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

Risk Assessment Report

Thiacloprid
(Pesticides)

Food Safety Commission of Japan (FSCJ)
October 2018

ABSTRACT

FSCJ conducted the risk assessment of a neonicotinoid insecticide, thiacloprid (CAS No. 111988-49-9), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy rice and tomatoes), residues in plants, subacute toxicity (rats, mice and dogs), acute and subacute neurotoxicity (rats) chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), genotoxicity, immunotoxicity (rats), and mechanisms of effects on thyroid hormones, liver metabolism enzymes, steroid hormone production, and reproduction.

Major adverse effects of thiacloprid observed are hepatocellular hypertrophy in the liver, hypertrophy of follicular epithelial cells in the thyroid and expantion of valuolation area in the adrenal x-zone (mice). Thiacloprid showed no developmental neurotoxicity, genotoxicity and immunotoxicity.
In carcinogenicity studies, treatment related increased incidences of thyroid follicular adenomas in male rats, uterine adenocarcinomas in female rats, and luteoma in the ovaries in mice were observed. Studies on the mechanism of uterine adenocarcinoma suggested that the increase in estrogen resulting from increased aromatase activity by the treatment was involved in carcinogenesis in the uterus. Although mechanisms for luteoma and of thyroid follicular adenomas remained unknown, the increses in either tumors are unlikely attributed to genotoxicity. Hence, it was considered possible to establish a threshold dose in the assessment.
In reproduction studies, stillbirth and difficult delivery were observed in rats. Developmental toxicity studies in rats showed increased incidence of skeletal anomaly and variations in fetuses at the dose with maternal toxicity. Teratogenicity was not observed in rabbits.
From the above results, thiacloprid (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 1.2 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.012 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of thiacloprid was 3.1 mg/kg bw/day obtained in the acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.031 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rats	90-day subacute toxicity study	0, 25, 100, 400, 1 600 ppm M : 0, 1.9, 7.3, 28.6, 123 F : 0, 2.0, 7.6, 35.6, 161	M : 7.3 F : 7.6 M : Increased TP and others F : Increased Chol
	90-day combined subacute toxicity/neurotoxicity study	0, 50, 400, 1 600 ppm M : 0, 2.94, 24.2, 101 F : 0, 3.41, 27.9, 115	M : 24.2 F : 27.9 M/F : Suppressed body weight (No subacute neurotoxicity was observed)
	Two-year combined chronic toxicity/carcinogenicity study	0, 25, 50, 500, 1 000 ppm M : 0, 1.2, 2.5, 25.2, 51.7 F : 0, 1.6, 3.3, 33.5, 69.1	M : 1.2 F : 1.6 M : Hypertrophy of follicular epithelial cells in the thyroid, and others F : Retinal atrophy (M : follicular cell adenomas in the thyroid. F : an increased incidence of uterine adenocarcinomas
	Two-generation reproduction	0, 50, 300, 600 ppm PM : 0, 3.5, 21, 41 PF : 0, 4.2, 26, 51 F1M : 0, 4.2, 26, 53 F1F : 0, 4.1, 25, 51	Parents (M/F), Offspring and Reproductivity: PM : 3.5 PF : 4.2 F1M : 4.2 F1F : 4.1 Parents (M/F) : Hepatocellular hypertrophy, and others Offspring : Suppressed body weight Reproductivity : Fatal cases due to difficult delivery, and others
	Developmental toxicity study	0, 2, 10, 50	Dams : 10 Fetuses : 10 Dams : Suppressed body weight, and others Fetuses : Increased number of late embryonic resorption, low body weight, and others (Fetuses : Increased incident of skeletal variations and skeletal anomaly)
	Developmental neurotoxicity study	0, 50, 300, 500 ppm	Dams : 4.4

[1] Major adverse effect observed at LOAEL

		0, 4.4, 25.6, 40.8	Offspring : 4.4 Dams/Offspring : Suppressed body weight (No developmental neurotoxicity was observed)
Mice	90-day subacute toxicity study	0, 50, 250, 1,250, 6 250 ppm M : 0, 19.9, 103, 542, 2 820 F : 0, 27.2, 139, 704, 3 350	M : 103 F : ― M : Decreases in Ht and MCV F : Expansion of vacuolation area in the adrenal x-zone
	Two-year carcinogenicity study	0, 30, 1,250, 6 250 ppm M : 0, 5.7, 234, 546 F : 0, 10.9, 475, 872	M : 5.7 F : 10.9 M/F : Mesenteric lymph nodes vacuolation, and others (Increased incidence of luteoma in the ovaries)
Rabbits	Developmental toxicity study	0, 2, 10, 45	Dams : 2 Fetuses : 2 Dams : Suppressed body weight, and others Fetuses : Low body weight (No teratogenicity was observed)
Dogs	15-week subacute toxicity study	0, 250, 1 000, 2 000 ppm M : 0, 8.5, 34.9, 68.0 F : 0, 8.9, 34.7, 65.3	M : 8.5 F : 65.3 M : Increase in absolute and relative weight of the prostate, and others F : No toxicity was observed
	One-year chronic toxicity study	0, 40, 100, 250, 1 000 ppm M : 0, 1.42, 3.60, 8.88, 34.4 F : 0, 1.39, 3.27, 8.30, 33.8	M : 34.4 F : 33.8 M/F : No toxicity was observed
ADI (cRfD)			NOAEL : 1.2 SF : 100 ADI : 0.012
The critical study for setting ADI			Combined two-year chronic toxicity/carcinogenicity study in rats

ADI: Acceptable Daily Intake; NOAEL: No-observed-adverse-effect level; NOEL: No-observed-effect-level;
SF: Safety factor; UF: Uncertainty factor; /: No description