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

Risk Assessment Report

Metominostrobin (Second edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
August 2021

ABSTRACT

The FSCJ conducted a risk assessment of metominostrobin (CAS No. 133408-50-1), a strobilurin fungicide, based on submitted documents. For this second edition, additional test results were submitted by the Ministry of Health, Labour and Welfare including residues in soil and residues in crops (mangoes).

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of metominostrobin were observed in the liver (including centrilobular hepatocellular hypertrophy), in the kidneys (including chronic progressive nephropathy) and blood (anemia). No effect on fertility was observed, nor was genotoxicity or immunotoxicity.

In a two-year combined chronic toxicity/carcinogenicity study in rats, increases in frequency of hepatocellular adenoma and large granular lymphocytic (LGL) leukemia were observed. However, the mode of action was considered to be non-genotoxic, and it was deemed possible to establish a threshold for evaluation.

In addition, although LGL leukemia is prevalent in Fischer rats, it is rare in humans and the characteristics of the tumor are significantly different from those in rats; therefore, it is considered that the increase in this tumor cannot be extrapolated to humans.

In a developmental toxicity study in rabbits, an increase in skeletal mutation was observed, whereas no increase in skeletal, external, or internal anomalies were observed. No adverse effect was observed in fetuses of rats. Consequently, metominostrobin was considered to have no teratogenicity.

Based on these results, metominostrobin (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and fishery products.

The lowest no-observed-adverse-effect level (NOAEL) from these studies was 1.6 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 0.016 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The NOAEL and lowest-observed-adverse-effect level (LOAEL) values were compared for potential adverse effects of a single oral administration of metminostrobin, of which the lowest value was a NOAEL of 78.1 mg/kg bw based on general pharmacology tests in mice and rabbits. The FSCJ specified an acute reference dose (ARfD) to be 0.78 mg/kg bw by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Rat	90-day subacute toxicity study	0, 50, 2 500, 5 000, 10 000 ppm M: 0, 3.3, 167, 335, 687 F: 0, 3.6, 178, 343, 68	M: 3.3 F: 3.6 M/F: Centrilobular hepatocellular hypertrophy, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 35, 350, 3 500 ppm M: 0, 1.6, 16.3, 167 F: 0, 1.9, 19.7, 212	M: 1.6 F: 1.9 F: Altered hepatocellular foci M: Glomerulosclerosis, etc. (Increased in frequency of hepatocellular adenoma and LGLleukemia in the male group administered 3 500 ppm)
	Two-generation reproductive toxicity study	0, 30, 300, 3 000 ppm PM: 0, 2.2, 22.6, 225 PF: 0, 2.5, 24.7, 244 F_1M: 0, 2.5, 25.2, 273 F_1F: 0, 2.8, 27.7, 289	Parent PM: 2.2 PF: 24.7 F_1M: 2.5 F_1F: 27.7 Offspring: PM: 22.6 PF: 24.7 F_1M: 25.2 F_1F: 27.7 Parent: M: Hyalin casts in the kidney, etc. F: Centrilobular hepatocellular hypertrophy, etc. Offspring: Centrilobular hepatocellular hypertrophy, etc. (No effect on fertility is observed.)
	Developmental toxicity study	0, 25, 75, 225	Dams: 25 Fetuses: 225 Dams: Increase in corrected and relative liver weights, etc. Fetuses: No adverse effect from administration is observed. (No teratogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Mouse	90-day subacute toxicity study	0, 300, 3 000, 10 000 ppm M: 0, 34.1, 348, 1 200 F: 0, 38.4, 384, 1 310	M: 34.1 F: 38.4 M: Hepatomegaly F: Periportal hepatocyte hypertrophy
	18-month carcinogenicity study	0, 30, 300, 3 000 ppm M: 0, 2.88, 30.5, 312 F: 0, 2.70, 26.9, 279	M: 2.88 F: 2.70 M/F: Periportal hepatocellular hypertrophy, etc. (No carcinogenicity is observed.)
Dog	90-day subacute toxicity study	0, 3, 120, 480	M: 3 F: 3 M/F: Centrilobular hepatocellular hypertrophy, etc.
	One-year chronic toxicity study	0, 2, 30, 300	M: 2 F: 2 M/F: Increased ALP, etc.
Rabbit	Developmental toxicity study	0, 30, 150, 750	Dams: 30 Fetuses: 150 Dams: Decreased body weight/suppressed body weight gain, decreased food intake Fetuses: Excess ribs (No teratogenicity is observed.)
ADI			NOAEL: 1.6 SF: 100 ADI: 0.016
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study (rat)

ADI, Acceptable daily intake; ALP, Alkaline phosphatase; LGLL, Large granular lymphocytic leukemia; 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 metominostrobin*

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 toxicity study	M/F: 0, 300, 390, 507, 659, 857, 1 114, 1 448	M/F: - Decreased locomotor activity, muscle hypotonia
Mouse	General pharmacological study (General condition)	M/F: 0, 78.1, 313, 1 250, 5 000	M: 78.1 M: Decreased locomotor activity
	Acute toxicity study	M/F: 0, 600, 780, 1 014, 1 318, 1 714, 2 228, 2 896	M: 780 F: 600 M/F: Decreased locomotor activity
	Micronucleus test	M/F: 125, 250, 500, 1 000	M/F: 125 M/F: Decreased locomotor activity
Rabbit	General pharmacological study (General condition)	M: 0, 78.1, 313, 1 250, 5 000	78.1 Decreased locomotor activity, hypotonia of limb and abdominal muscle, abnormal gait, etc.
	General pharmacological study (Electroencephalogram)	M: 0, 8.1, 78.1, 313, 1 250	78.1 Slow waves
	General pharmacological study (Body temperature)	M: 0, 8.1, 78.1, 313, 1 250	313 Decreased body temperature
	General pharmacological study (Respiration, blood pressure, electrocardiogram, heart rate)	M: 0, 78.1, 313, 1 250, 5 000	313 Decreased heart rate, decreased respiratory rate, etc.
	Developmental toxicity study	0, 30, 150, 750	150 Dams: Reduced body weight, decreased food intake
ARfD			NOAEL: 78.1 SF: 100 ARfD: 0.78
The critical study for setting ARfD			General pharmacological study (mouse, rabbit)

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor

-: NOAEL could not be specified.

[1)] The adverse effect observed at LOAEL