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

Risk Assessment Report

Fenarimol

(Pesticides)

Food Safety Commission of Japan (FSCJ)
June 2021

ABSTRACT

The FSCJ conducted a risk assessment of fenarimol (CAS No. 60168-88-9), a pyrimidine fungicide, based on submitted documents.

Test data used in the assessment include fate in animals (including rats and rabbits), fate in plants (including cucumbers and apples), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (rats), two- and three-generation reproductive toxicity (rats), three-generation reproductive toxicity (mice), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of fenarimol were observed in the body weight (suppressed weight gain) and in the liver (including increased liver weight, hepatocellular hypertrophy and fatty degeneration). No carcinogenicity, teratogenicity or biologically significant genotoxicity was observed.

In the two- and three-generation reproductive toxicity studies in rats, adverse effects including declines in copulation indices and reproductive rates, prolonged gestational periods and dystocia (obstructed labor) were observed in parent animals, and adverse effects including the decline in both live births and survival rates were observed in the offspring. While similar adverse effects were observed in mice, outcomes suggested that susceptibility in rats was higher than that of mice. The outcome of these studies investigating fenarimol's mode of action that interferes with fertility suggested that the declines in copulation indices and reproductive rates may be attributed to the suppression of male sexual behavior, whereby in addition to adverse effects on the brain, the central nervous system that plays a role in the sexual differentiation of the perinatal brain was also affected due to the inhibition of the conversion of androgen (testosterone) to estrogen (estradiol), possibly due to the aromatase inhibiting properties of fenarimol. The prolonged gestational period and dystocia (obstructed labor) observed in dams were likely due to the aromatase inhibiting properties of fenarimol having suppressed the secretion of estrogen whereby progesterone levels in the serum failed to drop moments before eutocia (normal delivery) thus having retained the luteal phase. No effect on fertility was observed in rabbits and guinea pigs.

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

No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values were compared, of which the lowest value was a NOAEL of 0.6 mg/kg bw per day in a three-generation reproductive toxicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.006 mg/kg bw per day by applying a safety factor 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of fenarimol was 0.8 mg/kg bw per day in a two-generation reproductive toxicity study (the 1st study) in rats. In addition, a NOAEL of 1.7 mg/kg bw per day was obtained in a three-generation reproductive toxicity study in rats. The discrepancy was attributed to different dose settings, and therefore, the appropriate NOAEL was reasoned to be 1.7 mg/kg bw per day. Since the effects observed at NOAELs in these studies were hypothesized to be due to fenarimol having affected the central nervous system involved in the sexual differentiation of the male brain in these lab animals, an acute reference dose (ARfD) of 0.017 mg/kg bw was specified for pregnant or potentially pregnant women by applying a safety factor of 100 to the NOAEL derived from the three-generation reproductive toxicity study in rats.

Suppressed expression of male sexual behavior was observed in exposure outside of the perinatal period also, thus the possibility of adverse effects by a single dose could not be ruled out. A NOAEL of 3.0 mg/kg bw per day was derived for the decline in copulation indices and reproductive rates of parental generation animals in a two-generation reproductive toxicity study (the 2nd study) in rats. The FSCJ specified an ARfD of 0.03 mg/kg bw per day for the general population by applying a safety factor of 100 to this NOAEL.

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

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, 50, 200, 800, 3 200 ppm M: 0, 3.8, 14.8, 62.1, 251 F: 0, 4.4, 16.5, 76.4, 286	M: - F: 4.4 M: Suppressed body weight gain F: Decreased T. Chol levels
	90-day subacute toxicity study (the 2nd study)	0, 140, 200, 275, 365, 500 ppm M: 0, 10.1, 14.8, 20.6, 27.1, 37.3 F: 0, 10.8, 15.4, 21.1, 30.0, 40.3	M: 37.3 F: 40.3 M/F: No toxicity
	90-day subacute toxicity study (the 3rd study)	0, 50, 200, 800 ppm 0, 2.5, 10, 40	Used as reference
	One-year chronic toxicity study	0, 50, 130, 350 ppm M: 0, 3.1, 8.0, 21.2 F: 0, 3.6, 9.0, 24.5	M: 8.0 F: 9.0 M: Pancreatic acinar atrophy, etc. F: Bile duct hyperplasia, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 50, 130, 350 ppm M: 0, 2.09, 5.45, 14.9 F: 0, 2.91, 8.05, 22.5	M: - F: 2.91 M: Fatty degeneration of hepatocytes F: Increase in absolute and relative weights of the ovaries, etc. (No carcinogenicity is observed)
	Two-year carcinogenicity study (the 1st study)	0, 12.5, 25, 50 ppm M: 0, 0.61, 1.20, 2.47 F: 0, 0.74, 1.46, 2.96	M: 1.20 F: 2.96 M: Suppressed body weight gain, decreased food intake and hepatocellular fatty degeneration F: No toxicity (Carcinogenicity could not be evaluated)
	Two-year carcinogenicity study (the 2nd study)	0, 12.5, 25, 50 ppm M: 0, 0.5, 1.0, 2.0 F: 0, 0.6, 1.2, 2.3	M: 1.0 F: 2.3 M: Fatty degeneration of hepatocytes F: No toxicity is observed (No carcinogenicity is observed)

	Comprehensive evaluation of two-year combined chronic toxicity/carcinogenicity study and the 1st and 2nd carcinogenicity studies		M: 1.20 F: 2.96 (No carcinogenicity is observed)
	Two-generation reproductive toxicity study (the 1st study)	0, 10, 50, 250 ppm PM: 0, 0.7, 3.6, 18.2 PF: 0, 0.8, 4.2, 20.4 F1M: 0, 0.8, 4.3, 21.9 F1F: 0, 0.9, 4.8, 22.9	Parent and reproductive performance: PM: 0.7 PF: 0.8 F1M: 0.8 F1F: 0.9 Offspring: PM: 3.6 PF: 4.2 F1M: 4.3 F1F: 4.8 Parent: M: Suppressed body weight gain, etc. F: Collagen fibrillogenesis at implantation sites in the endometrium, etc. Offspring: M/F: Reduced litter size, reduced survival rate, etc. Reproductive performance: Reduced conception rate
	Two-generation reproductive toxicity study (the 2nd study)	0, 50, 130, 350 ppm PM: 0, 3.0, 8.1, 21.6 PF: 0, 3.7, 8.9, 24.9 F1M: 0, 2.9, 7.3, 19.9 F1F: 0, 3.2, 9.2, 22.7	Parent and reproductive performance: PM: - PF: - F1M: - F1F: - Offspring: PM: 8.1 PF: 8.9 F1M: 7.3 F1F: 9.2 Parent: M: Suppressed body weight gain, reduced feed intake F: Reduced reproductive rate, etc. Offspring: Reduced number of live births, etc.
	Three-generation reproductive toxicity study	0, 12.5, 25, 50 ppm	Parent and reproductive performance PM: 1.2 PF: 1.7 F1M: 1.2 F1F: 1.7 F2M: 1.3

		PM: 0, 0.6, 1.2, 2.6 PF: 0, 0.8, 1.7, 3.2 F1M: 0, 0.6, 1.2, 2.5 F1F: 0, 0.9, 1.7, 3.5 F2M: 0, 0.7, 1.3, 2.7 F2F: 0, 1.0, 1.8, 3.8	F2F: 1.8 Offspring: PM: 0.6 PF: 0.8 F1M: 0.6 F1F: 0.9 F2M: 0.7 F2F: 1.0 Parent: M: Suppressed body weight gain F: Reduced reproductive rate, etc. Offspring: Reduced number of live births
	Developmental toxicity study (the 1st study)	0, 5, 20, 80	Dams: - Offspring: 5 Dams: Increased placental weight, placental congestion Fetuses: Reduced number of live fetuses, increased number of fetal resorption, increased fetal mortality rate, etc. (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 5, 13, 35	Dams: 35 Fetuses: 13 Dams: No toxicity Fetuses: Hydronephrosis (No teratogenicity is observed)
Mouse	90-day subacute toxicity study	0, 365, 620, 1 100, 2 000, 3 300 ppm	M: 116 F: 124 M/F: Increase in absolute and relative liver weights, periportal lipid droplets, etc.
		M: 0, 37.4, 72.9, 116, 171, 351 F: 0, 46.4, 87.8, 124, 200, 392	
	Two-year combined chronic toxicity/carcinogenicity study	0, 50, 170, 600 ppm	M: 19.7 F: 21.7 M: Suppressed body weight gain, fatty degeneration of hepatocytes, etc. F: Increase in absolute and relative liver weights, fatty degeneration of hepatocytes (No carcinogenicity is observed)
		M: 0, 5.68, 19.7, 69.4 F: 0, 6.50, 21.7, 77.7	
	Three-generation reproductive toxicity study	0, 35, 70, 140 ppm	Parent and offspring PM: 17.3

		PM: 0, 3.2, 6.4, 17.3 PF: 0, 3.8, 7.4, 15.8 F1M: 0, 3.2, 6.4, 13.6 F1F: 0, 3.8, 8.2, 15.8 F2M: 0, 3.2, 6.8, 13.6 F2F: 0, 4.0, 8.4, 15.8	PF: 15.8 F1M: 13.6 F1F: 15.8 F2M: 13.6 F2F: 15.8 Parent and offspring: No toxicity is observed. (No reproductive toxicity is observed)
Rabbit	Developmental toxicity study (the 1st study)	0, 3, 10, 35	Dams and fetuses: 35 Dams and fetuses: No toxicity is observed. (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 15, 15, 150	Dams and fetuses: 50 Dams: Reduced body weight/suppressed body weight gain, reduced food intake, etc. Fetuses: Declining trend in fetal survival, increased trend in supernumerary ribs (No teratogenicity is observed.)
Dog	90-day subacute toxicity study	0, 1.25, 5, 20	M/F: 20 M/F: No toxicity
	One-year chronic toxicity study	0, 1.25, 12.5, 125	M/F: 12.5 M/F: Increased ALP levels, increase in absolute and relative liver weights, etc.
ADI (cRfD)			NOAEL: 0.6 SF: 100 ADI: 0.006
The critical study for setting ADI (cRfD)			Three-generation reproductive toxicity study (rat)

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

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 (General condition)	M: 0, 5, 50, 500	50 Staggering gait, suppressed body weight, etc.
	Acute toxicity study	M/F: 0, 694, 833, 1 000, 1 200, 1 440, 1 730	M/F: - M/F: Decrease in locomotor activities, ataxia, spasmodic gait, etc.
	Acute toxicity study	M/F: 1 400, 2 000, 2 750, 3 650, 5 000	M/F: - M/F: Decrease in locomotor activities, limb weakness, loss of righting reflex, dyspnea, etc.
	Two-generation reproductive toxicity study (the 2nd study)	0, 50, 130, 350 ppm PM: 0, 3.0, 8.1, 21.6 PF: 0, 3.7, 8.9, 24.9 F_1M: 0, 2.9, 7.3, 19.9 F_1F: 0, 3.2, 9.2, 22.7	PM: 3.0 Parent: Decreased copulation index and reproductive rate
	Developmental toxicity study (the 1st study)	0, 5, 20, 80	Dams: 20 Dams: Decrease in body weight
	MoA study on reproductive performance	M/F: 0, 35	M: 35 Decreased copulation index and reproductive rate attributed to inhibited expression of male sexual behavior
Mouse	General pharmacological study (General condition)	M: 0, 5, 50, 500	50 Gait in prone position, prone position, staggering gait and diarrhea

	General pharmacology (Momentum in locomotor activity and motor coordination)	F: 0, 50, 500	50 Decreasing trend in locomotor activity momentum and decreasing trend in motor coordination
	Acute toxicity study	M: 0, 3 146, 3 932, 4 915, 6 144, 7 680, 9 600, 12 000, 15 000 F: 0, 2 517, 3 146, 3 932, 4 915, 6 144, 7 680, 9 600, 12 000, 15 000	M/F: - M/F: Decrease in locomotor activity, ataxic gait, decreased respiratory rate, decreased body temperature, etc.
	Acute toxicity study	M/F: 1 100, 1 600, 2 500, 3 000, 4 000	M/F: - M/F: Decrease in locomotor activity, limb weakness, loss of righting reflex, etc.
Rabbit	General pharmacological study (Body temperature)	M: 0, 50, 500	50 Decreased body temperature, prone and side positions due to limb paralysis
ARfD			NOAEL: 3.0 SF: 100 ARfD: 0.03
The critical study for setting ARfD			Two-generation reproductive toxicity study (the 2nd study) (rat)

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

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

(Women who are pregnant or might be pregnant)

Species	Study	Dose (mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw per day) [1)]
Rat	Two-generation reproductive toxicity study (the 1st study)	0, 10, 50, 250 ppm PM: 0, 0.7, 3.6, 18.2 PF: 0, 0.8, 4.2, 20.4 F_1M: 0, 0.8, 4.3, 21.9 F_1F: 0, 0.9, 4.8, 22.9	PF: 0.8 F_1P (M): Decreased conception rate
	Two-generation reproductive toxicity study (the 2nd study)	0, 50, 130, 350 ppm PM: 0, 3.0, 8.1, 21.6 PF: 0, 3.7, 8.9, 24.9 F_1M: 0, 2.9, 7.3, 19.9 F_1F: 0, 3.2, 9.2, 22.7	PF: 3.7 F_1P: Decreased copulation index and reproductive rate
	Three-generation reproductive toxicity study	0, 12.5, 25, 50 ppm PM: 0, 0.6, 1.2, 2.6 PF: 0, 0.8, 1.7, 3.2 F_1M: 0, 0.6, 1.2, 2.5 F_1F: 0, 0.9, 1.7, 3.5 F_2M: 0, 0.7, 1.3, 2.7 F_2F: 0, 1.0, 1.8, 3.8	P and F_1F: 1.7 F_1P and F_2P: Decreased copulation index and reproductive rate
ARfD			NOAEL: 1.7 SF: 100 ARfD: 0.017
The critical study for setting ARfD			Three-generation reproductive toxicity study (rat)

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

[1)] The adverse effect observed at LOAEL