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

Risk Assessment Report

Diquat

(Pesticides)

Food Safety Commission of Japan (FSCJ)
October 2019

ABSTRACT

FSCJ conducted the risk assessment of a bipyridinium herbicide, diquat (CAS No. 85-00-7), based on various data submitted by applicant.

The data used in the assessment include fate in animals (rats, goats, cattle and chicken), fate in plants (barley and wheat), residues in crops, subacute toxicity (rats), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity (mice), and MoA studies on cataract induced in rats and dogs.

Major adverse effects of diquat observed are suppressed body weight, cataract (rats and dogs), inflammation of the tongue and palate (rats), renal tubular dilatation and intratubular hyaline droplet formation (mice). Diquat showed no neurotoxicity, carcinogenicity, effects on reproductive activity, teratogenicity, genotoxicity relevant to human health, and immunotoxicity.

From the above results, diquat (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 value of the no-observed-adverse-effect level (NOAEL) in all tests was 0.58 mg/kg bw/day (as a converted value for diquat ion) in two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.0058 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 diquat was 75 mg/kg bw/day (as a converted value for diquat ion) obtained from body weight depression and reduced feed consumption in the acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.75 mg/kg bw (as a converted value for diquat ion) by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose[#] (mg/kg bw/day)	NOAEL[#] (mg/kg bw/day)[1)] Endpoint(s) at LOAEL
Rat	90-day subacute toxicity study	0, 20, 100, 500 ppm M: 0, 1.70, 8.53, 39.5 F: 0, 1.89, 9.20, 41.5	M: 8.53 F: 9.20 M/F: Cataract, etc.
	90-day subacute neurotoxicity study	0, 20, 100, 400 ppm M: 0, 1.6, 7.9, 32.4 F: 0, 1.9, 9.5, 38.5	M: 7.9 F: 9.5 M/F: Cataract-like changes (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study	0, 5, 15, 75, 375 ppm M: 0, 0.19, 0.58, 2.91, 14.9 F: 0, 0.24, 0.72, 3.64, 19.4	M: 0.58 F: 0.72 M/F: Cataract (No carcinogenicity)
	Two-generation reproduction study	0, 16, 80, 400/240 ppm PM: 0, 1.5, 7.2, 35.8 PF: 0, 1.6, 7.9, 24.0 F_1M: 0, 1.4, 7.2, 24.0 F, 1.6, 8.0, 31.2	Parent PM: 7.2 PF: 1.6 F_1M: 7.2 F_1F: 1.6 Offspring PM: 1.5 PF: 1.6 F_1M: 1.4 F_1F: 1.6 Parent M: Suppressed body weight, Cataract, etc. F: Cataract-like changes, etc. Offspring Suppressed body weight, etc. (No effect on reproductive activity)
	Developmental toxicity study	0, 4, 12, 40	Dams: 12 Fetuses: 12 Dams: Suppressed body weight, etc. Fetuses: Low body weight, etc. (No teratogenicity)

Species	Study	Dose[#] (mg/kg bw/day)	NOAEL[#] (mg/kg bw/day)[1)] Endpoint(s) at LOAEL
Mouse	104-week carcinogenicity study	0, 30, 100, 300 ppm M: 0, 3.56, 12.0, 37.8 F: 0, 4.78, 16.0, 48.3	M: 3.56 F: 4.78 M/F: Renal tubular dilatation (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 1, 3, 10	Dams: 1 Fetuses: 3 Dams: Suppressed body weight Fetuses: Low body weight, Delayed ossification of forearm and hindlimb phalanges (No teratogenicity)
Dog	One-year chronic toxicity study	0, 0.5, 2.5, 12.5 M: 0, 0.46, 2.42, 11.5 F: 0, 0.53, 2.53, 13.2	M: 2.42 F: 0.53 M/F: Cataract, etc.
ADI			NOAEL: 0.58 SF: 100 ADI: 0.0058
The critical study for setting ADI			Two-year combined chronic toxicity /carcinogenicity study in rats

ADI, Acceptable Daily Intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor

[1)], The adverse effect observed at LOAEL; [#], as a converted value for diquat ion

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

Species	Study	Dose# (mg/kg bw or mg/kg bw/day)	Endpoints and NOAEL(mg/kg bw or mg/kg bw/day)# for relevant to setting ARfD1)
Rat	General pharmacology (general signs)	M/F: 0, 160, 200, 240, 280	M: - Diarrhea, lacrimation, etc.
	Acute toxicity study	M/F: 100, 150, 200, 225, 250	M/F: 100 M/F: Piloerection, etc.
	Acute neurotoxicity study	M/F: 0, 25, 75, 150	M/F: 75 M/F: Diarrhea, piloerection, etc.
ARfD			NOAEL: 75 SF: 100 ARfD: 0.75
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, #, as a value converted for diquat ion.