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

Risk Assessment Report

Iprodione

(Pesticides)

Food Safety Commission of Japan (FSCJ)
November 2021

ABSTRACT

The FSCJ conducted a risk assessment of iprodione (CAS No.36734-19-7), a dicarboximide fungicide, based on submitted documents.

The data used in the assessment include fate in animals (rats, cattle, goats and chickens), fate in plants (including paddy rice and lettuce), residues in crops, subacute toxicity (rats and mice), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), three-generation reproductive toxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of iprodione were observed in body weight (suppressed weight gain), red blood cells (Heinz body in dogs), the liver (hepatocellular hypertrophy in mice), the adrenal gland (including hypertrophy of the zona glomerulosa cells in the adrenal cortex) and the testis (including testicular interstitial cell tumor in rats and mice). Neither teratogenicity nor genotoxicity was observed.

In carcinogenicity studies, an increased incidence of testicular interstitial cell tumors was observed in rats, and increased incidences of both hepatocellular tumors and hepatocellular carcinomas were observed in mice. However, the mode of action was considered to be non-genotoxic, and it was deemed possible to establish a threshold for evaluation.

In a two-generation reproduction study using rats, decreases were observed in both in the average number of offspring and the number of surviving pups after birth.

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

The lowest value among the no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) obtained from each study was a NOAEL of 4.12 mg/kg bw per day in male dogs from the one-year chronic toxicity study (the 1st study). An acceptable daily intake (ADI) of 0.041 mg/kg bw per day can be calculated by applying a safety factor of 100 to this NOAEL. Meanwhile, no NOAEL was identified in males of a two-year combined chronic toxicity/carcinogenicity study using rats (the 2nd study), with a LOAEL of 6.1 mg/kg bw per day. Considering an additional safety factor of 3 for this study, the resulting ADI is 0.02 mg/kg bw per day, which is lower than the 0.041 mg/kg bw per day

derived from the one-year chronic toxicity study using dogs (the 1st study). Therefore, the FSCJ determined that it is appropriate to establish the ADI based on the LOAEL in males from the two-year combined chronic toxicity/carcinogenicity study using rats (the 2nd study).

Accordingly, based on the LOAEL of 6.1 mg/kg bw per day obtained from the two-year chronic toxicity/carcinogenicity study (the 2nd study) in rats, the FSCJ specified an ADI of 0.02 mg/kg bw per day by applying a safety factor of 300, which includes the standard safety factor of 100 and an additional factor of 3 to account for the use of the LOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration was 90 mg/kg bw per day from a developmental toxicity study (the 2nd study) in rats, in which adverse effects observed were increases in small fetuses and cavities between visceral organs and body walls of fetuses at doses that were not maternally toxic. Therefore, the FSCJ specified an acute reference dose (ARfD) of 0.9 mg/kg bw for pregnant or potentially pregnant women by applying a safety factor of 100 to this NOAEL.

Regarding potential adverse effects of a single oral administration for the general population, NOAEL and LOAEL values were compared, of which the lowest value was a LOAEL of 900 mg/kg bw obtained from an acute toxicity study (the 1st study) in rats. Although no NOAEL was identified from the test results, it was considered to be above the cut-off level (500 mg/kg bw) after a comprehensive evaluation of acute toxicity studies in rats and mice, thus it was deemed unnecessary to specify an ARfD.

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

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, 300, 1 000, 3 000 ppm M: 0, 20.5, 70.0, 205 F: 0, 23.7, 81.8, 240	M: 20.5 F: 23.7 M/F: Hypertrophy of the zona glomerulosa cells of the adrenal cortex
	90-day subacute toxicity study (the 2nd study)	0, 250, 500, 800, 3 000 ppm M: 0, 15.1, 30.8, 48.9, 183 F: 0, 17.6, 35.8, 56.3, 229	M: 30.8 F: 35.8 M/F: Vacuolation of zona fasciculata and zona glomerulosa cells of the adrenal cortex, etc.
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 125, 250, 1 000 ppm M: 0, 5.3, 10.5, 42.9 F: 0, 6.7, 13.4, 55.1	M: 10.5 F: 13.4 M/F: Suppressed body weight gain and decreased food intake (No carcinogenicity is observed)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 150, 300, 1 600 ppm M: 0, 6.1, 12.4, 69 F: 0, 8.4, 16.5, 95	M: - F: 8.4 M: Micro-vacuolation of zona reticularis cells of the adrenal cortex F: Hypertrophy of the zona glomerulosa cells of the adrenal cortex, hemosiderin deposition in the spleen (Increased incidence of testicular interstitial cell tumor)
	Three-generation reproductive toxicity study	0, 125, 250, 1 000 ppm (First five weeks) 0, 250, 500, 2 000 ppm (Next eight weeks) PM: 0, 15, 29, 119 PF: 0, 17, 34, 136 F_1M: 0, 15.0, 29.6, 127 F_1F: 0, 16.5, 32.8, 135 F_2M: 0, 13.7, 27.5, 110 F_2F: 0, 15.0, 29.2, 123	Parent and offspring PM: 119 PF: 136 F_1M: 127 F_1F: 135 F_2M: 110 F_2F: 123 Parent and offspring: No toxicity (No effect on fertility is observed)
	Two-generation reproductive toxicity study	0, 300, 1 000, 3 000/2 000 ppm PM: 0, 16.7, 55.1, 159 PF: 0, 21.3, 71.4, 214 F_1M: 0, 20.6, 68.6, 165	Parent: PM: 16.7 PF: 21.3 F_1M: 20.6

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
		F_1F: 0, 24.8, 82.1, 191	F_1F: 24.8 Offspring: PM: 55.1 PF: 71.4 F_1M: 68.6 F_1F: 82.1 Parent: M/F: Decreased food intake, etc. Offspring: Low body weight, etc. Fertility PM: 55.1 PF: 71.4 F_1M: 68.6 F_1F: 82.1 (Decreases in the average number of newborns and postpartum survival)
	Developmental toxicity study (the 1st study)	0, 100, 200, 400	Dams: 200 Fetuses: 400 Dams: Suppressed body weight gain and decreased food intake Fetuses: No toxicity (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 40, 90, 200	Dams: 200 Fetuses: 90 Dams: No toxicity Fetuses: Increased number of small fetuses, etc. (No teratogenicity is observed)
Mouse	Four-week subacute toxicity study (the 1st study)	0, 600, 1 900, 6 000, 9 500, 15 000 ppm M: 0, 130, 390, 950, 1 500, 2 300 F: 0, 120, 420, 1 000, 1 500, 2 400	M: 390 F: 420 M/F: Vacuolation of hepatocytes, etc.
	Four-week subacute toxicity study (the 2nd study)	0, 1 900, 6 000, 9 500, 15 000 ppm 0, 290, 900, 1 400, 2 300	M/F: 290 M/F: Formation of crystals and granulomatous lesions etc., in the bladder, etc.

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	13-week subacute toxicity study	0, 1 500, 3 000, 6 000, 12 000 ppm M: 0, 260, 510, 1 100, 2 100 F: 0, 330, 660, 1 300, 2 600	M: - F: - M/F: Hepatocellular hypertrophy, hypertrophy and vacuolation of adrenocortical cells, etc.
	18-month carcinogenicity study	0, 200, 500, 1 250 ppm M: 0, 27.2, 69.8, 172 F: 0, 31.2, 77.7, 192	M: 172 F: 192 M/F: No toxicity (No carcinogenicity is observed)
	99-week carcinogenicity study	0, 160, 800, 4 000 ppm M: 0, 23, 115, 604 F: 0, 27, 138, 793	M: 23 F: 138 M: Hypertrophy and vacuolation of the testicular interstitial cells, etc. F: Suppressed body weight gain, decreased food intake, etc. (Increased incidence of hepatocellular adenomas and carcinomas)
Rabbit	Developmental toxicity study (the 1st study)	0, 100, 200, 400	Dams: 100 Fetuses: 100 Dams: Suppressed body weight gain and decreased food intake Fetuses: Increased number of embryo resorption (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 20, 60, 200	Dams: 20 Fetuses: 60 Dams: Suppressed body weight gain and decreased food intake Fetuses: Decreased number of survived fetuses, increased number of post-implantation embryonic mortality (No teratogenicity is observed)
Dog	One-year chronic toxicity study (the 1st study)	0, 100, 600, 3 600 ppm M: 0, 4.12, 24.9, 145 F: 0, 4.30, 28.2, 153	M: 4.12 F: 4.30 M/F: Heinz body in red blood cells

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) [1)]
	One-year chronic toxicity study (the 2nd study)	0, 200, 300, 400, 600 ppm M: 0, 7.8, 12.4, 17.5, 24.6 F: 0, 9.1, 13.1, 18.4, 26.4	M: 24.6 F: 26.4 M/F: No toxicity
	Comprehensive evaluation of the 1st and 2nd one-year chronic toxicity studies		
ADI (cRfD)			LOAEL: 6.1 SF: 300 ADI: 0.02
The critical study for setting ADI (cRfD)			Two-year combined chronic toxicity/carcinogenicity study (the 2nd study) (rat)

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

-, NOAEL could not be specified.

/: No study was described.

[1)] The adverse effect observed at LOAEL

Table 2-1. *Potential adverse effects of a single oral administration of iprodione* (General population)

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw) [1)]
Rat	Acute toxicity study (the 1st study)	M/F: 900, 1 350, 2 000, 3 000, 4 500	M/F: - M/F: Sedation, abnormal gait, etc.
Mouse	Acute toxicity study (the 1st study)	M/F: 600, 900, 1 350, 2 000, 3 000, 4 500	M/F: 900 M/F: Sedation, abnormal gait, etc.
	Acute toxicity study (the 2nd study)	M/F: 0, 1 300, 2 000, 3 000, 4 500, 6 700, 10 000	M/F: - M/F: Sedation, dyspnea
	Acute toxicity study (the 3rd study)	M/F: 0, 1 300, 2 000, 3 000, 4 500, 6 700, 10 000	M/F: - M/F: Sedation, dyspnea
ARfD			It is considered unnecessary to specify (Above the cut off level of 500 mg/kg bw)

ARfD, Acute reference dose
-, NOAEL could not be specified.
[1)] The adverse effect observed at LOAEL

Table 2-2. *Potential adverse effects of a single oral administration of iprodione* (Pregnant or potentially pregnant women)

Species	Study	Dose (mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw per day) [1)]
Rat	Developmental toxicity study (the 2nd study)	0, 40, 90, 200	Fetuses: 90 Fetuses: Increase in small fetuses and embryonic cavities between visceral organs and body walls
ARfD			NOAEL: 90 SF: 100 ARfD: 0.9
The critical study for setting ARfD			Developmental toxicity study in rats (the 2nd study)

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