B7-1.0 FENOPROP

B7-1.1 Background Information

IUPAC: (RS)-2-(2,4,5-trichlorophenoxy)propionic acid

CAS: 2-(2,4,5-trichlorophenoxy)propanoic acid

CASRN: 93-72-1

FENOPROP USAGE:

Fenoprop is a post-emergence selective herbicide against annual and perennial broadleaf weeds (CEPA, 2002). It was used in cereal, fruit crops and had aquatic weed control uses in ditches and riverbanks (Tomlin, 1995; Kaufman *et al*., 1998). Fenoprop was very effective as an herbicide, but its registration was cancelled by the U.S. EPA in 1986. It was judged to pose unacceptable human health risks due to its high propensity for contamination with its toxic by-products, notably 2,3,7,8-tetrachlorodibenzo-p-dioxin from its manufacturing processes. Fenoprop can be used as an acid, ester or a salt.

Fenoprop was sprayed at CFB Gagetown on designated plots during the CFS1966/67 Tests only.

Table B7-1 Fenoprop Usage at CFB Gagetown[a]

Year	Amount of Fenoprop Applied (kg)	Total Area Treated (ha)
1966	2.9E+00	8.7E-01
1967	2.9E+00	8.7E-01
Total	**5.9E+00**	**1.7E+00**

[a] Adapted from Boynton, 1969.

B7-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_9H_7Cl_3O_3$

Activity: A phenoxypropionic herbicide, with similar activity as the auxins. Fenoprop is a plant growth regulator (Morais *et al*., 2002).

Notes: Fenoprop is generally referred to as 2,4,5-TP in Europe, and Silvex in the United States. Various forms of fenoprop include: fenoprop-butometyl, fenoprop-butotyl, fenoprop-3-butoxypropyl [CASRN: 6047-17-2], fenoprop-butyl [CASRN: 13557-98-7], fenoprop-isoctyl, fenoprop-methyl [CASRN: 4841-20-7], fenoprop-potassium [CASRN: 2818-16-8].

Structure:

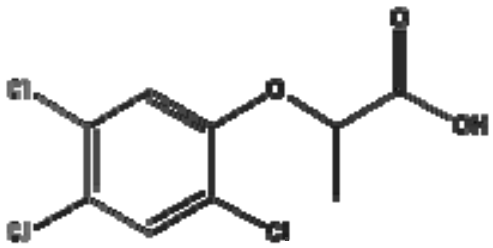

Figure B7-1 Fenoprop CASRN: 93-72-1 Structure

Table B7-2 Chemical and Physical Properties of Fenoprop

Chemical/Physical Property	Result	Reference
Colour/Form	White powder	HSDB, 2000
Dissociation Constant (pKa)	2.84	JW, 2006
Henry's Law constant	$9.06x10^{-09}$atm-m^3/mole at 25ºC	JW, 2006
Log K_{ow}	3.8	JW, 2006
Melting Point	181.6ºC	HSDB, 2000
Molecular Weight	269.51	JW, 2006
Vapour Pressure	$9.06x10^{-06}$mm Hg at 25ºC	JW, 2006
Water Solubility	71 mg/L at 25ºC	JW, 2006

B7-3.0 PMRA EVALUATION

PMRA has removed the evaluation requirements regarding fenoprop, since it is no longer registered for use in Canada (Government of Canada, 2005).

B7-4.0 TOXICOLOGICAL SUMMARY

The following toxicological profile for fenoprop is a short summary based on the California Environmental Protection Agency's (CalEPA) draft report entitled "Public Health Goal for Silvex in Drinking Water" and WHO's Guidelines for Drinking-water Quality. Only the toxicological studies appropriate for guideline development were highlighted below.

B7-4.1 Human Health Effects

Table B7-3 Human Health Effects Resulting from Acute Exposure to Fenoprop Containing Herbicides [a,b]

Exposure	Effects	Response
Acute		
	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.

Table B7-3 Human Health Effects Resulting from Acute Exposure to Fenoprop Containing Herbicides [a,b]

Exposure	Effects	Response
Acute		
	Respiratory	Ingestion of large amounts may cause bradypnea, respiratory failure, hyperventilation, or pulmonary edema.
	Neurologic	Low dose exposures: Vertigo, headache, malaise, and paresthesias may occur depending on the specific compound involved. High dose exposures: Muscle twitching, spasms, profound weakness, polyneuritis, and unconsciousness may occur depending on the specific compound involved. Idiosyncratic reactions: Peripheral neuropathies.
	Gastrointestinal	Nausea, vomiting, and diarrhea have been reported. Necrosis of the gastrointestinal mucosa has been reported.
	Hepatic	Elevated LDH, AST, and ALT have been reported.
	Genitourinary	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 haematologic effect. Leukopenia has also been reported.
	Dermalogic	Direct contact may cause skin irritation. Chlorodioxin contamination of products may produce chloracne with heavy exposure.
	Musculoskeletal	Muscle cramps, muscle rigidity, elevated creatinine kinase.

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

B7-4.2 Health Effects by Route of Exposure

B7-4.2.1 Oral Exposure

Table B7-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Fenoprop

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute		
Mice	1410[a]	U.S. EPA, 1987a
Rats	650	U.S. EPA, 1987a
Rats	600[b]	U.S. EPA, 1987a
Rats	620[a]	U.S. EPA, 1987a
Guinea pig	1250[a]	U.S. EPA, 1987a
Rabbit	750[b]	U.S. EPA, 1987a
Rabbit	819[a]	U.S. EPA, 1987a

[a] Propylene glycol butyl ether ester form of fenoprop used.
[b] Mixed butyl esters of fenoprop used.

Table B7-5 Mammalian Effects Resulting from Oral Exposure to Fenoprop

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Sub-chronic				
Rats	Diet	0, 10, 30, 100, 300 and 600 mg/kg/day for 90 days[a]	Slight enlargement of the liver. Decreased body weight gains. Histopathologic changes at highest doses indicating malnutrition.	Mullisson, 1966a

Table B7-5 Mammalian Effects Resulting from Oral Exposure to Fenoprop

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Rats	Diet	0, 100, 300, 1,000, 3,000, 10000 ppm in diet for 90 days[b]	Growth retardation, liver and kidney sizes were increased, histopathological changes including swelling, granular degeneration, necrosis of hepatocytes, swelling of renal tubule cells, vacuolation and degeneration of seminiferous tubules.	Mullisson, 1966a
Beagle dogs	Diet	0, 4, 13 and 40 mg/kg/day for 90 days[c]	Lower body weight for both sexes, increased serum alkaline phosphatase, decreased haemoglobin, and decreased haematocrit.	Mullisson, 1966a
Sheep	Gavage	100 mg/kg/day for 21 days followed by 10 days at 150 mg/kg/day[a]	Anorexia, depression, tense appearance and muscular spasms. Two animals died. Inflamed and swollen lymphatics, enteritis, enlarged and congested spleen, and rumen stasis, elevated serum levels of glutamic oxaloacetic transaminase and lactic dehydrogenase.	Wright *et al*., 1966
		Chronic		
Rats	Diet	0, 0.26, 0.8, 2.6, or 7.9 mg/kg/day for 18 mths[c]	Reduced body weights and increased relative kidney weights in males in highest dose levels.	Gehring *et al.*, 1978a
Rats	Diet	5.3, 16, 53, or 160 mg/kg of diet for 2 years	Increased kidney weights.	Mullisson, 1966b
Beagle dogs	Diet	30, 101, or 300 mg/kg of diet for 2 years[c]	Severe liver pathology observed in both sexes.	Mullisson, 1966b
Beagle dogs	Diet	0.9, 2.6, 8.2, or 9.9 mg/kg/day for 2 years[c]	Mild degeneration and necrosis of the hepatocytes and fibroblastic proliferation in both sexes at highest dose levels.	Gehring *et al.*, 1978a

[a] Propylene glycol butyl ether ester form of fenoprop used.
[b] Sodium salt of fenoprop used.
[c] Potassium salt of fenoprop was used.

Table B7-6 Mammalian Developmental Effects Resulting from Oral Exposure to Fenoprop

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
CD-1 Mice	Oral/ subc-utaneous administration	404 mg/kg/day gestation days 12-15	Maternal effects: increased weight gain, due to increases in liver size. Developmental effects: Subcutaneous administration caused increased fetal mortality. Both oral and subcutaneous administration caused decreased fetal weight gain. Cleft palate in pups was also observed in oral administrations.	Courtney, 1977
Rats	Oral	25-100 mg/kg/ day during gestation days 6-15[a]	Maternal effects: alopecia, loss of appetite and vaginal bleeding. Fetal effects: cleft palate, retarded ossification, extra cervical ribs, microphthalmia and cardiovascular changes.	U.S. EPA, 1987b

[a] Fenoprop containing less than 0.05 ppm of TCDD was used.

B7-4.2.1.1 No Observed Adverse Effect Levels

Table B7-7 Mammalian NOAELs and LOAELs for Oral Exposure to Fenoprop

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Sub-chronic				
Rats	NOAEL	10	Hepatic effects.	Mullisson, 1966a
Beagle dogs	NOAEL	13	Body weight changes and blood chemistry effects.	Mullisson, 1966a
Chronic				
Rats	NOAEL	2.6	Reduced body weights and increased relative kidney weights.	Gehring *et al.*, 1978a
Rats	NOAEL	3.18	Increased kidney weights.	Mullisson, 1966b
Beagle	NOAEL (M)	0.75	Liver pathology.	Mullisson, 1966b
	NOAEL (F)	2.5		
Beagle	NOAEL (M)	0.9	Systemic effects in the liver and serum enzyme effects.	Gehring *et al.*, 1978a
	NOAEL (F)	2.6		

B7-4.2.2 Dermal Exposure

No data found.

B7-4.2.3 Inhalation Exposure

No data found.

B7-4.3 Carcinogenicity

U.S. EPA has assigned fenoprop as a Group D (not classifiable as to human carcinogenicity) carcinogen. Fenoprop was not classifiable as to its carcinogenicity in humans due to lack of human data and inadequate animal testing (CEPA, 2002). Furthermore, genotoxicity studies of fenoprop returned negative results (Andersen *et al*., 1972; Mersch-Sundermann *et al*., 1988). It was shown that fenoprop was not mutagenic in the absence, and presence of an activation S9 microsomal fraction (Andersen *et al*., 1972; Mersch-Sundermann *et al*., 1988).

B7-4.4 Populations at Special Risk

No information found.

B7-4.5 Toxicokinetics

In a rat study, it was found that 94% of administered fenoprop was excreted in the urine (78%) and feces (16%) 192 hours after initial exposure (Sauerhoff *et al*., 1977a). In rats, fenoprop will be extensively absorbed. It was found that a significant amount of excreted fenoprop will be reabsorbed in rats during enterohepatic circulation. This was demonstrated by the more rapid excretion of fenoprop in bile duct-cannulated rats compared to bile duct-intact rats (Sauerhoff *et al*., 1977a). In humans, peak plasma levels of fenoprop were observed within two to four hour period after initial exposure to a dose of 1.0 mg/kg of fenoprop (Sauerhoff *et al*., 1977b). This demonstrated rapid absorption in the human volunteers. Furthermore, after 168 hours, approximately 80% of the fenoprop elicited was recovered in urine and feces (<3.2%) (Sauerhoff *et al*., 1977b). From the rat study (Sauerhoff *et al*., 1977a) it was found that fenoprop will distribute to the liver, kidneys, brain tissue, perirenal fat, abdominal fat, and muscle tissues. In general kidneys and the liver had the highest fenoprop distribution ratios (Sauerhoff *et al*., 1977a). Esters of fenoprop were found to rapidly hydrolyzed in the animal gut, followed by rapid absorption (CEPA, 200). In humans, fenoprop will either be excreted unchanged, or conjugate with glucuronic acid or amino acids (Leng, 1977). The basic fenoprop structure will not be readily altered (CEPA, 2002).

B7-4.6 Exposure Limits

Table B7-8 Existing RfD Values for Fenoprop Exposures

Reference Dose (mg/kg/day)	Reference	Endpoint	Study	Reference	NOAEL (mg/kg/day)	Uncertainty Factor	Study Classification
Acute/Short-term (1-7 days)							
No Information Found	--	--	--	--	--	--	--
Intermediate-term (7 days- Several months)							
No Information Found	--	--	--	--	--	--	--
Long-term (6 months to lifetime)							
0.003	WHO, 1996	Adverse effects on the liver	2 year Dog feeding study	Gehring *et al*., 1978a	0.9	300	--
0.008	U.S. EPA, 1988	Histo-pathological changes in the liver	Dog Chronic Oral Bioassay	Mullison, 1966c Gehring *et al*., 1978b	0.75	100	Acceptable, confidence in the RfD is Medium

A chronic RfD of 0.003 mg/kg/day (WHO, 1996) was selected for risk assessment purposes.

B7-5.0 ENVIRONMENTAL FATE AND EXPOSURE

Fenoprop has low vapour pressure and thus volatilization would only occur to a minor extent. Furthermore, fenoprop also has a low Henry's Law constant of $9.06x10^{-09}$atm-m^3/mole (JW, 2006). This indicates that it would have little tendency to escape from an aqueous solution. Hence, Fenoprop will not be expected to be found in air with the exception as a consequence of direct aerial application of compounds to agricultural and non agricultural areas. Fenoprop also reacts strongly with photochemically produced hydroxyl ions, leading to a relatively short half-life of 6.3 hrs in air (CEPA, 2002). Fenoprop will not hydrolyze in water. It will adsorb strongly to sediment and biodegrade at a relatively slow rate. However, near the water's surface, fenoprop is subjected to photooxidation (CEPA, 2002). Similarly, fenoprop will adsorb strongly to soil but it will biodegrade to 2,4,5-trichlorophenol. Fenoprop can migrate in sandy and clay soils with a reported half-life ranging from 12 to 17 days (CEPA, 2002).

B7-6.0 SUMMARY

Fenoprop is a post-emergent selective herbicide used against annual and perennial broadleaf weeds. While fenoprop was used in agriculture, landscaping, and the forestry industries, it is no longer registered for use in Canada and the United States (CEPA, 2002). Between 1966 and 1967, approximately 5.9 kg of fenoprop was applied in combination with 2,4-D on 1.7 ha of selected test plots at CFB Gagetown.

Acute exposures to fenoprop through the oral route caused systemic toxicity in mammalian studies. In rodents, fenoprop also caused noticeable developmental and/or reproductive effects during dietary feeding studies. Furthermore, the U.S. EPA has classified fenoprop as a Group D carcinogen (not classifiable as a human carcinogen).

B7-7.0 REFERENCES

Andersen, K.J., Leighty, E.G. and Takahashi, M.T. 1972. Evaluation of herbicides for possible mutagenic properties. J Agr Food Chem 20: 649-656. Cited In: CEPA, 2002.

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

CEPA. 2002. Public Health Goal for Silvex in Drinking Water-Draft. Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, Claifornia Environmental Protection Agency. June, 2002. Available at: http://www.oehha.ca.gov/water/phg/pdf/Silvexposting53002.pdf#search=%22silvex%20ban%22 [Sept 5, 2006]

Courtney, D.K. 1977. Prenatal effects of herbicides: evaluation by the Prenatal Development Index. Archives of environmental contamination and toxicology, 6:33-46. Cited In: CEPA, 2002.

Gehring, P.J. and Betso, J.E. 1978a. Phenoxy acids: effects and fate in mammals. Ecological bulletin (Stockholm) 27:122-133. Cited In: WHO, 1996.

Gehring, P.J. and J.E. Betso. 1978b. Phenoxy acids: Effects and fate in mammals. In: Chlorinated Phenoxy Acids and Their Dioxins, Vol. 27, C. Ramel, Ed. Ecol. Bull., Stockholm. p. 122-133. Cited In: U.S. EPA, 1988.

Government of Canada. 2005. Canada Gazette, Part 1, Section 19. Government of Canada Publications, Public Works and Government Services Canada. Ottawa, ON.

HSDB. 2000. 2,4,5-TP. Hazardous Substance Data Bank, National Library of Medicine. Online hazardous chemical database Available at: http://toxnet.nlm.nih.gov/cgibin/sis /htmlgen?SDB. Cited In: CEPA, 2002.

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.

Kaufmann, D.D. and Kearney, P.C. 1998. In: Herbicides, vol1, Chmistry, degradation, and mode of action, 2nd edn. Marcel Dekker, New York.

Leng. M.L. 1977. Comparative metabolism of phenoxy herbicides in animals. In: Fate of pesticides in large animals. Ivie GW and Dorough HW, eds. Academic Press, New York, pp. 53-76. Cited In: CEPA, 2002.

MEDITEXT®. 2006. TOMES® Information System Micromedex, Inc., Englewood, Co; CCIS Volume 130, expires Nov, 2006. Cited In: HSDB, 2000.

Mersch-Sundermann, V., Dickgiesser, N., Hablizel, U. and Gruber, B. 1988. Examination of mutagenicity of organic microcontaminants in the environment. Zentralbl Bakteriol Mikrobiol 183(3):247-260. Cited In: CEPA, 2002.

Morais, S., Casino, P., Marin, L., Puchades, R. and Maquieira A. 2002. Assessment of enzyme-linked immunosorbent assay for the determination of 2,4,5-TP in water and soil. Anal Bioanal Chem 374:262-268.

Mullison, W.R. 1966. Some toxicological aspects of silvex. In: Proceedings of the Nineteenth Annual Meeting of the Southern Weed Conference, January 18, 19, 20, 1966, Jacksonville, Florida, pp. 420-435. Cited In: WHO, 1996.

Mullison, W.R. 1966a. Some toxicological aspects of silvex. In: Proceedings of the ineteenth Annual Meeting of the Southern Weed Conference, January 18, 19, 20, 1966, Jacksonville, Florida, pp. 420-435. Cited In: CEPA, 2002.

Mullison, W.R. 1966c. Some toxicological aspects of silvex. In: Proc. 19th Ann. Meet., Southern Weed Conference, Jacksonville, FL. p. 420-435. Cited In: U.S. EPA, 1988.

Rumack, B.H., and Hall, A.H. Eds. 2006. POISINDEX® Information system Micromedex, Inc., Englewood, CO. CCIS Volume 130, expires Nov 2006. Cited In: HSDB, 2000.

Sauerhoff, M.W., Braun, W.H. and LeBeau, J.E. 1977a. Dose-dependent pharmacokinetics profile of silvex following intravenous administration in rats. J Tox Environ Health 2:605-618. Cited In: CEPA, 2002.

Sauerhoff, M.W., Chenoweth, M.B., Karbowski, R.J., Braun, W.H., Ramsey, J.C., Gehring, P.J. and Blau, G.E. 1977b. Fate of silvex following oral administration to humans. J Tox Environ Health 3:941-952. Cited In: CEPA, 2002.

Tomlin, C. 1995. The pesticide manual, 10th edn. British Crop Protection Council and The Royal Society of Chemistry, Bath. Cited In: Morais *et al*., 2002.

U.S. EPA. 1987a. Health advisory for 2,4,5-trichlorophenoxypropionic acid. Office f Water, U.S. Environmental Protection Agency. PB95-153904. Cited In: CEPA, 2002.

U.S. EPA. 1987b. Drinking water criteria document for 2(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP). US Environmental Protection Agency. Washington, DC. Cited In: WHO, 1996.

U.S. EPA. 1988. (2,4,5-Trichlorophenoxy) propionic acid. Integrated Risk Information System, U.S. Environmental Protection Agency. Available at: http://www.epa.gov/iris/subst/0323.htm [July 5, 2006]

WHO.1996. Chlorophenoxy herbicides (excluding 2,4-D and MCPA) in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva, Switzerland. Available at: http://www.who.int/ water_sanitation_health/dwq/chemicals/chlorophenoxyherb.pdf [August 23, 2006]

Wright, F.C., Palmer, J.S., Hunt, L.M. 1966. Preliminary study on toxicologic and biochemical effects of silvex on sheep. Am J Vet Res 27:172-176. Cited In: CEPA, 2002.