

# Isfetamid (Pesticides)

## Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of isfetamid (CAS No. 875915-78-9), a phenacyl amide fungicide, based on results from various studies. Major treatment-related effects of isfetamid were observed on liver (hepatocellular hypertrophy) and on thyroid (hypertrophy of follicular epithelial cell). None of neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, immunotoxicity and genotoxicity were observed. Based on the results from various studies, only parent isfetamid was identified as the relevant substance to the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-adverse-effect level (NOAEL) obtained in all the toxicity studies was 5.34 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ has established an acceptable daily intake (ADI) of 0.053 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. The lowest NOAEL for adverse effects that would be likely to be elicited by a single oral administration of isfetamid was 300 mg/kg bw/day, which is obtained on the maternal toxicity in rabbits. FSCJ specified an acute reference dose (ARfD) of 3 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

## Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of isfetamid (CAS No. 875915-78-9), a phenacyl amide fungicide, based on results from various studies.

The data used in the assessment include the fate in animals (rats, goats and chickens), fate in plants (lettuce and grapes), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), immunotoxicity (mice), genotoxicity, and also a study on the toxic mechanisms.

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immunotoxicity and genotoxicity were observed.

Based on the results from various studies, only parent isfetamid was identified as the relevant substance to the residue definition for dietary risk assessment in agricultural products.

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This is an English translation of excerpts from the original full report (October 2016-FS/641/2016). Only original Japanese texts have legal effects.

The original full report is available in Japanese at <http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20150113247&fileId=201>

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Levels relevant to toxicological evaluation of isofetamid

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints <sup>1)</sup>
Rat	90-day subacute toxicity study	0, 100, 1,000, 10,000 ppm M: 0, 6.65, 68.9, 637 F: 0, 7.83, 78.0, 741	M: 6.65 F: 7.83	M: 68.9 F: 78.0	F/M: Diffuse Hepatocellular hypertrophy, etc
	90-day subacute neurotoxicity study	0, 500, 3,000, 15,000 ppm M: 0, 34, 207, 1,050 F: 0, 40, 245, 1,210	M: 207 F: 1,210	M: 1,050 F: -	M: Depressed body weight F: No toxicological effects (Not neurotoxic)
	One-year chronic toxicity study	0, 30, 100, 500, 5,000 ppm M: 0, 1.39, 4.68, 22.7, 237 F: 0, 1.82, 5.92, 30.0, 311	M: 22.7 F: 30.0	M: 237 F: 311	F/M: Increased absolute/relative liver weights, Diffuse hepatocellular hypertrophy, etc
	Two-year carcinogenicity study	0, 30, 100, 500, 5,000 ppm M: 0, 1.21, 4.07, 20.3, 210 F: 0, 1.55, 5.02, 26.1, 263	M: 20.3 F: 26.1	M: 210 F: 263	F/M: Hypertrophy of thyroid follicular epithelial cell, etc (Not carcinogenic)
	Two-generation reproductive toxicity study	0, 100, 1,000, 10,000 ppm PM: 0, 5.76, 57.1, 594 PF: 0, 8.85, 90.5, 908 F <sub>1</sub> M: 0, 6.02, 60.1, 643 F <sub>1</sub> F: 0, 8.69, 89.1, 906	Parent PM: 57.1 PF: 8.85 F <sub>1</sub> M: 60.1 F <sub>1</sub> F: 8.69	Parent PM: 594 PF: 90.5 F <sub>1</sub> M: 643 F <sub>1</sub> F: 89.1	Parent F/M: Increased absolute/relative liver weights, etc.
			Offspring PM: 57.1 PF: 90.5 F <sub>1</sub> M: 60.1 F <sub>1</sub> F: 89.1	Offspring PM: 594 PF: 908 F <sub>1</sub> M: 643 F <sub>1</sub> F: 906	Offspring F/M: Depressed body weight, etc. (No effect on reproduction)
Developmental toxicity study	0, 100, 300, 1,000	Maternal: 300  Embryo/fetus: 1,000	Maternal: 1,000  Embryo/fetus: -	Maternal: Trend in increased absolute liver weights and increased relative liver weights Embryo/fetus: No toxicological effects (Not teratogenic)	
Mouse	90-day subacute toxicity study	0, 100, 1,000, 8,000 ppm M: 0, 13, 129, 1,070 F: 0, 16, 161, 1,310	M: 129 F: 161	M: 1,070 F: 1,310	F/M: Increased absolute/relative liver weights, etc
	78-week carcinogenicity study	0, 100, 800, 3,000(F), 4,000(M) ppm M: 0, 12, 92, 502 F: 0, 14, 118, 431	M: 12 F: 118	M: 92 F: 431	F/M: Depressed body weight, etc (Not carcinogenic)
Rabbit	Developmental toxicity study	0, 100, 300, 1,000	Maternal: 300  Embryo/fetus: 1,000	Maternal: 1,000  Embryo/fetus: -	Maternal: Depressed body weight, etc Embryo/fetus: No toxicological effects (Not teratogenic)
Dog	90-day subacute toxicity study	0, 100, 1,000, 10,000 ppm M: 0, 2.95, 29.3, 301 F: 0, 3.07, 32.7, 314	M: 2.95 F: 3.07	M: 29.3 F: 32.7	F/M: Increase in ALP, etc
	One-year chronic toxicity study	0, 60, 200, 6,000 ppm M: 0, 1.61, 5.34, 166 F: 0, 1.57, 5.58, 178	M: 5.34 F: 5.58	M: 166 F: 178	F/M: Increased absolute/relative liver weight, Centrilobular hypertrophy of hepatocytes, etc
ADI			NOAEL: 5.34 SF: 100 ADI: 0.053		
The critical study for setting ADI			One-year chronic toxicity study in dogs		

M, Male; F, Female; F/M, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F<sub>1</sub>M, Male in F<sub>1</sub> generation; F<sub>1</sub>F, Female in F<sub>1</sub> generation; -, LOAEL was not derived; <sup>1)</sup>, The adverse effect observed at LOAEL; ADI, Acceptable daily intake; SF, Safety factor

*Adverse effects possibly elicited by a single oral administration*

Species	Study	Dose (mg/kg bw/day)	NOAEL and end point for establishing acute reference dose (ARfD) <sup>1)</sup> (mg/kg bw/day)
Rabbit	Developmental toxicity study	0, 100, 300, 1,000	Maternal: 300 Maternal: Depressed body weight gain, lower feed consumption (gestation day 6 to 9)
ARfD			NOAEL: 300 SF: 100 ARfD: 3
The critical study for setting ARfD			Developmental toxicity study in rabbits

<sup>1)</sup>, The adverse effect observed at LOAEL; ARfD, Acute reference dose; SF, Safety factor