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

Risk Assessment Report

Tolfenpyrad (4th edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of a pyrazole insectide, tolfenpyrad (CAS No. 129558-76-5), based on various documents. For revising to the 4th edition, risk management organizations newly provided the data on fate in animals (*in vitro* study on metabolism using liver microsome), fate in plants (radish and leaf lettuce), residue in crops (Yamaimo, onions), and developmental toxicity (rabbits).

The data used in the assessment include fate in animals (rats), fate in plants (egg plants and head cabbage), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and newly submitted data.

Major adverse effects of tolfenpyrad observed are hepatocellular hypertrophy and hypertrophy of renal proximal tubular epithelium cells. Tolfenpyrad showed no neurotoxicity, carcinogenicity, teratogenicity and genotoxicity relevant to human health.
In a two-generation reproduction toxicity study in rats, prolonged gestational period was observed.
From the above results, FSCJ identified tolfenpyrad (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 0.56 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.0056 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 flupyrimin was 1 mg/kg bw/day obtained in developmental toxicity studies in rats. FSCJ specified an acute reference dose (ARfD) to be 0.01 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 15, 80, 160 ppm M: 0,0.91, 4.78, 9.33 F: 0, 1.01, 5.17, 9.32	M: - F: -	M: 0.91 F: 1.01	M: Increased relative organ weight of the liver F: Increased relative organ weight of the kidney
	90-day subacute neurotoxicity study	0, 15, 40, 80 ppm M: 0, 1.0, 2.7, 5.4 F: 0, 1.2, 3.2, 6.0	M: 2.7 F: 3.2	M: 5.4 F: 6.0	M/F: Suppressed body weight (No subacute neurotoxicity)
	Combined two-year chronic toxicity/carcinogenicity study	0, 15, 40, 80 ppm M: 0, 0.56, 1.50, 3.07 F: 0, 0.69, 1.85, 3.79	M: 0.56 F: 0.69	M: 1.50 F: 1.85	M: Increased relative organ weight of the liver and kidney F: Suppressed body weight (No carcinogenicity)
	Two-generation reproductive toxicity study	0, 0.75, 1.5, 3	Parent: M: 1.5 F: 0.75 Offspring: M: 0.75 F: 1.5 Reproduction: 1.5	Parent: M: 3 F: 1.5 Offspring: M: 1.5 F: 3 Reproduction: 3	Parent: M/F: Decreased feed intake Offspring: Suppressed body weight Reproduction: Prolonged gestational period
	Developmental toxicity study	0, 1, 3, 4.5	Dams: 1 Fetuses: 3	Dams: 3 Fetuses: 4.5	Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 15, 100, 300 ppm M: 0, 2.4, 15.9, 46.2 F: 0, 2.8, 27.1, 5.9	M: 15.9 F: 20.2	M: 46.2 F: 57.9	M/F: Increased relative organ weight of the liver
	18-month carcinogenicity study	0, 15, 150, 500/400/300[2)] ppm M:0, 2.2,20.8, 60.9 F: 0, 2.8, 27.1, 75.9	M: 2.2 F: 2.8	M: 20.8 F: 27.1	M: Suppressed body weight F: Decreased feed intake (No carcinogenicity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rabbit	Developmental toxicity study (the 1st study)	0, 1, 3, 6	Dams: 1 Fetuses: 6	Dams: 3 Fetuses: -	Dams: Body weight loss (Death after the loss) Fetuses: No toxicity was observed (No teratogenicity)
	Developmental toxicity study (the 2nd study)	0, 1, 3, 6	Dams: 1 Fetuses: 3	Dams: 3 Fetuses: 6	Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Dog	90-day subacute toxicity study (the 1st study)	0, 1, 5, 10	M: 1 F: 1	M: 5 F: 5	M/F: Vomiting
	90-day subacute toxicity study (the 2nd study)	0, 10, 30, 100	M: - F: -	M: 10 F: 10	M/F: Vomiting, loose stool
	Comprehensive evaluation of 90-day subacute toxicity study (the 1st study and the 2nd study)		M: 1 F: 1	M: 5 F: 5	
	One-year chronic toxicity study	0, 1, 5, 20/10[3)]	M: 1 F: 1	M: 5 F: 5	M/F: Decrease in T.Chol and phospholipids
ADI			NOAEL: 0.56 SF: 100 ADI: 0.0056		
The critical study for setting ADI			Combined two-year chronic toxicity/carcinogenicity study in rats		

ADI: Acceptable Daily Intake, NOAEL: No-Observed-Adverse-Effect level, SF: Safety Factor
-: LOAEL could not be specified.
[1)] The adverse effect observed at LOAEL
[2)] Dose was reduced to 400 ppm after 13 weeks of administration and 300 ppm after 20 weeks of administration.
[3)] Dose was reduced to 10 mg/kg bw/day from 5 weeks of administration.

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

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: 100, 150, 250, 500, 750 F: 50, 75, 100,150, 250	- M/F: Loose stool
		M/F: 40, 80, 160, 320, 640	- M/F: Diarrhea
		M/F: 20, 40, 80, 160, 320	- M/F: Diarrhea
	Acute neurotoxicity study	M: 0, 20, 40, 60 F: 0, 10, 20, 40	M: 20 F: 10 M: Suppressed body weight F: Suppressed body weight, decreased feed intake
	Developmental toxicity study	F: 0, 1, 3, 4.5	Dams: 1 Dams: Suppressed body weight, decreased feed intake
Mouse	Acute toxicity study	M/F: 25, 50, 100, 150, 250	M/F: 25 M/F: Decreased activity, ataxia
		M/F: 0, 25, 50, 80, 100, 150	M: - F: 25 M: Soiled perineal region F: Decreased motor activity
Dog	90-day subacute toxicity study (the 1st study)	M/F: 0, 1, 5, 10	M/F: 5 M/F: Vomiting
	90-day subacute toxicity study (the 2nd study)	M/F: 10, 30, 100	M/F: - M/F: Vomiting
	One-year chronic toxicity study	M/F: 0, 1, 5, 20/10[2)]	M/F: 5 M: Vomiting F: Vomiting, loose stool
ARfD			NOAEL: 1 SF: 100 ARfD: 0.01
The critical study for setting ARfD			Developmental toxicity study in rats

ARfD: Acute reference dose, NOAEL: No-observed-adverse effect level, SF: Safety factor
[1)] The adverse effect observed at LOAEL
[2)] Dose was reduced to 10 mg/kg bw/day from 5 weeks of administration.