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 toxicity	M: 5, 18, 98, 959 F: 5, 22, 115, 1 213	5 Elevated AST levels
Mouse	78-week carcinogenicity study	1, 4, 16, 69	4 Increased incidence of fatty liver F: Increased absolute/relative liver weights Not carcinogenic
Rat	4-week subacute toxicity study	M: 86, 346, 1 044 F: 90, 362, 1 017	M: 86 (LOAEL) 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 absolute/relative liver weight
Rat	90-day subacute toxicity	M: 4, 15, 74, 900 F: 4, 15, 81, 947	15 Increase in thromboplastin time F: Increase in T.Chol and PL, centrilobular hypertrophy of hepatocytes and increased absolute/relative liver weight
Rat	52-week chronic toxicity study	M: 3, 11, 54, 656 F: 3, 14, 67, 778	14 Increased absolute/relative liver weight
Rat	104-week carcinogenicity study	M: 5, 47, 578 F: 6, 57, 707	- Not carcinogenic

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Rat	Two-generation reproductive toxicity study	F0: prior to mating: 15.8, 119, 950 During pregnancy: 13.5, 103, 863 During lactation period: 32.3, 245, 2 055 F_1: prior to mating: 18.6, 141, 1 109 During pregnancy: 15.1, 114, 918 During lactation period: 30.8, 241, 2 028	Parent: 13.5 ~ 32.3 Increased absolute/relative liver weight, centrilobular hypertrophy of hepatocytes, cortical cell hypertrophy of the zona glomerulosa in the adrenal glands Offspring: 13.5 ~ 32.3 (LOAEL) Increased absolute/relative liver weight
Rat	Teratogenicity study	0, 100, 300, 1 000	1 000 Not teratogenic
Dog	4-week subacute toxicity	M: 161, 566, 1 217 F: 184, 561, 1 472	M: 161 (LOAEL), F: 184 (LOAEL) Increase in ALP, decreased absolute/relative thymus weight and increased absolute/relative adrenal weight
Dog	13-week subacute toxicity	M: 10, 107, 963 F: 11, 97, 1 176	(LOAEL) M: 10, F: 11 Small intestine (dilation of glands) F: Pancreas (increased apoptosis)
Dog	52-week chronic toxicity	M: 3, 10, 99 F: 3, 8, 91	3 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

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