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

Risk Assessment Report

Penthiopyrad (5th Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

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ABSTRACT

FSCJ conducted the risk assessment of a carboxylic acid amide fungicide, penthiopyrad (CAS No. 183675-82-3) for additional use of wheat. Documents newly submitted for the present assessment include data on fate in animals (goats and chicken), fate in plants (sugar beet), residues in crops (wheat) and residues in livestock products (cattle and chicken), and 28-day subacute toxicity study (metabolite A-3, rats).

Data used for the assessment include fate in animals (rats, goats and chicken), fate in plants (grape and tomato), residues in plants, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (mice and rats), two-generation reproduction (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), genotoxicity, immunotoxicity (rats and mice), and mechanisms of effects on the thyroid and liver.

Major adverse effects of penthiopyrad observed are suppressed body weight, liver hypertrophy, anemia and hypertrophy of follicular epithelial cell of the thyroid. Penthiopyrad showed no effects on reproduction, teratogenicity, developmental neurotoxicity and genotoxicity relevant to human health.
In a carcinogenicity study, increased incidences of follicular thyroid adenomas in rats, and of hepatocellular adenomas in mice were observed. However, a genotoxic mechanism was unlikely to be involved in the tumorigenesis, and FSCJ considered it reasonable to establish a threshold dose in the assessment.
Activity to produce antigen-specific antibodies lowered in mice in immunotoxicity studies, however, no immunotoxicity was observed in rats.
From the above results, penthiopyrad (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products, and penthiopyrad and its metabolite A-3 were identified for that in livestock products.
The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 8.10 mg/kg bw/day in one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.081 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. This ADI was the same as the previous assessment.
The lowest NOAEL for potential adverse effects of a single oral administration of flupyrimin was 125 mg/kg bw/day obtained in acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 1.2 mg/kg bw by applying a safety factor of 100 to the NOAEL.

FSCJ did not specify the ADI and ARfD of the metabolite A-3 despite that it was considered more toxic than the parent compound, because the residue amount was low in the residue studies in crops and livestock products, and because available data about toxicity were limited.

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

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, 40, 100, 250, 625 M: 0, 39.8, 99.9, 248, 660 F: 0, 39.7, 99.8, 250, 663	M: 39.8 F: 39.7	M: 99.9 F: 99.8	M/F: Increased relative weight of the liver, hepatocellular hypertrophy in the liver
	90-day subacute neurotoxicity study	0, 10, 40, 160, 640 M: 0, 11.0, 43.8, 177, 712 F: 0, 10.7, 42.5, 170, 686	M: 177 F: 42.5	M: 712 F: 170	M/F: Suppressed body weight (No subacute neurotoxicity)
	One-year chronic toxicity study	0, 6.25, 25, 100, 400 M: 0, 6.21, 24.9, 98.8, 397 F: 0, 6.26, 24.9, 100, 401	M: 24.9 F: 24.9	M: 98.8 F: 100	M/F: Increased relative weight of the liver
	Two-year carcinogenicity study	0, 9, 27, 83, 250 M: 0, 9.06, 27.0, 83.4, 252 F: 0, 9.11, 27.4, 83.2, 253	M: 27.0 F: 27.4	M: 83.4 F: 83.2	M: Periportal hepatocellular fatty degeneration F: Suppressed body weight (M: increased incidence of follicular cell adenomas in the thyroid)
	Two-generation reproduction study	0, 200, 1 000, 5 000 ppm PM: 0, 11.0, 54.0, 278 PF: 0, 18.1, 90.5, 439 F_1M: 0, 12.8, 64.2, 340 F_1F: 0, 19.0, 95.6, 480	Parent PM: 11.0 PF: 18.1 F_1M: 12.8 F_1F: 19.0 Offspring PM: 54.0 PF: 90.5 F_1M: 64.2 F_1F: 95.6	Parent PM: 54.0 PF: 90.5 F_1M: 64.2 F_1F: 95.6 Offspring PM: 278 PF: 439 F_1M: 340 F_1F: 480	Parent: Suppressed body weight Offspring: Low body weight (No effects on reproductivity)
	Developmental toxicity study	0, 62.5, 250, 1 000	Dams: 250 Fetuses: 250	Dams: 1 000 Fetuses: 1 000	Dams: Suppressed body weight Fetuses: Increased mortality of post-implantation embryo/fetuses (No teratogenicity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Developmental neurotoxicity study	0, 100, 250, 500	Dams: 100 Offspring: 100	Dams: 250 Offspring: 250	Dams: Decreased feed intake Offspring: Dirt in perianal region (No developmental neurotoxicity)
Mouse	90-day subacute toxicity study	0, 30, 100, 300, 1 000 M: 0, 29.5, 100, 299, 997 F: 0, 30.7, 102, 306, 1 030	M: 100 F: 102	M: 299 F: 306	M/F: Increased relative weight of the liver
	18-month carcinogenicity study	0, 20, 60, 200, 600 M: 0, 19.9, 59.8, 200, 602 F: 0, 20.0, 60.3, 201, 604	M: 59.8 F: 60.3	M: 200 F: 201	M/F: Hypertrophy of follicular epithelial cells of the thyroid (M: Increased incidence of hepatocellular adenomas)
Dog	90-day subacute toxicity study	0, 300, 3 000, 30 000 ppm M: 0, 8.01, 76.7, 811 F: 0, 8.18, 80.9, 864	M: 76.7 F: 80.9	M: 811 F: 864	M/F: Increased absolute/relative weight of the liver
	One-year chronic toxicity study	0, 310, 2 150, 15 000 ppm M: 0, 7.91, 54.4, 461 F: 0, 8.10, 56.6, 445	M: 54.4 F: 8.10	M: 461 F: 56.6	M: Suppressed body weight F: Increased ALP
Rabbit	Developmental toxicity study	0, 25, 75, 225	Dams: 75 Fetuses: 75	Dams: 225 Fetuses: 225	Dams: Miscarriage Fetuses: Low body weight (No teratogenicity)
ADI			NOAEL: 8.10 SF: 100 ADI: 0.081		
The critical study for setting ADI			One-year chronic toxicity study in dogs		

ADI: Acceptable daily intake, NOAEL: No-observed-adverse-effect level, SF: Safety factor
[1)]The adverse effect observed at LOAEL

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

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	General pharmacology (general conditions)	M: 0, 200, 600, 2 000	M: 600 Slight decrease in consciousness, slight decrease in mobility, trend of low body temperature
	General pharmacology (blood pressure, heart rate)	M: 0, 200, 600, 2 000	M: 600 Decreased heart rate
	Acute neurotoxicity study	M/F: 0, 125, 500, 2 000	M/F: 125 M/F: Hunchback position, low body temperature, decreased locomotor activity
Mouse	General pharmacology (general conditions)	F: 0, 200, 600, 2 000	F: 600 F: Mild sedation, ataxia, low body temperature
ARfD			NOAEL: 125 SF: 100 ARfD: 1.2
The critical study for setting ARfD			Acute neurotoxicity study in rats

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