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

Risk Assessment Report

Pendimethalin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
April 2021

ABSTRACT

FSCJ conducted the risk assessment of an insecticide, pendimethalin (CAS No. 40487-42-1), based on various documents. For revising to the 3rd edition, risk management organizations newly provided the data on residue in crops (licorice and cantaloupe), residue in livestock products (cattle and chicken) and acute neurotoxicity (rats).

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (maize and paddy rice), residues in crops, acute neurotoxicity (rats), subacute toxicity (rats, dogs and rabbits), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, neurotoxicity, and mechanism of thyroid tumor in rats.

Major adverse effects of pendimethalin observed are hepatocellular hypertrophy and hyperplasia of follicular epithelial cell of the thyroid. Pendimethalin showed no neurotoxicity, reproduction toxicity, teratogenicity and genotoxicity relevant to human health.
In a carcinogenicity study in rats, an increased incidences of follicular cell tumors in the thyroid in rats were observed. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and it was considered possible to establish a threshold dose in the assessment.

Pendimethalin (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 value of the no-observed-adverse-effect level (NOAEL) in all tests was 12.5 mg/kg bw/day in a two-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.12 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 pendimethalin was 100 mg/kg bw/day obtained in the acute neurotoxicity 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 pendimethalin*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Rat	90-day subacute toxicity study (the 1st study)	0, 500, 2 500, 12 500 ppm M: 0, 44.4, 227, 1 140 F: 0, 48.8, 252, 1 160	M: 227 F: 252 M/F: Suppressed body weight
	90-day subacute toxicity study (the 2nd study)	0, 100, 500, 5 000 ppm M: 0, 7.6, 39.2, 382 F: 0, 8.7, 43.4, 411	M: 39.2 F: 43.3 M/F: Increased organ weight (absolute and relative weight) of the liver
	90-day subacute neurotoxicity study	0, 600, 1 800, 5 400 ppm M: 0, 42.0, 127, 387 F: 0, 50.1, 152, 423	M: 127 F: 50.1 M/F: Suppressed body weight (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 100, 500, 5 000 ppm M: 0, 3.8, 19, 195 F: 0, 4.7, 24, 260	M: 19 F: 24 M/F: Increased organ weight (absolute and relative weight) of the thyroid (increased incidence of thyroid follicular cell adenomas)
	Two-generation reproductive toxicity study	0, 500, 2 500, 5 000 ppm	Parent PM: 25 F_1M: 25 PF: 35 F_1F: 35 Offspring F_1M: 25 F_2M: 25 F_1F: 35 F_2F: 35 Parent

		PM: 0, 25, 125, 250 F_1M: 0, 25, 125, 250 PF: 25, 175, 350 F_1F: 25, 175, 350	M/F: Suppressed body weight Offspring Suppressed body weight (No reproductive toxicity)
	14-day biliary excretion and the liver T4 metabolism studies	0, 100, 5 000 ppm	
	Developmental toxicity study	0, 125, 250, 500	Dams: 500 Fetuses: 500 Dams/Fetuses: No effect from administration of specimen (No teratogenicity)
Mouse	18-month carcinogenicity study	0, 100, 500, 5 000 ppm M: 0, 13.6, 69.4, 691 F: 0, 17.0, 87.0, 906	M: 69.4 F: 87.0 M/F: Increase in the absolute and relative organ weight of hepatic gallbladder. (No carcinogenicity)
	18-month carcinogenicity study	0, 100, 500, 2 500/5 000 ppm	
Rabbit	Developmental toxicity study	0, 15, 30, 60	Dams: 30 Fetuses: 60 Dams: Suppressed body weight Fetuses: No effect from administration of specimen (No teratogenicity)

Dog	90-day subacute toxicity study	0, 62.5, 250, 1 000	M: 62.5 F: 250 M/F: Suppressed body weight.
	Two-year chronic toxicity study	0, 12.5, 50, 200	M/F: 12.5 M/F: Chronic liver inflammation, increased cholestasis
ADI (cRfD)			NOAEL: 125 SF: 100 ADI: 0.12
The critical study for setting ADI (cRfD)			Two-year chronic toxicity study in dogs

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake; UF, Uncertainty factor; cRfD, chronic reference dose

-, NOAEL could not be specified. /, No study was described.

[1)], The adverse effect observed at LOAEL

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

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 (the 1st study)	M/F: 2 500, 5 000, 10 000	M/F: - M/F: Salivation, behavioral inactivity
	Acute toxicity study (the 2nd study)	M/F: 1 000, 3 000, 5 000, 7 000, 10 000	M/F: 3 000 M/F: Low locomotor activity
	Acute neurotoxicity study	M/F: 0, 100, 300, 1 000	M: 300 F: 100 M/F: Decrease in locomotor activity
Mouse	General pharmacology data (Motor coordination)	M: 0, 300, 1 000, 3 000	M:1 000 Increased incidence in fall in the test using rotating rod.
	Acute toxicity study	M/F: 3 500, 5 300, 8 000, 12 000	M/F: - M/F: Low locomotor activity
ARfD			NOAEL: 100 SF: 100 ARfD: 1
The critical study for setting ARfD			Acute neurotoxicity study in rats

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