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

Risk Assessment Report

Acynonapyr

(Pesticides)

Food Safety Commission of Japan (FSCJ)
April 2018

ABSTRACT

FSCJ conducted a risk assessment of Acynonapyr (CAS No. 1332838-17-1), an insecticide (an acaricide), based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (apples and mandarin oranges), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combind chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of acynonapyr observed are suppressed body weight, effects on hematopoietic system such as anemia, hepatocellular hypertrophy in the liver, and basophilic tubules in the kidney. Foamy cell accumulation/vacuolation in many organs (the lung, lymph nodes, thyroid, liver, and so on) were also observed. Acynonapyr showed no neurotoxicity, teratogenicity and genotoxicity relevant to human health.

Increased incidence of hemangioma in the mesenteric lymph node and thyroid follicular cell adenomas were observed in male rats in a two-year combined chronic toxicity/carcinogenicity study. Increased incidence of malignant lymphoma in lympho-hematopoitic system was observed in male mice in a carcinogenicity study. However, a genotoxic mechanism was unlikely to be involved in the tumor induction. It was thus considered possible to establish a threshold dose in the assessment.
Decrease in implantation number, decrease in conception rate and copulation index were observed in a reproduction study in rats.

Based on the results from various studies, acynonapyr and its metabolite C were identified as the substance relevant for the residue definition for dietary risk assessment in agricultural products, and acynonapyr (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in fishery products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 4 mg/kg bw/day in a one year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.04 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
Since the absence of any toxicological effects that would be likely to be elicited by a single dose of acynonapyr was observed, FSCJ considered it was unnecessary to specify the ARfD.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rats	90-day subacute toxicity study (the 1st study)	0, 60, 250, 1 000, 4 000 ppm M: 0, 3.7, 15.2, 60.5, 260 F: 0, 4.3, 18.4, 72.5, 290	M: 15.2 F: 18.4	M: 60.5 F: 72.5	M: Increased urinary pH F: Suppressed body weight
	90-day subacute toxicity study (the 2nd study)	0, 60, 250, 1 000, 4 000/2 000 ppm M: 0, 3.9, 17.1, 68.9, 286/125 F: 0, 4.6, 21.2, 83.5, 304/149	M: 17.1 F: 21.2	M: 68.9 F: 83.5	M/F: basophilic tubules in the kidney
	Two-year combined chronic toxicity/carcinogenicity study	0, 70, 250, 900 ppm (Chronic toxicity group) M: 0, 3.8, 13.5, 51.5 F: 0, 5.2, 17.5, 68.2 (Carcinogenicity group) M: 0, 3.5, 12.3, 45.1 F: 0, 4.6, 16.2, 60.9	M: 12.3 F: 16.2	M: 45.1 F: 60.9	M/F: Chronic progressive nephropathy (M: hemangioma in the mesenteric lymph node)
	Two-generation reproductive toxicity study	0, 80, 400, 1 000 ppm PM : 0, 4.8, 23.9, 61.7 PF : 0, 5.9, 30.0, 74.3 F_1M : 0, 5.3, 27.1, 71.5 F_1F : 0, 7.1, 35.9, 93.1	Parent PM : 4.8 PF : 5.9 F_1M : 5.3 F_1F : 7.1 Offspring PM : 23.9 PF : 30.0 F_1M : 27.1 F_1F : 35.9 Reproductivity PM : 23.9 PF : 30.0 F_1M : 27.1 F_1F : 35.9	Parent PM : 23.9 PF : 30.0 F_1M : 27.1 F_1F : 35.9 Offspring PM : 61.7 PF : 74.3 F_1M : 71.5 F_1F : 93.1 Reproductivity PM : 61.7 PF : 74.3 F_1M : 71.5 F_1F : 93.1	Parent M/F: Suppressed body weight Offspring lower body weights Reproductivity Decreased implantation number, conception rate and copulation index
	Developmental toxicity study	0, 20, 150, 1 000	Dams: 150 Fetuses: 150	Dams: 1 000 Fetuses: 1 000	Dams: Suppressed body weight and decreased feed consumption Fetuses: Low body weight and Delayed Ossification (No teratogenicity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Mice	90-day subacute toxicity study	0, 60, 320, 1 600, 8 000 ppm M: 0, 8.1, 39.9, 216, 1 130 F: 0, 9.3, 48.4, 256, 1 270	M: 39.9 F: 48.4	M: 216 F: 256	M/F: Adrenocortical hypertrophy, Increased extramedullary hematopoiesis in red pulp
	18-month carcinogenicity study	0, 100, 500, 2 500 ppm M: 0, 13.2, 69.7, 342 F: 0, 15.5, 79.3, 393	M: 69.7 F: 79.3	M: 342 F: 393	M: malignant lymphoma in the lymph-hematopoitic system F: chronic progressive nephropathy, and necrosis of hepatocytes (M: malignant lymphoma in the lymph-hematopoitic system)
Rabbits	Developmental toxicity study	0, 15, 50, 150	Dams: 50 Fetuses: 50	Dams: 150 Fetuses: 150	Dams: abortion Fetuses: low body weight (No teratogenicity)
Dogs	90-day subacute toxicity study	0, 10, 50, 200	M/F : 10	M/F : 50	M: increased hematopoiesis in the sterna and thigh bone. F: Increased T Bil
	One-year chronic toxicity study	0, 4, 20, 80	M/F : 4	M/F : 20	M/F: increased hematopoiesis in the sterna
ADI			NOAEL: 4 SF: 100 ADI: 0.04		
The critical study for setting ADI			One year chronic toxicity study in dog		

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