Fenquinotrione (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of fenquinotrione (CAS No. 1342891-70-6), a triketone herbicide, based on results from various studies. A major adverse effect of fenquinotrione was observed in ocular toxicity characterized as keratitis in rats, which is often observed with other 4-hydroxyphenylpyruvate dioxygenase (4-HPDDase) inhibitors in this species. Other effects included were centrilobular hepatocytes hypertrophy, and also cholecystolithiasis in mice. No effects were observed on neurotoxicity, fertility, teratogenicity and genotoxicity. A corneal squamous cell carcinoma found in a male rat, at a sub-highest dose in a two-year carcinogenicity study, was judged to be treatment-related, because this tumor is rare in rats. The occurrence was considered to be attributed to persistent stimulation of inflammation including keratitis. In addition, negative results were obtained from all of the genotoxicity studies. Therefore, a genotoxic mechanism was unlikely involved in the tumor development, and it enabled FSCJ to establish a threshold in the assessment. Fenquinotrione (parent compound only) was the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.166 mg/kg bw/day in a two-generation reproductive toxicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.0016 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. The lowest-observed-adverse-effect-level (LOAEL) for potential adverse effects of a single oral administration of fenquinotrione was 2,000 mg/kg bw based on soft feces and staining of perianal fur observed within one day after the oral administration in an acute toxicity study in rats. Thus the acute reference dose (ARfD) is not necessary, since the LOAEL was adequately above the cut off level (500 mg/kg bw).

Conclusion in Brief

FSCJ conducted a risk assessment of fenquinotrione (CAS No. 1342891-70-6), a triketone herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice), residues in crops, acute toxicity (rats), subacute toxicity (rats, mice, and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity. In subacute toxicity studies, blood concentration levels of tyrosine were determined to verify 4-hydroxyphenylpyruvate

dioxygenase (4-HPDDase) inhibitions in rats and dogs.

A major adverse effect of fenquinotrione was observed in ocular toxicity characterized as keratitis in rats, which is often observed with other 4-HPDDase inhibitors in this species. Other effects included were centrilobular hepatocytes hypertrophy, and also cholecystolithiasis in mice. No effects were observed on neurotoxicity, fertility, teratogenicity and genotoxicity.

A corneal squamous cell carcinoma found in a male rat, at a sub-highest dose in a two-year carcinogenicity study, was judged to be treatment-related, because this tumor is rare in rats. The occurrence was considered to be attributed to persistent stimulation of inflammation including keratitis. In addition, negative results were obtained from all of the

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The original full report is available in Japanese at <http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20160323543&fileId=201>

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genotoxicity studies. Therefore, a genotoxic mechanism was unlikely involved in the tumor development, and it enabled FSCJ to establish a threshold in the assessment.

Based on the results from various studies, fenquitrone (parent compound only) was the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.166 mg/kg bw/day in a two-generation reproductive toxicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.0016 mg/kg

bw/day by applying a safety factor of 100 to the NOAEL.

The lowest-observed-adverse-effect-level (LOAEL) for potential adverse effects of a single oral administration of fenquitrone was 2,000 mg/kg bw based on soft feces and staining of perianal fur observed within one day after the oral administration in an acute toxicity study in rats. Thus the acute reference dose (ARfD) is not necessary, since the LOAEL was adequately above the cut off level (500 mg/kg bw).

Table 1. Levels relevant to toxicological evaluation of fenquinotriol

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints ¹⁾
Rat	28-day subacute toxicity study	0, 2, 10, 100, 2 000, 20 000 ppm	M: 0.787 F: 8.52	M: 8.19 F: 181	M/F: Increased absolute/ relative liver weight, etc.
		M: 0, 0.157, 0.787, 8.19, 162, 1 640 F: 0, 0.168, 0.852, 8.52, 181, 1 790			
	90-day subacute toxicity study	0, 1, 10, 100, 2 000, 20 000 ppm	M: 0.631 F: 0.719	M: 6.38 F: 7.53	M/F: Keratitis, etc.
		M: 0, 0.0625, 0.631, 6.38, 131, 1 330 F: 0, 0.0720, 0.719, 7.53, 154, 1 500			
	90-day subacute neurotoxicity study	0, 200, 2 000, 20 000 ppm	M: - F: -	M: 12.2 F: 14.0	M: Rough fur F: Moist/soiled vulval fur
		M: 0, 12.2, 125, 1 280 F: 0, 14.0, 144, 1 460			
	One-year chronic toxicity study	0, 1, 20, 200, 2 000 ppm	M: 0.843 F: 1.06	M: 8.78 F: 11.0	M/F: Keratitis, colloid degeneration of the thyroid etc.
		M: 0, 0.0431, 0.843, 8.78, 89.4 F: 0, 0.0536, 1.06, 11.0, 111			
	Two-year carcinogenicity study	0, 20, 200, 2 000 ppm	M: 0.730 F: 0.936	M: 7.53 F: 9.69	M/F: Keratitis, etc. (Carcinogenicity, M: Corneal squamous cell carcinoma at 200 ppm)
		M: 0, 0.730, 7.53, 77.3 F: 0, 0.936, 9.69, 99.1			
Two-generation reproductive toxicity study	0, 3, 60, 1 200 ppm	Parent PM: 0.166 PF: 0.271 F ₁ M: 0.198 F ₁ F: 0.294 Offspring PM: 0.166 PF: 5.59 F ₁ M: 0.198 F ₁ F: 6.00	Parent PM: 3.40 PF: 5.59 F ₁ M: 4.11 F ₁ F: 6.00 Offspring PM: 3.40 F ₁ M: 110 PF: 4.11 F ₁ F: 121	Parent M/F: Keratitis, etc. Offspring M: Delayed preputial separation F: Keratitis, etc (No adverse effect on fertility)	
	PM: 0, 0.166, 3.40, 70.3 PF: 0, 0.271, 5.59, 110 F ₁ M: 0, 0.198, 4.11, 85.4 F ₁ F: 0, 0.294, 6.00, 121				
Developmental toxicity study	0, 1, 10, 1 000	Maternal: 1 Embryo/fetus: 1	Maternal: 10 Embryo/fetus: 10	Maternal: Reduced feed consumption Embryo/fetus: Suppressed body weight (Not teratogenic)	
Mouse	90-day subacute toxicity study	0, 10, 400, 4 000, 10 000 ppm	M: 56.0 F: 65.9	M: 560 F: 682	M/F: Centrilobular hypertrophy of hepatocytes, etc.
		M: 0, 1.39, 56.0, 560, 1 420 F: 0, 1.69, 65.9, 682, 1 730			
	18-month carcinogenicity study	0, 100, 1 000, 10 000 ppm	M: - F: -	M: 10.9 F: 10.7	M/F: Cholecystolithiasis (Not carcinogenic)
		M: 0, 10.9, 108, 1 110 F: 0, 10.7, 110, 1 090			
Rabbit	Developmental toxicity study	0, 1, 10, 1 000	Maternal: 10 Embryo/fetus: 1	Maternal: 1 000 Embryo/fetus: 10	Maternal: Miscarriage Embryo/fetus: 27 presacral vertebrae and supernumerary ribs (Not teratogenic)
Dog	90-day subacute toxicity study	0, 2, 10, 2,000, 7 000/4 000 ppm	M: 0.291 F: 0.310	M: 60.2 F: 62.0	M: Decreased absolute/relative thymus weight F: Increased extramedullary hematopoiesis in the spleen and liver
		M: 0, 0.0576, 0.291, 60.2, 149 F: 0, 0.0612, 0.310, 62.0, 146			
	One-year chronic toxicity study	0, 10, 200, 2 000 ppm	M: 5.98 F: 0.300	M: 59.8 F: 6.21	M: Increased urinary specific gravity F: Increased ALP, etc.
M: 0, 0.297, 5.98, 59.8 F: 0, 0.300, 6.21, 60.5					
ADI			NOAEL: 0.166 SF: 100 ADI: 0.0016		
The critical study for setting ADI			Two-generation reproductive toxicity study in rats		

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F₁M, Male in F₁ generation; F₁F, Female in F₁ generation; -, NOAEL could not be specified; ADI, Acceptable daily intake; ALP, alkaline phosphatase; SF, Safety factor; NOAEL, -; NOAEL or LOAEL could not be specified

¹⁾ The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL)

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

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints ¹⁾
Rat	Acute toxicity study	2 000	F: - F: Soiled periproctal hair coat and loose watery feces (six hours ~ one day after administration)
ARfD			Unnecessary (Above cutoff value (500 mg/kg bw))

ARfD, Acute reference dose; -, NOAEL could not be specified

¹⁾ Major adverse effects observed at LOAEL