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

Risk Assessment Report

Tioxazafen

(Pesticides)

Food Safety Commission of Japan (FSCJ)
September 2020

ABSTRACT

FSCJ conducted the risk assessment of a nematicide, tioxazafen (CAS No. 330459-31-9) composing of an oxadiazole ring in its structure, based on various documents.

The data used in the assessment include fate in animals (rats, mice and goats), fate in plants (soybean and maize), residues in crops, acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, mechanism of liver tumor induction (mice), and immunotoxicity (mice).

Major adverse effects of tioxazafen observed are increased organ weight and hypertrophy of hepatocytes in the liver, suppressed body weight, vacuolation of the adrenal cortex (rats), and increased bone in the metaphysis of femur (rats). Tioxazafen showed no reproduction toxicity, teratogenicity, genotoxicity or immunotoxicity.
In a combined two-year chronic toxicity/carcinogenicity study in mice, increased incidences of hepatocellular carcinomas in male and of hepatocellular adenomas in female were observed. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and FSCJ considered it possible to establish a threshold dose in the assessment.
FSCJ identified tioxazafen and its metabolite TX2 as the relevant substances for the residue definition for dietary risk assessment in agricultural products, livestock products.

The lowest no-observed-adverse-effect level (NOAEL) in all tests was 5 mg/kg bw/day in a two-generation reproductive toxicity study in rats and in developmental toxicity study in rabbits. 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 tioxazafen was 50 mg/kg bw/day obtained in developmental toxicity studies in rats. If an acute reference dose (ARfD) is specified based on this NOAEL applying a safety factor of 100, an ARfD of 0.5 mg/kg bw will be calculated. Meanwhile, no NOAEL could be determined for male and females rats in the acute neurotoxicity study and its LOAEL was 250 mg/kg bw. Even if an additional factor of 5 is added to a usual safety factor of 100 considering lack of NOAEL and findings observed at the LOAEL, an ARfD will be calculated to be 0.5 mg/kg bw, the same as that specified based on the NOAEL in developmental

toxicity study in rats. Therefore FSCJ considered that 0.5 mg/kg bw is a reliable value for ARfD. In conclusion, FSCJ specified ARfD to be 0.5 mg/kg bw based on the acute neurotoxicity study and the developmental toxicity study in rats.

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

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, 10, 50, 250, 750, 1 500 ppm M: 0, 1, 3, 16, 47, 91 F: 0, 1, 4, 19, 55, 113	M: 16 F: 19	M: 47 F: 55	M/F : Increased bone in the metaphysis of femur
	90-day subacute neurotoxicity study	0, 100, 300, 1 000 ppm M: 0, 7, 20, 67 F: 0, 8, 24, 75	M: 20 F: 8	M: 67 F: 24	M/F: Suppressed body weight, decreased feed intake (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study	0, 5, 25, 75, 250, 750 ppm M: 0, 0.3, 1.3, 3.9, 13.3, 39.6 F: 0, 0.3, 1.6, 4.9, 16.0, 48.1	M: 13.3 F: 16.0	M: 39.6 F: 48.1	M/F: Suppressed body weight, decreased feed intake (No carcinogenicity)
	Two-generation reproductive toxicity study	PM：0, 5, 21, 62 PF：0, 5, 20, 61 F_1M：0, 5, 21, 63 F_1F：0, 5, 21, 62	Parent: PM: 5 PF: 20 F_1M: 5 F_1F: 21 Offspring PM: 62 PF: 61 F_1M: 63 F_1F: 62	Parent PM: 21 PF: 61 F_1M: 21 F_1F: 62 Offspring PM：- PF：- F_1M：- F_1F：-	Parent: M: Vacuolation of zona fasciculata cells in the adrenals F: Suppressed body weight, decreased feed intake Offspring: No toxicity was observed (No effect on reproductive activity)
	Developmental toxicity study	0, 10, 50, 200	Dams: 10 Fetuses: 200	Dams: 50 Fetuses: -	Dams: Suppressed body weight, decreased feed intake Fetuses: No toxicity was observed. (No teratogenicity)
Mouse	28-day subacute toxicity study	0, 20, 100, 300, 1 000, 3 000 ppm	M: 58 F: 70	M: 184 F: 219	M/F: Increase in the absolute and relative

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
		M: 0, 4, 19, 58, 184, 437 F: 0, 5, 25, 70, 219, 399			weight of the liver, and centrilobular hypertrophy of hepatocytes.
	90-day subacute toxicity study	0, 10, 50, 200, 600, 1 250 ppm	M: 259 F: 54.4	M: - F: 174	M: No toxicity was observed F: Increased T.Bil, centrilobular hypertrophy of hepatocytes
		M: 0, 2.1, 10.3, 42.2, 125, 259 F: 0, 2.6, 13.8, 54.4, 174, 319			
	78-week carcinogenicity study	0, 5, 50, 250, 750, 1 750 (only male) ppm	M: 40.9 F: 10.2	M: 119 F: 49.7	M/F: Hypertrophy of hepatocytes, brown pigmentation in macrophage (M: increased incidences of hepatocellular carcinomas F: increased incidence of hepatocellular adenomas)
		M: 0, 0.8, 8.0, 40.9, 119, 281 F: 0, 1.0, 10.2, 49.7, 153			
Rabbit	Developmental toxicity study	0, 5, 20, 100	Dams: 5 Fetuses: 100	Dams: 20 Fetuses: -	Dams: Suppressed body weight, decreased feed intake Fetuses: No toxicity was observed. (No teratogenicity)
Dog	90-day subacute toxicity study	0, 1, 3, 10, 40, 120	M: 10 F: 40	M: 40 F: 120	M/F: Increased WBC and Neutrophils
ADI			NOAEL: 5 SF: 100 ADI: 0.05		
The critical study for setting ADI			1) Two-generation reproductive toxicity study in rats 2) Developmental toxicity study in rabbits		

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 tioxazefen*

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, 250, 750, 2 000	M/F: - M: Decreased locomotive activity F: Decreased locomotive activity, lowered body temperature
	Developmental toxicity study	0, 10, 50, 200	Dams: 50 Dams: suppressed body weight, decreased feed intake
ARfD and The critical study for setting ARfD			1) Acute neurotoxicity study in rats LOAEL: 250 SF: 500 2) Developmental toxicity study in rats NOAEL: 50 SF: 100 ARfD: 0.5

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