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

Risk Assessment Report

Pymetrozine (2nd edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

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ABSTRACT

FSCJ conducted the risk assessment of a pyridineazomethine insecticides, pymetrozine (CAS No. 123312-89-0), based on various documents. In the present assessment, the results of 28-day subacute toxicity study (rats) and developmental neurotoxicity study (rats) were newly available.

The data used in the assessment include fate in animals (rats, dogs, mice, goats and chicken), fate in plants (tomatoes and potatoes), residues in crops, acute toxicity (rats and mice), subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), genotoxicity and data on effects on liver, thyroid and testis.

Major adverse effects of pymetrozine are those changes in the liver and thyroid and hematological effect. Pymetrozine had no effects on reproduction. It showed neither teratogenicity nor developmental neurotoxicity, nor genotoxicity.

In a carcinogenicity study, incidence of hepatocellular adenomas and carcinomas increased in female rats, and in both male and female mice. However, all genotoxicity studies showed negative results, thus a genotoxic mechanism was unlikely to be involved in tumor induction. Therefore, FSCJ considered it possible to establish a threshold dose in the assessment.
FSCJ identified the relevant substance for the residue definition for dietary risk assessment in agricultural products to be pymetrozine (parent compound only).

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 1.30 mg/kg bw/day in a two-generation reproduction 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 pymetrozine was NOAEL of 10 mg/kg bw/day obtained in developmental toxicity studies in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.1 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints
Rat	28-day subacute toxicity study	0, 10, 100, 600	M/F: 10 M/F: Hyperplasia of white pulp
	90-day subacute toxicity study	0, 5, 500, 5 000 ppm M: 0, 3.42, 32.5, 360 F: 0, 3.63, 33.9, 370	M: 32.5 F: 33.9 M/F: Suppressed body weight
	90-day subacute neurotoxicity study	0, 500, 1 000, 3 000 ppm M: 0, 35, 68, 201 F: 0, 41, 81, 224	General toxicity M: 68 F: 81 M/F: Suppressed body weight, decreased feed intake Neurotoxicity M: 68 F: 81 M: Stereotyped behavior F: Gait on toe
	Combined two-year chronic toxicity/ carcinogenicity study	0, 10, 100, 1 000, 3 000 ppm M: 0, 0.357, 3.73, 39.3, 128 F: 0, 0.43, 4.45, 47.1, 154	M: 3.73 F: 4.45 M/F: Hepatocellular hypertrophy (F: Increased incidence of hepatocellular adenomas)
	Two-generation reproductive activity study	0, 20, 200, 2 000 ppm	Parent and offspring PM: 1.30 PF: 1.59 F_1M: 1.51 F_1F: 1.82 Offspring PM: 12.9 PF: 16.0 F_1M: 15.2

		PM: 0, 1.30, 12.9, 128 PF: 0, 1.59, 16.0, 152 F_1M: 0, 1.51, 15.2, 159 F_1F: 0, 1.82, 17.1, 186	F_1F: 17.1 Parent M: Hepatocellular hypertrophy F: Increase in absolute and relative weight of the adrenal grand Offspring: Low body weight (No effects on reproductive activity)
	Developmental toxicity study	0, 30, 100, 300	Dams and Fetuses: 30 Dams: Suppressed body weight, decreased feed intake Fetuses: Delayed ossification, skeletal variations
	Developmental toxicity study (Additional study)	0, 3, 30	Dams and Fetuses: 30 Dams and Fetuses: No toxicity (No teratogenicity)
	Developmental neurotoxicity study	0, 100, 500, 2 500 ppm (2 500 ppm was only for gestational period) Gestational period: 0, 8.1, 38.7, 173 Nursing period: 0, 16.8, 82.6	Dams and Offspring: 8.1 Dams: Suppressed body weight, decreased feed intake, an increase in offspring mortality Offspring: Increased mortality (No developmental neurotoxicity)
Mouse	18-month carcinogenicity study	0, 10, 100, 2 000, 5 000 ppm M: 0, 1.24, 12.0, 254, 678 F: 0, 1.17, 11.4, 243, 673	M: 12.0 F: 11.4 M/F: Suppressed body weight (M/F: Increase in liver tumors)
Rabbit	Developmental toxicity study	0, 10, 75, 125	Dams and Fetuses: 10 Dams: Suppressed body weight, decreased feed intake Fetuses: Pubic hypoplasia
Dog	90-day subacute toxicity study	0, 100, 500, 2 500 ppm M: 0, 3.12, 13.9, 53.4 F: 0, 3.24, 14.5, 60.2	M: 3.12 F: 3.24 M/F: Hepatic inflammatory cell infiltration and bile duct proliferation

	One-year chronic toxicity study	0, 20, 200, 1 000 ppm M: 0, 0.57, 5.33, 27.9 F: 0, 0.57, 5.03, 27.4	M: 5.33 F: 5.03 M: Decreased RBC, Hb, Ht. Prolonged PT F: Suppressed body weight
ADI (cRfD)			NOAEL: 1.30 SF: 100 ADI: 0.013
The critical study for setting ADI (cRfD)			Two-generation reproductive activity study in rats

ADI, Acceptable daily intake; NOEL, No-observed-adverse-effect level; LOAEL, Lowest-observed-adverse-effect level; NOEL, No-observed-effect level; SF, Safety factor; UF, Uncertainty factor; cRfD, Chronic reference dose
[1], The adverse effect observed at LOAEL.
/, No description in relevant reference

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

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 toxicity study	M/F: 4 000, 5 000, 6 000, 6 500, 7 000	M/F: - M: Decreased locomotor activity F: Dirty facial fur
	Acute neurotoxicity study	M/F: 0, 125, 500, 2 000	M/F: 125 M/F: Diminished arousal, decreased locomotor activity
	Developmental toxicity study	0, 30, 100, 300	Dams: 100 Dams: Suppressed body weight
Mouse	Acute toxicity study	M: 0, 800, 1 500, 2 000, 5 000 F: 0, 800, 2 000, 3 500, 5 000	M/F: 800 M/F: Decreased locomotor activity
Rabbit	Developmental toxicity study	0, 10, 75, 125	Dams: 10 Dams: Early embryonic resorption, suppressed body weight, decreased feed intake
ARfD			NOAEL: 10 SF: 100 ARfD: 0.1
The critical study for setting ARfD			Developmental toxicity study in rabbits

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