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

Risk Assessment Report

Ipflufenoquin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of an insecticide having a new skeleton structure, ipflufenoquin (CAS No. 1314008-27-9), based on various documents.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (paddy rice and kidney beans), residues in plants, subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, mechanisms about drug metabolism enzyme induction in the liver, effects on incisor or femur, and phototoxicity in vitro.

Major adverse effects of ipflufenoquin observed are depressed body weight, enamel hypoplasia of incisor (rats and rabbits), hypertrophy of hepatocytes in the liver, hypertrophy of follicular cells in the thyroid (rats), and mucosal epithelial hyperplasia in the colon (rats). Ipflufenoquin showed no neurotoxicity, carcinogenicity, effects on reproductive activity, teratogenicity and genotoxicity.

From the above results, FSCJ identified the relevant substances for the residue definition for dietary risk assessment in agricultural, livestock or fishery products to be ipflufenoquin and its metabolites [3 and 4], ipflufenoquin and the metabolites [11 and 17] or ipflufenoquin (parent compound only), respectively.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 4.84 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.048 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of ipflufenoquin was 125 mg/kg bw obtained in acute neurotoxicity studies in rats. FSCJ specified an acute reference dose (ARfD) to be 1.2 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	28-day subacute toxicity study	0, 50, 250, 1 000	M/F: 50	M/F: 250	M/F: Mucosal epithelial hyperplasia and regeneration in the colon
	90-day subacute toxicity study	0, 100, 400, 2 000, 8 000 ppm Main group M: 4.84, 24.8, 126 F: 6.76, 33.8, 177 Satellite group M: 5.52, 27.6, 142 F: 7.32, 40.0, 201	M: 26.8 F: 34.1	M: 137 F: 171	M: Increased absolute and relative weight of the live F: Decreased BuChE
	Combined two-year chronic toxicity/carcinogenicity study	0, 100, 500, 2 500 ppm M: 0, 11.0, 43.8, 177, 712 F: 0, 10.7, 42.5, 170, 686	M: 4.84 F: 6.76	M: 24.8 F: 33.8	M/F: Pale color of lower incisor (No carcinogenicity)
	Two-generation reproduction study	0, 250, 1 000, 4 000 ppm PM: 0, 14.4, 57.7, 237 PF: 0, 19.1, 75.9, 314 F_1M: 0, 16.4, 67.6, 279 F_1F: 0, 20.4, 81.5, 340	Parent PM: 57.7 PF: 75.9 F_1M: 67.6 F_1F: 81.5 Offspring PM: 57.7 PF: 75.9 F_1M: 67.6 F_1F: 81.5	Parent PM: 237 PF: 314 F_1M: 279 F_1F: 340 Offspring PM: 237 PF: 314 F_1M: 279 F_1F: 340	Parent: M/F: Pale color of incisor, mucosal pithelial hyperplasia in the colon Offspring: Suppressed body weight (No effects on reproductive activity)
	Developmental toxicity study	0, 40, 200, 1 000	Dams: 200 Fetuses: 1 000	Dams: 1 000 Fetuses: -	Dams: Suppressed body weight, decreased feed intake Fetuses: No toxicity (No teratogenicity)
Mouse	18-month carcinogenicity study	0, 60, 250, 1 000 ppm M: 0, 6.10, 24.8, 106 F: 0, 7.16, 29.5, 117	M: 24.8 F: 29.5	M: 106 F: 117	M: Pale color of incisor F: Incisor fracture (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 50, 150, 300	Dams: 50 Fetuses: 300	Dams: 150 Fetuses: -	Dams: Suppressed body weight, Emaciation Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute	0, 20, 60, 180	M: 60	M: 180	M: Suppressed body

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	toxicity study		F: 180	F: -	weight, decreased feed intake F: No toxicity
	One-year chronic toxicity study	0, 10, 60, 180 (M), 360 (F)	M: 180 F: 60	M: - F: 360	M: No toxicity F: Suppressed body weight, decreased feed intake
ADI			NOAEL: 4.84 SF: 100 ADI: 0.048		
The critical study for setting ADI			Combined two-year chronic toxicity/carcinogenicity study (rats)		

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

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

Species	Study	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw/day) [1]
Rat	Acute neurotoxicity study	0, 125, 500, 2 000	M/F: 125 M: Decreased body temperature F: Decreased body temperature, decreased locomotive activity (walking and mobility)
ARfD			NOAEL: 125 SF: 100 ARfD: 1.2
The critical study for setting ARfD			Acute neurotoxicity study in rats

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
[1)], The adverse effect observed at LOAEL