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

Risk Assessment Report

Teflubenzuron

(2nd edition)
(Pesticides and Veterinary medicinal products)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of teflubenzuron (CAS No. 83121-18-0), a benzoylphenylurea insecticide, based on various documents. New data on analyses of residue in crops (leaf of chrysanthemum) were submitted for the present assessment.

The data used in the assessment are on: fate in animals (rats and others), fate in plants (soybean, spinach and others), residues in crops, subacute toxicity (rats, mice, dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and mechanisms of hepatocarcinogenicity in mice.

Major adverse effects of teflubenzuron observed are: hepatocellular hypertrophy, hepatocellular necrosis, and altered cell foci of hepatocytes. No effects on reproductive ability, teratogenicity or genotoxicity were observed.

In a carcinogenicity study, an incidence of hepatocellular adenoma was increased in male mice. However, studies on the mechanism suggested that the carcinogenicity was unlikely to be attributable to genotoxic mechanism. Therefore, FSCJ considered it possible to establish a threshold dose in the assessment.

Based on the results from various studies, FSCJ specified the residue definition for this dietary risk assessment in agricultural products to be teflubenzuron (parent compound only).

The lowest NOAEL in the toxicological studies was 2.1 mg/kg body weight/day in a 78 weeks carcinogenicity study in mice. FSCJ specified the acceptable daily intake (ADI) to be 0.021 mg/kg body weight per day. The safety factor of 100 was applied to this NOAEL
Since any toxicological effect that would be likely to be elicited by a single dose of teflubenzuron was not observed, FSCJ considered it unnecessary to specify the ARfD.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	90-day subacute toxicity study	0, 100, 1 000, 10 000 ppm M: 0, 8.02, 81.6, 809 F: 0, 9.12, 94.0, 942	M: 8.02 F: 9.12 M/F: Increased AST
	Combined 120-week chronic toxicity/carcinogenicity study	0, 20, 100, 500 ppm M: 0, 1.0, 4.8, 24.8 F: 0, 1.2, 5.9, 29.9	M: 4.8 F: 5.9 M/F: Altered cell foci of hepatocyte (clear cell) (No carcinogenicity was observed)
	Combined two-year chronic toxicity/carcinogenicity study	0, 2,500, 10 000 ppm M: 0, 122, 487 F: 0, 154, 615	M: - F: - M/F: Altered cell foci of hepatocyte (basophilic type) (No carcinogenicity was observed)
	Two-generation reproductive toxicity study (the 1st study)	0, 20, 100, 500 ppm PM: 0, 1.5, 7.4, 36.9 PF: 0, 1.6, 8.1, 40.0 F_1M: 0, 1.9、9.6、48.2 F_1F: 0, 2.1, 10.5, 53.4 USA: M: 0, 1.5～1.9, 7.4～9.6, 39.6～48.2 F: 0, 2.2～2.5, 1.8～12.4, 54.9～61.5	Parent PM: 36.9 PF: 40.0 F_1M: 48.2 F_1F: 53.4 Offspring PM: 36.9 PF: 40.0 F_1M: 48.2 F_1F: 53.4 Dams and fetuses: No toxic effect (No effect on reproductivity)
	Two-generation reproductive toxicity study (the 2nd study)	0, 100, 10 000, 50 000 ppm PM: 0, 7.0, 713, 3 680 PF: 0, 10.7, 1 070, 5 060 F1M: 0, 7.5, 791, 4 150 F1F: 0, 9.5, 966, 5 060	Parent PM: 713 PF: 5,060 F_1M: 791 F_1 F: 5,060 Offspring

[1] Major adverse effect observed at LOAEL

			PM: 7.0 F_1M: 7.5 PF: 10.7 F_1F: 9.5 Parent M: Suppressed body weight F: No toxic effect Offspring: Suppressed body weight (No effect on reproductivity)
	Developmental toxicity study (the 1st study)	0, 10, 50, 250	Dams and fetuses: 250 Dams and fetuses: No toxic effect (No teratogenicity was observed)
	Developmental toxicity study (the 2nd study)	0, 100, 300, 1 000	Dams and fetuses: 1,000 Dams and fetuses: No toxic effect (No teratogenicity was observed)
Mice	90-day subacute toxicity study	0, 100, 1 000, 10 000 ppm M：0, 11.9, 115, 1 210 F：0, 13.7, 143, 1 450	M: 11.9 F: 13.7 M/F: Centrilobular hypertrophy of hepatocytes
	78-week carcinogenicity study	0, 15, 75, 375 ppm (Interim sacrifice group) M: 0, 2.1, 10.9, 61.2 F: 0, 3.4, 15.6, 74.7 (Ultimate sacrifice group) M：2.1, 10.5, 53.6 F：3.1, 15.4, 71.7	M: 2.1 F: 15.4 M/F: Hepatocellular necrosis (Increased incidence of hepatocellular adenomas in male)
Rabbits	Developmental toxicity study (the 1st study)	0, 10, 50, 250	Dams and fetuses: 250 Dams and fetuses: No toxic effect (No teratogenicity was observed)

	Developmental toxicity study (the 2nd study)	0, 1 000	Dams: - Fetuses: 1 000 Dams: Macroscopic findings of the liver (grossly granulated cut surface) Fetuses: No toxic effect (No teratogenicity was observed)
Dogs	90-day subacute toxicity study	0, 100, 1 000, 10 000 ppm M：0, 3.45, 33.7, 318 F：0, 3.97, 42.8, 417	M: 33.7 F: 3.97 M: Increased AST F: Focal gastritis
	90-day subacute toxicity study	0, 30, 100 ppm M: 0, 1.24, 4.42 F: 0, 1.49, 5.07	M: 4.42 F: 5.07 M/F: No toxic effect
	One-year chronic toxicity study	0, 30, 100, 500 ppm M: 0.98, 3.15, 17.3 F: 1.16, 4.02, 18.0	M: 17.3 F: 18.0 M/F: No toxic effect
ADI (cRfD)			NOAEL: 2.1 SF: 100 ADI: 0.021
The critical study for setting ADI			Mice 78-week carcinogenicity study

NOAEL, No-observed-adverse-effect level; LOAEL, Lowest-observed-adverse-effect level; SF, Safety factor; UF, Uncertainty factor; ADI, Acceptable Daily Intake; cRfD, Chronic Reference Dose
[1)], The adverse effect observed at LOAEL
－, NOAEL could not be specified