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

Risk Assessment Report

Trinexapac-ethyl

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2022

ABSTRACT

The FSCJ conducted the risk assessment of trinexapac-ethyl (CAS No. 95266-40-3), a cyclohexanedione plant growth regulator, based on results from various documents. In the revision of the second edition, the additional data of the following studies were submitted by the Ministry of Health, Labour and Welfare: fate in animals (goats and chicken), residues in crops (paddy rice and wheat), residues in livestock (cattle and chicken) and acute neurotoxicity (rats).

The test results used in the assessment include the data on fate in animals (rats, goats and chicken), fate in plants (paddy rice, wheat, etc.), residues in crops, acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity(rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity (mice), and others.

The major adverse effects of triexapac-ethyl in those test results were body weight (suppressed weight), kidney (renal tubule epithelium cell brown pigmentation, etc. in rats). No adverse effects were observed in the tests of carcinogenicity, teratogenicity, genotoxicity, immunotoxicity or effects on fertility.

Consequently, the FSCJ identified trinexapac-ethyl (parent compound) and metabolite B as the relevant substances for the residue definition on dietary risk assessment in agricultural products and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.59 mg/kg bw per day in two-generation reproductive toxicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.0059 mg/kg bw per day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for possible adverse effects of a single oral administration was 60 mg/kg bw in developmental toxicity study in rabbits. Accordingly, the FSCJ specified an acute reference dose (ARfD) to be 0.6 mg/kg bw by applying a safety factor of 100 to the NOAEL.

Table 1. *Levels relevant to toxicological evaluation of trinexapac-ethyl*

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Rat	90-day subacute toxicity study	0, 50, 500, 5 000, 20 000 ppm	M: 34 F: 395
		M: 0, 3, 34, 346, 1 350 F: 0, 4, 38, 395, 1 550	M: Renal tubular with crystal deposits F: Suppressed weight gain, etc.
	90-day subacute neurotoxicity study	3 750, 7 500, 15 000 ppm	M: 948 F: 1 170
		M: 233, 463, 948 F: 294, 588, 1 170	M/F: No toxicity (No subacute neurotoxicity is observed)
	Two-year combined chronic toxicity/carcinogenicity study	0, 10, 100, 3 000, 10 000, 20 000 ppm	M: 116 F: 147 M/F: Decrease of urine pH
		M: 0, 0.38, 3.87, 116, 393, 806 F: 0, 0.49, 4.88, 147, 494, 1 050	(No carcinogenicity is observed)
	Two-generation reproductive toxicity	0, 10, 1 000, 10 000, 20 000 ppm	Parent: PM: 0.59 PF: 737 F_1M: 0.59 F_1F: 765 Offspring: PM: 595 PF: 737 F_1M: 592 F_1F: 765 Parent: Suppressed weight gain, etc. Offspring: Low body weight, etc. (No effect on fertility is observed)
		PM: 0, 0.59, 60.0, 595, 1 170 PF: 0, 0.75, 74.8, 737, 1 410 F_1M: 0, 0.59, 59.1, 592, 1 260 F_1F: 0, 0.77, 77.2, 765, 1 560	
	Developmental toxicity study	0, 20, 200, 1 000	Dams and Fetuses: 1 000 Dams and Fetuses: No toxicity (No teratogenicity is observed)
Mouse	90-day subacute toxicity study	0, 10, 100, 1 000, 10 000 ppm	M: 1 550 F: 1 970
		M: 0, 1.6, 15.4, 161, 1 550 F: 0, 2.0, 19.8, 194, 1 970	M/F: No toxicity
	18-month carcinogenicity study	0, 7, 70, 1 000, 3 500, 7 000 ppm	M: 912 F: 1 070
		M: 0, 0.91, 9.01, 131, 451, 912 F: 0, 1.08, 10.7, 154, 539, 1 070	M/F: No toxicity (No carcinogenicity is observed)

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Rabbit	Developmental toxicity study	0, 10, 60, 360	Dams: 10 Fetuses: 60 Dams: Suppressed weight gain Fetuses: Decrease of fetus survival rates, etc. (No teratogenicity is observed)
Dog	90-day subacute toxicity study	0, 50, 1 000, 15 000, 30 000 ppm	M: 516 F: 582
		M: 0, 2.0, 34.9, 516, 927 F: 0, 1.9, 39.8, 582, 891	M/F: Diffuse chronic thymic atrophy, etc.
	One-year developmental toxicity study	0, 40, 1 000, 10 000, 20 000 ppm	M: 31.6 F: 1.37
		M: 0, 1.56, 31.6, 366, 727 F: 0, 1.37, 39.5, 357, 784	M: Mucous faces and Bloody faces, etc. F: Decrease of absolute and relative uterus weights
ADI		NOAEL: 0.59 SF: 100 ADI: 0.0059	
The critical study for setting ADI		Two-generation reproductive toxicity (rat)	

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake
[1)] The adverse effect observed at LOAEL

Table 2. *Potential adverse effects of a single oral administration of trinexapac-ethyl*

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	5 000	M: - F: Death
	Acute neurotoxicity study	0, 500, 1 000, 2 000	M/F: 1 000 M: Suppressed weight gain, decreased feed consumption F: Suppressed weight gain
Rabbit	Developmental toxicity study	0, 10, 60, 360	Dams: 60 Fetuses: 60 Dams: Suppressed weight gain Fetuses: Increased post-implantation mortality rate and decrease of survival fetuses
ARfD			NOAEL: 60 SF: 100 ARfD: 0.6
The critical study for setting ARfD			Developmental toxicity study (rabbit)

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