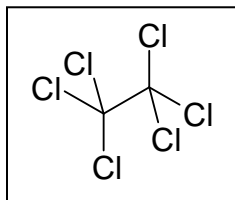**Hexachloroethane (HCE)**

CAS No. 67-72-1

Figure 1: Structure of Hexachloroethane

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on hexachloroethane (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for meeting the criteria for persistence and/or bioaccumulation and inherent toxicity to non-human organisms.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing

Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions.   The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca .

Information identified as of June 2004 was considered for inclusion in this Report. The critical information and considerations upon which the assessment is based are summarized below. Additional data identified between this date and the end of the external peer review period (December 2004) were also scoped and determined not to impact upon the conclusions presented here.

Identity, Uses and Sources of Exposure

A survey conducted pursuant to Section 71 of CEPA 1999 indicated that in Canada during the year 2000, approximately 150 tonnes of HCE were manufactured and 10–100 tonnes were imported (Environment Canada, 2001). HCE was reported to be used in Canada as a chemical intermediate, in the aluminum industry and as a flame retardant in an industrial resin (Environment Canada, 2001). Other uses of HCE noted in earlier reports were in military pyrotechnics, in the metallurgical industry, as a plasticizer, as an ignition suppressant, as a processing aid in various industrial processes, as a component of fungicidal and insecticidal formulations and (formerly) as an anthelmintic in veterinary medicine (IARC, 1979; Kirk-Othmer, 1993; ATSDR, 1997; NLM, 1999). Data on the use or presence of HCE in consumer products were not identified for Canada or other jurisdictions.

HCE releases to the environment in Canada are primarily atmospheric emissions from industrial processes. While exposure to HCE may occur from dermal contact with or ingestion of contaminated food, water or soil, the most likely route of exposure is expected to be inhalation of contaminated air. Exposure resulting from the use of consumer products is not expected to occur.

Exposure Assessment, Hazard Characterization and Risk Evaluation

Upper-bounding estimates of exposure to HCE for the general population range from 1.0 µg/kg-bw per day in the 60+ years age group to 3.1 µg/kg-bw per day in the 0.5–4 years age group, based on data from Canadian surveys of drinking water, indoor air, fish and soil (DeVault, 1985; OME, 1988, 1989; Fellin et al., 1992; Gizyn, 1994) (see Table 1). No further quantitative data for HCE levels in food were identified. The data available indicate that inhalation of indoor air is the most likely route of exposure, accounting for approximately 80–100% of total daily intake, depending on age. The sources of HCE in indoor air are unidentified, and no information on the presence of HCE in consumer products has been identified in the literature. Confidence in the database on exposure is considered low to moderate, since data on levels of HCE in indoor air in Canada are relatively recent, although limited.

In an assessment prepared by the International Agency for Research on Cancer (IARC, 1999), it was concluded that HCE was *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* in experimental animals and *inadequate evidence* in humans. A statistically significant increase in the incidence of hepatocellular carcinomas was observed in male and female mice exposed to a time-weighted average dose of 590 mg/kg-bw per day and higher by gavage for 78 weeks (Weisburger, 1977; NCI, 1978). There was a non-statistically significant increase in the incidence of kidney tubular cell adenomas in male rats at a time-weighted average dose of 212 mg/kg-bw per day administered by gavage for 78 weeks (Weisburger, 1977; NCI, 1978). Although there was no significant increase at the higher dose, high mortality may have precluded the observation of late-developing tumours (NCI, 1978). In a later study with rats, there was a significantly increased incidence of renal tubular adenomas and carcinomas combined in male rats exposed by gavage to 20 mg/kg-bw per day for 2 years, with no significant differences in survival (NTP, 1989). An increased incidence of pheochromocytomas of the adrenal gland was also observed in male rats, although the increase was significant only at the low dose (10 mg/kg-bw per day). There was no increase in tumour incidence in female rats exposed by gavage to up to 160 mg/kg-bw per day for 2 years compared with controls (NTP, 1989). In NTP (1989), it was concluded that there was "clear evidence" of carcinogenic activity of HCE in male rats based on the increased incidence of renal neoplasms and the possibly HCE-related marginally increased incidence of pheochromocytomas of the adrenal gland. There was "no evidence" of carcinogenic activity in female rats.

The pattern of renal histopathological effects (renal tubular hyperplasia, linear mineralization of the renal papillae and hyperplasia of the pelvic transitional epithelium) observed in male rats in the 2-year study, but not in female rats or mice, was consistent with those associated with alpha-2-urinary globulin nephropathy. In a 21-day study in male rats, HCE induced nephropathy, consisting of hyaline droplet accumulation and renal tubular regeneration, along with a dose-related increase in renal tubule cell labelling index (NTP, 1996). However, the potential for reversible binding of HCE to a specifically identified protein was not investigated in either study. Thus, although evidence for a role of alpha-2-urinary globulin nephropathy in the induction of renal tumours in rats by HCE is suggestive, it is not conclusive. In addition, the potential mode of induction by HCE of the liver tumours in mice has not been investigated.

The genotoxicity of HCE has been investigated in short-term screening assays addressing a wide range of endpoints (Table 2). While identified *in vivo* studies are limited to a micronucleus test and an assay for DNA damage in mice and DNA binding studies in rats and mice, *in vitro* data are more extensive. However, gene mutation tests in mammalian systems either *in vivo* or *in vitro* were not identified. With few exceptions, all reported results were negative. The only positive results of potential significance were those in a single report in which DNA binding was reported *in vivo* and *in vitro*; however, there was no clear evidence of adduct formation or mutation induction (Lattanzi et al., 1988). Modelled predictions of the genotoxicity of HCE and related compounds were also generally negative.

Although the mode of induction of tumours by HCE has not been well studied, the weight of evidence in a relatively robust data set on genotoxicity is negative, suggesting that the mechanism of carcinogenicity is likely to be non-genotoxic and that a level of exposure for which there is no probability of carcinogenic effects is a possibility. Therefore, the margin between the effect level for the non-neoplastic effect determined to be critical and the upper-bounding estimate of exposure is taken into consideration.

Although, based on consideration of the use patterns, physical-chemical properties and the upper-bounding estimate of exposure, inhalation in air is the predominant route of population exposure to HCE in Canada, the available toxicological database for inhaled HCE is much more limited than that for exposure to the substance via ingestion (i.e., the only identified long-term studies involve oral administration to experimental animals). The lowest oral lowest-observed-effect level (LOEL) for non-neoplastic effects identified was 10 mg/kg-bw per day (the lowest dose tested), which was associated with histopathological changes in the kidney in the male rat (NTP, 1989). Confidence in the toxicity database is considered to be moderate in a screening context, since, although it includes a considerable number of studies (including those for which animals were exposed for a significant proportion of their life span) addressing a wide range of endpoints, data on the toxicity of HCE for the principal route of exposure (inhalation) are sparse (see Table 2).

Comparison of the lowest oral effect level (10 mg/kg-bw per day) with an upper-bounding estimate of exposure (3.1 µg/kg-bw per day) results in a margin of 3200. Effects observed at this dose were those that preceded development of tumours in the target organ (i.e., the kidney); these effects were significantly increased only at the next higher dose (i.e., 20 mg/kg bw-per day), along with a significant increase in the incidence of tumours of the adrenal gland.

This margin was considered inadequate to address elements of uncertainty dealing with limitations of the database, including intraspecies variation and interspecies variation. Other uncertainties relevant to interpretation of the adequacy of the margin include the limitations of the database on the potential modes of induction of the observed neoplastic effects, which is inadequate to preclude that they result from direct interaction with genetic material. Uncertainties which are also relevant to interpretation of the adequacy of this margin is the limited characterization of dose–response in the critical study for non-neoplastic effects (a no-observed-effect level, or NOEL, was not identified), the severity of the effects observed at the critical LOEL (i.e., non-neoplastic effects in the kidney preceding tumour development at doses only 2-fold greater, along with increases in tumours of the adrenal gland) and the limitations of the database on levels of HCE in media of importance to human exposure.

The outcome of this evaluation on HCE is that it is suspected that this margin may not be adequate to account for the uncertainties in the mode of induction of tumours in experimental animals and the other uncertainties described above. Additional information to address uncertainties in intraspecies and interspecies variations in sensitivity and modes of induction of

the observed neoplastic effects, as well as uncertainties regarding the dose–response relationship for non-neoplastic effects, would permit a more definitive conclusion.

Table 1: Upper-bounding estimates of daily intake of hexachloroethane by the general population in Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of hexachloroethane by various age groups						
	0–6 months[1–3]		0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Formula fed	Not formula fed					
Ambient air[9]	2.4×10^{-4}		5.2×10^{-4}	4.0×10^{-4}	2.3×10^{-4}	2×10^{-4}	1.7×10^{-4}
Indoor air[10]	1.3		2.7	2.1	1.2	1	0.9
Drinking water[11]	2×10^{-3}	6×10^{-4}	7×10^{-4}	6×10^{-4}	3×10^{-4}	3×10^{-4}	4×10^{-4}
Food and beverages[12]		NA	0.4	0.3	0.2	0.2	0.1
Soil[13]	4×10^{-6}		6.5×10^{-6}	2.1×10^{-6}	5.1×10^{-7}	4.2×10^{-7}	4.2×10^{-6}
Total intake	1.3	1.3	3.1	2.4	1.4	1.2	1.0

1   Data on concentrations of HCE in breast milk were not identified.

2   Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (EHD, 1998).

3   For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of HCE in water used to reconstitute formula was based on a study of tap water from Union, Ontario, and Ottawa, Ontario (OME, 1988, 1989). Data on concentrations of HCE in formula were not identified. Approximately 50% of not-formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990).

4   Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (EHD, 1998).

5   Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (EHD, 1998).

6   Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

7   Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

8   Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

9   No Canadian data for HCE in ambient air were identified. The maximum measured mean outdoor concentration of HCE over various locations in the northern and southern Atlantic Ocean was 6.8×10^{-3} µg/m³ (Class and Ballschmiter, 1986). Data considered in the selection of critical data also included Ligocki et al. (1985) and Class and Ballschmiter (1987). Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998).

10   The maximum HCE level in indoor air recorded in a survey of 754 residential homes in Canada was 4.82 µg/m³ (Fellin et al., 1992). The detection limit was calculated as 5.2 µg/m³ using analysis of the calibration standard solutions. Uncertainty associated with analytical measurements may contribute to a lack of fit at the low or high end of an estimated calibration function and result in a detection limit lower or higher than the lowest or highest detected levels. The detection limit was used to represent an upper-bounding estimate for Canadian indoor air concentrations of HCE. Data considered in the selection of critical data also included Otson et al. (1994) and Kostiainen (1995). Canadians are assumed to spend 21 hours indoors each day (EHD, 1998).

11   The reported maximum value of HCE (1.6×10^{-2} µg/L) from 12 samples of tap water from Union, Ontario, and 24 samples of tap water from Ottawa, Ontario, in 1987 was used to calculate the intake estimate (OME, 1988,

1989). Data considered in the selection of critical data also included Clark et al. (1982), Otson et al. (1982), Environment Canada (1989) and City of Toronto (1990, 2002a,b,c,d).

[12] The maximum concentration of HCE (100 µg/kg) measured in various freshwater fish in the Ashtabula River, Ohio (DeVault, 1985), was used to calculate the intake from fish as described in EHD (1998). The Ashtabula River drains into Lake Erie, and the fish sampled in the study may be representative of fish consumed by the Canadian population. Data considered in the selection of critical data also included Oliver and Niimi (1983). HCE was not identified in any other foods.

[13] No quantitative data were identified for HCE levels in soil. The highest detection limit (1 µg/kg) from a study that measured HCE in soil samples from urban and rural locations in Windsor, Ontario, was used to calculate the intake estimate (Gizyn, 1994). Data considered in the selection of critical data also included Oliver and Kaiser (1986), Oliver and Pugsley (1986), Webber (1994) and Webber and Nichols (1995).

Table 2: Summary of health effects information for HCE

Endpoint	Lowest effect levels[1]/Results
Laboratory animals and *in vitro*	
Acute toxicity	Lowest **oral LD$_{50}$** = 4460 mg/kg-bw (Weeks et al., 1979) [Additional studies: Exxon Chemical Americas, 1962; Fowler, 1969; Kinkead and Wolfe, 1992] Lowest **dermal LD$_{50}$** >3160 mg/kg-bw (Exxon Chemical Americas, 1962) [No additional studies identified] Lowest **inhalation LC$_{50}$** >8230 mg/m^3 (Exxon Chemical Americas, 1962) [No additional studies identified]
Short-term repeated-dose toxicity	Lowest **oral (gavage) LOEL** (male rat) = 146.8 mg/kg-bw per day: increased absolute and relative kidney weights, hyaline droplet nephropathy and increased renal tubule cell labelling index (21-day study) (NTP, 1996) [Additional studies: Dow Chemical Co., 1977; Weeks et al., 1979; NTP, 1989] Lowest **inhalation LOEC** (male and female rats, male dogs and male guinea pigs) = 2517 mg/m^3: tremors and/or mortality (6-week studies) (Weeks et al., 1979) [No additional studies identified]
Subchronic toxicity	Lowest **oral (diet) LOEL** (male and female rats) = 15 mg/kg-bw per day: swelling of hepatocytes and kidney tubular degeneration (16-week study) (Gorzinski et al., 1985) [Additional studies: NTP, 1989]
Chronic toxicity	Lowest **oral (gavage) LOEL** (male rats) = 10 mg/kg-bw per day: histopathology (kidney mineralization, hyperplasia of the pelvic transitional epithelium and renal tubule hyperplasia) of the kidney (2-year study) (NTP, 1989) [Additional studies: Weisburger, 1977; NCI, 1978]

Endpoint	Lowest effect levels[1]/Results
Carcinogenicity	An increased combined incidence of **renal adenomas or carcinomas** (1/50, 2/50 and 7/50 at 0, 10 and 20 mg/kg-bw per day, respectively) was observed in male rats administered HCE by gavage for 2 years. The increase was significant only at the high dose (NTP, 1989).
	An increased incidence of **pheochromocytomas** of the adrenal gland (15/50, 28/45 and 21/49 at 0, 10 and 20 mg/kg-bw per day, respectively) was observed in male rats administered HCE by gavage for 2 years. The increase was significant only at the low dose (NTP, 1989).
	There were no increases in the incidence of tumours at any site in female rats administered HCE at up to 20 mg/kg-bw per day by gavage for 2 years (NTP, 1989).
	An increased incidence of **kidney tubular cell adenomas** (0/20, 0/20, 4/49 and 0/50 at 0 [naïve], 0 [vehicle], 212 and 423 mg/kg-bw per day, respectively) was observed in male rats administered HCE by gavage for 78 weeks. The increase was significant only at the low dose (NCI, 1978).[2]
	An increased incidence of **hepatocellular carcinomas** was observed in male (1/18, 3/20, 15/50 and 31/49 for 0 [naïve], 0 [vehicle], 590 and 1179 mg/kg-bw per day, respectively) and female (0/18, 2/20, 20/50 and 15/49 at 0 [untreated], 0 [vehicle], 590 and 1179 mg/kg-bw per day, respectively) mice exposed by gavage for 78 weeks. The increase was significant only at the high dose in males and the low dose in females (NCI, 1978).[3]
	No increase in a preneoplastic lesion (i.e., gamma glutamyltranspeptidase-positive foci) was observed in the liver of rats exposed to HCE at 500 mg/kg-bw by gavage followed by 0.05% phenobarbital in the diet for 7 weeks. An increased incidence of preneoplastic lesions was observed in rats exposed intraperitoneally to N-nitrosodiethylamine at 30 mg/kg-bw followed by HCE at 500 mg/kg-bw per day for 7 weeks (Story et al., 1986; Milman et al., 1988).
Genotoxicity and related endpoints: *in vivo*	**DNA binding (covalent)** **Positive results:** rat and mouse, liver, kidney, lung, stomach cells (Lattanzi et al., 1988) **Micronuclei induction** **Negative results:** mouse bone marrow (Crebelli et al., 1999) **DNA unwinding** **Negative results:** mouse (Taningher et al., 1991)

Endpoint	Lowest effect levels[1]/Results
Genotoxicity and related endpoints: *in vitro*	**Gene mutation** **Positive results:** *Saccharomyces cerevisiae* (Bronzetti et al., 1989) **Equivocal results:** *Drosophila* (Vogel and Nivard, 1993) **Negative results:** *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538, BA13, BAL13 (Weeks et al., 1979; Kinae et al., 1981; Haworth et al., 1983; Stanford Research Institute International, 1984; Milman et al., 1988; NTP, 1989; Roldan-Arjona et al., 1991) *Sacharomyces cerevisiae* (Weeks et al., 1979; Bronzetti et al., 1989) **Sister chromatid exchange** **Positive results:** Chinese hamster ovary cells (Galloway et al., 1987) **Micronuclei induction** **Equivocal results:** human blood cells (Tafazoli et al., 1998) **Negative results:** human lymphoblastoid cells (Doherty et al., 1996; Parry et al., 1996) **DNA binding (covalent)** **Positive results:** calf thymus DNA (Lattanzi et al., 1988) **Induction of repair** **Negative results:** prophage (Nakamura et al., 1987) **Differential toxicity** **Negative results:** *Bacillus subtilis* (Kinae et al., 1981) **Aneuploidy** **Negative results:** *Aspergillus nidulans* (Crebelli et al., 1988) **Cell transformation** **Negative results:** BALB/c-3T3 cells (Arthur D. Little Inc., 1983; Tu et al., 1985; Milman et al., 1988) **Chromosome aberrations** **Negative results:** Chinese hamster ovary cells (Galloway et al., 1987) **DNA damage** **Negative results:**

Endpoint	Lowest effect levels[1]/Results
	human lymphocytes (Tafazoli et al., 1998)
Developmental toxicity	Lowest **oral LOEL** (female rats) = 500 mg/kg-bw per day: lower gestation indices and number of live fetuses per dam and higher fetal resorption rates (gestation days 6–16) (Weeks et al., 1979) [No additional studies were identified] Lowest **inhalation LOEC** (female rats) = 465 mg/m^3: decreased body weight gain of dams, increased mucopurulent nasal exudate (gestation days 6–16) (Weeks et al., 1979) [No additional studies were identified]
Reproductive toxicity	No data identified
Behavioural toxicity/ neurotoxicity	Highest **inhalation NOEC** (male rats) = 2517 mg/m^3: no change in behaviour observed at any concentration tested (3 weeks and 6 weeks) (Weeks et al., 1979)
Humans	
Short-term repeated-dose toxicity	In an inhalation study of 11 munitions workers (5 males, 6 females) exposed to 10–20 mg/m^3 for 5 weeks, increases in S-creatinine, S-urate and S-bilirubin were observed; however, levels were within reference values. An increased prevalence of "dry skin/dry mucous membranes" was not statistically significant (Selden et al., 1994).
Carcinogenicity	In a cohort study (n = 1880) of male workers at aluminum foundries and aluminum smelters, **no significant association** was observed between exposure to HCE (levels were not quantified in secondary source) and incidences of anorectal, liver or lung cancer or malignant lymphoma (Selden et al., 1997).

[1] LC$_{50}$ = median lethal concentration; LD$_{50}$ = median lethal dose; LOEC = lowest-observed-effect concentration; LOEL = lowest-observed-effect level; NOEC = no-observed-effect concentration.

[2] Note that incidences were reported as 0/20, 5/49 and 0/50 for vehicle controls, low dose and high dose, respectively, in the publication of the study by Weisburger (1977).

[3] Note that incidences for males were reported as 3/20, 15/50 and 29/49 for vehicle controls, low dose and high dose, respectively, in the publication of the study by Weisburger (1977).

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