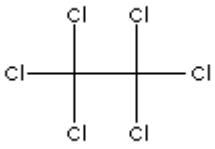
INITIAL TARGETED ASSESSMENT PROFILE

Category Name	Hexachloroethane
CAS No(s).	67-72-1
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present Initial Targeted Assessment Profile (ITAP) addresses the following human health endpoints: carcinogenicity and genotoxicity. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Human health endpoints included in the Canadian screening assessment that have not been presented to OECD member countries are not included in this ITAP.

"The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=CD3BB2EB-1]"

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) from 1999 to September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL. They were categorized to identify those that were: **inherently toxic** to humans or to the environment and that might be **persistent** and/or **bioaccumulative**; and substances to which people might have **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment, and subsequent assessment activities may have focused on either human health or ecological endpoints. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment, research and/or measures to control their use or release.

In Canada, the substance, hexachloroethane, was identified as an assessment priority because it was classified by other agencies as a possible carcinogen to humans and because it met the criteria for persistence, bioaccumulation and inherent toxicity to aquatic life.

Under the Canadian Environmental Protection Act (CEPA 1999), a screening assessment is conducted to determine whether a substance presents or may present a risk to the environment or to human health. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

Physical-chemical Properties

The substance, hexachloroethane, is characterized by colourless crystals with camphor-like odour at ambient temperature, has a melting point of 185-188°C, boiling point of 185-187°C (sublimes without decomposition) and a vapour pressure of 28-29 Pa at 20°C (all measured values). The measured octanol-water partition coefficient (log K_{ow}) is 3.34-5.31, and the measured water solubility is 7.7 mg/L at 25°C. The measured organic carbon-water partition coefficient (log K_{oc}) is 2.24-4.3.

Human Health

The majority of the studies described here have been reviewed by the International Agency for Research on Cancer (IARC 1999) or the US EPA (2011).

Genotoxicity: A sufficient genotoxicity database was available.

- The chemical was negative for gene mutations in the majority of *S. typhimurium* (bacterial) and *S. cerevisiae* (ascomycetes fungi) mutation assays conducted with and without metabolic activation.
- Chromosomal aberrations were negative with and without activation, whereas induction of sister chromatid exchanges (SCEs) were negative in Chinese hamster cells without metabolic activation, but positive only with activation at doses that induce cell cycle delay..
- It was negative for micronuclei in human lymphoblastoid cells but equivocal for micronuclei induction in human blood cells.
- DNA damage was negative in cultured human lymphocyte but positive in isolated human lymphocytes with and without activation.
- DNA binding was positive in calf thymus DNA with microsomal activation, and rat and mice liver, kidney, lung and stomach tissue with activation, but DNA adducts were not identified.
- Other indicator tests such as mitotic gene conversion in *S. cerevisiae* (ascomycetes fungi), aneuploidy in *A. nidulans* (yeast cells), SOS induction and strand damage using *S. typhimurium* (bacterial), differential toxicity in *B. subtilis* (bacterial) and cell transformation in mouse BALB/c-3T3 mouse cells, were all negative.

Overall, ***in vitro*** mutagenicity, clastogenicity and DNA damage assays showed negative results. Although DNA binding was positive in mammalian cells, there was no clear evidence of adduct formation.

A limited number of *in vivo* studies showed:

- *D. melanogaster* showed equivocal results for somatic gene mutation. DNA, RNA and protein binding were positive in liver, lung, kidney, and stomach cells, after i.p. administration of hexachloroethane to rats and mice, but the adducts were not identified.
- A micronuclei assay in mice was negative in bone marrow (hexachloroethane administered i.p.).

In vivo genotoxicity studies were equivocal overall. 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.

Carcinogenicity potential was determined on the basis of long-term and initiation-promotion oral studies.

In an oral carcinogenicity bioassay in F344/N rats exposed by gavage to hexachloroethane, 50 males/group were exposed to doses of 0, 10, or 20 mg/kg-bw per day and 50 females/group were exposed to 0, 80, or 160 mg/kg-bw per day, 5 days per week for 2 years. A statistically significant ($p < 0.01$) increase in the combined incidence of renal adenomas or carcinomas (1/50, 2/50 and 7/50, respectively) was observed in high dose males. An increased incidence of pheochromocytomas of the adrenal gland (15/50, 28/45 and 21/49, respectively) was

observed in males at both doses, with the increase being statistically significant ($p < 0.01$) at the low dose. There was no increase in the incidence of tumours at any site in females. There was no significant difference in survival between any groups of either sex. Since the adrenal tumours did not follow a dose response trend, Benchmark Dose (BMD) calculations could not be performed. For renal adenoma or carcinoma (combined) in male F344 rats, the lowest calculated $BMDL_{10}$ (the lower bound on the exposure associated with a 10% extra cancer risk) is 8.53 mg/kg-bw per day.

In an oral carcinogenicity study in Osborne-Mendel rats, 50 animals/sex were exposed by gavage to hexachloroethane 5 days per week for 22 weeks followed by a cyclic pattern of dosing for 56 weeks (1 dose free week followed by 4 weeks of dosing) at time-weighted average doses of 212 or 423 mg/kg-bw per day over the 78 week period, which was then followed by a dose-free observation period of 33 or 34 weeks. Twenty animals/sex/group were exposed by gavage to vehicle (corn oil) or placed on test as untreated controls without intubation. A non-statistically significant increased incidence of kidney tubular cell adenomas (0/20, 0/20, 4/49 and 0/50 at 0 [naive], 0 [vehicle], 212 and 423 mg/kg-bw per day, respectively) was observed in low dose males. Survival of male rats at 90 weeks was 19/50 for the high dose, 24/50 for the low dose, 14/20 for controls and 11/20 for vehicle controls. High mortality may have precluded the observation of late-developing tumours.

In an oral carcinogencitiy study in B6C3F1 mice, 50 animals/sex were exposed by gavage to hexachloroethane 5 days per week at time-weighted average doses of 590 or 1179 mg/kg-bw per day for 78 weeks, followed by a dose-free observation period of 12 or 13 weeks. Twenty animals/sex/group were exposed by gavage to vehicle (corn oil) or placed on test as untreated controls without intubation. An increased incidence of hepatocellular carcinomas was observed in both sexes (1/18, 3/20, 15/50 and 31/49 in males and 0/18, 2/20, 20/50 and 15/49 in females at 0 [untreated], 0 [vehicle], 590 and 1179 mg/kg-bw per day, respectively). When compared to vehicle controls, the increase was statistically significant ($p < 0.001$) only at the high dose in males and the low dose in females.

To assess initiation potential, 10 male Osborne-Mendel rats received 500 mg/kg-bw hexachloroethane by gavage 24 hours after partial hepatectomy. Six days later, the animals received a 0.05% dietary exposure to the tumour promoter phenobarbital for 7 weeks. No increase in preneoplastic lesions (i.e., gamma glutamyltranspeptidase positive foci) was observed in the liver of rats. To assess promotion potential, 10 male rats/group were i.p. injected with 30 mg of the tumour initiator, diethylnitrosamine or given 5 mL/kg bw water 24 hours after partial hepatectomy. Six days later, the animals received 500 mg/kg-bw hexachloroethane by gavage, 5 days/week for 7 weeks. A significantly increased incidence increased ($p < 0.05$) of preneoplastic lesions (liver foci) was observed in the animals. In summary, results were negative in the initiation study and positive in the promotion study.

Potential Mode of Action for Oral Carcinogenicity

No studies have been identified that presented immunohistochemical evidence of the presence of alpha-2µ-globulin in hyaline droplets in the kidneys of male rats exposed to hexachloroethane. Although evidence for a role of alpha-2 µ -globulin nephropathy in the induction of renal tumours in male rats by hexachloroethane is suggestive, it is not conclusive. In addition, the US EPA (2011) examined the mode of action of the kidney tumours in male rats and similarly concluded that the evidence was insufficient to conclude that kidney tumours were consequential to alpha-2µ-globulin accumulation. Furthermore, the potential mode of induction of the liver tumours in mice or adrenal tumours in rats by hexachloroethane have not been investigated.

Although the mode of induction of tumours by hexachloroethane has not been well studied, the available data on genotoxicity is generally negative, suggesting that the mechanism of carcinogenicity in some target tissues may be non-genotoxic In the absence of information indicating otherwise, the kidney tumours in male rats and liver tumours in male and female mice are considered relevant to humans.

Carcinogenicity Potential in Humans

In a cohort study (n = 1880) of male workers at aluminum foundries and aluminum smelters in Sweden, no significant association (in excess or trend over duration of employment) was observed between exposure to

hexachloroethane (exposure levels were not available, so proxy exposure variables like type of casting technique applied, duration of employment and job title were used) and incidences of anorectal, liver or lung cancer or malignant lymphoma. Confounding influences by co-exposures to agents such as polycyclic aromatic hydrocarbons or silica dust cannot be ruled out, and the power of the study was low.

Based on the available human and animal and in vitro data, the International Agency for Research on Cancer (IARC 1999), proposed that hexachloroethane was *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* in experimental animals and *inadequate evidence* in humans. Similarly,the U.S. EPA (2011) updated the Integrated Risk Information system and concluded that hexachloroethane was *likely to be carcinogenic to humans* by all routes of exposure.

Hexachloroethane possesses properties indicating a hazard for the one human health endpoint, carcinogenicity (kidney tumours and liver tumours via the oral route) targeted in this assessment.

Exposure Summary Information

Hexachloroethane is currently imported into Canada (sponsor country) for use as a degassing agent for oxides and hydrogen elimination from aluminum alloys during die casting at a quantity of less than 2000 kg per year. It was previously reported to be used in Canada as a chemical intermediate, as a flux agent for grain refining and degassing of aluminum alloys, and as a flame retardant in industrial laminating resins. It is no longer used in military smoke ammunition in Canada, and no evidence has been found for its current use as a flame retardant. Global uses of hexachloroethane noted in earlier scientific and technical literature 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. The production and uses of hexachloroethane are being phased out internationally. The European Commission prohibits the use of hexachloroethane in the manufacturing or processing of nonferrous metals. In the United States (US), there has been a trend away from using hexachloroethane flux in the secondary aluminum industry. Similarly, representatives of the aluminum industry in the US report that hexachloroethane is no longer used in most primary aluminum degassing.

Based on the most recent survey for this compound, approximately 150 tonnes of hexachloroethane were manufactured and 10–100 tonnes were imported in Canada during the 2000 calendar year. Although it is not manufactured for commercial distribution, hexachloroethane is formed during other processes in the chlorinated chemical industry; for example, this chemical is a by-product resulting from the 1,2-dichloroethane manufacturing process. Hexachloroethane can also be produced as a by-product of the chlorination of water and sewage and the incineration of chlorinated hydrocarbons.

Hexachloroethane can also be produced naturally by Rhodophyta algae. The halogenating capacity of the algae was established through incubation experiments.

Current Canadian sources of releases to the environment are minor but potentially numerous. They include possible releases from industrial facilities during manufacturing and processing, from the chlorination of water and sewage, from the incineration of chlorinated hydrocarbons, from municipal and industrial landfills by leaching and from the use of contaminated solvents (e.g., tetrachloroethylene).

Releases of hexachloroethane reported by Canadian industries to the National Pollutant Release Inventory indicated that there have been no releases at reporting thresholds since 2006, and prior to that year, all releases occurred to air and off-site disposal. From 1999 to 2005, on-site releases ranged from 0.001 to 0.012 tonne per year, and 0.004–19 tonnes per year were released to off-site disposal. Hexachloroethane is expected to be released by users (rather than producers) mostly to air, with smaller releases to water and soil. Releases of hexachloroethane associated with the die casting of aluminum products are expected to be minimal given the nominal amounts being used and the manner of processing.

According to the US Toxics Release Inventory, 467.2 kg of hexachloroethane were emitted to the atmosphere, 75.7 kg injected to underground wells, 164.6 kg to on site and off site landfills and 644.1 kg were released to other off site management facilities in the US in 2011.

Hexachloroethane has not been identified in consumer products in Canada and exposure from these sources are expected to be limited, as its use is being phased out or restricted in many countries.

Note: This document may only be reproduced integrally. The conclusions in this document are intended to be mutually supportive, and should be understood and interpreted together.