

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

Risk Assessment Report

Monepantel

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ) February 2017

ABSTRACT

FSCJ conducted a risk assessment of monepantel (CAS No.887148-69-8), a parasiticide based on results from various studies. Data on pharmacokinetics (cattle) and residues (cattle) were newly submitted.

The data used in the assessment include pharmacokinetics (rats, dogs and sheep), residues (sheep and cattle), genotoxicity, acute toxicity (rats), subacute toxicity (mice, rats and dogs), chronic toxicity (rats and dogs), reproductive and developmental toxicity (rats and rabbits) as well as general pharmacology data.

All genotoxicity studies were negative, while no genotoxicity relevant to human health was suggested. FSCJ, thus judged it possible to establish an acceptable daily intake (ADI). Monepantel did not show carcinogenicity in a 78-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats.

The effect observed at the lowest dose in various toxicological studies were decrease in thromboplastin time, adrenal hypertrophy and liver pathological changes in male dogs, as well as decreased albumin levels, decreased albumin/globulin ratio, increased alkaline phosphatase activity, and increased relative thyroid weight in female dogs in a 52-week chronic toxicity study at 300 ppm and higher. The no-observed-adverse-effect level (NOAEL) in this study was 100 ppm (equivalent to 3 mg/kg bw/day for both sexes).

Consequently, FSCJ specified an ADI for monepantel at 0.03 mg/kg bw/day, based on NOAEL of 3 mg/kg bw/day, obtained in dogs in the 52-week chronic toxicity study applying a safety factor of 100.

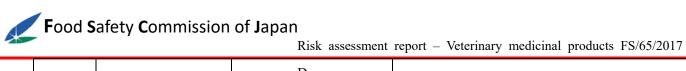


 Table 1. Levels relevant to toxicological evaluation of monepantel

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Mouse	13-week subacute	M: 5, 18, 98, 959	5
Wiodse	toxicity	F: 5, 22, 115, 1 213	Elevated AST levels
Mouse	78-week	1, 4, 16, 69	4
Wiodse	carcinogenicity study	1, 1, 10, 05	Increased incidence of fatty liver
	caremegement, sura,		F: Increased absolute/relative liver weights
			Not carcinogenic
Rat	4-week subacute	M: 86, 346, 1 044	M: 86 (LOAEL)
	toxicity study	F: 90, 362, 1 017	F: 90 (LOAEL)
	-		Centrilobular hypertrophy of hepatocytes
			M: Diffuse hypertrophy of thyroid follicular cells
			F: Increase in T.Chol, PL and TG as well as increased
Rat	90-day subacute	M: 4, 15, 74, 900	absolute/relative liver weight
Tut	toxicity	F: 4, 15, 81, 947	Increase in thromboplastin time
	temeny	1. 1, 10, 01, 21,	F: Increase in T.Chol and PL, centrilobular
			hypertrophy of hepatocytes and increased
			absolute/relative liver weight
Rat	52-week chronic	M: 3, 11, 54, 656	14
	toxicity study	F: 3, 14, 67, 778	Increased absolute/relative liver weight
Rat	104-week	M: 5, 47, 578	-
	carcinogenicity study	F: 6, 57, 707	Not carcinogenic

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Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Rat	Two-generation	F0: prior to mating: 15.8,	Parent: 13.5 ~
	reproductive toxicity	119, 950	32.3
	study		Increased absolute/relative liver weight, centrilobular
		103, 863	hypertrophy of hepatocytes, cortical cell hypertrophy
		During lactation period:	of the zona glomerulosa in the adrenal glands
		32.3, 245, 2 055	Offspring: 13.5 ~
		F ₁ : prior to mating: 18.6,	32.3 (LOAEL)
		141, 1 109	Increased absolute/relative liver weight
		During pregnancy: 15.1,	
		114, 918	
		During lactation period:	
		30.8, 241, 2 028	
Rat	Teratogenicity study	0, 100, 300, 1 000	1 000
			Not teratogenic
Dog	4-week subacute	M: 161, 566, 1 217	M: 161 (LOAEL), F: 184 (LOAEL)
	toxicity	F: 184, 561, 1 472	Increase in ALP, decreased absolute/relative thymus
			weight and increased absolute/relative adrenal weight
Dog	13-week subacute	M: 10, 107, 963	(LOAEL)
	toxicity	F: 11, 97, 1 176	M: 10, F: 11
			Small intestine (dilation of glands)
			F: Pancreas (increased apoptosis)
Dog	52-week chronic	M: 3, 10, 99	3
	toxicity	F: 3, 8, 91	M: Decrease in thromboplastin time and
			histopathological findings in the liver
			F: Decrease in Alb and A/G ratio, increase in ALP as
			well as increased relative thyroid weight
Rabbit	Teratogenicity	0, 100, 300, 1 000	1 000
			Not teratogenic
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Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Toxicological ADI (mg/kg bw/day)			0.03
			NOAEL: 3
			Safety factor: 100
The critical study for setting the ADI			52-week chronic toxicity study in dogs
ADI (mg/kg bw/day)			0.03