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

Risk Assessment Report

Bromofenofos

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
June 2018

ABSTRACT

FSCJ conducted a risk assessment of bromofenofos (CAS No.21466-07-9), a paraciticide based on a set of data submitted to the Ministry of Health, Labour and Welfare (MHLW).

The data used in the assessment include pharmocokinetics (rats, sheeps and cattle), residues (cattle), genotoxicity, acute toxicity, (mice and rats), subacute toxicity (rats), and reproductive and developmental toxicity (rats).

FSCJ judged that bromofenofos and its major metabolite, diphosphate bromofenofos, have no genotoxicity relevant to human health based on results from various genotoxicity studies. It was thus concluded possible to establish an acceptable daily intake (ADI) in the assessment.

The toxicological data submitted were limited (i.e., no data on long-term toxicity and developmental toxicity), however major adverse effects of bromofenofos observed were decreased body weight, increase in ALP, and degeneration/histological changes in seminiferous tubules.

Bromofenofos was considered to be toxic by changing to diphosphate bromofenofos in the body based on various toxicity and pharmacokinetics studies.

The lowest LOAEL (lowest-observed adverse effect level) in various toxicological studies was 2.5 mg/kg bw/day based on the reduced body weight gain in dams and lower body weight in fetuses observed in developmental toxicity study in rats. No NOAEL (no-observed-adverse-effect level) was established in this study)

FSCJ concluded it appropriate to apply an additional safety factor 10 for establishing an ADI due the following reasons.

① To specify an ADI on the basis of the LOAEL.

② Chronic toxicity and carcinogenicity study were not conducted.

③ The NOAEL for testicular toxicity was specified based on the data in subacute toxicity study, however, reproductive toxicity study was not conducted.

④ Diphosphate bromofenofos is a phenolic substance with polybrominated biphenyl (PBB) structure and PBB derivatives have generally concerns to be accumulated in the body. Diphosphate bromofenofos; however, showed low accumulation in the body of animals.

⑤ In a residue study in cattle, diphosphate bromofenofos was depleted within a short period after the administraion.

⑥ Induction of teratogenicity at high dose where the dams showed marked reduction of their body weights, and lethal rate of embryos was approximately 90%.

There was a sufficient safety margin between the teratogenic dose and the critical LOAEL for setting the ADI. Taking into account various factors comprehensively, FSCJ specified an ADI for bromofenofos at 0.0025mg/kg bw/day, based on the LOAEL of 2.5mg/kg bw/day obtained in developmental toxicity study in rats, applying a safety factor of 1000.

Table 1. *Adverse effects possibly elicited by a single oral administration*

Species	Studies	Dose (mg/kg bw day)	NOAEL (mg/kg bw day) FSCJ Expert Committee on Veterinary Medicinal Products
Rat	1-month subacute toxicity study	6, 12, 24, 48 (by gavage)	6 Suppressed body weight
Rat	22-week subacute toxicity study	8.4, 12.0, 16.7, 20.2 (by gavage)	8.4 (LOAEL) Increase in relative kidney weight (F) and increase in ALP (F, M)
Rat	6-month subacute toxicity study	6, 12, 24 (by gavage)	6 Increased ALP, decrease in relative testicular weight and testicular toxicity
Rat	Developmental toxicity study	2.5, 5, 10, 20 (by gavage)	Maternal: 2.5 (LOAEL) Suppressed body weight Offspring: 2.5 (LOAEL) Lower body weight
Toxicological ADI			LOAEL: 2.5 mg/kg bw/day SF: 1,000
The critical study for setting the ADI			Developmental toxicity study in rats
ADI			0.0025 mg/kg bw/day