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

Risk Assessment Report

Acequinocyl (Fourth edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2022

ABSTRACT

The FSCJ conducted the risk assessment of acequinocyl (CAS No. 57960-19-7), based on various documents. This substance is a quinon group insecticide (acaricide) having a naphthoquinone framework. In the revision of the fourth edition, the additional test results of the following studies were submitted by the Ministry of Health, Labour and Welfare: residues in crops (sweet corn and Leafy aquatic vegetables); and acute neurotoxicity (rats).

The data used in the assessment include the fate in animals (rats and goats), fate in plants (eggplants, apples and oranges), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and others.

The major adverse effects of administration of acequinocyl from those test results were identified in the mechanism of blood coagulation. Neurotoxicity, carcinogenicity, effects on fertility, teratoxicity and genotoxicity in organism were not identified.

Consequently, the FSCJ specified acequinocyl and metabolite AKM-05 as the relevant substances for the residue definition on dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) obtained from all the studies was 2.25 mg/kg bw per day in two-year combined chronic toxicity/carcinogenicity study in rats. On the basis of this value, the FSCJ established an acceptable daily intake (ADI) of 0.022 mg/kg bw per day by applying a safety factor of 100.

The lowest NOAEL for possible adverse effects of a single oral administration was 7.3 mg/kg bw per day in two-generation reproductive toxicity study in rats. Accordingly, the FSCJ specified an acute reference dose (ARfD) of 0.073mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Rat	90-day subacute neurotoxicity study	0, 100, 400, 1 600, 3 200 ppm M: 0, 7.57, 30.4, 120, 253[2)] F: 0, 8.27, 32.2, 129, 286[2)]	M: 30.4 F: 32.2 M/F: APTT extension, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 50, 200, 800, 1 600 ppm M: 0, 2.25, 9.02, 36.4, 74.0 F: 0, 2.92, 11.6, 46.2, 93.6	M: 2.25 F: 11.6 M: Enlargement of eyeball F: Congestion spleen (No carcinogenicity is observed)
	Two-generation reproduction activity study	0, 100, 800, 1 500 ppm PM: 0, 7.3, 58.9, 111 PF: 0, 8.7, 69.2, 134 F_1M: 0, 8.2, 65.5, 124 F_1F: 0, 8.9, 70.4, 136	Parent: PM: 7.3 PF: 8.2 F_1M: 69.2 F_1F: 70.4 Offspring: PM: 7.3 PF: 8.2 F_1M: 8.7 F_1F: 8.9 Parent: PM: Bleeding PF: Absolute weight increase of spleen Offspring: Bleeding, swelling, death, etc. (No effect on fertility is observed)
	Developmental toxicity study	0, 50, 150, 500, 750	Dams: 150 Fetuses: 500 Dams: Bloody vaginal discharge (Bleeding), etc. Fetuses: Increased frequency of skeletal variations (No teratogenicity is observed)
Mouse	90-day subacute toxicity study	0, 100, 500, 1 000 ppm M: 0, 16, 81, 151 F: 0, 21, 100, 231	M: 16 F: 21 M/F: Hepatocyte vacuolation

	18-month carcinogenicity study	0, 20, 50, 150, 500 ppm M: 0, 2.7, 7.0, 20.3, 66.0 F: 0, 3.5, 8.7, 26.3, 86.0	M: 2.7 F: 3.5 M/F: Hepatic macrophage brown pigmentation deposition, etc. (No carcinogenicity is observed)
Rabbit	Developmental toxicity study	0, 30, 60, 120	Dams and Fetuses: 60 Dams: Significant weight loss, decrease of food intake Fetuses: Increase of embryo absorption in the emergently slaughtered dams (No teratogenicity is observed)
Dog	90-day subacute neurotoxicity study	0, 40, 160, 640, 1000	M: 40 F: 40 M/F: Suppressed weight gain, etc.
	One-year chronic toxicity study	0, 5, 20, 80, 320	M: 5 F: 20 M/F: PLT increase, etc.
ADI (cRfD)			NOAEL: 2.25 SF: 100 ADI: 0.022
The critical study for setting ADI (cRfD)			Two-year combined chronic/carcinogenicity study (rat)

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

[1)] The adverse effect observed at LOAEL

[2)] Average sample intake by the time of death as all rats were emergently slaughtered.

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

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	General pharmacological study (Urine・Electrolyte)	M: 0, 200, 600, 2 000	M: - M: Decreased urine output, decreased NA^+, K^+, $C1^-$ and protein excretion
	General pharmacological study (Blood coagulation)	M: 0, 200, 600, 2 000	M: - M: Extension of PT (prothrombin time), APTT (activated partial thromboplastin tie) and whole blood clotting, increase of Fbg (fibrinogen)
	Acute toxicity study	0, 5 000	M/F: - M/F: Watery diarrhea
	90-day subacute toxicity study	0, 100, 400, 1 600, 3 200 ppm M: 0, 7.57, 30.4, 120, 253 F: 0, 8.27, 32.2, 129, 286	M: 120 F: 129 M/F: Death due to multi-organ bleeding or emergently slaughtered
	Two-generation reproductive toxicity study	0, 100, 800, 1 500 ppm P generation: M: 0, 7.3, 58.9, 111 F: 0, 8.7, 69.2, 134 F_1 generation: M: 0, 8.2, 65.5, 124 F: 0, 8.9, 70.4, 136	PM: 7.3 PF: 8.7 F_1M: 8.2 F_1F: 8.9 Offspring F_1/F_2: Bleeding, swelling, and death
	Developmental toxicity study	0, 50, 150, 500, 750[2)]	Dams: 150 Dams: Emergently slaughtered due to brown body surface and eyes, piroerection, bradyplea and bloody vaginal discharge (bleeding)
Mouse	Acute toxicity study	0, 5 000	M/F: - M/F: Watery diarrhea
Dog	90-day subacute toxicity study	0, 40, 160, 640, 1 000	M/F: 160 Decreased body weight, decreased feed consumption and vomiting
ARfD			NOAEL: 7.3 SF: 100 ARfD: 0.073
The critical study for setting ARfD			Two-generation developmental toxicity (rat)

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor
[1)] The adverse effect observed at LOAEL.
[2)] The administration was discontinued for the group dosed 750 mg/kg bw per day because significant toxicity was observed in 10-13 days pregnant dams.
-, NOAEL could not be specified.