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

Risk Assessment Report

Pyrimidifen

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of an insecticide (an acaricide), pyrimidifen (CAS No. 105779-78-0), based on various documents. Results of study on residues in crops (head cabbage and satsuma mandarin) were additionally presented for this assessment for new use. An acceptable daily intake (ADI) has been already specified in 2013. The present evaluation has focused on establishment of an acute reference dose (ARfD).
The data used in the assessment include fate in animals (rats), fate in plants (mandarin and apples etc.), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductivity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of pyrimidifen observed are suppressed body weight, effects on gastrointestinal tract (vomiting and watery stool in dogs), and increased organ weight in the liver and kidney. Pyridimifen showed no neurotoxicity, effects on reproductivity, teratogenicity and genotoxicity.

In a carcinogenicity study, an increased incidence of adrenal pheochromocytomas in male rats was observed. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and it was considered possible to establish a threshold dose in the assessment.
From the above results, pyridimifen (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 0.15 mg/kg bw/day in one-year chronic toxicity study in dogs. FSCJ specified an ADI of 0.0015 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. This ADI was specified in 2013.
The lowest NOAEL for potential adverse effects of a single oral administration of pyrimidifen was 4 mg/kg bw/day obtained from maternal toxicity in developmental toxicity studies in rabbits. FSCJ specified an ARfD to be 0.04 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)] Endpoint(s) at LOAEL
Rat	90-day subacute toxicity study	0, 10, 30, 100, 150 ppm M: 0, 0.600, 1.79, 5.98, 8.74 F: 0, 0.693, 2.02, 6.64, 9.43	M: 1.79 F: 2.02 M/F: Suppressed body weight, decreased feed-intake
	90-day subacute neurotoxicity study	0, 10, 30, 100 ppm M: 0, 0.68, 2.04, 6.56 F: 0, 0.81, 2.49, 7.71	M: 6.56 F: 7.71 M/F: No toxicity (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study	0, 3, 10, 30, 100 ppm M: 0, 0.101, 0.338, 1.02, 3.41 F: 0, 0.126, 0.427, 1.29, 4.47	M: 1.02 F: 0.427 M/F: Suppressed body weight (Increased adrenal pheochromocytomas in male rats)
	Two-generation reproduction study	0, 10, 30, 100 ppm PM: 0, 0.8, 2.2, 7.6 PF: 0, 0.8, 2.5, 8.3 F_1M: 0, 0.8, 2.5, 8.4 F_1F: 0, 0.9, 2.7, 9.5	Parent, Offspring PM: 2.2 PF: 2.5 F_1M: 2.5 F_1F: 2.7 Parent: M/F and Offspring: Suppressed body weight, etc. (No effect on reproductive activity)
	Developmental toxicity study	0,1, 5, 25	Dams: 5 Fetuses: 5 Dams: Suppressed body weight, etc. Fetuses: Low body weight, etc. (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 10, 30, 100, 300 ppm M: 0, 1.25, 3.96, 13.4, 39.7 F: 0, 1.77, 5.33, 17.7, 46.7	M: 13.4 F: 5.33 M: Centrilobular hypertrophy of hepatocytes in the liver F: Increase in absolute and relative weight of the liver

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)] Endpoint(s) at LOAEL
	86-week carcinogenicity study	0, 10, 30, 100, 300 ppm M: 0, 1.00, 2.84, 9.52, 27.8 F: 0, 0.896, 2.64, 9.37, 27.8	M: 9.52 F: 2.64 M/F: Suppressed body weight (No teratogenicity)
Rabbit	Developmental toxicity study	0, 1, 4, 20	Dams: 4 Fetuses: 4 Dams: Decreased body weight, suppressed body weight Fetuses: Delayed ossification (No teratogenicity)
Dog	90-day subacute toxicity study	0, 0.15, 0.5, 1.5, 4.5	M: 0.15 F: 0.15 M/F: Vomiting and watery stool
	One-year chronic toxicity study	0, 0.15, 0.75, 3.75	M: 0.15 F: 0.15 M/F: Vomiting and watery stool
ADI			NOAEL: 0.15 SF: 100 ADI: 0.0015
The critical study for setting ADI			1) One-year chronic toxicity study in dogs 2) 90-day subacute toxicity study in dogs

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 pyrimidifen*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints and NOAEL (mg/kg bw or mg/kg bw/day)[1)] for relevant to setting ARfD
Rat	Acute toxicity study	M/F: 21, 35, 60, 102, 173, 294, 500	M/F: 21 M/F: Death
Mouse	Acute toxicity study	M/F: 70, 120, 204, 346, 588, 1 000	M: 120 F: 70 M: Inactive behavior and death F: Bradypnea, Inactive behavior and death
Rabbit	Developmental toxicity study	0, 1, 4, 20	Dams: 4 Dams: Decreased/suppressed body weight
ARfD			NOAEL: 4 SF: 100 ARfD: 0.04
The critical study for setting ARfD			Developmental toxicity study in rabbits

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
[1)], The adverse effect observed at LOAEL