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

Risk Assessment Report

Propanil
(Pesticides)

Food Safety Commission of Japan (FSCJ)
December 2018

ABSTRACT

FSCJ conducted the risk assessment of an amide herbicide, propanil (CAS No. 709-98-8), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy rice), residues in crops, subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and mechanism studies on hemolytic anemia and testicular toxicity.

Major adverse effects of propanil observed are suppressed body weight, effects on blood such as methemoglobinemia and hemolytic anemia, increased organ weight of the liver, and brown pigmentation in renal proximal tubular epithelium cells (RPTECs). Propanil showed no teratogenicity and genotoxicity.

In a two-year combined chronic toxicity/carcinogenicity study in rats, an increased incidence of testicular interstitial cell tumors in male rats and increased trend in hepatocellular adenomas in female rats were observed. In addition, an increase in incidences of malignant lymphoma was observed in females in a carcinogenicity study in mice. 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.

From the above results, propanil (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) or the lowest observed adverse effect level (LOAEL) in all tests was the LOAEL of 5 mg/kg bw/day in one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.016 mg/kg bw/day by applying a safety factor of 300 (10 for species difference, 10 for individual difference, and 3 for additional factor due to usage of LOAEL.
The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of propanil was the NOAEL of 57 mg/kg bw/day based on no effect on MetHb on the next day of initial treatment at

this dose obtained from a mechanism study on methohemoglobin anemia in rats. FSCJ specified an acute reference dose (ARfD) to be 0.57 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

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, 160, 800, 4 000 ppm M: 0, 10.6, 53.0, 277 F: 0, 12.3, 61.0, 278	M: 10.6 F: 12.3	M: 53 F: 61	M/F : Suppressed body weight, Increased extramedullary hematopoiesis in the spleen
	Combined two-year chronic toxicity/carcinogenicity study	0, 200, 600, 1 800 ppm M: 0, 9.0, 27.7, 88 F: 0, 11.5, 38.3, 145	M: - F: -	M: 9.0 F: 11.5	M/F: Brown pigmentation in renal convoluted proximal tubular epithelium cells (RPTECs) (M: Increased incident of testicular interstitial cell tumors. F: Increased trend in the incidence of hepatocellular adenomas)
	Two-generation reproductive toxicity study	0, 60, 150, 600 ppm PM: 0, 4, 11, 43 PF: 0, 5, 13, 51 F_1M: 0, 5, 13, 53 F_1F: 0, 6, 16, 66	Parent PM: 11 PF: 13 F_1M: 13 F_1F: 16 Offspring PM: 11 PF: 13 F_1M: 13 F_1F: 16	Parent PM: 43 PF: 51 F_1M: 53 F_1F: 66 Offspring PM: 43 PF: 51 F_1M: 53 F_1F: 66	Parent: M/F: Brown pigmentation in macrophages of the spleen Offspring: M/F: Suppressed body weight (No effect on reproduction)
	Developmental toxicity study	0, 0.8, 4, 20, 100	Dams: 100 Fetuses: 100	Dams: - Fetuses: -	Dams/Fetuses: No toxic effect. (No teratogenicity)
Mouse	Two-year carcinogenicity study (the 1st study)	0, 5, 30, 180 ppm M: 0, 0.71, 4.39, 26.1 F: 0, 0.88, 5.35, 32.4	M: 26.1 F: 32.4	M: - F: -	M/F: No toxic effect (No carcinogenicity)
	Two-year carcinogenicity study (the 2nd study)	0, 500, 1 000 ppm M: 0, 74.9, 150 F: 0, 88.6	M: - F: -	M: 74.9 F: 88.6	M/F: Increased MetHb (F: Increased incidence of malignant lymphoma (All tissues and the spleen))

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Comprehensive evaluation of the results of two-year carcinogenicity study (the 1st and 2nd study)		M: 26.1 F: 32.4	M: 74.9 F: 88.6	
Rabbit	Developmental toxicity study	0, 4, 20, 100	Dams: 20 Fetuses: 100	Dams: 100 Fetuses: -	Dams: weight loss /suppressed body weight, death Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 2, 7, 24.5, 85.8	M/F: 7	M/F: 24.5	M/F: Increased MetHb
	One-year chronic toxicity study	0, 200, 1 600, 3 200 ppm M: 0, 5, 45, 79 F: 0, 6, 42, 85	M: - F: -	M: 5 F: 6	M/F: Decreased RBC and Hb
ADI			LOAEL: 5 SF: 300 ADI: 0.016		
The critical study for setting ADI			One year chronic toxicity study in dogs		

ADI, Acceptable daily intake; SF, Safety factor; LOAEL, Lowest-observed-adverse-effect level; Hb, Hemoglobin; MetHb, Methemoglobin
-, 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 propanil*

Species	Study[1)]	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day)[2)]
Rat	Acute toxicity	F: 980, 1 750	980 Drowsiness and abdominal breathing
	Acute toxicity	750, 1 080, 1 555	M/F: - M/F: Drowsiness, ataxia and death
	Effect on MetHb tests	0, 300, 500, 700	M: 57 F: 67 M/F: No effect on an increase of MetHb
		M: 0, 25, 41, 57 F: 0, 28, 41, 67	
ARfD			NOAEL: 57 SF: 100 ARfD: 0.57
The critical study for setting ARfD			Effect on MetHb tests in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
－, NOAEL could not be specified
[1)], This study was conducted as a mechanism study on methohemoglobin anemia in rats; [2)], The adverse effect observed at LOAEL