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

Risk Assessment Report

Cyflufenamid (3rd Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

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ABSTRACT

FSCJ conducted the risk assessment of an insecticide having Amidoxime skeleton, cyflufenamid (CAS No. 18409-60-3), based on various documents. Documents submitted newly in this 3rd version of assessment include data of residue in crops (hop) and of acute neurotoxicity study in rats. The current assessment was conducted focusing on newly submitted data and specifying acute reference dose (ARfD).

The data used in the assessment include fate in animals (rats and dogs), fate in plants (cucumber, apple and wheat), residues in crops, acute toxicity (rats), acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive activity (rats), developmental toxicity (rats and rabbits), genotoxicity, and mechanisms of various toxicities observed in rats, mice or dogs.

Major adverse effects of cyflufenamid observed are centrilobular hypertrophy of hepatocytes in the liver, vacuolation of renal tubular in the kidney, myocarditis, follicular cell hypertrophy of the thyroid (rats), testicular interstitial cell hyperplasia, and cerebral vacuolation. Cyflufenamid showed no neurotoxicity, effects on reproductive activity and genotoxicity.
In carcinogenicity studies, incidence of follicular adenomas in the thyroid and incidence of hepatocellular adenomas increased in male rats and in male mice, respectively. However, a genotoxic mechanism was unlikely to be involved in tumor induction, and FSCJ considered it possible to establish a threshold dose in the assessment.
In developmental toxicity studies in rabbits, incidence of external-, internal- and skeletal anomaly increased in the fetuses. In developmental toxicity studies in rats, no teratogenicity was observed.
From the above results, cyflufenamid (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 4.14 mg/kg bw/day in a one-year chronic toxicity study in dogs, and 4.4 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.041 mg/kg bw/day by applying a safety factor of 100 to the NOAEL of 4.14 mg/kg bw/day. This ADI was the same as the previous ADI.

Since the absence of any toxicological effects that would be likely to be elicited by a single dose of cyflufenamid was observed, FSCJ considered it was unnecessary to specify the ARfD.

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

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, 50, 300, 1 800, 10 800 ppm	M: 20.1 F: 24.7	M: 20.1 F: 24.7
		M: 0, 3.3, 20.1, 117, 673 F: 0, 4.1, 24.7, 144, 783	M/F: Increase in absolute and relative weight of the thymus, centrilobular hypertrophy of hepatocytes in the liver	M/F: Increase in absolute and relative weight of the thymus, centrilobular hypertrophy of hepatocytes in the liver
	90-day subacute neurotoxicity study	0, 200, 1 000, 5 000 ppm	M: 88 F: 98	M: 88 F: 98
		M: 0, 18, 88, 453 F: 0, 21, 98, 572	M: Suppressed body weight F: Suppressed body weight, decrease in dietary efficiency (No subacute neurotoxicity)	M: Suppressed body weight F: Suppressed body weight, decrease in dietary efficiency (No neurotoxicity)
	Combined two-year chronic toxicity/carcinogenicity study	0, 100, 500, 2 000 (F), 5 000 (M) ppm	M: 4.4 F: 5.5	M: 4.4 F: 5.5
		M: 0, 4.4, 22, 229 F: 0, 5.5, 28, 115	M: Pigmentation and hyaline droplet in renal tubular cells of the kidney cortex F: Increased relative weight of thyroid/parathyroid, centrilobular hypertrophy of hepatocytes in the liver (Increased incidence of thyroid follicular cell adenomas in male)	M: Pigmentation and hyaline droplet in renal tubular cells of the kidney cortex F: Increased relative weight of thyroid/parathyroid, centrilobular hypertrophy of hepatocytes in the liver (Increased incidence of thyroid follicular cell adenomas in male)
	Two-generation reproductive activity study	0, 80, 250, 800 ppm	Parent and offspring PM: 18.0 PF: 19.9	Parent and offspring PM: 18.0 PF: 19.9

[1] Major adverse effect observed at LOAEL

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[1]	
			FSCJ	Reference (Summary reports)
		PM: 0, 5.8, 18.0, 57.4 PF: 0, 6.5, 19.9, 66.2 F_1M: 0, 7.4, 23.0, 75.2 F_1F: 0, 7.8, 24.1, 78.2	F_1M: 23.0 F_1F: 24.1 Parent: Increased relative weight of the thyroid. Offspring: Suppressed body weight (No effect on reproductive activity)	F_1M: 23.0 F_1F: 24.1 Parent: Increased relative weight of the thyroid. Offspring: Suppressed body weight (No effect on reproductive activity)
	Developmental toxicity study	0, 100, 300, 1 000	Dams: 100 Fetuses: 1 000 Dams: Salivation, increased absolute- and relative-weight of the liver Fetuses: No toxicity (No teratogenicity)	Dams: 100 Fetuses: 1 000 Dams: Salivation, increased absolute- and relative-weight of the liver Fetuses: No toxicity (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 100, 400, 1 600, 7 000 ppm M: 0, 14.0, 50.7, 218, 808 F: 0, 17.6, 70.8, 295, 940	M: 50.7 F: 70.8 M/F: Increased absolute- and relative-weight of the liver, centrilobular hypertrophy of hepatocytes in the liver	M: 50.7 F: 70.8 M/F: Increased absolute- and relative-weight of the liver, centrilobular hypertrophy of hepatocytes in the liver
	18-month carcinogenicity study	0, 60, 50, 4 000/2 000 ppm M: 0, 7.1, 62.8, 325 F: 0, 9.0, 75.5, 404	M: 62.8 F: 9.0 M: Diffuse fat deposition in the liver F: Increase in absolute- and relative- weight of the liver. (Increased incidence of hepatocellular adenomas in male)	M: 62.8 F: 9.0 M: Diffuse fat deposition *in* the liver F: Increase in absolute- and relative- weight of the liver. (Increased incidence of hepatocellular adenomas in male)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints[1]	
			FSCJ	Reference (Summary reports)
Rabbit	Developmental toxicity study (the 1st study)	0, 10, 60, 300	Dams: - Fetuses: 10 Dams: Suppressed body weight, decreased feed intake Fetuses: Incomplete callus of epiphysis, metacarpal bone and phalangeal	Dams: - Fetuses: 10 Dams: Suppressed body weight, decreased feed intake Fetuses: Incomplete callus of epiphysis, metacarpal bone and phalangeal
	Developmental toxicity study (the 2nd study)	0, 5, 10	Dams: 10 Fetuses: 10 Dams and fetuses: No toxicity (No teratogenicity)	Dams: 10 Fetuses: 10 No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	0, 150, 500, 1 500 ppm M: 0, 6.5, 23.2, 76.2 F: 0, 7.5, 24.4, 70.5	M: 6.5 F: 7.5 M/F: Hepatocellular vacuolation and hypertrophy	M: 6.5 F: 7.5 M/F: Hepatocellular vacuolation and hypertrophy
	One-year chronic toxicity study	0, 30, 120, 480 ppm M: 0, 1.04, 4.14, 17.3 F: 0, 1.08, 4.41, 17.3	M: 4.14 F: 4.41 M/F: Increased ALP	M: 4.14 F: 4.41 M/F: Increased ALP
ADI			NOAEL: 4.14 SF: 100 ADI: 0.041	NOAEL: 4.14 SF: 100 ADI: 0.041
The critical study for setting ADI			One-year chronic toxicity study in dogs Combined two-year chronic toxicity/carcinogenicity study in rats	One-year chronic toxicity study in dogs Combined two-year chronic toxicity/carcinogenicity study in rats

ADI, Acceptable Daily Intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
[1)], The adverse effect observed at LOAEL
-, NOAEL could not be specified.