

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

Risk Assessment Report

Ipflufenoquin

(Pesticides)

Food Safety Commission of Japan (FSCJ) January 2020

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.

28-day subacute toxicity study 0, 50, 250, 1 000 M/F: 50 M/F: 250 M/F: Mucosal epithe hyperplasia and regeneration in the cc 90-day subacute toxicity study 0, 100, 400, 2 000, 8 000 ppm M/F: 34.1 M: 137 M: Increased absolu and relative weight o the live F: 0.73, 348, 126 90-day subacute toxicity study 0, 100, 400, 2 000, 8 000 ppm M: 4.84 F: 34.1 F: 171 M: Increased absolu and relative weight o the live F: Decreased BuChE Combined two-year chronic 0, 100, 500, 2500 ppm M: 5.52, 27.6, 142 M: 4.84 M: 24.8 M/F: Pale color of F: 6.76 F: 33.8 Combined two-year chronic 0, 100, 4000 ppm 90, 250, 1000, 4000 ppm M: 4.84 M: 24.8 M/F: Pale color of F: 6.76 M: M: regeneration f: 6.76 M: M: Resent f: 6.76 M: M: Resent f: 6.76 M: M: Resent f: 6.76 M: Resent f: 6.76 M: Resent f: 8.38 Two-generation reproduction study W: 0, 11.4, 45.7, 237 PF: 7.5.9 PF: 31.4 M: regeneration file M: Resent f: 8.15 M: 8.24 M: 006 Restus:	Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints ¹⁾
P0-day subacute toxicity study ppm F: 34.1 F: 171 and relative weight o the live F: Decreased BuChE 90-day subacute toxicity study 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 F: 171 and relative weight o the live F: Decreased BuChE Combined two-year chronic 0, 100, 500, 2 500 ppm M: 0, 500, 2 500 ppm M: 4.84 F: 6.76 M: 24.8 F: 33.8 M/F: Pale color of F: 6.76 toxicity/carcinogenicity study F: 0, 10.7, 42.5, 170, 686 Parent PM: 57.7 PArent PM: 57.7 PArent PM: 57.7 PArent PM: 57.7 PM: 237 Two-generation reproduction study Fig. 0, 19.1, 75.9, 314 Fig. 0, 15.4, 67.6, 67.99 Fig. 81.5 Pi: 81.5 Fig. 81.5 Pi: 81.5 Fig. 81.5 Pi: 67.0 Fig. 237 Pi: 67.0 Fig. 237 Developmental toxicity study 0, 400, 200, 1 000 Dams: 200 Fetuses: 1 000 Dams: 1000 Fetuses: 1 000 Dams: Suppressed bed weight, decreased fee intake Mouse 18-month earcinogenicity study 0, 60, 250, 1 000 ppm M: 24.8 F: 29.5 Pi: 117 Pi lace color of nici F: 117 M: 06 F: 0, 7.16, 29.5, 117 M: 24.8 F: 29.5 Pi: 1000 Fetuses: 300 M: 24.8 F: 117 Pi lace color of nici F: 1000 No carcinogenicity study 0, 50, 1	Rat	•	0, 50, 250, 1 000			M/F: Mucosal epithelial hyperplasia and regeneration in the colon
Rat Image: chronic toxicity/carcinogenicity study M: 0, 11.0, 43.8, 177, 712 F: 0, 10.7, 42.5, 170, 686 F: 6, 76 F: 33.8 lower incisor Rat		-	ppm Main group M: 4.84, 24.8, 126 F: 6.76, 33.8, 177 Satellite group M: 5.52, 27.6, 142			M: Increased absolute and relative weight of
Rat0, 250, 1000, 4000 ppmParent PM: 57.7Parent PM: 237Parent M/F: Pale color of incisor, mucosal pith hyperplasia in the col OffspringTwo-generation reproduction study $PM: 0, 14.4, 57.7, 237$ $PF: 0, 19.1, 75.9, 314PF: 75.9F_1N: 67.6PF: 314F_1M: 279hyperplasia in the colOffspringTwo-generationreproduction studyF_1M: 0, 16.4, 67.6, 279F_1F: 0, 20.4, 81.5, 340F_1N: 67.6F_1N: 67.6F_1M: 279F_1F: 314OffspringPM: 237PF: 75.9Suppressed body weiPM: 237PF: 75.9Developmental toxicitystudy0, 40, 200, 1000Dams: 200Fetuses: 1000Dams: 1000Fetuses: -1Dams: Suppressed bcweight, decreased feeintakeMouse18-monthcarcinogenicity study0, 60, 250, 1000 ppmM: 0, 6.10, 24.8, 106F: 0, 7.16, 29.5, 117M: 24.8F: 29.5M: 106F: 117M: 106F: 1ncisor fractureM: 0x carcinogenicity)RabbitDevelopmental toxicitystudy0, 50, 150, 300Dams: 50Fetuses: 300Dams: 150Fetuses: -Dams: Suppressed bcweight, EmaciationFetuses: No toxicity(No carcinogenicity)$		chronic				
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Rabbit Developmental toxicity study 0, 50, 150, 300 Dams: 50 Dams: 150 Dams: Suppressed box Rabbit Developmental toxicity study 0, 50, 150, 300 Dams: 0 Fetuses: 300 Fetuses: - weight, Emaciation	Mouse		M: 0, 6.10, 24.8, 106			M: Pale color of incisor F: Incisor fracture
	Rabbit					Fetuses: No toxicity
Dog 90-day subacute 0, 20, 60, 180 M: 60 M: 180 M: Suppressed body	Dog	90-day subacute	0, 20, 60, 180	M: 60	M: 180	M: Suppressed body

Table 1. Levels relevant to toxicological evaluation of ipflufenoquin



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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



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

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

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;

¹⁾, The adverse effect observed at LOAEL