B12-1.0 TRICHLOROACETIC ACID (TCA)

B12-1.1 Background Information

IUPAC: Trichloroethanoic acid

CAS: Trichloroacetic acid

CASRN: 76-03-9

TRICHLOROACETIC ACID USAGE:

TCA is a pre-emergence herbicide for the control of annual and perennial grasses in oilseed rape, sugar beet, fodder beet, asparagus, rhubarb, carrots, potatoes, tomatoes, peas, field beans, lettuce, alfalfa, sunflowers, sugar cane, cotton, flax, rice, gladioli and on non-crop areas.

TCA was used in conjunction with 2,4-D and 2,4,5-T, and it was only applied during the 1967 U.S. trials (Demaree *et al*., 1968).

Table B12-1 TCA Usage at CFB Gagetown[a]

Year	Total Area Treated (ha)	Total TCA Applied (kg)
1967	0.66	12
Total	**6.6E-01**	**1.2E+01**

[a] Adapted from Demaree *et al*., 1968.

B12-1.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: Cl_3CCOOH

Activity: TCA-sodium is a halogenated alkanoic acid systemic herbicide. It is absorbed by the roots of plants and will be translocated readily. Studies have shown that TCA tend to accumulate in meristematic tissues (Tomlin, 1995).

Notes: TCA was used as a sodium salt (Sodium Trichloroacetate) [CASRN: 650-51-1] in CFB Gagetown. TCA is known to cause non-selective leaf chlorosis. TCA is not registered for use in Canada or in United States.

Structure:

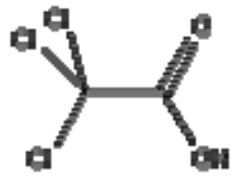

Figure B12-1 TCA CASRN: 76-03-9 Structure

Table B12-2 Chemical and Physical Properties of TCA

Chemical/Physical Property	Result	Reference
Colour/Form	Colourless hygroscopic crystals	Tomlin, 1995
	Yellowsih deliquescent powder[a]	
Dissociation Constant (pKa)	0.512-0.7	WHO, 2004
	0.512	JW, 2006
Henry's Law constant	$1.35x10^{-5}$atm-m^3/mole at 25ºC[a]	JW, 2006
Log K_{ow}	1.33 [a]	JW, 2006
Melting Point	55-58ºC	Tomlin, 1995
	165-200ºC [a]	
Molecular Weight	163.4	Tomlin, 1995
	185.37 [a]	JW, 2006
Vapour Pressure	2.60×10^{-08} mm Hg at 25ºC [a]	JW, 2006
Water Solubility	10kg/L at 25ºC	Tomlin, 1995
	1.2kg/L at 25ºC [a]	

[a] As a sodium salt.

B12-3.0 PMRA EVALUATION

No information found.

B12-4.0 TOXICOLOGICAL SUMMARY

B12-4.1 Human Health Effects

Table B12-3 Human Health Effects Resulting from Acute Exposure to Trichloroacetic Acid Containing Herbicides[a,b]

Exposure	Effects	Response
	Heent	Eye exposure may result in pain, swelling, corneal rosions and blindness.
	Cardiovascular	Cardiovascular collapse may develop soon after severe poisonings.
	Respiratory	Inhalation may produce dyspnea, pleuritic chest pain, upper airway edema, pulmonary edema, hypoxemia, bronchospasm, pneumonitis, and persistent pulmonary function abnormalities. Airway hyperreactivity has also been reported. The onset of respiratory symptoms may be delayed for several hours.

Table B12-3 Human Health Effects Resulting from Acute Exposure to Trichloroacetic Acid Containing Herbicides[a,b]

Exposure	Effects	Response
	Gastrointestinal	Ingestion of acids may result in burns, gastrointestinal bleeding, gastritis, perforations, dilation, edema, necrosis, vomiting, stenosis, fistula, and duodenal/jejunal injury.
	Hepatic	Systemic toxicity may result in acute hepatic injury.
	Genitourinary	Renal failure is a rare complication of severe poisonings. Haemoglobinuria may develop secondary to haemolysis.
	Acid-Base	Metabolic acidosis may develop following significant acid ingestion
	Fluid-electrolyte	Massive fluid and electrolyte shifts may occur with extensive dermal or gastrointestinal burns. Hyperkalemia may occur with haemolysis. Hyperphosphatemia, hypocalcemia and hyperchloremia have been reported.
	Hematologic	Haemolysis may occur following significant acid ingestion. Disseminated intravascular coagulation has been reported.
	Dermalogic	Chemical burns to the skin are often associated with concurrent thermal burns and trauma. Complications seen with thermal burns including cellulitis, sepsis, contractures, osteomyelitis, may occur as well as systemic toxicity from absorbed acid. Deep or extensive burns may require grafting. Alopecia was reported following application of an acidic formulation of a hair-relaxing product.

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

B12-4.2 Health Effects by Route of Exposure

B12-4.2.1 Oral Exposure

Table B12-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Trichloroacetic-Acid

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute		
Mice	4970	Woodard *et al*., 1941
Rats	3200	WHO, 2004b
Rats	3320	Woodard *et a*l., 1941

Table B12-5 Mammalian Effects Resulting from Oral Exposure to TCA

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Sub-chronic				
B6C3F_1 Mice	Drinking-water	0, 25, 125 or 500 mg/kg/day for 3 or 10 weeks	After 3 weeks, liver weight was increased in the two highest dose groups, accompanied by increased 12- hydroxylation of lauric acid. After 10 weeks, effects included increased absolute and relative liver weights in the two highest dose groups, a dose-related increase in cyanide-insensitive palmitoyl-CoA oxidase activity, increased 12-hydroxylation of lauric acid and increased peroxisome proliferation.	Parrish *et al*., 1996

Table B12-5 Mammalian Effects Resulting from Oral Exposure to TCA

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Male B6C3F$_1$ mice	Drinking-water	0, 75, 250 or 500 mg/kg/day for 14 days	Dose-related increase in liver weights.	Sanchez and Bull, 1990
Sprague-Dawley rats	Drinking-water	312 mg/kg/day for 10, 20 or 30 days	No systemic effects observed.	Parnell *et al*., 1988
F344 rats B6C3F$_1$	Gavage	500 mg/kg/day for 10 days	Relative liver weights and cyanide insensitive palmitoyl-CoA oxidation were increased. There was no effect on relative kidney weights.	Goldsworthy and Popp, 1987
Male Sprague-Dawley rats	Drinking-water	0, 4.1, 36.5, 355 mg/kg/day for 90 days	At the two highest dose levels, decreased absolute spleen weight and increased relative liver and kidney weights were observed. At the highest dose, there was focal hepatocellular enlargement, intracellular hepatic swelling, hepatic glycogen accumulation and increased hepatic peroxisomal β-oxidation activity.	Mather *et al*., 1990
Male Wistar rats	Drinking-water	0, 3.8 mg/kg/ day for 10 weeks	Decreased body weight, changes in serum markers for lipid and carbohydrate metabolism (increased succinate dehydrogenase activity, increased glycogen accumulation and decreased liver triglyceride and cholesterol levels) and decreased kidney glutathione levels. No changes in relative liver weight, serum liver enzyme activity or liver glutathione levels were observed	Acharya *et al*., 1995
Male Wistar rats	Drinking-water	0, 3.8 mg/kg/day for 10 weeks	Mild liver and kidney histopathology were observed	Acharya *et al*., 1997
Chronic				
Female B6C3F$_1$ mice	Drinking-water	0, 78, 262 or 784 mg/kg/day for 51 or 82 weeks	Decreased body weight and increased relative liver weights	Pereira, 1996
F344 rats	Drinking-water	0, 78, 262 or 784 mg/kg/day	Decreased body weight, decreased absolute (but not relative) liver weight, increased serum alanine aminotransferase activity, increased cyanide-insensitive palmitoyl-CoA oxidase activity and increased severity of hepatic necrosis. No changes in kidney, spleen or testis weights. There was no evidence of increased hepatocellular proliferation, as measured by radiolabelled thymidine incorporation rates. At 32.5 mg/kg of body weight per day, a significant decrease in serum aspartate aminotransferase activity was observed.	DeAngelo *et al*., 1997

Table B12-6 Mammalian Reproductive and Developmental Effects Resulting from Oral Exposure to TCA

est Organism (Species)	Exposure	Dose (mg/kg/day) (Duration)	Response	Reference
Pregnant Long Evans rats	Gavage	0, 330, 800, 1200 or 1,800 mg/kg/day on gestation days 6-15	At 330 mg/kg of body weight per day and higher, fetal weight and length were significantly reduced, and an increase in the incidence of soft tissue malformations, primarily involving the cardiovascular and renal systems, was observed. Skeletal malformations of the orbit and hydronephrosis were also noted.	Smith *et al*., 1989
Pregnant Sprague-Dawley rats	Drinking-water	0 or 290 mg/kg/day on gestation days 1-22	A significant decrease in body weight gain was observed in treated dams relative to controls. Reproductive effects included increased resorptions and increased cardiac soft tissue malformations.	Johnson *et al*., 1998

B12-4.2.1.1 No Observed Adverse Effect Levels

Table B12-7 Mammalian NOAELs and LOAELs for Oral Exposure to TCA

Test Organism (Species)	Effect	Value (mg/kg/day)	Endpoint	Reference
Sub-chronic				
B6C3F$_1$ Mice	LOAEL	500	Liver effects	Goldsworthy and Popp, 1987
B6C3F$_1$ Mice	NOAEL	25	Liver effects	Parrish *et al*., 1996
Male B6C3F$_1$ Mice	NOAEL	75	Dose-related increase in liver weight	Sanchez and Bull, 1990
Male Wistar rats	LOAEL	3.8	Systemic effects involving body weight, liver and kidney effects	Acharya *et al*., 1995
Male Wistar rats	LOAEL	3.8	Mild liver and kidney histopathology.	Acharya *et al*., 1997
F344 rats	LOAEL	500	Liver effects	Goldsworthy and Popp, 1987
Male Sprague-Dawley rats	NOAEL	36.5	Liver effects	Mather *et al*., 1990
Sprague-Dawley rats	NOAEL	312	Systemic effects	Parnell *et al*., 1988
Chronic				
F344 rats	NOAEL	32.5	Non neoplastic effects	DeAngelo *et al*., 1997
Female B6C3F$_1$ mice	NOAEL	78	Liver weight increases	Pereira, 1996

B12-4.2.2 Dermal Exposure

Table B12-8 Mammalian LD_{50} Values Resulting from Dermal Exposure to TCA

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute		
Rats	>2,000[a]	Health Canada, 2006

[a] As a sodium salt.

For dermatological effects of TCA to humans, refer to Table B12-8

B12-4.2.3 Inhalation Exposure

No data found.

B12-4.3 Carcinogenicity

IARC (2002) classified TCA as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). However, U.S. EPA (1994) classified TCA in group C, a possible human carcinogen, in accordance with the U.S. EPA, 1986 Guidelines for Carcinogen Risk Assessment. Under the 1999 U.S. EPA Draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), there was suggestive evidence of TCA being a carcinogen, but the data present were not sufficient enough to assess human carcinogenicity (U.S. EPA, 2002). For the risk assessment purposes of this report, TCA will not be assessed as a carcinogen.

Table B12-9 Animal Carcinogenicity Data

Test Subjects	Exposure	Dose	Response	Reference
Male B6C3F$_1$ Mice	Drinking-water	0, 178 or 319 mg/kg/day for 37 or 52 weeks	Increased incidence of hepatocellular carcinomas in males. No increase in the incidence of hepatocellular carcinoma in females.	Bull *et al*., 1990
Male B6C3F$_1$ Mice	Drinking-water	0, 8, 71 or 595 mg/kg/day for 60 weeks	Significant increases in the incidence of combined hepatocellular tumours, adenomas and carcinomas were observed relative to controls.	U.S. EPA, 1991
B6C3F$_1$ Mice	Drinking-water	583 mg/kg/day for 94 weeks.	Significant increased incidence of combined hepatocellular adenomas/carcinomas were observed in both male and females.	U.S. EPA, 1991
B6C3F$_1$ Mice	Drinking-water	0, 78, 262, 784 mg/kg /day for 51 or 82 weeks	Liver carcinomas, increased incidences of altered hepatocellular foci, adenomas and carcinoms. Lesions were predominantly basophilic or mixed basophilic/eosinophilic, lacked expression of glutathione-S-transferase-pi and were consistent with peroxisome proliferation involvement in tumourignesis.	Pereira, 1996
F344 rats	Drinking-water	0, 3.6, 32.5, 364 mg/kg/day for 104 weeks	No evidence of carcinogenicity.	DeAngelo *et al*., 1997

In male mice, TCA did not modify the incidence of mutations in exon 2 of H-*ras* in carcinomas, nor did it alter the mutational spectrum observed in tumours that bore a mutation in exon 2. In female mice, 27% of tumours promoted by TCA exhibited loss of heterozygosity at a minimum of two loci on chromosome 6 (Tao *et al*., 1996).

In mouse liver *in vivo*, measurements of TCA-induced 8-hydroxydeoxyguanosine DNA adducts gave different results depending on the route of administration (Von Tungeln *et al.*, 2002; Bhunya and Behere, 1987). TCA induced abnormal sperm in mice *in vivo* in one study and chromosomal aberrations in mouse bone marrow *in vivo* after administration at single high doses (Bhunya and Behere, 1987). The results of *in vivo* studies in rodents on the induction of DNA

strand breaks and micronuclei were inconsistent with these earlier findings (Styles *et al*., 1991; Nelson *et al*., 1989).

In human cells *in vitro*, TCA did not induce chromosomal aberrations or DNA strand breaks in single studies (Kurinnyi, 1984). In another study, renal cells from mice exposed *in vivo* to trichloroethylene (which was metabolized to TCA) no effect was observed in a DNA strand-break assay or a single-cell gel assay (Comet assay) (Mensing *et al*., 2002). TCA inhibited intercellular communication in cultured mouse but not in rat hepatocytes (Klaunig *et al*., 1989). TCA was assessed to be a very weak mutagen in the mouse lymphoma L5178Y/TK$^{+/-}$ assay (Harrington-Brock *et al.*, 1998). TCA did not cause mutation in the SOS chromatest but did show mutagenic activity in a strain of *Salmonella* (TA100) in a fluctuation test (Giller *et al.*, 1997). It was not mutagenic in a preincubation assay using several strains of *Salmonella* and different sources of microsomal activation (NTP, 1997).

The weight-of-evidence for TCA suggests that this substance is unlikely to be a mutagenic carcinogen (Harrington-Brock *et al.*, 1998; IARC, 2002).

B12-4.4 Populations at Special Risk

No information found.

B12-4.5 Toxicokinetics

Upon oral exposure, the gastrointestinal tract of both rats and humans will readily absorb TCA (Kim and Weisel, 1998; Schultz *et al*., 1999). Maximum blood TCA concentrations post dosing in rats occurred after 2 hours (Schultz *et al*., 1999). There was no evidence of dermal absorption of TCA in significant amounts observed in humans *in vivo* (Kim and Weisel, 1998), or *in vitro* using diffusion chambers (Xu *et al*., 2002).

TCA will be metabolized in the liver at relative small quantities. The main metabolites of TCA was found to be carbon dioxide, glyoxylic acid, oxalic acid, glycolic acid and dichloroacetic acid (DCA) in rats and mice following oral administrations of radio-labeled TCA (Health Canada, 2006). It had been suggested that TCA was metabolized by reductive dehalogenation to DCA (Larson and Bull, 1992). It was proposed that metabolism through a additional reductive dehalogenation would proceed *via* DCA to MCA and ultimately to thiodiglycolate (Bull, 2000). However, other investigators disputed previous findings of TCA metabolism and have suggested that metabolism to DCA may have been over-reported due to analytical methodologies that converted TCA to DCA due to the presence of a reagent. (Ketcha *et al*., 1996; Lash *et al*., 2000).

Oral and intravenous administration of TCA in rats indicated significant TCA plasma protein binding, and distribution to the liver (Templin *et al*., 1993; Schultz *et al*., 1999; Yu *et al*., 2000). Plasma protein binding of TCA varies across species and will be highest in humans (Lumpkin *et al*., 2003). The significant binding to plasma, only the free TCA would be available for tissue uptake and elimination (Yu *et al*., 2000).

Urine is the primary route for TCA excretion when it is administered either orally or intravenously (Templin *et al*., 1993; Schultz *et al*., 1999; Yu *et al*., 2000). The number of TCA metabolism studies is limited. In a human oral study involving volunteers, it was found that the elimination half-life of TCA from the blood was 50.6 hours (Muller *et al*., 1974). In another

study, five human volunteers drank tap water with TCA concentrations ranging from 50 to 80 µg/L, for the first 2 weeks, and then TCA free bottled water for the last 2 weeks (Bader *et al*. 2005). Urinary elimination rates were found to range from 2.1-6.3 days (Bader *et al*. 2005).

B12-4.6 Exposure Limits

Table B12-10 Existing RfD Values for TCA Exposures

Reference Dose (mg/kg/day)	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Acute/Short-term						
No information found	--	--	--	--	--	--
Intermediate- term						
No information found	--	--	--	--	--	--
Long-term						
0.0325	WHO, 2004; Health Canada, 2006	Decreased body weight, increased liver serum enzyme activity and liver histopathology	2 year Drinking-water rat study	DeAngelo *et al*., 1997	32.5	1,000

A chronic RfD of 0.0325 mg/kg/day (Health Canada, 2006) was selected for the risk assessment purposes of this report.

B12-5.0 ENVIRONMENTAL FATE AND EXPOSURE

TCA is miscible with water. It has a water solubility of 10 kg/L at 25ºC (Tomlin, 1995). TCA has low vapour pressure and thus volatilization would only occur to a minor extent. Furthermore, TCA also has a low Henry's Law constant of 1.35×10^{-5} atm-m^3/mole (JW, 2006). This indicates that it would have little tendency to escape from an aqueous solution. Hence, TCA will only be found in air as a consequence of direct aerial application to agricultural and non agricultural areas. Since TCA has low volatility, it is removed from the atmosphere by dry and wet deposition.

TCA will not be expected to adsorb onto sludge or soil and hence will not pollute agricultural soils (UNEP, 2000). The main release of TCA to soil is when it is being used as an herbicide. When released into the soil, TCA may biodegrade to a moderate extent and leach into groundwater. It has been proposed that TCA will undergo slow biological degradation by soil micro-organisms (UNEP, 2000). It was suggested that a biodegradation half-life of 150 days could be assumed for TCA-sodium salt, where dichloroacetic acid and monochloroacetic acid were the main metabolites in forest soils (UNEP, 2000).

TCA has a bioaccumulation factor between 0.4 to 1.0 and <1.7 (UNEP, 2000; JW, 2006). Hence, bioaccumulation in fish will be low (UNEP, 2000). In plants, a rapid uptake and translocation of TCA will occur (UNEP, 2000). However, elimination of TCA from the plant will be low leading to higher bioaccumulation rates of TCA in plants (UNEP, 2000).

B12-6.0 SUMMARY

TCA-sodium is a pre-emergent herbicide used for the control of annual and perennial weeds in a variety of food crops. However, TCA is no longer registered for use in Canada and the United States. In 1967, a small quantity of TCA was applied in a mixture with 2,4-D and 2,4,5-T on selected test plots at CFB Gagetown. Approximately 12 kg of TCA was applied over an area of 0.66 hectares (Demaree and Haws, 1968).

TCA has low acute toxicity. Long-term feeding studies showed that TCA will induce systemic effects, especially in the liver of rodents. Furthermore, developmental/reproductive effects were also observed. While TCA has been classified as a possible human carcinogen (Group C) by the U.S EPA (U.S. EPA, 1994), it has not received the same classification by IARC (2002). IARC (2002) classified TCA as a Group 3 carcinogen (non-human carcinogen).

B12-7.0 REFERENCES

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