

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

Risk Assessment Report

Flumioxazin (Second Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
October 2022

ABSTRACT

The FSCJ conducted a risk assessment of an N-phenyl phthalimide herbicide, flumioxazin (CAS No. 103361-09-7), based on results from various documents. In the revision of the second edition, the additional results of the following studies were submitted by the Ministry of Health, Labour and Welfare: residues in crops (domestic: garden peas, overseas: coffee beans); developmental toxicity study (rats, inhalation exposure); fetus anemia induction study; and others.

The test results used in the assessment includes the data on plant metabolism (mandarin oranges, soybeans, etc.), residues in crops, livestock metabolism(goats and chickens), fate in animals (rats and rabbits), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), acute neurotoxicity (rats), subacute neurotoxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity and others.

The major adverse effects of flumioxazin were observed in blood (anemia, etc.) and liver (hepatocyte hypertrophy, weight increase, etc.). Neurotoxicity, immunotoxicity, carcinogenicity, and biologically significant genotoxicity were not observed.

In a two-generation reproductive toxicity study, the decline of copulation index, delivery index, and viability index on day 4 was observed.

In a developmental toxicity study, cardiovascular malformation including ventricular septal defect (VSD) and skeleton malformation such as scapular curvature were observed in fetuses of rats.

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

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 1.8 mg/kg bw per day in a combined two-year chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.018 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.



The NOAEL and lowest-adverse-effect-level (LOAEL) values were compared for potential adverse effects of a single oral administration of flumioxazine, of which the lowest value was the NOAEL of 3 mg/kg bw per day in a developmental toxicity study (oral administration) in rats. The identified findings include fetal ventricular septal defect (VSD) at doses that do not cause adverse effects in dams. Accordingly, the FSCJ specified an acute reference dose (ARfD) of 0.03 mg/kg bw by applying a safety factor of 100 to this NOAEL for pregnant or potentially pregnant women.

For the general population, the lowest NOAEL for possible adverse effects from a single oral administration was 1,000 mg/kg bw per day, above the cut-off value (500 mb/kg bw), in the developmental toxicity study in rabbits. Accordingly, the FSCJ determined that specifying an ARfD is unnecessary.



 Table 1. Levels relevant to toxicological evaluation of flumioxazin

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) 1)
		0, 30, 300, 1 000, 3 000	M: 19.3
	90-day subacute	ppm	F: 2.2
	toxicity study	M: 0, 1.9, 19.3, 65.0, 196	
	(the 1 st study)	F: 0, 2.2, 22.4, 72.9, 218	M: Decrease of Hb, MCV, MCH, MCHC, etc.
			F: Decrease of MCV and MCH
	90-day subacute	0, 30, 300, 1 000, 3 000 ppm	1
	toxicity study (the 2 nd study)	M: 0, 2.3, 21, 70, 244	F: 22
		F: 0, 2.2, 22, 72, 230	
		0.50.500.1.000	M/F: Decrease of MCV, etc.
	Two-year combined	0, 50, 500, 1 000 ppm	M: 1.8
	chronic toxicity/	M: 0, 1.8, 18.0, 36.5	F: 2.2
	carcinogenicity	F: 0, 2.2, 21.8, 43.6	M/E. Extramedullar, homotomoiosis in the sulcan sta
	study		M/F: Extramedullary hematopoiesis in the spleen, etc. (No carcinogenicity is observed.)
		0.500.1500.4500	M: -
		0, 500, 1 500, 4 500 ppm M: 0, 37, 110, 323	F: 41
	90-day subacute	F: 0, 41, 124, 358	11.41
	neurotoxicity study	1.0, 41, 124, 330	M: Decrease of MCV and MCH
	nearotoxicity stady		F: Decrease of Hb, Ht, etc.
			(No subacute neurotoxicity is observed.)
D .		M: 0, 37, 110, 323	Parent
Rat		F: 0, 41, 124, 358	PM: 6.3
	Two-generation reproductive toxicity study	PM: 0, 3.2, 6.3,12.7, 18.9	PF: 15.1
		PF: 0, 3.8, 7.6, 15.1, 22.7	F ₁ M: 7.5
		F ₁ M: 0, 3.7, 7.5, 15.0, 22.4	F ₁ F: 17.2
		F ₁ F: 0, 4.3, 8.5, 17.2, 25.6	
			Offspring
			PM: 6.3
			PF: 7.6
			F ₁ M: 7.5
			F ₁ F: 8.5
			Fertility
			PM: 12.7
			PF: 15.1
			F ₁ M: 15.0
			F ₁ F: 17.2
			Parent
			_
			Parent M: Decrease of absolute and relative weight epididymis F: Suppressed body weight gain, etc.

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Mouse Developmental toxicity study Dams: No toxicity Fetuses: 3 Dams: No toxicity Fetuses: Ventricular Septal Defect (VSD), etc. Provided Mr. 20, 152, 420, 1370 Fr. 0, 165, 482, 1 700 Fr. 0, 165, 482, 1 700 Fr. 0, 30.6, 346, 859 Mr. Increase of absolute and relative weight of liver Provided Mr. 20, 300, 3000, 7000 ppm Mr. 31.1 Pr. 36.6 Mr. Hepatocyte hypertrophy, etc. Presuses: 3 000 Dams: 1 000 Pretuses: 3 000 Dams: 1 000 Pretuses: 3 000 Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Pretuses: No toxicity No teartogenicity is observed.) One-year chronic toxicity study One-year combined chronic toxicity/carcinogenicity study O	Species Study Dose (mg/		Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day) 1)	
M: Decrease of copulation index F: Decrease of delivery index				Offspring: Low body weight, etc.	
M: Decrease of copulation index F: Decrease of delivery index					
Developmental toxicity study				-	
Developmental toxicity study				-	
Developmental toxicity study				-	
Developmental toxicity study Dams: No toxicity Fetuses: Ventricular Septal Defect (VSD), etc.			0, 1, 3, 10, 30		
Dams: No toxicity Fetuses: Ventricular Septal Defect (VSD), etc.		Developmental		Fetuses: 3	
Application Section		-			
Mouse 28-day subacute toxicity study M: 0, 152, 420, 1 370 F: 165 M/F: Increase of absolute and relative weight of liver M: 0, 300, 3 000, 7 000 ppm M: 31.1 F: 36.6 M/F: Hepatocyte hypertrophy, etc. M/F: Hepatocyte hypertrophy				·	
Mouse			0 1 000 2 000 10 000	-	
Mouse Mous		28-day subacute	0, 1 000, 3 000, 10 000 ppm		
Mouse 18-month carcinogenicity study 0, 300, 3 000, 7 000 ppm M: 31.1		•			
Rabbit Developmental toxicity study Developmental toxicity study Dog One-year chronic toxicity study Dog ADI (cRfD) Ref P: 0, 36.1, 315, 754 F: 36.6 M/F: Hepatocyte hypertrophy, etc. No acrcinogenicity is observed.) Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity					
Rabbit Developmental toxicity study Dog One-year chronic toxicity study Cone-year chronic toxicity study Dog ADI (cRfD) Carcinogenicity F: 0, 36.6, 346, 859 M/F: Hepatocyte hypertrophy, etc. NooAmmediate hypertrophy, etc. M/F: Hepatocyte hypertrophy, etc. NooAmmediate hypertrophy, etc. M/F: Hepatocyte hypertrophy, etc. NooAmmediate hypertrophy, etc.	Mouse		0, 300, 3 000, 7 000 ppm	4	
Rabbit Developmental toxicity study Dog One-year chronic toxicity study Dog ADI (cRfD) Rabbit Study (No carcinogenicity is observed.) Dams: 1 000 Fetuses: 3 000 Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: 100 M/F: 100 M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity			M: 0, 31.1, 315, 754		
Rabbit Developmental toxicity study Dog O, 300, 1 000, 3 000 Dams: 1 000 Fetuses: 3 000 Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity Two-year combined chronic toxicity/carcinogenicity			F: 0, 36.6, 346, 859	M/F: Hepatocyte hypertrophy, etc.	
Rabbit Developmental toxicity study Dams: 1 000 Fetuses: 3 000 Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity		study			
Rabbit Developmental toxicity study Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity Two-year combined chronic toxicity/carcinogenicity					
Rabbit Developmental toxicity study Dams: Decreased body weight/suppressed body weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity		_	0, 300, 1 000, 3 000		
weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) 90-day subacute toxicity study One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity				Fetuses: 3 000	
weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) 90-day subacute toxicity study One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) weight gain and decreased food consumption Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc. NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity				Dames Dames d hada	
Fetuses: No toxicity (No teratogenicity is observed.) 90-day subacute toxicity study Dog One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) The critical study for setting ADI (cRfD) Fetuses: No toxicity (No teratogenicity is observed.) M/F: 100 M/F: 100 M/F: 10 M/F: Increase of ALP, etc. NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity	Rabbit				
One-year chronic toxicity study O, 10, 100, 1 000 M/F: 100 M/F: Increase of ALP, T. Chol, PL, etc.					
Dog One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) One-year chronic toxicity study One-year chronic toxicity/carcinogenicity NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity				retuses. No toxicity	
Dog One-year chronic toxicity study One-year chronic toxicity study ADI (cRfD) One-year chronic toxicity study One-year chronic toxicity/carcinogenicity NOAEL: 1.8 SF: 100 ADI: 0.018 Two-year combined chronic toxicity/carcinogenicity				(No teratogenicity is observed.)	
Dog One-year chronic toxicity study NOAEL: 1.8 SF: 100 ADI: 0.018 The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity			0, 10, 100, 1 000	M/F: 100	
One-year chronic toxicity study One-year chronic toxicity study One-year chronic toxicity study One-year chronic toxicity study NOAEL: 1.8 SF: 100 ADI: 0.018 The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity				M/F: Increase of ALP, T. Chol, PL, etc.	
M/F: Increase of ALP, etc. NOAEL: 1.8 ADI (cRfD) SF: 100 ADI: 0.018 The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity	Dog	One-year chronic	0, 10, 100, 1 000	M/F: 10	
NOAEL: 1.8 ADI (cRfD) SF: 100 ADI: 0.018 The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity					
ADI (cRfD) SF: 100 ADI: 0.018 The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity		toxicity study			
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The critical study for setting ADI (cRfD) Two-year combined chronic toxicity/carcinogenicity	ADI (cRfD)				
The critical study for setting ADI (cRtD)				ADI: 0.018	
The critical study for setting ADI (CKID)		The critical study for	setting ADI (cRfD)	Two-year combined chronic toxicity/carcinogenicity	
study (fat)		The critical study 101	soming ADI (CRID)	study (rat)	

NOAEL: No-observed-adverse-effect level, SF: Safety factor, ADI: Acceptable daily intake, UF: Uncertainty, cRfD: Chronic reference dose, Hb: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, ALP: Alkaline Phosphatase, PL: Phospholipids (PL), T. Chol: Total Cholesterol

¹⁾The adverse effect observed at LOAEL

^{-:} NOAEL could not be specified.

 Table 2-1. Potential adverse effects of a single oral administration of flumioxazin (General population)

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day) 1)
	General pharmacological study (General condition)	0, 1 500, 5 000	M/F: 1 500 M/F: Decrease in locomotor activities
Mouse	General pharmacological study (Momentum in locomotive activities)	M: 0, 1 500, 5 000	M: 1 500 M: Decreased momentum in locomotor activities
Rabbit Developmental toxicity study		0, 300, 1 000, 3 000	Dames: 1 000 Dames: Decreased body weight and decreased food consumption
ARfD			Not required [Above cut-off level (500 mg/kg bw)]

ARfD: Acute reference dose

 $^{^{1)}}$ The adverse effect observed at LOAEL

Table 2-2. Potential adverse effects of a single oral administration of flumioxazin (Pregnant or potentially pregnant women)

negnam we		Dose	Endpoints relevant to setting NOAEL and
Species	Study	(mg/kg bw or mg/kg	ARfD
	22	bw per day)	(mg/kg bw or mg/kg bw per day) 1)
	Developmental toxicity study	0, 1, 3, 10, 30	Fetus: 3
	(Oral administration)		Fetus: Ventricular septal defect (VSD), etc.
	Developmental toxicity study	0, 400	Fetus: -
	(Critical period of pregnancy examination)		Fetus: Death of embryo/fetus, low body
	,		weight and ventricular septal defect (VSD)
Rat	Developmental toxicity study	0, 1 000	Fetus: -
	(Pathological examination)		Fetus: Death of embryo
	Developmental toxicity study (Expression mechanism	0, 400	Fetus: -
	examination)		Fetus:Death of embryo/fetus
	Developmental toxicity study	0, 15, 30, 60	Fetus: -
	(Fetus anemia-induced		
	examination)		Fetus: Ventricular septal defect (VSD)
			NOAEL: 3
ARfD			SF: 100
			ARfD: 0.03
	The critical study for setting	g ARfD	Developmental toxicity study (rat)

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

¹⁾ The adverse effect observed at LOAEL.

^{-:} NOAEL could not be specified.