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

Risk Assessment Report

Carbaryl

(Pesticides and Veterinary medicines)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ established health based guidance values of carbaryl (CAS No.63-25-2), a carbamate insecticide, based on results from various studies in the risk assessment.

The data used in the assessment include fate in animals (rats, cattle, chickens), fate in plants (wheat, Japanese white radishes and others), residue in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats) and genotoxcity.

Major adverse effects of carbaryl were inhibition of cholinesterase (ChE) activity in the brain and erythrtocytes, centrilobular hepatocellular hypertrophy, renal pelvic transitional epithelial hyperplasia, transitional epithelium hyperplasia in the urinary bladder in rats, protein-like intracytoplasmic droplets in the transitional epithelium of the urinary bladder in mice, follicular cell hypertrophy in rats, and anemia in mice. No reproductive toxicity teratogenicity and genotoxicity relevant to human health was observed.

The treatment related increases or increased trend in incidences of tumors were observed in uninary bladder, liver, thyroid and kidney in rats, as well as liver, kidney, and blood vessesl mainly in the liver and kidney in mice. A genotoxic mechanism, however was unlikely involved in carcinogenesis of these tumors. It was thus considered possible to establish a threshold in the assessment.

On the basis of various studies, carbaryl (parent compound only) was identified as a relevant substance for residue definition for dietary risk assessment in agricultural and livestock products.

The lowest value of no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) were NOAELs of 1.0 mg/kg bw/day in a 90-day subacute neurotoxicity study in rat and the first

developmental neurotoxicity study in rats. An acceptable daily intake (ADI) of 0.01 mg/kg bw/day can be derived by applying a safety factor of 100 to the both NOAELs.

The expert committee of pesticides recognized that the NOAEL could not be specified in a carcinogenicity study in mice where the vascular tumors (hemangiosarcomas) were increased by the treatment in all treated groups for males. If an ADI is established on the basis of this LOAEL (14.7 mg/kg bw/day)) of the carcinogenicity study in mice, an additional safety factor of 20 would be applied in view of using the carcinogenic LOAEL for estblishment of ADI, and the ADI would be 0.0073 mg/kg bw/day. This value is lower than that of 0.01 mg/kg bw/day derived from the NOAEL in the 90-day subacute neurotoxicity study and the first developmental neurotoxicity studyin rats.

On the basis of the above, FSCJ specified the ADI of 0.0073 mg/kg bw/day by applying a safety factor of 2,000 (10 for species difference, 10 for individual difference, 2 for additional safety factor to account for the use of LOAEL, and 10 in view of using the carcinogenic LOAEL) based on the LOAEL of 14.7 mg/kg bw/day in the carcinogenicity study in mice.

Adverse effects that would likely to be elicited by a single oral administration of carbaryl was evaluated in the Expert Committee of Pescitides, FSCJ. Inhibition of ChE activity was considered the most sensitive endpoint for the single dose effect of choline esterase inhibitors including carbaryl. NOAELs could not be identified in the second and third acute neurotoxicity studies in rats, as well as the comparison study of ChE sensitivity due to the inhibition of brain or erythrocyte ChE activity. The Expert Committee of Pescitides, FSCJ however noted that the NOAELs of 1.0 mg/kg bw/day in the 90-day subacute neurotoxicity toxicity study and in the first developmental neurotoxicity study in rats were lower than the LOAELs of the two acute neurotoxicity and the comparison studies described above. Therefore, the Expert Committee of Pescitides, FSCJ judged the overall NOAEL of 1.0 mg/kg bw/day is appropriate based on the lowest NOAEL for adverse effects of eliciting single oral dose of carbaryl. Consequently, FSCJ specified the ARfD of 0.01 mg/kg bw for carbaryl based on the overall NOAELs of 1.0 mg/kg bw bw per day by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw day) Critical endpoints[1)]
Rat	The first 90-day subacute toxicity study	0, 250, 1 500, 7 500 ppm 0, 12, 75, 380	M : － M : Follicular epithelial cell hypertrophy in thyroid
	90-day subacute neurotoxicity study	0, 1, 10, 30	FM : 1 FM : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others
	Two-year combined chronic toxicity/carcinogenicity study	0, 250, 1 500, 7 500 ppm M : 0, 10.0, 60.2, 350 F : 0, 12.6, 78.6, 485	M : 60.2 F : 12.6 FM : Inhibition of erythrocyte ChE activity (more than 20%) and others FM : Increased incidences of tumors in bladder M : Increased incidences of tumors in kidney and thyroid F : Increased incidences of tumors in liver
	Two-generation reproductive toxicity study	0, 75, 300, 1 500 ppm PM : 0, 4.67, 31.3, 92.4 PF : 0, 5.56, 36.3, 111 F_1M : 0, 5.79, 23.5, 124 F_1F : 0, 6.41, 26.9, 136	Parent PM : 4.67 PF : 36.3 F_1M : 5.79 F_1F : 26.9 Offspring PM : 4.67 PF : 5.56 F_1M : 5.79 F_1F : 6.41 Parent FM : Suppressed body weight and others Offspring FM : Reduced 4-day survival rate (No effect on reproduction)
	The first developmental toxicity study	0, 1, 4, 30	Maternal and Offspring : 4 Maternal : Suppressed body weight and others Embryo/fetus : Low body weight (Not teratogenic)
	The second developmental neurotoxicity study	0, 0.1, 1.0, 10	Maternal : 1.0 Offspring : 10 Maternal : Inhibition of brain ChE activity

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw day) Critical endpoints[1)]
			(more than 20%) and others Offspring : No toxicological effects (No developmental neurotoxicity)
Mouse	Two-year carcinogenicity study	0, 100, 1 000, 8 000 ppm --- M : 0, 14.7, 146, 1 250 F : 0, 18.1, 181, 1 440	M : － F : 18.1 M : Vascular tumor F : Intracytoplasmic protein-like droplets in the transitional epithelium of the urinary bladder FM : Vascular tumor M : Renal tubular tumor F : Increase in liver tumor
Rabbit	Developmental toxicity study	0, 5.0, 50.0, 150	Maternal and Embryo/fetus : 50.0 Maternal : Inhibition of erythrocyte ChE activity (more than 20%) and others Embryo/fetus : Low body weight (Not teratogenic)
Dog	5-week subacute toxicity study	0, 20, 45, 125 ppm --- M : 0, 0.59, 1.43, 3.83 F : 0, 0.64, 1.54, 4.11	M : 3.83 F : 4.11 FM : No toxicological effects
	One-year chronic toxicity study	0, 125, 400, 1 250 ppm --- M : 0, 3.37, 11.2, 33.8 F : 0, 3.73, 11.1, 34.4	M : 3.37 F : － FM : Inhibition of brain ChE activity (more than 20%) and others
ADI(cRfD)			LOAEL : 14.7 SF : 2, 000 ADI : 0.0073
The critical study for setting the ADI			Two-year carcinogenicity study in mice

/, No test described; NOAEL, No-observed-adverse-effect level; LOAEL, Lowest-observed-adverse-effect level; LOEL, Lowest-observed-effect level; ADI, Acceptable daily intake; cRfD, Chronic reference dose; SF, Safety factor; -, NOAEL not derived; [1)], The adverse effect observed at LOAEL

Table 2. *Adverse effects possibly elicited by a single oral administration*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	NOAEL and end point for establishing acute reference dose (ARfD)[1)] (mg/kg bw or mg/kg bw/day)
Rat	Acute toxicity study	200, 500, 1, 000	FM : － FM : Sedation, dyspnea, tremor and others
	Acute neurotoxicity study (the 1st study)	0, 10, 50, 125	FM : 10 FM : Tremor, ataxia and others
	Acute neurotoxicity study (the 2nd study)	0, 10, 50, 125	FM : － FM : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others
	Acute neurotoxicity study (the 3rd study)	0, 10, 30, 90	FM : － FM : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others
	90-day subacute neurotoxicity study	0, 1, 10, 30	FM : 1 FM : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others
	Reproductive toxicity study (the 1st study)	0, 1, 4, 30	Maternal : 4 Maternal : Salivation
	Developmental neurotoxicity study (the 1st study)	0, 0.1, 1.0, 10	Maternal : 1.0 Maternal : Inhibition of brain and erythrocyte ChE activity (more than 20%) and others
	Review on hepatic drug-metabolizing enzyme activities and cell proliferation activity	0, 10, 40	FM : 10 FM : Decreased activity and others
	ChE Comparative Sensitivity Study	M : 0, 3, 7.5, 15, 30	M : － M : Inhibition of erythrocyte ChE activity in (more than 20%) and others
Rabbit	Reproductive toxicity study	Maternal: 0, 5.0, 50.0, 150	Maternal : 50 Maternal : Suppressed body weight
ARfD			NOAEL : 1.0 SF : 100 ARfD : 0.01
The critical study for setting ARfD			Overall NOAEL evaluation of 90-day subacute neurotoxicity study in rats, developmental neurotoxicity study (the1st study), acute neurotoxicity study (the 2nd study) and (the 3rd study), as well as comparison study of ChE sensitivity

－, NOAEL was not derived; ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor; [1)], The adverse effect observed at LOAEL