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

Risk Assessment Report

Prothiofos

(Pesticides)

Food Safety Commission of Japan (FSCJ)
October 2018

ABSTRACT

FSCJ established health based guidance values of prothiofos (CAS No.34643-64-4), an organophosphorus insecticide 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, Chinese cabbage and others), residue in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (mice), two-generation and three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxcity.

The major adverse effect of prothiofos was inhibition of cholinesterase (ChE) activity in the brain and erythrocyte, neurotoxicity (tremor etc.) and suppressed body weight. No carcinogenicity, reproductive toxicity or genotoxicity was observed.

Prothiofos increased the incidences of open eyelid, bent ribs and femoral dysplasia of fetus at the maternal toxic dose in a rabbit developmental toxicity study. No teratogenicity was observed in rats.

On the basis of various studies, prothiofos (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 studies was 0.27 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.027 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects of eliciting a single oral administration of prothiofos was 5 mg/kg bw/day obtained in acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.05 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) Critical endpoints[1)]
Rat	28-day subacute toxicity study	0, 1, 5, 25	FM : 5 M : Inhibition of brain ChE activity (more than 20%) F : Fatty change of hepatocytes and inhibition of brain and erythrocyte ChE activity (more than 20%)
	90-day subacute toxicity study	0, 8, 40, 200, 1 000, 5 000 ppm M : 0, 0.45, 2.26, 11.4, 58.5, 304 F : 0, 0.53, 2.78, 12.8, 69.8, 353	M : 0.45 F : 0.53 FM : Inhibition of erythrocyte ChE activity (more than 20%)
	13-week subacute neurotoxicity study	0, 5, 200, 1 000 ppm M : 0, 0.37, 11.2, 59.2 F : 0, 0.46, 13.6, 73.4	M : 0.37 F : 0.46 FM : Inhibition of erythrocyte ChE activity (more than 20%) and others
	6-month chronic toxicity study	0, 5, 50, 500, 5 000 ppm M : 0, 0.24, 2.46, 25.0, 268 F : 0, 0.30, 3.02, 28.8, 296	M : 0.24 F : 0.30 FM : Inhibition of whole blood ChE inhibition (more than 20%) and others
	Two-year combined chronic toxicity/carcinogenicity study	0, 5, 50, 500 ppm M : 0, 0.27, 2.67, 27.2 F : 0, 0.36, 3.68, 37.6	M : 0.27 F : 0.36 FM : Inhibition of erythrocyte ChE activity (more than 20%) (Not carcinogenic)
	Three-generation reproductive toxicity study	0, 3, 30, 180 ppm PM : 0, 0.193, 2.03, 12.4 PF : 0, 0.201, 2.05, 12.2 F_1M : 0, 0.277, 2.66, 15.4 F_1F : 0, 0.226, 2.37, 13.3 F_2M : 0, 0.267, 2.65,	Parent PM : 0.193 PF : 2.05 F_1M : 0.277 F_1F : 2.37 F_2M : 0.267 F_2F : 2.37 F_3M : 0.240 F_3F : 2.46 M : Inhibition of erythrocyte ChE activity (more than 20%) F : Inhibition of brain or erythrocyte ChE activity (more than 20%) Offspring PM : 12.4 PF : 12.2 F_1M : 15.4 F_1F : 13.3 F_2M : 16.7

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) Critical endpoints[1)]
		16.7 F_2F : 0, 0.226, 2.37, 13.5 F_3M : 0, 0.240, 2.43, 14.8 F_3F : 0, 0.242, 2.46, 13.5	F_2F : 13.5 F_3M : 14.8 F_3F : 13.5 Offspring : No toxicological effects (No effect on reproduction)
	Two-generation reproductive toxicity study	0, 5, 40, 320 ppm PM : 0, 0.5, 3.5, 29.0 PF : 0, 0.5, 4.5, 34.9 F_1M : 0, 0.64, 5.57, 49.9 F_1F : 0, 0.80, 6.49, 57.2	Parent PM : 0.5 PF : 0.5 F_1M : 0.64 F_1F : 0.80 FM : Inhibition of erythrocyte ChE activity (more than 20%) Offspring PM : 3.5 PF : 4.5 F_1M : 5.57 F_1F : 6.49 Offspring : Suppressed body weight (No effect on reproduction)
	Developmental toxicity study (the 1st study)	0, 10, 30, 100	Maternal : 10 Embryo/fetus : 30 Maternal : Decreased body weight/suppressed body weight Embryo/fetus : Low body weight, delayed ossification and others (Not teratogenic)
Mouse	90-day subacute toxicity study	0, 1, 5, 25, 125, 625, 3 125 ppm M : 0, 0.20, 0.97, 4.20, 21.0, 119, 601 F : 0, 0.23, 1.25, 6.55, 31.7, 163, 831	M : 0.97 F : 0.23 FM : Inhibition of erythrocyte ChE activity (more than 20%)
	Two-year combined chronic toxicity/carcinogenicity study	0, 1, 5, 500 ppm M : 0, 0.41, 1.76, 159 F : 0, 0.50, 2.66, 199	M : 1.76 F : 0.50 M : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others F : Glandular epithelial hyperplasia in the stomach (Not carcinogenic)
Rabbit	Developmental toxicity study (the 1st study)	0, 10, 30, 100	Maternal and Embryo/fetus : 10 Maternal : Suppressed body weight and others Embryo/fetus : Increase in the late resorption rate, complex malformations and others

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) Critical endpoints[1)]
			(External abnormalities (open eyelid), skeletal abnormalities (bent ribs and femoral dysplasia) as well as complex malformations)
	Developmental toxicity study (the 2nd study)	0, 10, 30, 100	Maternal : - Maternal : Inhibition of erythrocyte ChE activity (more than 20%)
	Overall evaluation of developmental toxicity study (the 1st study and 2nd study)		Maternal : - Embryo/fetus : 10
Dog	90-daysubacute toxicity study	0, 2, 20, 200 ppm M : 0, 0.07, 0.72, 7.29 F : 0, 0.08, 0.74, 7.52	M : 0.72 F : 0.74 FM : Inhibition of erythrocyte ChE activity (more than 20%)
	One-year chronic toxicity study (the 1st study)	0, 0.1, 0.4, 300, 750 ppm M : 0, 0.003, 0.012, 8.27, 22.7 F : 0, 0.003, 0.012, 8.13, 22.3	FM : 0.012 FM : Inhibition of erythrocyte ChE activity (more than 20%)
	One-year chronic toxicity study (the 2nd study)	0, 0.15, 0.3, 10	FM : 0.3 M : Inhibition of erythrocyte ChE activity (more than 20%) F : Inhibition of erythrocyte ChE activity (more than 20%) , increase in ALP and hemosiderin deposition in spleen
	Two-year chronic toxicity study	0, 0.3, 1, 75, 225/300 M : 0, 0.010, 0.037, 2.60, 9.03 F : 0, 0.010, 0.034, 2.39, 8.53	M : 2.60 F : 2.39 FM : Inhibition of erythrocyte ChE activity (more than 20%) and increase in ALP
ADI			NOAEL : 0.27 SF : 100 ADI : 0.0027
The critical study for setting the ADI			Two-year combined chronic toxicity/carcinogenicity study in rats

ADI, Acceptable daily intake; SF, Safety factor; NOAEL, No-observed-adverse-effect level;
－, NOAEL not derived; [1)],Adverse effect observed at LOAEL

Table 2. *Adverse effects possibly elicited by a single oral administration*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	NOAEL and end point for establishing acute reference dose (ARfD)[1)] (mg/kg bw or mg/kg bw/day)
Rat	Acute toxicity study	M : 1, 10, 100, 1 000, 1 400, 2 000, 3 550 F : 1, 10, 100, 1 000, 1 250, 1 400, 1 600, 2 000 (16-hour fasted group)	FM : 1 FM : Indifference, decreased activity and piloerection
	Acute toxicity study	M : 10, 100, 500, 1 000, 1 600, 2 500, 5 000 F : 10, 100, 500, 800, 900, 1 000, 1 250, 1 600, 2 500 (non-fasted group)	FM : 10 FM : Indifference and piloerection
	Acute neurotoxicity study	0, 2, 5, 50, 500	FM : 5 FM : Inhibition of erythrocyte ChE activity (more than 20%)
	Developmental toxicity study (the 1st study)	0, 10, 30, 100	Maternal : 10 Maternal : Low body weight/suppressed body weight
	Evaluation of ChE inhibitory activity	0, 1.1, 11, 56, 120, 336, 560	F : 56 F : Inhibition of brain and erythrocyte ChE activity (more than 20%)
Mouse	Acute toxicity study	10, 100, 1 000, 1 800, 2 000, 2 500, 3 150, 3 550	FM : 10 Indifference, decreased activity and others
Rabbit	Developmental toxicity study (the 2nd study)	0, 10, 30, 100	Maternal : 30 Maternal : Inhibition of erythrocyte ChE activity (more than 20%)
ARfD			NOAEL : 5 SF : 100 ARfD : 0.05
The critical dose for setting ARfD			Acute neurotoxicity study in rats

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed-adverse-effect level;
[1)],The adverse effect observed at LOAEL