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

Risk Assessment Report

Prochloraz

(Pesticides)

Food Safety Commission of Japan (FSCJ)
September 2020

ABSTRACT

FSCJ conducted the risk assessment of a fungicide, prochloraz (CAS No. 67747-09-5), based on various documents.

The data used in the assessment include fate in animals (rats, mice and dogs), fate in plants (wheat and rape-seed), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (mice and rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and mechanisms of metabolic enzyme inductions in the liver of mice and rats.

Major adverse effects of prochloraz observed are suppressed body weight, increased organ weight and hepatocellular hypertrophy in the liver, and decreased organ weight of the prostate (dogs). Prochloraz showed no teratogenicity and genotoxicity relevant to human health.

In a carcinogenicity study in mice, an increased incidence of liver tumors in both male and female. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and FSCJ considered it possible to establish a threshold dose in the assessment.

In a two-generation reproductive toxicity study in rats, prochloraz showed reproductive toxicity including death of dams due to difficulties with delivery, an extension of delivery time, prolonged gestational period, all litters loss, reduced number of newborn offspring and surviving offspring.

FSCJ identified prochloraz and its metabolites containing 2,4,6-trichlorophenoxy moiety as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 4.07 mg/kg bw/day in two-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.04 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of prochloraz was NOAEL of 160 mg/kg bw/day obtained in developmental toxicity studies in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.08 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose# (mg/kg bw/day)	NOAEL# (mg/kg bw/day)[1]	
			FSCJ	Reference (Summary reports)
Rat#	90-day subacute toxicity study (the 1st study)	0, 40, 150, 600, 2 000 ppm M: 0, 2.30, 8.65, 35.0, 116 F: 0, 2.71, 10.4, 40.3, 125	M: 2.30 F: 10.4 M: Suppressed body weight F: Fatty change of peripheral hepatocytes	M: 2.30 F: 10.4 M: Suppressed body weight F: Fatty change of peripheral hepatocytes
	90-day subacute toxicity study (the 2nd study)	0, 6, 25, 100	- M/F: Decreased Hb, MCV and others	
	Two-year combined chronic toxicity/carcinogenicity study	0, 37.5, 150, 625 ppm M: 0, 1.3, 5.1, 21.5 F: 0, 1.6, 6.4, 28.1	M: 5.1 F: 6.4 M/F: Suppressed body weight (No carcinogenicity)	M: 1.3 F: 1.6 M/F: hepatocellular swelling (No carcinogenicity)
	Two-generation reproductive toxicity study	0, 37.5, 150, 625 ppm PM: 0, 3.11, 12.7, 56.8 PF: 0, 3.45, 13.8, 58.4 F_1M: 0, 3.70, 15.5, 69.5 F_1F: 0, 4.48, 17.5, 80.8	Parent, offspring and reproductive activity PM: 12.7 PF: 13.8 F_1M: 15.5 F_1F: 17.5 Parent: Suppressed body weight, Offspring: Decreased number of survived offspring. Reproductive activity: Death by difficulties with delivery	Parent PM: 3.11 PF: 13.8 F_1M: 3.70 F_1F: 17.5 Offspring and reproductive activity PM: 12.7 PF: 13.8 F_1M: 15.5 F_1F: 17.5 Parent M: Extended duration of aggressive behavior F: Suppressed body weight Offspring: Decreased number of survived offspring Reproductive activity: Death by difficulties with delivery

	Developmental toxicity study	0, 6, 25, 100	Dams: 6 Fetuses: 25 Dams: Rubbing behavior, salivation Fetuses: Low body weight, etc. (No teratogenicity)	Dams: 6 Fetuses: 25 Dams: Rubbing behavior, salivation Fetuses: Low body weight, etc. (No teratogenicity)
Mouse	90-day subacute toxicity study (the 1st study)	0, 6, 25, 100, 400 ppm M: 0, 7, 29, 119, 611 F: 0, 8, 33, 125, 588	M: 29 F: 33 M/F: periportal fat droplet	M: 7 F: 33 M/F: increased absolute and relative weight of the liver
	90-day subacute toxicity study (the 2nd study)	0, 35, 140, 560 ppm M: 0, 4.33, 17.3, 67.4 F: 0, 4.75, 19.3, 79.4	M: 17.3 F: 19.3 M/F: Suppressed body weight	M: 17.3 F: 19.3 M/F: Suppressed body weight
	Two-year carcinogenicity study	0, 78, 325, 1 300 ppm M: 0, 7.5, 32.8, 134 F: 0, 8.8, 36.1, 149	M: 7.5 F: 8.8 M/F: Increased absolute weight of the liver	M: 7.5 F: 8.8 M/F: Increased incidence of liver tumors
Rabbit	Developmental toxicity study (the 1st study)	0, 3,12, 48	Dams: 12 Fetuses: 48 Dams: Increases in absolute and relative weight of the liver, liver discoloration Fetuses: No toxicity was observed. (No teratogenicity)	Dams: 12 Fetuses: 48 Dams: Increases in absolute and relative weight of the liver Fetuses: No toxicity was observed (No teratogenicity)
	Developmental toxicity study (the 2nd study)	0, 10, 40, 160	Dams: 40 Fetuses: 40 Dams: Suppressed body weight Fetuses: Increased number of embryonic and fetal resorption (No teratogenicity)	Dams: 40 Fetuses: 160 Dams: Increased number of embryonic and fetal resorption Fetuses: No toxicity was observed (No teratogenicity)
Dog##	90-day subacute toxicity study	0, 1, 2.5, 7, 20	M/F: 2.5 M/F: Increased ALP.	M/F: 2.5 M/F: Increases in absolute and relative weight of the liver

	Two-year chronic toxicity study	0, 30, 135, 600/1 300 ppm M: 0, 0.94, 4.47, 18.1/28.9 F: 0, 0.90, 4.07, 18.0/27.5	M: 4.47 F: 4.07 M/F: inflammatory cellular infiltration	M: 0.94 F: 4.07 M/F: Coarse structure of centrilobular cytoplasm of the liver, centrilobular hepatocellular swelling
ADI			NOAEL: 4.07 SF: 100 ADI: 0.04	NOAEL: 0.94 SF: 100 ADI: 0.009
The critical study for setting ADI			Two-year chronic toxicity study in dogs	Two-year chronic toxicity study in dogs

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake;
-, NOAEL could not be specified. /, No study was described.
[1)] The adverse effect observed at LOAEL, [#] as a converted value for diquation.
#, FSCJ judged the lowest NOAEL in all rat studies was 5.1 mg/kg bw/day.
##, FSCJ judged the lowest NOAEL in both dog studies was 4.07 mg/kg bw/day.

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

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: 2 063, 2 372, 2 728, 3 138, 3 608, 4 149, 4 772 F: 1 418, 1 673, 1 974, 2 330, 2 749, 3 244, 3 828, 4 517, 5 330	M/F: - M/F: Decreased locomotor activity
		M/F: 800, 1 600, 2 400	M/F: - M/F: Piloerection, diarrhea
Mouse	Acute toxicity study	M: 1 018, 1 171, 1 346, 1 548, 1 780, 2 048, 2 355, 2 708, 3 114 F: 0, 980, 1 127, 1 296, 1 490, 1 714, 1 971, 2 267, 2 607, 2 998	M/F: - M/F: Decreased locomotor activity
Rabbit	Developmental toxicity study (Preliminary study)	0, 200, 250	Dams: - Dams: Suppressed body weight, decreased feed intake
	Developmental toxicity study (Conclusive study)	0, 10, 40, 160	Dams: 160 Dams: No toxicity
	Comprehensive evaluation of preliminary and conclusive studies		Dams: 160 Dams: Suppressed body weight, decreased feed intake
ARfD			NOAEL: 160 SF: 100 ARfD: 1.6
The critical study for setting ARfD			Developmental toxicity study in rabbits

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed-adverse-effect level;
-, NOAEL could not be observed.

1) The adverse effect observed at LOAEL