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

Risk Assessment Report

Cyfluthrin

(Pesticides and Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The FSCJ conducted a risk assessment of cyfluthrin (CAS No. 68359-37-5), a pyrethroid insecticide, based on various documents. The FSCJ also conducted a concomitant risk assessment of β-cyfluthrin, which is comprised of the eight optical isomers of cyfluthrin in different percentages.

Test results used in the assessment include fate in animals (rats, cattles and chickens), fate in plants (including soy beans and apples), residues in crops, acute neurotoxicity (rats), subacute toxicity (rats, mice, and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two- and three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), genotoxicity and immunotoxicity.

Major adverse effects of cyfluthrin were observed in the nervous system (including salivation and abnormal gait) and body weight (suppressed weight gain), while neither carcinogenicity, effect on fertility, teratogenicity, genotoxicity nor immunotoxicity was observed. Major adverse effects of β-cyfluthrin were observed in the nervous system (including salivation and abnormal gait) and body weight (suppressed weight gain), while neither developmental neurotoxicity nor genotoxicity was observed.

Based on these results, cyfluthrin (parent compound only, including β-cyfluthrin) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from these studies on cyfluthrin and β-cyfluthrin was 2.38 mg/kg bw per day in a ninety-day subacute toxicity study for β-cyfluthrin in dogs. The FSCJ specified an acceptable daily intake (ADI) of 0.023 mg/kg bw per day for both cyfluthrin and β-cyfluthrin by applying a safety factor of 100 to this NOAEL.

Of the potential adverse effects of a single oral administration of cyfluthrin and β-cyfluthrin studied individually, the lowest NOAEL value was 2.38 mg/kg bw per day in a ninety-day subacute toxicity study on β-cyfluthrin in dogs. The FSCJ specified an acute reference dose (ARfD) of 0.023 mg/kg bw for both cyfluthrin and β-cyfluthrin by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Rat	Four-week subacute toxicity study (the 1st study)	0, 100, 300, 1 000 ppm M: 0, 8.27, 24.7, 78.9 F: 0, 8.44, 25.2, 77.9	M: 24.7 F: 25.2 M/F: Suppressed body weight gain, abnormal gait, increased absolute and relative weights of the submandibular gland, etc.
	Four-week subacute toxicity study (the 2nd study)	0, 100, 300, 1 000 ppm M: 0, 9.1, 26.0, 75.2 F: 0, 10.6, 28.9, 76.9	M: 26.0 F: 28.9 M/F: Suppressed body weight gain, decreased food intake, etc.
	Four-week subacute toxicity study (the 3rd study)	0, 5, 20, 40(80)	M/F: 20.0 M/F: Death, ataxia, etc.
	90-day subacute toxicity study (the 1st study)	0, 30, 100, 300 ppm M: 0, 2.24, 7.39, 22.5 F: 2.70, 8.83, 28.0	M: 22.5 F: 28.0 M/F: No toxicity
	90-day subacute toxicity study (the 2nd study)	0, 100, 300, 1 000 ppm M: 0, 6.20, 18.5, 61.0 F: 0, 7.24, 21.2, 68.5	M: 6.20 F: 21.2 M: Decreased glucose levels F: Suppressed body weight gain, decreased food intake, etc.
	90-day subacute neurotoxicity study	0, 50, 200, 800 ppm M: 0, 3.07, 12.5, 49.1 F: 0, 3.89, 15.3, 59.6	M: 49.1 F: 15.3 M: No toxicity F: Suppressed body weight gain, decreased food intake, etc. (No subacute neurotoxicity is observed.)
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 50, 150, 450 ppm M: 0, 2.02, 6.19, 19.2 F: 0, 2.71, 8.15, 25.5	M: 6.19 F: 8.15 M/F: Suppressed body weight gain (No carcinogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 50, 225, 450 ppm M: 0, 2.6, 11.6, 22.8 F: 0, 3.3, 14.4, 28.3	M: 2.6 F: 3.3 M/F: Suppressed body weight gain (No carcinogenicity is observed.)
	Three-generation reproductive toxicity study	0, 50, 150, 450 ppm PM: 0, 3.80, 11.4, 34.7 PF: 0, 5.14, 14.0, 46.9 F_1M: 0, 3.95, 13.6, 37.6 F_1F: 0, 5.53, 16.0, 48.6 F_2M: 0, 3.74, 11.8, 39.6 F_2F: 0, 5.40, 15.4, 50.2	Parent and offspring PM: 3.80 PF: 5.14 F_1M: 3.95 F_1F: 5.53 F_2M: 3.74 F_2F: 5.40 Parent: Suppressed body weight gain Offspring: Suppressed body weight gain, Decreased five-day survival rate, decreased lactation index, etc. (No effect on fertility is observed.)
	Two-generation reproductive toxicity study (the 1st study)	0, 50, 125, 400 ppm PM: 0, 3.4, 8.9, 28.8 PF: 0, 3.9, 9.9, 33.2 F_1M: 0, 3.3, 9.1, 30.1 F_1F: 0, 3.8, 10.6, 33.7	Parent PM: 3.4 PF: 9.9 F_1M: 3.3 F_1F: 10.6 Offspring: PM: 3.4 PF: 3.9 F_1M: 3.3 F_1F: 3.8 Parent: Suppressed body weight gain, decreased food intake Offspring: Tremor, suppressed weight gain (No effect on fertility is observed.)
	Two-generation reproductive toxicity study (the 2nd study)	0, 25, 50 ppm PM: 0, 1.91, 3.77 PF: 0, 2.10, 4.14 F_1M: 0, 1.88, 3.79 F_1F: 0, 2.16, 4.25	Parent and offspring: PM: 3.77 PF: 4.14 F1M: 3.79 F1F: 4.25 Parent and offspring: No toxicity (No effect on fertility is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	Developmental toxicity study (the 1st study)	0, 3, 10, 30	Dams: 3 Fetuses: 30 Dams: Abnormal gait Fetuses: No toxicity (No teratogenicity is observed.)
	Developmental toxicity study (the 2nd study)[a]	0, 1, 3, 10	Dams and fetuses: 10 Dams and fetuses: No toxicity (No teratogenicity is observed.)
Mouse	Four-week subacute toxicity study	0, 100, 300, 1 000 ppm M: 0, 43.1, 136, 407 F: 0, 50.4, 165, 433	M: 43.1 F: 50.4 M/F: Acinar cell hypertrophy of the submandibular salivary gland, etc.
	23-month carcinogenicity study	0, 50, 200, 800 ppm M: 0, 11.6, 45.8, 194 F: 0, 15.3, 63.0, 260	M: 45.8 F: 63.0 M/F: Suppressed body weight gain (No carcinogenicity is observed.)
	18-month carcinogenicity study	0, 200, 750, 1 400/1 600 ppm M: 0, 31.9, 115, 233 F: 0, 38.4, 141, 310	M: 31.9 F: 38.4 M/F: Suppressed body weight gain, etc. (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study (the 1st study)[a]	0, 5, 15, 45	Dams: 15 Fetuses: 45 Dams: Abortion, full-litter resorption Fetuses: No toxicity (No teratogenicity is observed.)
	Developmental toxicity study (the 2nd study)	0, 20, 60, 180	Dams: 20 Fetuses: 180 Dams: Suppressed body weight gain, decreased food intake, increased rate of post implantation loss Fetuses: No toxicity (No teratogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Dog	6-month subacute toxicity study	0, 65, 200, 600 ppm M: 0, 2.00, 6.57, 19.2 F: 0, 2.15, 6.74, 20.8	M: 6.57 F: 6.74 M/F: Decreased activity, abnormal gait, etc.
	One-year chronic toxicity study (the 1st study)	0, 40, 160, 640 ppm M: 0, 1.38, 5.54, 23.6 F: 0, 1.45, 5.70, 23.7	M: 5.54 F: 5.70 M/F: Soft feces, vomiting, etc.
	One-year chronic toxicity study (the 2nd study)	0, 50, 100, 360, 500 ppm M: 0, 1.36, 2.43, 10.6, 15.5 F: 0, 1.46, 3.61, 10.7, 18.0	M: 2.43 F: 3.61 M/F: Abnormal gait, abnormal posture

LOAEL, lowest-observed-adverse-effect level; NOAEL, No-observed-adverse-effect level
[1)] The adverse effect observed at LOAEL.
a, Aqueous solution preparations of Cremophor EL were used as solvent.

Table 2. *Levels relevant to toxicological evaluation of β-cyfluthrin*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)]
Rat	Four-week subacute toxicity study[a]	0, 0.25, 1, 4, 16	M/F: 1 M/F: Increased activity, salivation, etc.
	90-day subacute toxicity study	0, 30, 125, 500 ppm M: 0, 2.3, 9.5, 38.9 F: 0, 2.5, 10.9, 42.4	M: 9.5 F: 10.9 M/F: Abnormal gait, suppressed body weight gain, decreased food intake, etc.
	90-day subacute neurotoxicity study	0, 30, 125, 400 ppm M: 0, 2.02, 7.99, 26.8 F: 0, 2.34, 9.40, 30.8	M: 2.02 F: 2.34 M: Crust (auricle) F: Suppressed body weight gain, decreased food intake
	Developmental toxicity study[a]	0, 3, 10, 40	Dams and fetuses: 10 Dams: Decreased body weight, suppressed body weight gain, etc. Fetuses: Low body weight, delayed ossification (No teratogenicity is observed.)
	Developmental neurotoxicity study	0, 30, 125, 200 ppm Gestational period: 0, 2.4, 11.0, 17.8 Lactation period: 0, 5.9, 25.4, 40.9	Dams and fetuses: 11.0 Dams: Suppressed body weight gain, decreased food intake Fetuses: Suppressed body weight gain, etc. (No developmental neurotoxicity is observed.)
Dog	90-day subacute toxicity study	0, 10, 60, 360 ppm M: 0, 0.38, 2.38, 13.8 F: 0, 0.40, 2.46, 15.3	M: 2.38 F: 2.46 M/F: Ataxia, diarrhea, etc.

[1)] Adverse effect observed at LOAEL
a, Aqueous solution preparations of Cremophor EL were used as solvent

Table 3. *Potential adverse effects of a single oral administration of cyfluthrin*

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day)[1)]
Rat	Acute toxicity study (the 1st study)	M: 36, 73, 220, 280, 360, 460, 600, 780, 1 000, 1 300 F: 30, 60, 120, 360, 460, 600, 780, 1 000, 1 300, 1 700	M: 36 F: 30 M/F: Salivation, Straub's tail reaction, hypersensitivity to sound and touch stimuli, etc.
	Acute toxicity study (the 2nd study)	M: 10, 50, 80, 90, 100, 125, 140, 160, 180, 200, 250 F: 10, 50, 90, 100, 140, 160, 170, 180, 250	M/F: 10 M/F: Salivation, dyspnea, crouching and ataxic gait
	Acute toxicity study (the 3rd study) (Non-fasting)	M: 10, 50, 100, 500, 1 000, 1 500, 2 500 F: 10, 50, 100, 500, 750, 1 000, 1 500, 2 000, 2 500	M/F: 10 M/F: Restlessness, salivation, hyperactivity, etc.
	Acute toxicity study (the 3rd study)	M: 10, 50, 100, 250, 300, 350, 500, 750, 1 000, 2 500 F: 10, 50, 100, 500, 750, 1 000, 1 500, 2 500	M/F: 10 M/F: Restlessness, salivation, hyperactivity, etc.
	Acute toxicity study (the 4th study)[a]	M: 13, 15, 17.5, 20	M: - Death, tremor, circling, movement/breathing disorders
	Acute toxicity study (the 5th study)	M: 200, 250, 300, 350, 500	M: - Death, tremor, circling, movement/breathing disorders
	Acute toxicity study (the 6th study)	125, 150, 200, 350, 500, 750, 1 000	M: - Death, tremor, circling, movement/breathing disorders
	Acute toxicity study (the 7th study)	100, 250, 500, 1 000	M: - Tremor, circling, movement/breathing disorders

	Acute neurotoxicity study	M/F: 0, 5, 25, 75	M/F: 25 M/F: Salivation, decreased respiratory rate, abnormal gait, abnormal aerial righting reflex, etc.
	Four-week subacute toxicity study (the 1st study)	M: 8.27, 24.7, 78.9 F: 8.44, 25.2, 77.9	F: 25.2 F: Salivation
	90-day subacute toxicity study (the 2nd study)	M: 6.20, 18.5, 61.0 F: 7.24, 21.2, 68.5	M: 18.5 F: 21.2 M/F: Salivation, abnormal gait
Mouse	Acute toxicity study (the 1st study)	M: 15, 46, 60, 78, 100, 130, 170, 220, 280 F: 26, 78, 100, 130, 170, 220, 280	M: 15 F: 26 M/F: Salivation, hypersensitivity to sound and touch stimuli, etc.
	Acute toxicity study (the 2nd study)	M: 10, 50, 100, 500, 1 000, 2 000 F: 50, 100, 150, 500, 1 000, 2 000, 2 500	M: 10 F: 50 M/F: Restlessness, hyperkinesia, ataxia, etc.
	Four-week subacute toxicity study	M: 43.1, 136, 407 F: 50.4, 165, 433	M: 136 F: 165 M/F: Salivation
Rabbit	Acute toxicity study	M: 0, 100, 250, 500, 1 000	M: 100 M: Indifference, reduced appetite
Dog	Acute toxicity study	M: 0, 10, 50, 100	M: 10 M: Vomiting, indifference, reduced appetite

ARfD, Acute reference dose
-: NOAEL could not be specified.
[1)] The adverse effect observed at LOAEL
a, Aqueous solution preparations of Cremophor EL were used as solvent

Table 4. *Potential adverse effects of a single oral administration of β-cyfluthrin*

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day)[1)]
Rat	Acute toxicity study (the 1st study)	M: 0, 10, 50, 100, 250, 500, 710, 1 000, 1 400 F: 0, 10, 50, 100, 800, 1 000, 1 400, 1 500, 1 600, 2 000	M/F: 10 M/F: Increased activity, abnormal gait, salivation, etc.
	Acute toxicity study (the 1st study) (Non-fasting)	M: 0, 10, 100, 630, 800, 1 000, 1 400, 2 500 F: 0, 10, 100, 1 000, 1 400, 1 800, 2 000	M/F: 10 M/F: Increased activity, abnormal gait, salivation, etc.
	Acute toxicity study (the 2nd study)	M: 0, 1, 10, 50, 100, 250, 400, 500 F: 0, 1, 10, 100, 250, 315, 400, 500	M/F: 10 M/F: Lethargy, abnormal gait, salivation, etc.
	Acute toxicity study (the 2nd study) (Non-fasting)	M: 0, 1, 10, 100, 200, 250, 315, 355, 400, 500 F: 0, 1, 10, 100, 250, 355, 400, 450, 500	M/F: 10 M/F: Lethargy, abnormal gait, salivation, etc.
	Acute toxicity study (the 3rd study)	M: 0, 1, 10, 71, 100, 160, 250 F: 0, 1, 10, 63, 80, 100, 160	M/F: 1 M/F: Lethargy, abnormal gait, salivation, etc.
	Acute toxicity study (the 3rd study) (Non-fasting)	M: 0, 1, 10, 100, 160, 180, 200 F: 0, 1, 10, 71, 100, 160, 200, 250	M/F: 1 M/F: Lethargy, abnormal gait, salivation, etc.
	Acute neurotoxicity study (the 1st study)[a]	M/F: 0, 0.5, 2, 10	M: 2 F: 0.5 M: Ataxia, decreased activity, salivation, etc. F: Decreased locomotor activity and movement
	Four-week subacute toxicity study[a]	M/F: 0, 0.25, 1, 4, 16	M/F: 1 M/F: Increased activity, increased burrowing and grooming behaviors
	90-day subacute toxicity study	M: 0, 2.3, 9.5, 38.9 F: 0, 2.5, 10.9, 42.4	M: 9.5 F: 10.9 M/F: Abnormal gait
	Developmental toxicity study[a]	F: 0, 3, 10, 40	Dams: 10 Dams: Decreased activity, salivation, ataxia, reduced weight/suppressed weight gain, decreased food intake

Dog	90-day subacute toxicity study	M: 0, 0.38, 2.38, 13.8 F: 0, 0.40, 2.46, 15.3	M: 2.38 F: 2.46 M/F: Ataxia, diarrhea

[1)] The adverse effect observed at LOAEL.
a, Aqueous solution preparations of Cremophor EL were used as solvent.