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

Risk Assessment Report

Fluralaner

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
October 2018

ABSTRACT

FSCJ conducted a risk assessment of a paraciticide, fluralaner (CAS No. 864731-61-3), based on documents for IT application, evaluation reports from EMA (EPMAR) and others.

Data used in the assessment include pharmacokinetics (rats, rabbits, dogs and chiken), residues (chicken), genotoxicity, acute toxicity (rats), subacute toxicity (rats and dogs), chronic toxicity (dogs) and reproductive/developmental toxicity (rats and rabbits).

Residue analyses in chicken revealed high bio-accumulation of fluralaner, since the residue levels in eggs and in tissues decreased below the detection limit (2 ng/g) only after 28 and 35 days, repectively.

Since data of all genotoxicity studies were negative, FSCJ considered that fulralaner has no genotoxicity relevant to human health, and thus concluded that the acceptable daily intake (ADI) for fulralaner could be specified.

Although carcinogenicity study was not conducted, FSCJ judged that carcinogenic potential of fluralaner is unlikely since data of all genotoxicity studies were negative and precancerous lesion was not observed in subacute and chronic toxicity studies.

In the developmental toxicity study in rabbits, skeletal variations (slight adhesion of second cervical vertebra and vertebral arch) were increased in fetuses exposed to fluralaner at 25 mg/kg bw/day and above. Thus the NOAEL for fetus toxicity was specified to be 10 mg/kg bw/day.

Major adverse effects of fluralaner observed were changes of blood chemistry parameters related to lipid metabolism (decreases in Chol, PL and TG), fatty change of the liver, mucosal vacuolation of the intestinal villi, and aggregation of alveolar macrophage. These findings, suggesting metabolic disorder such as an inhibition of lipid absoption, were observed as interspecies toxicity. FSCJ also recognized that there is species difference in susceptibility to fluralaner because the changes of blood chemistry parameters related to lipid metabolism in dogs and rabbitts were observed at the dose lower than that in rats.The lowest NOAEL was determined 1 mg/kg bw/day based on the decreases in Chol and TG in male dogs in 52-week chronic toxicity study.

FSCJ concluded that this value was appropriate as the basis of the ADI for fluralaner and specified the ADI for fluralaner as 0.01 mg/kg bw/day applying a safety factor of 100 to this NOAEL. FSCJ also concluded that carcinogenic potential of fluralaner was low though carcinogenicity study was not conducted.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rats	28-day subacute toxicity study	0, 30, 60, 600 (gavage administration)	60 Suppressed body weight gain, decreased feed consumption, increased absolute and relative weights of the adrenal gland, thymic atrophy, decrease in zymogen granule of the pancreas, diffuse fatty change in the liver (M/F)
	13-week subacute toxicity study (the 1st study)	0, 20, 40, 400 (gavage administration)	20 (LOAEL) Fatty change in the liver (M/F)
	13-week subacute toxicity study (the 2nd study)	0, 2, 4, 8 (gavage administration)	8 No effects of the administration
	One-generation reproduction	0, 50, 100, 500 (gavage administration)	Parents (General toxicity): 50 (LOAEL) Fatty change in the liver Reproductivity : 100 Decreases in mean number of implantations, increase trend in embryonal resorption rate, decrease in the number of live pups (P, F_1F) Offspring : 50 Decrease in organ weight and relative weight of the thymus (F)
	Two-generation reproduction	0, 8, 50, 500 (gavage administration)	Parents: 8 Increase in organ weight and relative weight of the kidney, decrease in organ weight and relative weight of the thymus, inflammatory lesions in the lung peribronchial (F) Reproductivity : 50 Increase trend in embryonal resorption rate, increased offspring mortality, decrease in the number of live pups (P, F_1F) Offspring : 50 Deppressed body weight gain, development of fur, open eyelid, delayed preputial separation and delayed vaginal opening
	Developmental toxicity study	0, 100, 300, 1 000 (gavage administration)	Dams (General toxicity): 100 Decreased feed consumption, deppressed body weight gain Offspring : 100

[1] Major adverse effect observed at LOAEL

			Increase in the incident rate of supernumerary ribs
Rabbits	Developmental toxicity study (the 1st study)	0, 50, 250, 1 000 (gavage administration)	Dams (general toxicity) : 50 Decreased feed consumption Offspring : 50 (LOAEL) Decreased body weight, skeletal variations and skeletal anomaly (adhesion of second cervical vertebra and vertebral arch)
	Developmental toxicity study (the 2nd study)	0, 10, 25, 250 (gavage administration)	Dams (general toxicity): 10 (LOAEL) Decreases in Chol, PL and TG, fatty change in the liver Fetuses: 10 Skeletal variations (slight adhesion of second cervical vertebra and vertebral arch)
Dogs	4-week subacute toxicity study (the 1st study)	0, 100, 250, 750 (oral administration)	100 (LOAEL) Decreases in Chol and PL (M/F), vacuolation of the adrenocortical zone fasciculata (M)
	4-week subacute toxicity study (the 2nd study)	0, 20, 40, 100 (oral administration)	20 (LOAEL) Decreases in Chol (M/F), TG (M), and PL (F)
	13-week subacute toxicity study	0, 2, 4, 8 (oral administration)	4 Decreases in Chol and TG (M/F), increases in organ weight and the relative weight of thyroid (F)
	52-week chronic toxicity study	0, 1, 2, 4 (oral administration)	1 Decreases in Chol and TG (M)
Toxicological ADI (mg/kg bw/day)			0.01 NOAEL : 1 SF : 100
The critical study for setting Toxicological ADI			52-week chronic toxicity study (dogs)
ADI (mg/kg bw/day)			0.01