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

Risk Assessment Report

Chlorfluazuron
(Pesticides)

Food Safety Commission of Japan (FSCJ)
December 2017

ABSTRACT

FSCJ conducted a risk assessment of chlorfluazuron (CAS No. 71422-67-8), a benzoyl phenyl uea insecticides, based on results from various studies.

The data used in the assessment include fates in animals (rats), livestocks (goats and chicken), fate in plants (cabbage and cotton), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combind chronic toxicity/carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of chlorfluazuron are observed in the liver (increased organ weights and increased serum cholesterol level), and in the thyroids (C cell hyperplasia in rats). Chlorfluazuron showed no adverse effects on reproductivity, teratogenicity and genotoxicity relevant to human health.
Although a significant increase in the incidence of endometrial stromal sarcoma was observed in a combined two-year chronic toxicity/carcinogenicity study in mice, a genotoxic mechanism was unlikely to be involved in the tumor development. It was thus considered possible to establish a threshold in the assessment. Carcinogenicity was not observed in rats.

Based on the results from various studies, chlorfluazuron (parent compound only) was identified as the relevant substance for a residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 2.97 mg/kg bw/day in 90-day subacute toxicity study in male rats. FSCF considered the NOAEL of 3.3 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in female rats was appropriate to specify an acceptable daily intake (ADI) because the duration was long-term and the NOAEL in males was 125 mg/kg bw per day. FSCJ specified an acceptable daily intake (ADI) of 0.033 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
As the lowest NOAEL for potential adverse effects of single oral administration of chlorfluazuron was considered to be above the cut-off level (500 mg/kg bw), FSCJ considered it unnecessary to specify an acute reference dose (ARfD).

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	90-day subacute toxicity study (the 1st study)	0, 500, 2 000, 10 000 ppm M: 0, 41.6, 161, 796 F: 0, 47.0, 180, 882	M: 796 F: 882 M/F: No toxic effect
	90-day subacute toxicity study (the 3rd study)	0, 50, 4 000, 20 000 ppm M: 0, 2.97, 238, 1 200 F: 0, 3.24, 264, 1 300	M: 2.97 F: 3.24 M/F: Increased T.Chol
	28-day subacute neurotoxicity study	0, 200, 2 000, 20 000 ppm M: 0, 15.7, 159, 1 680 F: 0, 17.4, 174, 1 780	M: 1 680 F: 1 780 M/F: No toxic effect (Subacute neurotoxicity was not observed)
	Combined two-year chronic toxicity/carcinogenicity study	0, 10, 50, 2 500, 10 000 ppm M: 0, 0.49, 2.48, 125, 519 F: 0, 0.66, 3.30, 168, 679	M: 125 F: 3.30 M: Increased mortality F: Increase in T.Chol and E.Chol (No carcinogenicity was observed)
	Two-generation reproductive toxicity study	0, 50, 1 000, 20 000 ppm PM: 0, 3.51, 70.7, 1 430 PF: 0, 4.47, 89.1, 1 800 F_1M: 0, 3.58, 71.2, 1 450 F_1F: 0, 4.30, 88.8, 1 830 F_2M: 0, 3.96, 80.9, 1 670 F_2F: 0, 4.52, 97.4, 1 930	Parent and offspring PM: 1 430 PF: 1 800 F_1M: 1 450 F_1F: 1 830 F_2M: 1 670 F_2F: 1 930 Parent and offspring: No toxic effect (No effect on reproductivity)
	Developmental toxicity study	0, 10, 100, 1 000	Dams and fetuses: 1 000

[1] Major adverse effect observed at LOAEL

			Dams and fetuses: No toxic effect (No teratogenicity was observed)
Mice	90-day subacute toxicity study (the 1st study)	0, 500, 2 000, 10 000 ppm --- M: 0, 84, 326, 1 680 F: 0, 115, 463, 2 330	M: 326 F: 2 330 M: Decreased WBC F: No toxic effect
	Combined two-year chronic toxicity/carcinogenicity study	0, 10, 50, 2 500, 10 000 ppm --- M: 0, 1.60, 7.95, 396, 1 630 F: 0, 1.87, 9.25, 456, 1 900	M: 396 F: 9.25 M: Increased T.Chol F: Increase in absolute weight, weight relative to brain weight of the adrenal gland. (Increased endometrial stromal sarcoma)
Rabbits	Developmental toxicity study	0, 10, 100, 1 000	Dams and fetuses: 1 000 Dams and fetuses: No toxic effect (No teratogenicity was observed)
Dogs	90-day subacute toxicity study	0, 200, 2 500, 50 000 ppm --- M: 0, 7.87, 94.6, 2 070 F: 0, 8.03, 95.3, 2 050	M: － F: 8.03 M/F : Increased T.Chol
	78-week chronic toxicity study	0, 2, 500, 50 000 ppm --- M: 0, 85.2, 1 790 F: 0, 80.0, 1 760	M/F : － M/F: Increased T.Chol
	Integrated evaluation of 90-day subacute toxicity study and 78-week chronic toxicity study		M: 7.07 F: 7.28

ADI	NOAEL: 3.30 SF: 100 ADI : 0.033
The critical study for setting ADI	Combined two-year chronic toxicity/carcinogenicity study

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

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

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw) [1]
Rabbit	Acute toxicity study	5 000	M/F: － Sedation, Dyspnea, Unkempt fur and Hunchback position
Hamster	Acute toxicity study	5 000	M/F : － Dyspnea, Exophthalmos, Unkempt fur and Hunchback position
ARfD			Unnecessary to specify, since the NOAEL was above the cut-off level (500 mg/kg bw).

ARfD, Acuter reference dose
[1)], The adverse effect observed at LOAEL
－, NOAEL could not be specified