FOOD SAFETY

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Risk assessment report

Pyraziflumid (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of pyraziflumid (CAS No.942515-63-1), a carboxamide fungicide of pyrazine-biphenyl type, based on results from various studies. Major adverse effects of pyraziflumid observed were of single-cell necrosis hepatocytes and hypertrophy of follicular epithelial cell in the thyroid. No adverse effects were detected in fertility, teratogenicity and genotoxicity relevant to human health. Increased incidences of thyroid follicular cell adenomas and carcinomas in males, and also of hepatocellular adenomas in females were identified in a two-year combined chronic toxicity/carcinogenicity study in rats. Genotoxic mechanisms were, however, unlikely involved in the tumor developments, and these enabled FSCJ to establish a threshold in the assessment. Based on various studies, pyraziflumid (parent compound only) was the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-effect level (NOAEL) obtained from all the studies was 2.15 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.021 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. FSCJ considered it unnecessary to specify an acute reference dose (ARfD) in view of the absence of adverse effects that would be likely to be elicited by a single oral administration of pyraziflumid.

Conclusion in Brief

FSCJ conducted a risk assessment of pyraziflumid (CAS No.942515-63-1), a carboxamide fungicide of pyrazine-biphenyl type, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, lettuce and others), residues in crops, 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) and genotoxicity, and also on mechanism studies related to the tumor development in rats.

Major adverse effects of pyraziflumid observed were of single-cell necrosis hepatocytes and hypertrophy of follicular epithelial cell in the thyroid. No adverse effects were detected in fertility, teratogenicity and genotoxicity relevant to human health.

Increased incidences of thyroid follicular cell adenomas and carcinomas in males, and also of hepatocellular adenomas in females were identified in a two-year combined chronic toxicity/carcinogenicity study in rats. Genotoxic mechanisms were, however, unlikely involved in the tumor developments, and these enabled FSCJ to establish a threshold in the assessment.

Based on various studies, pyraziflumid (parent compound only) was the residue definition for dietary risk assessment in agricultural products.

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

FSCJ considered it unnecessary to specify an acute reference dose (ARfD) in view of the absence of adverse effects that would be likely to be elicited by a single oral administration of pyraziflumid.

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This is an English translation of excerpts from the original full report (March 2017−FS/189/2017). Only original Japanese texts have legal effect. The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20161018124&fileId=201
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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