HEXACHLOROETHANE

This substance was considered by previous working groups, in 1978 (IARC, 1979) and 1987 (IARC, 1987). Since that time, new data have become available and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

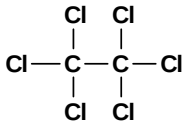
Chem. Abstr. Serv. Reg. No.: 67-72-1

Chem. Abstr. Name: Hexachloroethane

IUPAC Systematic Name: Hexachloroethane

Synonyms: Ethane hexachloride; 1,1,1,2,2,2-hexachloroethane; hexachloroethylene

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2Cl_6 Relative molecular mass: 236.74

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Crystals; camphorous odour (Budavari, 1996)

(*b*) *Boiling-point*: Triple-point sublimation temperature, 187°C (Lide, 1997)

(*c*) *Density*: 2.091 g/cm^3 at 20°C (Lide, 1997)

(*d*) *Solubility*: Insoluble in water; very soluble in ethanol and diethyl ether; soluble in benzene (Lide, 1997)

(*e*) *Volatility*: Vapour pressure, 53.2 Pa at 20°C; relative vapour density (air = 1), 8.16 (Verschueren, 1996)

(*f*) *Octanol/water partition coefficient (P)*: log P, 3.4 (Verschueren, 1996)

(*g*) *Conversion factor*: mg/m^3 = 9.68 × ppm

1.2 Production and use

Information available in 1995 indicated that hexachloroethane was produced in Brazil, China, India, Japan, the Russian Federation and the United States (Chemical Information Services, 1995).

Hexachloroethane is used in metallurgy for refining aluminium alloys, removing impurities from molten metals and recovering metal from ores or smelting products. It is used as a degassing agent for magnesium and to inhibit the explosiveness of methane and combustion of ammonium perchlorate. It is also used as a smoke generator in grenades, in pyrotechnics, as an ignition suppressant, as a component of fire extinguishing fluids, as a polymer additive, as a flame-proofing agent, as a vulcanizing agent and in the production of synthetic diamonds (Budavari, 1996).

1.3 Occurrence

1.3.1 *Natural occurrence*

Hexachloroethane is not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 8500 workers in the United States were potentially exposed to hexachloroethane. Occupational exposure to hexachloroethane may occur during its production and during its use as a refining agent, degassing agent, explosive inhibitor, smoke generator, ignition suppressant, component of fire extinguishing fluids, polymer additive, flame-proofing agent or vulcanizing agent (Budavari, 1996).

1.3.3 *Environmental occurrence*

Hexachloroethane has been detected occasionally in drinking-water systems and at low concentrations (nanograms per cubic meter) in the atmosphere. Limited data indicate that the typical background air concentrations in the northern hemisphere range from 48 to 68 ng/m^3. Hexachloroethane is rarely detected in surface waters or biota and has not been reported in ambient soil, sediments or commercial food products (Agency for Toxic Substances and Disease Registry, 1997).

According to the Environmental Protection Agency Toxic Chemical Release Inventory for 1987, 2600 kg hexachloroethane were released into the air, 89 kg were disposed of by underground injection and 230 kg were released onto the land from manufacturing and processing facilities in the United States. By 1996, 1300 kg were released into the air, 15 kg were released into water and 920 kg were disposed of by underground injection. These figures do not include releases from the manufacture and use of military smoke and pyrotechnic devices, since Federal facilities in the United States are not required to report releases (National Library of Medicine, 1998).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (1997) has recommended 9.7 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation for potential dermal absorption, for exposure to hexachloroethane in workplace

air. Values of 9.7–100 mg/m^3 have been used as standards or guidelines in other countries (International Labour Office, 1991).

No international guidelines have been established for hexachloroethane in drinking-water (WHO, 1993).

2. Studies of Cancer in Humans

One cohort study has been conducted of exposure to hexachloroethane (Seldén *et al.*, 1997), which was a retrospective follow-up study of cancer incidence during 1958–92 among 6454 workers at aluminium foundries and secondary aluminium smelters in Sweden, hexachloroethane being one of the agents to which some of the workers were exposed. No significant excess and no significant trend over duration of employment in the incidences of anorectal, liver or lung cancers or malignant lymphomas was found among the 1880 male workers who were considered to have been most heavily exposed to hexachloroethane and its by-products. The standardized incidence ratio for liver cancer among these workers was 1.1 (95% CI, 0.13–3.8), based on two cases with less than one year's employment. Malignant lymphomas were found in excess in this group (standardized incidence ratio, 2.3), but the excess was not significant (95% CI, 0.93–4.7; seven exposed cases). Confounding by agents such as polycyclic aromatic hydrocarbons, silica dust or hexachlorobenzene cannot be ruled out, and the power of the study was low, in particular for liver cancer.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Hexachloroethane was tested in one experiment in mice and one in rats by oral administration. It produced hepatocellular carcinomas in male and female mice. In rats, no statistically significant excess of tumours was observed; however, a marginal increase in the incidence of renal tubular tumours, rarely seen in control animals, was found in male rats (IARC, 1979).

New studies

3.1 Oral administration

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were given hexachloroethane (purity, > 99%) by oral gavage in corn oil at doses of 0, 10 or 20 mg/kg bw for males and 0, 80 or 160 mg/kg bw for females, on five days per week for 104 weeks. The survival rates at the end of the study were 31/50, 29/50 and 26/50 in males and 32/50, 27/50 and 32/50 in females at the three doses, respectively. Hexachloroethane increased the incidence of renal tubular adenomas and carcinomas combined in male rats at the high dose, the incidences being 1/50 (control), 2/50 (low dose) and 7/50 (high dose).

When adjusted for intercurrent mortality, the renal tumour incidences in male rats (expressed as percentages) were 2.6, 5.9 and 24% in the control, low-dose and high-dose groups, respectively. Male rats at the high dose also had a significant increase in the incidence of renal tubular hyperplasia. None of the females had renal tumours even though they were exposed to eightfold higher doses than the males. The incidence of phaeochromocytomas of the adrenal gland was marginally increased in males at the low dose (control, 15/50; low dose, 28/45; and high dose, 21/49). The incidence rates of phaeochromocytoma adjusted for survival were 41, 82 and 62% for the control, low-dose and high-dose male groups, respectively; none was observed in the females (National Toxicology Program, 1989).

3.2 Administration with known carcinogens or modifying factors

Rat: Hexachloroethane was tested in an initiation–promotion protocol in rats in which the end-point was development of foci of hepatocellular alteration, regarded as putative preneoplastic lesions predictive of liver tumour development. In an initiation study, groups of 10 male Osborne-Mendel rats weighing 180–230 g underwent a two-thirds hepatectomy and 24 h later received 500 mg/kg bw hexachloroethane (purity, 98%) by oral gavage in corn oil. Six days after the partial hepatectomy, phenobarbital was administered in the diet as a promoting agent at a concentration of 0.05% for seven weeks, followed by control diet for a further seven days before sacrifice. Positive controls were given an initiating dose of 30 mg/kg bw *N*-nitrosodiethylamine intraperitoneally, followed by the phenobarbital-containing diet as described above. Negative controls were given 2 mL/kg bw corn oil by gavage, followed by control diet. In the promotion phase of this study, groups of 10 male Osborne-Mendel rats were initiated with 30 mg/kg bw *N*-nitrosodiethylamine intraperitoneally or given 5 mL/kg bw water 24 h after a two-thirds hepatectomy. Six days later, the rats were given 500 mg/kg bw hexachloroethane in corn oil by gavage on five days per week for seven weeks or, for control rats, corn oil alone. The rats were killed one week after the end of the promotion phase. Foci of hepatocellular alteration were identified by morphological examination or immunohistochemical staining for γ-glutamyltranspeptidase. Hexachloroethane showed no evidence of initiating activity but significantly increased ($p < 0.05$) the number of liver foci in the promotion phase of the study (Story *et al*., 1986; Milman *et al*., 1988).

4. Other Data Relevant to and Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

After hexachloroethane was administered in the feed of male and female Fischer 344 rats at 62 mg/kg bw per day for eight weeks, the ratio of its concentration in blood: liver:kidney:fat was 1:1:20–40:100. The concentrations decreased in all organs examined in an apparent first-order manner, with half-lives of approximately 2.5 days (Gorzinski *et al.*, 1985).

4.2 Toxic effects

4.2.1 *Humans*

The possible short-term adverse effects of hexachloroethane were investigated in a group of 11 munition workers who were exposed to hexachloroethane at concentrations of 10–20 mg/m^3 or more for five weeks. They were compared with a sex- and age-matched unexposed control group. Mild skin and mucous membrane irritation were reported in the exposed group, but clinical and laboratory examinations revealed no adverse effects on blood, liver, kidney or lung function (Seldén *et al.*, 1994).

4.2.2 *Experimental systems*

Rats exposed by inhalation to 2500 mg/m^3 hexachloroethane for 8 h showed no adverse effects during exposure or for 14 days thereafter. In contrast, two of six rats exposed to 57 000 mg/m^3 died at the end of the 8-h exposure, and the body weights of the surviving animals were reduced. Subacute diffuse interstitial pneumonitis was diagnosed after 14 days, but no other gross lesions were observed. Male and female Sprague-Dawley rats, male beagle dogs, male Hartley guinea-pigs and male and female quail (*Coturnix japonica*) were treated with 15, 48 or 260 ppm (140, 460 and 2500 mg/m^3) hexachloroethane vapour for 6 h a day on five days a week for six weeks. No effects were seen with the two lower doses, while the dose of 260 ppm affected mainly the nervous system of dogs and to a lesser extent that of rats. The dogs developed tremor, facial muscular fasciculations and hypersalivation. The oxygen consumption of rats at the high dose was reduced, but pulmonary function tests showed no difference from reported normal values. The rats showed tremor, ruffled pelt and red exudate around the eyes but no changes in either avoidance performance or spontaneous motor activity. The only other adverse effects were increased organ:body-weight ratios for the kidney, spleen and testis in male rats and the liver in female rats. Guinea-pigs receiving the high dose showed body-weight reduction. No signs of toxicity were seen in quail. In the same study, hexachloroethane was given to groups of five male rabbits daily by gavage for 12 days; the experiment was terminated four days after the last dose. A dose of 100 mg/kg bw was not toxic, while doses of 320 and 1000 mg/kg bw reduced body weights, caused liver degeneration and necrosis and renal tubular nephrocalcinosis and decreased the serum potassium and glucose concentrations (Weeks *et al.*, 1979).

Hexachloroethane was administered in the diet at approximate doses of 0, 1, 15 and 62 mg/kg bw per day for 16 weeks to male and female Fischer 344 rats. The high dose was toxic to the kidney, as manifested by slightly increased kidney weights in males, but not in

females, and tubular atrophy, degeneration, hypertrophy and/or dilatation in males and to a lesser extent in females. The livers of both males and females at the high dose were heavier, while histopathological swelling of hepatocytes was observed only in males at the two higher doses (Gorzinski *et al.*, 1985).

In a 16-day study in Fischer 344 rats, oral administration of 187 or 375 mg/kg bw hexachloroethane produced hyaline droplet formation in the cytoplasm of the renal tubular epithelium in male rats, with tubular-cell regeneration. No renal effects were observed in female rats (National Toxicology Program, 1989).

In male and female rats dosed orally with 0, 47, 94, 188, 375 or 750 mg/kg bw hexachloroethane on five days a week for 13 weeks, the compound-related effects included increased relative weights of the liver, heart, kidney and brain in males and females at the highest dose. Renal changes were seen in all treated males (9/10 at the lowest dose), including increased hyaline droplet formation, tubular regeneration and tubular casts, and their severity was dose-related. No renal changes were observed in female rats. Hepatocellular necrosis was observed in females at 188 mg/kg bw and in both males and females at the two highest doses (National Toxicology Program, 1989).

A study of the effects of hexachloroethane on replicative DNA synthesis in hepatocytes from eight-week-old male B6C3F_1 mice that had been given a dose of 1000 mg/kg bw by gavage gave inconclusive results (Miyagawa *et al.*, 1995).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Hexachloroethane was detected at a mean concentration of 427 ppt [ng/mL] in 20% of samples of ovarian follicular fluid obtained from 150 Canadian women. It was not detected in serum (Foster *et al.*, 1996).

4.3.2 *Experimental systems*

In a study of developmental toxicity, groups of 22 female Sprague Dawley received 0, 50, 100 or 500 mg/kg bw hexachloroethane (purity, 99.8%) by gavage in corn oil or 0, 15, 48 or 260 ppm (0, 140, 460 or 2500 mg/m^3) via inhalation on days 6–16 of gestation. Tremors and decreased body-weight gain were observed after exposure to the high dose by either route. After oral exposure to 500 mg/kg bw, increased resorptions and decreased live litter size were noted (Weeks *et al.*, 1979). [The Working Group noted that few actual experimental results were contained in this summary article of research by the United States Army.]

Hexachloroethane was one of a number of organic chemicals present in three samples of materials used or originating in the manufacture of semiconductors that were tested for developmental toxicity. The concentrations of hexachloroethane in the three mixtures ranged from 0.30 to 10.95 mg/kg, which were low in comparison with those of the other organic chemicals present. The mixtures were administered to mice of three strains by oral gavage on days 6–15 of gestation. Two of the mixtures resulted in dose-related embryonic deaths, fetal growth retardation and malformations, primarily cleft palate, in all strains.

The authors suggested that the effects were the result of the presence of titanocene dichloride-like contaminants (Schmidt *et al*., 1995).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Hexachloroethane did not cause differential toxicity in the *Bacillus subtilis* rec system or SOS DNA repair in *Salmonella typhimurium*. It was not mutagenic to *S. typhimurium* TA100, TA98, TA1535 or TA1537 or *Saccharomyces cerevisiae*. Gene conversion was induced in *S. cerevisiae* in the absence of exogenous metabolic activation whereas crossing-over and aneuploidy were not induced in *Aspergillus nidulans*. Hexachlorethane induced somatic mutations in *Drosophila melanogaster.*

Hexachloroethane induced sister chromatid exchange, but not chromosomal aberrations in Chinese hamster ovary cells in culture. It did not induce micronuclei in human cells *in vitro* and did not transform BALB/c 3T3 mouse cells.

Hexachloroethane was reported to bind to DNA *in vitro* in the presence of an exogenous metabolic system. After a single intraperitoneal injection to mice and rats *in vivo*, it was bound to DNA, RNA and protein. The binding to DNA was weak but was greatest in mouse liver; it was very weak in mouse kidney, lung and stomach and in all organs of rats.

4.5 Mechanistic considerations

Hexachloroethane produces a spectrum of histopathological effects in the kidneys of male rats, but not of female rats or of mice, which are consistent with those typically induced by chemicals that cause α_{2u}-globulin nephropathy. It is structurally similar to pentachloroethane, which also causes renal tumours in male rats (National Toxicology Program, 1983). Pentachloroethane has been shown to increase the renal cortical concentrations of α_{2u}-globulin and stimulate renal cell proliferation (Goldsworthy *et al*., 1988). Although these comparisons suggest that hexachloroethane acts through an α_{2u}-globulin-associated mechanism, the available data are insufficient to fulfil the criteria for establishing this mechanism (Capen *et al*., 1999).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hexachloroethane may occur during its production and use in metal refining, in fire suppression and in other minor uses.

Table 1. Genetic and related effects of hexachloroethane

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Prophage, induction of SOS repair, strand breaks, cross-links	–	–	42	Nakamura *et al.* (1987)
Bacillus subtilis rec, differential toxicity	–	NT	10 µg/plate	Kinae *et al.* (1981)
Salmonella typhimurium, forward mutation, arabinose resistance (Ara^r)	–	–	7100 µg/plate	Roldán-Arjona *et al.* (1991)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	10000 µg/plate	Haworth *et al.* (1983)
Salmonella typhimurium TA100, TA98, TA1537, reverse mutation	–	–	10 µg/plate	Kinae *et al.* (1981)
Saccharomyces cerevisiae, gene conversion	+	–	1200	Bronzetti *et al.* (1989)
Saccharomyces cerevisiae, reverse mutation	–	–	3000	Bronzetti *et al.* (1989)
Aspergillus nidulans, crossing-over	–	NT	800	Crebelli *et al.* (1988)
Aspergillus nidulans, aneuploidy	–	NT	800	Crebelli *et al.* (1988)
Drosophila melanogaster, somatic mutation	+		2400 feed	Vogel & Nivard (1993)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	+	350	Galloway *et al.* (1987)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	NR	Galloway *et al.* (1987)
Cell transformation, BALB/c 3T3 mouse cells	–	NT	20	Tu *et al.* (1985)
Micronucleus formation, human lymphoblastoid AHH-1, MCL-5 and h2E1 cells *in vitro*	–	NT	24	Doherty *et al.* (1996)
Binding (covalent) to calf thymus DNA *in vitro*	NT	+	13	Lattanzi *et al.* (1988)
Binding (covalent) to DNA, male rat and mouse liver, kidney, lung and stomach cells *in vivo*	+		2 ip × 1	Lattanzi *et al.* (1988)
Binding (covalent) to RNA or protein, male rat and mouse liver, kidney, lung and stomach cells *in vivo*	+		2 ip × 1	Lattanzi *et al.* (1988)

[a] +, positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro test, : µg/mL; in-vivo study, mg/kg bw per day; NR, not reported; ip, intraperitoneal

5.2 Human carcinogenicity data

One cohort study of workers at aluminium foundries and aluminium smelters in Sweden showed no significant association between exposure to hexachloroethane and cancer incidence.

5.3 Animal carcinogenicity data

Hexachloroethane was tested in one experiment in mice and two experiments in rats by oral administration. It produced liver tumours in mice of each sex. In rats, it produced a statistically significantly increased incidence of renal tubular tumours in males in one study and a marginal increase in the incidence of renal tubular tumours in another study, also only in males. In a two-stage liver initiation–promotion assay in rats, hexachloroethane showed promoting but no initiating activity.

5.4 Other relevant data

No data were available to the Working Group on the absorption, distribution, metabolism or excretion of hexachloroethane in humans. It is absorbed in rats after oral administration, is concentrated in kidney and fat and is excreted by apparent first-order kinetics.

In humans, exposure by inhalation to hexachloroethane (10–20 mg/m^3) produced mild irritation of the skin and mucous membrane. Inhalation produced respiratory irritation in rodents.

After short-term exposure, hexachloroethane caused renal toxicity in male rats and hepatocellular necrosis in both male and female rats.

The data on reproductive toxicity were inadequate for evaluation.

No data were available on the genetic and related effects of hexachloroethane in humans. Hexachloroethane was found to bind to DNA in mouse liver after intraperitoneal injection; no other data were available on its genetic effects in experimental systems *in vivo*. It induced sister chromatid exchange in one study but did not induce chromosomal damage in mammalian cells *in vitro*. It induced gene mutation in *Drosophila* and yeast but was not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of hexachloroethane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of hexachloroethane.

Overall evaluation

Hexachloroethane is *possibly carcinogenic to humans (Group 2B)*.

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