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

Risk Assessment Report

Ethaboxam (2nd edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of a thiazole carboxamide fungicide, ethaboxam (CAS No. 162650-77-3), based on various documents. In addition to the data used for the first edition, the results of residue in crops (head cabbage and broccoli), acute neurotoxicity study (rats), 28-day subacute transdermal toxicity study (rats), genotoxicity study and 28-day immunotoxicity study were newly available in the present assessment.

The data used in the assessment include fate in animals (rats), fate in plants (grapes and potatoes), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity (rats), and mechanism of testicular toxicity in rats.

Major adverse effects of ethaboxam observed are testicular toxicity including seminiferous tubular atrophy (rats), hepatocellular hypertrophy and anemia (dogs). Ethaboxam showed no neurotoxicity, genotoxicity relevant to human health and immunotoxicity.
In two-generation reproductive toxicity study in male rats, decreases in mating ratio, insemination ratio and fertility ratio, and lowered sperm motility were observed as treatment-related changes. In developmental toxicity study in rats, increased incidences of organ malformations or anomalies and skeletal variations were observed in fetuses. No-observed-adverse-effect levels (NOAELs) for both studies were determined. Incidence of testicular interstitial cell adenomas was increased in male rats in a carcinogenicity study. However, a genotoxic mechanism was unlikely involved in the tumor induction and it was considered possible to establish a threshold dose in the assessment.
FSCJ identified ethaboxam (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest NOAEL obtained in all tests was 5 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.05 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of ethaboxam was the NOAEL of 75 mg/kg bw/day obtained in a developmental toxicity in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.75 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

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, 200, 650, 2 000 ppm M: 0, 16.3, 49.7, 154 F: 0, 17.9, 58.0, 164	M: 16.3 F: 17.9	M: 49.7 F: 58.0	M: Abnormal spermatogenic cells in epididymis F: Increase in relative and corrected* weight of the liver *: values adjusted for bodyweight as covariate
	90-day subacute neurotoxicity study	0, 250, 600, 1 500 ppm M: 0, 18, 43, 106 F: 0, 21, 50, 122	M: 43 F: 122	M: 106 F: -	M: Suppressed body weight, decreased feed intake F: No toxicity (No subacute neurotoxicity)
	Combined two-year chronic toxicity/carcinogenicity study	0, 100, 300, 650 ppm M: 0, 5.5, 16.4, 35.8 F: 0, 7.0, 21.0, 45.5	M: 5.5 F: 21.0	M: 16.4 F: 45.5	M: Decreased absolute weight of the epididymides F: Suppressed body weight (Increased incidence of testicular interstitial cell adenomas)
	Two-generation reproduction activity study	0, 65, 200, 650 ppm PM: 0, 5.2, 16.2, 52.6 PF: 0, 5.7, 17.6, 56.1 F_1M: 0, 5.8, 17.7, 60.4 F_1F: 0, 6.2, 18.5, 60.7	Parent, Offspring, Reproductive activity PM: 16.2 PF: 17.6 F_1M: 17.7 F_1F: 18.5	Parent, Offspring, Reproductive activity PM: 52.6 PF: 56.1 F_1M: 60.4 F_1F: 60.7	Parent and offspring: Suppressed body weight (Reproductive activity: decreases in mating ratio, insemination ratio and fertility ratio)
	Developmental toxicity study (the 1st study)	0, 100, 300, 1 000 ppm	Dams: 100 Fetuses: -	Dams: 300 Fetuses: 100	Dams: Suppressed body weight Fetuses: Low body weight (Increased incidences of organ malformations or anomalies, and of skeletal variations)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Developmental toxicity study (the 2nd study)	0, 10, 30, 100, 300	Dams: 30 Fetuses: 100	Dams: 100 Fetuses: 300	Dams: Increased alopecia on the back Fetuses: Increased incidences of variations (No teratogenicity)
	Comprehensive evaluation of developmental toxicity study (the 1st study) and (the 2nd study).		Dams: 30 Fetuses: 30	Dams: 100 Fetuses: 100	Dams: Increased alopecia on the back Fetuses: Low body weight
Mouse	90-day subacute toxicity study	0, 200, 450, 1 000, 2 500 ppm M: 0, 33, 74, 163, 405 F: 0, 41, 93, 195, 483	M: 33 F: 93	M: 74 F: 195	M/F: Centrilobular hypertrophy of hepatocytes
	18-month carcinogenicity study	0, 100, 300, 900 ppm M: 0, 11.8, 35.0, 117 F: 0, 13.8, 43.8, 135	M: 35.0 F: 43.8	M: 117 F: 135	M/F: Suppressed body weight (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 25, 75, 125	Dams: 25 Fetuses: 125	Dams: 75 Fetuses: -	Dams: Decreased feed intake Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 15, 40, 100	M/F: -	M/F: 15	M/F: Suppressed body weight
	One-year chronic toxicity study	0, 5, 10, 30	M/F: 5	M/F: 10	M/F: Hypertrophy of hepatocytes
ADI			NOAEL: 5 SF: 100 ADI: 0.05		
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 ethaboxam*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day)[1)]
Rat	Acute neurotoxicity study	0, 300, 1 000, 2 000	M: 300 F: 1 000 M/F: Suppressed body weight
	Developmental toxicity study (the 1st study)	0, 100, 300, 1 000	Dams: 300 Dams: Suppressed body weight, decreased feed intake
	Developmental toxicity study (the 2nd study)	0, 10, 30, 100, 300	Dams: 100 Dams: Suppressed body weight, decreased feed intake
	Micronucleus test	0, 500, 1 000, 2 000	M: - Piloerection, hypersensitive behavior, gait abnormality
Rabbit	Developmental toxicity study	0, 25, 75, 125	Dams: 75 Dams: Suppressed body weight, decreased feed intake
ARfD			NOAEL: 75 SF: 100 ARfD: 0.75
The critical study for setting ARfD			Developmental toxicity study in rabbits

ARfD; Acute reference dose, NOAEL; No-observed-adverse-effect level, SF; Safety factor
-: NOAEL could not be observed.
1) The adverse effect observed at LOAEL