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

Risk Assessment Report

Pyraflufen-ethyl (Third edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
June 2021

ABSTRACT

The FSCJ conducted a risk assessment of pyraflufen-ethyl (CAS No. 129630-19-9), a pyrazole herbicide, based on submitted documents. For this third edition, the Ministry of Health, Labour and Welfare submitted additional data including residues in crops (okras and sweet peppers, i.e., shishito peppers).

The data used in the assessment include fate in animals (rats), fate in plants (including wheat and satsuma mandarins), residues in crops, subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of pyraflufen-ethyl were in the liver (including hepatocellular hypertrophy and brown pigment deposits in Kupffer cells) and in the kidneys (including hyperplasia of transitional cell epithelium and necrosis and/or sloughing of renal papillae). Neither effect on fertility, teratogenicity nor biologically significant genotoxicity was observed.

A slight increase in hepatocellular adenoma was observed in a carcinogenicity study in mice. However, the mode of action was considered to be non-genotoxic, and it was deemed possible to establish a threshold for evaluation.

Based on these results, pyraflufen-ethyl (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 from these studies was 17.2 mg/kg bw per day in a two-year combined chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.17 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

Since there was no adverse effect likely to be elicited by a single oral administration of pyraflufen-ethyl, the FSCJ considered it unnecessary to specify an acute reference dose (ARfD).

Table 1. *Levels relevant to toxicological evaluation of pyraflufen-ethyl*

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
Rat	90-day subacute toxicity study	0, 200, 1 000, 5 000, 15 000 ppm M: 0, 17.8, 85.6, 456, 1 490 F: 0, 19.4, 95.4, 499, 1 500	M: 456 F: 499 M/F: Suppressed body weight gain, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 80, 400, 2 000, 10 000 ppm M: 0, 3.4, 17.2, 86.7, 468 F: 0, 4.4, 21.8, 112, 579	M: 17.2 F: 112 M: Increased urine volume, etc. F: Hyperplasia of transitional cell epithelium in the kidneys, etc. (No carcinogenicity is observed.)
	Two-generation reproductive toxicity study	0, 100, 1 000, 10 000 ppm PM: 0, 6.84, 70.8, 721 PF: 0, 7.78, 80.1, 813 F_1M: 0, 8.10, 82.3, 844 F_1F: 0, 9.06, 91.2, 901	Parent and offspring: PM: 70.8 PF: 80.1 F_1M: 82.3 F_1F: 91.2 Parent: Single-cell necrosis of the liver, inflammatory cell infiltration of the liver, etc. Offspring: Low body weight (No effect on fertility is observed.)
	Developmental toxicity study	0, 100, 300, 1 000	Dams: 1 000 Fetuses: 1 000 Dams and fetuses: No toxicity (No teratogenicity is observed.)
Mouse	18-month carcinogenicity study	0, 200, 1 000, 5 000 ppm M: 0, 21.0, 110, 547 F: 0, 19.6, 98.3, 524	M: 21.0 F: 19.6 Centrilobular hepatocyte hypertrophy, etc. (Increased incidence of hepatocellular adenoma)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
Rabbit	Developmental toxicity study	0, 20, 60, 150	Dams: 20 Fetuses: 150 Dams: Death Fetuses: No toxicity (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 40, 200, 1 000	M: 1 000 F: 1 000 M/F: No toxicity
	One-year chronic toxicity study	0, 40, 200, 1 000	M: 1 000 F: 1 000 M/F: No toxicity
ADI (cRfD)			NOAEL: 17.2 SF: 100 ADI: 0.17
The critical study for setting ADI (cRfD)			Two-year combined chronic toxicity/carcinogenicity study (rat)

ADI, Acceptable daily intake; cRfD, Chronic reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor; UF, Uncertainty factor

[1)] The adverse effect observed at LOAEL