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

Risk Assessment Report

Propargite (Second edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
June 2021

ABSTRACT

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of propargite (CAS No. 2312-35-8), a sulfite ester insecticide, based on various documents. For this 2nd edition, a risk management organization provided additional data including residues in crops (prune).

The following data were included in the assessment; fate in animals (including rats, goats and chickens), fate in plants (including apples and maize), residues in crops, subacute toxicity (rats 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 propargite were observed in body weight (suppressed weight gain) and blood (anemia), while no effect on fertility or genotoxicity were observed.

In a carcinogenicity study in rats, an increased incidence of undifferentiated sarcomas of the jejunum (derived from the interstitial cells of Cajal) was observed. Since carcinogenicity was not observed in other species, and no genotoxicity was observed, involvement of a genotoxic mode of action was unlikely, thus it was considered possible to establish a threshold dose for the assessment. In a developmental toxicity study in rabbits, hydrocephalus was observed at doses that caused significant toxicity in maternal animals. Teratogenicity was not observed in rats.

Based on these results, propargite (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.

No-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) obtained in each test was 2 mg/kg bw per day in a developmental toxicity study in rabbits (the 1st study). On the other hand, in a rat two-year combined chronic toxicity/carcinogenicity study (the 1st study), jejunal undifferentiated tumor was observed in females in all treatment groups, so LOAEL in this study was 2.95 mg/kg body weight per day. Based on these findings, the FSCJ specified an ADI of 0.0098 mg/kg bw per day by applying a safety factor of 300 (10 for species difference, 10 for individual difference, and an additional factor 3 for using a LOAEL value).

The lowest NOAEL for potential adverse effects of a single oral administration of propargite was 100 mg/kg bw per day from a general pharmacology study in mice, based on which the FSCJ specified an acute reference dose (ARfD) of 1 mg/kg bw by applying a safety factor of 100.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Rat	90-day subacute toxicity study (the 1st study)	0, 100, 1 000, 2 000 ppm M: 0, 7.07, 71.2, 144 F: 0, 8.31, 72.5, 149	M: 7.07 F: 8.31 M/F: Suppressed body weight gain, etc.
	90-day subacute toxicity study (the 2nd study)	0, 200, 400, 800, 2 000, 4 000 ppm M: 0, 10, 19, 41, 102, 214 F: 0, 11, 24, 47, 109, 240	M: 41 F: 47 M/F: Suppressed body weight gain, decreased food consumption
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 50, 80, 400, 800 ppm M: 0, 2.38, 3.83, 19.2, 38.9 F: 0, 2.95, 4.68, 23.6, 49.4	M: 3.83 F: - M/F: Undifferentiated sarcomas of the jejunum, etc. (M/F: Undifferentiated sarcomas of the jejunum)
	Two-generation reproductive toxicity study	0, 80, 400, 800 ppm PM: 0, 5.1, 25.2, 48.9 PF: 0, 6.3, 30.5, 58.2 F_1M: 0, 5.6, 27.1, 59.0 F_1F: 0, 6.8, 32.7, 88.0	Parent and offspring PM: 5.1 PF: 6.3 F_1M: 5.6 F_1F: 6.8 Parent: M/F: Suppressed body weight gain, decreased food intake Offspring: M/F: Low body weight (No effect on fertility is observed.)
	Developmental toxicity study (the 1st study)	0, 6, 25, 105	
	Developmental toxicity study (the 2nd study)	0, 6, 12, 18, 25, 105	Dams: 25 Fetuses: 105 Dams: Soiled perineal and trunk regions, decreased body weight/suppressed body weight gain, etc. Fetuses: No toxicity (No teratogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Mouse	18-month carcinogenicity study	0, 50, 160, 500, 1 000 ppm M: 0, 6.1, 19.0, 61.1, 118 F: 0, 7.2, 23.9, 72.9, 143	M: 61.1 F: 72.9 M/F: Amyloidosis, etc. (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study (the 1st study)	0, 2, 6, 10, 18	Dams and Fetuses: 2 Dams: Increased trend in mortality, etc. Fetuses: Delayed ossification of the skull, etc. (No teratogenicity observed at no toxic dosage for maternal animals)
	Developmental toxicity study (the 2nd study)	0, 2, 4, 6, 8, 10	Dams: 6 Fetuses: 8 Dams: Decreased body weight/suppressed body weight gain Fetuses: Increased sternal segmental fusion (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 2 000/2 500 ppm M: 0, 54.7 F: 0, 67.7	M/F: - M/F: Decreased body weight, etc.
	One-year year chronic toxicity study	0, 160, 1 250, 2 500/1 875 ppm M: 0, 5.3, 38, 44 F: 0, 5.2, 40, 42	M: 5.3 F: 5.2 M/F: Decreased body weight/ suppressed body weight gain, etc.
	Two-year chronic toxicity study	0, 100, 300, 900 ppm M: 0, 4.86, 16.0, 48.8 F: 0, 5.54, 16.1, 46.1	M: 48.8 F: 46.1 M/F: No toxicity
ADI			LOAEL: 2.95 SF: 300 ADI: 0.0098
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study (the 1st study) in rats (Based on the LOAEL regarding carcinogenicity)

ADI, Acceptable daily intake; cRfD, Chronic reference dose; LOAEL, Lowest-observed-adverse-effect level; NOAEL, No-observed-adverse-effect level; SF, Safety factor; UF, Uncertainty factor
[1)] The adverse effect observed at LOAEL.
-, NOAEL could not be specified; /, Not described.

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

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)]
Rat	Acute toxicity study	M: 1 154, 1 500, 1 950, 2 535 F: 888, 1 154, 1 500, 1 950, 2 535	M/F: - M: Decreased body weight F: Decreased activity
Mouse	General pharmacological study (General condition, Irwin test)	M: 0, 30, 100, 300, 1 000	100 Piloerection, prone position, lethargy
	General pharmacology (Motor coordination)	F: 0, 30, 100, 300	100 Shortened latency to fall (Coordination disorder)
	Acute toxicity study	M: 420, 546, 710, 923, 1 200, 1 560 F: 420, 546, 710, 923, 1 200	M/F: - M/F: Decreased activity
ARfD			NOAEL: 100 SF: 100 ARfD: 1
The critical study for setting ARfD			General pharmacology data in mouse

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