B16-1.0 DIQUAT DIBROMIDE (DIQUAT)

B16-1.1 Background Information

IUPAC: 9,10-dihydro-8a,10a-diazoniaphenanthrene;
6,7-dihydrodipyrido[1,2-a:2',1'-c]pyrazine-5,8-di-ium;
1,1'-ethylene-2,2'-bipyridyldiylium

CAS: 6,7-dihydrodipyrido[1,2-a:2',1'-c]pyrazinediium

CASRN: 85-00-7

DIQUAT USAGE:

Diquat is a non-selective contact herbicide, algicide, desicaant and defoliant. As a herbicide/algicide it is used to control broadleaf and grassy weeds in non-crop (including residential) and aquatic areas. As a desiccant/defoliant it is used in seed crops and potatoes.

Diquat was only applied on designated plots located within CFB Gagetown during the U.S. 1966/67 trials (Table B16-1).

Table B16-1 Diquat Usage at CFB Gagetown[a]

Year	Total Diquat Applied (kg)	Total Area Treated (ha)
1966	29.9	7.3
1967	124.7	28.9
Total	**1.5E+02**	**3.6E+01**

[a] Adapted from Demaree and Haws, 1968; Demaree *et al*., 1966; Demaree and Creager, 1968.
[b] Average maximum yearly application rate (kg/ha).

B16-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_{12}H_{12}N_2$

Activity: Herbicides (quaternary ammonium herbicides)

Notes: When this substance is used as a salt, its identity should be stated, for example diquat [85-00-7].

The name “deiquat” is used in Germany. The name “Reglone” was used in the former USSR, but Reglone is a registered trade mark in many countries.

Structure:

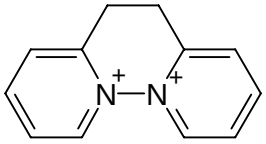

Figure B16-1 Diquat CASRN 85-00-7 & 2764-72-9

Table B16-2 Chemical and Physical Properties of Diquat

Chemical/Physical Property	Result	Reference
Boiling Point	--	
Colour/Form	Colourless to yellow Crystalline powder	Tomlin, 1997; WHO, 1991
Henry's Law constant	$1.4x10^{-13}$ atm cu m/mole[a]	Meylan and Howard, 1991; JW, 2006
Log K_{ow}	-4.60 at 20°C	Tomlin, 1997; JW, 2006
Melting Point	180°C	WHO, 1991
	300°C	California EPA, 1994
	335°C	NIOSH, 2001
	337°C	Lide, 2000
Molecular Weight	344.05 g/mol	Lide, 2000; JW, 2006
Odour	Odourless	WHO, 1991
Specific Gravity	1.22-1.27 at 20°C/20°C	Lide, 2000
	1.20 at 20°C	WHO, 1991
Vapour Density	--	
Vapour Pressure	$1.81x10^{-6}$ mm Hg at 25°C	JW, 2006
	$<< 1x10^{-7}$ mm Hg at 25°C	Ahrens, 1994
Water Solubility	677 g/L at 20°C	California EPA, 1994
	700 g/L at 20°C	WHO, 1991; NIOSH, 2001
	708 g/L at 20°C	Shiu *et al*., 1990; JW, 2006

[a] Estimated using a fragment constant estimation method.

B16-3.0 PMRA EVALUATION

PMRA (2004) is currently re-evaluating diquat through the PMRA Re-evaluation Program. Diquat requires a suitable foreign review that covers all of the main science areas required for Canadian Regulatory decisions and considers the active ingredient and main formulation used in Canada. U.S. EPA RED documents will be the primary source of foreign review information. Furthermore, PMRA re-evaluations will be based upon the U.S. EPA RED document, with emphasis on Canadian issues and use pattern.

B16-4.0 TOXICOLOGY SUMMARY

B17-4.1 Human Health Effects

The acute effects of diquat exposure are as follows (Table B16-3).

Table B16-3 Human Health Effects Resulting from Acute Exposure to Diquat[a,b]

Exposure	Effects	Response
Acute	HEENT	Eye contact results in severe irritation; no permanent eye damage reported in humans
	Cardiovascular	Ventricular dysrhythmia; myocardial necrosis
	Respiratory	Upper respiratory tract irritation with epistaxis; sore throat; coughing; chest tightness; breathing difficulties
	Neurologic	Approximately 50% of patients have neurologic effects: nervousness; agitated behaviour; combativeness; diminished reflexes; lethargy; inability to recognize familiar persons; nonsensical statements; stupor, coma; intracerebral bleeding; seizures
	Gastrointestinal	Burning sensation and irritation of the pharyngeal esophageal and gastric mucosa resulting in extensive vomiting and diarrhea after ingestion; first or second degree burns of the gastrointestinal tract and/or hemorrhagic ulcers; transient ileus
	Hepatic	Rise in liver transaminase activities
	Genitourinary	Renal tubule damage; acute renal failure; oliguric renal failure
	Fluid Electrolyte	Development of an ileus can contribute to dehydration and electrolyte imbalances
	Dermatologic	Severe skin irritation or burns

[a] Rumack and Hall, 2006.
[b] MEDITEXT®, 2006.

NIOSH (2001) indicates that the effects of short-term diquat exposure are: impaired functions and tissue lesions due to effects on the kidney, liver, cardiovascular system and gastrointestinal tract. Diquat is irritating to the eyes, skin and respiratory tract and exposure to high concentrations may result in death. Long term or repeated exposure to diquat may have an effect on the eyes resulting in cataract formation (NIOSH, 2001).

B16-4.2 Health Effects by Route of Exposure

B16-4.2.1 Oral Exposure

B16-4.2.1.1 Death

Oral exposure to diquat is slightly acutely toxic and has been placed in Toxicity Category III for these effects by the U.S. EPA (1995a).

Table B16-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Diquat

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Multiple Species (cow, dog, monkey, rabbit, mice, rats)	30-810	Walley, 1987; Clark and Hurst, 1970; Bingham *et al*., 2001; McCall and Robinson, 1990; Pritchard, 1986; Chevron Chemical Co., 1979a

Table B16-5 Mortality as a Result of Oral Exposure to Diquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Mouse (Alderley Park SPF)	1 mg/kg/day (11 days)	Mortality	Palmer *et al*., 1978

B16-4.2.1.2 Systemic Effects

Oral subchronic exposure of rats to diquat resulted in hemorrhages into vitreous and detachment of the retina was observed (Grant, 1986).

Table B16-6 Systemic Effects Resulting from Oral Exposure to Diquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Rat (Alpk: APfSD)	150 mg/kg (single dose)	Piloerection; diarrhea; staining around nose; urinary incontinence; upward curvature of the spine; hunched posture; tip toe gait; subdued behaviour; pinched sides; slightly decreased body weights; decreased body weight gains; decreased food consumption	Horner, 1992
Sub-chronic			
Rat (Alpk: APfSD)	32.4-38.5 mg/kg/day (21 days)	Opaque eyes; eye pallor; decreased visual placement response; decreased body weight; decreased body-weight gains and food utilization; increased incidence of cataracts and/or posterior lens opacities	Horner, 1992
Chronic			
Mouse (CD-1) (M)	≥11.96-16.0.3 mg/kg/day (2 years)	Increased kidney weight	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Mouse (CD-1) (M/F)	37.83-48.27 mg/kg/day (2 years)	Increased incidence of eye discharge; increased incidence of thin appearance (M); subdued behaviour; decreased body weight; decreased food consumption; increase in microscopic lesions in the kidney (tubular dilatation and tubular hyaline droplet formation (F)), liver (extramedullary hemopoiesis) and lymph node, and mesenteric (lymphoid proliferation (F)); decreased brain weight (F)	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Rat	≥0.58-0.72 mg/kg/day (2 years)	Cataracts	Colley *et al*., 1985
Rat (M)	≥2.91-3.64 mg/kg/day (2 years)	Increased incidence of nephropathy in the kidneys	Colley *et al*., 1985
Rat	14.88-19.44 mg/kg/day (2 years)	Decreased body weight gain; depression in average food consumption	Colley *et al*., 1985
Rat (M)	14.88-19.44 mg/kg/day (2 years)	Increased incidence of arteritis/periarteritis in blood vessels and paracortical cell hyperplasia in the lymph nodes	Colley *et al*., 1985
Dog (M/F)	12.5 mg/kg/day	Decreased body-weight gains (during first 2 weeks); bilateral lens opacity; increased kidney weights; cataracts; chronic inflammatory changes in the large intestine, colon, rectum and cecum	Hopkins, 1990

(M) Effects observed in males only.
(F) Effects observed in females only.

B16-4.2.1.3 Neurological Effects

Table B16-7 Neurological Effects Resulting from Oral Exposure to Diquat

Test Type	Test Organism (Species)	Dose (Duration)	Response	Reference
Acute	Rat (Alpk: APfSD/M)	150 mg/kg	Increased landing foot splay	Horner, 1992

B16-4.2.1.4 Reproductive/Developmental Effects

Table B16-8 Reproductive and Developmental Effects Resulting from Oral Exposure to Diquat

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Mouse (Alderley Park SPF/F)	Gavage	<1 mg/kg/day (days 6 through 15 of gestation)	Decreased body-weight gain	Palmer *et al*., 1978
Mouse (Alderley Park SPF/F)	Gavage	≥1 mg/kg/day (days 6 through 15 of gestation)	Increased incidence of minor skeletal abnormalities (incomplete ossification, extra ribs, variant sternebrae) and evidence of major malformations	Palmer *et al*., 1978
Mouse (Alderley Park SPF/F)	Gavage	≥2 mg/kg/day (days 6 through 15 of gestation)	Maternal effects: increased incidence of gastrointestinal disorders and ruptured lungs; congested lungs; severe pulmonary changes; increased incidence of clinical signs of toxicity (piloerection,dyspnea, respiratory noise, abnormal posture, lethargy, tremors, unsteadiness on feed, emaciation, ptosis);	Palmer *et al*., 1978
Mouse (Alderley Park SPF/F)	Gavage	4 mg/kg/day (days 6 through 15 of gestation)	Fetal effects: decreased fetal body weight and litter weight	Palmer *et al*., 1978
Rat (Alpk: APfSD)(M/F)	Diet	12 mg/kg/day (12 weeks; 2 generation study)	Maternal effects: decreased body-weight gains during gestation; decreased food consumption during gestation and lactation	Hodge, 1990
			Fetal effects: ulceration of the hard palate; increased incidence of pyelitis, ureteritis and cortical tubular dilatation; distended caecum; ocular opacity; increased incidence of hyptertrophy and hyperplasia of the collecting duct opithelium in the kidney; cystitis; pyelitis; slight cortical tubular dilatation; decreased mean number of live pups/litter and mean pup body weight	
Rat (Alderley Park SPF/F)	Gavage	40 mg/kg/day (days 7 through 16 of gestation)	Maternal effects: increased incidence of piloerection; subdued behaviour; decreased body-weight gains; decreased food consumption	Wickramaratne, 1989
			Fetal effects: decreased gravid uterine weight; decreased mean litter weight and mean fetal body weight; increased incidence of hemorrhagic kidney and poorer ossification (skeletal alterations)	
Rabbit (New Zealand White/F)	Gavage	1.0 mg/kg/day (days 7 to 19 of gestation)	Fetal: significantly delayed ossification; increased malformations (altered cell migration)	Hodge, 1989
Rabbit (New Zealand White/F)	Gavage	10 mg/kg/day	Maternal effects: Increased incidence of diarrhea, subdued appearance, and thin appearance; decreased food consumption	Hodge, 1989
			Fetal effects: increased incidence of friable and mottled livers; increase in percent of fetuses with extra 13^{th} ribs; increased incidence of partially-ossified 6^{th} sternebrae and 27 pre-sacral vertebrae; Increased incidence of sternebrae not ossified.	

B16-4.2.1.5 No Observed Adverse Effect Levels

Table B16-9 NOAELs and LOAELs for Oral Exposure to Diquat[a]

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Acute				
Rat (Alpk: APfSD)	LOAEL	150	Systemic toxicity (clinical signs, decreased body-weight gain)	Horner, 1992
Rat (Alpk: APfSD)	NOAEL	75	Systemic toxicity	Horner, 1992
Rat (Alpk: APfSD)	NOAEL	150	Motor activity	Horner, 1992
Sub-chronic				
Rat (Alpk: APfSD)	LOAEL	32.4-38.5	Systemic toxicity (cataracts; decreased body-weight gain; food utilization)	Horner, 1992
Rat (Alpk: APfSD)	NOAEL	8.0-9.5	Systemic toxicity	Horner, 1992
Rat (Alpk: APfSD)	NOAEL	32.4-38.5	Neurotoxicity (functional observational battery, motor activity assessment, gross/histopathological examination)	Horner, 1992
Chronic				
Mice (CD-1)	LOAEL	11.96-16.03	Clinical signs (eye discharge (M), subdued behaviour (F)) and decreased body weight/body-weight gain (M)	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Mice (CD-1)	NOAEL	3.56-4.78	Systemic	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Mice (CD-1)	NOAEL	37.83-48.27	Hematology parameters; gross pathology	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Rat	LOAEL	2.91-3.64	Eye lesions (total cataracts)	Colley *et al*., 1985
Rat	NOAEL	0.58-0.72	Eye lesions (total cataracts)	Colley *et al*., 1985
Rat (Alpk: APfSD/MF)	NOAEL	4	Systemic parental	Hodge, 1990
Rat	NOAEL	14.88-19.44	Mortality; Clinical signs of toxicity (exception of effects on the eye)	Colley *et al*., 1985
Dog (F)	NOAEL	0.5	Unilateral cataracts	Hopkins, 1990
Dog	NOAEL	12.5	Survival; clinical signs; hematology; clinical chemistry; urinalysis; gross pathology	Hopkins, 1990

[a] Obtained from U.S. EPA, 2001.

Table B16-10 Diquat Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Mice (Alderley Park SPF/F)	LOAEL	2 mg/kg/day	Maternal toxicity (clinical signs, death, macroscopic lesions)	Palmer *et al*., 1978
Mice (Alderley Park SPF/F)	LOAEL	4 mg/kg/day	Developmental toxicity (decreased fetal body weight and increased incidence of skeletal alterations)	Palmer *et al*., 1978

Table B16-10 Diquat Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Mice (Alderley Park SPF/F)	NOAEL	1 mg/kg/day	Maternal toxicity	Palmer *et al*., 1978
Mice (Alderley Park SPF/F)	NOAEL	2 mg/kg/day	Developmental toxicity	Palmer *et al*., 1978
Mice (Alderley Park SPF/F)	NOAEL	4 mg/kg/day	Pregnancy rate; number of implantations and live fetuses/dam; fetal sex ratio; pre-and post-implantations losses; litter size; minor visceral abnormalities	Palmer *et al*., 1978
Rat (Alpk: APfSD)(M/F)	LOAEL	4 mg/kg/day	Parental systemic toxicity (increased incidence of clinical signs	Hodge, 1990
Rat (Alderley Park SPF/F)	LOAEL	12 mg/kg/day	Maternal toxicity (decreased maternal body-weight gain and food consumption)	Wickramaratne, 1989
Rat (Alpk: APfSD)(M/F)	LOAEL	12 mg/kg/day	Reproductive/Developmental toxicity (decreased number of live pups per litter and weight gain; increased incidence of kidney lesions)	Hodge, 1990
Rat (Alderley Park SPF/F)	LOAEL	40 mg/kg/day	Developmental toxicity (decreased fetal body weight, decreased litter weight, poorer ossification, increased incidence of hemorrhagic kidney)	Wickramaratne, 1989
Rat (Alpk: APfSD)(M/F)	NOAEL	0.8 mg/kg/day	Parental systemic toxicity	Hodge, 1990
Rat (Alderley Park/F)	NOAEL	4 mg/kg/day (days 7 to 16 of gestation)	Maternal (reduced food consumption and body weight gain)	Hodge, 1990
Rat (Alderley Park SPF/F)	NOAEL	4 mg/kg/day	Maternal toxicity	Wickramaratne, 1989
Rat (Alpk: APfSD)(M/F)	NOAEL	4 mg/kg/day	Reproductive/Developmental toxicity	Hodge, 1990
Rat (Alderley Park SPF/F)	NOAEL	12 mg/kg/day	Developmental toxicity	Wickramaratne, 1989
Rat (ALpk:APfSD/MF)	NOAEL	0.8 mg/kg/day (2 generation study)	Systemic pup effects	Hodge, 1990
Rat (Alpk: APfSD)(M/F)	NOAEL	12 mg/kg/day	Female fertility (live birth index, viability index, lactation index, fetal sex distribution)	Hodge, 1990
Rabbit (New Zealand White)	LOAEL	3 mg/kg/day	Maternal toxicity (body-weight loss, decreased food consumption)	Hodge, 1989
Rabbit (New Zealand White)	LOAEL	10 mg/kg/day	Developmental toxicity (increased incidence of friable and or/mottled livers and poorer ossification)	Hodge, 1989
Rabbit (New Zealand White/F)	NOAEL	<1.0 mg/kg/day (days 7 to 19 of gestation)	Developmental (increased rate of malformations resulting from faulty cell migration)	Hodge, 1989
Rabbit (New Zealand White)	NOAEL	1 mg/kg/day	Maternal toxicity	Hodge, 1989
Rabbit (New Zealand White)	NOAEL	3 mg/kg/day	Developmental toxicity	Hodge, 1989

Table B16-10 Diquat Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Rabbit (New Zealand White)	NOAEL	10 mg/kg/day	Reproductive success (numbers of corpora lutea/doe, implantations/doe, % pre- and post-implantation losses, gravid uterine weight, mean litter size, mean litter weight, mean fetal body weight or % males)	Hodge, 1989
Dog (M)	LOAEL	> 2.5 mg/kg/day (1 year)	Reduced epididymal weights	Hopkins, 1990

[a] Obtained from U.S. EPA, 2001.

B16-4.2.2 Dermal Exposure

Diquat causes slight dermal irritation and has been placed in Toxicity Category IV for this effect by the U.S. EPA (1995a). It is not a skin sensitizer. However, it can cause slight to severe eye irritation and has been placed in Toxicity Category II for acute dermal and eye irritation effects (U.S. EPA, 1995a).

B16-4.2.2.1 Death

Table B16-11 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Diquat

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Multiple Species (Rabbit, Guinea Pig, Mouse, Rat)	262-650	Chevron Chemical Co., 1979b; Bingham *et al*., 2001

Table B16-12 Mortality Resulting from Dermal Exposure to Diquat

Test Type	Test Organism (Species)	Dose (Duration)	Response	Reference
Sub-chronic	Rat (M/F)	20-80 mg/kg/day (21 days)	Mortality (hypothermia, hypoactivity, dyspnea, cyanosis, pale extremities, anogenital staining, little or no stool, general poor condition, emaciated appearance)	Auletta, 1987

B16-4.2.2.2 Systemic Effects

Table B16-13 Systemic Effects Resulting from Dermal Exposure to Diquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Rat (M/F)	20 – 40 mg/kg/day (21 days)	Decreased food consumption; decreased body-weight gains	Auletta, 1987
Sub-chronic			
Rat (M/F)	$\geq$ 5 mg/kg/day (21 days)	Dermal irritation (erythema, edema and desquamation) and tissue destruction (necrosis and eschar formation) observed at the site of application	Auletta, 1987
Rat (M/F)	$\geq$ 20 mg/kg/day (21 days)	Sores, severe erythema, fissures, acute necrotizing purulent dermatitis and degeneration of the hair follicles and sebaceaous glands at the site of application	Auletta, 1987

B16-4.2.2.3 Neurological Effects

No data was found.

B16-4.2.2.4 Reproductive/Developmental Effects

No data was found.

B16-4.2.2.5 No Observed Adverse Effect Level

Table B16-14 NOAELs and LOAELs for Dermal Exposure to Diquat

Test Organism (Species)	Value	Effect	Endpoint	Reference
Sub-chronic				
Rat	LOAEL	5 mg/kg/day	Dermal toxicity based on dermal application at application site	Auletta, 1987
Rat	LOAEL	20 mg/kg/day	Systemic Toxicity based on dose response mortality and clinical signs (hypothermia; hypoactivity, dyspnea, cyanosis, pale extremities, general poor condition, *etc*.)	Auletta, 1987
Rat	NOAEL	5 mg/kg/day	Systemic Toxicity	Auletta, 1987
Rat	NOAEL	<5 mg/kg/day	Dermal toxicity	Auletta, 1987
Rabbit	NOAEL	20 mg/kg	Systemic effects	Clayton and Clayton, 1982

B16-4.2.3 Inhalation Exposure

Diquat is slightly acutely toxic through inhalation exposure and has been placed in Toxicity Category III for these effects by the U.S. EPA (1995a).

B16-4.2.3.1 Death

Table B16-15 Mammalian Acute LD_{50} Value Resulting from Inhalation Exposure to Diquat

Test Organism (Species/Sex)	LD_{50} (µg/L)	Reference
Rat (Sprague-Dawley CD)(M/F)	121-132[a]	Bruce, 1985
Rat (M)	800 -1,090	U.S. EPA, 2001

[a] Whole body exposure to aerosol; 4-hr exposure

B16-4.2.3.2 Systemic Effects

Table B16-16 Systemic Effects Resulting From Exposure to Diquat *via* Inhalation

Test Organism (Species)	Dose (Duration)	Response	Reference
Sub-chronic			
Rat (M/F)	>0.49 µg/L (21 days)	Microscopic lesions in the lungs (multi-focal chronic interstitial pneumonia and alveolar macrophages; Increased lung weight (M); mottling and/or reddening of the lungs (M)	Bruce and Griffis, 1987
Rat (M/F)	>1.1 µg/L (21 days)	Decreased food consumption; Increased lung weight (F); mottling and/or reddening of the lungs (F)	Bruce and Griffis, 1987
Rat (M/F)	3.8 µg/L (21 days)	Abnormal respiratory sounds; anogenital discharge; decreased body weight; decreased body weight gains; microscopic lesions in the anterior nasal tissues (epithelial dysplasia, erosion and rhinitis); microscopic lesions in the lungs (alveolar edema)	Bruce and Griffis, 1987

(M) Effects observed in males only.
(F) Effects observed in females only.

B16-4.2.3.3 Neurological Effects

No data found.

B16-4.2.3.4 Reproductive/Developmental Effects

No data found.

B16-4.2.3.5 No Observed Adverse Effect Level

Table B16-17 NOAELs and LOAELs for Diquat Exposure *via* Inhalation

Test Organism (Species)	Effect	Value	Endpoint	Reference
Sub-chronic				
Rat	LOAEL	0.49 µg/L	Microscopic lesions in the lungs	Bruce and Griffis, 1987
Rat	NOAEL	0.1 µg/L	Increased lung weight	Bruce and Griffis, 1987
Rat	NOAEL	0.1 µg/L	--	Chevron Chemical Co., 1988
Rat	NOAEL	3.8 µg/L	Hematology; clinical chemistry; ophthalmological parameters	Bruce and Griffis, 1987

B16-4.3 Carcinogenicity

Diquat is not classifiable as a human carcinogen (American Conference of Governmental Industrial Hygienists TLVs and BEIs, 2005). In addition, the U.S. EPA (2001) classified diquat as Category E: evidence of non-carcinogenicity to humans.

Table B16-18 Animal Carcinogenicity Data[a]

Test Subjects	Exposure	Dose	Response	Reference
Mice	Water	2-4 mg/kg/day (2 years)	No tumorigenicity	Bingham *et al*., 2001
Mice (CD-1)	Diet	37.83-48.27 mg/kg/day (2 yars)	No carcinogenic effects	Hodge, 1991; Ishmael, 1993a; Ishmael, 1993b; Ishmael, 1993c
Mice	Diet	75 mg/kg/day (2 years)	No tumorigenicity	Bingham *et al*., 2001
Rat	Water	2.6 mg/L (2 years)	No tumorigenicity	Bingham *et al*., 2001
Rat (CD)	Diet	14.88-19.44 mg/kg/day (2 years)	Incidence of comparatively rare osteosarcoma observed in males (0/50,1/50,0/50,0/50, and 3/50 for control and increasing dose groups, respectively).	Colley *et al*., 1985
Rat	Diet	14.88-19.44 mg/kg/day (2 years)	No treatment-related increase in any tumour type	Colley *et al*., 1985
Rat	Diet	720 mg/kg (long term)	No carcinogenic effects	WHO, 1991
Rat	Diet	720 mg/kg (2 eayrs)	No tumorigenicity	Bingham *et al*., 2001

[a] Obtained from U.S. EPA, 2001; HSDB, 2005.

B16-4.4 Populations at Special Risk

Data provided no indication of increased sensitivity of rats, mice or rabbits to *in utero* and/or post-natal exposure to diquat. In a 2 generation reproduction study in rats and rabbits, effects in the offspring were observed only at or above treatment levels that resulted in evidence of parental toxicity. Therefore, diquat does not show special sensitivity to infants and children (U.S. EPA, 2001).

B16-4.5 Toxicokinetics

B16-4.5.1 Absorption

Diquat is poorly absorbed from the intestinal tract and skin as it is a cation (WHO, 1991; The Chemical Society, 1970; Kearney and Kaufman, 1975; Bingham *et al*., 2001; Daniel and Henson, 1960). For instance, radiolabeled diquat was applied to the forearms of six human male volunteers and maintained for 24 hours (Feldmann and Maibach, 1974). A total of 0.3% of the applied dose was recovered in the urine. Wester and Maibach (1985) demonstrated that a dermally applied dose of diquat on humans led to 1.4% being absorbed. Daniel and Henson (1960) demonstrated that diquat was absorbed to a small extent when administered to rats orally in an aqueous solution.

Dermal Absorption

The U.S. EPA (2001) determined a dermal absorption factor of 4.1% for diquat. The dermal absorption of diquat through intact rat skin is considered very low based on a *in vivo* percutaneous absorption study (Brorby and Griffis, 1989). Diquat was applied dermally to the shaved backs of four Sprague-Dawley rats. The dermal absorption factor was determined based on the exposure patter and duration of exposure of the low dose after 2 hours of exposure (U.S. EPA, 2001).

B16-4.5.2 Distribution

Diquat has been shown to accumulate in the kidneys, but not the lungs (WHO, 1991; Bingham *et al*., 2001). Dairy cattle and sheep feed on diquat-treated silage had no diquat residues in their milk, meat or organs after sacrifice (Menzie, 1969).

Following an oral feeding of diquat to rats, there was no retention of diquat in the brain, liver, lung, stomach, small and large intestine, muscle, and blood. In addition, little retention was observed in the kidneys (Litchfield *et al*., 1973). Following a dose of radiolabeled diquat administered intravenously, diquat was found to concentrate in the cartilaginous tissues, the liver and bladder. However, after an hour, radioactivity decreased in most tissues, and after 72 hours diquat was only detected in the intestines of the rats (Litchfield *et al*., 1973).

B16-4.5.3 Metabolism

In the body, diquat monopyridone and diquat dypridone are the primary and secondary metabolites, respectively (WHO, 1991). Both of these metabolites are considerably less toxic than their parent compound diquat. Diquat is primarily metabolized in the gastrointestinal tract

by microflora, as little evidence of biliary excretion has been observed (WHO, 1991; Bingham *et al*., 2001; Daniel and Gage, 1966; Mills, 1976). Diquat is also suggested to be metabolized in the liver as free radicals were shown to be produced when diquat was incubated in the presence of reduced NADP and liver microsomes (Doull *et al*., 1980).

Only a small percentage of diquat appears to be metabolized within the body. For instance, after an oral administration of diquat to rats, 77% of the dose was excreted in feces as diquat and only 12% as metabolites. Diquat monopyridone made up the majority of the metabolites (Kearney and Kaufman, 1975). In addition, the WHO (1991) states that when an oral dose is administered less than 20% is metabolized.

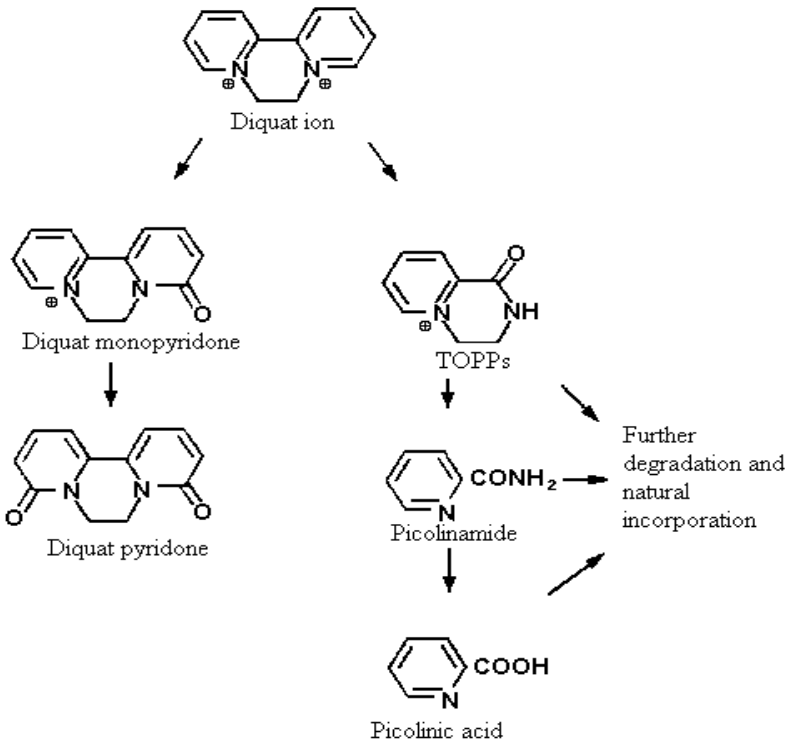

Figure B16-2 Diquat metabolism in various laboratory animals and humans [TOPPs- 1,2,3,4-tetrahydro-1-oxopyrido-2*H*-[1,2-a]-5-pyrazinium ion

B16-4.5.4 Elimination and Excretion

The kidneys are the major route of excretion for diquat and its metabolites (WHO, 1991; Fuke *et al*., 1996; Bingham *et al*., 2001; Daniel and Henson, 1960). However, this only applies through exposure *via* injection (Mills, 1976; Menzie, 1969). For instance, after a subcutaneous administration of 10 mg/kg bw of diquat to Wistar rats, 87 and 5% of the dose was excreted in the urine and feces, respectively (Mills, 1976). Conversely, when diquat was administered as an oral dose in an aqueous solution by gavage, 6 and 89% were excreted in urine and feces, respectively (Mills, 1976). Therefore, when administered orally the main route of diquat

excretion is through feces (Griggs and Davis, 1975; Menzie, 1969; Johnston *et al*., 1990; The Chemical Society, 1970; Hemingway *et al*., 1974; Leahy *et al*., 1976).

Diquat can also be excreted in the bile depending on the animal species; however, levels of excretion are significantly lower than levels reported in feces and urine (WHO, 1991).

B16-4.6 Exposure Limits

Table B16-19 Existing RfD Values For Diquat Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor	Study Classification
Acute/Short-term (1-7 days)								
0.75	Oral	U.S. EPA, 2001	Clinical signs and decreased body weight gain	Acute rat neurotoxicity	Horner, 1992	75	100	Acceptable
Intermediate-term (7 days- Several months)								
No information found		--	--	--	--	--	--	--
Long-term (6 months to lifetime)								
0.0022	Oral	U.S. EPA, 1995b	Minimal lens opacity	2 years feeding study of rats	Colley *et al*., 1985	0.22	100	High quality; confidence in the RfD is medium to high
0.005	Oral	U.S. EPA, 2001	Cataracts (F) and decreased adrenal and epididymides weights (M)	1 year Chronic dog toxicity	Hodge, 1990	0.5	100	Acceptable
0.008[a]	Oral	WHO, 1991; Health Canada, 1986; 2004	Cataract formation	Rats	--	0.75	100	--

[a] Acceptable Daily Intake (ADI) - The amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects.

Table B16-20 Summary of the Toxicological Dose and Endpoints for Diquat Used In Human Risk Assessment by the U.S. EPA (2001)

Exposure Scenario	Reference Dose (mg/kg/day)	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	MOE	Reference
Incidental Oral (short term)	0.01	Decreased body-weight gain and food consumption	Development toxicity rabbit	1	3	100	Hodge, 1989
Incidental Oral (intermediate-term)	0.005	Cataracts (F) and decreased adrenal and epididymis weights	Chronic oral toxicity dog	0.5	2.5	100	Hopkins, 1990
Dermal [ab] (short term)	0.01	Decreased body-weight gain and food consumption	Development toxicity rabbit	1	3	100	Hodge, 1989
Dermal [ab] (intermediate term)	0.005	Cataracts (F) and decreased adrenal and epididymis weights	Chronic oral toxicity dog	0.5	2.5	100	Hopkins, 1990
Dermal [ab] (long-term)	0.005	Cataracts (F) and decreased adrenal and epididymis weights	Chronic oral toxicity dog	0.5	2.5	100	Hopkins, 1990
Inhalation (short term)	$2.9x10^{-4}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	21 d inhalation toxicity rat	0.1[c]	0.49	100	Bruce and Griffis, 1987
Inhalation (intermediate term)	$2.9x10^{-4}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	21 d inhalation toxicity rat	0.1[c]	0.49	100	Bruce and Griffis, 1987
Inhalation (long term)	$2.9x10^{-4}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	21 d inhalation toxicity rat	0.1[c]	0.49	100	Bruce and Griffis, 1987

[a] Dermal absorption factor of 4.1% should be used.

[b] Since an oral route was selected, route-to-route extrapolation should be followed.

[c] Units µg/l. The NOEL was converted to mg/kg/day using a body weight of 70 kg and a breathing rate of 20 m^3/day.

Based on the general population (Table B16-19) and occupational (Table B16-20) reference doses, the following exposure limits were selected for risk assessment purposes of this report (Table B16-21).

Table B16-21 Summary of Selected TRVs for Diquat

COC	TRV Type	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
Diquat	Acute/Short-term RfD (1-7 days)	Oral	0.01	Decreased body-weight gain and food consumption	Oral	U.S. EPA, 2001
		Dermal				
		Inhalation	$2.9x10^{-4a}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	Inhalation	U.S. EPA, 2001
	Intermediate-term RfD (1 week to several months)	Oral	0.005	Cataracts (F) and decreased adrenal and epididymis weights	Oral	U.S. EPA, 2001
		Dermal				
		Inhalation	$2.9x10^{-4a}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	Inhalation	U.S. EPA, 2001
	Long-term RfD (>6 months)	Oral	0.005	Cataract formation	Oral	U.S. EPA, 2001
		Dermal	0.005	Cataracts (F) and decreased adrenal and epididymis weights	Oral	U.S. EPA, 2001
		Inhalation	$2.9x10^{-4a}$	Increased mean lung weight (M); mottling and reddening of lungs (F); lung lesions	Inhalation	U.S. EPA, 2001

B16-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B16-5.1 Air

B16-5.1.1 Transport and Partitioning

Diquat is not volatile; however, during spray application droplets of the solution may be present in the air as an aerosol (WHO, 1991). According to the model of gas/particle partitioning of semi-volatile organic compounds in the atmosphere, diquat will exist in the particulate phase (Bidleman, 1988). Particulate phase diquat may be removed from the air by wet or dry deposition.

B16-5.1.2 Transformation and Degradation

Diquat is susceptible to UV decomposition (absorption maximum at 310 nm); however, once it is adsorbed onto particulate matter no photodegradation will occur (Weber, 1972).

Table B16-22 Half-life of Diquat in Air

Half-life	Reference
48 hours[a]	Funderburk, 1967

[a] Exposed to sunlight.

B16-5.2 Water

B16-5.2.1 Transport and Partitioning

Diquat residues disappear rapidly from water through adsorption to aquatic weeds and by strong absorption to soil sediment and organic matter (WHO, 1991). Diquat is a divalent cation. Cations generally adsorb to organic carbon and clay more strongly than their neutral counterparts (Doucette, 2000). Volatilization from water surfaces is not expected based on an estimated Henry's Law constant (Meylan and Howard, 1991).

B16-5.2.2 Transformation and Degradation

Following its use as an aquatic herbicide diquat residues have been found to decrease rapidly to undetectable levels within seven to 14 days (WHO, 1991). Diquat is stable in neutral or acidic solutions; however it hydrolyzes in alkaline water (Ahrens, 1994). Diquat is also rapidly oxidized by chlorine oxide above and below a pH of 8.14 and 7.12, respectively (Faust, 1975). Therefore, the compound would dissipate rapidly from chlorinated drinking water, which is slightly alkaline in nature (Faust, 1975). In addition, diquat solutions are readily reduced (autooxidizable).

Microorganisms are capable of degrading diquat in various sediment-water systems, but at a very slow rate (Simsiman and Chesters, 1976). For instance, diquat adsorbed on the internal faces of clay in an aqueous soil-nutrient solution was not degraded by microorganisms over a one year period (Weber, 1972). Furthermore, after 65 days only 0.88 and 0.21% of diquat present in a solution was converted to carbon dioxide under aerobic and anaerobic conditions, respectively, using water and sediment from a eutrophic lake (Simsiman and Chesters, 1976). Therefore,

biodegradation is not expected to be an important environmental fate process for diquat in aqueous systems (Chemicals Inspection and Testing Institute, 1992).

Diquat is susceptible to UV decomposition (absorption maximum at 310 nm). For example, after exposure to UV radiation for 192 hours, no diquat remained in an aqueous solution (Funderburk, 1967). When a solution containing 5 ppm of diquat was exposed to sunlight during May and June, seventy percent of the diquat was degraded within 3 weeks (Smith and Grove, 1969). The major photoproducts were picolinic acid and TOPPs (Smith and Grove, 1969). When diquat is adsorbed onto particulate matter, no evidence of photodegradation was reported (Weber, 1972).

Table B16-23 Half-life of Diquat in Water

Conditions	Half-life	Reference
In the water column	< 48 hours	JW, 2005
Exposed to sunlight	74 days	Tegala and Skidmore, 1987; JW, 2006
In sediments	160 days	JW, 2005

B16-5.3 Sediment and Soil

B16-5.3.1 Transport and Partitioning

Diquat becomes tightly bound to clay minerals in the soil, which chemically inactivates the herbicidal activity of the compound (WHO, 1991). Diquat is a divalent cation. Cations generally adsorb to organic carbon and clay more strongly than their neutral counterparts (Doucette, 2000). Adsorbed diquat is persistent and immobile, and is not expected to be a ground water contaminant (U.S. EPA, 1995a; Weber, 1972). Based on a classification scheme, an estimated K_{oc} value of 2,000 was determined from a structure estimation model (Meylan *et al*., 1992). Diquat is expected to have only slight mobility in soil. Volatilization from moist or dry soil surfaces is not expected to occur based on the estimated Henry's Law constant and vapour pressure (Meylan and Howard, 1991). Field and laboratory studies have indicated that diquat usually remains in the top inch of soil for long periods of time after its application (JW, 2005).

B16-5.3.2 Transformation and Degradation

Rapid photochemical degradation of diquat on soil surfaces minimizes the risk to the environment as the breakdown products are of lower toxicity than diquat (WHO, 1991). However, once diquat is adsorbed in the interlayer spacings of clay, the compound will persist indefinitely in its original form, although in a biologically inactive state (Weber, 1972).

Biodegradation within the soil is not expected to occur due its strong adsorption to soil (Chemicals Inspection and Testing Institute, 1992). For instance, diquat adsorbed on the internal faces of clay in an aqueous soil-nutrient solution was not degraded by microorganisms over a one year period (Weber, 1972). Diquat dibromide is highly persistent with reported field half-lives of greater than 1000 days (JW, 2005).

B16-5.4 Other Environmental Media

B16-5.4.1 Transport and Partitioning

Diquat has a BCF range of <0.6 to 2.5 (Chemicals Inspection and Testing Institute, 1992; JW, 2006), therefore bioconcentration in aquatic organisms is expected to be low. Microcosm and field studies have shown no bioaccumulation occurs in the organs or tissues of fish exposed to diquat. (Garten and Trabalka, 1983; Funderburk, 1967) and no residues were found in the organs or tissues of channel catfish exposed to diquat.

B16-5.4.2 Transformation and Degradation

Refer to section 4.5 Toxicokinetics.

B16-6.0 SUMMARY

Diquat is a non-selective contact herbicide, algicide, desiccant and defoliant. As an herbicide/algicide it is used to control broadleaf and grassy weeds in non-crop (including residential) and aquatic areas. As a desiccant/defoliant diquat is used on seed crops and potatoes. Diquat was only applied on designated plots located at CFB Gagetown during the 1966/67 U.S. trials. Approximately 150 kg of diquat was applied over an area of 36 ha (Demaree and Haws, 1968; Demaree and Creager, 1968; and, Demaree *et al*., 1966).

Oral exposures to diquat cause low acute toxicity and have been placed in Toxicity Category III by the U.S. EPA (1995a). However, diquat will cause reproductive and developmental effects (decreased fetal body weight and increased incidence of skeletal alteration, decreased maternal body-weight gains during gestation; decreased food consumption during gestation and lactation). Furthermore, slight dermal irritation was associated with diquat exposures (Toxicity Category IV) (U.S. EPA, 1995a). While diquat is not a skin sensitizer, it can cause slight to severe eye irritation. Hence, it has been placed in Toxicity Category II for acute dermal and eye irritation effects (U.S. EPA, 1995a). *Via* the inhalation route of exposure, diquat is only slightly toxic and has been placed in Toxicity Category III by the U.S. EPA (1995a). Chronic animal studies have shown that diquat is not classifiable as a human carcinogen (American Conference of Governmental Industrial Hygienists TLVs and BEIs, 2005). Similarly, the U.S. EPA (2001) classified diquat as a Category E carcinogen (evidence of non-carcinogenicity to humans).

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