B23-1.0 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D)

B23-1.1 Background Information

IUPAC: (2,4-dichlorophenoxy)acetic acid

CAS (2-4-dichlorophenoxy) acetic acid

CASRN: 94-75-7

In 1983, the manufacturing process for 2,4-D was modified, and a production limit of "not detectable at 1 ppb" was established for 2,3,7,8-tetrachlordibenzo-*p*-dioxin (2,3,7,8-TCDD). Based on the current manufacturing process, the precursor phenol (2,4,5-trichlorophenol) that forms 2,3,7,8-substituted isomers is not used to manufacture 2,4-D. Furthermore, as a result of the review in 1981, improved methods of synthesis are employed to lower the levels of non-2,3,7,8-substituted dioxins in 2,4-D. Thus, with refined manufacturing processes, contamination of 2,4-D with dioxins and furans is not seen, nor is it expected (PMRA, 2005).

Contaminants: 2,3,7,8-TCDD (historically)

2,4-D USAGE

2,4-D was first registered in Canada in 1946 and has been labeled for use on lawn/turf since the 1960s. 2,4-D is a systemic chlorophenoxy herbicide used widely in Canada for the control of broadleaf weeds in cereal cropland and on industrial property, lawns, turf, pastures and non-cropland. In addition, 2,4-D is also used to control aquatic weeds.

2,4-D was applied extensively at CFB Gagetown between 1956 and 2000 (JW, 2006). 2,4-D was utilized for 27 years to treat the range and training area (RTA) on a yearly basis. In addition, it was applied in 1966 and 1967 on designated plots during the U.S. trials and CFS tests. Furthermore, in 1990 2,4-D was applied during Dow Chemical trials. In total 290,000 kg of 2,4-D was applied over a total area of 55,000 ha (Table B23-1). 2,4-D was applied as a low volatile ester, amine salt, diamine salt, or butoxy-ethanol ester.

Table 23-1 Usage of 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D) at CFB Gagetown[a,b]

Year	Total 2,4-D Applied (kg)	Total Area Treated (ha)
1956	5,028	1,492
1957	5,290	1,570
1963	52,023	3,706
1964	55,256	3,936
1965	5,033	1,867
1966	15,198	3,468
1967	18,369	4,235
1968	9,921	2,301
1969	6,766	1,502
1970	14,274	3,338
1971	16,800	3,895
1972	17,826	4,133

Table 23-1 Usage of 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D) at CFB Gagetown[a,b]

Year	Total 2,4-D Applied (kg)	Total Area Treated (ha)
1973	15,123	3,506
1974	7,233	1,677
1977	566	132
1978	161	4
1983	1,799	541
1984	8,607	2,990
1985	5,418	1,523
1986	1,026	285
1987	9,720	2,700
1988	2,200	1,134
1989	6,149	1,492
1990	4,080	1,150
1991	4,242	1,178
1993	1,186	824
1994	531	139
2000	56	15
Total	**2.9E+05**	**5.5E+04**

[a] Adapted from Demaree and Haws, 1968; Demaree *et al*., 1966; Demaree and Creager, 1968; Boynton, 1969; and, JW, 2006.

[b] Average maximum yearly application rate (kg/ha).

B23-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_8H_6Cl_2O_3$

Activity: herbicides (phenoxyacetic herbicides); plant growth regulators (auxins)

Notes: When this substance is used as an ester or a salt, its identity should be stated, for example 2,4-D-ammonium [2307-55-3], 2,4-D-butotyl [1929-73-3], 2,4-D-2-butoxypropyl [1320-18-9], 2,4-D-3-butoxypropyl [1928-45-6], 2,4-D-butyl [94-80-4], 2,4-D-diethylammonium [20940-37-8], 2,4-D-dimethylammonium [2008-39-1], 2,4-D-diolamine [5742-19-8], 2,4-D-dodecylammonium [2212-54-6], 2,4-D-2-ethylhexyl [1928-43-4], 2,4-D-heptylammonium [37102-63-9], 2,4-D-isobutyl [1713-15-1], 2,4-D-isoctyl [25168-26-7], 2,4-D-isopropyl [94-11-1], 2,4-D-isopropylammonium [5742-17-6], 2,4-D-lithium [3766-27-6], 2,4-D-meptyl [1917-97-1], 2,4-D-methyl [1928-38-7], 2,4-D-octyl [1928-44-5], 2,4-D-pentyl [1917-92-6], 2,4-D-propyl [1928-61-6], 2,4-D-sodium, 2,4-D-tefuryl [15146-99-3], 2,4-D-tetradecylammonium [28685-18-9], 2,4-D-triethylammonium [2646-78-8], 2,4-D-trolamine [2569-01-9].

Structure:

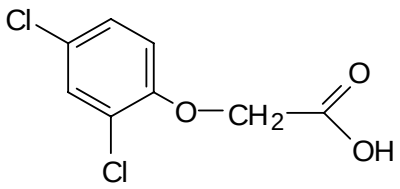

Figure B23-1 2,4-D acetic Acid CASRN 94-75-7

Table B23-2 Chemical and Physical Properties of 2,4-D Acid (Applied as Amine Salts, Dimethylamine Salt, Diethanolamine Salt, or Other Amine Salts)

Chemical/Physical Property	Result	Reference
Dissociation Constant (pKa)	2.73	JW, 2006
	2.8	PMRA, 2005
Henry's Law constant	3.54 x10^{-8} Pa·m^3/mol	JW, 2006
Log K_{ow}	2.81	JW, 2006
Molecular Weight	221.01 g/mol	JW, 2006
Vapour Pressure	8.25x10^{-5} mm Hg at 25°C	JW, 2006
Water Solubility	677 mg/L	JW, 2006

2,4-D can be applied in various forms depending on the individual formulation. For example, 2,4-D can be applied as an amine salt, dimethylamine salt, diethanolamine salt, sodium salt, or low volatile esters (JW, 2006). The low volatile esters of 2,4-D, such as 2,4-D butoxyethyl ester (BEE) have slightly different physical properties than the 2,4-D acid (Table B23-3)

Table 23-3 Chemical and Physical Properties of 2,4-D (Present as Low Volatile Esters)

Chemical/Physical Property	Result	Reference
Henry's Law constant	9.56 x10^{-5} Pa·m^3/mol at 25°C	JW, 2006
Log K_{ow}	6.73	JW, 2006
Molecular Weight	334.26 g/mol	JW, 2006
Vapour Pressure	7.06x10^{-6} mm Hg at 25°C	JW, 2006
Water Solubility	0.0324 mg/L at 25°C	JW, 2006

B23-3.0 PMRA EVALUATION

PMRA (2005) concluded that the use of 2,4-D to treat lawns and turf does not involve an unacceptable risk of harm to human health or the environment. This review examined 2,4-D as an acid, butoxyethyl ester (BEE), ethylhexyl ester (EHE), dimethylamine (DMA) and diethanolamine (DEA). The DEA form of 2,4-D has a different toxicological profile compared to the other forms examined in the PMRA decision document (PMRA, 2005).

B23-4.0 TOXICOLOGICAL SUMMARY

2,4-D is an extensively studied herbicide active ingredient that is constantly under evaluation and review. The following reviews and evaluations have been released by several regulatory agencies:

- Re-registration eligibility decision for 2,4-D (U.S. EPA, 2005);
- Re-evaluation of the Lawn and Turf Uses of (2,4-D) [2,4-D] (PMRA, 2005);
- 2,4-D Integrated Risk Information System (U.S. EPA, 1988);
- Pesticide residues in food: 1996 evaluations Part II Toxicological: 2,4-D (WHO, 1996);
- 2,4-D Canadian Water Quality Guidelines (Health Canada, 1991);
- 2,4-D in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality (WHO, 2003);
- Review report for the active substance 2,4-D (European Commission, 2001);
- The reconsideration of approvals of the active constituent 2,4-D, registrations of products containing 2,4-D and their associated labels: Preliminary Review Findings (Environment) Part 1: 2,4-D Esters, Volume 1: Review Summary and Volume 2: Technical Report (Australian Pesticides and Veterinarian Medicines Authority, 2006); and,
- Report of the Pesticides Board Expert Panel on 2,4-D (New Zealand Pesticides Board, 2000).

Due to the large volume of recent reviews and toxicological summaries on 2,4-D specific toxicological information was only provided for those studies used to derive TRVs established by regulatory agencies. Please refer to these recent reviews for additional information.

B23-4.1 Human Health Effects

Table B23-4 Human Health Effects Resulting from Acute and Chronic Exposure to 2,4-D[a,b]

Exposure	Effects	Response
Acute	Vital Signs	
	HEENT	Eye, nose, and mouth irritation are possible with direct contact.
	Cardiovascular	Tachycardia, bradycardia, ECG abnormalities, asystole, other dysrhythmias, and hypotension have been reported with overdose. Deaths have resulted from cardiorespiratory arrest
	Respiratory	Ingestion of large amounts may cause bradypnea, respiratory failure, hyperventilation, or pulmonary edema.
	Neurologic	Vertigo, headache, malaise, and paresthesias may occur during low dose exposures; Muscle twitching, spasms, profound weakness, polyneuritis, and unconsciousness may occur at higher dose levels. Peripheral neuropathies may occur as an idiosyncratic reaction.
	Gastrointestinal	Nausea, vomiting, and diarrhea have been reported. Necrosis of the gastrointestinal mucosa has been reported.
	Hepatic	Elevated LDH, AST (SGOT), and ALT (SGPT) have been reported.
	Genitournary	Albuminuria and porphyria may occur; renal failure due to rhabdomyolysis is also possible.
	Fluid-Electrolyte	Ingestion of 2,4-D has produced hypocalcemia, hyperkalemia, and hypophosphatemia
	Hematologic	Thrombocytopenia is the primary hematologic effect. Leukopenia has also been reported.
	Dermatologic	Direct contact may cause skin irritation. Chlorodioxin contamination of products may produce chloracne with heavy exposure.
	Musculoskeletal	Muscle cramps, muscle rigidity, elevated creatinine kinase, and rhabdomyolysis were reported after ingestion of MCPP. EMG abnormalities were described in a case of 2,4-D ester exposure.
	Endocrine	Hypoglycemia has been reported in cases of acute 2,4-D poisoning. Animal studies showed decreased T3 and T4 levels, but this effect has not been reported in humans.

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

B23-4.2 Carcinogenicity

IARC

IARC (1987) has classified chlorophenoxy herbicides (including 2,4-D) as possibly carcinogenic to humans (Group 2B). This is based on limited evidence for carcinogenicity to humans and inadequate evidence for carcinogenicity to animals.

Major reviews of 2,4-D in the public domain

Reviews of the toxicology and epidemiology and health effects associated with exposure to 2,4-D have been carried out by several regulatory authorities or have appeared in the scientific and medical literature. Key conclusions of these reports are presented below:

U.S. EPA

Numerous studies on 2,4-D and related chlorophenoxy herbicides and the development of soft-tissue sarcoma and non-Hodgkin's lumphoma have produced conflicting results. A number of experts and expert panels have examined all of the studies in detail and have concluded that while some of the studies suggest a possible association between 2,4-D exposure and an increase in these tumours in humans, other epidemiological studies fail to support this conclusion (PMRA, 2005; U.S. EPA, 2005). In 1996, a U.S. EPA Carcinogenicity Peer Review Committee examined both animal carcinogencity and epidemiology studies using 2,4-D. The committee decided that 2,4-D should remain classified as a Group D carcinogen (not classifiable as to human carcinogenicity). This classification was established by the Committee during a review held in 1992 (U.S. EPA, 2005).

Since the review in 1996 the U.S. EPA has reviewed the epidemiological studies linking cancer to 2,4-D twice. Both reviews conducted in 2004, concluded, that there is no additional evidence to suggest that 2,4-D is a cause of cancer (U.S. EPA, 2005).

PMRA

Since the U.S. EPA Peer Review Committee report was released in 1997 additional epidemiological and animal evidence have been released which also indicate that there is inadequate evidence that 2,4-D is a human carcinogen (Gandhi *et al.*, 2000; Garabrant and Philbert, 2002; De Roos *et al.*, 2003; Alavanja *et al.*, 2002; 2004). The World Health Organization (WHO), the U.S. Department of Agriculture (USDA), the European Commission (EC), and Joint WHO/FAO Meeting on Pesticide Residues are all in agreement that there is no evidence of carcinogenicity in the animal toxicity studies, and that the epidemiology studies do not show a clear association between exposure to phenoxy herbicides and cancer in humans (PMRA, 2005). Therefore, PMRA (2005) also agrees that 2,4-D cannot be classified as to its human carcinogenicity.

Health Canada

Despite the availability of numerous epidemiological studies, it is still inconclusive as to whether or not 2,4-D is carcinogenic. The majority of the studies have dealt with multiple exposures to mixtures of chlorophenoxy herbicides, other pesticides and other organic compounds that focus on three endpoints (soft-tissue sarcomas, non-Hodgkin's lymphoma and Hodgkin's disease) (Health Canada, 1991). Several case control studies suggested a causal association between farming, chlorophenoxy herbicide use and non-Hodgkin's lymphoma. However, these results were not consistent with results from other studies, particularly occupational cohort studies. The association of chlorophenoxy herbicides with soft-tissue sarcomas, commonly attributed to dioxins, is inconsistent and weak (Health Canada, 1991). Limited evidence of carcinogenicity has been observed in animal studies. 2,4-D has therefore been classified in Group III (possibly carcinogenic to humans) in accordance with the classification scheme adopted for drinking water (Health Canada, 1991).

Other Jurisdictions

The Ontario Pesticide Advisory Committee of the Ontario Ministry of the Environment (Anders *et al*., 1987) concluded that there is limited evidence of carcinogenicity in man based on exposure to phenoxyacetic acid herbicides. In addition, evidence for 2,4-D specifically is still regarded as inadequate to classify it as a carcinogen (Anders *et al*., 1987).

A panel at the Harvard School of Public Health (1990) stated that the epidemiological evidence of an association between 2,4-D and non-Hodgkins lymphoma is suggestive and required further investigation (Ibrahim *et al*., 1991). In addition, little evidence was found to associate 2,4-D with soft-tissue sarcoma or Hodgkin's disease, and there was no evidence of an association between 2,4-D and any other type of cancer.

B23-4.3 Populations at Special Risk

There is qualitative evidence of susceptibility of infants and children to 2,4-D. In the rat developmental toxicity study using 2,4-D acid, fetal effects were observed at a dose level that produced less severe maternal toxicity (Taylor, 2000).

There is no evidence of increased susceptibility in the prenatal developmental toxicity study in rabbits or the two generation reproductive study in rats on 2,4-D. In addition, there was no evidence of increased susceptibility during prenatal developmental toxicity studies on rats and rabbits on any of the amine salts or esters of 2,4-D (Taylor, 2000).

B23-4.4 Toxicokinetics

B23-4.4.1 Absorption

2,4-D acid is rapidly and almost completely absorbed (>90%) in mammals within a 48 hour period (European Commission, 2001). In a study, human volunteers were provided with 2,4-D (5 mg/kg as slurry in milk or as a powder chased with water), the mean half-life for 2,4-D absorption were found to be 3.8h in healthy human males (Sauerhoff, 1977). Dermal absorption is considered to be 10% of the oral dose and inhalation absorption is considered to be 100%

(default value) of the oral dose by PMRA (2005).

Human dermal absorption for 2,4-D is better defined than for virtually any other pesticide (Ross *et al.*, 2005). Uncertainty is limited by the there are five human dermal absorption studies where either 2,4-D acid or its dimethylamine salt (DMA) was applied to the forearm or hand. These areas constitute skin surfaces with high potential for exposure for pesticide handlers. The results of these investigations have provided remarkably consistent results despite the fact that they were performed at widely separated points in time, at different laboratories by different personnel on different human subjects (Ross *et al.*, 2005). The percent dermal absorption of 2,4-D applied to the hand, forearm or backhand produced a weighted average of 5.7% (Std Dev 3.4) based on data from studies that applied either the acid or the dimethylamine salt to skin in water, acetone or ethanol (Feldmann and Maibach, 1974; Maibach and Feldmann, 1974; Harris and Solomon, 1992; Moody *et al.*, 1992; Wester *et al.*, 1998; Ross *et al.*, 2005).

Studies in other species have also produced repeatable and consistent findings with several different forms of 2,4-D. Monkeys gave similar (within 2-fold) results to humans when the same free acid or salt was tested at the same anatomic site in each species (Wester and Maibach, 1976; Moody *et al.*, 1990). Rats absorbed about 3-fold more than humans (Pelletier *et al.*, 1989) consistent with results of other pesticides tested in both species (Ross *et al.*, 2001). And rabbits absorbed even more than rats (Moody *et al.*, 1990), which is also consistent with other observations of relative skin permeability between species (Ross *et al.*, 2005).

The U.S. EPA (2005) historically selected a dermal absorption factor of 5.8% based on the average absorbed dose from a human dermal absorption study. However, in order to account for variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 to 10%.

B23-4.4.2 Distribution

Higher distribution of 2,4-D acid was found in the kidneys and the liver in mammals (European Commission, 2001). 2,4-D acid is soluble in water and is expected to distribute widely throughout the body (Garabrant and Philbert, 2002). Its apparent volumes of distribution will also increase with dose, ranging from 143 to 300 ml/kg (Garabrant and Philbert, 2002). At physiological pH (7.4), the parent 2,4-D acid (pKa=3.0) will exist predominately in the ionized form and will not be expected to diffuse across the lipid bi-layer of cellular membranes readily (Berndt and Koschier, 1973; Pritchard, 1980; Kim and O'Tuama, 1981). Hence, active transport of the parent 2,4-D ions are required for cellular entry (Berndt and Koschier, 1973; Pritchard, 1980; Kim and O'Tuama, 1981). Furthermore, 2,4-D acid does not accumulate in tissues and will not cross the blood brain barrier (Clark *et al*., 1975; Tyynela *et al*., 1990). However, some 2,4-D acids have been identified in the central nervous system (European Commission, 2001). This is probably caused by the saturation of the anionic transporter required for the transport of 2,4-D out of the brain (at doses of 100 to 200 mg/kg). The compromise of anionic transported will allow for moderate accumulation of 2,4-D in the parenchyma within the brain and in the cerebrospinal fluids (Elo and Ylitalo, 1977; Tyynela *et al*., 1990; Ylitalo *et al*., 1990). Furthermore, adverse physiological response within the brain (focal vascular damage) was observed within mammals that received high dosages (300 to 600mg/kg) of 2,4-D (Elo *et al*., 1988). This indicates the compromise of the blood brain barrier along with discharge (extravasation) of albumin in the medulla oblongata and cortex (Elo *et al*., 1988).

B23-4.4.3 Metabolism

The salts and esters of 2,4-D will uniformly undergo acid or enzymatic hydrolysis *in vivo* to produce 2,4-D acid (Garabrant and Philbert, 2002). Since around 97% of 2,4-D is excreted unchanged, only minor conjugation is expected to occur that will produce 2,4-D metabolites (European Commission, 2001). In rats that received subcutaneous injections of 2,4-D butyl ester, taurine and glycine conjugates of 2,4-D were frequently found (Grunow and Bohme, 1974). In human workers that was exposed to 2,4-D esters, acid-hydrolyzable conjugates were found in the urine (Sauerhoff, 1977). However, in other human studies, no 2,4-D conjugates were identified using gas chromatography (35). Reactive intermediates of 2,4-D metabolism have not been identified in any species to date (Garabrant and Philbert, 2002). However, renal transport of 2,4-D can be rapidly saturated due to the fact that 2,4-D can exceed the anion transport capacity of the organic anion kidney transporters of some mammals(Garabrant and Philbert, 2002). Generally, the metabolic fate of 2,4-D and its esters is independent of dose or gender of the animal (WHO, 1996; Dryzga *et al*., 1992).

B23-4.4.4 Elimination and Excretion

2,4-D is primarily (>90%) excreted *via* the renal route in mammals. However, at higher dosages, 2,4-D and its metabolites can appear in the feces (Garabrant and Philbert, 2002). Furthermore, human studies revealed that excretion of 2,4-D and its metabolites is also through the urinary route following first-order kinetics (Sauerhoff, 1977).

The Pharmacokinetics of 2,4-D exposed through the dermal route is different from the oral exposure. Blood concentrations of 2,4-D in mammals tend to plateau between 2 and 8 hours after dermal exposure, which is followed by rapid decline in its blood concentrations (Pelletier *et al*., 1989). 2,4-D's plasma clearance after dermal exposure will follow biphasic kinetics. With first phase occurring after 8 hour after initial exposure and a second face occurring after 25 to 29 hours (Garabrant and Philbert, 2002). 2,4-D's half life ranges between 0.6 to 2.3 hours in the first phase, and 25 to 29h in the second phase (Garabrant and Philbert, 2002). It has been found that the kinetics of the second phase represent a dermal reservoir of 2,4-D, which contributes to a slowed increase in plasma clearance during later phases of elimination (Garabrant and Philbert, 2002).

B23-4.5 Exposure Limits

Table B23-5 Existing RfD Values for 2,4-D Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Acute/Short-term (1-7 days)							
0.025 (Females 13-49)	Oral	U.S. EPA, 2005	Skeletal abnormalities	Rat Development Toxicity	Rodwell *et al*., 1983; Nemec *et al*., 1983	25	1,000
0.067 (General population)	Oral	U.S. EPA, 2005	Gait abnormalities	Acute Neurotoxicity in Rats	Mattsson *et al*., 1994	67	1,000
0.08 (Females 13-50)	Oral	PMRA, 2005	Increased skeletal variations	Rat developmental		25	300
0.25 (General population)	Oral	PMRA, 2005	Increased in-coordination and slight gait abnormalities	Acute rat neurotoxicity	NR	75	300
Intermediate-term (7 days- Several months)							
No Information found.							
Long-term (6 months to lifetime)							
0.003[a]	Oral	PMRA, 2005	Kidney effects	2 year rat study	NR	1.0	300
0.017	Oral	PMRA, 2007	-	-	-	-	-
0.005	Oral	U.S. EPA, 2005	Decreased body-weight gain (F) and food consumption (F); alterations in hematology, and clinical chemistry parameters; decreased T4, glucose (F), cholesterol and triglycerides (F)	Rat Chronic toxicity study	Jeffries *et al*., 1995	5.0	1,000

Table B23-5 Existing RfD Values for 2,4-D Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
0.01	Oral	WHO, 1996	Changes in serum chemistry and lesions in kidney and liver Renal lesions	1 year dog toxicity study; Two year rat study	Dalgard, 1993 Serota, 1986	1.0	100
0.01[b]	Oral	U.S. EPA, 1988	Hematologic, hepatic and renal toxicity	90 day rat oral bioassay; 1 year Interim report from a 2 year rat oral bioassay	Dow Chemical Co., 1983	1.0	100
0.01[a]	Oral	Health Canada, 1991; 2004	Tubular cell pigmentation in the kidney	Two year dietary toxicity/ oncogenicity study in rats	Industry task force on 2,4-D research data, 1986	1.0	100
0.05[a]	Oral	EC, 2001	Kidney/histopathology	Long term rat/mouse study	NR	5.0	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.

[b] U.S. EPA (1988) classified the study as medium, and has medium confidence in the RfD.

NR Reference was not provided.

To establish reference values, the PMRA utilized a standard safety factor of 100 (10x for interspecies variation and 10x intraspecies variation) in addition to a 3x safety factor to protect for potential sensitivity of the young noted in a series of published neurotoxicity studies (PMRA, 2005). The U.S. EPA (2005) applied an uncertainty factor of 1,000 (10x intraspecies variability, 10x interspecies variability, 10x database uncertainty) to determine both acute and chronic RfDs in some cases; however, in IRIS (U.S. EPA, 1988) an uncertainty factor of 100 was applied (10x interspecies variability, 10x interhuman variability). PMRA (2007) have indicted that a re-evaluation of the chronic oral toxicity of 2,4-D, to be released in the spring of 2007, will indicated an oral TRV of 0.017 mg/kg/day.

Table B23-6 Summary of the Toxicological Dose and Endpoints for 2,4-D Acid, DMA and EHE used in the 2,4-D Lawn/turf Risk Assessment Conducted by PMRA (2005)

Exposure Scenario	Reference Dose (mg/kg/day)	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for MOE (residential)
Dermal and Inhalation[a] Short-term (1-7 day) (Females 13-50)	0.03	Increased maternal deaths and morbidity	Rabbit developmental	30	90	1,000
Dermal and Inhalation[a] Short-term (1-7 day) (General population)	0.04	Decreased body-weight gain	Rat developmental	12.5	50	300
Incidental oral Short-term (1-7 day) (Toddlers)	0.04	Decreased body-weight gain	Rat developmental	12.5	50	300
Dermal and Inhalation[a] Short-term (8-30 day) (Females 13-50)	0.03	Increased maternal deaths and morbidity	Rabbit developmental	30	90	1,000
Dermal and Inhalation[a] Short-term (8-30 day) (General population)	0.04	Decreased body-weight gain	Rat developmental	12.5	50	300
Aggregate (1-7 day) all routes (Females 13-50)	0.03	Increased maternal deaths and morbidity	Rabbit developmental	30	90	1,000
Aggregate (1-7 day) all routes (General population)	0.04	Decreased body-weight gain	Rat developmental	12.5	50	300

[a] A dermal absorption value of 10% was incorporated into the dermal estimates of exposure for all scenarios.

The PMRA considers 2,4-D butylethyl ester (BEE) to be toxicologically equivalent to 2,4-D acid (PMRA, 2006). Therefore, the toxicological endpoints for 2,4-D BEE are the same as those selected for 2,4-D acid. However, the NOAEL was lower in the rabbit developmental study conducted with 2,4-D BEE (10 *vs*.30 mg/kg/day). As a result the risk assessment toxicological

endpoints for some exposure routes to females (13 to 50) were different (Table B23-7). All other endpoints remained the same as the acid (PMRA, 2005).

Furthermore, PMRA does not consider the diethyl acid (DEA) form of 2,4-D to be toxicologically equivalent to the other forms of 2,4-D. Additional information regarding this form has been submitted to PMRA for consideration. Mitigation measures of the DEA from of 2,4-D may be proposed at a later date (PMRA, 2005).

Table B23-7 Summary of the Toxicological Dose and Endpoints for 2,4-D BEE used in the 2,4-D Lawn/turf Risk Assessment Conducted by PMRA (2005)

Exposure Scenario	Reference Dose (mg/kg/day)	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for MOE (residential)
Dermal and Inhalation Short-term (1-7 day) (Females 13-50)	0.01	Increased maternal deaths and morbidity	Rabbit developmental	10	30	1,000
Dermal and Inhalation Short-term (8-30 day) (Females 13-50)	0.01	Increased maternal deaths and morbidity	Rabbit developmental	10	30	1,000
Aggregate (1-7 day) all routes (Females 13-50)	0.01	Increased maternal deaths and morbidity	Rabbit developmental	10	30	1,000

Table B23-8 Summary of the Toxicological Dose and Endpoints for 2,4-D used in Human Risk Assessment by the U.S. EPA (2005)

Exposure Scenario	Reference Dose	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for MOE	Reference
Oral Short-term incidental (1-30 day)	0.025	Decreased maternal body-weight gain	Rat developmental toxicity	25	75	1,000	Rodwell *et al*., 1983; Nemec *et al*., 1983
Oral Intermediate-term incidental (1-6 months)	0.015	Decreased body weight/body weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation	Rat Subchronic oral	15	100	1,000	Schulze, 1991a,b,c
Dermal[a] Short-term	0.025	Decreased maternal body-weight gain and skeletal abnormalities	Rat Developmental study	25	75	1,000	Rodwell *et al*., 1983; Nemec *et al*., 1983
Dermal[a] Intermediate-term	0.015	Decreased body weight/body weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation	Rat Subchronic oral	15	100	1,000	Schulze, 1991a,b,c
Dermal[a] Long-term	0.005	Decreased body-weight gain (F) and food consumption (F); alterations in hematology, and clinical chemistry parameters; decreased T4, glucose (F), cholesterol and triglycerides (F)	Rat Chronic toxicity study	5	75	1,000	Jeffries *et al*., 1995
Inhalation[b] Short-term	0.025	Decreased maternal body-weight gain and skeletal abnormalities	Rat Developmental study	25	75	1,000	Rodwell *et al*., 1983; Nemec *et al*., 1983

Table B23-8 Summary of the Toxicological Dose and Endpoints for 2,4-D used in Human Risk Assessment by the U.S. EPA (2005)

Exposure Scenario	Reference Dose	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for MOE	Reference
Inhalation[b] Intermediate-term	0.015	Decreased body weight/body weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation	Rat Subchronic oral	15	100	1,000	Schulze, 1991a,b,c
Inhalation[b] Long-term	0.005	Decreased body-weight gain (F) and food consumption (F); alterations in hematology, and clinical chemistry parameters; decreased T4, glucose (F), cholesterol and triglycerides (F)	Rat Chronic toxicity study	5	75	1,000	Jeffries *et al*., 1995

[a] The dermal absorption rate is 5.8%.
[b] The inhalation absorption rate is 100%.

Based on the general population (Table B23-5) and occupation (Table B23-6,7,8) reference doses, the following exposure limits were selected for the risk assessment purposes of this report (Table B23-9).

Table B23-9 Summary of the Selected TRVs for 2,4-D

COC	TRV Type[a]	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
2,4,-D	Short-term RfD	Oral / Dermal / Inhalation	0.04	Decreased body-weight gain	Oral	PMRA, 2005
	Intermediate-term RfD	Oral	0.015[b]	Decreased body weight/body weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation	Oral	U.S. EPA, 2005
		Dermal / Inhalation	0.01[cd]	Increased maternal deaths and morbidity	Oral	PMRA, 2005
	Long-term RfD	Oral	0.017	-	Oral	PMRA, 2007
		Dermal / Inhalation	0.005	Decreased body-weight gain (F) and food consumption (F); alterations in hematology, and linical chemistry parameters; decreased T4, glucose (F), cholesterol and triglycerides (F)	Oral	U.S. EPA, 2005

[a] Exposure durations were as follows unless otherwise indicated: short-term RfD (1 to 7 days); intermediate-term RfD (7 day to several months); Long-term RfD (6 months to lifetime.
[b] Exposure duration of 1 to 6 months.
[c] Acute dietary RfD for females 13 to 50 years of age.
[d] Exposure duration of 8 to 30 days.
[e] Acceptable Daily Intake (ADI).

B32-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B23-5.1 Air

B23-5.1.1 Transport and Partitioning

2,4-D may contaminate the atmosphere due to volatilization and drift from spray application. In the atmosphere 2,4-D residues are typically found in the form of isopropyl and butyl esters (Health Canada, 1991).

B23-5.1.2 Transformation and Degradation

2,4-D is removed from the atmosphere through photooxidation and rainfall, with a half life of less than one day (Health Canada, 1991).

B23-5.2 Water

B23-5.2.1 Transport and Partitioning

The extent to which 2,4-D will leach into groundwater is inversely related to the organic matter content and directly related to the soil pH (Health Canada, 1991). 2,4-D is not expected to accumulate in bottom sediments or muds in aqueous environments (Health Canada, 1991).

Despite the short half-life of 2,4-D in soil and aquatic environments, the compound has been detected in groundwater supplies and at very low concentrations in surface water (JW, 2005).

B23-5.2.2 Transformation and Degradation

2,4-D esters are rapidly hydrolyzed in alkaline aqueous environments, and 2,4-D amine salts rapidly dissociate in water (U.S. EPA, 2005). However, 2,4-D esters may persist under sterile acidic aquatic conditions.

2,4-D is rapidly biodegraded in water, however, some degradation may be a result of photolysis occurring at the surface (Health Canada, 1991).

Microoganisms readily break down 2,4-D in aqueous environments. The rate of breakdown is directly proportional to the amount of nutrients, sediment load and dissolved organic carbon.

Table B23-10 Half-life of 2,4-D in Water

Conditions	Half-life	Reference
Oxygenated	~7-21 day	JW, 2005
Aerobic	15 day	U.S. EPA, 2005
Anaerobic	41-333 day	U.S. EPA, 2005
Anaerobic	80-120 day	Health Canada, 1991

B23-5.3 Sediment and Soil

B23-5.3.1 Transport and Partitioning

2,4-D has a low binding affinity (K_{ad} <3 and K_{de}<1) in mineral soils and sediment. The mobility of 2,4-D in supplemental thin layer chromatography (TLC) studies were classified as intermediately mobile to very mobile in "sieved" mineral soils (U.S. EPA, 2005).

Table B23-11 Freundlich Kads and K_{oc} Values for 2,4-D in Various Soil Types

Soil Type	K_{oc} (mL/g)	Freundlich K_{ads} values
Sandy loam	70	0.17
Sand	76	0.36
Silty clay loam	59	0.52
Loam	117	0.28

B23-5.3.2 Transformation and Degradation

2,4-D esters are rapidly hydrolyzed in moist soils into the free acid (Health Canada, 1991; U.S. EPA, 2005). The free acid is rapidly degraded in soil under many environmental conditions. However, 2,4-D esters may persist on dry soil.

2,4-D is eliminated from the soil mainly through biodegradation (Health Canada, 1991).

2,4-D has low soil persistence. Soil microbes are primarily responsible for its disappearance (JW, 2006).

Table B23-12 Half-life of 2,4-D in Soil

Conditions	Half-life	Reference
Moist soil types	4-7 d	Health Canada, 1991
	<7 d	JW, 2005
Aerobic mineral soils	6.2 d	U.S. EPA, 2005
Acidic soils	~ 42 d	Health Canada, 1991

B23-5.4 Other Environmental Media

B23-5.4.1 Transport and Partitioning

2,4-D has a bioconcentration factor of 3.162 when present as amine or sodium salts, however, as a low volatile ester 2,4-D has a BCF of 30,570 (JW, 2006).

B23-5.4.2 Transformation and Degradation

Refer to Section B23-4.4 Toxicokinetics.

B23-6.0 SUMMARY

2,4-D was first registered in Canada in 1946 and has been labeled for use on lawn/turf since the 1960s. 2,4-D is a systemic (auxin like growth regulator), chlorophenoxy herbicide used widely in Canada. The main uses of 2,4-D include the control of broadleaf weeds in cereal cropland, industrial properties, lawns, turfs, and pastures. In addition, 2,4-D can also be used to control aquatic weeds. Between 1986 and 2000, approximately 290,000 kg of 2,4-D was applied over an area of 55,000 ha at CFB Gagetown (JW, 2006). While 2,4-D is an acid, it can also be applied as an amine salt, dimethylamine salt, diethanolamine salt, sodium salt, or low volatile esters (JW, 2006). The low volatile esters of 2,4-D, such as 2,4-D butoxyethyl ester (BEE) have slightly different physical properties than the 2,4-D acid.

Low acute toxicity was associated with 2,4-D exposures through all three routes (oral, dermal and inhalation) of exposure in rodents (U.S. EPA, 2005). Severe eye irritation was associated with human accidental exposures to 2,4-D. Long-term rodent studies demonstrated that 2,4-D would lead to fluctuations in body weight and blood chemistry. Furthermore, reproductive/developmental effects such as decreased maternal weight gain and skeletal abnormalities in the fetus were observed. IARC (1987) classified chlorophenoxy herbicides (including 2,4-D) as possible carcinogens in humans (Group 2B). However, numerous carcinogenicity studies on 2,4-D and related chlorophenoxy herbicides have produced conflicting results (PMRA, 2005; U.S. EPA, 2005). In 1996, U.S. EPA classified 2,4-D as a Group D carcinogen (not classifiable as a human carcinogen) (U.S. EPA, 2005). Similarly, PMRA (2005) has agreed that 2,4-D cannot be classified as a human carcinogen. Health Canada, in 1991, classified 2,4-D in Group III (possibly carcinogenic to humans) in accordance with the classification scheme adopted for drinking water (Health Canada, 1991).

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