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

Risk Assessment Report

Tebufenpyrad

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2018

ABSTRACT

FSCJ conducted a risk assessment of tebufenpyrad (CAS No. 119168-77-3), an acaricide containing a pyrazole ring, based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (crab apples and eggplants), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and mechanism of liver tumor in rats.

Major adverse effects of tebufenpyrad observed are suppressed body weight and increased organ weight of the liver. Tebufenpyrad showed no adverse effects on reproductivity and teratogenicity, and no genotoxicity relevant to human health
Increases in the incidence of hepatocellular adenomas in male rats were identified in a two-year combined chronic toxicity/carcinogenicity test. However, a genotoxic mechanism was unlikely to be involved in the tumor development. It was thus considered possible to establish a threshold in the assessment.

Based on the results from various studies, tebufenpyrad (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 0.82 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity test in rats. FSCJ specified an acceptable daily intake (ADI) of 0.0082 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for adverse effects which are likely elicited by a single oral administration of tebufenpyrad was 12.5 mg/kg bw obtained in a general pharmacological study in rabbits (general symptoms and respiration rate). However, this NOAEL was obtained from the study used small number animals (three animals) and one sex (females only). Similar NOAEL to this study was obtained from a developmental toxicity study in rabbits and the NOAEL of this study was 15 mg/kg bw/day. Comprehensively judging these facts, FSCJ considered it is appropriate to specify the ARfD on the basis of the NOAEL obtained in the developmental toxicity study. Thus, FSCJ specified the ARfD as 0.15 mg/kg bw applying the safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 10, 100, 400 ppm M: 0, 0.69, 6.81, 29.0 F: 0, 0.72, 7.27, 31.6	M: 0.69 F: 0.72 M/F: Increase in absolute and relative weight of the liver
	Two-year combined chronic toxicity/carcinogenicity study	0, 5, 20, 150, 300 ppm M: 0, 0.21, 0.82, 6.52, 13.4 F: 0, 0.26, 1.01, 8.13, 17.0	M: 0.82 F: 1.01 M/F: Suppressed body weight (M: Increased incidence of hepatocellular adenomas)
	Two-generation reproductive toxicity study	0, 20, 100, 200 ppm PM: 0, 1.67, 8.32, 16.68 PF: 0, 1.92, 9.60, 19.39 F_1M: 0, 1.67, 8.39, 16.82 F_1F: 0, 1.90, 9.63, 19.31	Parent PM: 8.32 PF: 19.4 F_1M: 8.39 F_1F: 19.3 Offspring PM: 8.32 PF: 9.60 F_1M: 8.39 F_1F: 9.63 Parent M: Suppressed body weight and decreased feed consumption F: No toxic effect was observed Offspring Suppressed body weight (No effect on reproductivity)
	Developmental toxicity study (the 1st study)	0, 15, 50, 150	Parent: 15 Fetuses: 50 Dams: Suppressed body weight Fetuses: Low body weight, delayed ossification (No teratogenicity was observed)
	Developmental toxicity study (the 2nd study)	0, 15, 50, 90	Parent: 15 Fetuses: 15 Dams: Suppressed body weight and increase in water intake Fetuses: Increased skeletal

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1)]
			variations (increased accessory 14th ribs) (No teratogenicity was observed)
Mouse	90-day subacute toxicity study	0, 30, 300, 1 200 ppm M：0, 4.39, 40.9, 176 F：0, 5.77, 56.2, 211	M：4.39 F：5.77 M/F：Increase in absolute and relative weight of the heart
	18-month carcinogenicity study	0, 30, 500, 1 000 ppm M: 0, 3.6, 64.4, 132 F: 0, 4.2, 71.3, 162	M: 4.39 F: 5.77 M/F: Suppressed body weight (No carcinogenicity was observed)
Rabbit	Developmental toxicity study	0, 5, 15, 40	Dams: 15 Fetuses: 40 Dams: Suppressed body weight Fetuses: No toxic effect (No teratogenicity was observed)
Dog	90-day subacute toxicity study (the 1st study)	0, 1, 3, 6	M/F: 6 M/F: No toxic effect
	90-day subacute toxicity study (the 2nd study)	0, 2, 10, 20	M/F: 2 M/F: Vomiting and diarrhea/ loose stool
	12-month chronic toxicity study	0, 1, 6, 20	M/F: 1 M/F: Vomiting and chronic gastritis
ADI			NOAEL: 0.82 SF: 100 ADI: 0.0082
The critical study for setting			Two-year combined chronic toxicity/carcinogenicity study in rats

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

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

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)]
Rat	Acute toxicity study	M: 81 M/F : 128, 320, 506, 800, 1 265	M: 81 F: - M/F: Prone position, decreased motor activity
	Acute toxicity study	F: 50, 300, 2 000	F: 50 F: Decreased locomotive activity, staggering walk
	Developmental toxicity study (the 1st study)	0, 15, 50, 150	Dams: 50 Dams: Suppressed body weight
Mouse	General pharmacology (General status)	0, 25, 50, 100, 200, 400, 800	M/F: 50 M/F: Cognitive function decline, decreased motor activity
	Acute toxicity study	M: 81 M/F: 128, 161, 202, 320, 506, 800	M/F: - M/F: Ataxia, lethargy
Rabbit	General pharmacology (General status)	M : 0, 12.5, 25, 50, 100	M: 12.5 M: Behavioral disorder
	General pharmacology (Respiration rate)	M: 0, 6.25, 12.5, 25, 100	M: 12.5 M: Decreased respiration rate
	Developmental toxicity study	0, 5, 15, 40	Dams: 15 Dams: Suppressed body weight, decreased feed consumption
ARfD			NOAEL: 15 SF: 100 ARfD: 0.15
The critical study for setting ARfD			Developmental toxicity study in rabbits

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