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

Risk Assessment Report

Bixafen (Periodic evaluation)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted the risk assessment of bixafen (CAS No. 581809-46-3), a fungicide of the structure containing a pyrazole ring and a biphenyl ring, based on various documents. In the present assessment, data of studies on fate in plants (potatoes and tomatoes), residue in crops (wheat, maize and soybeans) and acute neurotoxicity (rats) were newly available.

The data used in the assessment include fate in animals (rats, goats and chicken), fate in plants (wheat and soybeans), residues in plants, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction activity (rats), developmental toxicity (rats and rabbits), genotoxicity, mechanism of effect on liver and thyroid, and acute neurotoxicity.

Major adverse effects of bixafen observed are hepatocellular hypertrophy in the liver and follicular cell hypertrophy in the thyroid. Bixafen showed no carcinogenicity, effects on reproductive activity and genotoxicity.

In developmental toxicity study in rabbits, incidence in esophageal travel of right subclavian artery and number of anterior sacral vertebrae in fetuses were increased at a serious maternal toxic dose. FSCJ judged that bixafen has no teratogenicity, since bixafen did not induce abnormality at the dose without maternal toxicity in rabbits and internal- and skeletal anomaly at the highest dose tested in rats.

From the above results, FSCJ identified bixafen (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products, and and bixafen and its metabolite M21 as that for dietary risk assessment in livestock products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 1.98 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study (the 2nd study) in rats. FSCJ specified an acceptable daily intake (ADI) of 0.019 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. This ADI was the same as that of the previous evaluation.
The lowest NOAEL for potential adverse effects of a single oral administration of flupyrimin was 20 mg/kg bw/day obtained in developmental toxicity studies in rats. FSCJ specified an acute reference dose (ARfD) to be 0.2 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 50, 200, 800, 2 000 ppm M: 0, 3.2, 12.9, 50.4, 130 F: 0, 3.9, 15.0, 59.2, 153	M: 12.9 F: 15.0	M: 50.4 F: 59.2	M: Centrilobular hypertrophy of hepatocytes in the liver F: Increased relative – and absolute-organ weight in the liver.
	Combined two-year chronic toxicity/carcinogenicity study (the 1st study)	0, 50, 300, 2 000 ppm F: 0, 2.81, 17.4, 117	F: 2.81	F: 17.4	F: Centrilobular hypertrophy of hepatocytes in the liver (No carcinogenicity)
	Combined two-year chronic toxicity/carcinogenicity study (the 2nd study)	0, 50, 300, 2 000 ppm F: 0, 1.98, 12.1, 80.5	M: 1.98	M: 12.1	M: Centrilobular hypertrophy of hepatocytes in the liver (No carcinogenicity)
	Two-generation reproductive activity study	0, 50, 400, 2 500 ppm M: 0, 3.4, 26.9, 173 F: 0, 4.0, 31.3, 196	Parent: PM: 3.4 PF: - Offspring: F_1M: 26.9 F_1F: 31.3	Parent: PM: 26.9 PF: 4.0 Offspring: F_1M: 173 F_1F: 196	Parent: M/F: Increased absolute- and relative-weight of the liver. Offspring: Suppressed body weight (No effect on reproductive activity)
	Developmental toxicity study	0, 20, 75, 250	Dams and Fetuses: 20	Dams and Fetuses: 75	Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Mice	90-day subacute toxicity study	0, 50, 200, 500 ppm M: 0, 8.5, 34.3, 88 F: 0, 10.4, 42.9, 110	M: 8.5 F: 42.9	M: 34.3 F: 110	M/F: Centrilobular hypertrophy of hepatocytes in the liver
	18-month carcinogenicity study	0, 50, 150, 500 ppm M: 0, 6.7, 20.4, 69.0 F: 0, 8.6, 25.5, 85.0	M: 6.7 F: -	M: 20.4 F: 8.6	M/F: Increased absolute- and relative-weight of the liver (No carcinogenicity)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rabbit	Developmental toxicity study	0, 25, 100, 400	Dams: 100 Fetuses: 25	Dams: 400 Fetuses: 100	Dams: Abortion, sacrifice in extremis, suppressed body weight Fetuses: Delayed ossification (5th sternebrae)
Dog	90-day subacute toxicity study	0, 100, 300, 1 000 ppm	M/F: 300	M/F: 1 000	M/F: Centrilobular hypertrophy of hepatocytes in the liver
	One-year chronic toxicity study	0, 10, 100, 1 000 ppm	M/F: 100	M/F: 1 000	M/F: Centrilobular hypertrophy of hepatocytes in the liver
ADI			NOAEL: 1.98 SF: 100 ADI: 0.019		
The critical study for setting ADI			Combined two-year chronic toxicity/carcinogenicity study (the 2nd study) in rats		

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

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

Species	Study	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]
Rat	Acute neurotoxicity study	0, 250, 1 000, 2 000	M/F: 250 M/F: Decreased motor activity, low body temperature
	Developmental toxicity study	0, 20, 75, 250	Dams: 20 Dams: Decreased body weight/Suppressed body weight, decreased feed intake
Rabbit	Developmental toxicity study	0, 25, 100, 400	Dams: 100 Dams: Decreased body weight/Suppressed body weight
ARfD			NOAEL: 20 SF: 100 ARfD: 0.2
The critical study for setting ADI			Developmental toxicity study in rats

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