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Risk assessment report

Dicyclanil (Veterinary Medicinal Products)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (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 also the Australian government. In an 18-month chronic toxicity/carcinogenicity study in mice, increased incidences of hepatocellular adenomas and carcinomas were observed in females in the 500 ppm group. In spite of a recent experiment implying the possible indirect genotoxicity of dicyclanil on the carcinogenicity, dicyclanil is unlikely to exert the carcinogenicity *in vivo* through the genotoxic mechanism judging from other studies. FSCJ recognized it as feasible to set the threshold value. Adverse effects detected at the lowest dose in various toxicological studies were the increased plasma levels of 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 20 ppm (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 long term study, a 12-month chronic toxicity study in dogs was 25 ppm (equivalent to 0.71 mg/kg bw/day in males) based on increased level of plasma cholesterol observed only in males 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 levels in plasma were common in both studies in dogs. It was appropriate to choose the NOAEL for the effect on cholesterol in the longer term treatment, and thus FSCJ 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 the 12-month chronic toxicity study in dogs, by applying a safety factor of 100.

Conclusion in Brief

Food Safety Commission of Japan (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 also the Australian government.

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

Major adverse effects of dicycranil observed were suppressed body weights, elevated levels of cholesterol, hepatocellular hypertrophy, and increases in absolute and relative weights of the liver.

In an 18-month chronic toxicity/carcinogenicity study in mice, increased incidences of hepatocellular adenomas and carcinomas were observed in females in the 500 ppm group.

In spite of a recent experiment implying the possible indirect genotoxicity of dicyclanil on the carcinogenicity, dicyclanil is unlikely to exert the carcinogenicity *in vivo* through the genotoxic mechanism judging from other studies. FSCJ recognized it as feasible to set the threshold value.

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The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20070306022&fileId=201
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Suppressed body weight in dams, and delayed ossification and other toxicities in fetuses were observed in reproductive and developmental studies. The adverse effects on fetuses were observed at maternal toxic levels. No treatment-related teratogenicity was observed.

Adverse effects detected at the lowest dose in various toxicological studies were the increased plasma levels of 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 20 ppm (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 long term study, a 12-month chronic toxicity study in dogs was 25 ppm (equivalent to 0.71 mg/kg bw/day in males) based on increased level of plasma cholesterol observed only in males 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 levels in plasma were common in both studies in dogs. It was appropriate to choose the NOAEL for the effect on cholesterol in the longer term treatment, and thus FSCJ 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 the 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 1 500 ppm were sacrificed before the termination (during 58 or 59 weeks of treatment)