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

Risk Assessment Report

1,3-Dichloropropene (Fifth edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The FSCJ conducted a risk assessment of 1,3-dichloropropene (CAS No.542-75-6), an insecticide, based on submitted documents. For this fifth edition, a request for reevaluation was made in accordance with the Agricultural Chemicals Regulation Act, whereby additional test results were submitted by the Ministry of Agriculture, Forestry and Fisheries, including results from acute oral toxicity (rats), subacute inhalation toxicity (rats and mice), genotoxicity studies, as well as reports on published scientific literature.

Test results used in the assessment include fate in plants (including lettuce and spinach), residues in crops, fate in animals (rats and mice), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (mice), reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and immunotoxicity (rats).

Major adverse effects of 1,3-dichloropropene were observed in the stomach (including hyperplasia of the forestomach squamous epithelium and hyperkeratosis), bladder (transitional cell hyperplasia), and blood (anemia). No effects on fertility, teratogenicity, biologically significant genotoxicity, or immunotoxicity were observed. Although reproductive and developmental toxicity studies have not been conducted by oral administration, based on the pulmonary absorption rate derived from the animal fate study conducted by inhalation exposure in rats, the estimated sample intake for the reproductive and developmental toxicity studies conducted by inhalation exposure was considered to not fall below the sample intake in long-term toxicity studies. There were no findings in humans that raised concerns over adverse health effects of 1,3-dichloropropene ingested through food.

In carcinogenicity studies, an increased incidence of hepatocellular adenomas was observed in male and female rats and an increased incidence of bronchioloalveolar adenomas was observed in male and female mice. However, the mode of action was considered to be non-genotoxic, and it was deemed possible to establish a threshold for evaluation.

Based on these results, 1,3-dichloropropene (parent compound only) was identified as the relevant substance for the residue definition of dietary risk assessment in agricultural products.

Although the lowest no-observed-adverse-effect level (NOAEL) among the studies conducted was 2 mg/kg bw per day in the two-year combined chronic toxicity/carcinogenicity study in rats (the 1st study), the NOAEL in the two-year chronic toxicity/carcinogenicity study in rats (the 2nd study) was 2.5 mg/kg bw per day, with the discrepancy likely due to differences in dose settings. Therefore, it was considered reasonable to establish a NOAEL of 2.5 mg/kg bw per day in rats. Based on the above, the FSCJ specified an acceptable daily intake (ADI) of 0.025 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 1,3-dichloropropene was 20 mg/kg bw per day in a two-week subacute toxicity study in dogs.
The FSCJ specified an acute reference dose (ARfD) of 0.2 mg/kg bw by applying a safety factor of 100 to this NOAEL.

Table 1. *Levels relevant to toxicological evaluation of 1,3-dichloropropene*

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
Rat	90-day subacute toxicity study (the 1st study)	0, 5, 25, 50, 100	M/F: 5 M/F: Hyperplasia and hyperkeratosis of the forestomach squamous epithelium
	90-day subacute toxicity study (the 2nd study)	0, 5, 15, 50, 100	M: - F: 5 M: Suppressed body weight gain F: Hyperkeratosis of the forestomach squamous epithelium, basal cell hyperplasia, suppressed body weight gain
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 2, 10, 25	M/F: 2 M/F: Hyperplasia and hyperkeratosis of the forestomach squamous epithelium, etc. (No carcinogenicity is observed.)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 2.5, 12.5, 25	M/F: 2.5 M/F: Suppressed body weight gain, decreased TG, basal cell hyperplasia of the forestomach (Increased incidence of hepatocellular adenoma)
	A comprehensive evaluation of the 1st and 2nd two-year combined chronic toxicity/carcinogenicity studies		M/F: 2.5
	Two-generation reproductive toxicity study (inhalation exposure)	0, 5, 20, 60 ppm (Until day seven of administration) 0, 10, 30, 90 ppm (Day eight of administration and onward)	Parents M/F: 18.5 Offspring: 55.5 Parents M: Suppressed body weight gain, hyperplasia and degeneration of the respiratory epithelium F: Stomach ulcer Offspring: No toxicity (No effect on fertility is observed.)
		0, 6.2, 18.5, 55.5 (Oral dose equivalent on day eight of administration and onward) 0, 3.1, 9.25, 27.8 (Estimated sample intake considering pulmonary absorption rate)	

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	Developmental toxicity study (the 1st study) (inhalation exposure) [a]	0, 10, 30, 90 ppm 0, 8.6, 25.9, 77.6 (Oral dose equivalent) 0, 4.3, 13.0, 38.8 (Estimated sample intake considering pulmonary absorption rate)	Dams: 25.9 Fetuses: 77.6 Dams: Suppressed body weight gain, decreased food and water intake Fetuses: No toxicity (No teratogenicity is observed.)
	Developmental toxicity study (the 2nd study) (inhalation exposure) [a]	0, 20, 60, 120 ppm 0, 17.3, 51.8, 104 (Oral dose equivalent) 0, 8.65, 25.9, 52.0 (Estimated sample intake considering pulmonary absorption rate)	Dams: - Fetuses: 51.8 Dams: Suppressed body weight gain, decreased food intake Fetuses: Increased incidence of delayed ossification of the centrum vertebrae (No teratogenicity is observed.)
	90-day subacute inhalation toxicity study [a]	0, 10, 30, 90, 150 ppm 0, 5.7, 17.0, 51.1, 85.1 (Oral dose equivalent)	M/F: 17.0 M/F: Suppressed body weight gain, etc. (Changes in the nasal epithelium were observed in males at 30 ppm and above, and females at 90 ppm and above as primary stimulus)
	Two-year combined chronic toxicity/carcinogenicity study (inhalation exposure)	0, 5, 20, 60 ppm 0, 2.8, 11.3, 34.0 (Oral dose equivalent) 0, 1.4, 5.65, 17.0 (Estimated sample intake considering pulmonary absorption rate)	M/F: 11.3 M/F: Suppressed body weight gain (Changes in the nasal epithelium were observed in both males and females at 60 ppm as primary stimulus) (No carcinogenicity is observed.)
Mouse	90-day subacute toxicity study (the 1st study)	0, 10, 50, 100, 200	M/F: 10 M/F: Hyperkeratosis of the forestomach, hyperplasia of the forestomach squamous epithelium, etc.
	90-day subacute toxicity study (the 2nd study)	0, 15, 50, 100, 175	M/F: 15 M/F: Suppressed body weight gain

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	Two-year combined chronic toxicity/carcinogenicity study	0, 2.5, 25, 50	M/F: 2.5 M/F: Suppressed body weight gain, decreased food intake (No carcinogenicity is observed.)
	18-month carcinogenicity study	0, 2, 10, 25	M/F: 10 M/F: Hyaline changes in the bladder, etc. (No carcinogenicity is observed.)
	90-day subacute inhalation toxicity study [a]	0, 10, 30, 90, 150 ppm --- 0, 10.3, 31.0, 93.0, 155 (Oral dose equivalent)	M: 31.0 F: 10.3 M: Suppressed body weight gain, etc. F: Infiltration of submucosal mononuclear cells in the bladder (Changes in the nasal epithelium were observed in females at 90 ppm as primary stimulus)
	Two-year combined chronic toxicity/carcinogenicity study (inhalation exposure)	0, 5, 20, 60 ppm --- 0, 5.2, 20.7, 62.0 (Oral dose equivalent)	M/F: 5.2 M/F: Epithelial hyperplasia in the bladder (Changes in the nasal epithelium were observed in males and females at 20 ppm as primary stimulus) (Increased incidence of bronchioloalveolar adenomas)
Rabbit	Developmental toxicity study (inhalation exposure) [a]	0, 20, 60, 120 ppm --- 0, 12.3, 36.8, 73.5 (Oral dose equivalent)	Dams: 12.3 Fetuses: 73.5 Dams: Decreased weight, suppressed body weight gain Fetuses: No toxicity (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 130, 380, 1 000 ppm --- M:0, 4.7, 14.5, 40.9 F:0, 5.0, 16.2, 41.4	M: 4.7 F: 5.0 M/F: Suppressed body weight gain, etc.

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	One-year chronic toxicity study	0, 0.5, 2.5, 15	M/F: 2.5 M/F: Suppressed body weight gain, etc.
ADI			NOAEL: 2.5 SF: 100 ADI: 0.025
The critical study for setting ADI			Comprehensive evaluation of the 1st and 2nd two-year combined chronic toxicity/carcinogenicity studies (rat)

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor; TG, triglyceride
[1)] The adverse effect observed at LOAEL.
-, NOAEL could not be specified
[a], Produced using technical grade active ingredient with epichlorohydrin added as stabilizer

Table 2. *Potential adverse effects of a single oral administration of 1,3-dichloropropene*

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	100, 500, 1 000	M/F: - M/F: Diarrhea
	Acute toxicity study	F: 300, 2 000	F: - F: Diarrhea, decreased locomotor activities, etc.
	Acute toxicity study	F: 300, 2 000	F: - F: Diarrhea, decreased locomotor activities, etc.
Mouse	General pharmacological study (general condition)	M: 0, 3, 10, 30, 100, 300, 1 000	M: 30 M: Decreased grooming and locomotor activities
Dog	Two-week subacute toxicity study	0, 10, 20, 40	M/F: 20 M/F: Increased frequency of vomiting (day two of administration and onward)
ARfD			NOAEL: 20 SF: 100 ARfD: 0.2
The critical study for setting ARfD			Two-week subacute toxicity study (dog)

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