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

Risk Assessment Report

Flupyrimin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
July 2018

ABSTRACT

FSCJconducted the risk assessment of an insecticide, flupyrimin (CAS No. 1689566-03-7), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy rice and head cabbage), residues in plants, subacute toxicity (rats, mice and dogs), chronic toxicity (rats and dogs), carcinogenicity (mice and rats), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and mechanisms on liver and thyroid effects in rats.

Major adverse effects of flupyrimin observed are centrilobular hypertrophy and necrosis of hepatocytes in the liver, and hypertrophy of follicular epithelial cells in the thyroid (rats). Flupyrimin showed no teratogenicity and genotoxicity.
In a carcinogenicity study, incidences of hepatocellular adenomas and carcinomas in both males and females, and total incidences of follicular adenomas and carcinomas in the thyroid in males were increased in rats. In mice, total incidences of hepatocellular adenomas and carcinomas in males and an incidence of hepatocellular adenomas in females were increased. A genotoxic mechanism was unlikely to be involved in tumor induction, and it was considered possible to establish a threshold dose in the assessment.
In a two-generation reproduction toxicity study in rats, reduced number of newborn offspring was observed.
From the results above, flupyrimin (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.
The lowest no-observed adverse effect level (NOAEL) in all studies was 1.12 mg/kg bw/day in the carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.011 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of flupyrimin was 8 mg/kg bw/day obtained in developmental toxicity studies in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.08 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rats	90-day subacute toxicity study	0, 10, 20, 100, 1 000, 3 000 ppm M: 0, 0.637, 1.28, 6.55,63.4, 192 F : 0, 0.756, 1.54, 7.68, 75.6, 208	M : 6.55 F : 7.68	M : 63.4 F : 75.6	M / F: Centrilobular hypertrophy of hepatocytes
	One-year chronic toxicity study	0, 30, 60, 300, 1 000 ppm M : 0, 1.33, 2.69, 13.3, 47.1 F : 0, 1.68, 3.50, 17.6, 59.1	M : 2.69 F : 3.50	M : 13.3 F : 17.6	M / F: Centrilobular hypertrophy of hepatocytes (M: Increased incidences of follicular adenomas in the thyroid)
	Two-year carcinogenicity study	0, 30, 60, 300, 1 000 ppm M : 0, 1.12, 2.24, 11.4, 39.3 F : 0, 1.39, 2.84, 14.6, 51.7	M : 1.12 F : 2.84	M : 2.24 F : 14.6	M / F: Centrilobular hypertrophy of hepatocytes (M / F at dose of 1,000 ppm: An increased incidence of hepatocellular adenomas and carcinomas. M at 300 ppm and above: increases in total incidences of follicular adenomas and carcinomas in the thyroid, and total incidences of hepatocellular adenomas and carcinomas.)
	Two-generation reproductive toxicity study	0, 30, 60, 300, 1 500 ppm PM : 0, 1.86, 3.77, 18.8, 94.8 PF : 0, 2.28, 4.62, 23.7, 107 F_1M : 0, 2.23, 4.52, 22.6, 119 F_1F : 0, 2.52, 5.16, 25.6, 132	Parent PM : 3.77 PF : 4.62 F_1M : 4.52 F_1F : 5.16 Offspring and reproductive ability: PM : 18.8 PF : 23.7 F_1M : 22.6 F_1F : 25.6	Parent PM : 18.8 PF : 23.7 F_1M : 22.6 F_1F : 25.6 Offspring and reproductive ability: PM : 94.8 PF : 107 F_1M : 119 F_1F : 132	Parent: Centrilobular hypertrophy of hepatocytes Offspring: Suppressed body weight Reproductive ability: Reduced number of newborn offspring

	Developmental toxicity study	0, 5, 20, 80	Dams : 20 Fetuses : 80	Dams : 80 Fetuses : －	Dams: Decreased body weight / suppressed body weight, decreased feed consumption. Fetuses: No toxicity observed. (No teratogenicity)
mice	90-day subacute toxicity study	0, 30, 100, 500, 2 000 ppm M : 0, 4.27, 14.3, 72.1, 273 F : 0, 4.93, 17.1, 82.4, 332	M : 14.3 F : 82.4	M : 72.1 F : 332	M / F: Centrilobular hypertrophy of hepatocytes.
	18-month carcinogenicity study	0, 30, 100, 500, 1 000 ppm M : 0, 3.14, 10.1, 52.2, 108 F : 2.93, 9.88, 51.7, 105	M : 10.1 F : 51.7	M : 52.2 F : 105	M: Systemic amyloidosis. F: Centrilobular hypertrophy of hepatocytes. (M: Increased total incidences of hepatocellular adenomas and carcinomas. F: Increased incidences of hepatocellular adenomas)
Rabbits	Developmental toxicity study	0, 3, 8, 20	Dams and Fetuses : 8	Dams and Fetuses : 20	Dams: Decreased body weight, decreased feed consumption. Fetuses: Low body weight. (No teratogenicity)
Dogs	90-day subacute toxicity study	0, 30, 100, 300 ppm M : 0, 0.96, 2.80, 8.60 F : 0, 0.91, 2.96, 9.25	M : 2.80 F : 9.25	M : 8.60 F : －	M: Increased AST. F: No toxicity observed.
	One-year chronic toxicity study	0, 30, 100, 300 ppm M : 0, 0.83, 2.71, 8.51 F : 0, 0.82, 2.58, 8.43	M : 2.71 F : 2.58	M : 8.51 F : 8.43	M: Increased AST F: Increased ALT, ALP, and GGT
ADI			NOAEL : 1.12 SF : 100 ADI : 0.011		
The critical study for setting ADI			Two-year carcinogenicity study in rats.		

NOAEL : no-observed-adverse-effect level SF : Safety factor ADI : Acceptable Daily Intake
[1)] the adverse effect observed at LOAEL
－: NOAEL could not be specified

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

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]
Rats	Acute toxicity	F : 300, 2 000	－ Sedation, ptosis
	Acute neurotoxicity	M / F : 0, 50, 100, 200	M / F : 50 M : mydriasis F : Decreased locomotive activity, increase in the Forelimb grip strength
	Developmental toxicity	0, 5, 20, 80	Dams : 20 Dams : Decreased body weight
Mice	General pharmacology (General status)	M / F : 0, 30, 100, 300	M / F : 100 M / F : Ptosis, deterioration in vigilance performance.
Rabbits	Developmental toxicity	0, 3, 8, 20	Dams : 8 Dams : Decreased body weight
ARfD			NOAEL : 8 SF : 100 ARfD : 0.08
The critical study for setting ARfD			Developmental toxicity study in rats

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