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

Risk Assessment Report

Thifluzamide (Fourth edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
November 2023

ABSTRACT

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of thifluzamide (CAS No. 130000-40-7), an amide fungicide, based on results from submitted documents. For the fourth edition, the Ministry of Agriculture, Forestry and Fisheries submitted additional information, including genotoxicity test results and reports on published scientific literature, along with a request for review of the assessment in accordance with the Agricultural Chemicals Regulation Act.

The data used in the assessment include fate in plants (including paddy rice and peanuts), residues in crops, fate in livestock (goats and chickens), residues in livestock products, fate in animals (rats), subacute toxicity (rats, mice, and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of thifluzamide were observed in the liver (including vacuolation of hepatocytes in rats), the adrenal glands (increase in organ weight, adrenocortical vacuolation in dogs), the kidneys (including renal tubular dilation), and the nervous system (axonal degeneration and myelin alteration in dogs) (Table 1). No adverse effects on carcinogenicity, fertility, teratogenicity, and genotoxicity were observed .

Based on these results, thifluzamide (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural and fishery products, while thifluzamide and its metabolite (2) were likewise identified as the relevant substances for the residue definition for dietary risk assessment in livestock products.

The lowest no-observed-adverse-effect level (NOAEL) was 1.40 mg/kg bw per day from a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ established an acceptable daily intake (ADI) of 0.014 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The lowest NOAEL for potential adverse effects after a single oral administration of thifluzamide was 25 mg/kg bw per day from the results of the developmental toxicity studies in both rats and rabbits (Table 2). FSCJ established an acute reference dose (ARfD) of 0.25 mg/kg bw by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 40, 200, 1 000, 5 000, 10 000 ppm M: 0, 2.6, 13.4, 67.3, 322, 620 F: 0, 3.4, 16.9, 82.3, 382, 691	M: 2.6 F: 3.4	M: 13.4 F: 16.9	M/F: Suppressed body weight gain, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 2, 10, 30, 100, 200 ppm M: 0, 0.10, 0.48, 1.40, 4.75, 9.37 F: 0, 0.13, 0.64, 2.02, 6.54, 13.5	M: 1.40 F: 2.02	M: 4.75 F: 6.54	M/F: Centrilobular fatty change of hepatocytes (No carcinogenicity observed)
	Two-generation reproductive toxicity study	0, 40, 200, 600 ppm PM: 0, 2.6, 12.8, 37.6 PF: 0, 3.0, 15.0, 45.0 F_1M: 0, 2.8, 14.1, 42.8 F_1F: 0, 3.3, 16.2, 50.0	Parents PM: - PF:3.0 F_1M: - F_1F: 3.3 Offspring PM: 12.8 PF: 15.0 F_1M: 14.1 F_1F: 16.2	Parents PM: 2.6 PF: 15.0 F_1M: 2.8 F_1F: 16.2 Offspring PM: 37.6 PF: 45.0 F_1M: 42.8 F_1F: 50.0	Parents M/F: Centrilobular/ midlobular hepatocyte vacuolation, etc. Offspring: Suppressed body weight gain (No effect on fertility observed)
	Developmental toxicity study	0, 5, 25, 125	Dams: 25 Fetuses: 25	Dams:125 Fetuses: 125	Dams: Suppressed body weight gain, etc. Fetus: Low body weight (No teratogenicity observed)
Mouse	90-day subacute toxicity study	0, 50, 500, 2 500, 5 000 ppm M: 0, 9.2, 98.3, 489, 1 050 F: 0, 15.0, 164, 799, 1 660	M: 9.2 F:164	M: 98.3 F: 799	M: Suppressed body weight gain F: Decreases in absolute and relative weights of the kidneys, etc.
	18-month carcinogenicity study	0, 2, 10, 50, 250, 500 ppm M: 0, 0.35, 1.8, 9.2, 44.3, 91.6 F: 0.51, 2.8, 14.2, 72.6, 143	M: 91.6 F: 143	M/F: -	M/F: No toxicity (No carcinogenicity observed)

Rabbit	Developmental toxicity study	0, 10, 25, 45	Dams: 25 Fetuses: 25	Dams: 45 Fetuses: 45	Dams: Emaciation, etc. Fetus: low body weight (No teratogenicity observed)
Dog	90-day subacute toxicity study	0, 1, 30, 300, 1 000	M/F: 30	M/F: 300	M/F: Increase in cholesterol levels, etc.
	One-year chronic toxicity study	0, 1, 10, 100, 1 000	M/F: 10	M/F: 100	M/F: Increase in cholesterol levels, etc.
ADI			NOAEL: 1.40 SF: 100 ADI: 0.014		
The critical study for setting ADI			Combined chronic toxicity/carcinogenicity study (rat)		

ADI, Acceptable daily intake; LOAEL, Lowest-observed-adverse-effect level; NOAEL, No-observed-adverse-effect level; SF, Safety factor
[1)] The adverse effect observed at LOAEL
-: NOAEL/LOAEL could not be specified.

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

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day)[1)]
Rat	Acute toxicity study	M/F: 2 000, 3 846, 4 000, 5 000, 6 000, 6 500	M/F: - M/F: Decreased locomotor activity, ataxia, etc.
		M/F: 5 000	M/F: - M/F: Abnormal grooming
	Developmental toxicity study	0, 5, 25, 125	Dams: 25 Dams: Decrease in body weight
Mouse	Acute toxicity study	M/F: 5 000	M/F: - M/F: Loose feces F: Decreased locomotor activity
Rabbit	Developmental toxicity study	0, 10, 25, 45	Dams: 25 Dams: Decrease in body weight and food intake
ARfD			NOAEL: 25 SF: 100 ARfD: 0.25
The critical study for setting ARfD			Developmental toxicity studies (rat, rabbit)

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