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

Risk Assessment Report

Mefentrifluconazole

(Pesticides)

Food Safety Commission of Japan (FSCJ)

January 2020

ABSTRACT

FSCJ conducted the risk assessment of a triazole fungicide, mefentrifluconazole (CAS No. 1417782-03-6), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (wheat and soybean), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive activity (rats), developmental toxicity (rats and rabbits), genotoxicity, plasma concentration in 90-day studies in rats, mice and dogs, and toxicity studies of a metabolite F022.

Major adverse effects of mefentrifluconazole observed are suppressed body weight, hypertrophy and necrosis of hepatocytes in the liver (mice). Mefentrifluconazole showed no neurotoxicity, carcinogenicity, teratogenicity and genotoxicity.
Slight decreases in number of implantations in F1 dams and decrease in number of offspring were observed in the two-generation reproductive toxicity study in rats.

Based on the above results, FSCJ identified the relevant substance for the residue definition for dietary risk assessment in agricultural products and in livestock products to be mefentrifluconazole (parent compound only) and mefentrifluconazole and its metabolite F022 (including the conjugate), respectively.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 3.5 mg/kg bw/day in an 18-month carcinogenicity study in mice. FSCJ specified an acceptable daily intake (ADI) of 0.035 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL/LOAEL for potential adverse effects of a single oral administration of mefentrifluconazole was 600 mg/kg bw obtained in an acute neurotoxicity study in rats. FSCJ considered it unnecessary to specify an acute reference dose (ARfD), since the NOAEL was above the cut-off level (500 mg/kg bw).

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

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, 400, 1 200, 3 600 ppm M: 0, 27.2,76.3, 256 F: 0, 30.4, 90.5, 314	M: 27.2 F: 30.4	M: 76.3 F: 90.5	M/F: Increased ALP
	Combined two-year chronic toxicity/carcinogenicity study	0, 100, 600, 3 600 ppm M: 0, 4.6, 28.5, 185 F: 0, 6.4, 41.4, 312	M: 4.6 F: 41.4	M: 28.5 F: 312	M/F: Increased ALP (No carcinogenicity)
	Two-generation reproductive toxicity study	0, 25, 75, 200 PM: 0, 24.1, 72.2, 191 PF: 0, 24.3, 72.9, 194 F_1M: 0, 23.9, 72.1, 192 F_1F: 0, 24.1, 72.2, 193	Parent PM: 24.1 PF: 24.3 F_1M: 23.9 F_1F: 24.1 Offspring PM: 72.2 PF: 72.9 F_1M: 72.1 F_1F: 72.2 Reproductive ability PM: 72.2 PF: 72.9 F_1M: 72.1 F_1F: 72.2	Parent PM: 72.2 PF: 72.9 F_1M: 72.1 F_1F: 72.2 Offspring PM: 191 PF: 194 F_1M: 192 F_1F: 193 Reproductive ability PM: 191 PF: 194 F_1M: 192 F_1F: 193	Parent: Increased ALP Offspring: Suppressed body weight Reproductive toxicity: Decreased number of implantation
	Developmental toxicity study	0, 50, 150, 400	Dams: 150 Fetuses: 400	Dams: 400 Fetuses: -	Dams: Suppressed body weight, decreased feed intake Fetuses: No toxic effect (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 10, 50, 250, 750 ppm M: 0, 2, 11, 58, 174 F: 0, 3, 15, 67, 211	M: 2 F: 15	M: 11 F: 67	M/F: Increase in absolute- and relative-weight of the liver, centrilobular and diffuse hypertrophy of hepatocytes in the liver, decreased T.Chol.
	18-month carcinogenicity study	M: 0, 20, 50, 200 ppm M/F: 0, 20, 50, 250 ppm	M: 3.5 F: 4.9	M: 9.1 F: 12.6	M: Hepatocellular fatty change (macro vesicular) F: Suppressed body weight (No carcinogenicity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
		M: 0, 3.5, 9.1, 36.8 F: 0, 4.9, 12.6, 61.5			
Rabbit	Developmental toxicity study	0, 5, 15, 25	Dams: 25 Fetuses: 25	Dams: - Fetuses: -	Dams: No toxicity Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 15, 90, 180	M: 15 F: 90	M: 90 F: 180	M/F: Eosinophilic changes in centrilobular hepatocytes, Increased ALP
	One-year chronic toxicity study	0, 10, 30, 150	M: 30 F: 30	M: 150 F: 150	M/F: Centrilobular/diffuse hypertrophy of hepatocytes
ADI			NOAEL: 3.5 SF: 100 ADI: 0.035		
The critical study for setting ADI			18-month carcinogenicity study in mice		

ADI, Acceptable daily intake; SF, Safety factor;
-, LOAEL could not be specified
[1)], The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw/day) [1]
Rat	Acute toxicity study	F: 2 000	- Crouching, poor performance status, piloerection
	Acute neurotoxicity study	0, 200, 600, 2 000	M/F: 600 M/F: Coordination disorder (unsteady gait), decreased locomore activity
ARfD			Specification not required (above the cut-off value (500 mg/kg bw))

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