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

Risk Assessment Report

Dimethomorph (Fourth edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
February 2023

ABSTRACT

The FSCJ conducted the risk assessment of dimethomorph (CAS No. 110488-70-5), a cinnamic acid derivative fungicide, based on various documents. 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 (cabbage, leaves, etc.); metabolism in livestock (goats and chickens); residues in livestock products (lactating cows); fate in animals (rats); acute neurotoxicity (rats); one-generation reproductive toxicity (rats); and others.

The test results used in the assessment include the data on metabolism in plants (grapes, potatoes, etc.), residues in crops, metabolism in livestock (goats and chickens) , residues in livestock products, fate in animals (rats), subacute toxicity (rats and dogs), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), acute neurotoxicity (rats), subacute neurotoxicity (rats), one and two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity and others.

The major adverse effects of dimethomorph were observed in body weight (suppressed weight gain) and liver (increased organ weights, hepatocyte vacuolation, etc.). Carcinogenicity, effects on fertility, teratogenicity, biologically significant genotoxicity and immunotoxicity were not identified.

Although a decrease of momentum in locomotor activities was observed in an acute neurotoxicity study using rats, the effects due to the dose of dimethomorph were not observed in a neuropathological examination.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 11.3 mg/kg bw per day in a two-year carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.11 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of dimethomorph was 30 mg/kg bw in a general pharmacological study using mice and the lowest-observed-effect-level (LOEL) was 100 mg/kg bw. Meanwhile, despite different species, the NOAEL was 60 mg/kg bw per day and the

lowest-observed-adverse-effect-level (LOAEL) was 120 or more mg/kg bw per day in an acute neurotoxicity study (the second study) and a developmental toxicity study in rats. Accordingly, the FSCJ specified an acute reference dose (ARfD) of 0.6 mg/kg bw by applying a safety factor of 100 to the NOAEL of 60 mg/kg bw per day in an acute neurotoxicity study (the second study) and a developmental toxicity study in rats, after comprehensive consideration of the difference in setting dose in each test, observed toxic effects and their levels.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
Rat	90-day subacute toxicity study	0, 40, 200, 1 000 ppm M: 0, 2.9, 14.2, 73 F: 0, 3.2, 15.8, 82	M: 73 F: 82 M/F No toxicity
	Two-year chronic toxicity study	0, 200, 750, 2 000 ppm M: 0, 9.4, 36.3, 99.9 F: 0, 11.9, 57.7, 158	M: 36.3 F: 11.9 M: Suppressed body weight gain, etc. F: Suppressed body weight gain, etc.
	Two-year carcinogenicity study	0, 200, 750, 2 000 ppm M: 0, 8.8, 33.8, 94.6 F: 0, 11.3, 46.3, 133	M: 33.8 F: 11.3 M: Suppressed body weight gain, etc. F: Suppressed body weight gain, etc. (No carcinogenicity is observed.)
	Acute neurotoxicity study (the 1st study)	0, 250, 500, 2 000	M/F: Less than 250 M/F: Decreased momentum in locomotor activities, etc.
	Acute neurotoxicity study (the 2nd study)	F: 0, 30, 60, 120	F: 60 F: Decreased momentum in locomotor activities
	90-day subacute neurotoxicity study	0, 300, 800, 2 400 ppm M: 0, 21.5, 58.7, 178 F: 0, 25.5, 69.6, 204	M: 58.7 F: 69.6 M/F: Suppressed body weight gain, decreased food consumption, etc. (No subacute neurotoxicity is observed.)
	One-generation reproductive toxicity study	0, 300/150, 800/400, 1 600/800 ppm PM: 0, 23.4, 63.0, 128 PF: 0, 25.0, 66.8, 137 F_1M: 0, 27.8-28.1, 73.7-75.8, 152-154 F_1F: 0, 28.0-28.7, 73.4-74.1, 158-159	PM: 63.0 PF: 25.0 F_1M: 27.8-28.1 F_1F: 28.0-28.7 P M/F: Suppressed body weight gain F_1M: Reduction in the length of anogenital distance (AGD), etc. F_1F: Suppressed body weight gain, etc. (No effect on fertility is observed.)
	Two-generation reproductive toxicity study	0, 100, 300, 1 000 ppm PM: 0, 6.9, 20.8, 69.0 PF: 0, 8.0, 24.0, 79.3 F_1M: 0, 7.9, 23.7, 78.6 F_1F: 0, 8.9, 27.0, 89.2	Parent: PM: 69.0 PF: 24.0 F_1M: 78.6 F_1F: 27.0 Offspring: PM: 69.0

Species	Study	Dose (mg/kg bw per day)	NOAEL[1)] (mg/kg bw per day)
			PF: 79.3 F_1M: 78.6 F_1F: 89.2 <u>Parent:</u> M: No toxicity F: Suppressed body weight gain, etc. <u>Offspring:</u> No toxicity (No effect on fertility is observed.)
	Developmental toxicity study	0, 20, 60, 160	Dams: 60 Fetuses: 60 Dams: Suppressed body weight gain, decreased food consumption Fetuses: Slight increase in post-implantation embryo mortality rate (No teratogenicity is observed.)
Mouse	Two-year carcinogenicity study	0, 10, 100, 1 000 Actual measurement M: 0, 9.8, 98.0, 978 F: 0, 9.8, 96.8, 977	M: 98.0 F: 96.8 M/F: Suppressed body weight gain (No carcinogenicity is observed.)
Rabbit	Developmental toxicity study	0, 135, 300, 650	Dams: 300 Fetuses: 650 Dams: Suppressed body weight gain, decreased food consumption, increase in miscarriages Fetuses: No toxicity. (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 150, 450, 1 350 ppm M: 0, 5.0, 15.3, 43.1 F: 0, 6.0, 15.5, 43.7	M: 15.3 F: 15.5 M/F: Increase of ALP, etc.
	One-year chronic toxicity study	0, 150, 450, 1 350 ppm M: 0, 4.9, 14.7, 44.6 F: 0, 5.0, 15.7, 47.0	M: 14.7 F: 15.7 M/F Increase of ALP, increase of liver weight, etc.
ADI (cRfD)			NOAEL: 11.3 ADI: 0.11 SF: 100
The critical study for setting ADI			Two-year carcinogenicity study (rat)

NOAEL: No-observed-adverse-effect level, SF: Safety factor, ADI: Acceptable daily intake,
UF: Uncertainty, cRfD: Chronic reference dose, ALP: Alkaline Phosphatase

[1)] The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD [a)] (mg/kg bw or mg/kg bw per day)
Rat	Acute toxicity study (the 1st study)	3 200, 4 000, 5 000	M/F: － M/F: Piloerection, hunchback position, gait abnormality, lethargy, slowing of breathing rate, drooping eyelids, Raynaud's syndrome symptoms, etc.
	Acute toxicity study (the 2nd study)	2 000	F: － F: Deterioration of generalized condition, breathing difficulty, and piloerection
	Acute toxicity study (Material E)	4 000, 5 000	M/F: － M/F: Piloerection, half-closed eyes, retraction of abdomen, motor inhibition, breathing difficulty, pale feces, etc.
	Acute toxicity study (Material Z)	4 000, 5 000	M/F: － M/F: Pale feces
	Acute neurotoxicity study (the 1st study)	0, 250, 500, 2 000	M/F: － M/F: Decreased times of standups and decreased momentum in locomotor activities
	Acute neurotoxicity study (the 2nd study)	F: 0, 30, 60, 120	F: 60 F: Decreased momentum in locomotor activities
	Developmental toxicity study	0, 20, 60, 160	Dams: 60 Dams: Suppressed body weight gain and decreased food consumption
Mouse	Acute toxicity study	M: 5 000 mg/kg F: 1 000, 1 500, 2 230, 3 340, 5 000 mg/kg	M: － F: 1 000 M: Prostration, piloerection and soiled fur F: Piloerection, ataxia and soiled fur
	General pharmacological study (General condition)	30, 100, 300	M: 30 M: Apathy, gasping respiration and piloerection F: Increased aggression (of mice) in a cage and apathy
Rabbit	Developmental toxicity study	0, 135, 300, 650	Dams: 300 Dams: Decreased food consumption
ARfD			NOAEL: 60 SF: 100 ARfD: 0.6
The critical study for setting ARfD			Acute neurotoxicity study (the 2nd study) and developmental toxicity study (rat)

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

－: NOAEL could not be specified.

[a)] The adverse effect observed at LOAEL.