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

Risk Assessment Report

Metobromuron

(Pesticides)

Food Safety Commission of Japan (FSCJ)
August 2022

ABSTRACT

The FSCJ conducted a risk assessment of a urea herbicide, metobromuron (CAS No. 3060-89-7), based on results from various studies.

The tests used in the assessment includes the data on fate in animals (rats), fate in plants (potatoes, lamb's lettuce, etc.), residues in crops, acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and others.

The major adverse effects of administration of metobromuron from those test results were observed in blood (hemolytic anemia). Neurotoxicity, carcinogenicity, effects on fertility, teratogenicity and genotoxicity were not observed.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.46 mg/kg bw per day in one-year chronic toxicity study in dogs. The FSCJ specified an acceptable daily intake (ADI) of 0.0046 mg/kg bw per day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of metobromuron was 1.59 mg/kg bw per day in one-year chronic toxicity study in dogs. Based on this, the FSCJ specified an acute reference dose (ARfD) of 0.015 mg /kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints [a]
Rat	Twenty eight-day subacute neurotoxicity study	0, 50, 250, 1 000 ppm M: 0, 4.16, 19.2, 73.4 F: 0, 4.32, 22.3, 81.0	M: - F: -	M: 4.16 F: 4.32	M/F: Enhancement of extramedullary hematopoiesis in the spleen
	Ninety-day subacute neurotoxicity study	0, 25, 100, 250 ppm M: 0, 1.51, 6.00, 15.0 F: 0, 1.80, 7.06, 18.0	M: 1.51 F: 1.80	M: 6.00 F: 7.06	M/F: Hemosiderin deposits in the spleen, etc.
	Two-year chronic toxicity study	0, 5, 15, 50, 150, 250 ppm M: 0, 0.3, 0.8, 2.7, 8.0, 16.4 F: 0, 0.3, 1.0, 3.3, 10.4, 19.5	M: 2.7 F: 1.0	M: 8.0 F: 3.3	M: Increase of Heinz bodies, hemosiderin deposits in the spleen, etc. F: Decrease of Hb, RBC and Ht
	Twenty four-month carcinogenicity study	0, 5, 15, 50, 150 ppm M: 0, 0.26, 0.8, 2.6, 7.9 F: 0, 0.34, 1.0, 3.4, 9.9	M: 2.6 F: 3.4	M: 7.9 F: 9.9	M/F: Hemosiderin deposits in the liver and the spleen, etc. (No carcinogenicity is observed.)
	Two-generation reproductive toxicity study	0, 15, 50, 150 ppm PM: 0, 1.36, 4.53, 13.5 PF: 0, 1.49, 4.98, 15.1 F_1M: 0, 1.59, 5.29, 16.0 F_1F: 0, 1.69, 5.71, 17.5	Parent: PM: 1.36 PF: 1.49 F_1M: 1.59 F_1F: 1.69 Offspring: PM: 13.5 PF: 15.1 F_1M: 16.0 F_1F: 17.5	Parent: PM: 4.53 PF: 4.98 F_1M: 5.29 F_1F: 5.71 Offspring: PM: - PF: - F_1M: - F_1F: -	Parent M/F: Hemosiderin deposits in the spleen Offspring M/F: No toxicity (No effect on fertility is observed.)
	Developmental toxicity study	0, 10, 30, 90	Dams: 10 Fetuses: 30	Dams: 30 Fetuses: 90	Dames: Decline of incremental rate of adjusted body weight and decreased food consumption Fetuses: Thoracic vertebrae with dumbbell-shaped body and unossified 13th rib (No teratogenicity is observed.)
Mouse	Twenty eight-day	0, 50, 200, 800 ppm	M: - F: -	M: 11.7	M/F: Increase of Heinz bodies,

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints [a]
	subacute neurotoxicity study	M: 0, 11.7-16.7, 45.7-70.1, 189-256 F: 0, 13.6-16.8, 50.3-59.6, 243-257		F: 13.6	etc.
	Twenty four-month carcinogenicity study	0, 3, 12, 50 ppm M: 0, 0.8, 3, 12 F: 0, 0.8, 3, 12	M: 0.8 F: 0.8	M: 3 F: 3	M/F: Increase of Heinz bodies, etc. (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study	0, 10, 30, 100	Dams: 30 Fetuses: 30	Dams: 100 Fetuses: 100	Dams: Death, decreased body weight/suppressed body weight gain, decreased food consumption, etc. Fetuses: Decreased number of live fetuses, etc. (No teratogenicity is observed.)
Dog	Ninety-day subacute toxicity study	0, 20, 80, 250 ppm M: 0, 0.651, 2.69, 8.27 F: 0, 0.696, 2.98, 9.71	M: 2.69 F: 2.98	M: 8.27 F: 9.71	M/F: Decrease of RBC and MCHC, increase of Heinz bodies, etc.
	One-year chronic toxicity study	0, 5, 15, 50, 250 ppm M: 0, 0.16, 0.46, 1.59, 7.88 F: 0, 0.18, 0.54, 1.71, 8.49	M: 0.46 F: 0.54	M: 1.59 F: 1.71	M/F: Increase of Heinz bodies, etc.
ADI			NOAEL: 0.46 SF: 100 ADI: 0.0046		
The critical study for setting ADI			One-year chronic toxicity study (dog)		

ADI: Acceptable daily intake, NOAEL: No-observed-adverse-effect level, SF: Safety factor, Hb: haemoglobin, RBC: Red Blood Cell, Ht: hematocrit MCHC: Mean Corpuscular Hemoglobin Concentration

-: NOAEL nor LOAEL could not be specified.

[a]: The adverse effect observed at LOAEL.

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

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD[1)] (mg/kg bw or mg/kg bw per day)
Rat	General pharmacological study (General condition) Multidimensional observation Test	M/F: 0, 100, 500, 1 000	M/F: 100 M/F: Decrease of grooming frequency, decrease in locomotor activities, decrease of pain reaction, abnormal posture, abnormal gait, decrease of righting reflex, decrease of grip strength, half closed eyelid, miosis, etc.
	Acute toxicity study	M/F: 500, 1 000, 2 000, 3 000, 5 000, 6 000	M/F: - M/F: Calming, difficult breathing , exophthalmos, unkempt fur and crouching
	Acute toxicity study	F: 2 000	- Decrease in locomotor activities and slow respiration
	Acute neurotoxicity study	M/F: 0, 30, 100, 300	M: 30 F: 100 M: Suppressed body weight gain F: Suppressed body weight gain and decreased momentum in locomotor activities
Mouse	General pharmacological study (General condition) Irwin Test	M/F: 0, 100, 1 000, 2 000	M/F: 100 M/F: Decrease of anaphylaxia, decrease in locomotor activities, decrease of righting reflex, half closed eyelid, etc.
	General pharmacological study (Central nervous system) Momentum in locomotive activities	M: 0, 100, 1 000, 2 000	100 Decreased momentum in locomotor activities
	Acute toxicity study	M/F: 775, 1 290, 2 150, 3 170, 3 590	M/F: - M/F: Calming, difficult breathing , exophthalmos, unkempt fur, crouching and abdominal position
Dog	One-year chronic toxicity study	0, 5, 15, 50, 250 ppm --- M: 0, 0.16, 0.46, 1.59, 7.88 F: 0, 0.18, 0.54, 1.71, 8.49	M: 1.59 F: 1.71 M/F: Increase of MetHb

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD[1)] (mg/kg bw or mg/kg bw per day)
ARfD			NOAEL: 1.59 SF: 100 ARfD: 0.015
The critical study for setting ARfD			One-year chronic toxicity study (dog)

ARfD: Acute reference dose, SF: Safety factor, NOAEL: No-observed-adverse-effect level, MetHb: Methemoglobinemia

-: NOAEL could not be specified.

[1)] : The adverse effect observed at LOAEL.