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

Risk Assessment Report

Dicyclanil

(Veterinary medicinal products)

Food Safety Commission of Japan (FSCJ)
August 2017

ABSTRACT

FSCJ conducted a risk assessment of dicycranil (CAS No.112636-83-6), a pyrimidine-derived insect growth regulator, using the evaluation reports from the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Medicines Agency (EMEA), and the Australian government.

The data used in the assessment include pharmocokinetics (rats and sheep), residues (sheep), genotoxicity, acute toxicity (rats), subacute toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (mice, rats and dogs), reproductive/developmental toxicity (rats and rabbits).

Major adverse effects of dicycranil observed were suppressed body weight, increased cholesterol, hepatocellular hypertrophy and increase in absolute and relative weight of the liver.

In an 18-month chronic toxicity/carcinogenicity study in mice, incidences of hepatocellular adenomas and carcinomas were increased in females in the 500 ppm group. Considering the weight of evidence from the genotoxicity studies, FSCJ considered it unlikely that dicyclanil exerts the carcinogenicity through a genotoxic mechanism, and thus recognized it as feasible to set the threshold value.

In a developmental toxicity studies, suppressed body weight in dams and delayed ossification and other findings in fetuses were observed. The doses of adverse effects on fetuses were the same or higher than the maternal toxic levels. No teratogenicity was observed.

The adverse effects at the lowest dose in various toxicological studies were increases in plasma cholesterol and phospholipid at 100 ppm (equivalent to 2.7 mg/kg bw/day in males and 3.5 mg/kg bw/day in females) in a 90-day subacute toxicity study in dogs. No observed adverse effect level (NOAEL) of this study was 20ppm (equivalent to 0.61 mg/kg bw/day in males and 0.71 mg/kg bw/day in females).

On the other hand, the NOAEL in a 12-month chronic toxicity study in dogs, a longer term study, was 25 ppm (equivalent to 0.71 mg/kg bw/day in males) based on increased level of plasma cholesterol observed in males only at 150 ppm(equivalent to 4.4 mg/kg bw/day in males and 5.1 mg/kg bw/day in females). The increased cholesterol in plasma was common in both studies in dogs. Therefore FSCJ judged that it was appropriate to choose the NOAEL for the effect on cholesterol in a longer term study, and thus adopted the NOAEL of 0.71 mg/kg bw/day.

Consequently, FSCJ specified the ADI of 0.0071 mg/kg bw/day for dicyclanil based on the NOAEL of 0.71 mg/kg bw/day in a 12-month chronic toxicity study in dogs, by applying a safety factor of 100.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Mouse	18 month chronic toxicity/carcinogenicity study	0, 10, 100, 500, 1 500 ppm* (in the diet, M: 0, 1.1, 12, 59, 210, F: 0, 1.1, 12, 65, 200)	M: 1.1 F: 12 Necrosis of hepatocytes and pigmentation (M), Suppressed body weight (F/M) Carcinogenic (F: 500 ppm)
Rat	28-day subacute toxicity study	0, 5, 30, 300, 1 000 (Dermal study)	-
	90-day subacute toxicity study	0, 5, 25, 125, 500 ppm (in the diet, M: 0, 0.31, 1.6, 8.0, 33, F: 0, 0.31, 1.7, 8.4, 34)	M: 1.6 F: 1.7 Decrease in Glu (F/M) Decrease in body weight gain (M)
	24-month chronic toxicity/ carcinogenicity study	0, 5, 25, 125, 500 ppm (in the diet M: 0, 0.19, 0.97, 4.8, 22, F: 0, 0.23, 1.2, 6.0, 26)	M: 0.97 F: 1.2 Decrease in body weight gain (F/M) (Not carcinogenic)
	Two-generation reproductive toxicity study	0, 5, 30, 200, 500 ppm (in the diet)	Parental toxicity: 2 Suppressed body weight and decreased feed consumption (No effect on reproduction) Offspring: 21 Low body weight
	Developmental toxicity study	0, 1, 5, 25, 75 (by gavage)	Maternal: 5 Suppressed body weight Embryo/fetus: 25 (Not teratogenic)
Rabbit	Developmental toxicity study	0, 1, 3, 10, 30 (by gavage)	Maternal: 3 Suppressed body weight Embryo/fetus: 10 Low body weight of embryo/fetus and delayed ossification (Not teratogenic)
Dog	90-day subacute toxicity study	0, 20, 100, 500, 1 500 ppm (in the diet F: 0, 0.61, 2.7, 14, 42, M: 0, 0.71, 3.5, 17, 42)	M: 0.61 F: 0.71 Increase levels in Cholesterol and *phospholipid* (F/M) Atrophy of the prostate tissue (M) Increase in inflammatory change with urothelial cell hypeplasia in urinary bladder (F)

	12-month chronic toxicity study	0, 5, 25, 150, 750 ppm (in the diet F: 0, 0.16, 0.71, 4.4, 23, M : 0, 0.15, 0.77, 5.1, 23)	M: 0.71 F: 5.1 *Increase in plasma cholesterol* (M) Changes in general condition, and in blood chemistry (F)
Toxicological ADI (mg/kg bw/day)			0.0071 NOAEL: 0.71 SF: 100
The critical study for setting ADI			12-month chronic toxicity study in dogs
ADI (mg/kg bw/day)			0.0071

M, Male; F, Female; F/M, both sexes; ADI, Acceptable daily intake; SF, Safety factor; NOAEL, No-observed-adverse-effect level; -, NOAEL could not be specified; *, All rats at 1500 ppm were sacrificed before the termination (during 58 or 59 weeks of treatment)