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

Risk Assessment Report
Permethrin

(Pesticides and Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
May 2019

ABSTRACT

FSCJconducted the risk assessment of a pyrethroid insecticides, permethrin (CAS No. 52645-53-1), based on various documents.

Permethrin consists of four different types of stereoisomers. JMPR has conducted assessment of a group of permethrin which consists of *cis*- and *trans*-isomers with the ratio 25:75 ~ 40:60, and the technical grade permethrin used as both pesticides and veterinary medicinal products in Japan consist of the *cis*- and *trans*-isomers in this range of ratio. Therefore, FSCJ conducted this assessment of a group of permethrin used as pesticides and veterinary medicinal products which consists of *cis*- and *trans*-isomers with the ratio 25:75 ~ 40:60. In addition, a group of permethrin consisting of *cis*- and *trans*-isomers in a ratio 80:20 is reported to be used for veterinary use in abroad, and JECFA and EMEA conducted the risk assessment of permethrin of this group for veterinary use. Accordingly, FSCJ also evaluated the food safety risk of permethrin for veterinary use consisting of *cis*- and *trans*-isomer in a ratio 80:20 despite that it is out of use in Japan.

The data used in the assessment include fate in animals (rats, human, cattle, goats and chicken), fate in plants (cucumbers and apples), residues in crops, residues in livestock products (cattle, pigs and chicken), subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), three-generation reproduction toxicity (rats and mice), developmental toxicity (rats and rabbits), genotoxicity and mechanisms including human relevance on liver and lung tumors in mice.
Major adverse effects of permethrin observed are tremor, suppressed body weight, liver weight increase and fatty vacuolation in hepatocyte (rats), and a restricted form of cortical degeneration/necrosis of the adrenal (dogs). Permethrin showed no effect on reproductive activity, and no teratogenicity and genotoxicity.
Increase in the incident of benign tumors in the liver and lung of female mice were observed in two-year combined chronic toxicity/carcinogenicity studies (the 2nd study in Table 1). 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, permethrin (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests, with a group of permethrin of the *cis*- and *trans*-isomers ratio 25:75 ~ 40:60, was 5 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.05 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. FSCJ considered it also appropriate to specify an ADI to be 0.05 mg/kg bw/day for 80:20 *cis:trans* permethrin by applying a safety factor of 100 to the NOAEL of 5 mg/kg bw/day comprehensively analysing the toxicological profiles of permethrin of various isomer ratios including 80:20 *cis:trans* permethrin.

The lowest NOAEL for potential adverse effects of a single oral administration of permethrin was 50 mg/kg bw/day obtained in an acute neurotoxicity study and developmental toxicity study in rats (the 1st study in Table 2). FSCJ specified an acute reference dose (ARfD) to be 0.5 mg/kg bw by applying a safety factor of 100 to the NOAEL

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	28-day subacute toxicity study	0, 200, 500, 1 000, 2 500, 5 000, 10 000 ppm	M/F: 50
		0, 20, 50, 100, 250, 500, 1 000	Tremor
	90-day subacute toxicity study	0, 50, 75, 100, 500 ppm	M/F: 50
		0, 5, 7.5, 10, 50	No toxic effect
	6-month subacute toxicity study	0, 375, 750, 1 500, 3 000 ppm	M: 92.9 F: 110
		M: 0, 22.5, 46.0, 92.9, 185 F: 0, 27.5, 52.3, 110, 221	M/F: Hypersensitivity, tremor
	28-day subacute neurotoxicity study	0, 100, 750, 1 500, 3 000, 4 000, 5 000 ppm	M/F: 38 Tremor
	90-day subacute neurotoxicity study (the 1st study)	0, 300, 1 000, 3 000 ppm	M: 63.7 F: 75.1
		M: 0, 18.4, 63.7, 195 F: 0, 22.9, 75.1, 248	M/F: Tremor, restlessness
	90-day subacute neurotoxicity study (the 2nd study)	0, 250, 1 500, 2 500 ppm	M: 15.5 F: 18.7
		M: 0, 15.5, 91.5, 150 F: 0, 18.7, 111, 190	Tremor
	90-day subacute neurotoxicity study (the 3rd study)	M: 0, 86, 160, 340 F: 0, 110, 170, 350	M: 86 F: 110 Tremor
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 20, 100, 500 ppm	M: 24.3 F: 29.7
		M: 0, 0.94, 47, 243 F: 0, 1.24, 6.0, 29.7	M/F: No toxic effect (No carcinogenicity)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 500, 1 000, 2 500 ppm	M: 41.9 F: 47.7 M/F: Tremor, hepatocellular vacuolation
		M: 0, 20.6, 41.9, 107 F: 0, 24.1, 47.7, 121	(No carcinogenicity)

[1] Major adverse effect observed at LOAEL

	Two-year combined chronic toxicity/carcinogenicity study (the 3rd study)	0, 10, 50, 250	M: 10 F: 50 M: Fatty vacuolation in hepatocyte F: Tremor (No carcinogenicity)
	Three-generation reproductive toxicity study (the 1st study)	0, 5, 30, 180	Parent: 180 Offspring: 180 Parent and offspring: No toxic effect (No effect on reproductive activity)
	Three-generation reproductive toxicity study (the 2nd study)	0, 500, 1 000, 2 500 ppm 0, 25, 50, 125	Parent: 50 Offspring: 125 Parent: Tremor Offspring: No toxic effect (No effect on reproductive activity)
	Developmental toxicity study (the 1st study)	0, 15, 50, 150	Dams: 50 Fetuses: 50 Dams: Tremor Fetuses: Low body weight, supernumerary ribs (No teratogenicity)
	Developmental toxicity study (the 2nd study)	0, 4, 41, 83	Dams: 83 Fetuses: 83 Dams and Fetuses: No toxic effect (No teratogenicity)
Mouse	28-day subacute toxicity study	0, 200, 400, 1 000, 2 000, 4 000, 80/10 000 ppm 0, 28, 56, 140, 280, 560 (Except 80/10 000 ppm administered group)	M/F: 280 Suppressed body weight
	98-week combined chronic toxicity/carcinogenicity study	0, 250, 1 000, 2 500 ppm M: 0, 26.3, 106, 269 F: 0, 29.4, 125, 316	M: 106 F: 125 M/F: Suppressed body weight (No carcinogenicity)

	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 20, 500/5 000, 100/4 000 ppm M: 0, 1.9, 54.9, 286 F: 0, 2.1, 59.3, 295	M: 1.9 F: 59.3 M/F: Heart mononuclear cell infiltration, and atrial thrombosis (No carcinogenicity)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	M: 0, 100/20, 2 500/500, 5 000/2 000 ppm F: 0, 100/20, 2 500, 5 000 ppm M: 0, 4.7, 115, 369 F: 0, 5.4, 462, 928	M: 115 F: 5.4 M: hypoplasia of testis (atrophy) F: Increase in the absolute and relative organ weight of the liver. (F: Increases in the incidence of hepatocellular adenomas and small bronchial-alveolar epithelial adenomas)
	Three-generation reproductive toxicity study	0, 300, 1 000, 3 000 ppm PM: 0, 69.7, 255, 764 PF: 0, 106, 332, 971 F_1M: 0, 70.3, 242, 688 F_1F: 0, 97.1, 318, 917 F_2M: 0, 84.3, 268, 819 F_2F: 0, 104, 371, 1 080	Parent PM: 69.7 PF: 971 F_1M: 70.3 F_1F: 917 F_2M: 84.3 F_2F: 1 080 Offspring PM: 255 PF: 332 F_1M: 242 F_1F: 318 F_2M: 268 F_2F: 371 Parent M: Suppressed body weight F: No toxic effect Offspring M/F: Suppressed body weight (No effect on reproductive activity)
Rabbit	Developmental toxicity study	0, 600, 1 200, 1 800	Dams: - Fetuses: 600 Dams: Suppressed body weight Fetuses: Increase in the post implantation embryo mortality. (No teratogenicity)

Dog	13-week subacute toxicity study	0, 10, 100, 2 000	M/F: 100 M/F: Tremor
	One-year chronic toxicity study	0, 5, 100, 2 000/1 000	M/F: 5 M: Localized degeneration/necrosis in the adrenal cortex F: Suppressed body weight
ADI (mg/kg bw/day)			NOAEL: 5 SF: 100 ADI: 0.05
The critical study for setting Toxicological ADI			One-year chronic toxicity study (dog)

ADI, Acceptable daily intake; SF, Safety factor; LOAEL, lowest-observed-adverse-effect level;
-, 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 Permethrin*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day)[1]
Rat	Acute toxicity	100, 130, 170, 220, 284, 385, 500, 650, 845, 1 000	M/F: 170 M/F: Decreased locomotor activity, piloerection, muscle spasm, and tremor.
	Acute toxicity	100, 200, 296, 384, 500, 650, 845, 1 000	M/F: 100 M/F: Decreased locomotor activity, respiratory stimulation, muscle spasm
	Acute neurotoxicity (the 1st study)	0, 10, 50, 200	M/F: 50 M/F: Tremor, decreased locomotor activity, increased auditory response
	Acute neurotoxicity (the 2nd study)	0, 10, 150, 300	M/F: 150 M/F: Tremor, ataxia
	6-month subacute toxicity	0, 375, 750, 1 500, 3 000 ppm M: 0, 22.5, 46.0, 92.9, 185 F: 0, 27.5, 52.3, 110, 221	M: 92.9 F: 110 M/F: Hypersensitivity and tremor
	90-day subacute neurotoxicity (the 1st study)	0, 300, 1 000, 3 000 ppm M: 0, 18.4, 63.7, 195 F: 0, 22.9, 75.1, 248	M: 63.7 F: 75.1 M/F: Tremor
	90-day subacute neurotoxicity (the 3rd study)	M: 0, 86, 160, 340 F: 0, 110, 170, 350	M: 86 F: 110 M/F: Tremor, irregular excitability
	Developmental toxicity (the 1st study)	0, 15, 50, 150	Dams: 50 Dams: Tremor, head shaking
Mouse	Acute toxicity	100, 130, 170, 220, 284, 385, 500, 650, 845, 1 000, 1 300, 1 700	M/F: 170 M/F: Decreased locomotor activity, piloerection, jumping, muscle spasm
	Acute toxicity	100, 200, 296, 384, 500, 650, 845, 1 000	M/F: 100 M/F: Decreased locomotor activity, piloerection, muscle spasm
Dog	13-week subacute toxicity	0, 10, 100, 2 000	M/F: 100 M/F: Tremor
	One-year chronic toxicity	0, 5, 100, 2 000/1 000	M/F:100 M/F: Convulsions, tremor
ARfD			NOAEL: 50 SF: 100 ARfD: 0.5
The critical study for setting ARfD			Acute neurotoxicity study in rats (the 1st study) Developmental toxicity study in rats (the 1st study)

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