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

Risk Assessment Report

Uniconazole P (2nd edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The FSCJ conducted the risk assessment of a triazole plant growth regulator, uniconazole P (CAS No. 83657-17-4), based on various documents. For revising to the 2nd edition, risk management organizations newly provided the data on residue in crops (tomatoes).

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice and tomatoes), residues in crops, 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, and MoA data on liver tumor in mice.

Major adverse effects of uniconazole P observed are suppressed body weight, increased liver weight and hepatocellular hypertrophy (rats, mice, and dogs), hepatocellular vacuolation and single cell necrosis of hepatocyte (rats and mice). Uniconazole P showed no reproduction toxicity, teratogenicity and genotoxicity relevant to human health.

Although very weak hepatocarcinogenicity was observed in mice, the tumor induction mechanism was non-genotoxic mechanism, and it was considered possible to establish a threshold dose in the assessment. Uniconazole P (parent compound only) and (*E*)-(*R*) form were identified as the relevant substance for the residue definition for dietary risk assessment in agricultural product.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 2 mg/kg bw per day in a one-year chronic toxicity study in dogs. The FSCJ specified an acceptable daily intake (ADI) of 0.02 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 uniconazole P was 5 mg/kg bw/day based on the increased incidence of accessory 14th ribs in fetuses observed in developmental toxicity studies in rats the FSCJ specified an acute reference dose (ARfD) for women of child-bearing age to be 0.05 mg/kg bw by applying a safety factor of 100 to the NOAEL of 5 mg/kg bw per day. For general population, the FSCJ specified an acute reference dose (ARfD) to be 1 mg/kg bw by applying a safety factor of 100 to the NOAEL of 100 mg/kg bw per day obtained in an acute toxicity study in rats.

Table 1. *Levels relevant to toxicological evaluation of uniconazole P*

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Rat	90-day subacute toxicity study	0, 30, 100, 1 000, 3 000 ppm M: 0, 2.25, 7.48, 73.0, 228 F: 0, 2.42, 8.36, 79.4, 229	M: 2.25 F: 8.36 M: Intracytoplasmic vacuolization of the thyroid F: Suppressed body weight gain
	Two-year combined chronic toxicity/carcinogenicity study	0, 10, 40, 200, 1 000 ppm M: 0, 0.42, 1.64, 8.29, 43.1 F: 0, 0.53, 2.17, 10.9, 56.7	M: 8.29[2)] F: 2.17[2)] M: Suppressed body weight gain, centrilobular vacuolation of hepatocytes F: Centrilobular vacuolation of hepatocytes (No carcinogenicity)
	Two-generation reproductive toxicity study	0, 15, 150, 1 500 ppm PM: 0, 1.13, 11.1, 112 PF: 0, 1.43, 14.2, 135 F_1M: 0, 1.10, 11.2, 120 F_1F: 0, 1.27, 12.7, 133	Parent and offspring PM: 11.1 PF: 14.2 F_1M: 11.2 F_1F: 12.7 Parent: Suppressed body weight gain, vacuolation of hepatocyte Offspring: Suppressed body weight gain, decreased survived rate (No effect on reproductive activity)
	Developmental toxicity study	0, 1, 5, 25, 50	Dams: 5 Fetuses: 5 Dams: Suppressed body weight gain Fetuses: Increased incidence of skeletal variations (No teratogenicity)
Mouse	18-month carcinogenicity study[3)]	0, 10, 40, 200, 1 500 ppm	M: 27.4 F: 35.0

		M: 0, 1.37, 5.44, 27.4, 208 F: 0, 1.71, 6.75, 35.0, 256	M/F: Hepatocellular hypertrophy, vacuolation of hepatocytes (Very weak hepatocarcinogenicity in male)
Rabbit	Developmental toxicity study	0, 1, 3, 10, 20	Dams: 10 Fetuses: 20 Dams: Suppressed body weight gain Fetuses: No toxicity was observed (No teratogenicity)
Dog	90-day subacute toxicity study	M/F: 0, 5, 20, 80, 320	M/F: 20 M/F: Increased ALP, ALT
	One-year chronic toxicity study	M/F: 0, 2, 20, 200	M/F: 2 M/F: Increased ALP
ADI			NOAEL: 2 SF: 100 ADI: 0.02
The critical study for setting ADI			One-year chronic toxicity study in dogs

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor; UF, Uncertainty factor
[1)] The adverse effect observed at LOAEL.
[2)] Variance of LOAEL is due to the different calculation of sample intake.
[3)] This particular study was performed with animals of main-, middle-, and killing-group, and sample intake was calculated for individual groups. Therefore, the dose corresponds to the lowest value in three groups for each dose.

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

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)]
Rat	Acute toxicity study	M/F: 25, 100, 200, 280, 390, 550, 770, 1 080, 1 500	M/F: 100 M: Decreased motor activity, ataxia, quadriplegia, loss of righting reflex, irregular breathing, vacuolation of hepatocyte F: Decreased motor activity, ataxia, quadriplegia, loss of righting reflex, irregular breathing
Mouse	General pharmacology data (General condition, motor activity)	M: 200, 500, 1 000, 2 000	M: 200 M: Changes in body posture and limb position, ataxia, loss of righting reflex
	Acute toxicity study	M/F: 50, 250, 1 000, 1 400, 1 800, 2 300, 3 000, 3 900, 5 000	M/F: 50 M/F: Muscle twitch, decreased motor activity, ataxia, quadriplegia, loss of righting reflex
	Comprehensive evaluation of general pharmacology data and acute toxicity study		M: 200
ARfD			NOAEL: 100 SF: 100 ARfD: 1
The critical study for setting ARfD			Acute toxicity study in rats

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