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

Risk Assessment Report

Carbosulfan

(Pesticides)

Food Safety Commission of Japan (FSCJ)
February 2020

ABSTRACT

FSCJ conducted the risk assessment of a carbamate insecticide, carbosulfan (CAS No. 55285-14-8), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy rice and maze), acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), combined chronic toxicity/carcinogenicity (rats and mice), three-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of carbosulfan observed are inhibition of brain and RBC ChE activity, suppressed body weight, iris atrophy and retinal degeneration in the eye (rats). Carbosulfan showed no carcinogenicity, teratogenicity and genotoxicity.

In a three-generation reproduction toxicity study in rats, reduced number of newborn offspring and decrease in survival rate at four postnatal days were observed.

The relevant substance for the residue definition for dietary risk assessment in agricultural and livestock products and that in fishery products were identified as carbosulfan, its metabolite B (carboflan) and C (including conjugated form of either), and carbosulfan and its metabolite B (carboflan) respectively.

The lowest value of the no-observed-adverse-effect level (NOAEL) or LOAEL in all tests was the 0.5 mg/kg bw/day of NOAEL in an acute neurotoxicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.005 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL or LOAEL for potential adverse effects of a single oral administration of carbosulfan was 0.5 mg/kg bw/day of NOAEL in an acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.005 mg/kg bw by applying a safety factor of 100 to the NOAEL.

The lowest value of LOAEL for metabolite B (carbofuran), 0.03 mg/kg bw obtained by the comprehensive evaluation on ChE activity inhibition in rats, was lower than that of carbosulfan. FSCJ specified an ADI and an ARfD for the metabolite B (carbofuran) as 0.00015 mg/kg bw/day and 0.00015 mg/kg bw respectively, applying a safety factor of 200 (10 for interspecies difference, 10 for interindividual difference, an additional factor of 2 for using LOAEL) to the LOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	Acute neurotoxicity study	0,0.5, 5, 30 ppm M: 0, 1, 6.2, 38.7 F: 0, 1.1, 6.8, 43.5	M/F: 0.5 M/F: RBC and brain ChE activity inhibition (more than 20%)
	90-day subacute toxicity study (the 1st study)	0, 10, 20, 100, 500, 1 000 ppm M: 0, 0.8, 1.5, 7.8, 39.4, 81.8 F: 0, 0.9, 1.7, 8.4, 43.9, 91.5	M: 7.8 F: 8.4 M/F: Suppressed body weight
	90-day subacute toxicity study (the 2nd study)	0, 10, 20, 500 ppm M: 0, 0.7, 1.5, 38.0 F: 0, 0.9, 1.8, 46.0	M: 1.5 F: 1.8 M/F: RBC and brain ChE activity inhibition (more than 20 %)
	90-day subacute neurotoxicity study	0, 20, 1 000, 2 000 ppm M: 0, 1.2, 64.8, 131 F: 0, 1.4, 78.9, 152	M: 1.2 F: 1.4 M/F: Suppressed body weight
	Combined two-year chronic toxicity/carcinogenicity study	0, 10, 20, 500, 2 500 ppm M: 0, 0.5, 1.0, 26.8, 153 F: 0, 0.6, 1.2, 34.7, 213	M: 1.0 F: 1.2 M/F: Brain ChE activity inhibition (more than 20%) (No carcinogenicity)
	Three-generation reproduction activity study	0, 10, 20, 250 ppm PM: 0, 0.72, 1.39, 18.3 PF: 0, 0.82, 1.69, 22.8 F_1M: 0, 0.82, 1.53, 22.2 F_1F: 0, 0.92, 1.86, 27.5 F_2M: 0, 0.83, 1.80, 23.8 F_2F: 0, 0.97, 2.00, 27.4	Parent, offspring and reproductive activity PM: 1.39 PF: 1.69 F_1M: 1.58 F_1F: 1.86 F_2M: 1.80 F_2F: 2.00 Parent and offspring: Suppressed body weight Reproductive activity: Reduced number of newborn offspring and decrease in survival rate at four postnatal days

[1] Major adverse effect observed at LOAEL

	Developmental toxicity study	0, 2, 10, 20	Dams: 2 Fetuses: 2 Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 9, 20, 100, 500, 1 120 ppm M: 0, 1.16, 2.76, 12.8, 65.9, 140 F : 0, 1.52, 3.48, 16.9, 80.8, 176	M: 2.76 F: 16.9 M/F: Suppressed body weight
	Two-year carcinogenicity study	0, 10, 20, 500, 2 500 ppm M: 0, 1.3, 2.5, 61.5, 320 F: 0, 1.5, 3.1, 71.9, 337	M: 2.5 F: 3.1 M/F: RBC and brain ChE activity inhibition (more than 20 %) (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 2, 5, 10	Dams: 5 Fetuses: 10 Dams: Suppressed body weight Fetuses: No toxicity (No teratogenicity)
Dog	6-month subacute toxicity study	0, 50, 500, 1 000 ppm M: 0,1.7, 17.0, 31.2 F: 0, 2.0, 16.9, 31.7	M:1.7 F: 16.9 M: Hypersalivation, RBC ChE activity inhibition (more than 20 %) F: RBC and brain ChE activity inhibition (more than 20 %)
ADI			NOAEL: 0.5 SF: 100 ADI: 0.005
The critical study for setting ADI			Acute neurotoxicity study in rats

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor
[1)] The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw) [1]
Rat	Acute toxicity study	M: 57, 180, 570 F: 57, 180	M/F: - M: Reduced stool volume, piloerection F: Reduced stool volume, decreased locomotor activity, tremor
	Acute toxicity study	M/F: 64, 73, 92, 110, 129, 156, 184	M/F: - M/F: Decreased locomotor activity, tremor, hygrostomia
	Acute toxicity study	M/F: 68.8, 103, 154, 231, 348, 520	M/F: - M/F: Piloerection, lacrimation, hygrostomia, tremor, miosis
	Acute neurotoxicity study	M/F: 0, 0.5, 5, 30	M/F: 0.5 M/F: RBC and brain ChE activity inhibition (more than 20%)
Mouse	Acute toxicity study	M/F: 120, 144, 173, 207, 249, 299	M/F: - M/F: Decreased locomotor activity, tremor, lacrimation
	Acute toxicity study	M/F: 50.0, 65.8, 87.1, 115, 152, 200	M/F: - M/F: Diarrhea, tremor, lacrimation
ARfD			NOAEL: 0.5 SF: 100 ARfD: 0.005
The critical study for setting ARfD			Acute neurotoxicity study in rats

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