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

Risk Assessment Report

Emamectin benzoate

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The FSCJ conducted a risk assessment of emamectin benzoate (CAS No. 155569-91-8, a mixture of emamectin B1a benzoate and emamectin B1b benzoate), a 16-membered macrocyclic lactone insecticide, based on submitted documents.

Test results used in the assessment include fate in plants (including cabbage and maize), residues in crops, fate in livestock etc. (goats, chickens and salmon), fate in cultured fishes (salmon and cod), residues in livestock and aquatic products, fate in animals (including rats and dogs), subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), acute neurotoxicity (rats), subacute neurotoxicity (rats), chronic neurotoxicity (rats), developmental neurotoxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and immunotoxicity (mice).

Major adverse effects of emamectin benzoate were observed in body weight (suppressed weight gain) and the nervous system (including degeneration of the brain, spinal cord, and sciatic nerve). No carcinogenicity, teratogenicity, genotoxicity, or immunotoxicity was observed.

In a two-generation reproductive toxicity study, both conception and fertilization rates decreased at doses that were toxic to parental animals.

In a developmental neurotoxicity study, a reduction in auditory startle response was observed in offspring at doses that were toxic to parental animals.

Based on these results, relevant substances for residue definition of dietary risk assessment were identified as emamectin benzoate and its metabolite (Ca/b) in agricultural products, emamectin benzoate (parent compound only) in livestock products, and emamectin B1a in aquatic products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from these studies was 0.25 mg/kg bw per day from the 90-day subacute toxicity study and the one-year chronic toxicity study in dogs. Taking into account the histopathological changes observed in the brain, spinal cord and peripheral nervous system at the lowest-observed-adverse-effect level (LOAEL) of 0.5 mg/kg bw per day and the small gap between the NOAEL and LOAEL obtained from these two tests, it was considered appropriate to adopt an

additional safety factor of 5. Consequently, an acceptable daily intake (ADI) of 0.0005 mg/kg bw per day (free base equivalent) was specified by applying a safety factor of 500 to the NOAEL of 0.25 mg/kg bw per day from the 90-day subacute toxicity study and the one-year chronic toxicity study in dogs.

Regarding potential adverse effects of a single oral administration of emamectin benzoate, while a NOAEL in an acute neurotoxicity study in rats was 5 mg/kg bw, potential adverse effects could not be ruled out for single oral administration in dogs at higher doses, since no test in this category was submitted for dogs. Moreover, tests on dogs revealed no neural symptoms at the highest dose of 1.5 mg/kg bw per day from the 90-day subacute toxicity study, nor from the exploratory five-week repeated-dose neurotoxicity study, nor were there any adverse effects observed in the nervous system in histopathological testing at one week of administration. After a comprehensive evaluation of these results, the FSCJ specified an acute reference dose (ARfD) of 0.015 mg/kg bw (free base equivalent) by applying a safety factor of 100 to the NOAEL of 1.5mg/kg bw per day from the 90-day subacute toxicity study and the exploratory five-week repeated-dose neurotoxicity study in dogs.

Table 1. *Levels relevant to toxicological evaluation of emamectin benzoate*

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Rat	90-day subacute toxicity study	0, 0.5, 2.5,12.5/8/5 M: 0, 0.5, 2.5, 6.7 F: 0, 0.5, 2.6, 7.1	M: 0.5 F: 2.6 M/F: Neuronal vacuolation in the brain, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 0.25, 1.0, 5.0/2.5 M: 0.25, 1.01, 4.85/2.63 F: 0.25, 1.01, 4.99/2.76	M/F: 1.01 M/F/: Neuronal vacuolation in the brain and spinal cord, etc. (No carcinogenicity is observed.)
	90-day subacute neurotoxicity study	0, 0.25, 1.0, 5.0 M: 0, 0.23, 0.95, 4.66 F: 0, 0.24, 0.95, 4.81	M/F: 0.95 M/F: Tremor, neuronal vacuolation in the brain and spinal cord, etc.
	One-year chronic neurotoxicity study	0, 0.1, 1.0, 2.5 (M), 5.0/2.5(F) M: 0, 0.10, 1.00, 2.50 F: 0, 0.10, 1.00, 3.34	M/F:1.0 M/F: Neuronal vacuolation in the brain and spinal cord, etc.
	Developmental neurotoxicity study	0, 0.1, 0.6, 3.6/2.5	Dams and offspring: 0.6 Dams: Suppressed body weight gain Offspring: Tremor, suppressed body weight gain, reduced auditory startle response, etc.
	Two-generation reproductive toxicity study (the 1st study)	0, 0.1, 0.6, 3.6/1.8 PM: 0, 0.10, 0.59, 3.62 PF: 0, 0.10, 0.60, 3.65 F_1M: 0, 0.1, 0.62, 3.69 F_1F: 0, 0.10, 0.63, 1.95	Parents, offspring, and fertility: PM: 0.59 PF: 0.60 F_1M: 0.62 F_1F: 0.61 Parents: Suppressed body weight gain, neuronal vacuolation in the brain and spinal cord, etc. Offspring: Tremor, suppressed body weight gain, etc. (Reduced conception and fertilization rates are observed.)

Rat (Cont'd)	Two-generation reproductive toxicity study (the 2nd study)	0, 0.1, 0.6, 1.8 PM: 0.10, 0.62, 1.86 PF: 0.10, 0.61, 1.84 F_1M: 0.11, 0.64, 1.90 F_1F: 0.11, 0.63, 1.89	Parents and offspring: PM: 0.59 PF: 0.56 F_1M: 0.60 F_1F: 0.55 Parents: M/F: Suppressed body weight gain, decreased food intake and decreased absolute weight of the brain Offspring: Tremor, decreased absolute weight of the brain, neuronal vacuolation in the brainstem, etc. (No effect on fertility is observed.)
	Developmental toxicity study	0, 2, 4, 8	Dams: 2 Fetuses: 4 Dams: Suppressed body weight gain Fetuses: Increases in skeletal variations and incomplete ossifications (No teratogenicity is observed.)
Mouse	90-day subacute toxicity study	0, 0.5, 1.5/10, 4.5, 15 M: 0, 0.49, 1.46/10.5, 4.46, 15.2 F: 0, 0.52, 1.53/10.4, 4.70, 15.6	(Reference material)
	18-month carcinogenicity study	0, 0.5, 2.5, 12.5/7.5/5.0(M), 12.5/7.5(F) M: 0, 0.50, 2.56, 6.57 F: 0, 0.51, 2.52, 10.63	M: 2.56 F: 2.52 M/F: Increased mortality, suppressed body weight gain (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study	0, 1.5, 3, 6	Dams: 3 Fetuses: 6 Dams: Mydriasis, loss of pupillary reflex and suppressed body weight gain Fetuses: No toxicity (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 0.5/0.25, 1.0/0.5, 1.5/1.0	M/F: 0.25 M/F: Degeneration of white matter in the brain, skeletal muscle atrophy, etc.

	One-year chronic toxicity study	0, 0.25, 0.5, 0.75, 1.0	M/F: 0.25 M/F: Degeneration of axons of the brain and peripheral nerves, etc.
ADI (cRfD)			NOAEL: 0.25 SF: 500 ADI: 0.0005
Critical studies for setting ADI			90-day subacute toxicity study (dog) and one-year chronic toxicity study (dog)

ADI, Acceptable daily intake; cRfD, Chronic reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor

Table 2. *Potential adverse effects of a single oral administration of emamectin benzoate*

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)	F: 40, 60, 90, 135 (solvate)	F: - Ataxia, tremor, etc.
		F: 40, 60, 90, 135 (hydrate)	F: - Ataxia, tremor, etc.
	Acute toxicity study (the 2nd study)	F: 40, 68, 116, 196, 344 (solvate)	F: - Tremor, decreased activity, etc.
		F: 40, 68, 116, 196, 344 (hydrate)	F: - Tremor, decreased activity, etc.
	Acute toxicity study (the 3rd study)	M/F: 32, 41.6, 54.1, 70.3, 91.4 (hydrate)	M/F: - Tremor
	Acute toxicity study (the 4th study)	F: 20.8, 65.8, 208, 657.9 (hydrate)	F: 65.8 Tremor, decreased activity, death
	Acute toxicity study (the 5th study)	M/F: 44.4, 66.6, 100, 150, 225 (hydrochloride salt)	M/F: - Tremor, ataxic gait, salivation, etc.
	90-day subacute toxicity study	M/F: 0.5, 2.5, 12.5/8/5 (hydrochloride salt) M: 0.5, 2.5, 11.0/6.8/4.8 F: 0.5, 2.6, 11.6/7.3/5.1	M: 2.5 F: 2.6 Tremor
	Acute neurotoxicity study (the 1st study)	M/F: 0, 27.4, 54.8, 82.2 (hydrochloride salt)	M/F: - Tremor, degeneration of white matter in the brain, degeneration of spinal cord white matter, sciatic nerve degeneration, etc.
	Acute neurotoxicity study (the 2nd study)	M/F: 0.5, 2.5, 5.0, 10, 25 (solvate)	M/F: 5.0 Tremor, irritability
Mouse	Acute toxicity study (the 1st study)	F: 60, 90, 135, 202 (solvate)	F: 60 Tremor, ataxia, decreased activity, etc.
		F: 60, 90, 135, 202 (hydrate)	F: 60 Tremor, ataxia, decreased activity, etc.
	Acute toxicity study (the 2nd study)	F: 5, 10, 20, 40, 80, 144, 259, 466 (solvate)	F: 40 Tremor, ataxia, decreased activity, etc.
		F: 5, 10, 20, 40, 80, 144, 259, 466 (hydrate)	F: 40 Tremor, ataxia, decreased activity, etc.
	Acute toxicity study (the 3rd study)	M/F: 70, 120, 192, 307(F) (hydrate)	M/F: - M: Tremor, ataxia, decreased activity, etc. F: Tremor
	Acute toxicity study (the 4th study)	F: 55, 175 (hydrate)	F: - Decreased activity, stooping position, etc.

	General pharmacological study (General condition)	M: 0, 20, 40, 80 (hydrate)	M: 40 Tremor, decreased locomotor activities, decreased startle response, decreased grip strength, etc.
Rabbit	General pharmacological study (General condition)	M: 0, 10, 20, 40, 80 (hydrate)	M: 20 Tremor, mydriasis, indifference, paralysis, etc.
Dog	90-day subacute toxicity study	M/F: 0, 0.5/0.25, 1.0/0.5,1.5/1.0 (hydrochloride salt)	M/F: 1.5 M/F: No neural symptoms observed at one week of administration
	Exploratory five-week repeated-dose neurotoxicity study	M/F: 0, 0.5, 1.5 (hydrochloride salt)	M/F: 1.5 M/F: No neural symptoms observed at one week of administration
ARfD			NOAEL: 1.5 SF: 100 ARfD: 0.015
Critical studies for setting ARfD			90-day subacute toxicity study (dogs) and exploratory five-week repeated-dose neurotoxicity study (dogs)

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