B5-1.0 PICLORAM

B5-1.1 Background Information

PICLORAM potassium salt (K-salt) (formulation used in Tordon 22K) triisopropanolamine salt (TIPA-salt) (formulation used in Tordon 101) isooctyl ester (IOE) (formulation used in M-2993)picloram acid (P-acid) (active ingredient)

IUPAC: 4-amino-3,5,6-trichloropyridine-2-carboxylic acid
4-amino-3,5,6-trichloropicolinic acid

CAS: 4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid

CASRN: 1918-02-1 **CASRN: potassium salt:** 2545-60-0

PICLORAM USAGE

Picloram is an active ingredient in many herbicide formulations such as Tordon 22K, Tordon 101 and M-2993. These herbicides are used in the control of a number of broadleaf weeds and undesirable brush.

Picloram was used extensively at CFB Gagetown between 1965 and 1993 (JW, 2006). Picloram was utilized for 24 years to treat the range and training area (RTA) on a yearly basis; in addition, it was applied in 1966 and 1967 on designated test plots during the U.S. trials and CFS tests. Furthermore, in 1990 picloram was applied during Dow Chemical trials.

Table B5-1 Plcloram Usage at CFB Gagetown[a,b]

Year	Total Picloram Applied (kg)	Total Area Treated (ha)
1965	1,365	1,867
1966	4,029	3,443
1967	5,021	4,244
1968	2,687	2,301
1969	1,588	1,358
1970	3,872	3,338
1971	4,557	3,895
1972	6,648	4,673
1973	4,096	3,506
1974	6,256	2,951
1975	11,603	3,444
1976	7,298	2,166
1977	6,868	2,124
1978	5,579	1,653
1979	4,069	1,208
1980	681.8	202.3
1981	274.5	107.0
1982	5,818	1,531
1985	1,433	1,470
1986	277.9	285

Table B5-1 Plcloram Usage at CFB Gagetown[a,b]

Year	Total Picloram Applied (kg)	Total Area Treated (ha)
1987	2632.6	2700.0
1989	1095.1	936.0
1990	1105.0	1150.0
1991	1001.3	1027.0
1993	321.4	823.7
Total	**9.0E+04**	**5.2E+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).

B5-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: Triisopropanolamine salt (**TIPA-salt**) – $C_{15}H_{24}C_{l3}N_3O_5$
Potassium salt (**K-salt**) – $C_6H_2Cl_3KN_2O_2$
Picloram Acid (**P-acid**) – $C_6H_3C_{l3}N_2O_2$
Picloram isooctyl ester (**IOE**) – $C_{14}H_{19}C_{l3}N_2O_2$

Activity: Herbicides (picolinic acid herbicides; pyridine herbicides)

Notes: When this substance is used as an ester or a salt, its identity should be stated, for example picloram-2-ethylhexyl [36374-99-9], picloram-isoctyl [26952-20-5], picloram-methyl [14143-55-6], picloram-potassium [2545-60-0], picloram-triethylammonium [35832-11-2].

Technical grade picloram contains hexachlorobenzene (U.S. EPA, 1995b). The U.S. EPA (1995b) stated that the maximum levels of hexachlorobenzene (HCB) allowed in the technical grade is 200 ppm.

Structure:

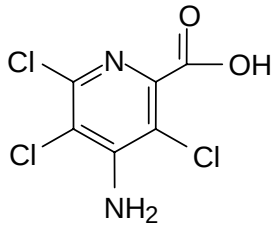

Figure B5-1 Picloram Acid CASRN 2545-60-0 K^+

Acid Equivalency:

Picloram acid equivalents:	0.86	K-salt
	0.68	IOE
	0.56	TIPA-salt

Table B5-2 Chemical and Physical Properties of Picloram Acid

Chemical/Physical Property	Result	Reference
Boiling Point	NA[a]	FAO, 2004
Dissociation Constant (pKa)	1.9	USDA, 1995
	2.3 at 22°C	Baker, 1989; JW, 2006
	3.6	Budavari *et al*., 1989
Henry's Law constant	$5.33x10^{-14}$ atm·m^3/mol at 25°C	JW, 2006
Log K_{ow}	-0.05 at pH 5-9	USDA, 1995
	0.26	Bidlack, 1980
	0.3	JW, 2006
	1.9	Washburn, 2002; Baker, 1989
	1.4	SRC, 1998
Melting Point	174-183°C	FAO, 2004
Molecular Weight	241.48 g/mol	U.S. EPA, 1995a; JW, 2006
Vapour Pressure	$6.16x10^{-7}$ mm Hg at 35°C	Burdavari *et al*., 1989
	6.0x10-^{10} mm Hg at 35°C	Baker, 1989
	$7.21x10^{-11}$ mm Hg at 20°C	Dobbs, 1984; JW, 2006
Water Solubility	430 mg/L	USDA, 1995; JW, 2006
	560 mg/L	FAO, 2004; U.S. EPA, 1995b

[a] Boiling point is not determined as picloram decomposes around the melting point.

Table B5-3 Chemical and Physical Properties of Picloram K Salt

Chemical/Physical Property	Result	Reference
Melting Point	>260°C	FAO, 2004
Molecular Weight	280.6 g/mol	Budavari *et al*., 1989
Water Solubility	200 g/L	Durkin and Follansbee, 2003
	430 g/L	Neary *et a*l., 1993
	530 g/L at 20°C	FAO, 2004
	740 g/L at 20°C	U.S. EPA, 1995b

Table B5-4 Chemical and Physical Properties of Picloram TIPA

Chemical/Physical Property	Result	Reference
Melting Point	61-66°C	FAO, 2004
Molecular Weight	432.6 g/mol	Durkin and Follansbee, 2003
Water Solubility	>675 g/L at 20°C	FAO, 2004

Table B5-5 Chemical and Physical Properties of Picloram IOE

Chemical/Physical Property	Result	Reference
Molecular Weight	353.5 g/mol	Durkin and Follansbee, 2003
Water Solubility	0.23 mg/L	U.S. EPA, 1995b

B5-3.0 PMRA EVALUATION

In 2004, PMRA approved an application for the registration of a new product containing picloram as the active ingredient (Health Canada, 2004). This product will be utilized to control deep-rooted perennial and biennial broadleaf weeds in barley, wheat, grass pastures and rangeland as a post-emergent treatment.

Picloram is currently being re-evaluated by PMRA in the 2005 to 2009 re-evaluation programs. The approach of the current re-evaluations is to build on available foreign reviews and expand work-sharing arrangements with the U.S. EPA.

B5-4.0 TOXICOLOGY SUMMARY

B5-4.1 Human Health Effects

The acute effects of picloram exposure are as follows (Table B5-6).

Table B5-6 Human Health Effects Resulting from Acute Exposure to Picloram[a,b]

Exposure	Effects	Response
Acute	HEENT	Eye irritation
	Respiratory	Irritating to the respiratory tract (picloram dust)
	Neurologic	Seizures have developed in animals
	Gastrointestinal	Nausea
	Hematologic	Decreased leucocyte levels
	Dermatologic	Mild irritating to the skin

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

NIOSH (1995) indicated that picloram is irritating to the eyes, skin and respiratory tract during short-term exposures. Picloram may have effects on the liver if a person is subjected to long-term or repeated exposure (NIOSH, 1995).

B5-4.2 Health Effects by Route of Exposure

B5-4.2.1 Oral Exposure

Picloram and its derivatives are only slightly toxic by the oral route, and has been placed in Toxicity Category III by the U.S. EPA. (1995a).

B5-4.2.1.1 Death

Table B5-7 Mammalian acute LD_{50} Values resulting from Oral Exposure to Picloram

Compound	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
IOE	Rat (M/F)	>3,500	Jeffrey *et al*., 1987a
K-salt	Rat (F)	3,536	Jeffrey *et al*., 1987a
P-acid	Rat (F)	4,012	Jeffrey, 1987
K-salt	Rat (M)	>5,000	Jeffrey *et al*., 1987a
TIPA-salt	Rat (M/F)	>5,000	Berdasco *et al*., 1989
P-acid	Rat (M)	>5,000	Jeffrey, 1987a
K-salt	Rat (M/F)	>5,000	FAO, 2004

B5-4.2.1.2 Systemic Effects

Table B5-8 Systemic Effects Resulting from Oral Exposure to Picloram

Compound	Test Organism (Species)	Dose (mg/kg/day) (Duration)	Response	Reference
Acute				
K-salt	Rabbit (New Zealand white)	172 (12 days)	Decreased body weight	John *et al*., 1984
Sub-chronic				
IOE	Rat (F344)	220 (13 weeks)	Increased liver weights (M/F); slight/very slight hepatocellular hypertrophy (M); increased kidney weight (M)	Barna-Lloyd *et al*., 1991
TIPA-salt	Rat (F344)	550 (13 weeks)	Heptacellular hypertrophy (M	Szabo and Grandjean, 1990
TIPA-salt	Rat (F344)	1,800 (13 weeks)	Heptacellular hypertrophy (F); increased liver and kidney weights (F); decreased body weight gain (M/F)	Szabo and Grandjean, 1990
P-acid	Dog	175 (6 months)	Decreased body weight gain, food consumption, liver weights, alkaline phosphatase and alanine transaminanse	Barna-Lloyd *et al*., 1982
Chronic				
P-acid	Mice (B6C3F1) (M)	1,000 (2 years)	Systemic toxicity (increase in absolute and relative kidney weights	Stott *et al*., 1992
P-acid	Rat (F344) (M)	250 (2 years)	Chronic toxicity (increased incidence and severity of glomerulonephropathy; increased absolute and relative kidney weight)	Cosse *et al*., 1992
P-acid	Rat (F344) (F)	500 (2 years)	Chronic toxicity (increased glomerulonephropathy; increased absolute and relative kidney weight)	Cosse *et al.*, 1992
P-acid	Rat	100 (2 generation reproductive study)	Histopathological effects on the kidney; signs of kidney damage	Breslin *et al.*, 1991

B5-4.2.1.3 Neurological Effects

Picloram is an indirect neurotoxicant as it might produce neurologic effects that are secondary to other forms of toxicity (Durkin and Diamond, 2002). For instance, high doses of picloram have been shown to cause ataxia, tremors, convulsions and weakness (U.S. EPA, 1992a). Therefore, neurotoxicity studies have not been requested by the U.S. EPA for picloram or its derivatives (U.S. EPA, 1995a).

B5-4.2.1.4 Reproductive/Developmental Effects

Table B5-9 Reproductive and Developmental Effects Resulting from Oral Exposure to Picloram

Compound	Test Organism (Species)	Exposure	Dose (mg/kg/day) (Duration)	Response	Reference
TIPA-salt	Rat (CD)	Gastric intubation	1,000 (days 6 through 15 of gestation)	Excessive salivation; decreased body weight gain and decreased food consumption	Schroeder, 1990a
IOE	Rabbit (New Zealand White)	Gavage	100 (days 7 through 19 of gestation)	Decreased body weight gain	Zablotny *et al.*, 1991
TIPA-salt	Rabbit (New Zealand white)	Gavage	$\geq$ 180 (days 7 through 19 of gestation)	Increased rate of abortions; decreased food consumption and body weight gain	Vedula *et al.*, 1992
IOE	Rabbit (New Zealand White)	Gavage	500 (days 7 through 19 of gestation)	Maternal toxicity (decreased feces)	Zablotny *et al.*, 1991
TIPA-salt	Rabbit (New Zealand white)	Gavage	$\geq$ 538 (days 7 through 19 of gestation)	Increased incidence of clinical signs	Vedula *et al.*, 1992

B5-4.2.1.5 No Observed Adverse Effect Levels

During sub-chronic oral exposure different forms of picloram exhibited varying degrees of toxicity. For instance in the rat P-acid was most toxic followed by IOE and TIPA-salt (Table B5-10). This was also observed for reproductive and developmental effects in rats (Table B5-11). However, for reproductive and development effects in New Zealand White Rabbits IOE was the most toxic followed by K-salt and TIPA-salt (Table B5-10).

Table B5-10 NOAELs and LOAELs from Oral Exposure to Picloram[a]

Compound	Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Acute					
K-salt	Rat	NOAEL	5,000	Mortality or signs of toxicity	Jeffrey *et al.*, 1987b
Sub-chronic					
P-acid	Rat (F344)	LOAEL	150	Liver weight change; minimal microscopic changes in the liver	Gorzinski *et al.*, 1982
IOE	Rat (F344)	LOAEL	220	Increased liver weights (M/F); slight/very slight hepatocellular hypertrophy (M); increased kidney weight (M)	Barna-Lloyd *et al.*, 1991
TIPA-salt	Rat (F344)	LOAEL	550	Systemic toxicity (hepatocellular hypertrophy (M))	Szabo and Grandjean, 1990
P-acid	Rat (F344)	NOAEL	50	Clinical signs (liver weight change; minimal microscopic changes in the liver)	Gorzinski *et al.*, 1982

Table B5-10 NOAELs and LOAELs from Oral Exposure to Picloram[a]

Compound	Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
IOE	Rat (F344)	NOAEL	73	Systemic toxicity	Barna-Lloyd *et al*., 1982
TIPA-salt	Rat (F344)	NOAEL	90	Systemic toxicity (hepatocellular hypertrophy (M))	Szabo and Grandjean, 1990
P-acid	Dog	LOAEL	175	Systemic toxicity (decreased body weight gain, food consumption, liver weights, alkaline phosphatase and alanine transaminanse)	Barna-Lloyd *et al*., 1982
P-acid	Dog	NOAEL	35	Systemic toxicity	Barna-Lloyd *et al*., 1982
Chronic					
P-acid	Mice (B6C3F1)	NOAEL	500	Systemic toxicity	Stott *et al*., 1992
P-acid	Rat (F344)	LOAEL	60	Altered size and tinctorial properties of centrilobular hepatocytes; increased absolute and/or relative liver weights	Landry *et al*., 1986
P-acid	Rat (F344)	NOAEL	20	Toxicity	Landry *et al*., 1986
TIPA-salt	Dog	LOAEL	175	Increased liver weight (absolute and relative)	Young, 1988
TIPA-salt	Dog	NOAEL	35	Increased liver weight (absolute and relative)	Young, 1988

[a] Obtained from Durkin and Follansbee, 2003; U.S. EPA, 1992b; and, U.S. EPA, 1995b.

Table B5-11 Picloram Reproductive and Developmental NOAEL and LOAEL Values[a]

Compound	Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
K-salt	Rat (CD)	LOAEL	347	Excessive salivation	Schroeder, 1990b
IOE	Rat (CD)	LOAEL	500	Maternal toxicity (decreased body weight gain during gestation days 6-9)	Vedula *et al*., 1991
TIPA-salt	Rat (CD)	LOAEL	1000	Maternal toxicity (excessive salivation; decreased body weight gain and decreased food consumption)	Schroeder, 1990b
IOE	Rat (CD)	NOAEL	100; $\geq$1000	Maternal; Developmental toxicity	Vedula *et al*., 1991
K-salt	Rat (CD)	NOAEL	174; $\geq$ 347	Maternal; Developmental toxicity	Schroeder, 1990
TIPA-salt	Rat (CD)	NOAEL	500; 1000	Maternal, Developmental toxicity	Schroeder, 1990b
P-acid	Rat	NOAEL	$\geq$1000	Reproductive performance	Breslin *et al*., 1991
IOE	Rabbit (New Zealand white)	LOAEL	100	Maternal toxicity (increased incidence of clinical signs)	Zablotny *et al*., 1991

Table B5-11 Picloram Reproductive and Developmental NOAEL and LOAEL Values[a]

Compound	Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
K-salt	Rabbit (New Zealand white)	LOAEL	172-200	Parental toxicity (decreased body weight)	John *et al*., 1984; Breslin, 1989
TIPA	Rabbit (New Zealand white)	LOAEL	180	Maternal toxicity (increased rate of abortions, decreased food consumption and body weight gain)	Vedula *et al*., 1992
IOE	Rabbit (New Zealand white)	NOAEL	20; >500	Maternal toxicity; Developmental toxicity	Zablotny *et al*., 1991
K-salt	Rabbit (New Zealand White)	NOAEL	34-40; 344-400	Maternal toxicity; Developmental toxicity	John *et al*., 1984; Breslin, 1989
TIPA-salt	Rabbit (New Zealand white)	NOAEL	54; ≥1000	Maternal toxicity; Developmental toxicity	Vedula *et al*., 1992

[a] Obtained from U.S. EPA, 1995b.

B5-4.2.2 Dermal Exposure

Picloram and its derivatives are only slightly toxic by the dermal route, and have been placed in Toxicity Category IV for these effects. The potassium salt of picloram is classified as a moderate eye irritant (Category III) but as a non-irritant to the skin (Category IV) (U.S. EPA, 1995a). Most of the picloram derivatives are not skin irritants (Category IV), with the exception of IOE (Category III). The three derivatives are skin sensitizers, while picloram acid is not (U.S. EPA, 1995a).

Tordon 22K (Gilbert, 1996) caused transient skin irritation in standard acute dermal studies. Furthermore, Tordon 22K produced a delayed hypersensitivity reaction in Hartley guinea pigs 48 hours after exposure (Haut and Bell, 1997).

B5-4.2.2.1 Death

Table B5-12 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Picloram

Compound	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute			
K-salt; TIPA-salt; P-salt; IOE	Rabbit (M/F)	> 2,000	Jeffrey *et al*., 1987c,d,e; Mizell *et al*., 1989
K-salt (as Tordon 22K)	Rabbit (M/F)	> 5,000	FAO, 2004

B5-4.2.2.2 Systemic Effects

Table B5-13 Systemic Effects Resulting from Dermal Exposure to Picloram

Compound	Test Type	Test Organism (Species)	Dose (Duration)	Response	Reference
Sub-Chronic					
K salt	Sub-chronic	Rabbit (New Zealand white)(M/F)	75.3 mg/kg/day (15 applications)	Dermal irritation (very slight to well defined edema and/or erythema)	Atkin *et al*., 1990a
TIPA	Sub-chronic	Rabbit (New Zealand white)(M/F)	132 mg/kg/day (15 applications)	Dermal irritation (very slight to well defined edema and/or erythema)	Atkin *et al*., 1990b

B5-4.2.2.3 Neurological Effects

Picloram is an indirect neurotoxicant as it might produce neurologic effects that are secondary to other forms of toxicity (Durkin and Diamond, 2002). For instance, high doses of picloram have been shown to cause ataxia, tremors, convulsions and weakness (U.S. EPA, 1992a). Therefore, neurotoxicity studies have not been requested by the U.S. EPA for picloram or its derivatives (U.S. EPA, 1995a).

B5-4.2.2.4 Reproductive/Developmental Effects

No data was found.

B5-4.2.2.5 No Observed Adverse Effect Level

Table B5-14 NOAELs and LOAELs for Dermal Exposure to Picloram[a]

Compound	Test Organism (Species)	Effect	Value (mg/kg/day)	ndpoint	Reference
Acute					
K-salt (as Tordon 22K)	Rabbit (New Zealand white)	NOAEL	407	Systemic toxicity	Jeffrey *et al*., 1987g
K salt; TIPA-salt	Rabbit (M/F)	NOAEL	>2,000	Systemic toxicity	Jeffrey *et al*., 1987c; Mizell *et al*., 1989
Sub-Chronic					
IOE	Rabbit	LOAEL	500	Increased bilirubin (M); increased BUN (M/F)	Lockwood and Szabo, 1991
IOE	Rabbit	NOAEL	250	Systemic toxicity	Lockwood and Szabo, 1991
K-salt	Rabbit (New Zealand white)	NOAEL	$\geq$ 753	Toxicity	Atkin *et al*., 1990a
TIPA	Rabbit (New Zealand white)	NOAEL	$\geq$ 1,320	Toxicity	Atkin *et al*., 1990b

[a] Obtained from U.S. EPA, 1995b.
(M) Effects observed in males only.
(F) Effects observed in females only.

B5-4.2.3 Inhalation Exposure

Picloram acid is highly toxic, and its three derivatives are moderately toxic by the inhalation route placing in Toxicity Categories I and II, respectively (U.S. EPA, 1995a).

B5-4.2.3.1 Death

Table B5-15 Mammalian LD_{50} Value Resulting from Inhalation Exposure to Picloram

Compound	Test Type	Test Organism (Species/Sex)	LD_{50} (mg/L)	Reference
P acid	Acute	Rat (M/F)	> 0.035	Streeter *et al*., 1987a
IOE	Acute	Rat (M/F)	> 0.35	Streeter *et al*., 1987b
K salt	Acute	Rat (M/F)	> 0.54	Streeter *et al*., 1987c
TIPA	Acute	Rat (M/F)	> 0.07	Nitschke and Lomax, 1989
K-salt (as Tordon 22K)	Acute	Rabbits (M/F)	> 8.11	FAO, 2004

B5-4.2.3.2 Systemic Effects

Table B5-16 Systemic Effects Resulting from Exposure to Picloram *via* Inhalation

Compound	Test Type	Test Organism (Species)	Dose (mg/L)	Response	Reference
K-salt (as Tordon K)	Acute	Rat (M)	0.54 a.e	Transient decrease in body weight	Streeter *et al*., 1987c
K-salt (as Tordon 22K)	Acute	Rat (M/F)	18.3	Transient decrease in body weight	Streeter *et al*., 1988

B5-4.2.3.3 Neurological Effects

Picloram is an indirect neurotoxicant as it might produce neurologic effects that are secondary to other forms of toxicity (Durkin and Diamond, 2002). For instance, high doses of picloram have been shown to cause ataxia, tremors, convulsions and weakness (U.S. EPA, 1992a). Therefore, neurotoxicity studies have not been requested by the U.S. EPA for picloram or its derivatives (U.S. EPA, 1995a).

B5-4.2.3.4 Reproductive/Developmental Effects

No data found.

B5-4.2.3.5 No Observed Adverse Effect Level

Table B5-17 NOAELs and LOAELs for Picloram Exposure *via* Inhalation

Compound	Test Type	Test Organism (Species)	Effect	Value (mg/L)	Endpoint	Reference
P. acid	Acute	Rat (F344)	NOAEL	0.0351	Clinical signs	Streeter *et al*., 1987a
K-salt (as Tordon 22k)	Acute	Rat (Fisher 344)	NOAEL	1.95	Clinical signs	McGuirk and Cieszlak, 1996

B5-4.3 Carcinogenicity

Picloram has been classified as Group E: evidence of non-carcinogenicity for humans (U.S. EPA, 1995b). This classification applies to picloram acid and the picloram potassium salt form as acceptable carcinogenicity studies were available. Carcinogenicity studies have not been required for the other forms of picloram.

IARC (1991) states that picloram is not classifiable as to its carcinogenicity to humans (Group 3). This overall evaluation is based on limited evidence for carcinogenicity of picloram technical grades in experimental animals. Technical-grade picloram increased the incidence of liver-cell tumours (mainly benign) in male and female rats, and C-cell adenomas of the thryroid in female rats in another study. However, an increase in tumour incidence was not observed in mice (IARC, 1991). Furthermore, the American Conference of Governmental Industrial Hygienists TLVs and BEIs (2005) also determined that picloram is not classifiable as a human carcinogen.

Table B5-18 Animal Carcinogenicity data Evaluated by the U.S. EPA (1995b)

Compound	Test Subjects	Exposure	Dose (mg/kg/day)	Response	Reference
P acid	Rat (F344)	Oral	500	No evidence of carcinogenicity	Cosse *et al.*, 1992
P acid	Mice (B6C3F1)	Oral	1,000	No evidence of carcinogenicity	Stott *et al*., 1992

Genetic Toxicology

TIPA-salt, P-acid and IOE were evaluated in the Ames test using *Salmonella typhimurium*. None of the salts or acid induced a mutagenic response in the presence of absence of activation (Samson and Gollapudi, 1990a,b). Another study conducted by Linscombe and Gollapudi (1987) evaluated picloram acid for gene mutation in mammalian cells. The compound was found to be negative for inducing forward mutation in Chinese hamster ovary (CHO) cells. No evidence of a mutagenic response occurred at any dosage level of IOE either in the presence or absence of S-9 activation during a Chinese Hamster Ovary Cell HGPRT forward gene mutation assay (Cifone, 1992). Picloram acid did not produce cytogenic effects on bone marrow cells of rats *via* intragastric exposure (Mensik *et al*., 1976). TIPA-salt was also evaluated for genotoxic potential when admistered to primary rat hepatocyte cultures. The test material was negative for inducing unscheduled DNA synthesis up to toxic levels (McClintock and Gollapudi, 1990a). In addition, picloram IOE was shown to have no potential for inducing chromosomal aberrations when evaluated using a rat lymphocyte cytogenetic assay, with and without S9 activation (U.S. EPA, 1995b). Picloram IOE was non-clastogenic in mice as shown by the lack of mutagenic effects at doses up to lethality (McClintock and Gollapudi, 1990b).

A study conducted by McClintock and Gollapudi (1990b) evaluated picloram TIPA salt administered to mice orally in the mouse bone marrow micronucleus test. Picloram IOE was evaluated in the mouse micronucleus assay, and was found not to be clastogenic (Samson and Gallapudi, 1991a).

Table B5-19 Genetic Toxicity of Picloram

Test	Form of Picloram		
	TIPA-salt	P-acid	IOE
Ames/Salmonella	--	--	--
CHO mutations	NP	--	--
CHO chromosomal abberations	--	NP	NP
Micronucleus	--	--	--
Unscheduled DNA synthesis	--	--	--

-- No effects
NP Not performed

B5-4.4 Populations at Special Risk

No specific groups identified.

B5-4.5 Toxicokinetics

B5-4.5.1 Absorption

Picloram and its derivatives are rapidly absorbed, distributed and excreted following oral administration and injection in both humans and laboratory animals (Reitz *et al*., 1989; Dimoradzki *et al*., 1991; Domoradzki *et al*., 1992; Nolan *et al*., 1980). In the human gastrointestinal tract picloram was rapidly absorbed ($t_{1/2}$= 20 minute), however, picloram was poorly absorbed through human skin ($t_{1/2}$=12 hour)(Nolan *et al*., 1984). Only a small fraction of picloram applied to the skin was absorbed (0.2%), based on the amount recovered in the urine.

The U.S. EPA (1995) used a dermal absorption factor of 100% as an adequate dermal absorption study was not available.

B5-4.5.2 Distribution

As picloram and its derivatives are rapidly absorbed through the gastrointestinal tract and rapidly excreted, it is not expected to be widely distributed throughout the body. Tissue retention was found to be minimal after a dietary administration of picloram to cattle. At the highest dose (1600 mg/kg) tissue concentrations were measured as 15 to 18, 1.4 to 2, 1.1 to 1.6, and 0.3 to 0.5 mg/kg in the kidney, blood, liver, and muscle and fat, respectively (HSDB, 2005).

B5-4.5.3 Metabolism

Picloram is not metabolized within laboratory animals or humans. After six male volunteers received an oral dose of picloram, over 90% was excreted unchanged in the urine (Nolan *et al*., 1984).

The major metabolite after an oral dose of picloram IOE was 2-ethyl-1,6-hexanoic acid (Dimordadzki *et al*., 1991). Therefore, picloram IOE is hydrolyzed rapidly to picloram acid and 2-ethyl hexanol. In addition, picloram TIPA is also rapidly hydrolyzed to picloram acid.

B5-4.5.4 Elimination and Excretion

Following administration of an oral dose of picloram IOE, the ester is excreted rapidly (Dimoradzki *et al*., 1991). For instance, 24 hours after the exposure 67% of the radioactivity was recovered. After 48 hours post-exposure 96.4% of the radioactivity was recovered. The urine was the major metabolite route, followed by feces and expired CO_2 with levels of radioactivity of 68%, 16.35 and 10.16%, respectively.

After 6 healthy male volunteers ingested an oral dose of picloram, over 90% of the dose was recovered as unchanged picloram in the urine (Nolan *et al*., 1984).

B5-4.6 Exposure Limits

Table B5-20 Existing RfD Values for Picloram Exposure

Reference Dose (mg/kg/day)	Form	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Acute/Short-term (1-7 days)								
Not Required	Picloram acid, potassium salt, triisopropanol amine and isooctyl ester	Oral Dermal Inhalation	U.S. EPA, 1995b	There are no short term toxicological concerns indicated for occupational exposure.	--	--	--	--
Intermediate-term (7days- Several months)								
5.0	Picloram isooctyl ester	Inhalation Dermal Oral	U.S. EPA, 1995b	Increased bilirubin (males) and increased BUN (males/females).	21 day dermal rabbit studies	Bond, 1993	500[b]	100
Long-term (6month to lifetime)								
0.02[a]	--	Oral	Health Canada, 1988, 2004	Changes in liver, body weights, and clinical chemistry parameters	2 years rat toxicity study	Johnson *et al*., 1986	20	1,000
0.07	Picloram acid	Oral	U.S. EPA, 1992b	Increased liver weights	6 months dog feeding study	Dow Chemical Company, 1982	7	100
0.20	Picloram acid	Oral	U.S. EPA, 1995b	Increasd size and altered tinctorial properties of the centrilobular hepatocytes	2 years rat oral toxicity	Landry *et al.*, 1986	20	100

[a] Negligible Daily Intake (NDI) - 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] LOAEL used.

Based on the available general population and occupational reference doses (Table B5-20) the following exposure limits were selected for the risk assessment purposes of this report (Table B5-21).

Table B5-21 Summary of Selected TRVs for Picloram

COC	TRV Type	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
Picloram	Acute/Short-term RfD	Oral	Not required	There are no short term toxicological concerns indicated for occupational exposure.		U.S. EPA, 1995b
		Dermal				
		Inhalation				
	Intermediate-term RfD	Oral	5.0	Increased bilirubin (males) and increased BUN (males/females)	Dermal	U.S. EPA, 1995b
		Dermal				
		Inhalation				
	Long-term RfD	Oral	0.02[a]	Changes in liver, body weights, and clinical chemistry parameters	Oral	Health Canada, 2004
		Dermal	NA			
		Inhalation	NA			

[a] Neglible daily intake (NDI).

Although different forms of picloram have been shown to possess slightly different toxicological properties, separate RfDs have not been established for different forms (IOE, TIPA-salt).

The Food Directorate of the Department of National Health and Welfare (Health Canada, 1988) determined an NDI for picloram of 0.02 mg/kg/day based upon a NOAEL of 20 mg/kg/day for changes in liver, body weights and clinical chemistry parameters during a 2 year rat study (Johnson *et al*., 1986). An uncertainty factor of 1,000 was applied based upon interspecies variation (10), intraspecies variation (10) and deficiencies in the data base which lacked longer-term studies on a non-rodent species and a mammalian point mutation study (10). U.S. EPA (1995b) established an RfD of 0.20 mg/kg/day based upon a NOAEL of 20 mg/kg/day for increased size and altered tinctorial properties of the centrilobular hepatocytes during a 2 year rat oral toxicity study (Landry *et al*., 1986) and an uncertainty factor of 100 (interspecies and intraspecies variation). The U.S. EPA (1992b) has also established an oral RfD of 0.07 mg/kg/day based upon a NOAEL of 7 mg/kg/day for increased liver weights in dogs during a 6 months feeding study, and an uncertainty factor of 100 (Dow Chemical Company, 1982). The U.S. EPA (1992b) has medium confidence in this RfD. A chronic oral RfD of 0.02 mg/kg/day (Health Canada, 1988) was selected for the risk assessment purpose of this report.

Due to the low acute toxicity of picloram *via* the oral, dermal, and inhalation routes, an acute RfD was not established by the U.S. EPA (U.S. EPA, 1995b). Furthermore, no short term dermal and or dermal toxicological endpoints of concern were addressed by the U.S. EPA (U.S. EPA, 1995b).

B5-5.0 ENVIRONMENTAL FATE AND EXPOSURE

All four active ingredients are expected to have very similar fate and transport characteristics in the environment (U.S. EPA, 1995a). For picloram acid, TIPA and IEO the part of the molecule which is biologically active is the anion (*i.e.*, active ingredient); which is chemically identical for all three. When these active ingredients enter the environment they will dissociate to yield the free anion. Picloram IOE is expected to rapidly degrade in the environment to forms with the same anion as the acid and its salts. Therefore, picloram IOE is also expected to have similar environmental fate characteristics to the other active ingredients (U.S. EPA, 1995a).

B5-5.1 Air

B5-5.1.1 Transport and Partitioning

Based on a model gas/particle partitioning of semi-volatile organic compounds in the atmosphere, picloram is expected to exist solely in the particulate phase in the ambient atmosphere (Bidleman, 1988). Particulate phase picloram may be removed from the air by wet and dry deposition.

B5-5.1.2 Transformation and Degradation

Picloram is expected to undergo direct photolysis in the atmosphere based on photodegradation half-lives in sunlight water (Zepp, 1991; Hedlund and Youngson, 1972).

B5-5.2 Water

B5-5.2.1 Transport and Partitioning

Picloram, in all of its forms, is among the most mobile pesticides (U.S. EPA, 1995a). Therefore, it has high potential to contaminate surface water runoff from use areas. Regardless of the original chemical form of picloram applied, substantial quantities of the anion will be available for several months following application due to its environmental persistence (U.S. EPA, 1995a).

Picloram easily leaches into groundwater, and may contaminate surface water in places where groundwater discharges into surface water (U.S. EPA, 1995a). Based on K_d values of picloram it is expected that in surface water and runoff picloram will be dissolved in the water rather than adsorbed to particulate matter (U.S. EPA, 1995a).

B5-5.2.2 Transformation and Degradation

Picloram is expected to be persistent in surface water, except in clear shallow water with substantial mixing or water with short hydraulic residence times (U.S. EPA, 1995a). Picloram may undergo direct photolysis in water, but not abiotic hydrolysis or volatilization. Under both aerobic and anaerobic conditions biological degradation of picloram will be slow (U.S. EPA, 1995a). Its major dissipation route appears to be leaching (U.S. EPA, 1995b).

Table B5-22 Half-life of Picloram in Water

Conditions	Half-life	Reference
Sunlit water	0.7 days	Hedlund and Youngson, 1972
Surface water *via* photolysis at 25°C	2.6 days	Woodburn *et al*., 1989; JW, 2006
Sunlit water	9.58 days	Zepp, 1991
Field Dissipation	14 days	USDA, 1989a,b
Field Dissipation	15 days	Scifres *et al*., 1977

B5-5.3 Sediment and Soil

B5-4.3.1 Transport and Partitioning

Picloram is more persistent and mobile in a course-textured soil than in a finer textured soil (U.S. EPA, 1995b). Picloram has a soil adsorption coefficient of 16 (JW, 2006).

B5-5.3.2 Transformation and Degradation

In some soils picloram is nearly recalcitrant to all degradation processes (U.S. EPA, 1995b). Therefore, leaching is the major route for picloram to dissipate from the soil (U.S. EPA, 1995b). It is expected to easily contaminate groundwater due to its high solubility.

Based on the low vapour pressure of picloram, volatilization from soils is not an important dissipation mechanism (U.S. EPA, 1995b). Aerobic soil metabolism of picloram occurs at slow rates. The major degradate is carbon dioxide and the two minor degradates are 4-amino-3,5-dichloro-2-pyridinol and 4-amino-2,3,5-trichloro pyridine (U.S. EPA, 1995b). Picloram is stable to anaerobic degradation as greater than 90% of the chemical remained after a 300 day

incubation period. In addition, picloram acid is stable to photolysis when applied on soil (U.S. EPA, 1995b). However, photodegradation may occur at the soil surface (JW, 2005).

The half-life of picloram in soil varies (Table B5-22). Picloram's half-life in soil increases with increasing organic content (JW, 2005).

Table B5-23 Half-life of Picloram in Soil[a]

Conditions	Half-life	Reference
Aerobic	20-300 days	JW, 2005
Aerobic	90 days	Havens *et al.*, 2001
Field Dissipation	90 days	Durkin and Follansbee, 2003
Field Dissipation	108 days	USDA, 1995
Field Dissipation	131 days	Michael and Neary, 1993
Various soils (7 types)	167-513 days	U.S. EPA, 1995a
Field Dissipation; silt loam	203 days	Close *et al.*, 1998
Field Dissipation; sandy loam	244 days	Close *et al.*, 1998

[a] Obtained from U.S. EPA, 1995a; Durkin and Follansbee, 2003; and, JW, 2006.

B5-5.4 Other Environmental Media

B5-5.4.1 Transport and Partitioning

Picloram has a bioconcentration factor of 3.162; therefore significant bioaccumulation in aquatic organisms in not expected (U.S. EPA, 1995a; JW, 2006).

B5-5.4.2 Transformation and Degradation

See section 4.5 Toxicokinetics.

B5-6.0 SUMMARY

Picloram is part of the picolinic pyridine family of herbicides and is often used to control broadleaf weeds and undesirable brushes. While being inherently an acid, picloram can also be used either as an ester or a salt. Furthermore, technical grade picloram contains hexachlorobenzene, with a maximum allowed level of 200ppm (U.S. EPA, 1995d). During 1965 and 1993, approximately 90,000 kg of picloram was applied over an area of 52,000 ha at CFB Gagetown (JW, 2006).

As an acid, picloram is highly toxic *via* both the oral and inhalation routes of exposure (Toxicity Categories I and II, respectively) (U.S. EPA, 1995c). Conversely, picloram and its derivatives are only slightly toxic by the dermal route (Toxicity Category IV) (U.S. EPA, 1995c). During intermediate-term oral exposure studies, different forms of picloram exhibited varying degrees of toxicity in rodents. The varying degrees of toxicity were also observed in reproductive/developmental rodent studies as well. Picloram is also an indirect neurotoxicant as it may produce neurologic effects that are secondary to other forms of toxicity (Durkin and Diamond, 2002). For example, high doses of picloram have been shown to cause ataxia, tremors, convulsions and weakness (U.S. EPA, 1992). Picloram has been classified as a Group E carcinogen (evidence of non-carcinogenicity in humans) by the U.S EPA (U.S. EPA, 1995d).

IARC (1991b) has classified picloram in Group 3 (not classifiable as to its carcinogenicity in humans). Furthermore, the American Conference of Governmental Industrial Hygienists TLVs and BEIs (2005) has also classified picloram as a non-human carcinogen.

B5-7.0 REFERENCES

American Conference of Governmental Industrial Hygienists TLVs and BEIs. 2005. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indicies. Cincinatti, OH, p. 47. Cited In: HSDB, 2005.

Atkin, L., Stott, W., and Stebbins, K. 1990a. Picloram, Potassium Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits: Lab Project Study ID: K-050731-008. Unpublished study prepared by Dow Chemical Co., Toxicology Research Laboratory, Health and Environmental Sciences, 160 p. Cited In: U.S. EPA, 1995b.

Atkin, L., Stott, W., and Stebbins, K. 1990b. Picloram, Triisopropanolamine Salt: 21-Day Dermal Toxicity Study in New Zealand White Rabbits: Lab Project Study ID: K-049877-011. Unpublished study prepared by Dow Chemical Co., Toxicology Research Laboratory, Health and Environmental Sciences, 162 p. Cited In: U.S. EPA, 1995b.

Baker, R. 1989. Product Chemistry: Picloram. Unpublished study prepared by Dow Chemical U.S.A., 5 p. Cited In: Durkin and Follansbee, 2003.

Barna-Lloyd, T., Taylor, H., Swaim, L., *et al*. 1982. Results of a Six-month Dietary Toxicity Study of Picloram ..., Administered in the Diet to Male and Female Beagle Dogs: Study TXT:K-038323 (28). Final report. Unpublished study submitted by Dow Chemical U.S.A., Midland, MI; CDL:248162-A. Cited In: U.S. EPA, 1995b.

Barna-Lloyd, T., Szabo, J., and Davis, N. 1991. Picloram 2-Ethylhexyl Ester (Picloram EHE): Subchronic Dietary Toxicity Study in Fischer 344 Rats: Lab Project Number: DR-0044-1725-002. Unpublished study prepared by The Dow Chemical Co., 213p. Cited In: U.S. EPA, 1995b.

Berdasco, N., Schuetz, D., Jersey, G., *et al*. 1989. Picloram Triisopropanolamine Salt: Acute Oral Toxicity Study in Fischer 344 Rats: Final Report: Lab Project Study ID: K-049877-006A. Unpublished study prepared by The Dow Chemical Co., Toxicology Research Laboratory, 21 p. Cited In: U.S. EPA, 1995b.

Bidlack, H. 1980. Determination of the Bioconcentration Factor for Picloram in Bluegill Sunfish during Continuous Aqueous Exposure: GH-C 1384. Unpublished study submitted by Dow Chemical U.S.A., Midland, MI; CDL:250517-A. Cited In: Durkin and Follansbee, 2003.

Bidleman, T.F. 1988. Environ Sci Technol 22: 361-367. Cited In: HSDB, 2005.

Bond, D. 1993. Picloram 2-Ethylhexyl Ester (Picloram EHE): Probe and 21-Day Dermal Toxicity Studies in New Zealand White Rabbits: Supplement to MRID 42171601: Lab Project Number: DR-0044-1725-005. Unpublished study prepared by DowElanco. 34p. Cited In: U.S. EPA, 1995b

Boynton, J.C. 1969. Trials of Herbicides for Brush Control at Base Gagetown. Internal Report M-46. Forest Research Laboratory, Fedricton, NB.

Breslin, W. 1989. Historical Control Data in New Zealand White Rabbits: Picloram: Project ID: K-050731-003. Unpublished study prepared by Dow Chemical, U.S.A., 75 p. Cited In: U.S. EPA, 1995b.

Breslin, W., Zielke, G., and Kociba, R. 1991. Picloram: Two-Generation on Diet Reproduction Study in Sprague-Dawley Rats: Lab Project Number: K-038323-057F0: K-038323-057F1W: K-038323-057F1. Unpublished study prepared by The Toxicology Research Lab. & The Dow Chemical Co., 1225 p. Cited In: U.S. EPA, 1995b.

Budavari, S., O'Neil, M.J., Smith, A., and Heckelman, P.E. (Eds). 1989. The Merck Index : An Encyclopedia of Chemicals, Drugs, and Biologicals 11th Edition Centennial Edition. Rahway, N.J. Cited In: Durkin and Follansbee, 2003.

Cifone, M. 1992. Mutagenicity Test on Picloram-2-ethylhexyl Ester in the CHO/HGPRT Forward Mutation Assay: Lab Project Number: DR-0044-1725-010;14880-0-435DR. Unpublished study prepared by Hazleton Washington, Inc.,Vienna, 40 p. Cited In: U.S. EPA, 1995b.

Close, M.E., Pang, L., Watt, J.P.C., and Vincent, K.W. 1998. Leaching of picloram, atrazine and simazine through two New Zealand soils. Geoderma 84 (1-3): 45-63. Cited In: Durkin and Follansbee, 2003.

Cosse, P., Stebbins, K., Sames, K., *et al*. 1992. Picloram: Two-year Dietary Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats: Lab Project Number: K-038323-056. Unpublished study prepared by The Dow Chemical Co., 983 p. Cited In: U.S. EPA, 1995b.

Demaree, K.D., Creager, R.A., Frank, J.R., Darrow, R.A., Truchelut, G.P., and Hart, W.J. 1966. Program for experimental herbicidal sprays. Base Gagetown, New Brunswick, Canada. Crops Department, Biological Sciences Laboratory. Dated August, 1966

Demaree, K.D., and Creager, R.A. 1968. Defoliation tests in 1966 at Base Gagetown, New Brunswick, Canada. Technical Memorandum 141. Plant Sciences Laboratory, Plant Physiology Division, Department of the Army, Fort Detrick, Frederick, MD.

Demaree, K.D., and Haws, A.R. 1968. Chemical defoliation of northern tree species. Technical Memorandum 145. Plant Sciences Laboratory, Plant Physiology Division, Department of the Army, Fort Detrick, Frederick, MD.

Dobbs, A.J. 1984. Chemosphere 13: 687-92. Cited In: HSDB, 2005.

Domoradzki, J., Brzak, K., Bormett, G., *et al*. 1991. Picloram 2Ethylhexyl Ester: Hydrolysis in vitro and in vivo in Fixcher 344 Rats: Lab Project Number: DR-0044-1725-009. Unpublished study prepared by The Dow Chemical Co., 55 p. Cited In: U.S. EPA, 1995b.

Domoradzki, J., Hiser, M., Bormett, G., *et al*. 1992. Picloram, Triisopropanolamine Salt: Dissociation and Metabolism in Male Fisher 344 Rats: Lab Project Number: K-049877-013. Unpublished study prepared by The Dow Chemical Comp., 40 p. Cited In: U.S. EPA, 1995b.

Dow Chemical Company. 1982. MRID No. 000110534, 00110535; HED Doc. No. 003954. Available from EPA. Write to FOI, EPA, Washington, CD 20460. Cited In: U.S. EPA, 1992.

Durkin, P.R., and Diamond, G. 2002. Neurotoxicity, Immunotoxicity, and Endocrine Disruption with Specific Commentary on Glyphosate, Triclopyr, and Hexazinone: Final Report. SERA TR
01-43-08-04a. Available at: www.fs.fed.us/foresthealth/pesticide/risk.htm.

Durkin, P.R., and Follansbee, M. 2003. Picloram- Revised Human Health and Ecological Risk Assessment- Final Report. Prepared for: USDA, Forest Service Forest Health Protection. SERA TR 03-43-16-01b.

FAO. 2004. Picloram: FAO Specifications and Evaluations for Agriculutral Pesticides. Food and Agriculture Organization of the United Nations.

Gilbert, K. 1996. Tordon 22K: Acute Dermal Toxicity Study in New Zealand White Rabbits: Lab Project Number: M-004713-005. Unpublished study prepared by The Dow Chemical Co. 28 p. MRID 43959603. Cited In: Durkin and Follansbee, 2003.

Gorzinski, S., Johnson, K., Campbell, R., *et al*. 1982. Technical Grade Picloram: Results of a 13-week Dietary Toxicity Study in Fischer 344 Rats: Laboratory Report Code HET K-038323-(32). Final rept. Unpublished study submitted by Dow Chemical U.S.A., Midland, MI; CDL: 248162-D. Cited In: U.S. EPA, 1992.

Haut, K., and Bell, T. 1997. Tordon 22K: Dermal Sensitization Potential in Hartley Albino Guinea Pigs. Final Report: Lab Project Number: 971122: T1.05-003-000-025. Unpublished study prepared by The Dow Chemical Co. 37 p. MRID 44389101. Cited In: Durkin and Follansbee, 2003.

Havens, P., Murrow, D., and Pottinger, M. 2001. State Groundwater Surveillance Monitoring Program for Picloram Herbicide: Field Progress Report: Lab Project Number: 980054: 96-330:

Health Canada. 1988. Guidelines for Canadian Drinking Water Quality: Picloram. Available at: http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/doc_sup-appui/picloram-piclorame/index_e.html. [July 20, 2006].

Health Canada. 2004. Regulations amending the food and drug regulations (1400-picloram). Government of Canada, Canada Gazette 138 (45).

Hedlund, R.T., and Youngson, C.R. 1972. Fate of Organic Pesticides in the Aquatic Systems. pp. 159-72. Cited In: HSDB, 2005.

HSDB (Hazardous Substances Data Bank). 2005. U.S. National Library of Medicine's Toxicology Data Network (TOXNET). Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. [April 27, 2006].

IARC. 1991. IARC Summaries and Evaluations: Picloram. International Agency for Research on Cancer. 53: 481. Available at: http://www.inchem.org/documents/iarc/vol53/15-picloram.html. [April 26, 2006].

Jeffrey, M. 1987. Picloram Acid (Picloram Technical): Acute Oral Toxicity Study in Fischer 344 Rats: Final Rept.: K-038323-042A. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 26 p. Cited In: U.S. EPA, 1995b.

Jeffrey, M., Schuetz, D., and Eisenbrandt, D. 1987a. Picloram Isooctyl Ester: Acute Oral Toxicity Study in Fischer 344 Rats: Study No. K-041284-005A. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 22 p. Cited In: U.S. EPA, 1995b.

Jeffrey, M., Battjes, J., and Yano, B. 1987b. Tordon 22K Weed Killer: Acute Oral Toxicity Study in Fischer 344 Rats: Project ID: M-004713-002A. Unpublished study prepared by Dow Chemical Co., 16 p., MRID 40677401. Cited In: Durkin and Follansbee, 2003.

Jeffrey, M., Phillips, J., and Lomax, L. 1987c. Tordon K Salt Liquor: Acute Dermal Toxicity Study in New Zealand White Rabbits: Final Rept.: K-050731-004D. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 18 p. Cited In: U.S. EPA, 1995b.

Jeffrey, M., Schuetz, D., and Jersey, G. 1987d. Picloram Acid (Picloram Technical): Acute Dermal Toxicity Study in New Zealand White Rabbits: Final Rept.: K-038323-041D. Unpublished study prepared By The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 17 p. Cited In: U.S. EPA, 1995b.

Jeffrey, M., Schuetz, D., and Yano, B. 1987e. Picloram Isooctyl Ester: Acute Dermal Toxicity Study in New Zealand White Rabbits: Study ID K-041284-005D. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 18 p. Cited In: U.S. EPA, 1995b.

Jeffrey, M., Battjes, J., and Johnson, K. 1987f. Tordon 22K Weed Killer: Acute Dermal Toxicity Study in New Zealand White Rabbits: Project ID: M-004713-002D. Unpublished study prepared by Dow Chemical Co. 18 p. MRID 40677402. Cited In: Durkin and Follansbee, 2003.

John, J., Ouellette, J., and Johnson, K. 1984. Picloram Potassium Salt: Oral Teratology study in Rabbits: HET K-050731-003. Unpublished study submitted by Dow Chemical U.S.A., Midland, MI. MRID 00138703. Cited In: U.S. EPA, 1995b.

Johnson, K.A., Landry, T.D., Gorzinsky, S., Cieszlak, F., Kropscott, B. and Wolfe, E.L. 1986. Picloram: A two-year chronic toxicity and oncogenicity study in Fischer 344 rats. Toxicologist, 6: 83.

JW. 2006. Final Report. Task 2A: The History and Science of Herbicide Use at CFB Gagetown From 1952 to Present. Report to: Department of National Defence. Jacques Whitford, May 19, 2006.

Landry, T., Johnson, K., Cieszlak, F., *et al*. 1986. Picloram: A Two-year Dietary Chronic Toxicity-oncogenicity Study in Fischer 344 Rats. Unpublished study prepared by Dow Chemical U.S.A., 1243 p. Cited In: U.S. EPA, 1995b.

Linscombe, V., and Gollapudi, B. 1987. Evaluation of Picloram in the Chinese Hamster Ovary Cell/Hypoxanthine-guanine-phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay: Final Report: File No. TXT: K-038323-041. Unpublished study prepared by The Dow Chemical Co., 18 p. Cited In: U.S. EPA, 1995b.

Lockwood, D., and Szabo, J. 1991. Picloram 2-Ethylhexyl Ester (Picloram EHE): Probe and 21-Day Dermal Toxicity Studies in New Zealand White Rabbits: Lab Project Number: DR-0044-1725-005. Unpublished study prepared by Dow Chemical Co., 123 p. Cited In: U.S. EPA, 1995b.

McClintock, M., and Gollapudi, B. 1990a. Evaluation of a Formulation Containing Picloram Triisopropanolamine Salt (Picloram TIPA) in Rat Hepatocyte Unschedule DNA Synthesis (UDS) Assay: Lab Project Number: TXT:K- 049877-004. Unpublished study prepared by The Dow Chemical Co., 41 p. Cited In: U.S. EPA, 1995b.

McClintock, M., and Gollapudi, B. 1990b. Evaluation of a Formulation Containing Picloram Triisopropanolamine Salt in the Mouse Bone Marrow Micronucleus Test: Lab Project Number: TXT:K-049877-005. Unpublished study prepared by The Dow Chemical Co., Lake Jackson Research Center, 29 p. Cited In: U.S. EPA, 1995b.

McGuirk, R., and Cieszlak, F. 1996. Tordon 22K Weed Killer: Acute Aerosol Inhalation Toxicity Study with Fischer 344 Rats: Lab Project Number: M-004713-004. Unpublished study prepared by The Dow Chemical Co. 38 p. MRID 43959605. Cited In: Durkin and Follansbee, 2003.

MEDITEXT®. 2006. TOMES® Information System Micromedex, Inc., Englewood, Co; CCIS Volume 128, expires May, 2006. Cited In: HSDB, 2005.

Mensik, D.C., Johnston, R.V., Pinkerton, M.N., *et al*. 1976. The Cytogenetic Effects of Picloram on the Bone Marrow Cells of Rats. Unpublished study prepared in cooperation with Univ. of Texas, Medical Branch, submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:247156-I. Cited In: U.S. EPA, 1995b.

Michael, J.L., and Neary, D.G. 1993. Herbicide dissipation studies in southern forest ecosystems. Environ Toxicol Chem. 12 (3): 405-410. Cited In: Durkin and Follansbee, 2003.

Mizell, M., Jersey, G., and Schuetz, D. 1989. Picloram TIPA: Acute Dermal Toxicity Study in New Zealand White Rabbits: Final Report: Laboratory Project Study ID: K-049877-006D. Unpublished study prepared by The Dow Chemical Co., Toxicology Research Laboratory, 19 p. Cited In: U.S. EPA, 1995b.

Neary, D.G., Bush, P.B., and Michael, J.L. 1993. Fate, dissipation and environmental effects of pesticides in southern forests: A review of a decade of research progress. Environ Toxicol Chem. 12 (3):411-428. Cited In: Durkin and Follansbee, 2003.

NIOSH. 1995. International Chemical Safety Cards: Picloram. National Institute for Occupational Safety and Health. Available at: http://www.cdc.gov/niosh/ipcsneng/neng1246.html. [April 26, 2006].

Nitschke, K., and Lomax, L. 1989. Picloram Triisopropanolamine: Acute Aerosol LC50 Study in Fischer 344 Rats: Final Report: Lab Project Study ID: K-049877-007. Unpublished study prepared by The Dow Chemical Co., Toxicology Research Laboratory, 30 p. Cited In: U.S. EPA, 1995b.

Nolan, R.J., Smith, F.A., Muller, C.J., *et al*. 1980. Kinetics of 14C-labeled Picloram in Male Fischer 344 Rats. Unpublished study submitted by Dow Chemical U.S.A., Midland, Mich. CDL:247156-H. Cited in: U.S. EPA, 1995b.

Reitz, R., Dryzga, M., Helmer, D., *et al*. 1989. Picloram: General Metabolism Studies in Female Fischer 344 Rats: Project ID K-038-323-044. Unpublished study prepared by Dow Chemical Co., 57 p. Cited In: U.S. EPA, 1995b.

Rumack, B.H., and Hall, A.H (Eds.). 2006. POISINDEX® Information system Micromedex, Inc., Englewood, CO. CCIS Volume 128, expires May 2006. Cited In: HSDB, 2005.

Samson, Y., and Gollapudi, B. 1990a. Evaluation of a Formulation Containing Picloram Triisopropanolamine Salt in the Ames Salmonella/Mammalian-microsome Bacterial Mutagenicity Assay: Lab Project Study I.D.: TXT:K-049877-003. Unpublished study prepared by The Dow Chemical Co., Health and Environmental Sciences-Texas, 26 p. Cited In: U.S. EPA, 1995b.

Samson, Y., and Gollapudi, B. 1990b. Evaluation of Picloram in the Ames Salmonella/Mammalian-microsome Bacterial Mutagenicity Assay: Lab Project Study I.D.: TXT:K-038323-046. Unpublished study prepared by The Dow Chemical Co., Health and Environmental Sciences, 25 p. Cited In: U.S. EPA, 1995b.

Samson, Y., and Gollapudi, B. 1991. Evaluation of Picloram EHE in the Ames Salmonella/Mammalian Bacterial Mutagenicity Assay.: Lab Project Number: DR-0044-1725-001. Unpublished study prepared by Dow Chemical Co., 30 p. Cited In: U.S. EPA, 1995b.

Samson, Y., and Gollapudi, B. 1991. Evaluation of Picloram EHE in the Mouse Bone Marrow Micronucleus Test: Lab Project Number: DR-0044-1725-003. Unpublished study prepared by Dow Chemical Co., 32 p. Cited In: U.S. EPA, 1995b.

Schroeder, R. 1990. A Teratogenicity Study in Rats with Picloram K Salt: Final Report: Lab Project Number: 89-3459. Unpublished study prepared by Bio/dynamics, Inc., 434 p. Cited In: U.S. EPA, 1995b.

Schroeder, R. 1990b. A Teratogenicity Study in Rats with Picloram Triisopropanolamine: Final Report: Lab Project Number: 89-3461. Unpublished study prepared by Bio/dynamics, Inc, 472 p. Cited In: U.S. EPA, 1995b.

Scifres, C.J., McCall, H.G., Mazey, R., and Tai, H. 1977. Residual properties of 2,4,5-T and picloram in sandy rangeland soils. J Environ Qual. 6 (1):36-42. Cited In: Durkin and Follansbee, 2003.

SRC (Syracuse Research Corporation). 1998. Estimation Program for Log $K_{o/w}$. Syracuse Research Corporation. Available at: http://www.syrres.com/. Cited In: Durkin and Follansbee, 2003.

Stott, W., Yano, B., Haut, K., *et al*. 1992. Picloram: Two-year Dietary Oncogenicity Study in B6C3F1 Mice: Lab Project Number: K-038323-058. Unpublished study prepared by The Dow Chemical Co., 919 p. Cited In: U.S. EPA, 1995b.

Streeter, C., Battjes, J., and Johnson, K. 1987a. Picloram Isooctyl Ester: An Acute Aerosol Inhalation Study in Fischer 344 Rats: K-041284-006. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 21 p. Cited In: U.S. EPA, 1995b.

Streeter, C., Battjes, J., and Johnson, K. 1987b. Picloram Acid: An Acute Aerosol Inhalation Study in Fischer 344 Rats: Final Report.: K-038323-043. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory. 21 p. MRID 40479415. Cited In: Durkin and Follansbee, 2003 and U.S. EPA, 1995b.

Streeter, C., Battjes, J., and Yano, B. 1987c. Tordon K Salt Liquor: An Acute Aerosol Inhalation Study in Fischer 344 Rats: Final Rept.: K-050731-005. Unpublished study prepared by The Dow Chemical Co., Mammalian and Environmental Toxicology Research Laboratory, 20 p. Cited In: U.S. EPA, 1995b.

Streeter, C., Eisenbrandt, D., and Battjes, J. 1988. Tordon 22K Weed Killer: An Acute Aerosol Inhalation Study in Fischer 344 Rats: Project ID: M-004713-003. Unpublished study prepared by Dow Chemical Co., 20 p. Cited In: Durkin and Follansbee, 2003.

Szabo, J., and Grandjean, M. 1990. Picloram Triisopropanolamine: 13 Week Dietary Toxicity Study in Fischer 344 Rats: Lab Project Study ID: TXT:K-049877-009. Unpublished study prepared by Dow Chemical Co., Lake Jackson Research Center, 239 p. Cited In: U.S. EPA, 1995b.

USDA. 1995. Picloram: Pesticide Fact Sheet. U.S. Department of Agriculture/Forest Service Prepared by Information Ventures, Inc. under U.S. Forest Service Contract. Cited In: Durkin and Follansbee, 2003.

USDA. 1989a. Final Environmental Impact Statement: Vegetation Management in the Coastal Plain/Piedmont, Management Bulletin R8-MB-23. U.S. Department of Agriculture/Forest Service, 1213 p. Cited In: Durkin and Follansbee, 2003.

USDA. 1989b. Pesticide Background Statements: Volume 1. Herbicides. U.S. Department of Agriculture/Forest Service. Available from NTIS. PB89-226682. Cited In: Durkin and Follansbee, 2003.

U.S. EPA. 1992a. Drinking water criteria document for picloram. United States Environmental Protection Agency. Health and Ecological Criteria Division.

U.S. EPA. 1992b. Picloram. Integrated Risk Information System, U.S. Environmental Protection Agency. Available at: http://www.epa.gov/iris/subst/0256.htm. [April 24, 2006].

U.S. EPA. 1995a. R.E.D. Facts: Picloram. U.S. Environmental Protection Agency, Prevention, Pesticides, and Toxic Substances, EPA 738–F-95-018.

U.S. EPA. 1995b. Reregistration eligibility decision (RED) for picloram. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Washington, DC. EPA 738-R95-019. Available at: http://www.epa.gov/oppsrrd1/REDs/0096.pdf. [April 26, 2006].

Vedula, U., Stebbins, K., and Breslin, W. 1991. 2-Ethylhexyl Ester of Picloram: Oral Gavage Teratology Study in Sprague-Dawley Rats: Lab Project Number: DR-0044-1752-007. Unpublished study prepared by Dow Chemical Co., 193 p. Cited In: U.S. EPA, 1995b.

Vedula, U., Stebbins, K., and Breslin, W. 1992. Picloram Triisopropanolamine Salt: Oral Gavage Teratology Study in New Zealand White Rabbits: Lab Project Number: K-049877-015. Unpublished study prepared by The Dow Chemical Co., 422 p. Cited In: U.S. EPA, 1995b.

Young, J. 1988. Picloram: 12-Month Dog Chronic Dietary Toxicity Study: Project Study ID: TXT:K-038323-040. Unpublished study prepared by Dow Chemical Co., 154 p. Cited In: U.S. EPA, 1995b.

Washburn, K. 2002. Product Chemistry: Technical Grade Product: Picloram Technical: Final Report: Lab Project Number: 6811-01. Unpublished study prepared by StillMeadow, Inc., 31 p. Cited In: Durkin and Follansbee, 2003.

Woodburn, K.B., Fontaine, D.D., and Bjerke, E.L. 1989. Photolysis of picloram in dilute aqueous solution. Environ Toxicol Chem. 8 :769-775. Cited In: Durkin and Follansbee, 2003.

Zablotny, C., Stebbins, K., and Breslin, W. 1991. 2-Ethylhexyl Ester of Picloram: Oral Gavage Teratology Study in New Zealand White Rabbits: Lab Project Number: DR-0044-1725-008. Unpublished study prepared by Dow Chemical Co., 260 p. Cited In: U.S. EPA, 1995b.

Zepp, R.G. 1991. Pestic Chem: Adv Int Res, Dev, Legis, Proc Int Congr Pestic Chem, 7th 1990, Environ Res Lab, US EPA, Athens, GA, pp. 329-45. Cited In: HSDB, 2005.