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

Risk Assessment Report

Carbofuran

(Pesticides)

Food Safety Commission of Japan (FSCJ)
February 2019

ABSTRACT

FSCJ conducted the risk assessment of a carbamate insecticide, carbofuran (CAS No. 1563-66-2), using assessment data by foreign assessment organizations and various documents on carbosulfan of which metabolite is carbofuran.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy Rice and potatoes), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), genotoxicity. FSCJ also used data on comparison of ChE inhibition between adult and juvenile animals (rats), and studies on sequential changes of ChE inhibition after single oral dose treatment.

Major adverse effects of carbofuran observed are the RBC, brain ChE inhibition and suppressed body weight. Carbofuran showed no carcinogenicity, teratogenicity and genotoxicity relevant to human health.

In a two-generation reproduction toxicity study and developmental neurotoxicity study in rats, survival rate of offspring reduced. Increased number of stillborn babies and developmental retardation of offspring were observed in developmental neurotoxicity study in rats.

From the above results, carbofuran and its metabolite C (including conjugated from) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products and livestock products

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The lowest value of the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) in all tests was the LOAEL of 0.03 mg/kg bw/day in a comprehensive evaluation of ChE inhibition study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.00015 mg/kg bw/day by applying a safety factor of 200 (interspecies difference: 10, interindividual difference: 10, and additional factor of 2 for use of the LOAEL).

The lowest NOAEL/LOAEL for potential adverse effects of a single oral administration of carbofuran in all tests was the LOAEL of 0.03 mg/kg bw/day in a comprehensive evaluation of ChE inhibition study in rats. 8 mg/kg bw/day obtained in developmental toxicity studies in rabbits. FSCJ specified an acute

reference dose (ARfD) to be 0.00015 mg/kg bw by applying a safety factor of 200 (interspecies difference: 10, interindividual difference: 10, and additional factor of 2 for use of the LOAEL).

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]	
			FSCJ	Reference (summary reports)
Rat	90-day subacute toxicity study	0, 20, 120, 720 ppm M: 0, 1, 6.2, 38.7 F: 0, 1.1, 6.8, 43.5	M: 1 F: 1.1 M/F: Brain ChE activity inhibition (more than 20%)	
	90-day subacute neurotoxicity study	0, 50, 500, 1 000 ppm M: 0, 3.17, 34.2, 67.5 F: 0, 3.75, 40.8, 81.2	General toxicity M: - F: 40.8 Neurotoxicity M: 3.17 F: 3.75 General toxicity M/F: Suppressed body weight Neurotoxicity M/F: Tremor	
	Combined two-year chronic toxicity/carcinogenicity study (the 1st study)	0, 10, 20, 100 ppm M: 0, 0.40, 0.80, 4.28 F: 0, 0.52, 1.02, 5.68	M: 0.80 F: 1.02 M/F: Brain ChE activity inhibition (more than 20%) (No carcinogenicity)	M: 0.40 F: 0.53 (No carcinogenicity)
	Combined two-year chronic toxicity/carcinogenicity study (the 2nd study)	0, 10, 20, 100 ppm M: 0, 0.463, 0.91, 4.92 F: 0, 0.63, 1.17, 6.17	M: 0.463 F: 1.17 M: Suppressed body weight, decreased diet efficiency F: Suppressed body weight (No carcinogenicity)	
	Two-generation reproductive activity	0, 20, 50, 100 ppm	Parent and offspring M: 1.17	

[1] Major adverse effect observed at LOAEL

	study	M: 0, 1.17, 2.94, 6.19 F: 0, 1.35,3.91, 7.96	F: 1.35 Fertility M: 2.94 F: 3.91 Parent: Suppressed body weight Offspring: Suppressed body weight Fertility: Decreased survival rate	
	Developmental toxicity study (the 1st study)	0, 0.1, 0.3, 1.0	Dams: 0.1 Fetuses: 1.0 Dams: Lethargy . Fetuses: No toxicity (No teratogenicity)	Dams：- Fetuses：1.0 Dams: Lethargy . Fetuses: No toxicity (No teratogenicity)
	Developmental toxicity study (the 2nd study)	0, 0.25, 0.5, 1.20	Dams and fetuses: 1.20 Dams and fetuses: No toxicity (No teratogenicity)	Dams and fetuses: 1.20 Dams and fetuses: No toxicity (No teratogenicity)
	Developmental toxicity study (the 3rd study)	0, 0.3, 1, 2	Dams: 0.3 Fetuses: 1 Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)	
	Developmental neurotoxicity study	0, 20, 75, 300 ppm	Dams: 1.7 Fetuses: 1.7 Dams: Suppressed body weight Fetuses: Decreased survival rate of postnatal four days	

		0, 1.7, 5, 20	(Developmental delay in learning and memorization, and swimming performance (head angle maintenance))	
	Examination of dose-response relationship in ChE activity inhibition (the 2nd study)	M/F (Juvenile and young adult rats): 0, 0.3, 0.6, 1.0	M/F (Juvenile and young adult rats): - M/F (Juvenile and young adult rats): Brain ChE activity inhibition (more than 20%)	M/F (Juvenile and young adult rats): - M/F (Juvenile and young adult rats): Brain ChE activity inhibition (more than 20%)
	Examination of dose-response relationship in ChE activity inhibition (the 3rd study)	M/F (Juvenile rats): 0, 0.03, 0.1, 0.3	M/F: 0.03 M/F: RBC and brain ChE activity inhibition (more than 20%)	
	Examination of dose-response relationship in ChE activity inhibition (the 4th study)	M/F (Juvenile and adult rats) : 0, 0.03, 0.1, 0.3	M (Juvenile rats): 0.03 F (Juvenile rats): - M/F (Young adult rats) : 0.03 M/F: Brain ChE activity inhibition (more than 20%)	M/F (Young adult rats): 0.03 M/F: Brain ChE activity inhibition (more than 20 %)
	Comprehensive evaluation of Examination of dose-response relationship in ChE activity inhibition (the 2nd, 3rd and 4th study)			
	Examination of dose-response relationship in ChE activity inhibition (the 5th study)	M (Juvenile and adult rats): 0, 0.1, 0.3, 0.6, 1.0	Juvenile rats: - Adult rats: 0.1 RBC and brain ChE activity inhibition (more than 20 %)	
	Examination of dose-response relationship in ChE activity inhibition (the 6th study)	M (Juvenile rats): 0, 0.1, 0.3, 0.6, 1.0	- RBC and brain ChE activity inhibition (more than 20 %)	
	Examination of dose-response relationship in ChE activity inhibition (the 7th study)	M (Adult rats): 0, 0.1, 0.3, 0.5, 0.75, 1.5	0.1 RBC and brain ChE activity inhibition (more than 20%), and decreased locomotor activity	
	ChE acitivity inhibition study in pregnant animals	0, 0.05, 0.25, 2.5	Dams: - Fetuses: -	

			Dams: The liver AChE activity inhibition (more than 20%) Fetuses: Whole blood AChE activity inhibition (more than 20%)	
	Comprehensive evaluation of Examination of dose-response relationship in ChE activity inhibition (the 5th, 6th and 7th study)			
	Comprehensive evaluation of Examination of dose-response relationship in ChE activity inhibition (the 2nd, 4th and 7th study)			
	Comprehensive evaluation of ChE activity inhibition study		- Brain ChE activity inhibition (more than 20%) in juvenile rats (11 day old)	
Mouse	Combined two-year chronic toxicity/carcinogenicity study	0, 20, 125, 500 ppm M：0, 2.71, 16.9, 67.1 F：0, 3.21, 19.3, 74.4	M: 2.71 F: 3.21 M/F: Brain ChE activity inhibition (more than 20%) (No carcinogenicity)	M: 2.71 F: 3.21 M/F：Brain ChE activity inhibition (more than 20%) (No carcinogenicity)
	Two-year carcinogenicity study	0, 20, 100, 500, 1 000 ppm M: 0, 2.95, 14.1, 69.3, 141 F: 0, 3.49, 17.3, 81.8, 162	M: 2.95 F: 3.49 M/F: RBC ChE activity inhibition (more than 20 %) (No carcinogenicity)	
Rabbit	Developmental toxicity study (the 1st study)	0, 0.2, 0.6, 2.0	Dams: 0.6 Fetuses: 2.0 Dams: Death, tremor Fetuses: No toxicity (No teratogenicity)	Dams: 0.6 Fetuses: 2.0 Dams: Death, tremor Fetuses: No toxicity (No teratogenicity)
	Developmental toxicity study (the 2nd study)	0, 0.12, 0.5, 2	Dams and fetuses: 0.5 Dams: Suppressed body weight, Fetuses: Skeletal variations (Disarrangement of sternebra) (No teratogenicity)	

	Developmental toxicity study (the 3rd study)	0, 0.2, 0.7, 2.5	Dams: 0.2 Fetuses: 2.5 Dams: Soft stool and suppressed body weight Fetuses: No toxicity (No teratogenicity)	
Dog	90-day subacute toxicity study	0, 10, 70, 500/250 ppm M: 0, 0.45, 3.11, 10.9 F: 0, 0.41, 2.99, 10.4	M/F: - M/F: Hygrostomia, RBC ChE activity inhibition	
	28-day subacute toxicity study (Supplemental study)	M: 0, 5 ppm 0, 0.22	0.22 No toxicity	
	One-year chronic toxicity study (the 1st study)	0, 10, 20, 500 ppm M: 0, 0.41, 0.84, 14.6 F: 0, 0.31, 0.63, 13.4	M: 0.41 F: 0.31 M/F: Hepatocellular fatty degeneration	M: 0.41 F: 0.31 M: Plasma ChE activity inhibition
	One-year chronic toxicity study (the 2nd study)	0, 0.1, 1, 10	M/F: 0.1 M/F: Miosis, RBC ChE activity inhibition (more than 20%)	
Chicken	28-day subacute delayed neurotoxicity study	0, 0.5, 1, 2	0.5 Histopathological alteration (Chromatolysis of the Nissle bodies, Purkinje cell degeneration) (No delayed neurotoxicity)	
ADI (cRfD)			LOAEL: 0.03 SF: 200 ADI: 0.00015	NOAEL: 0.31 SF: 100 ADI: 0.003
The critical study for setting ADI (cRfD)			Comprehensive evaluation of ChE activity inhibition study	One-year chronic toxicity study in dogs (the 1st study)

ADI, Acceptable daily intake; cRfD, Chronic reference dose; NOAEL, No-observed-adverse-effect level
LOAEL, lowest-observed-adverse-effect level; SF, Safety factor
[1)], The adverse effect observed at LOAEL; -, NOAEL could not be specified
/, No description in relevant reference

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

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw) [1]
Rat	Acute toxicity study with oral dose	M: 4~20 F: 2~20	M/F: - Tremor, decreased locomotor activity, hygrostomia
	Developmental toxicity study (the 3rd study)	0.3, 1, 2	Dams: 0.3 Hygrostomia, the lower jaw tremor
	Comparative ChE study	M/F (Newborn, juvenile and mature rats): 2.2~4 M/F (juvenile and mature rats): 0.03~1.5 Pregnant animals: 0.05, 0.25, 2.5	F (Juvenile rats): - F (Mature rats): 0.1 M (Juvenile and mature rats): 0.1 Dams: - Fetuses: - Juvenile and mature rats: Brain ChE activity inhibition (more than 20%) Dams: Liver AChE acitivity inhibition Fetuses: Whole blood AChE activity inhibition (more than 20%)
Mouse	Acute toxicity study with oral dose	5~40	M/F: - Tremor and hygrostomia
Dog	90-day subacute toxicity study	10, 70, 500/250 ppm M: 0, 0.45, 3.11, 10.9 F: 0, 0.41, 2.99, 10.4	M/F: - Hygrostomia
	One-year chronic toxicity study	10, 20, 500 ppm M: 0, 0.41, 0.84, 14.6 F: 0, 0.31, 0.63, 13.4	M: 0.41 Vomiting
Rabbit	Developmental toxicity study (the 2nd study)	0, 0.12, 0.5, 2	Dams: 0.5 Suppressed body weight
ARfD			LOAEL: 0.03 SF: 200 ARfD: 0.00015
The critical study for setting ARfD			Comprehensive evaluation of ChE activity inhibition study in rats.

ARfD, Acute reference dose; LOAEL, Lowest-observed-adverse-effect level; SF, Safety factor;
-, NOAEL could not be observed; [1], The adverse effect observed at LOAEL