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

Risk Assessment Report

Benzpyrimoxan

(Pesticides)

Food Safety Commission of Japan (FSCJ)
December 2019

ABSTRACT

FSCJ conducted the risk assessment of an insecticide, benzpyrimoxan (CAS No. 1449021-97-9), based on various documents.

The data used in the assessment include fate in animals (rats), livestock (goats and chicken), fate in plants (paddy rice), residues in plants, 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), and genotoxicity. The data on metabolite M4 were also included.

Major adverse effects of benzpyrimoxan observed are suppressed body weight, anemia, increased liver weight and hepatocellular hypertrophy, obstructive nephropathy and epithelial hyperplasia of renal pelvis. Renal toxicity observed in rats and mice was caused by crystal formation in the urinary tract. Benzpyrimoxan showed no neurotoxicity, carcinogenicity, teratogenicity and genotoxicity.

In a two-generation reproductive activity study, a decrease in survival rate of offspring in F_1 and F_2 generations and a slight decrease in birth rate of a dam in F_1 generation were observed. These findings were considered to be secondary effects of poor nursing on dams affected with the suppressed body weight by the treatment.

From the above results, FSCJ identified benzpyrimoxan and its metabolite M4 as the relevant substance for the residue definition for dietary risk assessment in agricultural products, while benzpyrimoxan (parent compound only) as that for dietary risk assessment in livestock products and fishery products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 2.68 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.026 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of benzpyrimoxan was 10 mg/kg bw/day obtained in developmental toxicity studies in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.1 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

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, 100, 300, 1 000, 3 000 ppm M: 0, 6.26, 18.7, 64.2, 194 F: 0, 7.41, 22.2, 78.1, 227	M: 18.7 F: 22.2	M: 64.2 F: 78.1	M/F: Crystal in the renal pelvis
	Combined two-year chronic toxicity/carcinogenicity study	0, 60, 300, 1 500 ppm Chronic toxicity study group: M: 0, 2.66, 13.9, 68.7 F: 0, 3.56, 17.5, 90.1 Carcinogenicity study group: M: 0, 2.29, 11.7, 59.4 F: 0, 2.92, 14.7, 77.9	M: 11.7 F: 14.7	M: 59.4 F: 77.9	M/F: Obstructive nephropathy (No carcinogenicity)
	Two-generation reproductive activity study	0, 60, 300, 2 000 ppm PM: 0, 3.12, 15.5, 105 PF: 0, 4.66, 23.6, 156 F1M: 0, 3.59, 18.2, 125 F1F: 0, 4.95, 25.0, 171	Parent: PM: 15.5 PF: 23.6 F1M: 18.2 F1F: 25.0 Offspring: F_1M: 15.5 F_1F: 23.6 F2M: 18.2 F2F: 25.0	Parent: PM: 105 PF: 156 F1M: 125 F1F: 171 Offspring: F_1M: 105 F_1F: 156 F2M: 125 F2F: 171	Parent: M/F: Suppressed body weight Offspring: Suppressed body weight
	Developmental toxicity study	0, 10, 50, 250	Dams: 50 Fetuses: 250	Dams : 250 Fetuses: -	Dams: Suppressed body weight, decreased feed intake Fetuses: No toxicity (No teratogenicity)
Mouse	90-day subacute toxicity study	M: 0, 400, 2 000, 4 000 ppm F: 0, 400, 2 000, 6 000 ppm M: 0, 56.4, 282, 523 F: 0, 66.1, 327, 971	M: 56.4 F: 66.1	M: 282 F: 327	M: Single cell necrosis in the liver F: Obstructive nephropathy
	78-week carcinogenicity study	M: 0, 80, 400, 2 000 ppm F: 0, 80, 400, 1 500 ppm	M: 7.7 F: 44.4	M: 39.9 F: 163	M: Increased incidence of gallstone.

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
		M: 0, 7.7, 39.9, 195 F: 0, 8.9, 44.4, 163			F: Centrilobular hepatocellular vacuolation (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 3, 10, 30	Dams and Fetuses: 10	Dams and Fetuses: 30	Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Dog	90-day subacute toxicity study	0, 100, 500, 2 500 ppm M: 0, 2.92, 14.6, 70.6 F: 0, 2.68, 14.3, 67.3	M: 2.92 F: 2.68	M: 14.6 F: 14.3	M/F: Increased T.Chol. and PL
	One-year chronic toxicity study	0, 100, 500, 2 500 ppm M: 0, 2.92, 14.6, 70.6 F: 0, 2.68, 14.3, 67.3	M: 2.92 F: 2.68	M: 14.6 F: 14.3	M/F: pigmentation in hepatocytes
ADI			NOAEL: 2.68 SF: 100 ADI: 0.026		
The critical study for setting ADI			One-year chronic toxicity study in dogs		

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
-, NOAEL or LOAEL could not be specified
[1)], The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]
Rat	Acute toxicity study	M: 2 000	- M/F: Tubular/collecting duct dilatation
	Acute neurotoxicity study	M/F: 0, 500, 1 000, 2 000	M: 500 M: Suppressed body weight
	Developmental toxicity study	0, 10, 50, 250	Dams: 50 Dams: Suppressed body weight, decreased feed intake
Rabbit	Developmental toxicity study	0, 3, 10, 30	Dams: 10 Dams: Decreased body weight/Suppressed body weight, decreased feed intake
ARfD			NOAEL: 10 SF: 100 ARfD: 0.1
The critical study for setting ADI			Developmental toxicity study in rabbits

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