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

Risk Assessment Report

Pyriproxyfen (4th Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
August 2019

ABSTRACT

FSCJ established health based guidance values of pyriproxyfen (CAS No.95737-68-1), an insecticide having 4-phenoxyphenyl structure based on results from various studies in the risk assessment. Data including acute neurotoxicity study (rats), 90-day subacute neurotoxicity study (rats), four-week immunotoxicity study (mice), and residues in crops (Japanese wild parsley, citrus and coffee beans) were newly submitted for application of new use and import tolerance.

The data used in the assessment include fate in animals (rats), fate in plants (cucumbers, oranges and others), residue in crops, acute toxicity (mice and rats), subacute toxicity (rats, mice 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), genotoxcity, immunotoxicity (mice) and screening assays for endocrine disruptors, which have already been submitted.

Major adverse effects of pyriproxyfen were effects on hematopoietic system such as anemia, hepatocellular hypertrophy, liver fibrosis in dogs and chronic progressive nephropathy in mice.
No neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, genotoxicity or immunotoxicity was observed.

On the basis of various studies, pyriproxyfen (parent compound only) was identified as a relevant substance for residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all tests was 10 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.1 mg/kg bw/day, which was the same as previous one, by applying a safety factor of 100 to the NOAEL.

The lowest value of NOAEL for adverse effects of eliciting a single oral administration of pyriproxyfen was NOAEL of 300 mg/kg bw/day obtained in the developmental toxicity study in rats and the administration study in rats during the perinatal and lactation period. FSCJ specified an acute reference dose (ARfD) to be 3 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

Table 1. *Levels relevant of toxicological evaluation of pyriproxyfen*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoint[1]
Rat	90-day subacute toxicity study	0, 400, 2 000, 5 000, 10 000 ppm M: 0, 23.5, 118, 309, 642 F: 0, 27.7, 141, 356, 784	M: 23.5 F: 27.7	M: 118 F: 141	FM: Hepatocellular hypertrophy and others
	90-day subacute neurotoxicity study	0, 1 500, 5 000, 15 000 ppm M: 0, 108, 359, 1 110 F: 0, 120, 407, 1 210	M: 359 F: 407	M: 1 110 F: 1 210	FM: Suppressed body weight and others (No subacute neurotoxicity)
	Six-month subacute toxicity study	0, 80, 400, 2 000, 10 000 ppm M: 0, 4.80, 24.0, 121, 682 F: 0, 5.36, 27.5, 136, 688	M: 24.0 F: 27.5	M: 121 F: 136	M: Decrease in RBC, Hb, Ht and others F: Increase in sodium and others
	Two year combined chronic toxicity/carcinogenicity study	0, 120, 600, 3 000 ppm M: 0, 5.42, 27.3, 138 F: 0, 7.04, 35.1, 183	M: 27.3 F: 35.1	M: 138 F: 183	FM: Suppressed body weight and others (Not carcinogenic)
	Two-generation reproductive toxicity study	0, 200, 1 000, 5 000 ppm PM: 0, 15.5, 76.4, 386 PF: 0, 17.7, 87.3, 442 F_1M: 0, 19.4, 97.3, 519 F_1F: 0, 20.6, 105, 554	Parent PM: 15.5 PF: 87.3 F_1M: 19.4 F_1F: 105 Offspring PM: 76.4 PF: 87.3 F_1M: 97.3 F_1F: 105	Parent PM: 76.4 PF: 442 F_1M: 97.3 F_1F: 554 Offspring PM: 386 PF: 442 F_1M: 519 F_1F: 554	Parent M: Increase in relative kidney and liver weights F: Suppressed body weight, decreased feed consumption and others Offspring FM: Suppressed body weight (No effect on reproduction)

[1] The adverse effect observed at LOAEL

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoint[1]
	Developmental toxicity study	0, 100, 300, 1 000	Maternal: － Embryo/fetus: 100 Newborn: 1 000	Maternal: 100 Embryo/fetus: 300 Newborn: －	Maternal: Suppressed body weight and others Embryo/fetus: Opening of the foramen transversarium of the seventh cervical vertebra Newborn: No toxicological effect (Not teratogenic)
	Study of treatment before and during the early stages of gestation	0, 100, 300, 500, 1 000	Parent M: － F: － Embryo/fetus: 1 000	Parent M: 100 F: 100 Embryo/fetus: －	Parent FM: Increase in absolute kidney weight and others Embryo/fetus: No toxicological effect (Not teratogenic)
	Study of treatment during the perinatal and lactation periods	0, 30, 100, 300, 500	Maternal: 100 Offspring: 100	Maternal: 300 Offspring: 300	Maternal: Suppressed body weight and others Offspring: Suppressed body weight and others (Not teratogenic)
Mouse	90-day subacute toxicity study	0, 200, 1 000, 5 000, 10 000 ppm M: 0, 28.2, 149, 838, 2 030 F: 0, 37.9, 197, 964, 2 350	M: 28.2 F: 37.9	M: 149 F: 197	M: Decrease in MCH F: Increase in T.Chol
	18-month carcinogenicity study	0, 120, 600, 3 000 ppm M: 0, 16.4, 81.3, 423 F: 0, 21.1, 107, 533	M: 16.4 F: 107	M: 81.3 F: 533	FM: Reduced survival rate, Systemic amyloidosis and others (Not carcinogenic)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoint[1]
Rabbit	Developmental toxicity study	0, 100, 300, 1 000	Maternal: 100 Embryo/fetus: 300	Maternal: 300 Embryo/fetus: 1 000	Maternal: Decreased locomotor activity and others Embryo/fetus: Decreased embryo survival (Not teratogenic)
Dog	90-day subacute toxicity study	0, 100, 300, 1 000	M: 100 F: 100	M: 300 F: 300	M: Increase in absolute/relative liver weight F: Hepatocellular hypertrophy and others
	One-year chronic toxicity study (The 1st study)	0, 30, 100, 300, 1 000	M: － F: 30	M: 30 F: 100	FM: Increase in T.Chol and others
	One-year chronic toxicity study (The 2nd study, additional study)	0, 3, 10	M: 10 F: 10	M: － F: －	No toxicological effects
ADI			NOAEL: 10 SF: 100 ADI: 0.1		
The critical study for setting the ADI			One-year chronic toxicity study in dogs		

ADI, Acceptable daily intake; NOAEL, No-observed-adverse effect level; SF, Safety factor
－: NOAEL or lowest-observed-adverse-effect level (LOAEL) was not derived

Table 2. *Adverse effects possibly elicited by a single oral administration*

Species	Studies	Dose (mg/kg bw or mg/kg bw/day)	NOAEL and endpoint for establishing acute reference dose (mg/kg bw or mg/kg bw/day)[1)]
Rat	Acute toxicity study	FM: 0, 1 000, 2 500, 5 000	M: 1 000 F: 2 500 FM: Decreased locomotor activity
	Acute neurotoxicity study	FM: 0, 300, 1 000, 2 000	FM: 1 000 M: Decrease in total motor activity and locomotion activity and others F: Eyelid closure and others
	Developmental toxicity	F: 0, 100, 300, 1 000	Maternal: 300 Maternal: Suppressed body weight, decreased feed consumption and soft stool/diarrhea
	Study of treatment before and during the early stages of gestation	FM: 0, 100, 300, 500, 1 000	FM: 500 FM: Suppressed body weight and soft stool/diarrhea
	Study of treatment during the perinatal and lactation periods	F: 0, 30, 100, 300, 500	Maternal: 300 Maternal: Soft stool/diarrhea
Mouse	General pharmacological study (General condition)	FM: 0, 200, 1 000, 5 000	FM: 1 000 FM: Soft stool/diarrhea
	Acute toxicity study	FM: 0, 1 000, 2 000, 5 000	M: 1 000 F: 2 000 FM: Ataxic gate, irregular respiration and others
ARfD			NOAEL: 300 SF: 100 ARfD: 3
The critical study for setting the ARfD			Developmental toxicity study in rats Study of treatment during the perinatal and lactation period in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor

[1)] The adverse effect observed at LOAEL