B15-1.0 PARAQUAT DICHLORIDE (PARAQUAT)

B15-1.1 Background Information

IUPAC: 1,1'-dimethyl-4,4'-bipyridinium

CAS: 1,1'-dimethyl-4,4'-bipyridinium

CASRN: 4685-14-7 dibromide CASRN 27041-84-5

PARAQUAT USAGE:

Paraquat dichloride was first registered for use in Canada in 1963. Paraquat is an herbicide currently registered for use on aquatic non-food sites, forests and woodlots, terrestrial feed crops, terrestrial food crops, turf, ornamental outdoor and vegetation control for non-food sites (PMRA, 2004).

Paraquat was sprayed at CFB Gagetown on designated plots during the U.S. 1967 Trial only (Table B15-1).

Table B15-1 Paraquat Usage at CFB Gagetown[a]

Year	Total Pentachlorophenol Applied (kg)	Total Area Treated (ha)
1967	30	7.3
Total	**3.0E+01**	**7.3E+00**

[a] Adapted from Demaree and Haws, 1968.

B15-1.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_{12}H_{14}N_2$

Activity: herbicides (quaternary ammonium herbicides)

Notes: When this substance is used as a salt, its identity should be stated, for example paraquat dichloride [1910-42-5].

Structure:

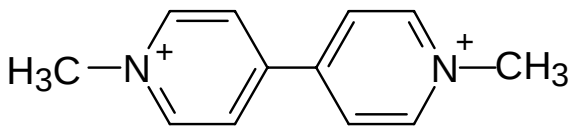

Figure B15-1 Paraquat CASRN 4685-14-7

Table B15-2 Chemical and Physical Properties of Paraquat Dichloride

Chemical/Physical Property	Result	Reference
Colour/Form	Colourless to yellow solid	Mackison *et al*., 1980; Lewis, 1993
Henry's Law constant	$<1x10^{-9}$ atm·m^3/mol	Seiber and Woodrow, 1984; JW, 2006
Log K_{ow}	-4.2	NIOSH, 2001
	-4.22 at pH 7.4	Platford, 1983
	-4.5	JW, 2006
Melting Point	175-180°C	NIOSH, 2001
Molecular Weight	186 g/mol	Clayton and Clayton, 1982
	257.2 g/mol	NIOSH, 2001; JW, 2006
Odour	Odourless	Mackison *et al*., 1980
Specific Gravity	1.24 at 20°C	Sunshine, 1969
Vapour Pressure	0 mm Hg at 20°C	Mackison *et al*., 1980
	$<1.0x10^{-7}$ mm Hg at 20°C	Weed Science Society of America, 1983
	$1.01x10^{-7}$ mm Hg at 25°C	JW, 2006
Water Solubility	700 g/L at 20°C	NIOSH, 2001; JW, 2006

B15-2.0 PMRA EVALUATION

Paraquat dichloride was re-evaluated by the PMRA under Re-evaluation Program 1 (PMRA, 2004). Under this program the PMRA relies as much as possible on foreign reviews, typically the U.S. EPA Re-registration Eligibility Decision (RED) documents, to assess Canadian pest products.

The U.S. EPA conducted a re-evaluation of paraquat dichloride and based on health and environmental health risk assessments concluded that it was eligible for re-registration with several mitigation measures. The evaluation of paraquat dichloride conducted by PMRA based its conclusions on this 1997 RED document taking into account the Canadian use pattern and Canadian issues (*e.g*., the federal Toxic Substances Management Policy). PMRA also conducted a review of the chemistry of Canadian products.

Based on the comparison of American and Canadian use patterns the U.S. EPA assessment described in the RED document is considered to be an adequate basis for the proposed Canadian re-evaluation decision by PMRA. The details of the U.S. EPA assessment are presented in the RED document for paraquat dichloride.

PMRA (2004) has determined that paraquat dichloride is acceptable for continued registration provided that specific mitigation measures are adopted.

B15-3.0 TOXICOLOGICAL SUMMARY

B15-3.1 Human Health Effects

Table B15-3 Human Health Effects Resulting from Acute and Chronic Exposure to Paraquat[a,b]

Exposure	Effects	Response
Acute	Vital Signs	Hypotension may develop after large ingestion
	HEENT	Protracted opacification of the cornea; mucosal irritant; epistaxis; and. sore throat may develop after inhalation
	Cardiovascular	Ventricular arrhythmias, hypotension and cardiorespiratory arrest may occur after large ingestions
	Respiratory	Progressive pulmonary fibrosis associated with dyspnea and pulmonary edema; pulmonary hemorrhage
	Neurologic	Lethargy; headache; malaise; cerebral edema may occur
	Gastrointestinal	Nausea; vomiting; diarrhea; abdominal pain; pancreatitis; caustic to the oral, esophageal and gastric mucosa
	Hepatic	Transient reversible liver injury
	Genitournary	Delayed glomerulonephritis; renal failure and functional renal insufficiency secondary to hypovolemia
	Hematologic	Methemoglobinemia after ingestion
	Dermatologic	Dermatitis associated with dry and cracking skin following dermal exposure; nail atrophy
	Musculoskeletal	Painful weakness of extremities; rhabdomyolysis
	Endocrine	Adrenal cortical necrosis
	Reproductive	Adverse reproductive effects observed in humans and experimental animals after ingestion of paraquat
Chronic	HEENT	Nosebleeds; upper respiratory tract irritation
	Respiratory	Altered pulmonary function tests; minor x-ray abnormalities; mild parenchymal changes on lung biopsy; pulmonary symptoms
	Dermatologic	Dry, cracking dermatitis; dermal burns; slow-healing narcosis; slow healing of small cuts and scratches; nail atrophy
	Musculoskeletal	Painful weakness of extremities

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

Short term exposure to paraquat dichloride may adversely affect the kidneys, liver, gastrointestinal tract, cardiovascular system and lungs (NIOSH, 2001). These effects may result in impaired functions and tissue lesions including hemorrhage and lung fibrosis. Inhalation may cause lung oedema. In addition, paraquat is irritating to the eyes, skin and respiratory tract. Exposure to high concentrations may result in the death (NIOSH, 2001). Prolonged or repeated dermal contact with paraquat may cause dermatitis. The substance may also result in nail damage (NIOSH, 2001).

B15-3.2 Health Effects by Route of Exposure

B15-3.2.1 Oral Exposure

Paraquat was determined to be moderately toxic (Category II) by the oral route (U.S. EPA, 1997a).

B15-3.2.1.1 Death

Table B15-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Paraquat

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute		
Mice	98	Hayes and Laws, 1991
Rat	126	Murray and Gibson, 1972
Rat	155-203	Verschueren, 1983
Rat (SPF Wistar, F)	283	Duerden, 1994a
Rat (SPF Wistar, M)	344	Duerden, 1994a
Guinea pig	22	Hayes and Laws, 1991; Murray and Gibson, 1972
Cat (F)	35	Hayes and Laws, 1991
Monkey	50	Hayes and Laws, 1991; Murray and Gibson, 1972
Sheep	50-75	WHO, 1984
Cow	50-75	WHO, 1984
Turkey	250-280	Smalley, 1973
Chicken (F)	262	Hayes and Laws, 1991

Table B15-5 Mortality Resulting from Oral Exposure to Paraquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Mice (Alderley Park)	40 mg/kg/day [a] (9 days)	100% mortality (dark red lungs or dark red patches on the lungs)	Hodge *et al*., 1977a
Rat (Alderley Park)	10 mg/kg/day [a] (11 days)	Increased mortality	Hodge *et al*., 1977b
Sub-chronic			
Dog (Beagle, M/F)	3.0 mg/kg (13 wks)	High mortality (2/3 males and 2/3 females during study days 16-23)	Sheppard, 1981
Chronic			
Rat (Alderley Park)	7.5 mg/kg/day [a] (multi-generation study)	Mortality (lung damage)	Lindsay *et al*., 1982

[a] Dose expressed as paraquat cation.

B15-3.2.1.2 Systemic Effects

Effects of acute oral toxicity in rats included: anorexia, adipsia, diarrhea, hyperpnea, dyspnea, tachycardia, necrosis of the liver, kidney and gastrointestinal tract with primary lesions in the lungs (Murray and Gibson, 1972).

Table B15-6 Systemic Effects Resulting from Oral Exposure to Paraquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Buffalo calves	100 mg/kg (single dose)	Dullness; depression; staggering gait; inco-ordination; stiff neck; irregular and feeble heart beat; laboured breathing; rumen stasis and bloat; severe muscular weakness; and, prostration and convulsions leading to coma	Humphreys, 1988

Table B15-6 Systemic Effects Resulting from Oral Exposure to Paraquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Subchronic			
Dog (Beagle, M/F)	3.0 mg/kg (13 weeks)	Increased absolute and relative lung weight, alveolitis and alveolar collapse; weight loss; decreased food intake; marked dyspnea; harsh rales; slow and/or irregular heart beat; and, large lesions in the lungs	Sheppard, 1981
Chronic			
Rat (Fischer 344)	3.75 mg/kg/day[a] (> 2years)	Increased incidence of: opacities/cataracts, ptosis/swollen eyelids (F), and non-neoplastic lung lesions (M)	Woolsgrove *et al*., 1983
Rat (Alderley Park)	> 3.75 mg/kg/day [a] (multi-generation study)	Increased incidence of alveolar histiocytosis in the lungs	Lindsay *et al*., 1982
Rat (Fischer 344)	$\geq$ 3.75 mg/kg/day[a] (> 2 years)	Increased incidence of ocular lesions	Woolsgrove *et al*., 1983
Rat (Fischer 344)	7.5 mg/kg/day[a] (> 2years)	Slightly decreased food consumption; decreased body weight gain; increased relative weight of the lungs; increased incidence of hydrocephalus (F); increased incidence of alveolar macrophages (M); and, increased incidence of alveolar epithelization and slight peribronchial lymphoid hyperplasia (M)	Woolsgrove *et al*., 1983
Rat (Wistar)	12.25-15.29 mg/kg/day[a] (2years)	Decreased erthrocytes, hemoglobin, and serum protein; decreased hematocrit, glucose, and corpuscular cholinesterase activity (M); decreased leucocytes, albumin/globulin ratio and alkaline phosphatase, GOT (glutamic-oxaloacetic transaminase) and GPT (glutamic-pyruvic transaminase) (F); increased polymorphonucleocytes (M); increased potassium and glucose (F); decreased absolute and/or relative weights of heart, liver (F), and brain (F); decreased absolute weights of kidneys (M); and, ovaries (F)	Toyoshima *et al.*, 1982a
Dog (Alderley Park beagle)	$\geq$ 0.93-1.0 mg/kg/day[a] (1 year)	Increased severity and extent of chronic pneumonitis	Kalinowski *et al*., 1983
Dog (Alderley Park beagle)	1.51-1.58 mg/kg/day[a] (1 year)	Increased group mean lung and spleen weights; hyperpnea; and, increased vesicular sound	Kalinowski *et al*., 1983

[a] Dose expressed as paraquat cation.
(M) Effects observed in males only.
(F) Effects observed in females only.

B15-3.2.1.3 Neurological Effects

There is currently no evidence to suggest the need for neurological studies as paraquat does not inhibit cholinesterase activity or affect morphology of the central and peripheral nervous systems (U.S. EPA, 1997b; Lambert and Bondy, 1989).

B15-3.2.1.4 Reproductive/Developmental Effects

Table B15-7 Reproductive and Developmental Effects Resulting from Oral Exposure to Paraquat

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Mice (Alderley Park)	Gavage	≥ 5 mg/kg/day [a] (days 6 through 15 of gestation)	Maternal effects: reduced body weight gain	Hodge *et al*., 1977a
Mice (Alderley Park)	Gavage	10 mg/kg/day [a] (days 6 through 15 of gestation)	Fetal effects: increased number of litters and fetuses with partially ossified 4th sternebrae	Hodge *et al*., 1977a
Mice (CrL:CDI BR)	Gavage	25 mg/kg/day [a] (days 6 through 15 of gestation)	Maternal effects: clinical signs (piloerection, laboured respiration, hunched posture, hypothermia, hypoactivity and/or pale extremities and eyes); death; decreased body weight and body weight gain; dark red lung lobes; increased lung with trachea and kidney weights; and, possible decrease in pregnancy rate	U.S. EPA, 1997b
			Fetal effects: decreased mean fetal weights; skeletal effects (increased number of litters with retarded ossification of the occipital, < 6 caudal centra, uni- or bilateral extra 14th ribs or non-ossified astragalus in the hindlimb)	
Rat (Alderley Park)	Diet	> 3.75 mg/kg/day [a] (multi-generation study)	Parental effects: increased incidence of alveolar histiocytosis in the lungs	Lindsay *et al*., 1982
Rat (Alderley Park)	Gavage	≥ 5 mg/kg/day [a] (days 7 through 15 of gestation	Maternal effects: Clinical signs (piloerection, thin and hunched appearance, decreased body weight gain); respiratory distress; and, histopathological findings in the lungs and kidneys	Hodge *et al*., 1977b
			Fetal effects: delayed ossification in the forelimb and hindlimb digits	

[a] Dose expressed as paraquat ion.

B15-3.2.1.5 No Observed Adverse Effect Levels

Table B15-8 NOAELs and LOAELs for Oral Exposure to Paraquat[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Subchronic				
Dog (Beagle, M/F)	LOAEL	1.5 mg/kg/day	Systemic toxicity	Sheppard, 1981
Dog (Beagle, M/F)	NOAEL	0.5 mg/kg/day	Systemic toxicity	Sheppard, 1981
Chronic				
Rat (Fischer 344; Alderley Park)	LOAEL	3.75 mg/kg/day[b]	Systemic toxicity	Woolsgrove *et al*., 1983; Lindsay *et al.*, 1982
Rat (Wistar)	LOAEL	12.25-15.29 mg/kg/day[b]	Systemic toxicity	Toyoshima *et al.*, 1982a

Table B15-8 NOAELs and LOAELs for Oral Exposure to Paraquat[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Rat (Fischer 344; Alderley Park)	NOAEL	1.25 mg/kg/day[b]	Systemic toxicity	Woolsgrove *et al*., 1983; Lindsay *et al*., 1982
Rat (Wistar)	NOAEL	4.15-5.12 mg/kg/day[b]	Systemic toxicity	Toyoshima *et al*., 1982a
Rat	NOAEL	170 mg/kg	--	Worthing and Walker, 1987
Dog (Alderley Park beagle)	LOAEL	0.93-1.0 mg/kg/day[b]	Systemic toxicity	Kalinowski *et al*., 1983
Dog (Alderley Park beagle)	NOAEL	0.45-0.48 mg/kg/day[b]	Systemic toxicity	Kalinowski *et al*., 1983
Dog	NOAEL	34 mg/kg	--	Worthing and Walker, 1987

[a] Obtained from U.S. EPA, 1997b U.S. EPA, 1993.
[b] Does expressed as paraquat cation.

Table B15-9 Diquat Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Mice (Alderley Park)	LOAEL	10 mg/kg/day[b]	Maternal and developmental toxicity	Hodge *et al*., 1977a
Mice (Crl:CD1 BR)	LOAEL	25 mg/kg/day[b]	Maternal (clinical signs; death; decreased body weight and body weight gain; dark red lung lobes; increases in lung and trachea and kidney weight; possible decrease in pregnancy rate) and developmental (decreased mean fetal weights; retarded ossification of the occipital; and, increased number with < 6 caudal central) toxicity	U.S. EPA, 1997b
Mice (Alderley Park)	NOAEL	10 mg/kg/day[b]	Maternal and developmental toxicity	Hodge *et al*., 1977a
Mice (Crl:CD1 BR)	NOAEL	15 mg/kg/day[b]	Maternal and developmental toxicity	U.S. EPA, 1997b
Rat (Alderley Park)	LOAEL	5 mg/kg/day[b]	Maternal and developmental toxicity	Hodge *et al*., 1977b
Rat (Alderley Park)	NOAEL	1 mg/kg/day[b]	Maternal and developmental toxicity	Hodge *et al*., 1977b
Rat (Alderley Park)	NOAEL	$\geq$ 7.5 mg/kg/day[b]	Reproductive toxicity	Lindsay *et al*., 1982
Rat (Alderley Park)	NOAEL	8 mg/kg/day[b]	Developmental and maternal toxicity	U.S. EPA, 1997b
Rat	NOAEL	100 ppm[b]	Growth and fertility	Zenz, 1988

[a] Obtained from U.S. EPA, 1997b; HSDB, 2005.
[b] Value expressed as paraquat cation.

B25-3.2.2 Dermal Exposure

Paraquat is slightly toxic (Category III) by the dermal route (U.S. EPA, 1997a). Paraquat will cause moderate to severe eye irritation and minimal dermal irritation, and has been placed in toxicity categories II and IV for these effects (U.S. EPA, 1997a; Lambert and Bondy, 1989).

B15-3.2.2.1 Death

Table B15-10 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Paraquat

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Rat (M)	80	Hayes and Laws, 1991
Rat (F)	90	Hayes and Laws, 1991
Rabbit	236	Hayes and Laws, 1991
Rabbit	>663	Verschueren, 1983
Rat (SPF Wistar, M/F)	>2000	Duerden, 1994b

B15-3.2.2.2 Systemic Effects

Table B15-11 Systemic Effects Resulting from Dermal Exposure to Paraquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Subchronic			
Rabbit (New Zealand White)	2.6 mg/kg[a] (21 days)	Scabbing at the dosing site	Cox, 1986
Rabbit (New Zealand White)	6.0 mg/kg[a] (21 days)	At the dosing site: scabbing; slight to well-defined erythema; minimal to moderately severe inflammation; acanthosis; hyperkeratosis (F); and, slight to severe erosion/ulceration and surface exudates General: decreased absolute and relative weight of testes (M)	Cox, 1986

[a] Dose expressed as paraquat cation

B15-3.2.2.3 Neurological Effects

There is currently no evidence to suggest the need for neurological studies as paraquat does not inhibit cholinesterase activity or affect morphology of the central and peripheral nervous systems (U.S. EPA, 1997b; Lambert and Bondy, 1989).

B15-3.2.2.4 Reproductive/Developmental Effects

No data found.

B15-3.2.2.5 No Observed Adverse Effect Level

Table B15-12 NOAELs and LOAELs for Dermal Exposure to Paraquat

Test Organism (Species)	Effect	Value	Endpoint	Reference
Subchronic				
Rabbit (New Zealand white)	LOAEL	2.6 mg/kg/day[a]	Dermal irritation	Cox, 1986
Rabbit (New Zealand white)	NOAEL	1.15 mg/kg/day[a]	Dermal irritation	Cox, 1986
Rabbit (New Zealand white)	NOAEL	17.9 mg/kg/day	Gross histological changes in the lung	Cox, 1986

[a] Value expressed as paraquat cation.

B15-3.2.3 Inhalation Exposure

In acute toxicity studies with laboratory animals, paraquat has been shown to be highly toxic when exposure occurs by the inhalation route, and has been placed in toxicity category I for acute inhalation effects (U.S. EPA, 1997a). However, the U.S. EPA (1997b) has determined that the particles used in agricultural practices (400 to 800 µm) are well beyond the respirable range. Therefore, inhalation toxicity is not a toxicological endpoint of concern (U.S. EPA, 1997b).

B15-3.2.3.1 Death

Table B15-13 Mammalian LD_{50} Value Resulting from Inhalation Exposure to Paraquat

Test Type	Test Organism (Species/Sex)	LD_{50}	Reference
Acute	Rat (Alderley Park SPF, M/F)	1µg/L	Gage, 1968

Table B15-14 Mortality Resulting from Inhalation of Paraquat

Test Type	Test Organism (Species)	Dose (Duration)	Response	Reference
Acute	Rat (Sprague-Dawley)	1.0 µg/L (Single exposure)	Mortality (respiratory failure)	Hardy *et al*., 1979

B15-3.2.3.2 Systemic Effects

Inhalation of paraquat aerosols for several hours produced severe congestion, alveolar edema and bronchial irritation two to three hours after the exposure in test organisms (Doull *et al*., 1980).

Table B15-15 Systemic Effects Resulting from Inhalation Exposure to Paraquat

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Rabbit (New Zealand White)	250 mg/100 mL water as an aerosol (2 exposures 5 days apart)	Decreased body weight; hypoxia; decreased breathing frequency; decreased lung capacity; increased lung weight; increase A-a O_2 gradient; decreased percent of macrophages in brochio-alveolar lavage fluid; and, increased percent of neutrophils (Changes not observed in rabbits that were able to recover for 6 weeks after exposure)	Seidenfeld *et al*., 1985
Subchronic			
Rat (Sprague-Dawley)	0.1 µg/L (3 weeks)	Nasal discharge; squamouse keratinizing metaplasia; and/or, hyperplasia of the epithelium of the larynx	Hardy *et al*., 1979
Rat (Sprague-Dawley)	0.5 µg/L (3 weeks)	Extensive ulceration; necrosis; inflammation and squamous keratinizing metaplasia, marked/moderate hyperplasia of adjacent epithelia in the larynx; aggregations of foamy macrophages in the bronchioles or alveoli; hypertrophy of the epithelium; and, thickened alveolar walls in the lungs	Hardy *et al*., 1979

B15-3.2.3.3 Neurological Effects

There is currently no evidence to suggest the need for neurological studies as paraquat does not inhibit cholinesterase activity or affect morphology of the central and peripheral nervous systems (U.S. EPA, 1997b; Lambert and Bondy, 1989).

B15-3.2.3.4 Reproductive/Developmental Effects

No data found.

B15-3.2.3.5 No Observed Adverse Effect Level

Table B15-16 NOAELs and LOAELs for Inhalation Exposure to Paraquat

Test Organism (Species)	Effect	Value (µg/L)	Endpoint	Reference
Subchronic				
Rat (Sprague-Dawley)	LOAEL	0.10	Inhalation toxicity (mortality; toxic signs)	Hardy *et al*., 1979
Rat (Sprague-Dawley)	NOAEL	0.01	Inhalation toxicity (mortality; toxic signs)	Hardy *et al*., 1979

B15-3.3 Carcinogenicity

The U.S. EPA (1993) has classified paraquat as category C: possible human carcinogen as paraquat produced squamous cell carcinoma in the head region (ear, skin, and oral and nasal cavities) in both sexes of Fischer 344 rats when the treated animals were compared with concurrent or historical controls (Woolsgrove *et al*., 1983). However, it was contended that the tumour sites (ear, skin, and oral and nasal cavities) should not be combined. When each of the sites was considered separately the incidence of squamous cell carcinomas between the treated and control rats was not statistically significant different (U.S. EPA, 1997b).

In 1989 the third Toxicology Branch Peer Review Committee met and classified paraquat as Category E: no evidence of carcinogenicity in animal studies. This decision was based on the re-examination of the study conducted by Woolsgrove *et al*. (1983) as well as subsequent (negative) carcinogenicity studies with rats and mice (Table B15-17)(U.S. EPA, 1997b).

Table B15-17 Animal Carcinogenicity Data[a]

Test Subjects	Exposure	Dose	Response	Reference
Mice (JCL:ICR)	Diet	4.15-5.12 mg/kg/day	Paraquat was not carcinogenic in this study; gross, non-neoplastic and neoplastic lesions were observed in various organs of the mice, but were not treatment related	Toyoshima *et al*., 1982b
Mice (Alderley Park)	Diet	18.7 mg/kg/day	No effect on the incidence of benign and malignant neoplasms	Litchfield *et al*., 1981
Mice (SPF Swiss)	Diet	125 ppm	No treatment-related tumours	Imperial Chemical Industries, 1981

Table B15-17 Animal Carcinogenicity Data[a]

Test Subjects	Exposure	Dose	Response	Reference
Rat (Fisher 344)	Diet	7.5 mg/kg/day	Paraquat was not considered carcinogenic in the lungs or head region; the incidence of pheochromocytoma or parafollicular adenomas and carcinomas did not appear to be paraquat related as they fell within the ranges reported for the historical controls	Woolsgrove *et al*., 1983; Chrevron Chemical Co., 1985; Willis, 1987; Ishmael, 1987; ICI Americal Inc., 1989
Rat (Wistar)	Diet	12.25-15.29 mg/kg/day	Paraquat was not carcinogenic; gross non-neoplastic and neoplastic lesions were observed in various organs but did not appear to be treatment related	Toyoshima *et al*., 1982a

[a] Obtained from U.S. EPA, 1997b; U.S. EPA, 1993.

Genotoxicity of Paraquat

Studies *in vitro*

Paraquat was negative in reverse mutation assays in *Salmonella* with or without metabolic activation using hepatic microsomal homogenates (Anderson *et al*., 1972; Benigni *et al*., 1979).

Paraquat was positive in *S. typhimurium* for induction of resistance to 8-Azaguanine (Benigni *et al*., 1979).

In plant cells (*Vicia faba*) Ma (1982) did not observe chromosomal aberrations. In stationary non-growing cells of the yeast *Saccharomyces cerevisiae* paraquat was positive for mutations (gene conversion) without a requirement for an added activation system (Zimmermann *et al*., 1984). In another strain of yeast, treatment with paraquat increased the frequency of intrachromosomal recombination (DEL) in years strain RS112 (Brennan *et al*., 1994), with no increased frequency in interchromosomal (ICR) mutations. Hydrogen peroxide (H_2O_2) is a potent inducer of mutations at these loci in yeast suggesting that super oxide generated by paraquat is responsible for mutation in yeast (Brennan *et al*., 1994).

Paraquat generates reactive oxygen species (super oxide) as a result of repeated cycles of reduction and reoxidation during metabolism (Hassan and Fridovich, 1979; Takeyama *et al*., 2004). Exposure of Chinese hamster lung fibroblasts *in vitro* to paraquat increased super oxide dismutase (SOD) enzyme levels from 10 to 50% in a dose-dependent manner (Nicotera *et al*., 1985). Mitotic indices in these cells decreased with dose, but both the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) increased with exposure to paraquat (Nicotera *et al*., 1985). A human cell lung cell line that did not exhibit P53 protein induction did not demonstrate the cytotoxic effect of paraquat that was noted in a cell line with normal P53 function (Takeyama *et al*., 2004). Oxidative-stress induced apoptosis was mediated by paraquat exposure through increased expression of P53 protein in G1 of the cell cycle (Takeyama *et al*., 2004).

The genotoxic potential of paraquat has been examined *in vitro* in Chinese hamster V79 cells (Speit *et al*., 1998). At high levels of exposure, paraquat induced the expected cytotoxicity and the associated chromosomal aberrations, but did not induce gene mutations at the HPRT locus.

Paraquat failed to produce a positive response for DNA breakage in the Comet assay (Speit *et al*., 1998).

Animal studies *in vivo*

Paraquat was not a mutagen according to results of the dominant lethal assay in the mouse (Green *et al*., 1985; Pasi *et al*., 1974).

The molecular mechanism of paraquat genotoxicity involves the generation of free radicals (Rios *et al*., 1995; Melchiorri *et al*., 1998). *In vivo* treatment of BALB/c mice (8 to 10 weeks old) with paraquat by intraperitoneal (i.p.) injection for 10 consecutive days produced chromosomal aberrations in somatic cells isolated from bone marrow (total dose 7, 15 and 23 mg/kg) (Rios *et al*., 1995). Only at the highest dose was an increase in chromosomal aberrations (gaps, breaks, fragments or exchanges) reported as a result of exposure to paraquat. However, paraquat did produce a significant decrease in mitotic index. In another test, male mice were given 5 daily i.p. injections and examined several weeks later for evidence of germ line mutation as reflected in sperm anomalies (Rios *et al*., 1995). In the latter experiment, significant anomalies were detected in spermatozoa, spermatids and spermatogonial cells of treated mice.

Treatment of adult ICR male mice with paraquat produced a dose-dependent increase (maximum reported at 48 h post exposure) in the production of micronucleated polychromatic erythrocytes in both peripheral blood and in bone marrow ((Melchiorri *et al*., 1998). This effect could be abolished by the pretreatment of the mice with melatonin. Melatonin was hypothesized to reduce the level of superoxide production, and this was presumed to be responsible for the protective effect (Melchiorri *et al*., 1998; Ortiz *et al*., 2000).

Dermal exposure of paraquat (dissolved in water) in rats resulted in the induction of micronuclei in a dose-dependent fashion (D'Souza *et al*., 2005). In tests using 9 to 11 week old Sprague-Dawley rats treated with the equivalent dermal exposure to 1/15, 1/6 and 1/3 of the LD_{50} for paraquat, the maximal increase in the number of MNPCEs in rat bone marrow was observed 48 hours after exposure. Recovery as monitored in maturing polychromatic erythrocytes and normochromatic erythrocytes was significant and dose-dependent at 72 hours post exposure (D'Souza *et al*., 2005).

The findings of D'Souza *et al*. (2005) suggest that both dermal and oral exposure to paraquat should be avoided.

B15-3.4 Populations at Special Risk

People with impaired pulmonary function may be at increased risk from paraquat exposure, due to its tendency to accumulate and impact respiratory function (Mackison *et al*., 1981).

B15-3.5 Toxicokinetics

B15-3.5.1 Absorption

Paraquat was poorly adsorbed after oral administration to rats, dogs and mice (Woolsgrove *et al*., 1983; Kalinowski *et al*., 1983; Toyoshima *et al*., 1982a). In addition, a dermal absorption study using healthy adult male volunteers showed that only 0.3% of the applied ^{14}C-paraquat

dichloride was absorbed through intact skin (forearms, back of the hands, lower legs) during a 24 hour exposure period (Wester *et al*., 1984).

B15-3.5.2 Distribution

After oral administration of paraquat to rats, dogs and mice, the compound was rapidly distributed to most tissues but the highest concentrations were found in the lungs and kidneys. However, tissues other than the lungs did not retain paraquat (Woolsgrove *et al*., 1983; Kalinowski *et al*., 1983; Toyoshima *et al*., 1982a).

B15-3.5.3 Metabolism

Paraquat was not metabolized by rats (Daniel and Gage, 1966). After oral administration of paraquat dichloride most of the radioactivity (69 to 96%) was excreted in feces as the unchanged parent compound. After subcutaneous injection unchanged paraquat appeared mostly in the urine (73 to 96% of radioactivity). However, further studies indicate that after oral exposure to paraquat up to 30% of the dose appeared within feces in a degraded form (Daniel and Gage, 1966). Degradation occurred as a result of microbial degradation in the gut demonstrated with an *in vitro* experiment (Daniel and Gage, 1966).

B15-3.5.4 Elimination and Excretion

Elimination and excretion of paraquat dichloride occurs through the feces when administered to rats as an oral dose, or in urine, when exposure *via* injection occurs (Daniel and Gage, 1966). After the administration of radiolabeled paraquat, the parent compound was excreted within 2 to 3 days after dosing in feces and within one day after dosing in urine (Daniel and Gage, 1966).

B15-4.6 Exposure Limits

Table B15-18 Existing RfD Values for Paraquat Cation Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Acute/Short-term							
0.00003	Inhalation	U.S. EPA, 1997a	Parameters examined included observations for toxic signs, body weights and food consumption.	Repeated dose inhalation toxicity study,	Hardy *et al*., 1979	0.01 µg/L = 0.0029 Assume a generic adult weights 70 Kg and breaths 20 m^3/day	100
0.0042 (females 13-50 years of age)	Oral	U.S. EPA, 2001	Increased incidence of aveolar histiocytes	3 generation reproduction study	Lindsay *et al.*, 1982	1.25	UF=100 FQPA SF = 3X
0.006	Oral	FAO, 2004	Histopathological changes in the lungs	13 week dog feeding study	--	0.55	100
0.03	Dermal	U.S. EPA, 1997a	Scabbing; slight to well-defined erythema; minimal to moderately severe inflammation; acanthosis; hyperkeratosis (F); and, slight to severe erosion/ulceration and surface exudates	21 day Dermal Toxicity study in rabbits	Cox, 1986	0.3	100
0.0125 (general population including infants and children)	Oral	U.S. EPA, 2001	Increased incidence of aveolar histiocytes	3 generation reproduction study	Lindsay *et al.*, 1982	1.25	UF=100 FQPA SF = 1X
Intermediate- term							
0.03	Dermal	U.S. EPA, 1997a	scabbing; slight to well-defined erythema; minimal to moderately severe inflammation; acanthosis; hyperkeratosis (F); and, slight to severe erosion/ulceration and surface exudates	21 day Dermal Toxicity study in rabbits	Cox, 1986	0.3	100

Table B15-18 Existing RfD Values for Paraquat Cation Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Long-term							
0.004	Oral	WHO, 1986	--	--	--	--	--
0.0045	Oral	U.S. EPA, 1993	Chronic pneumonitis	1 year dog feeding study	Kalinowski *et al*., 1983	0.45	100
0.0045	Oral	U.S. EPA, 1997a	Chronic pneumonitis	1 year dog feeding study	Kalinowski *et al*., 1983	0.45	100
0.0045	Oral	U.S. EPA, 2001	Chronic pneumonitis	1 year dog feeding study	Kalinowski *et al*., 1983	0.45	100
0.005[a]	Oral	FAO, 2004	Chronic pneumonitis	1 year dog feeding study	Kalinowski *et al*., 1983	0.45	100
0.0007	Oral	Health Canada, 2004	--	Diet study in the rat	FAO/WHO, 1983	1.5	--

[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.

FAO (2004) established an acute RfD for paraquat based upon a NOAEL of 0.55 mg/kg/day for histopathological changes in the lungs during a 13 week dog feeding study and an uncertainty factor of 100. The U.S. EPA (2001) however, established an acute RfD of 0.0125 mg/kg/day based upon a NOAEL of 1.25 mg/kg/day during a three generation reproduction study, and an uncertainty factor of 100. An increased incidence of alveolar histiocytes was observed at the next dosage level (3.75 mg/kg/day).

All of the jurisdictions investigated based their chronic RfD values on a one year dog feeding study conducted by Kalinowski *et al*. (1983). RfD values ranged between 0.004 to 0.005 mg/kg/day based upon a systemic NOEL of 0.45mg/kg/day and an uncertainty factor of 100. Chronic pneumonitis was observed at the next dose level (0.93 mg/kg/day).

Table B15-19 Summary of the Toxicological Dose and Endpoints for the Paraquat Cation used in Human Health 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)	LOC for MOE (residential)	Reference
Short- and Intermediate-term dermal [a]	0.0125	Increased incidence of alveolar histiocytes	3 generation reproduction study	1.25	3.75	100	Lindsay *et al*., 1982
Long-term dermal (several months to lifetime)[a]	0.0045	Increase in severity and extent of chronic pneumonitis	1 yr feeding study in dogs	0.45	0.93	100	Kalinowski *et al*., 1983
Inhalation (any time period)	0.00003	Squamous keratinizing metaplasia and/or hyperplasia of the epithelium of the larynx; Increased incidence of alveolar histocytes	21 day inhalation study	0.01[b]	0.1[b]	100	Hardy *et al.*, 1979
Inhalation (any time period)	0.0125	Increased incidence of alveolar histiocytes	3 generation reproduction study	1.25[c]	3.75	100	Lindsay *et al*., 1982

[a] Dermal absorption rate is 0.3% where applicable.
[b] Respirable particles; units of µg/L. Converted to mg/kg/day assuming a body weight of 70 kg and a breathing rate of 20 m^3/day.
[c] Non-respirable particles.
LOC Level of concern.

Based on the general population (Table B15-18) and occupational (Table B15-19) reference doses, the following exposure limits were selected for the risk assessment purposes of this report (Table B15-20).

Table B15-20 Summary of Selected TRVs for Paraquat

Chemical of Concern	TRV Type	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
Paraquat	Acute/Short-term RfD (1-7 days)	Oral	0.0125	Increased incidence of aveolar histiocytes	Oral	U.S. EPA, 2001
		Dermal				
		Inhalation	$3.0x10^{-5}$ [a]	Parameters examined included observations for toxic signs, bodyweights and food consumption.	Inhalation	U.S. EPA, 1997a
	Intermediate-term RfD (1 week to several months)	Oral	NA			
		Dermal	0.03	Increased incidence of aveolar histiocytes	Oral	U.S. EPA, 2001
		Inhalation	$3.0x10^{-5}$ [a]	Parameters examined included observations for toxic signs, bodyweights and food consumption.	Inhalation	U.S. EPA, 1997a
	Long-term RfD (>6 months)	Oral	0.0007	Not reported	Oral	Health Canada, 2004
		Dermal	0.0045	Increase in severity and extent of chronic pneumonitis	Oral	U.S. EPA, 2001
		Inhalation	$3.0x10^{-5}$ [a]	Parameters examined included observations for toxic signs, bodyweights and food consumption.	Inhalation	U.S. EPA, 1997a

[a] Assumed a generic adult weights 70 Kg and breaths 20 m^3/day.

B15-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B15-5.1 Air

B15-5.1.1 Transport and Partitioning

Based on the vapour pressure of paraquat, it will exist predominantly in the particulate phase in the atmosphere. Due to its high solubility, particulate and vapour phase paraquat may be partially removed from the air by rain and snow. Particulate paraquat may also be removed by dry deposition.

Spray drift of paraquat could pose a potential environmental risk as it is extremely biologically active and toxic to plants and animals before it becomes adsorbed to clay particles in the soil (U.S. EPA, 1997b). Due to the tendency of paraquat to bind tightly to soil, transport (post-application) does not occur in the vapour phase but it is tied to sediment transport processes (Amdur *et al*., 1991). For example, during the spraying of cotton fields downwind air samples taken 2 to 4 hours after spraying contained one to 10% of the amount dispersed. No paraquat was detectable in air samples taken five to seven hours after spraying (WHO, 1984).

B15-5.1.2 Transformation and Degradation

No data found.

B15-5.2 Water

B15-5.2.1 Transport and Partitioning

The major route of environmental dissipation of paraquat is adsorption to biological matter and soil clay particles (U.S. EPA, 1997b). Therefore, paraquat could potentially be found in surface water systems associated with soil particles carried by erosion.

Due to an extremely high adsorption coefficient paraquat is not expected to be a contaminant of groundwater. However, a minor photodegradate of paraquat, QINA (4-carboxy-1-methylpyridinium) was determined to be mobile. QINA is not expected to be an environmental concern due to the very slow degradation rate of paraquat (U.S. EPA, 1997b).

B15-5.2.2 Transformation and Degradation

Paraquat does not hydrolyze and is resistant to microbial degradation under both aerobic and anaerobic conditions (U.S. EPA, 1997b). Paraquat is stable at a pH of 5,7 and 9. In addition, based on Henry's Law constant (Table 2-2), volatilization of paraquat from water is not expected to occur (Seiber and Woodrow, 1984).

Paraquat dichloride did not photodegrade when continuously irradiated with a xenon arc lamp for 32 days at 25°C (Parker and Leahey, 1988). Paraquat dichloride accounted for 90.2 to 98% of applied radioactivity throughout the study in both the irradiated and dark control samples. No degradates were identified through TLC or HPLC analyses (Parker and Leahey, 1988). However, 0.15% of the applied radioactivity was recovered as CO_2.

Table B15-21 Half-life of Paraquat in Water

Conditions	Half-life	Reference
Laboratory stream water column settings	13.1 hours to 23 weeks	JW, 2005
Soil:water system	< 2 weeks	U.S. EPA, 1997b

B15-5.3 Sediment and Soil

B15-5.3.1 Transport and Partitioning

The primary route of environmental dissipation of paraquat is adsorption to biological materials and soil clay particles (U.S. EPA, 1997b). Once adsorbed to clay particles paraquat is inactive, as bound residues are environmentally unavailable. This strong affinity for adsorption by soil particles may limit the bioavailability of paraquat to plants, earthworms and microorganisms (JW, 2006). Paraquat dichloride was immobile in silty clay loam, loam, loamy sand and sand soils (Robbins *et al*., 1988). At high application rates $K_{adsorption}$ values ranged from 69 to 50,000 mL/g. Desorption from these soils did not occur (Robbins *et al*., 1988). Paraquat was found not to leach below the 0 to 3.5 inch soil depth after application to loamy sand soil planted with soybeans (U.S. EPA, 1997b).

B15-5.3.2 Transformation and Degradation

Paraquat did not photodegrade when mixed with sterile soil and exposed to natural sunlight for 85 weeks (U.S. EPA, 1997b). Furthermore, paraquat dichloride did not degrade in sandy loam soil incubated under aerobic conditions at 20°C for 180 days. The parent compound comprised 93% of the applied radioactivity at 180 days post-treatment. No degradates were detected through TLC or HPLC analysis and no volatile radioactivity was detected (U.S. EPA, 1997b). Paraquat was found not to degrade in sandy loam soil incubated under anaerobic conditions for 60 days, following a 30-day aerobic incubation. The parent compound comprised 88.8% of the recovered radioactivity at 90 days post-treatment. A trace amount of radioactivity (0.29%) was detected in the water phase. No degradates were reported through TLC or HPLC analyses and no volatile radioactivity was detected (Earl *et al*., 1989).

Paraquat degraded very slowly on loamy sand soil planted with soybeans. Residues decreased from an average of 1.1 mg/kg soil immediately after application to 0.76 mg/kg 86 days after treatment, and remained at 0.42 to 0.50 mg/kg from 296 to 657 days after application (U.S. EPA, 1997b). Due to a low vapour pressure and extremely high adsorption coefficient paraquat is not expected to volatilize once applied to the soil (U.S. EPA, 1997b).

Table B15-22 Half-life of Paraquat in Soil

Conditions	Half-life	Reference
Aerobic laboratory conditions	16 months	JW, 2005
	> 1,000 d (~33 months)	JW, 2005
Field study	13 years	JW, 2005

B15-5.4 Other Environmental Media

B15-5.4.1 Transport and Partitioning

The log K_{ow} for paraquat dichloride is -4.5 at 20°C indicating that bioaccumulation is unlikely (Table 2-2). Paraquat has a bioconcentration factor of 3.162 (JW, 2006).

B15-5.4.2 Transformation and Degradation

Refer to section 4.5 Toxicokinetics.

B15-6.0 SUMMARY

Paraquat is in the quaternary ammonium family of herbicides. Paraquat is an herbicide currently registered for use on aquatic non-food sites, forests and woodlots, terrestrial feed crops, terrestrial food crops, turf, ornamental outdoor and vegetation control for non-food sites (PMRA, 2004). Paraquat was sprayed on designated plots during the U.S. 1967 Trial at CFB Gagetown. Approximately 30 kg of paraquat was applied over an area of 7.3 ha (JW, 2006).

Short-term exposures to paraquats may adversely affect the kidneys, liver, gastrointestinal tract, cardiovascular system and lungs of humans (NIOSH, 2001). These effects may result in impaired functions and tissue lesions including hemorrhage and lung fibrosis. Inhalation of paraquat may cause lung oedema. In addition, paraquat is an irritant to the eyes, skin and the respiratory tract. Exposure to high concentrations of paraquat may also result in death (NIOSH, 2001). Furthermore, prolonged or repeated dermal contact with paraquat may cause dermatitis and nail damage in humans (NIOSH, 2001). The U.S. EPA (1993) has classified paraquat as category C carcinogen (possible human carcinogen) (U.S. EPA, 1997). In 1989, the third Toxicology Branch Peer Review Committee of the U.S. EPA classified paraquat as a category E carcinogen (no evidence of carcinogenicity in animal studies) (U.S. EPA, 1997).

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