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

Risk Assessment Report

Tolclofos-methyl

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2019

ABSTRACT

FSCJ conducted the risk assessment of an organophosphate fungicide, tolclofos-methyl (CAS No. 57018-04-9), based on various documents.

The data used in the assessment include fate in animals (rats and mice), livestock (goats and chicken), fate in plants (sugar beet and lettuce), residues in plants, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (mice and rats), three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and immunotoxicity.

Major adverse effects of tolclofos-methyl observed are suppressed body weight, inhibition of ChE activity in erythrocytes and the brain, anemia (dogs), increased organ weight and hepatocellular hypertrophy in the liver. Tolclofos-methyl showed no carcinogenicity, effects on reproductive activity, teratogenicity, genotoxicity and immunotoxicity.

From the above results, tolclofos-methyl (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural product.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 6.45 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in mice. FSCJ specified an acceptable daily intake (ADI) of 0.064 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 tolclofos-methyl was 13.8 mg/kg bw/day obtained in 9-month subacute toxicity studies in mice. FSCJ specified an acute reference dose (ARfD) to be 0.13 mg/kg bw by applying a safety factor of 100 to the NOAEL.

Table 1. *Levels relevant to toxicological evaluation of tolclofos-methyl*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1)]
Rat	5-week subacute toxicity study	0, 200, 1 000, 5 000, 20 000 ppm M: 0, 16.2, 79.1, 414, 1 640 F: 0, 17.8, 88.3, 452, 1 830	M: 414 F: 88.3 M/F: Inhibition of ChE activity (20% and above) in the brain
	13-week subacute toxicity study	0, 100, 1,000, 10 000 ppm M: 0, 6.46, 66.1, 653 F: 0, 7.13, 71.0, 696	M: 66.1 F: 71.0 M: Suppressed body weight F: Inhibition of RBC ChE activity (20% and above)
	13-week subacute neurotoxicity study	0, 300, 1 800, 10,000 ppm M: 0, 20.6, 122, 736 F: 0, 23.1, 136, 763	M: 122 F: 136 M/F: Suppressed body weight, decreased feed intake (No subacute neurotoxicity)
	6-month subacute toxicity study	0, 300, 1 000, 3 000, 10 000 ppm M: 0, 15.8, 51.2, 166, 547 F: 0, 18.3, 65.9, 186, 629	M: 166 F: 65.9 M: Suppressed body weight F: Proliferation of oval cells in the liver
	28/30-month combined chronic toxicity/ carcinogenicity study	0, 100, 300, 1 000 ppm M: 0, 4.12, 12.3, 41.6 F: 0, 4.78, 14.7, 48.6	M: 41.6 F: 48.6 M/F: No toxic effects (No carcinogenicity)
	Three-generation reproductivity study	0, 100, 300, 1 000 ppm	PM: 70.6 PF: 90.5 F_1M: 79.6 F_1F: 98.5 F_2M: 78.2 F_2F: 96.1

[1)] Major adverse effect observed at LOAEL

		PM: 0, 6.9, 20.5, 70.6 PF: 0, 8.9, 26.2, 90.5 F_1M: 0, 7.9, 23.4, 79.6 F_1F: 0, 9.2, 26.9, 98.5 F_2M: 0, 7.6, 23.8, 78.2 F_2F: 0, 9.0, 28.4, 96.1	P, F_1 and F_2 M/F: No toxic effect (No effects on reproductivity)
	Developmental toxicity study	0, 100, 300, 1 000	Dams : 300 Fetuses: 1 000 Dams: Suppressed body weight, Decreased feed intake Fetuses: No toxicity (No teratogenicity was found)
Mouse	9-month sub-acute toxicity study	0, 10, 30, 100, 3 000 ppm M: 0, 1.20, 3.78, 12.2, 513 F: 0, 1.42, 4.14, 13.8, 564	M: 3.78 F: 13.8 M/F: Inhibition of RBC ChE activity (20% and above)
	Two-year combined chronic toxicity/carcinogenicity study	0, 10, 50, 250, 1 000 ppm M: 0, 1.28, 6.45, 32.2, 134 F: 0, 1.32, 6.86, 34.1, 137	M: 6.45 F: 6.86 M/F: Inhibition of RBC ChE activity (20% and above) (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 300, 1 000, 3 000	Dams: 300 Fetuses: 3 000 Dams: Suppressed body weight, decreased feed intake Fetuses: No toxic effects (No teratogenicity)
Dog	6-month chronic toxicity study	0, 200, 600, 2 000 ppm M: 0, 6.63, 23.5, 69.9 F: 0, 5.97, 20.8, 62.9	M: 23.5 F: 20.8 M/F: Decrease in RBC and Hb

	One-year chronic toxicity study	0, 80, 400, 2 000 ppm	M: 11.4 F: 11.2
		M: 0, 2.15, 11.4, 58.7 F: 0, 2.56, 11.2, 61.9	M/F: Decrease in RBC, Ht and Hb.
ADI (mg/kg bw/day)			NOAEL: 6.45 SF: 100 ADI: 0.064
The critical study for setting Toxicological ADI			Two-year combined chronic toxicity/carcinogenicity study in mice

NOAEL, No-observed-adverse-effect level; SF, Safety factor; UF, Uncertainty factor; ADI, Acceptable daily intake
-, NOAEL or LOAEL could not be specified; [1)], The adverse effect observed at LOAEL

Table 2. *Potential adverse effects of a single oral administration of tolclofos-methyl*

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)]
Mouse	General pharmacology (clinical signs)	M: 0, 125, 250, 500, 1 000	M: 500 M: Deceased locomotor activity, gait abnormality, etc.
	General pharmacology (locomotor activity)	M: 0, 125, 250, 500, 1 000	M: 500 M: Decreased locomotor activity
	9-month subacute toxicity	M/F: 0, 10, 30, 100, 3 000 ppm M: 0, 1.20, 3.78, 12.2, 513 F: 0, 1.42, 4.14, 13.8, 564	F: 13.8 F: Inhibition of ChE activity in RBC (20 % and above, 2-week administration)
ARfD			NOAEL: 13.8 SF: 100 ARfD: 0.13
The critical study for setting ARfD			9-month subacute toxicity study in mice

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
1), The adverse effect observed at LOAEL