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

Risk Assessment Report

Validamycin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
September 2020

ABSTRACT

FSCJ conducted the risk assessment of a glycoside fungicide, validamycin (CAS No. 37248-47-8), based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice and lettuce), residues in plants, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (mice and rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, effects on microbiome.

Major adverse effects of validamycin observed are suppressed body weight (rats), disorders in the gastrointestinal tracts (diarrhea and loose stools). Validamycin showed no neurotoxicity, carcinogenicity, reproductive toxicity, and genotoxicity relevant to human health.
In a developmental toxicity study in rabbits, external- and skeletal anomalies were observed in fetuses at the highest dose (2000 mg/kg bw), in which the does showed serious toxicities. No teratogenicity was observed in rats.
Validamycin (parent compound only) was identified 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 40.4 mg/kg bw/day (36.8 mg/kg bw/day[1]) in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.36 mg/kg bw/day (converted into validamycin A) by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of validamycin was 500 mg/kg bw/day (327 mg/kg bw/day[1]) obtained from early change observed in a 90-day subacute toxicity study in dogs. FSCJ specified an acute reference dose (ARfD) to be 3.2 mg/kg bw (converted into validamycin A) by applying a safety factor of 100 to the NOAEL.

[1] The values in parenthesis are the converted values into validamycin A.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	Three-month subacute toxicity study	0, 1 000, 10 000, 100 000 ppm M/F: 0, 100, 1 000, 10 000 (0, 79.4, 794, 7 940)	M/F: 1 000 (794)	M/F: 10 000 (7 940)	M/F: Diarrhea, loose stools, and increased absolute weight of the caecum
	93-day subacute toxicity study	0, 1 000, 10 000, 100 000 ppm M/F: 0, 100, 1 000, 10 000 (0, 79.4, 794, 7 940)	M: 100 (79.4) F: 1 000 (794)	M: 1 000 (794) F: 10 000 (7 940)	M/F: Increased absolute weight of the caecum
	28-day subacute neurotoxicity study	0, 1 000, 3 000, 10 000 ppm M: 0, 87.3, 260, 886 (0, 58.2, 177, 591) F: 0, 93.1, 277, 897 (0, 62.1, 185, 599)	M: 886 (591) F: 897 (599)	M: - F: -	M/F: No toxicity was observed. (No subacute neurotoxicity)
	Two-year combined chronic toxicity/ carcinogenicity study	0, 100, 1 000, 10 000 ppm M: 0, 4.05, 40.4, 414 (0, 3.69, 36.8, 377) F: 0, 4.59, 47.2, 469 (0, 4.12, 43.0, 427)	M: 40.4 (36.8) F: 469 (427)	M: 414 (377) F: -	M: Suppressed body weight F: No toxicity was observed. (No carcinogenicity)
	Two-generation reproductive toxicity study (The 1st study)	0, 2 000, 6 000, 20 000 ppm PM: 0, 123, 371, 1 250 (0, 86.6, 261, 882) PF: 0, 156, 456, 1 490 (0, 110, 321, 1 050) F_1M: 0, 153, 460, 1 540 (0, 108, 324, 1 080) F_1F: 0, 175, 521, 1 760 (0, 123, 367, 1 240)	Parent and offspring: PM: 371 (261) PF: 456 (321) F_1M: 460 (324) F_1F: 521(367)	Parent and offspring: PM: 1 250 (882) PF: 1 490 (1 050) F_1M: 1 540 (1 080) F_1F: 1 760 (1 240)	Parent and offspring: M/F: Suppressed body weight (No reproductive toxicity)
	Developmental toxicity study	0, 100, 300, 1 000 (0, 70.4, 211, 704)	Dams and fetuses: 1 000 (704)	Dams and fetuses: -	Dams and fetuses: No toxicity was observed. (No teratogenicity)
Mouse	Three-month subacute toxicity study	0, 1 000, 10 000, 100 000 ppm M/F: 0, 143, 1430, 14 300 (0, 114, 1 140, 11 400)	M/F: 1 430 (1 140)	M/F: 14 300 (11 400)	M/F: Increased absolute weight of the caecum

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	89-day subacute toxicity study	0, 1 000, 10 000, 100 000 ppm M/F: 0, 143, 1430, 14 300 (0, 114, 1 140, 11 400)	M/F: 1 430 (1 140)	M/F: 14 300 (11 400)	M/F: Diarrhea, loose stools
	Two-year combined chronic toxicity/ carcinogenicity study	0, 100, 1 000, 10 000 ppm M: 0, 11.6, 114, 1 170 (0, 10.6, 114, 1 170) F: 0, 10.4, 101, 1 120 (0, 9.5, 91.9, 1 202)	M: 1 170 (1070) F: 1 120 (1 020)	M: - F: -	M/F: No toxicity was observed (No carcinogenicity)
Rabbit	Developmental toxicity study	The 1st study: 0, 125, 500, 2 000 (0, 115, 460, 1 840) Additional study: 0, 1 000, 2 000 (0, 913, 1 830)	Dams: 500 (460) Fetuses: 1 000 (913)	Dams: 1 000 (913) Fetuses: 2 000 (1 830)	Dams: Death, miscarriage Fetuses: skeletal and external anomaly)[2)]
Dog	90-day subacute toxicity study	0, 250, 500, 1 000 (0, 163, 327, 653)	M/F: 250 (163)	M/F: 500 (327)	M/F: Loose stools
	One-year chronic toxicity study	0, 50, 150, 500 (0, 32.7, 98.0, 327)	M/F: 150 (98.0)	M/F: 500 (327)	M/F: Loose stools
ADI			NOAEL: 36.8 SF: 100 ADI: 0.36 (converted into validamycin A)		
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study in rats		

Note: Parentheses are the values converted into validamycin A.
ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
-, NOAEL or LOAEL could not be specified.
[1)] The adverse effect observed at LOAEL
[2)] The anomaly was observed in the additional study

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

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]
Rat	Acute toxicity study (The 1st study)	10 000, 15 000, 20 000	M/F: - M/F: Diarrhea
	Acute toxicity study (The 3rd study)	F: 2 000 (1 270)	F: - F: Mucous stool
	93-day subacute toxicity study	0, 100, 1 000, 10 000 (0, 79.4, 794, 7 940)	M/F: 1 000 (794) M/F: Diarrhea, loose stools
Mouse	General pharmacology data (Body temperature)	0, 1 500, 5 000, 15 000	M: 1 500 M: Decreased body temperature
	Acute toxicity study (The 1st study)	10 000, 15 000, 20 000	M/F: - M/F: Diarrhea
	89-day subacute toxicity study	0, 143, 1 430, 14 300 (0, 114, 1 140, 11 400)	M/F: 1 430 (1 140) M/F: Diarrhea, loose stools
Dog	90-day subacute toxicity study	0, 250, 500, 1 000 (0, 163, 327, 653)	M/F: 500 (327) M/F: Loose stools
ARfD			NOAEL: 327 SF: 100 ARfD: 3.2 (converted into validamycin A)

Note: Parentheses are the values converted into validamycin A.
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