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Risk assessment report

Desmedipham (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of desmedipham (CAS No. 13684-56-5), a carbanilate herbicides, based on results from various studies. Major adverse effects of desmedipham were suppressed body weight, hemolytic anemia, methemoglobinemia and follicular cell hypertrophy in thyroid. Neither carcinogenicity, reproductive toxicity, nor genotoxicity relevant to human health was observed on desmedipham. Desmedipham, at the dose with maternal toxicity, caused external anomalies such as mandibular malformation and cleft palate, visceral anomalies such as ventricular septum defect, and skeletal anomalies such as defect of sternum and asymmetric alignment of seternebral hemicentres in developmental toxicity studies in rats. No teratogenetic effects were observed in rabbits. The lowest no-observed-effect level (NOAEL) obtained in all studies was 3.2 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity in rats. FSCJ specified an acceptable (ADI) of 0.032 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. The lowest NOAEL for adverse effects elicited by a single oral administration of desmedipham was 90 mg/kg bw/day obtained from the developmental toxicity study in rabbits (the 2nd study in the Table 2). Consequently, FSCJ specified an acute reference dose (ARfD) of 0.9 mg/kg bw applying a safety factor of 100 to the NOAEL.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of desmedipham (CAS No. 13684-56-5), a carbanilate herbicides, based on results from various studies.

The data used in the assessment include on the fate in animals (rats, cattle and chickens), fate in plants (sugar beets), residues in crops, subacute toxicity (rats and dogs), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, and a mechanism of hemolytic anemia in dogs.

Major adverse effects of desmedipham were suppressed body weight, hemolytic anemia, methemoglobinemia and follicular cell hypertrophy in thyroid. Neither carcinogenicity, reproductive toxicity, nor genotoxicity relevant to human health was observed on desmedipham.

Desmedipham, at the dose with maternal toxicity, caused external anomalies such as mandibular malformation and cleft palate, visceral anomalies such as ventricular septum defect, and skeletal anomalies such as defect of sternum and asymmetric alignment of seternebral hemicentres in developmental toxicity studies in rats. No teratogenetic effects were observed in rabbits.

Based on the data on various studies, desmedipham (parent compound only) was identified as the substance relevant to the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-effect level (NOAEL) obtained in all studies was 3.2 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity in rats. FSCJ specified an acceptable (ADI) of 0.032 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects elicited by a single oral administration of desmedipham was 90 mg/kg bw/day

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obtained from the developmental toxicity study in rabbits (the 2nd study in the Table 2). Consequently, FSCJ specified an acute reference dose (ARfD) of 0.9 mg/kg bw applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[a]
Rat	13-week subacute toxicity study (the 1st study)	0, 6, 30, 60, 300 ppm	M: 5.2 F: 5.6 F/M: Increase in MetHb, and Ret, etc.
		M: 0, 0.5, 2.6, 5.2, 26 F: 0, 0.5, 2.7, 5.6, 27	
	13-week subacute toxicity study (the 2nd study)	0, 160, 800, 4 000 ppm	M: 10.6 F: 12.3 M: Congestive spleen, etc. F: Decrease in RBC, Ht and Hb, etc.
		M: 0, 10.6, 54, 275 F: 0, 12.3, 60, 339	
	One-year chronic toxicity study	0, 100, 400, 1 200 ppm	M: 6.5 F: 31.7 F/M: Increase in T.Bil, etc.
		M: 0, 6.5, 25.2, 75.0 F: 0, 7.9, 31.7, 97.1	
	Two-year chronic toxicity/ carcinogenicity study	0, 60, 300, 1 500 ppm	M: 3.2 F: 3.9 F/M: Increase in MetHb and Ret, etc
		Chronic toxicity study M: 0, 3.2, 15.7, 79.9 F: 0, 3.9, 19.8, 101 Carcinogenicity study M: 0, 3.3, 16.1, 84.0 F: 0, 4.1, 20.2, 104	(Not carcinogenic)
	Two-year carcinogenicity study	0, 100, 400, 1 200 ppm	M: 5.4 F: 6.8 M: Increase in alveolar macrophage F: Increase in T.Bil (Not carcinogenic)
		M: 0, 5.4, 21.6, 64.4 F: 0, 6.8, 28.4, 86.6	
	Two-generation reproductive toxicity study (the 1st study)	0, 50, 250, 1 250 ppm	Parent and Offspring: PM: 4.0 PF: 4.6 F1M: 4.4 F1F: 4.9 Parent: F/M: Hemosiderin deposition in spleen Offspring: Suppressed body weight (No effect on reproduction)
		PM: 0, 4.0, 20.5, 106 PF: 0, 4.6, 23.3, 120 F1M: 0, 4.4, 22.5, 118 F1F: 0, 4.9, 25.3, 130	

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[a]
Rat	Two-generation reproductive toxicity study (the 2nd study)	0, 100, 400, 1 200 ppm	Parent and Offspring: PM: 32.5 PF: 38.8 F_1M: 37.6 F_1F: 42.5 Parent: F/M: Suppressed body weight and decreased feed consumption Offspring: lower weight (at birth) /Suppressed body weight (during lactation period) (No effect on reproduction)
		PM: 0, 8.04, 32.5, 97.0 PF: 0, 9.67, 38.8, 118 F_1M: 0, 9.31, 37.6, 117 F_1F: 0, 10.5, 42.5, 128	
	Developmental toxicity study (the 1st study)	0, 10, 100, 1 000	Maternal: 100 Embryo/fetus: 100 Maternal: Suppressed body weight and decreased feed consumption Embryo/fetus: External anomalies such as cleft palate and mandibular malformation
	Developmental toxicity study (the 2nd study)	0, 10, 100, 500	Maternal: 10 Embryo/fetus: 100 Maternal: Increase in MetHb Embryo/fetus: lower body weight, etc.
	Developmental toxicity study (the 3rd study)	0, 60, 250, 1 000	Maternal: 60 Embryo/fetus: 250 Maternal: Increase in absolute spleen weight Embryo/fetus: lower body weight and external anomalies such as cleft palate
Mouse	Two-year carcinogenicity study	0, 30, 150, 750 ppm	M: 21.7 F: 30.8
		Intermittent sacrifice M: 0, 4.24, 22.7, 141 F: 0, 6.25, 34.3, 187 Carcinogenicity study M: 0, 4.2, 21.7, 109 F: 0, 5.8, 30.8, 145	M: Increase in MetHb, etc. F: Decrease in Hb and Ht, etc. (Not carcinogenic)
	80-week carcinogenicity study	0, 400, 1 000, 2 500 ppm	M: 60.8 F: 71.9
		M: 0, 60.8, 153, 403 F: 0, 71.9, 178, 503	F/M: Necrosis of hepatocytes (Not carcinogenic)

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[a]
Rabbit	Developmental toxicity study (the 1st study)	0, 50, 150, 450	Maternal: 150 Embryo/fetus: 50 Maternal: Suppressed body weight and feed consumption Embryo/fetus: lower body weight (Not teratogenic)
	Developmental toxicity study (the 2nd study)	0, 30, 90, 270	Maternal: 30 Embryo/fetus: 90 Maternal: Increase in absolute weight of spleen Embryo/fetus: lower body weight, delayed ossification of sternum and incompletely ossified phalanges (Not teratogenic)
Dog	13-week subacute toxicity study (the 1st study)	0, 1, 5, 150 ppm	M: 4.97
		M: 0, 0.035, 0.17, 4.97 F: 0, 0.035, 0.19, 5.50	M: 4.97 F: 5.50 F/M: No toxicity
	13-week subacute toxicity study (the 2nd study)	0, 100, 500, 1 500 ppm	M: 18.6 F: 4.22
		M: 0, 3.73, 18.6, 55.6 F: 0, 4.22, 21.0, 62.2	F/M: Follicular cell hypertrophy, etc.
	One-year chronic toxicity study	0, 300, 1 500, 7 500/5 000 [b] ppm	M: 9.7 F: 10.4
		M: 0, 9.7, 52.5, 168 F: 0, 10.4, 57.4, 201	F/M: Hemolytic anemia, etc.
	Effect on MetHb formation	0, 75, 150, 200, 300, 500, 1 500 ppm	M: 15.5 F: 11.1
		M: 0, 2.5, 5.1, 6.5, 9.7, 15.5, 45.0 F: 0, 2.5, 4.3, 5.3, 11.1, 15.7, 49.2	
ADI			NOAEL: 3.2 SF: 100 ADI: 0.032
The critical study for setting ADI			Two-year combined chronic toxicity/carcinogenicity study in rats

M, Male; F, Female; F/M, both sexes; PM, Male in Parent (P) generation; PF, Female in P generation; F_1M, Male in F_1 generation; F_1F, Female in F_1 generation; ADI, Acceptable daily intake; cRfD, Chronic reference dose; SF, Safety factor; UF, Uncertainty factor; NOAEL, No-observed-adverse-effect level; -, NOAEL could not be specified; MetHB, methohemoglobin; Ret, Reticulocytes; Ht, Hemotocrit; T.Bil, Total bilirubin

[a], The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL); [b], Administered at 7 500 ppm for the first 28 days, (reduced to) 5 000 ppm after 28 days

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[a]
Rat	Acute toxicity study	5 000	F/M: - F/M: Sedation, dyspnea, flexion, suppressed body weight, rough fur and blanching
	Developmental toxicity study (the 1st study)	0, 10, 100, 1 000	Maternal: 100 Maternal: Suppressed body weight and decreased feed consumption
	Developmental toxicity study (the 2nd study)	0, 10, 100, 500	Maternal: 100 Maternal: Suppressed body weight and decreased feed consumption
	Developmental toxicity study (the 3rd study)	0, 60, 250, 1 000	Maternal: 250 Maternal: Suppressed body weight and decreased feed consumption
Mouse	Acute toxicity study	3 500	M: 3 500 F: - F: Dyspnea, hypothermia and coma
Rabbit	Developmental toxicity study (the 1st study)	0, 50, 150, 450	Maternal: 150 Maternal: Suppressed body weight and feed consumption
	Developmental toxicity study (the 2nd study)	0, 30, 90, 270	Maternal: 90 Maternal: Suppressed body weight and feed consumption
ARfD			NOAEL: 90 SF: 100 ARfD: 0.9
The critical study for setting ARfD			Developmental toxicity study in rabbits (the 2nd study)

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

[a], The adverse effect observed at LOAEL