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

Risk Assessment Report

Bentazone

(Pesticides)

Food Safety Commission of Japan (FSCJ)
June 2021

ABSTRACT

The FSCJ conducted a risk assessment of bentazone (bentazone, CAS No. 25057-89-0; bentazone sodium, CAS No. 50723-80-3) a heterocyclic herbicide, based on submitted documents.

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

Major adverse effects of bentazone and bentazone sodium were observed in body weight (suppressed weight gain), blood (prolonged coagulation) and the kidneys (including increased blood urea nitrogen levels and increased kidney weight). No carcinogenicity, effect on fertility, teratogenicity, biologically relevant genotoxicity or immunotoxicity was observed.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained from these studies for bentazone and bentazone sodium was 9 mg/kg bw per day in a combined two-year chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.09 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of bentazone and bentazone sodium was 50 mg/kg bw in an acute neurotoxicity study in rats. The FSCJ specified an acute reference dose (ARfD) of 0.5 mg/kg bw by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
Rat	90-day subacute toxicity study (the 1st study)	0, 70, 200, 800, 1 600 ppm M: 0, 5, 14, 54, 128 F: 0, 6, 16, 62, 120	M: 128 F: 120 M/F: No toxicity
	90-day subacute toxicity study (the 2nd study)	0, 400, 1 200, 3 600 ppm M: 0, 25.3, 77.8, 243 F: 0, 28.9, 86.1, 258	M: 77.8 F: 86.1 M: Extended PT and APTT, etc. F: Suppressed body weight gain, etc.
	90-day subacute toxicity study (the 4th study) [a)]	0, 475, 1 430, 4 280 ppm M: 0, 31, 91, 290 F: 0, 42, 98, 304	M: 91[76] F: 98[82] M: Suppressed body weight gain, extended PT and APTT, etc. F: Suppressed body weight gain, increased absolute and relative kidney weights, etc.
	90-day subacute neurotoxicity study	0, 300, 1 000, 3 500 ppm M: 0, 21.9, 73.6, 258 F: 0, 27.0, 86.4, 306	M: 258 F: 306 M/F: No toxicity (No subacute neurotoxicity is observed.)
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 200, 800, 4 000 ppm Twenty-six-week interim sacrifice group M: 12, 47, 233 F: 14, 55, 274 Fifty-six-week interim sacrifice group M: 0, 9, 39, 197 F: 0, 12, 48, 249 Carcinogenicity group M: 0, 9, 35, 180 F: 0, 11, 45, 244	M: 9 F: 11 M/F: Increased water intake, increased BUN levels, extended APTT, etc. (No carcinogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	Two-generation reproductive toxicity study	0, 200, 800, 3 200 ppm PM: 0, 14.8, 58.5, 238 PF: 0, 17.0, 66.9, 269 F_1M: 0, 13.7, 56.9, 227 F_1F: 0, 15.9, 64.4, 262	Parent: PM: 58.5 PF: 66.9 F_1M: 56.9 F_1F: 64.4 Offspring: PM: 14.8 PF: 17.0 F_1M: 13.7 F_1F: 15.9 Parent and offspring: Suppressed body weight gain (No effect on fertility is observed.)
	Developmental toxicity study (the 1st study)	0, 40, 100, 250	Dams and fetuses: 100 Dams: Decreased feed intake Fetuses: Increased postimplantation loss, low body weight, etc. (No teratogenicity is observed.)
Mouse	Two-year combined chronic toxicity/carcinogenicity study	0, 100, 400, 2 000 ppm M: 0, 12, 47, 242 F: 0, 12, 48, 275	M: 12 F: 48 M: Extended PT, etc. F: Nodular hyperplasia of thehepatocytes (No carcinogenicity is observed.)
	82- to 95-week carcinogenicity study	0, 100, 350, 1 600 ppm M: 0, 8.4, 29.7, 138 F: 0, 9.5, 34.3, 153	M: 138 F: 153 M/F: No toxicity (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study (the 1st study)	0, 75, 150, 375	Dams: 150 Fetuses: 375 Dams: Decreased food intake Fetuses: No toxicity (No teratogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
Dog	90-day subacute toxicity study (the 1st study)	0, 100, 300, 1 000, 3 000 ppm	M/F: 40 M/F: Suppressed bodyweight gain, etc.
		M: 0, 4, 12, 40, 115 F: 0, 4, 12, 40, 113	
	90-day subacute toxicity study (the 2nd study)	0, 15, 50, 150	M/F: 50 M/F: Increased AST and ALT, etc.
	One-year chronic toxicity study	0, 100, 400, 1 600 ppm	M: 13.1 F: 13.2
		M: 0, 3.04, 13.1, 49.7 F: 0, 3.29, 13.2, 54.8	M/F: Extended APTT, etc.
ADI (cRfD)			Bentazone NOAEL: 9 SF: 100 ADI: 0.09
The critical study for setting ADI (cRfD)			Two-year combined chronic toxicity/carcinogenicity study (the 1st study) (rat)

ADI, Acceptable daily intake; ALT, Alanine transaminase; APTT, Activated partial thromboplastin time; AST, Aspartate aminotransferase time; BUN, Blood urea nitrogen; cRfD, Chronic reference dose; NOAEL, No-observed-adverse-effect level; PT, Prothrombin time; SF, Safety factor; UF, Uncertainty factor

[1)] The adverse effect observed at LOAEL.

[a)] Bentazone sodium administration, [ ]: Expressed as bentazone equivalent

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

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	200, 400, 800, 1 000, 1 250, 1 600	- Dyspnea, piloerection, etc.
		500, 640, 800, 1 000, 1 250	- Dyspnea, tremor, etc.
		500, 640, 800, 1 000, 1 250, 1 600, 2 000	800 Dyspnea, etc.
		1 500, 1 800, 2 160, 2 592, 3 110, 3 732	- Decrease in locomotor activity, irregular respiration, etc.
		M/F: 825, 1 210, 1 780, 2 610	M/F: - M/F: Dyspnea, etc.
		M/F: 562, 825, 1 210, 1 780, 2 610	M/F: 562 M/F: Dyspnea, piloerection, etc.
	Acute toxicity study [a)]	800, 1 000, 1 250, 1 600, 2 000	- Dyspnea
		900, 1 080, 1 296, 1 555, 1 866	- Decrease in locomotor activity, staggering gait, irregular respiration, etc.
	Acute neurotoxicity study	M/F: 50, 150, 400	M: 50 F: 150 M: Decrease in locomotor activity F: Decrease in exploration, decrease in movement, etc.
	Developmental toxicity study (the 1st study)	0, 40, 100, 250	Fetuses: 100 Fetuses: Increased postimplantation loss, etc.
Mouse	Acute toxicity study	510, 714, 1 000, 1 200, 1 400, 1 680, 1 960	- Suppressed locomotor activity, tremor, etc.
	Acute toxicity study [a)]	909, 1 000, 1 100, 1 210, 1 331	- Decrease in locomotor activity, clonic convulsion, irregular respiration, etc.

Guinea pig	Acute toxicity study	M/F: 400, 800, 1 200, 1 600, 3 200	M/F: 400 Death
	Acute toxicity study [a)]	640, 800, 1 000, 1 250, 1 600	1 000 Collapse (prone position, side position), tachypnea, etc.
Cat	Acute toxicity study	250, 500, 1 000, 2 000	250 Staggering gait, vomiting, tremor, etc.
ARfD			NOAEL: 50 SF: 100 ARfD: 0.5
The critical study for setting ARfD			Acute neurotoxicity study in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor
[1)] The adverse effect observed at LOAEL
[a)] Administered bentazone sodium