FOOD SAFETY

doi: 10.14252/foodsafetyfscj.2017003s
Food Safety 2017; Vol. 5, No. 2, 61–66

Risk assessment report

Captan (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of captan (CAS No. 133-06-2), a phthalimide fungicide, based on results from various studies. Major adverse effects of captan were observed in suppressed body weight, and also in duodenal mucosal hyperplasia in mice. No adverse effect on fertility was detected. Increases in incidence of duodenal adenoma and adenocarcinoma were identified in mice. Negative results were however obtained from a gene mutation assay of the target in transgenic mice. No genotoxicity relevant to human health of captan was recognized 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, captan, at the doses causing maternal toxicity, increased external alterations as well as skeletal and soft tissue alterations in the fetus of rabbits and hamsters. No captan-induced teratogenicity was detected in rats. Captan (parent compound only) was identified as the residue definition for dietary risk assessment in agricultural and livestock products. The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 10 mg/kg bw/day. 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 captan was 30 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ specified an acute reference dose (ARfD) of 0.3 mg/kg bw, for women who are or may be pregnant, by applying a safety factor of 100 to the NOAEL. In addition, FSCJ specified an ARfD of 3 mg/kg bw, for general population, by applying a safety factor of 100 to the no-observed-effect level (NOEL) of 300 mg/kg bw obtained from a general pharmacology study in mice.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of captan (CAS No. 133-06-2), a phthalimide fungicide, based on results from various studies.

The data used in the assessment include fate in animals (rats, goats and chickens), fate in plants (tomatoes, lettuce and others), residues in crops, chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), one and three generation reproductive toxicity (rats), developmental toxicity (rats, rabbits, hamsters and monkeys) and genotoxicity, and also general pharmacology studies and mechanism studies related with tumor development of duodenum in mice.

Major adverse effects of captan were observed in suppressed body weight, and also in duodenal mucosal hyperplasia in mice. No adverse effect on fertility was detected.

Increases in incidence of duodenal adenoma and adenocarcinoma were identified in mice. Negative results were however obtained from a gene mutation assay of the target in transgenic mice. FSCJ evaluated comprehensively a number of genotoxicity studies including the experiment described above. No genotoxicity relevant to human health of captan was recognized 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, captan, at the doses causing maternal toxicity, increased external alterations

Published online: 30 June 2017
This is an English translation of excerpts from the original full report (March 2017–FS/129/2017). Only original Japanese texts have legal effect.
The original full report is available in Japanese at https://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20091214002&fileId=201
Acknowledgement: FSCJ wishes to thank the members of Expert Committee on Pesticides for the preparation of the original full report.
Suggested citation: Food Safety Commission of JAPAN. Captan: Summary. Food Safety. 2017; 5 (2): 61–66.
doi:10.14252/foodsafetyfscj.2017003s

as well as skeletal and soft tissue alterations in the fetus of rabbits and hamsters. No captan-induced teratogenicity was detected in rats.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 10 mg/kg bw/day, based on toxicities observed in developmental toxicity studies in rabbits (the 2nd and 3rd 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 captan was 30 mg/kg bw/day based on the adverse effect on dams (increase of postimplantation loss rate and the number of dead embryos) and on fetuses (external, skeletal and soft tissue alterations) in a developmental toxicity study in rabbits (the 3rd study in **Table 2**). FSCJ specified an acute reference dose (ARfD) of 0.3 mg/kg bw, for women who are or may be pregnant, by applying a safety factor of 100 to the NOAEL. In addition, FSCJ specified an ARfD of 3 mg/kg bw, for general population, by applying a safety factor of 100 to the no-observed-effect level (NOEL) of 300 mg/kg bw obtained from a general pharmacology study in mice.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[1)]
Rat	Two-year combined chronic toxicity study/carcinogenicity study	M: 0, 25, 98, 250 F: 0, 25, 99, 244	M/F: 25 M/F: Suppressed body weight, etc. (Not carcinogenic)
	130-week carcinogenicity study	0, 125, 500, 2 000 ppm M/F: 0, 5, 24, 98	M/F: 24 M/F: Suppressed body weight (Not carcinogenic)
	Three-generation reproduction study	0, 25, 100, 250, 500	Parental/offspring M/F: 25 Embryo/fetus: 250 Parental/offspring: Suppressed body weight Embryo/fetus: Lower body weight (No effect on fertility)
	One-generation reproduction study	0, 6, 12.5, 25	Parental/offspring: 25 Parental/offspring: No toxicity (No effect on fertility)
	Developmental toxicity study	0, 18, 90, 450	Maternal: 18 Embryo/fetus: 90 Maternal: Suppressed body weight, etc. Embryo/fetus: Lower body weight (Not teratogenic)
Mouse	26-month carcinogenicity study	0, 6 000, 10 000, 16 000 ppm M: 0, 599, 1 030, 1 890 F: 0, 634, 1 080, 1 880	M/F: - M/F: Duodenal mucosal hyperplasia, etc. (Carcinogenicity) Observed at 6 000 ppm and above M/F: Increased duodenal adenoma and adenocarcinoma
	22-month carcinogenicity study	0, 100, 400, 800, 6 000 ppm M: 0, 15.1, 60.9, 123, 925 F: 0, 17.7, 70.4, 142, 1 040	M: 123 F: 70.4 M/F: Lymphoid infiltration in the duodenum, etc. (Carcinogenicity) Observed at 6 000 ppm M/F: Increased duodenal adenoma and adenocarcinoma
	80-week carcinogenicity study	0, 8 000, 16 000 ppm M/F: 0, 900, 2 400	M/F: 900 M/F: Lower average body weight, etc. (Carcinogenicity) Observed at 16 000 ppm M/F: Increased duodenal adenoma

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[1)]
Rabbit	Developmental toxicity study (the 1st study)	0, 6, 12, 25, 60	Maternal: 12 Embryo/fetus: 25 Maternal: Suppressed body weight Embryo/fetus: Lower body weight (Not teratogenic)
	Developmental toxicity study (the 2nd study)	0, 10, 40, 60	Maternal: 10 Embryo/fetus: 40 Maternal: Suppressed body weight Embryo/fetus: Skeletal variation (Not teratogenic)
	Developmental toxicity study (the 3rd study)	0, 10, 30, 100	Maternal/embryo/fetus: 10 Maternal: Suppressed body weight, etc. Embryo/fetus: Skeletal variation (Teratogenicity) Observed at the maternally toxic dose (100)
Hamster	Developmental toxicity study	0, 50, 200, 400	Maternal/embryo/fetus: 200 Maternal: Increased mortality rate, etc. Embryo/fetus: Suppressed body weight, etc. (Teratogenicity) Observed at the maternally toxic dose (400)
Dog	One-year chronic toxicity study	0, 12.5, 60.0, 300	M/F: 300 M/F: No toxicity
Monkey	Developmental toxicity study	0, 6.25, 12.5, 25.0	Maternal/embryo/fetus: 12.5 Maternal: Miscarriage, etc. Maternal/embryo/fetus: Death (Not teratogenic)
ADI (cRfD)			NOAEL: 10 SF: 100 ADI: 0.1
The critical study for setting ADI			Developmental toxicity studies in rabbits (the 2nd and 3rd studies)

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

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

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

Species	Study		Dose (mg/kg bw/day)	NOAEL(mg/kg bw/day) and critical endpoints[1)]
Rat	Acute toxicity study		M: 0, 100, 1 000, 3 160, 5 630, 10 000, 15 000	M: 5 630 M: Suppressed body weight
			5 000, 6 500, 7 800(M)/7 200(F), 8 300, 10 800, 14 000	M: - F: - M: Hematuria, diarrhea. F: Reduced motor activity, diarrhea, etc.
			M: 1 800, 2 700, 4 050, 6 075, 9 113 F: 1 690, 2 197, 2 856, 3 713, 4 827, 6 275, 8 157, 10 604, 13 786	M: - F: - M/F: Rhinorrhea, lacrimation, salivation and loose watery feces
Mouse	General pharmacology study	General conditions (Irwin method)	M: 0, 300, 1 000, 3 000	M: 300 M: Reduced motor activity and loose watery feces
		Motor activity level	M: 0, 300, 1 000, 3 000	M: 300 M: Reduced motor activity
Rabbit	Developmental toxicity study		M: 0, 100, 1 000, 3 160, 10 000	M: 1 000 M: Death
ARfD				NOAEL: 300 SF: 100 ARfD: 3
The critical study for setting ARfD				General pharmacology studies in mice

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed-adverse-effect level; -, NOAEL could not be specified

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

Table 2-2. *Potential adverse effects of a single oral administration of captan (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 2nd study)	0, 10, 40, 160	Maternal: 40 Maternal: Increased embryo resorption and postimplantation loss
	Developmental toxicity study (the 3rd study)	0, 10, 30, 100	Maternal: 30 Embryo/fetus: 30 Maternal: Increase of postimplantation loss rate and the number of dead embryos Embryo/fetus: External, skeletal and soft tissue alterations
Hamster	Developmental toxicity study (the 1st study)	0, 50, 200, 400	Maternal: 200 Embryo/fetus: 200 Maternal: Increased embryo resorption and decreased the number of viable fetuses Embryo/fetus: Tail deformation, whole body edema, complex abnomalty, etc.
ARfD			NOAEL: 30 SF: 100 ARfD: 0.3
The critical study for setting ARfD			Developmental toxicity study in rabbits (the 3rd study)

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

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