APPENDIX B

TOXICOLOGICAL PROFILES

APPENDIX B

TOXICOLOGICAL PROFILES

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B-1.0 APPENDIX B DATA INCLUSION CRITERIA

Toxicological information on herbicides was compiled for the human health risk assessment (HHRA) of the Canadian Forces Base in Gagetown, New Brunswick, Canada.

B-1.1 Overview

The hazard or toxicity assessment methodology was based on the fundamental dose response principle. That is, the response of biological systems to chemical exposure increases in proportion to the concentration of chemicals in critical target tissues, where adverse effects may occur. Hazard assessment involves the identification of the potentially toxic effects of chemicals, and the determination of the maximum chemical dose that humans can receive without experiencing adverse health effects. In addition, the hazard assessment results in identification of exposure limits, [*i.e.*, the amount of chemical exposure that can occur without any adverse health effects (threshold chemicals), or that is associated with an acceptable level of risk (non-threshold chemicals)].

B-1.1.1 Purpose of Toxicological Profiles

The primary purpose of the toxicological profiles was to provide a summary of relevant human health toxicity data for all the herbicide active ingredients that were used. In addition, the profiles will provide the following:

- Relevant exposure limits (TRVs) for assessing health risks of the herbicide active ingredients within the HHRA;
- Information on the physical/chemical properties of each herbicide, general fate and transport properties and levels in typical environments; and,
- Information on ranges of effects observed, and factors that modify toxicity.

B-1.1.2 Methodology Used to Develop the Toxicological Profiles

The toxicological profiles were completed using data in the scientific literature and regulatory reviews. The exposure limits employed in the current assessment were obtained from regulatory agencies including Ontario Ministry of the Environment (OMOE), Health Canada, the Canadian Council of the Ministers of the Environment (CCME), the World Health Organization (WHO), the United States Environmental Protection Agency (U.S. EPA) and the Pest Management Regulatory Agency (PMRA). When toxicity data for a particular active ingredient were available from multiple regulatory agencies, all exposure limits were reviewed and professional judgement was used to select the most appropriate regulatory exposure limit for the current assessment.

The most critical considerations in selecting TRVs were the source (it must be derived by a reputable agency), the date it was derived (it must be as up to date as possible) and its relevance in terms of duration and route of exposure.

B-1.1.3 Factors to Consider when Reviewing the Toxicological Profiles

Certain factors should be considered when interpreting the data contained within the toxicological profiles. For example, not all herbicide active ingredients have reliable human-based toxicological data. The HHRA must rely on laboratory animal-to-human extrapolation as some of the available toxicological reference values were derived from laboratory animal studies. Due to the use of regulatory documents toxicity categories as defined by the U.S. EPA are defined in Table B-1.

Table B-1 Toxicity Categories

Type of Study	Category I	Category II	Category III	Category IV
Acute Oral	Up to and including 50 mg/kg	> 50 thru 500 mg/kg	> 500 thru 5,000 mg/kg	> 5,000 mg/kg
Acute Dermal	Up to and including 200 mg/kg	> 200 thru ,2000 mg/kg	> 2,000 thru ,5000 mg/kg	> 5,000 mg/kg
Acute Inhalation (4hr)	Up to and including 0.05 mg/liter ($\leq$ 0.05 µg/m^3)	> 0.05 thru 0.5 mg/liter (>0.05 – 0.5 µg/m^3)	> 0.5 thru 2 mg/liter (> 0.5 thru 2 µg/m^3)	> 2 mg/l (> 2 µg/m^3)
Primary Eye Irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or other eye irritation clearing in 8-21 days	Corneal involvement or other eye irritation clearing in 7 days or less	Minimal effects clearing in less than 24 hours
Primary Skin Irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	Mild or slight irritation at 72 hours (no irritation or slight erythema)

B1-1.0 BROMACIL

B1-1.1 Background Information

IUPAC: 5-bromo-3-sec-butyl-6-methyluracil

CAS: 5-bromo-6-methyl-3-(1-methylpropyl)-2,4(1H,3H)-pyrimidinedione

CASRN: 314-40-9

BROMACIL LITHIUM SALT

IUPAC: lithium (*RS*)-5-bromo-1-*sec*-butyl-4-methyl-6-oxo-1,6-dihydropyrimidin-2-olate

CAS: 5-bromo-6-methyl-3-(1-methylpropyl)-2,4(1*H*,3*H*)-pyrimidinedione lithium salt

CASRN: 53404-19-6

BROMACIL USAGE

Bromacil was first registered by the U.S. EPA in 1961. It is a broad-spectrum herbicide used to control broadleaf weeds, grasses and brush on non-cropland areas. Some of these non-cropland uses include: drainage systems, outdoor industrial areas, rights-of-way/fence rows/hedge rows, paved area, non-agricultural uncultivated areas and power stations.

Bromacil, which is one of the active ingredients in Krovar®, was applied once at Gagetown in 1994. Krovar® is mainly root absorbed, and has activity on many annual and perennial broadleaf and grass weed species (DuPont, 2006). Krovar® has the ability to control young weeds; however, a knockdown herbicide is required for established weeds (DuPont, 2006).

Bromacil was utilized in 1994 year to treat the range and training area (RTA) in CFB Gagetown (Table B1-1).

Table B1-1 Bromacil Usage at CFB Gagetown (JW, 2006)

Year	Total Bromacil Applied (kg)	Total Area Treated (ha)
1994	2.6E+03	3.6E+02

B1-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_9H_{13}BrN_2O_2$

Activity: Substituted Urea [inhibits photosynthesis]

Notes:

Structure:

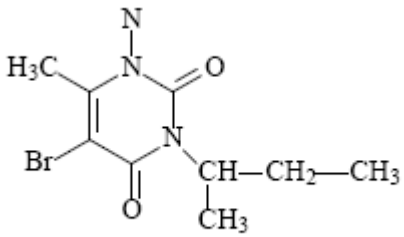

Figure B1-1 Bromacil [CAS No. 341-40-9] Structure

Table B1-2 Chemical and Physical Properties of Bromacil

Chemical/Physical Property	Result	Reference
Colour/Form	White to light tan; crystalline solid at 25°C	U.S. EPA, 1996
Dissociation Constant (pKa)	9.3	JW, 2006
Henry's Law constant	$1.29x10^{-10}$ at 25°C	JW, 2006
Log K_{ow}	1.53 (pH 5); 1.88 (pH 7); 1.63 (pH 9)	JW, 2006
Melting Point	158-159°C at 760 mm Hg	U.S. EPA, 1996
Molecular Weight	261.12	U.S. EPA, 1996; JW, 2006
Vapour Pressure	$3.07x10^{-7}$ mm Hg at 20°C	JW, 2006
Water Solubility	815 mg/L at 25°C	U.S. EPA, 1996; JW, 2006

B1-3.0 PMRA EVALUATION

PMRA (2004) re-evaluated Bromacil under the PMRA Re-evaluation Program 1. Bromacil is currently not registered for any food or feed crops in Canada, therefore, there are no maximum residue limits specified for bromacil. Currently, any residues of bromacil on food imported into Canada must not exceed 0.1ppm (PMRA, 2004).

B1-4.0 TOXICOLOGICAL SUMMARY

The following toxicological profile for bromacil is a short summary based on the U.S. EPA RED document, in accordance with PMRA. Only the toxicological studies appropriate for guideline development were highlighted below.

B1-4.1 Human Health Effects

Table B1-3 Human Health Effects Resulting from Acute Exposure to Urea-substituted Herbicides [a,b]

Exposure	Effects	Response
Acute	HEENT	Eye exposure may result in ocular irritation. Irritation of the respiratory mucous membranes may be noted following prolonged heavy contact.
	Cardiovascular	CNS depression and hypoxemia may be noted if methemoglobinemia is present.
	Gastrointestinal	Nausea, vomiting, and diarrhea may be noted following ingestion.
	Genitournary	Some metabolites may cause irritation of the urinary tract.
	Hematologic	Methemoglobinemia may result from effects of metabolites of some urea-based herbicides.
	Dermatologic	Cyanosis unresponsive to oxygen therapy may be noted in patients with methemoglobinemia due to absorption of excessive amounts of these agents.

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

B1-4.2 Health Effects by Route of Exposure

B1-4.2.1 Oral Exposure

Acute toxicity of bromacil through oral exposure was categorized in the lowest possible toxicity category (Toxicity Category IV) (U.S. EPA, 1996).

Single exposure of rabbits to Bromacil *via* ingestion resulted in incoordination, salivation, vomiting, weakness, and tearing and dilated pupils (DuPont, 2005). Repeated exposure caused liver changes, increased liver, adrenal, and heart weights, decreased kidney and spleen weights, and thyroid changes. Long-term exposure caused reduced weight gain, slight thyroid effects and liver effects (DuPont, 2005).

Table B1-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Bromacil

Test Type	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute	Rat (F)	3,998	U.S. EPA, 1996
	Rat (M)	5,126	U.S. EPA, 1996

Table B1-5 General Effects Resulting from Oral Exposure to Bromacil

Test Organism (Species)	Exposure	Dose (mg/kg/day) (Duration)	Response	Reference
Chronic				
Mice (CD-1)(M)	Diet	40 (18 months)	Increased incidence in hepatocellular hypertrophy, single cell and centrilobular necrosis, hepatocellular lysis with RBC accumulation, and centrilobular vacuolation	Kaplan *et al*., 1980

Table B1-5 General Effects Resulting from Oral Exposure to Bromacil

Test Organism (Species)	Exposure	Dose (mg/kg/day) (Duration)	Response	Reference
Rat (Cr1:CD) (M/F)	Diet	103-144 (2 years)	Decreased body weight gain; increased incidence of cystic follicles and ultimo-branchial cysyts (of or pertaining to the fifth pharangeal pouch) of the thyroid (M); increased incidence of epithelial hyperplasia of the thymus (F).	Bogdanffy, 1989
Dog (Beagle) (M/F)	Diet	17.3-17.8 (1 year)	Decreased body weight gain	Bogdanffy, 1991

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

Table B1-6 Reproductive and Developmental Effects Resulting from Oral Exposure to Cacodylic Acid

Test Organism (Species)	Exposure	Dose (mg/kg/day) (Duration)	Response	Reference
Rabbit (NZW)	Gavage	500 (gestation days 7-19)	Significant increase in the mean percentage of skeletal variations	Zellers, 1987

B1-4.2.1.1 No Observed Adverse Effect Levels

Table B1-7 NOAELs and LOAELs for Oral Exposure to Bromacil[a]

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Chronic				
Mice (CD-1) (M)	LOAEL	40	Liver effects	Kaplan *et al.*, 1980
Rat (Cr1:CD) (M/F)	LOAEL	103-144	Decreased body weight gain	Bogdanffy, 1989
Rat (Cr1:CD) (M/F)	NOAEL	9.82-13.3	General toxicity (decreased body weight gain)	Bogdanffy, 1989
Dog (Beagle) (M/F)	LOAEL	17.3-17.8	Decreased body weight gain	Bogdanffy, 1991
Dog (Beagle) (M/F)	NOAEL	4.6-4.65	General toxicity (decreased body weight gain)	Bogdanffy, 1991

[a] Obtained from U.S. EPA, 1996.

Table B1-8 Bromacil Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Rat (Cr1:CD BR)	LOAEL	75	Maternal toxicity (decreased body-weight gain and food consumption during the first two days of dosing)	Alvarez, 1988
Rat (Cr1:CD BR)	LOAEL	125 (2 generation reproductive study)	Parental toxicity (increased incidence of hydronephrosis)	Miller, 1991

Table B1-8 Bromacil Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Rat (Cr1:CD BR)	LOAEL	200	Developmental toxicity (increased incidence of rudimentary lumbar ribs and extra thoracic vertebrae	Alvarez, 1988
Rat (Cr1:CD BR)	NOAEL	12.5 (2 generation reproductive study)	Parental toxicity	Miller, 1991
Rat (Cr1:CD BR)	NOAEL	20	Maternal toxicity	Alvarez, 1988
Rat (Cr1:CD BR)	NOAEL	75	Developmental toxicity	Alvarez, 1988
Rat (Cr1:CD BR)	NOAEL	>125	Reproductive toxicity	Miller, 1991
Rabbit (NZW)	LOAEL	300	Maternal toxicity (Decreased body-weight gain and food consumption); Developmental toxicity (increase in the percentage of late post-implantation loss)	Zellers, 1987
Rabbit (NZW	NOAEL	100	Maternal and developmental toxicity	Zellers, 1987

[a] Obtained from U.S. EPA, 1996.

B1-4.2.2 Dermal Exposure

Acute toxicity of bromacil through dermal exposure was categorized in the lowest possible toxicity category (Toxicity Category IV) (U.S. EPA, 1996). Rabbits exposed dermally to bromacil did not show any clinical signs of toxicity, and no gross tissue changes were observed (DuPont, 2005). Bromacil is a mildly irritating to the eye (U.S. EPA, 1996).

Table B1-9 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Bromacil

Test Type	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute	Rabbit	>5,000	U.S. EPA, 1996

B1-4.2.3 Inhalation Exposure

Acute toxicity of bromacil through inhalation exposure was categorized in the lowest possible toxicity category (Toxicity Category IV) (U.S. EPA, 1996). Exposure of rabbits to a single dose of bromacil *via* inhalation resulted in rapid and deep respiration (DuPont, 2005). Repeated exposure caused slightly increased platelet counts, lower serum cholesterol, and slightly increased liver weights in some animals. The remaining animals remained normal after a 14-day exposure (DuPont, 2005).

Table B1-10 Mammalian LC50 Value Resulting from Inhalation Exposure to Bromacil

Test Type	Test Organism (Species/Sex)	LC50 (mg/L)	Reference
Acute	Rat	>14.4	U.S. EPA, 1996

B1-4.3 Carcinogenicity

The U.S. EPA (1996) classified bromacil as Group C; possible human carcinogen. This decision was based on the increased incidence of liver tumours in male mice, and positive trends in thyroid tumours in male rats. An analysis of structural activity relationship to similar compounds was also considered. Bromacil is not considered mutagenic (U.S. EPA, 1996). The U.S. EPA (1996) recommended that the Reference Dose (RfD) approach be used for the quantification of human risk to bromacil.

Table B1-11 Animal Carcinogenicity Data[a]

Test Subjects	Exposure	Dose (mg/kg/day)	Response	Reference
Mice (CD-1) (M)	Diet	871 (18 months)	Significant increase in combined hepatocellular adenomas and/or carcinomas; significant dose-related trend for hepatocellular carcinoma and for combined hepatocellular adenomas and/or carcinoma	Kaplan *et al*., 1980
Rat (Cr1:CD (M)	Diet	103 (2 years)	Increased trends in thyroid C-cell adenomas and thyroid follicular cell adenomas and/or carcinomas combined	Bogdanffy, 1989

[a] Obtained from U.S. EPA, 1996.

B1-4.4 Populations at Special Risk

Developmental studies have indicated that developmental effects occurred at doses that were the same or higher than doses that cause maternal toxicity (U.S. EPA, 1996). No effects on reproductive performance were observed in the two generation rat study. The developmental and reproduction toxicity studies for bromacil did not indicate any additional sensitivity of young organisms to bromacil (U.S. EPA, 1996). It was concluded that women and children are not at special risk to bromacil exposure.

B1-4.5 Toxicokinetics

B1-4.5.1 Absorption

Bromacil was readily absorbed from the gastrointestinal tract by rats during a metabolism study (McCooey, 1989).

Dermal absorption

The U.S. EPA (1996) established an interim estimate of 20% dermal absorption for bromacil. This value was estimated using a non-guideline absorption study and surrogate data from other pesticides. A 1965 skin absorption study, in rabbits, estimated the dermal absorption of bromacil during a workday to be 4.6% (U.S. EPA, 1996). Literature searches for *in vitro* human absorption values however, suggest an absorption rate of 14% for 5-fluorouracil, a surrogate substituted uracil. Therefore, an interim value of 20% was currently accepted until further dermal studies can be conducted (U.S. EPA, 1996).

B1-4.5.2 Distribution

After administration of radio-labeled bromacil to rats through single and multiple doses, radio label was found in all of the tissues examined; however, there was no evidence of accumulation (McCooey, 1989).

B1-4.5.3 Metabolism

Bromacil was extensively metabolized in rats by hydroxylation at the 6-methyl position and on the sec-butyl moiety (McCooey, 1989).

B1-4.5.4 Elimination and Excretion

The majority of radiolabeled bromacil administered to rats in single (low or high) and multiple doses (low) was rapidly excreted through the urine, except for multiple low dose males where excretion in the urine and feces was equal (McCooey, 1989). The major metabolite of bromacil in the urine of rats was 5-bromo-6-hydroxylmethyl-3-sec-butyl-uracil. Trace levels of the parent compound and two other unidentified metabolites were also excreted through the urine (McCooey, 1989).

B1-4.6 Exposure Limits

Table B1-12 Existing RfD Values for Bromacil 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)							
Not Required	Oral	U.S. EPA, 1996	Acutely toxic effects are not expected at concentrations of bromacil which are likely to be found in food	--	--	--	--
Intermediate-term (1 week to several months)							
0.2	Dermal	U.S. EPA, 1996	Decrease in body weight and food consumption during the dosing period	Developmental toxicity study in rats	Miller, 1991	20	100
0.2	Inhalation	U.S. EPA, 1996	Decrease in body weight and food consumption during the dosing period	Developmental toxicity study in rats	Miller, 1991	20	100
Long-term (greater than 6 months to lifetime)							
0.1	Oral	U.S. EPA, 1996	Decreased body weight gains	Chronic rat toxicity study	Bogdanffy, 1989	9.82	100

Based on the available general population and occupational reference doses (Table B1-12) the following exposure limits were selected for the risk assessment purposes of this report (Table B1-13).

Table B1-13 Summary of Selected TRVs for Bromacil

COC	TRV Type	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
Bromacil	Acute/Short-term RfD (1-7 days)	Oral	Not required	Acutely toxic effects are not expected at concentrations of bromacil which are likely to be found in food		U.S. EPA, 1996
		Dermal	NA			
		Inhalation	NA			
	Intermediate-term RfD (1 week to several months)	Oral	NA			
		Dermal	0.2	Decrease in body weight and food consumption during the dosing period	Oral	U.S. EPA, 1996
		Inhalation				
	Long-term RfD (>6 months to lifetime)	Oral	0.1	Decreased body weight gains	Oral	U.S. EPA, 1996
		Dermal	NA			
		Inhalation	NA			

B1-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B1-5.1 Air

Bromacil is expected to exist in both the vapour and particulate phases in the ambient atmosphere. Vapour phase bromacil is degraded by reacting with photochemically produced hydroxyl radicals or ozone, with half-lives of 20 and 7 days, respectively (HSDB, 2005). Particulate phase bromacil may be removed from the air by wet and dry deposition.

B1-5.2 Water

There is evidence that bromacil will contaminate groundwater, and will move off-site and contaminate surface water; due to its high mobility in soil (U.S. EPA, 1996).

The primary route of bromacil dissipation in water appears to be photolysis under alkaline conditions (U.S. EPA, 1996). However, during laboratory studies bromacil was stable to hydrolysis and photodegradation in water at pHs 5 and 7. Alkaline conditions ionize bromacil (pK_a 9.1) making it susceptible to photolysis due to a shift in the absorption spectrum (U.S. EPA, 1996).

Table B1-14 Half-life of Bromacil in Water

Conditions	Half-life	Reference
pH 9 buffered solution	4-7 days	U.S. EPA, 1996
Clean, low sediment waters	2 months	JW, 2006

B1-5.3 Sediment and Soil

Bromacil has been shown to be highly mobile and moderately to highly persistent in soil (U.S. EPA, 1996; JW, 2006). Bromacil is very mobile in sand, sandy loam, clay loam and silt loam soils. Even aged bromacil residues are very mobile in silt loam soils (U.S. EPA, 1996).

Bromacil has a soil adsorption coefficient (Koc) of 2.3 to 3.3, and therefore adsorbs to soil particles (JW, 2006). However, based on its high soil mobility, bromacil is expected to leach readily into groundwater. Leaching is dependent on the soil type, and will be greatest in sandy soils (JW, 2005). Bromacil generally has a leaching depth of 2 to 3 feet in other soil types (JW, 2005).

The primary route of dissipation of bromacil in soil is microbial degradation in anaerobic soil (U.S. EPA, 1996). Laboratory studies have shown that bromacil is resistant to photodegradation on soil and aerobic soil metabolism.

Table B1-15 Half-life of Bromacil in Soil

Conditions	Half-life	Reference
	2-8 months	JW, 2005
Field dissipation study	124-155 days	U.S. EPA, 1996
Microbial degradation in aerobic soil	275 days	U.S. EPA, 1996

B1-5.4 Other Environmental Media

Bromacil has been shown to slightly accumulate in aquatic organisms; however it depurates rapidly (U.S. EPA, 1996). It has a bioconcentration factor ranging from 2.1 to 8.3 (JW, 2006).

B1-6.0 SUMMARY

Bromacil was first registered by the U.S. EPA in 1961 (U.S. EPA, 1996). It is in the substituted urea class of herbicide used to control broadleaf weeds, grasses and brushes on non-cropland areas. In 1994, bromacil was used to treat the range and training areas (RTA) at CFB Gagetown. Approximately 2,600 kg of bromacil was applied over an area of 360 ha (JW, 2006).

Acute exposures to bromacil through the oral, dermal and inhalation routes were categorized in the lowest toxicity category (Toxicity Category IV) by the U.S. EPA (1996). Rodent feeding studies of bromacil demonstrated reproductive/developmental effects. Furthermore, systemic effects in the liver and thyroid glands have also been observed in long-term rodent feeding studies. The U.S. EPA (1996) classified bromacil as a Group C (possible human carcinogen) carcinogen. This decision was based on the increased incidence of liver tumours in male mice, and positive trends of thyroid tumours in male rats. However, the U.S. EPA (1996) recommended that the RfD approach should be used for the quantification of human risks of bromacil.

B1-7.0 REFERENCES

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