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

Risk Assessment Report

Tetradifon

(Pesticides)

Food Safety Commission of Japan (FSCJ)
September 2018

ABSTRACT

FSCJ established health based guidance values of tetradifon (CAS No.116-29-0), an acaricide having a diphenylsulfone skeleton structure based on results from various studies in the risk assessment.

The data used in the assessment include fate in animals (rats), fate in plants (apples, egg plants and others), residue in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxcity.

Major adverse effects of tetradifon were hepatocellular hypertrophy, single cell necrosis of hepatocytes, increased thyroid weight in rats and aggregation of alveolar macrophages. No neurotoxicity, reproductive toxicity teratogenicity and genotoxicity was observed.

Increase in the incidence of thyroid follicular cell adenomas was observed by the treatment in male and female rats in a two-year combined chronic toxicity/carcinogenicity study, however, a genotoxic mechanism was unlikely involved in the tumor induction. It was thus considered possible to establish a threshold in the assessment.

On the basis of various studies, tetradifon (parent compound only) was identified as a relevant substances for residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all tests was 1.39 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.013 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

FSCJ judged it unnecessary to specify an acute reference dose (ARfD), since no adverse effects would be likely to be elicited by a single oral administration of tetradifon.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 30, 150, 750, 3 000 ppm M : 0, 1.76, 8.82, 44.0, 180 F : 0, 3.63, 11.1, 55.6, 227	M : 44.0 F : 55.6 FM : Centrilobular hepatocellular hypertrophy, increased absolute/relative thyroid weight and others
	28-day subacute neurotoxicity study	0, 500, 3 000, 20 000 ppm M : 0, 42.0, 254, 1 730 F : 0, 44.3, 270, 1 820	M : 42.0 F : 44.3 FM : Increased absolute/relative liver weight and others (No acute neurotoxicity)
	Two-year chronic toxicity/carcinogenicity study	0, 15, 30, 300, 3 000 ppm M : 0, 0.70, 1.39, 14.1, 144 F : 0, 0.84, 1.62, 17.4, 181	M : 1.39 F : 1.62 FM : Aggregation of alveolar macrophages and others (FM : Increase in thyroid follicular adenoma)
	Two-generation reproductive toxicity study	0, 40, 200, 1 000 ppm PM : 0, 2.66, 13.5, 68.9 PF : 0, 3.13, 15.6, 77.9 F_1M : 0, 2.58, 13.1, 68.0 F_1F : 0, 2.43, 15.4, 78.0	Parent and offspring PM : 68.9 PF : 77.9 F_1M : 68.0 F_1F : 78.0 Parent and offspring : No toxicological effects (No effect on reproduction)
	Developmental toxicity study	0, 40, 200, 1 000	Maternal : 200 Embryo/fetus : 1 000 Maternal : Dyspnea, decreased body weight and decreased body weight and decreased feed consumption Embryo/fetus : No toxicological effects (Not teratogenic)
Mouse	18-month carcinogenicity study	0, 5, 10, 80, 640 ppm M : 0, 0.7, 1.4, 11.6, 92.2 F : 0, 0.8, 1.7, 13.3, 108	M : 11.6 F : 13.3 M : Centrilobular hepatocellular hypertrophy, centrilobular hepatocellular necrosis and others F : Aggregation of alveolar macrophages and others (Not carcinogenic)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) Critical endpoints[1)]
Rabbit	Developmental toxicity study	0, 90, 270, 810	Maternal : 90 Embryo/fetus : 270 Maternal : Miscarriage and others Embryo/fetus : Increase in dwarf and others (Not teratogenic)
Dog	90-day subacute toxicity study	0, 25, 50, 200	FM : 50 FM : Hepatocellular single-cell necrosis and others
ADI			NOAEL : 1.39 SF : 100 ADI : 0.013
The critical study for setting the ADI			Two-year combined chronic toxicity/carcinogenicity study in rats

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake;
[1)], Adverse effect observed at LOAEL