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

Risk Assessment Report

Triflumezopyrim

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of triflumezopyrim (CAS No. 1263133-33-0), a mesoionic insecticide, based on results from various studies.

The data used in the assessment include the fate in animals (rats, goats and chiken), fate in plants (paddy rice), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), reproductive toxicity (rats), developmental toxicity (rats and rabbits), immunotoxicity (rats), and genotoxicity.

Major adverse effects of triflumezopyrim observed were suppressed body weight, effects on hematopoietic system such as anemia, increased liver weights and increased total cholesterol. No teratogenicity, immunotoxicity and genotoxicity relevant to human health were observed. Decreased blood prolactine level was detected in female mice.

Increased incidence of uterine squamous cell carcinomas and of hepatocellular adenomas were increased in a two-year combined chronic toxicity/carcinogenicity study in rats and in 18-month carcinogenicity study in male mice, respectively. A genotoxic mechanism was unlikely involved in the tumor development, and it enabled FSCJ to establish a threshold in the assessment.

Although no effect on reproduction was observed in a two-generation reproductive toxicity study in rats, decreased numbers of implantations and pups at birth were observed in one-generation at higher doses reproductive toxicity study. Delayed tendencty of development of reproductive activity was also observed in males and females in the first generation (F_1) at higher doses in this study.
Based on the results from various studies, triflumezopyrim (parent compound only) was identified as a substance relevant for the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 3.23 mg/kg bw/day in a two-year combind chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.032 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for adverse effects likely elicited by a single oral administration of triflumezopyrim was 100 mg/kg bw /day obtained in an acute neurotoxicity study and in a developmental toxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 1 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	28-day subacute toxicity study	0, 200, 800, 4 000, 20 000/10 000 ppm M: 0, 16.6, 64.9, 309, 653 F: 0, 16.1, 63.6, 317, 627	M: 309 F: 63.6	M: 653 F: 317	M/F: Decreased RBC, etc.
	90-day subacute toxicity study (the 1st study)	0, 100, 400, 1 500, 6 000 ppm M: 0, 4.5, 18, 70, 274 F: 0, 6.0, 23, 83, 316	M: 70 F: 83	M: 274 F: 316	M/F: Suppressed body weight and decreased feed consumption
	90-day subacute toxicity study (the 2nd study)	0, 100, 400, 1 500, 6 000 ppm M: 0, 4.17, 17.0, 63.9, 257 F: 0, 5.13, 20.4, 74.3, 278	M: 63.9 F: 74.3	M: 257 F: 278	M/F: Suppressed body weight and decreased feed consumption
	Two-year combined chronic toxicity/carcinogenicity study	0, 100, 500, 2 000, 8 000 ppm M: 0, 3.03, 15.9, 70.6, 284 F: 0, 3.23, 17.3, 73.8, 396	M: 15.9 F: 3.23	M: 70.6 F: 17.3	M/F: Suppressed body weight (F: Increased incidence of squamous cell carcinomas in uterine including cervix)
	One-generation reproductive toxicity study	0, 400/240, 1 500/900, 6 000/3 600 ppm PM: 0, 28.1, 106, 375 PF: 0, 28.1, 99.0, 369 F_1M: 0, 29.0, 109, 465 F_1F: 0, 29.1, 109, 449			(Decreases in number of implantations and resulted decrease in birth number)
	Two-generation reproductive toxicity study	0, 100/60, 500/300, 1 500/900, 3 000/1 800 ppm PM: 0, 6.29, 31.7, 92.8, 184 PF: 0, 6.34, 30.7, 93.4, 182 F_1M: 0, 7.21, 36.0, 106, 211 F_1F: 0, 6.59, 32.7, 95.3, 193	Parent PM: 31.7 PF: 30.7 F_1M: 36.0 F_1F: 32.7 Offspring PM: 92.8 PF: 30.7 F_1M: 106 F_1F: 32.7	Parent PM: 92.8 PF: 93.4 F_1M: 106 F_1F: 95.3 Offspring PM: 184 PF: 93.4 F_1M: 211 F_1F: 95.3	Parent M/F: Suppressed body weight and decreased feed consumption Offspring M/F: Decreases in absolute and relative weight of spleen (No effect on reproduction)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Developmental toxicity study	0, 25, 50, 100, 200	Dams: 100 Fetuses: 200	Dams: 200 Fetuses: -	Dams: Suppressed body weight and decreased feed consumption Fetuses: No toxicity (No teratogenicity)
Mouse	28-day subacute toxicity study	0, 200, 800, 2 500, 7 000 ppm M: 0, 33.6, 129, 416, 1 100 F: 0, 40.7, 161, 504, 1 340	M: 416 F: 504	M: 1 100 F: 1 340	M/F: Centrilobular hypertrophy of hepatocytes, and increase in total cholesterol
	90-day subacute toxicity study	0, 200, 800, 2 500, 7 000 ppm M: 0, 31.4, 125, 417, 1 130 F: 0, 44.1, 177, 476, 1 530	M: 1 130 F: 1 530	M: - F: -	M/F: No toxicity
	18-month carcinogenicity study	0, 200, 800, 2 500, 7 000 ppm M: 0, 20.1, 84.5, 248, 727 F: 0, 21.8, 88.0, 283, 810	M: 248 F: 88.0	M: 727 F: 283	M: Centrilobular hypertrophy of hepatocytes F: Increases in absolute and relative weight of liver (M: Increased incidence of hepatocellular adenomas)
Rabbit	Developmental toxicity study	0, 50, 100, 250, 500	Dams: 250 Fetuses: 500	Dams: 500 Fetuses: -	Dams: Suppressed body weight and decreased feed consumption Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 100, 400, 1 000, 4 000 ppm M: 0, 3.05, 12.2, 26.6, 115 F: 0, 2.69, 12.2, 26.9, 131	M: 26.6 F: 26.9	M: 115 F: 131	M/F: Suppressed body weight

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	One-year chronic toxicity study	0, 40, 100, 400, 1 000/2 000(F), 2 000(M) ppm M: 0, 1.53, 3.31, 11.1, 53.2 F: 0, 1.20, 3.37, 10.8, 55.9	M: 53.2 F: 55.9	M: - F: -	M/F: No toxicity
ADI			NOAEL: 3.23 SF: 100 ADI: 0.032		
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study		

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F_1M, Male in F_1 generation; F_1F, Female in F_1 generation; ADI, Acceptable daily intake; SF, Safety factor; NOAEL, No-observed-adverse-effect level; -, LOAEL could not be specified; /, Not applicable

[1)], The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw)	NOAEL (mg/kg bw/day) and critical endpoints[1)]
Rat	Acute toxicity study (the 1st study)	M: 5 000 F: 2 500, 3 750, 4 375, 5 000	M: - F: - M: Reduced body weight, high posture, ptosis F: High posture, stained fur
	Acute toxicity study (the 2nd study)	F: 4 390, 5 000	F: 4 390 F: Reduced amount of stools
	Acute neurotoxicity study	0, 100, 500, 2 000	M/F: 100 M/F: Reduced body weight and reduced feed intake, decrease in body temperature, suppressed locomotor activity, and decrease in the number of total movement
	Developmental toxicity study	0, 25, 50, 100, 200	Dams: 100 Dams: Suppressed body weight
Mouse	General pharmacology (Central nervous system)	0, 80, 400, 2 000	M/F: 400 M/F: Suppressed locomotor activity
ARfD			NOAEL: 100 SF: 100 ARfD: 1
The critical study for setting ARfD			Acute neurotoxicity study in rats 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