

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 2<sup>nd</sup> 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.

Risk assessment report - Pesticides and Veterinary Medicinal Products FS/15/2019

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 1<sup>st</sup> 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

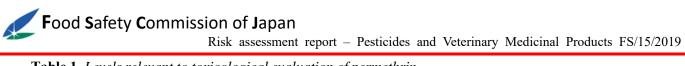
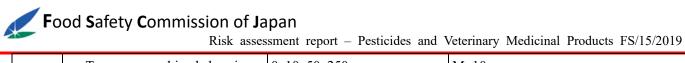


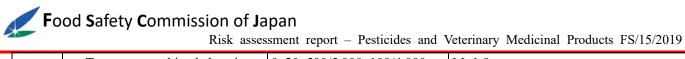
 Table 1. Levels relevant to toxicological evaluation of permethrin

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

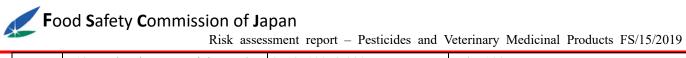
<sup>&</sup>lt;sup>1</sup> Major adverse effect observed at LOAEL



	Two-year combined chronic	0, 10, 50, 250	M: 10
	toxicity/carcinogenicity study		F: 50
	(the 3 <sup>rd</sup> study)		
			M: Fatty vacuolation in hepatocyte
			F: Tremor
			(No carcinogenicity)
	Three-generation reproductive	0, 5, 30, 180	Parent: 180
	toxicity study		Offspring: 180
	(the 1 <sup>st</sup> study)		
			Parent and offspring: No toxic effect
			(No effect on reproductive activity)
	Three-generation reproductive	0, 500, 1 000, 2 500 ppm	Parent: 50
	toxicity study (the 2 <sup>nd</sup> study)	0, 25, 50, 125	Offspring: 125
	•		Parent: Tremor
			Offspring: No toxic effect
			(No effect on reproductive activity)
	Developmental toxicity study	0, 15, 50, 150	Dams: 50
	(the 1 <sup>st</sup> study)		Fetuses: 50
			Dams: Tremor
			Fetuses: Low body weight, supernumerary
			ribs
			(No teratogenicity)
	Developmental toxicity study	0, 4, 41, 83	Dams: 83
	(the 2 <sup>nd</sup> study)		Fetuses: 83
			Dams and Fetuses: No toxic effect
			(No teratogenicity)
Mouse	28-day subacute toxicity study	0, 200, 400, 1 000, 2 000,	M/F: 280
		4 000,	
		80/10 000 ppm 0, 28, 56, 140, 280, 560	Suppressed body weight
		(Except 80/10 000 ppm	
		administered group)	
	98-week combined chronic	0, 250, 1 000, 2 500 ppm	M: 106
	toxicity/carcinogenicity study	M 0 262 106 260	F: 125
		M: 0, 26.3, 106, 269 F: 0, 29.4, 125, 316	M/F: Suppressed body weight
		2. 0, 27. 1, 123, 310	(No carcinogenicity)



	Two-year combined chronic	0, 20, 500/5 000, 100/4 000	M: 1.9
	toxicity/carcinogenicity study	ppm	F: 59.3
	(the 1 <sup>st</sup> study)		
	• •	M: 0, 1.9, 54.9, 286	M/F: Heart mononuclear cell infiltration,
		F: 0, 2.1, 59.3, 295	and atrial thrombosis
			and atrial unonnoosis
			(No carcinogenicity)
	Two-year combined chronic	M: 0, 100/20, 2 500/500,	M: 115
	toxicity/carcinogenicity study	5 000/2 000 ppm	F: 5.4
	(the 2 <sup>nd</sup> study)	F: 0, 100/20, 2 500, 5 000	
	•	ppm	M: hypoplasia of testis (atrophy)
		M: 0, 4.7, 115, 369	F: Increase in the absolute and relative
		F: 0, 5.4, 462, 928	organ weight of the liver.
		, , ,	
			(F: Increases in the incidence of
			hepatocellular adenomas and small
			bronchial-alveolar epithelial adenomas)
	Three-generation reproductive	0, 300, 1 000, 3 000 ppm	Parent
	toxicity study		PM: 69.7
		PM: 0, 69.7, 255, 764	PF: 971
		PF: 0, 106, 332, 971	$F_1M: 70.3$
		F <sub>1</sub> M: 0, 70.3, 242, 688	F <sub>1</sub> F: 917
		F <sub>1</sub> F: 0, 97.1, 318, 917	F <sub>2</sub> M: 84.3
		F <sub>2</sub> M: 0, 84.3, 268, 819	F <sub>2</sub> F: 1 080
		F <sub>2</sub> F: 0, 104, 371, 1 080	
			Offspring
			PM: 255
			PF: 332
			F <sub>1</sub> M: 242
			F <sub>1</sub> F: 318
			F <sub>2</sub> M: 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: -
	1 7 7		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
		NOAEL: 5	
ADI (mg/kg bw/day)		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; <sup>1)</sup>, 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) <sup>1</sup>
	Acute toxicity	100, 130, 170, 220, 284, 385, 500, 650, 845, 1 000	M/F: 170
		363, 300, 030, 643, 1 000	M/F: Decreased locomotor activity,
		100 200 206 204 500	piloerection, muscle spasm, and tremor.
		100, 200, 296, 384, 500,	M/F: 100
	Acute toxicity	650, 845, 1 000	M/F: Decreased locomotor activity, respiratory stimulation, muscle spasm
		0, 10, 50, 200	M/F: 50
	Acute neurotoxicity (the 1 <sup>st</sup> study)		M/F: Tremor, decreased locomotor activity, increased auditory response
	Acute neurotoxicity	0, 10, 150, 300	M/F: 150
	(the 2 <sup>nd</sup> study)		M/F: Tremor, ataxia
Rat		0, 375, 750, 1 500, 3 000	M: 92.9
			F: 110
	6-month subacute toxicity	ppm   M: 0, 22.5, 46.0, 92.9, 185   F: 0, 27.5, 52.3, 110, 221	M/F: Hypersensitivity and tremor
	00 day aula auta	0, 300, 1 000, 3 000 ppm	M: 63.7
	90-day subacute neurotoxicity	M: 0, 18.4, 63.7, 195	F: 75.1
	(the 1 <sup>st</sup> study)	F: 0, 22.9, 75.1, 248	M/F: Tremor
		M. 0. 96, 160, 240	M: 86
	90-day subacute neurotoxicity	M: 0, 86, 160, 340 F: 0, 110, 170, 350	F: 110
	(the 3 <sup>rd</sup> study)		M/F: Tremor, irregular excitability
	Developmental toxicity (the 1 <sup>st</sup> study)	0, 15, 50, 150	Dams: 50
	(the 1 study)		Dams: Tremor, head shaking
	Acute toxicity	100, 130, 170, 220, 284, 385, 500, 650, 845, 1 000,	M/F: 170
1.6		1 300, 1 700	M/F: Decreased locomotor activity, piloerection, jumping, muscle spasm
Mouse	Acute toxicity	100, 200, 296, 384, 500,	M/F: 100
		650, 845, 1 000	M/F: Decreased locomotor activity, piloerection
			muscle spasm
	13-week subacute toxicity	0, 10, 100, 2 000	M/F: 100
_	13 week subucute toxicity		M/F: Tremor
Dog	One-year chronic toxicity	0, 5, 100, 2 000/1 000	M/F:100
			M/F: Convulsions, tremor
ARfD  The critical study for setting ARfD			NOAEL: 50
			SF: 100
			ARfD: 0.5
			Acute neurotoxicity study in rats (the 1 <sup>st</sup> study)
			Developmental toxicity study in rats
			(the 1 <sup>st</sup> study)

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