

Folpet (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of folpet (CAS No. 133-07-3), a phthalimide fungicide, based on results from various studies. Major adverse effects of folpet were observed in hyper-keratosis in rats and in duodenal mucosal hyperplasia in mice. No neurotoxicity and adverse effect on fertility were detected. Increases in the incidence of duodenal adenoma and adenocarcinoma were identified in carcinogenicity studies in mice. FSCJ recognized no genotoxicity relevant to human health of folpet in spite of the positive results *in vitro*. Therefore, a genotoxic mechanism was unlikely involved in the tumor development, and it enabled us to establish a threshold in the assessment. In developmental toxicity studies, no adverse effects observed in fetus at the dose without maternal toxicity. No folpet-induced teratogenicity was detected in rats. Folpet (parent compound only) was identified as the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-adverse-effect level (NOAEL) obtained in all the studies was 10 mg/kg bw/day in several studies in dogs, rats and rabbits. FSCJ specified an acceptable daily intake (ADI) of 0.1 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. The lowest NOAEL for potential adverse effects of a single oral administration of folpet was 10 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ specified an acute reference dose (ARfD) of 0.1 mg/kg bw/day, for women who are or may be pregnant, by applying a safety factor of 100 to the NOAEL. FSCJ considered it unnecessary to specify ARfD for general population.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of folpet (CAS No. 133-07-3), a phthalimide fungicide, based on results from various studies.

The data used in the assessment include fate in animals (rats, mice and goats), fate in plants (tomatoes and grapes), subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity, and also mechanism studies related with tumor development of duodenum in mice.

Major adverse effects of folpet were observed in hyper-keratosis in rats and in duodenal mucosal hyperplasia in mice. No neurotoxicity and adverse effect on fertility were

detected.

Increases in the incidence of duodenal adenoma and adenocarcinoma were identified in carcinogenicity studies in mice. FSCJ comprehensively evaluated a number of genotoxicity studies *in vitro* and *in vivo*, and mechanism studies. Negative results were obtained from *in vivo* studies, including a comet study in the duodenum of mice treated with the high doses (up to four-times excess of the carcinogenicity study). FSCJ, thus, recognized no genotoxicity relevant to human health of folpet in spite of the positive results *in vitro*. Therefore, a genotoxic mechanism was unlikely involved in the tumor development, and it enabled us to establish a threshold in the assessment.

In developmental toxicity studies, folpet, at the dose causing maternal toxicity, increased incidences of hydrocephalus (lateral ventricular enlargement) and abnormality of the stomach in the rabbit fetus. No adverse effects observed in

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The original full report is available in Japanese at <http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20060718035&fileId=201>
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fetus at the dose without maternal toxicity. No folpet-induced teratogenicity was detected in rats.

Based on the results from studies available, folpet (parent compound only) was identified as the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 10 mg/kg bw/day based on the adverse effects in a one-year chronic toxicity study in dogs (the 2nd study in **Table 1**), a developmental toxicity study in rats (the 1st study in **Table 1**) and developmental toxicity studies in rabbits (the 1st and 2nd studies in **Table 1**). FSCJ specified an acceptable daily intake (ADI) of 0.1 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single

oral administration of folpet was 10 mg/kg bw/day based on the adverse effect on fetuses (hydrocephalus) in a developmental toxicity study in rabbits (the 2nd study in **Table 2**). FSCJ specified an acute reference dose (ARfD) of 0.1 mg/kg bw, for women who are or may be pregnant, by applying a safety factor of 100 to the NOAEL. In addition, FSCJ considered it unnecessary to specify ARfD for general population in view of the absence of adverse effects that would be likely to be elicited by a single oral administration of folpet.

Table 1. Levels relevant to toxicological evaluation of folpet

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints ¹⁾
Rat	90-day subacute toxicity study (the 1 st study)	0, 2 000, 4 000, 8 000 ppm M: 0, 116, 233, 456 F: 0, 126, 252, 482	M/F: - M/F: Diffuse hyper-keratosis in the fore-stomach, etc.
	90-day subacute neurotoxicity study (the 2 nd study)	0, 2 500, 5 000, 10 000 ppm M: 0, 181, 363, 701 F: 0, 201, 397, 790	M:181 F: 397 M/F: Suppressed body weight, etc. (No subacute neurotoxicity)
	Two-year chronic toxicity study	0, 250, 1 500, 5 000 ppm M: 0, 12.4, 83.2, 296 F: 0, 15.7, 104, 359	M: 12.4 F: 15.7 M/F: Diffuse hyper-keratosis in the fore-stomach
	Two-year combined chronic toxicity/carcinogenicity study	0, 200, 800, 3 200 ppm M: 0, 9.93, 40.0, 161 F: 0, 12.5, 50.5, 207	M: 40.0 F: 50.5 M/F: Hyper-keratosis in the fore-stomach, acanthosis, etc. (Not carcinogenic)
	Two-year carcinogenicity study	0, 500, 1 000, 2 000 ppm M: 0, 27.6, 54.8, 108 F: 0, 33.5, 66.5, 133	M: 27.6 F: 33.5 M/F: Diffuse hyper-keratosis in the fore-stomach epithelium, etc. (Not carcinogenic)
	Two-generation developmental toxicity study (the 1 st study)	0, 200, 800, 3 600 ppm PM: 0, 14.4, 59.1, 263 PF: 0, 18.1, 73.2, 315 F _{1b} M: 0, 22.0, 90.6, 421 F _{1b} F: 0, 23.4, 94.8, 434	Parent and offspring PM: 59.1 PF: 73.2 F ₁ M: 90.6 F ₁ F: 94.8 Parent: Diffuse hyper-keratosis in the fore-stomach Parent and offspring: Suppressed body weight (No adverse effect on fertility)
	Two-generation developmental toxicity study (the 2 nd study)	0, 250, 1 500, 5 000 ppm PM: 0, 18.9, 112, 370 PF: 0, 22.5, 133, 436 F ₁ M: 0, 25.2, 150, 520 F ₁ F: 0, 28.4, 168, 565	Parent and offspring PM: 18.9 PF: 22.5 F ₁ M: 25.2 F ₁ F: 28.4 Parent M/F: Hyper-keratosis in the fore-stomach, etc. Offspring: Suppressed body weight (No adverse effect on fertility)
	Developmental toxicity study (the 1 st study)	0, 10, 60, 360	Maternal: 10 Embryo/fetus: 360 Maternal: Suppressed body weight, etc. Embryo/fetus: No toxicity (Not teratogenic)
	Developmental toxicity study (the 2 nd study)	0, 150, 550, 2 000	Maternal: 150 Embryo/fetus: 150 Maternal: Decreased weights of pregnant uterus, etc. Embryo/fetus: Delayed ossification, etc. (Not teratogenic)
	Developmental toxicity study (the 3 rd study)	0, 20, 100, 800	Maternal: 100 Embryo/fetus: 800 Maternal: Suppressed body weight, etc. Embryo/fetus: No toxicity (Not teratogenic)

Table 1. Levels relevant to toxicological evaluation of folpet (continued)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints ¹⁾
Mouse	Two-year carcinogenicity study (the 1 st study)	0, 1 000, 3 500, 7 000 ppm M: 0, 123, 564, 1 260 F: 0, 141, 608, 1 300	M/F: - M/F: Diffuse hyper-keratosis in the fore-stomach mucosa, etc. (Carcinogenicity) Observed at 1 000 ppm and above M/F: Increased adenoma and carcinoma of duodenum F: Increased papilloma and carcinoma of fore-stomach
	Two-year carcinogenicity study (the 2 nd study)	0, 1 000, 5 000, 12 000 ppm M: 0, 93.0, 502, 1 280 F: 0, 95.5, 515, 1 280	M/F: - M/F: Duodenal mucosal hyperplasia (Carcinogenicity) Observed at and above 5 000 ppm M/F: Increased adenoma and adenocarcinoma duodenum Observed at 1 2000 ppm M: Increased adenocarcinoma of jejunum F: Increased adenoma and adenocarcinoma of jejunum
	Two-year carcinogenicity study (the 3 rd study)	0, 150, 450, 1 350 ppm M: 0, 16.2, 46.7, 151 F: 0, 16.0, 51.3, 154	M: 46.7 F: 51.3 M: Suppressed body weight, etc. F: Keratoacanthosis of stomach, etc. (Carcinogenicity) Observed at 1 350 ppm F: Increased squamous cell papillomas of stomach
Rabbit	Developmental toxicity study (the 1 st study)	0, 10, 40, 160	Maternal and Embryo/fetus: 10 Maternal: Suppressed body weight Fetus: The 13 th rib, etc. (Not teratogenic)
	Developmental toxicity study (the 2 nd study)	0, 10, 20, 60	Maternal and Emryo/fetus: 10 M: Suppressed body weight, etc. Embryo/fetus: Hydrocephalus, etc. (Teratogenicity) Observed at the maternally toxic dose (20 and above)
Dog	90-day subacute toxicity study	0, 20, 50, 500	M/F: - M/F: Centrilobular vacuolation of hepatocyte
	One-year chronic toxicity study (the 1 st study)	0, 325, 650, 1 300	M: - F: 325 M: Decreased TP, etc. F: Suppressed body weight, etc.
	One-year chronic toxicity study (the 2 nd study)	0, 10, 60, 120	M/F: 10 M/F: Suppressed body weight, etc.
ADI			NOAEL: 10 SF: 100 ADI: 0.1
The critical study for setting ADI			A one-year chronic toxicity study in dogs (the 2 nd study) A developmental toxicity study in rats (the 1 st study) Developmental toxicity studies in rabbits (the 1 st and 2 nd studies)

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F₁M, Male in F₁ generation; F₁F, Female in F₁ generation; -, NOAEL could not be specified; ADI, Acceptable daily intake; SF, Safety factor

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

Table 2. Potential adverse effects of a single oral administration of folpet (Women who are or may be pregnant)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints ¹⁾
Rabbit	Developmental toxicity study (the 1 st study)	0, 10, 40, 160	Maternal: 40 Maternal: Increased postimplantation loss rate
	Developmental toxicity study (the 2 nd study)	0, 10, 20, 60	Embryo/fetus: 10 Embryo/fetus: Hydrocephalus
ARfD			NOAEL: 10 SF: 100 ARfD: 0.1
The critical study for setting ARfD		Developmental toxicity study in rabbits (the 2 nd study)	

ARfD, Acute reference dose; SF, Safety factor

¹⁾ The adverse effect observed at LOAEL