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

Risk Assessment Report

Pydiflumetofen

(Pesticides)

Food Safety Commission of Japan (FSCJ)
November 2019

ABSTRACT

FSCJ conducted the risk assessment of an insecticide, pydiflumetofen (CAS No. 1228284-64-7), based on various documents.

The data used in the assessment include fate in animals (rats, mice and rabbits), fate in plants (wheat and tomatoes), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction (rats), developmental toxicity (rats and rabbits), genotoxicity, and MoA study of liver tumor in mice.

Blood concentration of pydiflumentofen was measured in 90-day toxicity studies in rats, mice and dogs, and a developmental toxicity study in rabbits. Since the blood concentration of pydiflumetofen showed non-linear temporal changes in these studies, their absorption in these studies seemed to be saturated. The results of blood concentration also indicated species difference and sex difference of the blood level where females showed higher concentrations except in dogs. Blood concentration was not measured in chronic toxicity or carcinogenicity studies in rats or mice, or reproductive or developmental toxicity studies in rats.

Major adverse effects of pydiflumetofen observed are suppressed body weight, increased organ weight and hypertrophy of hepatocytes in the liver, and increased organ weight in the thyroid. Pydiflumetofen showed no effects on reproductive activity, teratogenicity and genotoxicity relevant to human health. In a carcinogenicity study, an increased incidence of hepatocellular adenomas and carcinomas in male mice was observed. However, studies on the mechanism and genotoxicity suggested that a genotoxic mechanism was unlikely to be involved in tumor induction, thus FSCJ considered it possible to establish a threshold dose in the assessment. Moreover, study on the MoA suggested hepatocarcinogenesis of pydiflumetofen in mice was little exploitable into human.

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

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 9.9 mg/kg bw/day in a combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.099 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of pydiflumetofen was 30 mg/kg bw/day obtained from maternal toxicity in developmental toxicity studies in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.3 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

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, 250, 1 500, 8 000, 16 000 ppm M: 0, 18.6, 111, 578, 1 190 F: 0, 21.6, 127, 727, 1 330	M: 18.6 F: 127	M: 111 F: 727	M/F: Hepatocellular hypertrophy, hypertrophy of follicular epithelial cell of the thyroid
	Two-year combined chronic toxicity/carcinogenicity study	M: 0, 200, 1 000, 6 000 ppm F: 0, 150, 450, 1 500 ppm M: 9.9, 51.0, 319 F: 10.2, 31.0, 102	M: 9.9 F: 10.2	M: 51.0 F: 31.0	M/F: Suppressed body weight, decreased feed intake (No carcinogenicity)
	Two-generation reproductive activity study	M: 0, 150, 750, 4 500 ppm F: 0, 150, 450, 1 500 ppm PM: 0, 9.1, 46.1, 277 PF: 0, 11.9, 36.1, 116 F_1M: 0, 11.9, 59.1, 364 F_1F: 0, 14.1, 42.4, 141	Parent: PM: 46.1 PF: 116 F_1M: 59.1 F_1F: 141 Offspring PM: 46.1 PF: 36.1 F_1M: 59.1 F_1F: 42.4	Parent PM: 277 PF: - F_1M: 364 F_1F: - Offspring PM: 277 PF: 116 F_1M: 364- F_1F: 141	Parent: M: Increase in the absolute and corrected weight of the liver. F: No toxicity Offspring: Suppressed body weight (No effect on reproductive activity)
	Developmental toxicity study	0, 10, 30, 100	Dams: 30 Fetuses: 100	Dams: 100 Fetuses: -	Dams: Suppressed body weight Fetuses: No toxicity (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 100, 500, 4 000, 7 000 ppm M: 0, 17.5, 81.6, 630, 1 160 F: 0, 20.4, 106, 846, 1 480	M: 81.6 F: 846	M: 630 F: 1 480	M/F: Increased Chol, Increase in the absolute and relative weight of the liver.
	80-week carcinogenicity study	0, 75, 375, 2 250 ppm M: 0, 9.2, 45.4, 288 F: 0, 9.7, 48.4, 306	M: 45.4 F: 48.4	M: 288 F: 306	M/F: Suppressed body weight, decreased feed intake (M: Increased incidence of hepatocellular adenomas And carcinomas)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rabbit	Developmental toxicity study	0, 10, 100, 500	Dams: 500 Fetuses: 500	Dams: - Fetuses: -	Dams/Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 30, 300, 1 000	M/F: 30	M/F: 300	M: Increased ALP and TG F: Decrease in body weight, suppressed body weight
	One-year chronic toxicity study	0, 30, 100, 300	M/F: 100	M/F: 300	M/F: Increase in the absolute, relative and corrected organ weight of the liver
ADI			NOAEL: 9.9 SF: 100 ADI: 0.099		
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study in rats.		

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 pydiflumetofen*

Species	Study	Dose# (mg/kg bw or mg/kg bw/day)	Endpoints and NOAEL (mg/kg bw or mg/kg bw/day)# for relevant to setting ARfD1)
Rat	General pharmacology (general signs)	F: 0, 100, 300, 2 000	100 M/F: abnormal gait , abnormal posture
	General pharmacology (locomotive activity)	F: 0, 100, 300, 2 000	- Decreased locomotive activity
	General pharmacology (body temperature)	F: 0, 100, 300, 2 000	100 Decreased body temperature
	Acute neurotoxicity (the 1st study)	M/F: 0 100 (F) 300 (M), 1 000, 2 000	M: 300 F: 100 M: Decreased body weight/suppressed body weight F: Decreased locomotive activity
	Acute neurotoxicity (the 2nd study)	F: 0, 100, 300, 1 000	100 Decreased locomotive activity, decreased body temperature
	Developmental toxicity	F: 0, 10, 30, 100	Dams: 30 Dams: Suppressed body weight
ARfD			NOAEL: 30 SF: 100 ARfD: 0.3
The critical study for setting ARfD			Developmental toxicity study in rats

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