, 17, 174, 1 670	M: 14 F: 17	M: 140 F: 174	FM: Vacuolated intestinal epithelial cells, alveolar macrophage accumulation and others
	90-day subacute neurotoxicity study	0, 160, 1 600, 16 000 ppm M: 0, 9.96, 102, 1 030 F: 0, 12.2, 121, 1 190	M: 102 F: 121	M: 1 030 F: 1 190	FM: Vacuolated intestinal epithelial cells (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study	0, 20, 200, 2 000, 20 000 ppm M: 0, 0.85, 8.6, 89, 899 F: 0, 1.2, 12.1, 120, 1 250	M: 0.85 F: 1.2	M: 8.6 F: 12.1	FM: Centrilobular hepatocellular vacuolation and others (FM: Thyroid follicular cell adenomas)
	Two-generation reproductive toxicity study	0, 10, 20, 60, 200 ppm PM: 0, 0.82, 1.6, 4.7, 16.2 PF: 0, 0.90, 1.8, 5.5, 18.2 F_1M: 0, 0.97, 1.9, 5.5, 19.2 F_1F: 0, 1.11, 2.1, 6.2, 20.1	Parent PM: 4.7 PF: 18.2 F_1M: 5.5 F_1F: 20.1 Offsprings PM: 1.6 PF: 5.5 F_1M: 1.9 F_1F: 6.2	Parent: PM: 16.2 PF: — F_1M: 19.2 F_1F: — Offsprings PM: 4.7 PF: 18.2 F_1M: 5.5 F_1F: 20.1	Parent M: Increase in the percentage of morphologically abnormal sperm and others F: No toxicological effect Offsprings M: Delayed preputial separation F: Abdominal distension and others (No effect on reproduction)
	Developmental toxicity study	0, 100, 300, 1 000	Maternal: 1 000 Embryo/fetus: 100	Maternal: - Embryo/fetus: 300	Maternal: No toxicological effect Embryo/fetus: Supernumerary ribs and others (Not teratogenic)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	NOAEL[1)]
Mouse	18-month carcinogenicity study	0, 10, 100, 1 000, 8 000 ppm --- M: 0, 0.99, 10.1, 104, 877 F: 0, 1.10, 11.1, 114, 951	M: 0.99 F: 11.1	M: 10.1 F: 114	FM: Liver effects including increased absolute/relative liver weight (M: Hepatocellular adenomas)
Rabbit	Developmental toxicity study	0, 100, 300, 1 000	Maternal: 300 Embryo/fetus: 300	Maternal: 1000 Embryo/fetus: 1000	Maternal: Suppressed body weight and others Embryo/fetus: Abnormal lobation of the lungs and others (Not teratogenic)
Dog	90-day subacute toxicity study	0, 100, 300, 1 000	M: 1,000 F: 1,000	M: － F: －	FM: No toxicological effect
	One-year chronic toxicity study	0, 10, 100, 1 000	M: 100 F: 100	M: 1 000 F: 1 000	FM: Decrease 33 in T.Chol and others
ADI			NOAEL: 0.85 SF: 100 ADI: 0.0085		
The critical study for setting the ADI			Two-year combined chronic toxicity/carcinogenicity study in rats		

ADI, Acceptable daily intake; SF, Safety factor; NOAEL, No-observed-adverse-effect level
－, NOAEL could not be specified
[1], The adverse effect observed at NOAEL