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

Risk Assessment Report

Flutriafol

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2018

ABSTRACT

The FSCJ evaluated the health guidance values of flutriafol (CAS No. 76674-21-0)[1], a triazole fungicide in the risk assessment. New data submitted were fates of the pesticide in goats and hens, residue in cherries and others. The FSCJ established an acute reference dose.

The data used in the assessment include fate in animals (rats), livestocks (cattle, goats and chickens), fate in plants (barley, wheat and others), subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity. The FSCJ revised the toxicological monograph of triazole derivatives including 1,2,4-triazole, triazole acetic acid or triazole alanine based on the revised toxicological monograph of the Joint FAO/WHO Meeting of Pesticide Residue 2015, and referred it at evaluations of triazole derivatives.

Major adverse effects of flutriafol include suppressed body weight, hepatocellular fatty changes in hepatocytes and centrilobular hypertrophy of hepatocytes (rats and mice), hemosiderosis in the liver (dogs) and effects on blood such as anemia and others. No neurotoxicity, carcinogenicity, reproductive toxicity and genotoxicity was observed.

Developmental toxicity studies in rats showed that the test item at the dose with maternal toxicity caused increased skeletal anomalies in fetuses, however no teratogenicity was observed in rabbits.

On the basis of the results obtained above, flutriafol (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) in the toxicological studies was 1.05 mg/kg body weight/day in a two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.01 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 flutriafol was 7.5 mg/kg bw/day for maternal toxicity obtained in a developmental toxicity study in rabbits. FSCJ

specified an acute reference dose (ARfD) to be 0.075 mg/kg bw by applying a safety factor of 100 to the NOAEL.

[1] This pesticide had firstly evaluated March 2012 by Food Safety Commission of Japan

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoins[1)]
Rat	90-day subacute toxicity study	0, 20, 200, 2 000 ppm M: 0, 1.4, 13.3, 149 F: 0, 1.6, 16.9, 148	M: 13.3 F: 1.6	M: 149 F: 16.9	M: Suppressed body weight and others F: Increase in absolute and relative liver weights
	90-day subacute neurotoxicity study	0, 500, 1 500, 3 000 ppm M: 0, 28.9, 84.3, 172 F: 0, 32.6, 97.6, 185	M: 28.9 F: 32.6	M: 84.3 F: 97.6	FM: Suppressed body weight and decreased feed consumption (Not neurotoxic for subacute administration)
	Two-year chronic toxicity/carcinogenicity study	0, 20, 200, 2 000 ppm M: 0, 1.05, 10.2, 103 F: 0, 1.3, 12.7, 129	M: 1.05 F: 12.7	M: 10.2 F: 129	FM: Increased absolute/ relative liver weights and others (Not carcinogenic)
	Two-generation reproductive toxicity (the 1st study)	0, 60, 240, 1 000 ppm M: 0, 3.5, 13.5, 56.0 F: 0, 3.75, 14.4, 57.9	Parent M: 3.5 F: 14.4 Offspring M: 13.5 F: 14.4	Parent M: 13.5 F: 57.9 Offspring M: 56.0 F: 57.9	Parent M: Fatty change in hepatocytes F: Suppressed body weight and others Offspring: Decrease in the survival rate and others (No effect on reproduction)
	Two-generation reproductive toxicity (the 2nd study)	0, 30, 80, 150, 300 ppm PM: 0, 2.0, 5.5, 10.2, 20.8 PF: 0, 2.3, 6.2, 11.6, 23.9 F_1M: 0, 2.2, 5.7, 10.8, 22.1 F_1F: 0, 2.4, 6.3, 14.8, 24.5	Parent PM: 10.2 PF: 11.6 F_1M: 10.8 F_1F: 14.8 Offspring PM: 20.8 PF: 23.9 F_1M: 22.1 F_1F: 24.5	Parent PM: 20.8 PF: 23.9 F_1M: 22.1 F_1F: 24.5 Offspring PM: - PF: - F_1M: - F_1F: -	Parent FM: Increased relative liver weight and centrilobular hypertrophy of hepatocytes Offspring: No toxicity (No effect on reproduction)
	Developmental toxicity study (the 1st study)	0, 10, 50, 125	Maternal: 50 Embryo/fetus: 10	Maternal: 125 Embryo/fetus: 50	Maternal: Suppressed body weight and others Embryo/fetus: Increased skeletal variations (cervical rib and 14th rib) (Not teratogenic)

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoins[1)]
	Developmental toxicity study (the 2nd study)	0, 2, 5, 10, 75	Maternal: 10 Embryo/fetus: 10	Maternal: 75 Embryo/fetus: 75	Maternal: Suppressed body weight and others Embryo/fetus: Increase in skeletal anomalies including the hyoid bone
Mouse	Two-year carcinogenicity study	0, 10, 50, 200 ppm M: 0, 1.21, 6.01, 24.9 F: 0, 1.52, 7.42, 30.4	M: 1.21 F: 1.52	M: 6.01 F: 7.42	M: Fatty change in centrilobular hepatocytes F: Suppressed body weight (Not carcinogenic)
Rabbit	Developmental toxicity study	0, 2.5, 7.5, 15	Maternal: 7.5 Embryo/fetus: 7.5	Maternal: 15 Embryo/fetus: 15	Maternal: Suppressed body weight and others Embryo/fetus: Increased post implantation loss, delayed cranial ossification and other effects (Not teratogenic)
Dog	90-day subacute toxicity study	0, 1, 5, 15	M: 5 F: 5	M: 15 F: 15	FM: Increase in the number of hemosiderin-laden Kupffer cells, increase in ALP and others
	One-year chronic toxicity study	0, 1, 5, 20	M: 5 F: 5	M: 20 F: 20	FM: Suppressed body weight, effect on erythroid cells and others
ADI			NOAEL: 1.05 SF: 100 ADI: 0.01		
The critical study for setting ADI			Two-year chronic toxicity/carcinogenicity study in rats		

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

Table 2. *Adverse effects possibly elicited by a single oral administration*

Species	Studies	Dose (mg/kg bw or mg/kg bw day)	NOAEL and end point for establishing acute reference dose (ARfD)[1)] (mg/kg bw/day)
Rat	General pharmacology data (clinical signs)	M: 0, 80, 250, 750	M: 80 M: Ptosis, stained fur
	Acute toxicity study	750, 1 000, 1 500, 2 000, 2 500	M: - F: 750 FM: Decreased activity, decrease in abdominal tone, dehydration, piloerection, abdominal cavity and hunched posture
	Acute neurotoxicity study	0, 125, 250, 750	FM: 125 FM: Suppressed body weight and decreased feed consumption
	Developmental toxicity study (the 1st study)	0, 10, 50, 125	Maternal: 50 Maternal: Suppressed body weight
	Developmental toxicity study (the 2nd study)	0, 2, 5, 10, 75	Maternal: 10 Maternal: Suppressed body weight
Rabbit	Acute toxicity study	F: 100, 200, 300, 400, 500	F: 100 F: Decreased activity, restlessness, salivation, diarrhea
	Developmental toxicity study	0, 1.5, 7.5, 15	Maternal: 7.5 Maternal: Suppressed body weight
Guinea pig	Acute toxicity study	M: 100, 200, 300, 400, 500	M: 100 M: Decreased activity, restlessness, salivation and absence of some forelimb reflexes
ARfD			NOAEL: 7.5 SF: 100 ARfD: 0.075
The critical study for setting ARfD			Developmental toxicity study in rabbits

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed-adverse-effect level
1), The adverse effect observed at LOAEL; -, NOAEL was not derived