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

Risk Assessment Report

Fosthiazate

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of an organophosphorus amides insecticide, fosthiazate (CAS No. 98886-44-3), based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (tomatoes and potatoes), residues in plants, acute neurotoxicity (rats), subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, ChE activity inhibition (rats), immunotoxicity (mice), and inhibition of ChE activity in animals of various age.

Major adverse effects of fosthiazate observed are inhibition of RBC and brain ChE activity, cytoplasmic vacuolation of the adrenocortical zone fasciculate, and anemia. With regard to the inhibition of ChE activity in rats, female seemed more susceptible than male. Carcinogenicity, teratogenicity and immunotoxiciy were not observed.
In a two-generation reproduction toxicity study in rats, disturbance of estrous cyclicity, prolonged period for mating and prolonged gestational period were observed.

FSCJ identified fosthiazate (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products.
The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 0.205 mg/kg bw/day obtained in an AChE activity inhibition study with 104-week feeding in rats. FSCJ specified an acceptable daily intake (ADI) of 0.002 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 fosthiazate was 0.1 mg/kg bw/day of NOAEL for inhibition of RBC ChE activity in pregnant animals obtained in a study of age-specific susceptibility to inhibition of ChE activity (gestational exposure test) (hereinafter refer to as gestational exposure test) in rats.

FSCJ considered that pregnant animals are more susceptible to inhibition of ChE activity by the treatment than non-pregnant animals based on comprehensive consideration on the following evidences:
1. The gestational exposure test was done with repeated dose.

2. Data to show the inhibition of RBC ChE activity by a single administration in pregnant animals are not available in the present assessment.
3. There was no remarkable bioaccumulation by fosthiazate administration in the ADME study in rats.
4. Inhibition of RBC ChE activity was not clearly different by sample collecting times in the repeated dose studies.
5. A NOAEL of 0.7 mg/kg bw/day for inhibition of RBC ChE activity in non-pregnant animals was obtained in the gestational exposure test.

Moreover, FSCJ could not exclude a possibility that inhibition of RBC ChE activity (20 % and more) may be induced by a single administration of 0.7 mg/kg bw/day of fosthiazate, which is the LOAEL in the gestational exposure test.

Magnitude of the RBC ChE activity inhibition at 0.7 mg/kg bw/day in the gestational exposure test was similar to that observed at the LOAEL (0.510 mg/kg bw/day) in a 104-week feeding study on AChE activity inhibition in rats, where the NOAEL was 0.205 mg/kg bw/day. Hence, FSCJ specified an acute reference dose (ARfD) for pregnant or may be pregnant women to be 0.002 mg/kg bw based on the NOAEL of 0.205 mg/kg bw/day in the 104-week feeding study on AChE activity inhibition in rats. A safety factor of 100 was applied.
For general population, FSCJ specified the ARfD to be 0.007 mg/kg bw based on the NOAEL of 0.7 mg/kg bw/day in non-pregnant rats obtained in the gestational exposure test on ChE activity inhibition, applying a safety factor of 100.

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

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	NOAEL (mg/kg bw or mg/kg bw/day)[1]	
			FSCJ	Reference (Summary reports)
Rat	28-day subacute toxicity study	0, 0.5, 1, 5, 10, 100, 400 ppm	M: 0.97 F: 0.50 M/F: Inhibition of RBS AChE activity (20 % and more)	M: 0.97 F: 0.50 M/F: Inhibition of RBS AChE activity (20 % and more)
		M: 0, 0.05, 0.10, 0.48, 0.97, 9.69, 40.9 F: 0, 0.05, 0.10, 0.50, 1.00, 10.7, 43.5		
	90-day subacute toxicity study	0, 1.07, 10.7, 53.6, 429 ppm	M: 0.77 F: 0.89 M/F: Inhibition of RBC and brain ChE activity (20 % and more)	M: 0.77 F: 0.89 M/F: Inhibition of RBC and brain ChE activity (20 % and more)
		M: 0, 0.08, 0.77, 4.12, 36.4 F: 0, 0.09, 0.89, 4.74, 41.0		
	90-day subacute neurotoxicity study	0, 0.05, 0.5, 2.4 ppm	M: 0.56 F: 0.57 M: Inhibition of RBC and brain (Brain Cortex) ChE activity (20 % and more) F: Inhibition of RBC and brain (Brain Cortex, cerebellum and brain stem) ChE activity (20 % and more)	M: 0.56 F: 0.57 M/F: Inhibition of RBC and brain (Brain Cortex, cerebellum and brain stem) ChE activity (20 % and more)
		M: 0, 0.07, 0.56, 2.4 F: 0, 0.08, 0.57, 2.5		
	Two-year combined chronic toxicity/carcinogenicity study	0, 1, 10, 50, 200 ppm	M: 0.41 F: 0.055 M: Inhibition of RBC and brain AChE activity (20 % and more) (No carcinogenicity)	M: 0.41 F: 0.055 M: Inhibition of RBC and brain AChE activity (20 % and more) (No carcinogenicity)
		M: 0, 0.042, 0.41, 2.08, 8.94 F: 0, 0.055, 0.54, 2.63, 12.5		
	Two-generation reproductive toxicity study	0, 3, 10, 30, 100 ppm	Parent and Reproductive activity PM: 7.21 PF: 0.26 F_1M: 2.70 F_1F: 3.14	Parent and Reproductive activity PM: 2.09 PF: 2.62 F_1M: 2.70 F_1F: 3.14
		PM: 0, 0.21, 0.69, 2.09, 7.21 PF: 0, 0.26, 0.86, 2.62, 9.34 F_1M: 0, 0.27, 0.88, 2.70		

		F_1F: 0, 0.31, 1.02, 3.14	Offspring: PM: 0.69 PF: 0.86 F_1M: 0.88 F_1F: 1.02 Parent: M: No toxicity was observed. F: Disturbance of estrous cyclicity, prolonged period for mating and prolonged gestational period Offspring: Decreased survival rate	Offspring: PM: 2.09 PF: 2.62 F_1M: 2.70 F_1F: 3.14 Parent: M: No toxicity was observed. F: Increase in absolute organ weight of the adrenal grand and hypertrophy of zona glomerulosa of the adrenal cortex Offspring: Decreased survival rate, growth retardation
	Developmental toxicity study	0, 3, 5, 10	Dams: 5 Fetuses: 10 Dams: Suppressed body weight Fetuses: No toxicity was observed. (No teratogenicity)	Dams: 5 Fetuses: 10 Dams: Suppressed body weight Fetuses: No toxicity was observed. (No teratogenicity)
	18-week AChE activity inhibition study with feeding.	0, 0.5, 1, 5, 10 ppm --- 0, 0.05, 0.1, 0.5, 1 (Calculated value)	M: 1 F: 0.5 M: No toxicity was observed. F: Inhibition of RBC AChE activity (20% and more)	M: 1 F: 0.5 M: No toxicity was observed. F: Inhibition of RBC AChE activity (20% and more)
	104-week feeding study for AChE activity inhibition	F: 0, 2, 4, 10 --- F: 0, 0.104, 0.205, 0.510	0.205 F: Inhibition of RBC AChE activity (20% and more)	0.205 F: Inhibition of RBC AChE activity (20% and more)
	Comprehensive evaluation of combined 2-year chronic toxicity/carcinogenicity study and 104-week AChE activity inhibition study with feeding		M: 0.41 F: 0.205 M: Inhibition of RBC and brain AChE activity (20% and more)	

	Study of age-specific susceptibility to inhibition of ChE activity 1) Gestational exposure test. 2) Maximum inhibition period in offspring. 3) Effects of a single dose. 4) Effects of a repeated dose.	0, 0.1, 0.7, 5	1) Gestational exposure: Dams: 0.1 Fetuses: 0.7 2) Maximum inhibition period in offspring: 11-day old (M/F): 0.7 21-day old (M/F): 0.7 3) Effects of a single dose: 11-day old (M/F): 0.7 21-day old (M/F): 0.7 4) Effects of a repeated dose: 11-day old (M/F): 0.7 Young adult (M/F): 0.7 Dams: Inhibition of RBC ChE activity (20% and more) Fetuses, offspring and young adult: Inhibition of RBC ChE activity (20% and more)	Dams: 0.1 Fetuses: 0.7 Offspring: 0.7 Young adult: 0.7 Dams: Inhibition of RBC ChE activity (20% and more) Fetuses, offspring and young adult: Inhibition of RBC ChE activity (20% and more)
Mouse	Two-year carcinogenicity study	0, 10, 30, 100, 300 ppm --- M: 0, 1.09, 3.32, 11.1, 32.7 F: 0, 1.19, 3.43, 11.2, 42.0	M: 3.32 F: 3.43 M/F: Ceroid deposit in cortico-medullary junction of the adrenal grand (No carcinogenicity)	M: 3.32 F: 3.43 M/F: Ceroid deposit in cortico-medullary junction of the adrenal grand (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 0.5, 1, 1.5, 2	Dams: 2 Fetuses: 1.5 Dams: No toxicity Fetuses: Increased incident of dwarf (No teratogenicity)	Dams: 2 Fetuses: 1.5 Dams: No toxicity Fetuses: Increased incident of dwarf (No teratogenicity)
Dog	90-day subacute toxicity study	0, 0.054, 0.11, 0.54, 5.4	M/F: 0.54 M/F: Inhibition of RBC- and brain(barin cortex)- AChE activity (20% and more).	M/F: 0.54 M/F: Inhibition of RBC- and brain(barin cortex)- AChE activity (20% and more).

	One-year chronic toxicity study	0, 0.05, 0.1, 0.5, 5.0	M/F: 0.5 M/F: Changes of zona glomerulosa of the adrenal cortex into clear cells	M/F: 0.5 M/F: Changes of zona glomerulosa of the adrenal cortex into clear cells
ADI(cRfD)			NOAEL: 0.205 SF: 100 ADI: 0.002	NOAEL: 0.205 SF: 100 ADI: 0.002
The critical study for setting ADI			104-week AChE activity inhibition study with feeding in rats	104-week AChE activity inhibition study with feeding in rats

NOAEL: No-observed-adverse-effect level, SF: Safety factor, UF: Uncertainty factor, ADI: Acceptable daily intake, cRfD: Chronic reference dose, $BMDL_{10}$: the lower confidence limit of benchmark dose BMD_{10} (the dose that shows 10% inhibition rate of ChE activity obtained by bench mark dose rule).
[1)] The adverse effect observed at LOAEL
/: No description in the referred documents.

Table 2-1. *Potential adverse effects of a single oral administration of fosthiazate*

(General population)

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)]
Rat	Acute oral toxicity study	41, 51, 64, 81, 128	M/F: - M/F: Decreased locomotor activity, hunchback position
	Acute neurotoxicity study	M: 0. 0.4, 10, 40 F: 0, o.4, 10, 20	M/F: 0.4 M/F: Inhibition of RBC- and brain (brain cortex, cerebellum, brain stem)-ChE activity
	Study of age-specific susceptibility to inhibition of ChE activity (Maximum inhibition period in offspring)	0, 0.1, 0.7, 5	M/F (11-day and 21-day old offspring): 0.7 M/F (11-day and 21-day old offspring): Inhibition of RBC- and brain-ChE activity (20% and more)
	Study of age-specific susceptibility to inhibition of ChE activity (Effects of a single administration)	0, o.1, 0.7, 5	M/F (11-day and 21-day old offspring, and young animals): 0.7 M/F (11-day and 21-day old offspring, and young animals): Inhibition of RBC-ChE activity (20% and more)
Mouse	General pharmacology data (Behavior observation)	0, 5, 15, 50	M/F: 15 M/F: Slight Straub's tail reaction, slight decrease in righting reflex
	Acute oral toxicity study	51, 81, 102, 128, 161	M/F: 81 M/F: Decreased locomotor activity, ataxia
	Micronucleus Test	12.5, 25, 50	M/F: 25 M/F: Sedation
ARfD			NOAEL: 0.7 SF: 100 ARfD: 0.007
The critical study for setting ARfD			Study of age-specific susceptibility to inhibition of ChE activity in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
-: NOAEL could not be specified.
1) The adverse effect observed at LOAEL

Table 2-2. *Potential adverse effects of a single oral administration of fosthiazate*

(Pregnant or may be pregnant women)

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)]
Rat	104-week AChE activity inhibition study	F: 0, 2, 4, 10 ppm F: 0, 0.104, 0.205, 0.510	0.205 F: Inhibition of RBC-AChE activity (20% and more)
	Study of age-specific susceptibility to inhibition of ChE activity (Gestational exposure test)	0, 0.1, 0.7, 5	Dams: 0.1 Inhibition of RBC-ChE activity (20% and more)
ARfD			NOAEL: 0.205 SF: 100 ARfD: 0.002
The critical study for setting ARfD			104-week study of age-specific susceptibility to inhibition of ChE activity in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor

[1)] The adverse effect observed at LOAEL