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

Risk Assessment Report

Tolpyralate

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of an herbicide acting as an inhibitor of 4-4-hydroxyphenyl propionic acid oxygenase (4-HPPDase), tolpyralate (CAS No. 1101132-67-5), based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (maize), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (mice and rats), two-generation reproductive activity (rats), developmental toxicity (rats and rabbits), genotoxicity, and immunotoxicity (mice). The data also include mechanisms on various toxicities observed by the treatment including increased incidence of anomaly in rats, liver or thyroid effects in rats and mice or involvement of increased levels of blood thyroxine concentration by this 4-HPPD inhibitor in the toxicities.

Major adverse effects of tolpyralate observed are keratitis in the eye, vacuolation in the molecular layer of the cerebellum (rats), basophilic change in the renal tubules, hepatocellular hypertorophy, and gallbladder stone (mice). Tolpyralate showed no teratogenicity and genotoxicity. Hence, FSCJ considered it possible to establish a threshold dose in the assessment. The incidences of corneal squamous papillomas and corneal squamous cell carcinoma increased by the treatment in a two-year carcinogenicity study in rats. FSCJ considered this tumor induction attributable to persisted inflammation, but not a genotoxic mechanism.

From the above results, FSCJ identified the relevant substance for the residue definition for dietary risk assessment in agricultural products to be tolpyralate (parent compound only).

The lowest value of the no-observed-adverse-effect level (NOAEL) in all test was 0.323 mg/kg bw/day based hyaline droplets in renal tubules in 90-day subacute toxicity study in rats, while the NOAEL in a two-year carcinogenicity study in rats was 0.765 mg/kg bw/day. FSCJ considered the toxicological significance of this renal lesion to be low because of no reproducibility of this lesion or no enhancement

of renal toxicity in the two-year carcinogenicity study. Therefore, it is appropriate to choose the value of 0.765 mg/kg bw/day as the NOAEL in rats. There was no NOAEL specified in a carcinogenicity study in mice, and its lowest-observed-adverse-effect level (LOAEL) was 7.25 mg/kg bw/day. Considering the fact that this value of LOAEL in mice was approximately 10 times higher than the NOAEL in rats, FSCJ predicted that the value of the NOAEL in rats covers the level of NOAEL in mice.

Taken together, FSCJ specified an acceptable daily intake (ADI) of 0.0076 mg/kg bw/day based on the NOAEL in two-year carcinogenicity study in rats applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of tolpyalate was 10 mg/kg bw/day obtained in developmental toxicity studies in rats. 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 tolpyralate*

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, 5, 20, 2 000, 20 000 ppm M: 0, 0.323, 1.34, 133, 1 360 F: 0, 0.380, 1.58, 159, 1 650	M: 0.323 F: 1.58	M: 1.34 F: 159	M: Increased hyaline droplets in renal proximal tubules F: Keratitis and others
	90-day subacute neurotoxicity study	0, 20, 560, 16 000 ppm M: 0, 1.31, 37.7, 1 040 F: 0, 1.63, 42.6, 1 230	M: 1.31 F: 1.63	M: 37.7 F: 42.6	M/F: Keratitis and others (No subacute neurotoxicity)
	One-year chronic toxicity study	0, 5, 20, 2 000, 10 000 (M), 20 000 (F) ppm M: 0, 0.229, 0.925, 97.0, 482 F: 0, 0.303, 1.18, 126, 1 340	M: 0.925 F: 1.18	M: 97.0 F: 126	M/F: Keratitis and others
	Two-year carcinogenicity study	0, 5, 20, 2 000, 10 000 ppm M: 0.196, 0.765, 83.8, 426 F: 0.255, 1.01, 108, 554	M: 0.765 F: 1.01	M: 83.8 F: 108	M/F: Keratitis and others (No carcinogenicity)
	Two-generation reproduction study	0, 5, 50, 1 000 ppm PM: 0, 0.270, 2.70, 54.9 PF: 0, 0.41, 4.27, 81.8 F_1M: 0, 0.297, 3.07. 63.3 F_1F: 0, 0.438, 4.57, 90.2	Parent PM: 2.70 PF: 4.27 F_1M: 3.07 F_1F: 4.57 Offspring PM: 2.70 PF: 4.27 F_1M: 3.07 F_1F: 4.57	Parent PM: 54.9 PF: 81.8 F_1M: 63.3 F_1F: 90.2 Offspring PM: 54.9 PF: 81.8 F_1M: 63.3 F_1F: 90.2	Parent: PF: Keratitis and others Offspring: Suppressed body weight (No effects on reproductive activity)
	Developmental toxicity study	0, 1, 10, 500	Dams: 10 Fetuses: 10	Dams: 500 Fetuses: 500	Dams: Suppressed body weight, decreased feed intake Fetuses: low body weight, increased skeletal variations (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 50, 500, 2 000, 7 000 ppm	M: 284 F: 331	M: 1 060 F: 81.5	M: hypertrophy of follicular epithelial cells of the thyroid and others

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
		M: 0, 7.17, 70.8, 284, 1 060 F: 0, 7.94, 81.5, 331, 1 180			F: localized hepatocellular necrosis and others.
	18-month carcinogenicity study	0, 70, 700, 7 000 ppm M: 0, 7.37, 78.5, 793 F: 0, 7.25, 72.6, 732	M: - F: -	M: 7.37 F: 7.25	M/F: Gallbladder stone (No carcinogenicity)
Rabbit	Developmental toxicity study (the 1st study)	0, 0.5, 5, 500	Dams: 5 Fetuses: 5	Dams: 500 Fetuses: 500	Dams: Suppressed body weight Fetuses: Increased skeletal variations (No teratogenicity)
Dog	90-day subacute toxicity study	0, 200, 2 000, 20 000 ppm M: 0, 6.47, 64.6, 699 F: 0, 6.98, 65.3, 671	M: 64.6 F: 65.3	M: 699 F: 671	M: hyperostosis of hindlimb and nasal bone and others F: Keratitis and others
	One-year chronic toxicity study	0, 100, 1 000, 10 000 ppm M: 0, 2.91, 28.1, 321 F: 0, 2.62, 28.5, 295	M: 28.1 F: 28.5	M: 321 F: 295	M: the eye mucosa mucosal edema and congestion and others F: Increased ALT and ALP
ADI			NOAEL: 0.765 SF: 100 ADI: 0.0076		
The critical study for setting ADI			Two-year carcinogenicity study in rats		

ADI: Acceptable daily intake, NOAEL: No-observed-adverse-effect level, SF: Safety factor

1) The adverse effect observed at LOAEL

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

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, 500, 1 000, 2 000	M: 1 000 M: Suppressed body weight
	Developmental toxicity study	0, 1, 10, 500	Dams: 10 Dams：Decreased body weight and decreased feed intake
ARfD			NOAEL: 10 SF: 100 ARfD: 0.1
The critical study for setting ARfD			Developmental toxicity study in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;

1) The adverse effect observed at LOAEL