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

Risk Assessment Report

Fenpropidin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
March 2024

ABSTRACT

The FSCJ conducted a risk assessment of fenpropidin (CAS No. 67306-00-7), a piperidine fungicide, based on submitted documents.

Test results used in the assessment include fate in plants (including wheat and sugar beet), residues in crops, fate in livestock (goats and chickens), fate in animals (rats), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), developmental neurotoxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of fenpropidin were observed in body weight (suppressed weight gain), the stomach (including hyperkeratosis in rats and mice), esophagus (including hyperkeratosis in rats and mice), and bladder (including epithelial hyperplasia in rats and dogs). Neither carcinogenicity, developmental neurotoxicity, effects on fertility nor genotoxicity was observed.

In the developmental toxicity study in rabbits, increases in fetal abnormality rates (persistent truncus arteriosus, severe segmental alignment abnormalities of the sternum, etc.) were observed at doses that caused significant toxicity in dams.

Based on these results, fenpropidin (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

Although the lowest no-observed-adverse-effect level (NOAEL) obtained from these studies was 1.14 mg/kg bw per day in the 90-day subacute toxicity study in rats (the 1st study), the NOAEL value of 1.68 mg/kg bw per day in the two-year combined chronic toxicity/carcinogenicity study in rats was considered more suitable for use as NOAEL in rats based on its longer study term. Therefore, the FSCJ specified an acceptable daily intake (ADI) of 0.016 mg/kg bw per day by applying a safety factor of 100 to this latter NOAEL.

The lowest NOAEL value for potential adverse effects of a single oral administration of fenpropidin was 10 mg/kg bw per day from a developmental toxicity study in rabbits. Since an increase in fetal abnormality rate was observed in this study, the FSCJ specified an acute reference dose (ARfD) of 0.1

mg/kg bw for pregnant or possibly pregnant women by applying a safety factor of 100 to this NOAEL. For the general population, the FSCJ specified an ARfD of 3.5mg/kg bw by applying a safety factor of 100 to the NOAEL value of 359 mg/kg bw per day in the 90-day subacute toxicity study in mice.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
Rat	28-day subacute toxicity study	0, 50, 200, 1 000, 2 000 ppm M: 0, 5.40, 20.1, 105, 200 F: 0, 5.62, 19.9, 103, 212	M: 5.40 F: 5.62	M: 20.1 F: 19.9	M: Increased keratinization of the esophageal epithelium F: Decreased MCV
	90-day subacute toxicity study (the 1st study)	0, 20, 150, 1 500 ppm M: 0, 1.14, 9.84, 89.9 F: 0, 1.24, 10.1, 97.3	M: 1.14 F: 1.24	M: 9.84 F: 10.1	M: Increased keratinization of the esophageal and forestomach epithelium F: Increased keratinization of the esophageal epithelium
	90-day subacute toxicity study (the 2nd study)	0, 20, 60, 120 M: 0, 20.0, 60.1, 119 F: 0, 20.0, 60.4, 121	M: - F: 20.0	M: 20.0 F: 60.4	M: Suppressed body weight gain, worsened fur conditions, etc. F: Suppressed body weight gain and decreased Chol levels
	Two-year combined chronic toxicity/carcinogenicity study	0, 5/2, 25/10, 125/50, 625/250 ppm M: 0, 0.07, 0.34, 1.68, 8.53 F: 0, 0.09, 0.45, 2.27, 11.8	M: 1.68 F: 2.27	M: 8.53 F: 11.8	M/F: Increased potassium levels, etc. (No carcinogenicity is observed.)
	Developmental neurotoxicity study	0, 40, 100, 400 ppm	Dams: 3 Offspring: 7	Dams: 7 Offspring: 27	Dams and offspring: Suppressed body

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
		0, 3, 7, 27			weight gain (No developmental neurotoxicity is observed.)
	Two-generation reproductive toxicity study (the 1st study)	0, 25, 100, 500, 1 000 ppm PM: 0, 2, 8, 42, 80 PF: 0, 2, 8, 45, 88 F_1M: 0, 3, 10, 58, 126 F_1F: 0, 3, 11, 56, 114	Parents and offspring PM: 8 PF: 8 F_1M: 10 F_1F: 11	Parents and offspring PM: 42 PF: 45 F_1M: 58 F_1F: 56	Parents and offspring: Suppressed body weight gain, etc. (No effect on fertility is observed.)
	Two-generation reproductive toxicity study (the 2nd study)	0, 6.25, 25, 100 ppm PM: 0, 0.40, 1.61, 6.43 PF: 0, 0.48, 1.91, 7.79 F_1M: 0, 0.50, 2.03, 8.02 F_1F: 0, 0.56, 2.35, 9.31	Parents and offspring PM: 6.43 PF: 7.79 F_1M: 8.02 F_1F: 9.31	Parents and offspring PM: - PF: - F_1M: - F_1F: -	Parents and offspring: No toxicity (No effect on fertility is observed.)
	Developmental toxicity study (the 1st study)	0, 10, 60, 90	Dams and fetuses: 90	Dams and fetuses: -	Dams and fetuses: No toxicity (No teratogenicity is observed)
Mouse	90-day subacute toxicity study	0, 625, 1 250, 2 500, 5 000 ppm M: 0, 58, 155, 359, 547 F: 0, 87, 179, 361, 566	M: 58 F: -	M: 155 F: 87	M: Increased irritability or agitation F:Suppressed body weight gain
	80-week combined chronic toxicity/carcinogenicity	0, 30, 100, 300, 1 000 ppm	M: 4.12 F: 5.47	M: 13.5 F: 17.7	M/F: Increased keratinization of the esophageal

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
	study	M: 0, 4.12, 13.5, 41.9, 144 F: 0, 5.47, 17.7, 51.7, 166			epithelium (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study	0, 5, 10, 20	Dams and fetuses: 10	Dams and fetuses: 20	Dams: Decreased fecal volume, suppressed body weight gain, etc. Fetuses: Increased fetal abnormalities rate
Dog	26-week subacute toxicity study	0, 2, 5, 12	M/F: 2	M/F: 5	M/F: Vomiting
	One-year chronic toxicity study	0, 2, 5, 20	M/F: 5	M/F: 20	M/F: Cataract and epidermal hyperplasia, etc.
ADI			NOAEL: 1.68 SF: 100 ADI: 0.016		
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study (rat)		

ADI, Acceptable daily intake; Chol, Cholesterol; LOAEL, Lowest-observed-adverse-effect level; MCV, Mean corpuscular volume; NOAEL, No-observed-adverse-effect level
-, NOAEL or LOAEL could not be specified.
[1)] The adverse effect observed at LOAEL

Table 2-1. *Potential adverse effects of a single oral administration of fenpropidin*

(General population)

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day) [1)]
Rat	Acute toxicity study	M:1 872, 2 136, 2 401, 3 205, 4 273, 5 341 F: 539, 1 068, 1 333, 1 470, 1 607, 1 872, 2 136, 3 205	M/F: - M: Death, ataxia, piloerection, etc. F: Ataxia, piloerection, etc.
	Acute toxicity study	M/F: 913, 1 461, 2 283, 3 652	M/F: - M/F: Piloerection, hunchback position, etc.
Mouse	90-day subacute toxicity study	M: 58, 155, 359, 547 F: 87, 179, 361, 566	M: 359 F: 361 M/F: Decreased momentum in locomotor activities
	Micronucleus test	M/F: 385, 770, 1 540	M/F:385 M/F: Death
ARfD			NOAEL: 359 SF: 100 ARfD: 3.5
The critical study for setting ARfD			90-day subacute toxicity study (mouse)

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

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

(Women who are pregnant or possibly pregnant)

Species	Study	Dose (mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw per day) [1)]
Rabbit	Developmental toxicity study	0, 5, 10, 20	Fetuses: 10 Fetuses: Increased fetal abnormalities rate
ARfD			NOAEL: 10 SF: 100 ARfD: 0.1
The critical study for setting ARfD			Developmental toxicity study (rabbit)

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