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

Risk Assessment Report

Oxolinic acid (4th edition)

(Veterinary Medicinal Products and pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of oxolinic acid (CAS No. 14698-29-4), a fungicide (antimicrobial) having quinolone skeleton, using results from various studies. Note that data on residue in crops (young corn, Japanese white radish, etc.) were provided for assessment of new use of this substance for crops as a pesticide this time. The acceptable daily intake (ADI) for use as pesticide and veterinary medicine has been already specified in 2008. The present evaluation focused on establishment of an acute reference dose (ARfD) for use as a pesticide.

Data used in the assessment include fate in animals (rats and humans), fate in plants (paddy rice and Chinese cabbage), residue in crops, residue in livestock animals (cattle and pigs), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of oxolinic acid observed are suppressed body weight, hyperplasia of testicular interstitial cell (rats), increased ovarian weight (rats), neurological effects on excitatory neurologic manifestation and behavior.
In a combined chronic toxicity/carcinogenicity study, an increased incidence of testicular interstitial cell tumors was observed in rats. However, a genotoxic mechanism was unlikely involved in the tumor induction and it was considered possible to establish a threshold dose in the assessment.
From the above results, oxolinic acid (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) in the toxicological studies was 2.18 mg/kg body weight/day in a two-generation reproductivity study in rats. Applying the safety factor of 100 to the lowest NOAEL, FSCJ specified the acceptable daily intake (ADI) to be 0.021 mg/kg body weight/day.
Microbiological ADI was specified to be 0.031 mg/kg bw/day in accordance with the VICH[1] guideline

[1] The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

36.

Since ADI obtained from microbiological data was greater than that obtained from toxicological data, FSCJ considered it appropriate to specify ADI as 0.021 mg/kg body weight/day for establishing residue standards of oxolinic acid. This ADI was specified in 2008.

The lowest NOAEL for potential adverse effects of a single oral administration of oxolinic acid was 6 mg/kg bw/day obtained in acute neurotoxicity studies in rats. FSCJ specified an acute reference dose (ARfD) to be 0.06 mg/kg bw by applying a safety factor of 100 to the NOAEL.

Table 1. *Levels relevant to toxicological evaluation of oxolinic acid*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	30-day subacute toxicity study[#]	0, 125, 250, 500, 1 000	M: 125 F: -	M: 250 F: 125	M/F: Increase in absolute or/and relative organ weight of the adrenal grand
	90-day subacute toxicity study	0, 100, 300, 1 000, 3 000 ppm M: 0, 5.68, 17.2, 62.2, 204 F: 0, 6.48, 19.9, 77.4, 264	M: 17.2 F: 6.48	M: 62.2 F: 19.9	M: Suppressed body weight, decreased TP, decreased Glob etc F: Decreased GLU, etc
	6-month subacute toxicity study[#]	0, 1 000, 3 000, 10 000, 30 000 ppm M: 0, 0.06, 0.23, 0.79, 2.72 F: 0, 0.08, 0.31, 1.25, 3.60 (g/kg bw/day)	M: - F: 0.08 (g/kg bw/day)	M: 0.06 F: 0.31 (g/kg bw/day)	M: Decreased WBC F: Suppressed body weight
	90-day subacute neurotoxicity study	0, 50, 300, 1 800 ppm M: 3.24, 19.4, 132 F: 3.87, 24.4, 175	M: 19.4 F: 3.87	M: 132 F: 24.4	M/F: Excitatory neurologic manifestation and behavioral effects
	Two-year combined chronic toxicity/ carcinogenicity study	0, 30, 100, 300, 1 000 ppm M: 0, 1.06, 3.60, 10.9, 37.6 F: 0, 1.28, 4.38, 13.2, 49.1	M: 3.60 F: 13.2	M: 10.9 F: 49.1	M: Red discharge of eye, increased intake of feeds F: Wasting (Increased incidence of testicular interstitial cell tumors)
	Two-generation reproductive activity study	0, 50, 150, 500 ppm PM: 3.41, 10.3, 34.7 PF: 3.91, 12.1, 41.8 F_1M: 4.11, 12.4, 41.2 F_1F: 4.49, 13.8, 46.9	Parent PM: 3.41 PF: 12.1 F_1M: - F_1F:13.8 Offspring F_1M: 10.3 F_1F: 12.1 F_2M: 41.2 F_2F: 46.9	Parent PM: 10.3 PF: 41.8 F_1M: 4.11 F_1F: 46.9 Offspring F_1M: 43.7 F_1F: 41.8 F_2M: - F_2F: -	Parent: M/F: Suppressed body weight, etc. Offspring: Suppressed body weight (No effect on reproductive activity)
	Two-generation reproductive activity study (Additional study)	0, 15, 30 ppm PM: 1.07, 2.18 PF: 1.19, 2.44 F_1M: 1.25, 2.52 F_1F: 1.41, 2.82	Parent and offspring PM: 2.18 PF: 2.44 F_1M: 2.52 F_1F: 2.82	Parent and offspring PM: - PF: - F_1M: - F_1F: -	Parent: No toxicity findings Offspring: No toxicity

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
	Developmental toxicity study (the 1st study)	0, 3, 30, 150 (Treatment period: Gestation Day 6 to 15)	Dams: 3 Fetuses: 150	Dams: 30 Fetuses: -	Dams: Suppressed body weight Fetuses: No toxicity (No teratogenicity)
	Developmental toxicity study (the 2nd study)[#]	0, 125, 250, 500, 1 000 (Treatment period: Gestation Day 7 to 21days after delivery, Examination of fetuses/pups, Gestation day 0 and Postnatal day 20)	Dams: 250 Offsrping: 500	Dams: 500 Offsrping: 1 000	Dams: Cannibalism , decreased nursing rate Offspring: Low body weight (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 100, 300, 1 000, 3 000 ppm M: 0, 11.2, 34.7, 145, 507 F: 0, 13.8, 47.1, 184, 493	M: 34.7 F: 47.1	M: 145 F: 184	M/F: Suppressed body weight, increased feed intake, decreased dietary efficiency, wasting/small figure etc
	18-month carcinogenicity study	0, 50, 150, 500 ppm M: 0, 4.86, 15.2, 59.7 F: 0, 5.33, 15.7, 57.9	M: 15.2 F: 5.33	M: 59.7 F: 15.7	M: Skin lesions, increased mortality, suppressed body weight F: Suppressed body weight, decreased dietary efficiency (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 250, 500, 1 000, 2 000	Dams: 2 000 Fetuses:2 000	Dams: - Fetuses: -	Dams: No toxicity Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study	M: 0, 8, 40, 200 F: 0, 8, 40, 200	M: 8 F: 8	M: 40 F: 40	M: Suppressed body weight, decreased Glob. F: Suppressed body weight
	One-year chronic toxicity study	M: 0, 8, 40, 200 F: 0, 8, 40, 200	M: 8 F: 8	M: 40 F: 40	M: Corneal white point F: Corneal white point, suppressed body weight
ADI			NOAEL: 2.18 SF: 100 ADI: 0.021		
The critical study for setting ADI			Two-generation reproductive activity 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; #, Studies submitted for toxicological evaluation as veterinary medical product. Others were submitted as pesticide use.

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

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD[1)] (mg/kg bw or mg/kg bw/day)
Rat	Acute toxicity	M/F: 0, 20, 50, 200, 500, 630, 780, 1 000	M/F: 20 M/F: Increased locomotor activity
	Acute neurotoxcity	M/F: 0, 6, 30, 150	M/F: 6 M/F: Increased locomotor activity
	6-month subacute toxicity	M: 0, 0.06, 0.23, 0.79, 2.72 F: 0, 0.08, 0.31, 1.25, 3.60 (g/kg bw/day)	M: 0.06 F: 0.08 (g/kg bw/day) M/F: Neurological symptoms
	Developmental toxicity (the 1st study)	0, 3, 30, 150	Dams: 30 Dams: Self-biting, suppressed body weight, decreased feed intake
Mouse	Acute toxicity	M/F: 0, 10, 30, 800, 1 200, 1 800, 2 7000, 4 000, 6 000	M/F: 10 M: Increased locomotor activity, hunchback position.
Dog	90-day subacute toxicity	M/F: 0, 8, 40, 200	M/F: 40 M/F: Corneal white point
	One-year chronic toxicity	M/F: 0, 8, 40, 200	M/F: 8 M/F: Corneal white point
ARfD			NOAEL: 6 SF: 100 ARfD: 0.06
The critical study for setting ARfD			Acute neurotoxicity study in rats

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