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

Risk Assessment Report

Dichlorprop

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of dichlorprop (CAS No. 120-36-5), a chlorophenoxy plant growth regulator, based on results from various studies. In the same assessment, FSCJ also evaluated dichlorprop P (CAS No. 15165-67-0) using data from the assessments conducted in Europe, the United States of America, and Australia. Dichlorprop P is a pesticide of racemic mixture which contains racemic body of dichlorprop as an active ingredient.

The data used in the assessment include the fate in animals (rats and goats), fate in plants (wheat and apple), residues in crops, subacute toxicity (rats, mice and dogs), combined subacute toxicity/neurotoxicity (rats), chronic toxicity (dogs), combind chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two- and three-generation reproductivity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of dichlorprop and dichlorprop P observed were suppressed body weight, hepatocellular hypertrophy and necrosis in tha liver, and increased kidney weight. No neurotoxicity, carcinogenicity, teratogenicity and genotoxicity relevant to human health was observed. In a two-generation reproductivity study of dichlorprop in rats, decreased copulation index and birth rate were observed.

Based on the results from various studies, dichlorprop (parent compounds, including dichlorprop P) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all tests was 3.64 mg/kg bw/day in a two-year combind chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.036 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest value of NOAEL or LOAEL for potential adverse effects of single oral administration of dichlorprop was 30 mg/kg bw, NOEL obtained in an general pharmacological study in mice. FSCJ specified an acute reference dose (ARfD) to be 0.3 mg/kg bw by applying a safety factor of 100 to the NOAEL.

Table 1. *Levels relevant to toxicological evaluation of dichlorprop and dichlorprop P*

Technical product	Species	Study	Dose (mg/kg bw/day)	NOAEL[1)] (mg/kg bw/day)
Dichlorprop	Rat	90-day subacute toxicity study	0, 100, 500, 2 500 ppm 0, 5, 25, 125	M/F: 25 M/F: Suppressed body weight
		Two-year combined chronic toxicity/carcinogenicity study	0, 100, 300, 1 000, 3 000 ppm M: 0, 3.64, 11.0, 36.5, 116 F: 0, 4.42, 13.1, 45.7, 147	M: 3.64 F: 13.1 M/F: Decreased urinary specific gravity (No carcinogenicity)
		Three-generation reproductive toxicity study	0, 125, 500, 2 000/1 000 ppm PM: 0, 11.1, 42.5, 172 F_1M: 0, 11.3, 44.2, 99.2 F_2M: 0, 12.5, 52.6, 107 PF: 0, 11.3, 45.3, 179 F_1F: 0, 10.7, 43.2, 86.1 F_2F: 0, 12.3, 50.7, 93.4	Parent and Offspring PM: 42.5 F_1M: 44.2 F_2M: 52.6 PF: 45.3 F_1F: 43.2 F_2F: 50.7 Parent and Offspring: Suppressed body weight (No effect on reproduction)
		Two-generation reproductive toxicity study	0, 80, 400, 2 000 ppm M: 0, 8.0, 40.1, 220 F: 0, 8.7, 43.0, 233	Parent M: 40.1 F: 43.0 Offspring M: 40.1 F: 43.0 Dams: Suppressed body weight, and effects on the liver and kidney Offspring: A decrease in survival rate Reproductivity M:40.1 F: 43.0 Reproductivity A decrease in birth rate

		Developmental toxicity study	M/F: 0, 8, 20, 50, 125	Dams and fetuses: 125 Dams and fetuses: No observed toxicity (No teratogenicity)
	Mouse	90-day subacute toxicity study	0, 100, 300, 1 000, 3 000 ppm M: 0, 12.1, 37.1, 121, 365 F: 0, 14.2, 43.6, 146, 447	M: 37.1 F: 146 M/F: Multinucleated epithelial cells in distal convoluted tubules
	Rabbit	Developmental toxicity study	0, 12, 30, 75	Dams and fetuses: 75 Dams and fetuses: No observed toxicity (No teratogenicity)
	Dog	90-day subacute toxicity study	0, 78, 303, 1 210 ppm 0, 3, 12, 48	M/F: 3 M/F: decreased excretion of phenol sulfonphthalein (PSP) in urine
		One-year chronic toxicity study	0, 3, 8, 20	M/F: 8 M: Acidophil in the kidney F: Microgranuloma of the liver
Dichlorprop P	Rat	90-day subacute toxicity study	0, 100, 500, 2 500 ppm 0, 5, 25, 125	M: 25 F: 25 M/F: Effects on body weight
		90-day combined subacute toxicity/subacute neurotoxicity study	0, 100, 500, M: 2,000 F: 3 000 ppm M: 0, 7, 35, 144 F: 0, 8, 42, 245	M: 35 F: 42 M/F: Suppressed body weight (No subacute neurotoxicity)
		Developmental toxicity study	0, 20, 80, 160	Dams and fetuses: 20 Dams: Suppressed body weight Fetuses: Increased cervical rib (No teratogenicity)
	Mouse	90-day subacute	0, 100, 1 000, 2 500	M: 224

		toxicity study	M: 0, 20, 224, 683 F: 0, 33, 380, 1 040	F: 380 M/F: Eosinophilic hepatocytes
		78-week carcinogenicity study	0, 40, 400, 800 ppm M: 0, 6, 59 F: 0, 8, 75, 143	M: 6 F: 8 M: Suppressed body weight F: Chronic progressive nephropathy (No carcinogenicity)
	Rabbit	Developmental toxicity study	0, 20, 50, 100	Dams and fetuses: 50 Dams: Death, decreased body weight and decreased feed consumption. Fetuses: Increased accessory13th ribs (No teratogenicity)
	Dog	90-day subacute toxicity study	0, 25, 175, 525 ppm M: 0, 0.7, 5.1, 15.7 F: 0, 0.8, 5.8, 18.1	M: 5.1 F: 5.8 M/F: Diarrhea and a decrease in RBC
		One-year chronic toxicity study	0, 120, 240, 720 ppm M: 0, 3.5, 7.0, 22.2 F: 0, 3.9, 7.7, 26.1	M: 7.0 F: 7.7 M: Lymphocyte infiltration in the kidney F: Suppressed body weight
ADI (cRfD)				NOAEL: 3.64 SF: 100 ADI: 0.036
The critical study for setting ADI (cRfD)				Two-year combined chronic toxicity/carcinogenicity study in rats

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F_1M, Male in F_1 generation; F_2M, Male in F_2 generation; F_1F, Female in F_1 generation; F_2F, Female in F_2 generation; ADI, Acceptable daily intake; cRfD, Chronic reference dose; UF, Uncertainty factor; SF, Safety factor; NOAEL, No-observed-adverse-effect level; NOEL, No-observed-effect level; -, NOAEL could not be specified

[1)], The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL)

Table 2. *Potential adverse effects of a single oral administration of dichlorprop or dichlorprop P*

Technical product	Species	Study	Dose (mg/kg bw)	NOAEL (mg/kg bw/day) and critical endpoints[1)]
Dichlorprop	Rat	Acute toxicity study	M: 650, 740, 850, 970, 1 100, 1 250, 1 430, 1 860, 2 410 F: 650, 850, 1 100, 1 430, 1 860, 2 410	M/F: - Depression, muscle hypertonia, gait disturbance
			M/F: 200, 400, 600, 800, 1 000	M/F: - M/F: Suppressed locomotor activity
			M/F: 464, 825, 1 470, 2 150	M/F: 464 M/F: Breathing difficulty, ataxic gait, aggravation of general symptoms F: Indifference
	Mouse	General pharmacology data (General state)	M: 0, 30, 100, 300	M: 30 M: Abnormal walking, suppressed locomotor activity
		General pharmacology data (Locomotor activity)	M: 0, 30, 100, 300	M: 30 Decrease in locomotor activity
		Acute toxicity study	M: 650, 850, 1 100, 1 430, 1 860, 2 410 F: 850, 1 100, 1 430, 1 860, 2 410	M: - F: - M/F: Depression, muscle hypertonia, abnormal walking due to spasmodic gait, lacrimation, clonus
			M/F: 100, 200, 400, 600, 800, 1 000	M/F: - M/F: Ataxia, hypersensitivity, Straub tail
Dichlorprop P	Rat	Acute neurotoxicity study	0, 125, 250, 400, 500	M/F: 125 Decrease in locomotor activity
	Rabbit	Developmental toxicity study	0, 20, 50, 100	Dams: 50 Dams: decrease in body weight and food intake
ARfD				NOAEL: 30 SF: 100 ARfD: 0.3
The critical study for setting ARfD				General pharmacology data in mouse

-, NOAEL could not be specified
[1)], The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL)