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

Risk Assessment Report

Triazole Metabolites

(Revised Edition)
(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2018

This document is a summary of the currently available data on triazole analogs and related information to be reffered for the toxicological evaluation of triazole pesticides.

ABSTRACT

For the purpose of using as the reference documents for the toxicological evalaution of triazole pesticides, FSCJ reviewed the reports on toxicological evaluation of the common metabolite of Triazole pesticides, such as 1,2,4-triazole (CAS No. 288-88-01), triazole acetic acid (CAS No. 28711-29-7) and triazole alanine (CAS No. 10109-05-4), conducted by JMPR and the USA. FSCJ recognized that both reports summarized up-to-date scientific findings of the metabolites, and judged the informaions were useful as the reference for the evalaution of triazole pesticides by FSCJ if not available some of detailed information.

The data used in the assessment include fate in animals (rats), acute toxicity (rats, mice and rabbits), subacute toxicity (rats, mice and dogs), combind subacute toxicity/neurotoxicity (rats), combined chronic toxicity/neurotoxicity (rats), one- and two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of 1,2,4-triazole observed are apoptic bodies of the seminiferous tubular epithelium and decrease in the absolute weight in the teseis and suppressed body weight. Treatment related neurotoxicity including tremor, decrease in the absolute weight of the brain, neural tissue degeneration/necrosis of the cerebellum, and degeneration of the peripheral nerve fibers wase observed in a 90-day combind subacute toxicity/neurotoxicity study in rats. Decrease in conception rate and increased number of abnormal spermatozoa were observed in reproductive toxicity study in rats. In a developmental toxicity study in rats, incidences in cleft palate and skeletal variation were increased in fetuses at the doses where the suppressed body weight was observed in dams. Genotoxicity was not observed.

Major adverse effect of triazole asetic acid and triazole alanine was suppressed body weight. Neurotoxicity, reproductive toxicity, teratogenicity and genotoxicity were not observed.

Table 1. *Levels relevant to toxicological evaluation of 1,2,4-Triazole*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)] and Critical Endpoint
Rat	90-day subacute toxicity study	0, 100, 500, 2 500 ppm M: 0, 7.8, 37.9, 212 F: 0, 10.2, 54.2, 267	M: 37.9 F: 54.2 F/M: Suppressed body weight
	90-day combined subacute toxicity/ neurotoxicity study	0, 250, 500, 3 000, 1 000/4 000 ppm M: 0, 16, 33, 183, 210 F: 0, 19, 41, 234, 276	M: 33 F: 41 M/F: Suppressed body weight, tremor
	12-month combined chronic toxicity/ neurotoxicity study	0, 125, 375, 1 000, 2 000 ppm M: 0, 6.9, 21, 58, 113 F: 0, 8.3, 26, 71, 136	M: 21 F: 26 M/F: Suppressed bodyweight
	Two-generation reproduction study	0, 250, 500, 3 000 ppm[2)] PM: 0, 15.4, 30.9, 189 PF: 0, 17.5, 36.2, 218 F_1M: 0, 16.0, 32.0 F_1F: 0, 18.9, 37.5 [M:0, 15, 31, 189 F:0, 18, 36, 218][3)]	Parent PM: - PF: 36.2 F_1M: － F_1F: 37.5 Offspring PM: 30.9 PF: 36.2 F_1M: 32.0 F_1F: 37.5 Reproductive ability PM: 15.4 PF: 17.5 F_1M: 16.0 F_1F: 18.9

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)] and Critical Endpoint
			Parent M: Suppressed body weight F: Suppressed body weight, degeneration/necrosis of the cerebellum, Offspring: No toxic effect was observed. Reproductive ability: Increased number of abnormal spermatozoa, decreases in number of corpora lutea, and delayed vaginal opening
	Developmental Toxicity study (the 1st study)	0, 25, 100	Dams: 100 Fetuses: 100 Dams and Fetuses: No toxic effect (No teratogenicity)
	Developmental Toxicity study (the 2nd study)	0, 10, 30, 100	Dams: 30 Fetuses: 30 Dams: Suppressed body weight Fetuses: Low body weight
	Developmental Toxicity study (the 3rd study)	0, 100, 200	Dams: - Fetuses: - Dams: Suppressed body weight Fetuses: Low body weight (Cleft palate, Hind limb malformations)
Mouse	28-day subacute toxicity study	0, 50, 250, 500, 2 000 ppm M: 0, 9, 47, 90, 356 F: 0, 12, 60, 120, 479	M: 90 F: 479 M: Degeneration in the testis, seminiferous tubular atrophy F: No toxic effects

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)] and Critical Endpoint
	90-day subacute toxicity study	0, 500, 1 000、3 000, 6 000 ppm M: 0, 80, 161, 487, 988 F: 0, 105, 215, 663, 1 350	M: 161 F: 663 M/F: Tremor, decrease in the brain absolute weight
Rabbit	Developmental toxicity study	0, 5, 15, 30, 45	Dams: 30 Fetuses: 30 Dams: Dying, suppressed body weight, decreased feed consumption, clinical symptoms, decreased weight of the uterus during pregnancy Fetuses: Low body weight (Urinary tract malformation)

-, NOAEL was not derived

[1)], The adverse effect observed at LOAEL;

[2)], Studies on F_1 generation were conducted only with animals exposed to 250 and 500 ppm, since number of F_1 offspring was insufficient in the group exposed to 3,000 ppm;

[3)], The value reported in the document from the U.S.A.

Table 2. *Levels relevant to toxicological evaluation of Triazole acetic acid*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical Endpoint[1)]
Rat	14-day subacute toxicity study	0, 100, 1 000, 8 000 ppm M: 10.6, 103, 788 F: 10.1, 97.2, 704	M: 788 F: 704 M/F: No toxic effect
	29-day subacute toxicity study	0, 3 250, 6 500, 13 000 ppm M: 0, 243, 483, 993 F: 0, 260, 519, 940	M: 993 F: 940 M/F: No toxic effect
	13-week combined subacute toxicity/neurotoxicity study	0, 100, 300, 1 000 M: 0, 94, 495, 1 000 F: 0, 119, 627, 1 180	M: 1 000 F: 1 180 M/F: No toxic effect (No subacute neurotoxicity)
	One-generation reproduction study	0, 100, 300, 1 000 PM: 0, 96, 287, 959 PF: 0, 98, 293, 976 F_1M: 0, 93, 280, 926 F_1F: 0, 78, 246, 770	Parent PM: 287 PF: 976 F_1M: 280 F_1F: 770 Offspring PM: 959 PF: 976 F_1M: 926 F_1F: 770 Parent M: Suppressed body weight and decreased feed consumption F: No toxic effect Offspring：No toxic effect (No effect on reproduction ability)
	Developmental toxicity study	0, 100, 300, 1 000	Dams: 300 Fetuses: 300 Dams: Clinical symptoms, suppressed body weight and decreased feed consumption Fetuses: No toxic effect at and below 300 mg/kg bw/day

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical Endpoint[1)]
			(No teratogenicity at and below 300 mg/kg bw/day)
Mouse	28-day subacute toxicity study	0, 1 000, 3 000, 7 000 ppm --- M: 0, 159, 483, 1 070 F: 0, 183, 542, 1 360	M: 1 070 F: 1 360 M/F: No toxic effect
Rabbit	Developmental toxicity study	0, 100, 750, 1 000	Dams: 100 Fetuses: 100 Dams: Death, clinical symptoms, suppressed body weight Fetuses: Low body weight (No teratogenicity)

[1)], The adverse effect observed at LOAEL

Table 3. *Levels relevant to toxicological evaluation of Triazole alanine*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical Endpoint[1]
Rat	28-day subacute toxicity study	0, 25, 100, 400	M/F: 400 M/F: No toxic effect
	90-day subacute toxicity study	0, 1 250, 5 000, 20 000 ppm ---------- M: 0, 90, 370, 1 510 F: 0, 160, 400, 1 680	M: 370 F: 1 680 M: Suppressed body weight F: No toxic effect
	12-month combined chronic toxicity/neurotoxicity study	0, 600, 2 000, 6,000, 20 000 ppm ---------- M: 0, 28, 93, 278, 916 F: 0, 36, 120, 375, 1 270	M: 916 F: 1 270 M/F: No toxic effect (No chronic neurotoxicity)
	Two-generation reproduction study	0, 500, 2 000, 10 000 ppm ---------- PM: 0, 50, 213, 1 100 PF: 0, 51, 223, 1 110 F_1M: 0, 47, 192, 929 F_1F: 0, 49, 199, 988	Parent PM: 1 100 PF: 1 110 F_1M: 929 F_1F: 988 Offspring PM: 213 PF: 223 F_1M: 192 F_1F: 199 Parent: No toxic effect Offspring: Reduced weight of litters (No effect on reproduction ability)
	Developmental toxicity study	0, 100, 300, 1 000	Dams: 1 000 Fetuses: 100 Dams: No toxic effect Fetuses: Retarded ossification (No teratogenicity)
Rabbit	Developmental toxicity	0, 30, 100, 250	Dams: 100

[1] The adverse effect observed at LOAEL.

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical Endpoint[1]
	study		Fetuses: 100 Dams: Suppressed body weight Fetuses: Low body weight, increased skeletal variations (No teratogenicity)
Dog	90-day subacute toxicity study	0, 3 200, 8 000, 20 000 ppm M: 0, 144, 322, 850 F: 0, 150, 345, 902	M: 850 F: 345 M: No toxic effect F: Suppressed body weight and decreased feed consumption

1), The adverse effect observed at LOAEL