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

Risk Assessment Report

Pyraziflumid (Second edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2022

ABSTRACT

The FSCJ conducted a risk assessment of pyraziflumid (CAS No.942515-63-1), a pyrazine biphenyl-type carboxamide group fungicide, based on results from various studies. This is the second edition of the report including additional results of the following studies submitted by the Ministry of Health, Labour and Welfare: fate in animals (goats and chicken); residues in crops (carrots, garlics, etc.); residues in livestock (cattle and chicken); acute neurotoxicity (rats); and others.

The data used in the assessment include the fate in animals (rats, goats and chicken); fate in plants (paddy rice, lettuce and others); residues in crops and livestock; acute neurotoxicity (rats); 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); genotoxicity; and others.

As the results of various toxicity studies, the major adverse effects of pyraziflumid were observed in the liver (single-cell necrosis, etc.) and the thyroid (hypertrophy of follicular epithelial cell). No adverse effects were observed in neurotoxicity, fertility, teratogenicity and genotoxicity relevant to human health.

Increased incidences of thyroid follicular cell adenoma and carcinoma in males, and of hepatocellular adenoma in females were identified in a two-year combined chronic toxicity/carcinogenicity study in rats. Genotoxic mechanisms were, however, unlikely to be involved in the tumor development. A threshold could be established in the assessment.

Based on the results of various studies, the FSCJ identified pyraziflumid (parent compound only) of the residue definition for the dietary risk assessment in agricultural and livestock products.

The lowest no-observed-effect level (NOAEL) obtained from all studies was 2.15 mg/kg bw per day in a two-year combined chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.021 mg/kg bw per day, applying a safety factor of 100 to the NOAEL.

The possible LOAEL via the single acute oral administration, etc. of pyraziflumid was 500 mg/kg bw in an acute neurotoxicity study in rats. The finding was a decrease of motor activity only. Given this, the FSCJ specified an acute reference dose (ARfD) of 1.6 mg/kg bw applying a safety factor of 300 (species difference:10, individual difference: 10, additional factor attributed to the LOAEL: 3).

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

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	M: 0, 100, 500, 5 000/2 000 ppm F: 0, 100, 500, 2 000 ppm M: 0, 7.1, 36.2, 435/151 F: 0, 8.6, 41.9, 172	M: 7.1 F: 8.6	M: 36.2 F: 41.9	M/F: Increased absolute/relative liver weight, etc.
	Two-year combined chronic toxicity/ carcinogenicity study	0, 50, 100, 300, 1 000 ppm M: 0, 2.15, 4.34, 13.3, 45.7 F: 0, 2.88, 5.72, 18.1, 66.3	M: 2.15 F: 2.88	M: 4.34 F: 5.72	M: Centrilobular hypertrophy of hepatocytes/hepatocellular fatty change, etc. F: Pigmentation in tubular epithelium of renal cortex urinary, etc. (M: Increased incidences of thyroid follicular cell adenomas and carcinomas F: Increased incidences of hepatocellular adenomas)
	Two-generation reproductive toxicity study	0, 50, 100, 300, 1 000 ppm PM: 0, 2.8, 5.6, 16.6, 56.9 PF: 0, 3.5, 7.0, 20.8, 69.9 F_1M: 0, 3.6, 7.1, 21.2, 71.8 F_1F: 0, 4.3, 8.7, 25.8, 88.2	Parent and offspring PM: 5.6 PF: 7.0 F_1M: 7.1 F_1F: 8.7	Parent and offspring PM: 16.6 PF: 20.8 F_1M: 21.2 F_1F: 25.8	Parent and offspring PM/PF/F_1M/F_1F: Centrilobular hypertrophy of hepatocytes, etc. (No adverse effect on fertility)
	Developmental toxicity study	0, 20, 100, 500	Maternal: 20 Embryo/fetus: 500	Maternal: 100 Embryo/ fetus: -	Maternal: Suppressed body weight, decreased feed intake Embryo/fetus: No toxicity (Not teratogenic)
Mouse	78-week carcinogenicity study	0, 200, 2 000, 8 000 ppm M: 0, 21, 227, 905 F: 0, 25, 251, 1 030	M: 21 F: 25	M: 227 F: 251	M/F: Diffuse hypertrophy of hepatocytes/ hepatocellular fatty change, etc. (Not carcinogenic)
Rabbit	Developmental toxicity study	0, 10, 30, 100	Maternal: 30 Embryo/fetus: 100	Maternal: 100 Embryo/ fetus: -	Maternal: Suppressed body weight, decreased feed intake, etc. Embryo/fetus: No toxicity (Not teratogenic)

Dog	90-day subacute toxicity study	M: 0, 200, 1 000, 10 000/5 000 ppm F: 0, 200, 1 000, 10 000 ppm M: 0, 5.99, 29.1, 167 F: 0, 6.16, 30.9, 320	M: 29.1 F: 30.9	M: 167 F: 320	M/F: Single-cell necrosis hepatocytes, etc.
	One-year chronic toxicity study	0, 200, 1 000, 5 000/2 000 ppm M: 0, 5.38, 28.3, 50.8 F: 0, 5.53, 27.6, 47.6	M: 28.3 F: 27.6	M: 50.8 F: 47.6	M/F: Single-cell necrosis hepatocytes, etc.
ADI			NOAEL: 2.15 SF: 100 ADI: 0.021		
The critical study for setting ADI			A two-year combined chronic toxicity/carcinogenicity study in rats		

ADI, Acceptable daily intake; SF, Safety factor; NOAEL, No-observed-adverse-effect level;
[1)] The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL)
-, NOAEL could not be specified

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

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 neurotoxicity study	0, 500, 1000, 2000	M : - F: A decrease of locomotor activity (total volume of physical activity and walking volume)
ARfD			LOAEL: 500 SF: 300 ARfD: 1.6
The critical study for setting ARfD			Acute neurotoxicity study (rat)

ARfD, Acute reference dose; LOAEL, Lowest-observed-adverse-effect level; SF, Safety factor
[1)] The adverse effect observed at LOAEL.
-, NOAEL could not be specified.