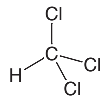
Chloroform
CAS No. 67-66-3

Reasonably anticipated to be a human carcinogen
First Listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Chloroform ($CHCl_3$) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (NCI 1976, IARC 1972, 1979, 1982, 1987, 1999). When administered by gavage (in corn oil), the compound induced hepatocellular carcinomas in mice of both sexes. It also induced increased incidences of kidney epithelial tumors in male rats when administered by the same route (NCI 1976). When administered orally (in olive oil), chloroform induced hepatomas and cirrhosis in female mice (IARC 1979). Chloroform in toothpaste or arachis oil, administered to four strains of mice by gavage, induced kidney epithelial tumors in males of one strain (Roe *et al.* 1979). When administered orally in drinking water, chloroform induced increased incidences of renal tubular cell adenomas and/or adenocarcinomas in male rats, but no renal or hepatic tumors were induced in male or female mice (Jorgenson *et al.* 1985). Another recent study reported the development of hepatic adenofibrosis in rats of both sexes and neoplastic nodules in females when chloroform was administered in the drinking water (Tumasonis *et al.* 1987).

There is inadequate evidence for the carcinogenicity of chloroform in humans (IARC 1982, 1987, 1999). Several epidemiological and ecological studies indicate that there is an association between cancer of the large intestine, rectum, and/or urinary bladder and the constituents of chlorinated water (EPA 1985). Although data may suggest a possible increased risk of cancer from exposure to chloroform in chlorinated drinking water, the data were insufficient to evaluate the carcinogenic potential of chloroform.

Properties

Chloroform is a colorless, volatile liquid that is nonflammable. It is slightly soluble in water and is miscible with oils, ethanol, ether, and other organic solvents. Chloroform has a pleasant, nonirritating odor. It is unstable when exposed to air, light, and/or heat, which cause it to break down to phosgene, hydrochloric acid, and chlorine. It is usually stabilized by the addition of 0.5% to 1% ethanol. When heated to decomposition, chloroform emits toxic fumes of hydrochloric acid and other chlorinated compounds (WHO 1994, HSDB 2001).

Use

Approximately 96% to 98% of the chloroform produced in the United States is used to make hydrochlorofluorocarbon-22 (HCFC-22) (ATSDR 1997, HSDB 2001). HCFC-22 is used as a refrigerant (70% of the HCFC-22 produced) and in the production of fluoropolymers (30%). However, this use is expected to diminish because of the phaseout of chlorine-containing fluorocarbons. Although the ozone depleting potential of HCFC-22 is relatively low, it is expected to be phased out in the United States by 2010 (HSDB 2001).

Other uses include the following: as a solvent in the extraction and purification of some antibiotics, alkaloids, vitamins, and flavors; as a solvent for lacquers, floor polishes, and adhesives; in artificial silk manufacturing; in resins, fats, greases, gums, waxes, oils, and rubber; as an industrial solvent in photography and dry cleaning; as a heat transfer medium in fire extinguishers; as an intermediate in the preparation of dyes and pesticides; and as a fumigant for stored grain crops (WHO 1994, ATSDR 1997, HSDB 2001). It is also used in certain medical procedures, such as dental root canal surgeries, and in combination with other ingredients as an experimental treatment of herpes zoster, or for control of screw worm in animals. It was used as an anesthetic prior to World War II, but this use has been banned. In addition, the U.S. FDA has banned its use in drugs, cosmetics, and food packaging (Kirk-Othmer 1979, ATSDR 1997).

Production

One U.S. manufacturer began chloroform production in 1903, but commercial production was not reported until 1922 (IARC 1979). Since the early 1980s, the production of chloroform has increased by 20% to 25%, primarily due to the great demand for the refrigerant HCFC-22 (ATSDR 1997). In 1994, 565 million lb of chloroform was produced in the United States (CEN 1996). There are currently at least two manufacturers and 38 suppliers of chloroform in the United States (ATSDR 1997, HSDB 2001, Chem Sources 2001).

Imports of chloroform decreased from a high of 38 million lb in 1989 to 5.3 million lb in 1994 (USDOC 1990; ATSDR 1997). In 2000, the U.S. imported approximately 406,000 lb of chloroform (ITA 2001). Exports increased from 33.5 million lbs in 1985 to 93 million lb by 1994 (ATSDR 1997). In 2000, U.S. exports exceeded 220 million lb (ITA 2001).

Exposure

The primary routes of potential human exposure to chloroform are ingestion, inhalation, and dermal contact with water (e.g., while showering, swimming, cleaning, and cooking). Therefore, practically all humans are exposed to low levels of the chemical (NCI 1976, IARC 1979, 1999, ATSDR 1997). Ingestion of contaminated water is expected to be a primary source because many drinking water supplies contain chloroform as a by-product of chlorination for disinfection purposes. The concentration of chloroform in drinking water increases with time with typical levels ranging from 2 to 68 ppb. Typical levels of exposure to chloroform from drinking water are estimated to range from 0.5 µg/kg b.w. per day to 10 µg/kg b.w. per day. Foods such as dairy products, oils/fats, vegetables, bread, and beverages may also contain small amounts of chloroform; typical average levels range from 52 to 71 µg/kg with an estimated average daily intake of 1 µg/kg b.w. per day (WHO 1994, IARC 1999). Chloroform was detected in the atmosphere at concentrations ranging from 0.10 to 10.0 µg/m^3 and in indoor air at 1.0 to 20.0 µg/m^3 (ATSDR 1997). Exposure via inhalation results in 60% to 80% absorption. Placental transfer of chloroform has also been demonstrated (WHO 1994).

A recent investigation demonstrated that water temperature exerts a very strong effect on dermal absorption of chloroform while bathing (Gordon *et al.* 1998). Among ten subjects, the mean amounts of chloroform exhaled at the lowest bath-water temperature (30°C) was 0.2 µg, while at the highest temperature (40°C) it was 7 µg, an increase by a factor of 35.

Although much emphasis has been given to trihalomethane exposures resulting from ingestion of chlorinated water, several studies have shown that inhalation and dermal exposure are important. Lindstrom *et al.* (1997) examined dermal and inhalation exposures that occur from swimming in a chlorinated pool. In this case, two college students (one male and one female) were monitored during a typical two-hour workout. Chloroform breath concentrations, found to be as high as 371 µg/m^3 and 339 µg/m^3 for the subjects, were more than two times the maximum possible inhalation-only level. Furthermore, the maximum alveolar breath concentrations ultimately rose to more than twice the indoor chloroform level, suggesting that dermal absorption was more important than inhalation in this case. The dermal contribution was estimated at greater than 80% of the total exposure.

Occupational exposure may occur during the manufacture or use of chloroform. Persons working at wastewater and other treatment plants can be exposed to significant levels of the chemical (ATSDR 1997). Other industries using chloroform include building and paperboard industries, iron and steel manufacturing, internal combustion engine industries, pesticide manufacturing, breweries, dry cleaning, and food processing industries. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 215,000 workers were potentially exposed to chloroform in the workplace (NIOSH 1976). The National Occupational Exposure Survey (1981-1983) indicated that 95,330 total workers, including 40,973 women, potentially were exposed to chloroform (NIOSH 1984). EPA's Toxic Chemical Release Inventory (TRI) listed 154 industrial facilities that reported environmental releases of chloroform in 1999 (TRI99 2001). Reported environmental releases of chloroform showed a steady decline from approximately 28 million lb in 1988 to 5.5 million lb in 1999.

Regulations

DOT

Chloroform is considered a hazardous material and special requirements have been set for marking, labeling, and transporting this material

EPA

Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

NSPS: Manufacture of substance is subject to certain provisions for the control of Volatile Organic Compound (VOC) emissions

Prevention of Accidental Release: Threshold Quantity (TQ) = 20,000 lb

Urban Air Toxics Strategy: Identified as one of 33 HAPs that present the greatest threat to public health in urban areas

Clean Water Act

Effluent Guidelines: Listed as a Toxic Pollutant

Water Quality Criteria: Based on fish/shellfish and water consumption = 5.7 μg/L; based on fish/shellfish consumption only = 470 μg/L

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 10 lb

Emergency Planning and Community Right-to-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

Reportable Quantity (RQ) = 10 lb

Threshold Planning Quantity (TPQ) = 10,000 lb

Resource Conservation and Recovery Act

Characteristic Toxic Hazardous Waste: TCLP Threshold = 6.0 mg/L

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - K044, K009, K010, K019, K020, K021, K029, K073, K116, K149, K150, K151, K158

Listed as a Hazardous Constituent of Waste

Safe Drinking Water Act

Maximum Contaminant Level (MCL) = 0.080 mg/L (sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform)

FDA

Chloroform may not be used as an ingredient in drug products or in pharmaceutical compounding

Chloroform may not be used as an ingredient in cosmetic products

OSHA

Ceiling Concentration = 50 ppm (240 mg/m^3)

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 10 ppm

NIOSH

Immediately Dangerous to Life and Health (IDLH) = 500 ppm

Short-term Exposure Limit (STEL) = 2 ppm (9.78 mg/m^3) (60 minute exposure)

Listed as a potential occupational carcinogen

REFERENCES

ATSDR. 1997. Toxicological Profile for Chloroform. Update (Final Report). NTIS Accession No. PB98-101140. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 337 pp.

CEN. 1996. Organic Chemicals: Mixed Results, but Production of Most Grew in 1995. Chem Eng News 74(26): 42.

ChemSources. 2001. Chemical Sources International, Inc. http://www.chemsources.com.

EPA. 1985. Health Assessment Document for Chloroform. EPA Report No. 600/8-84-004F. Washington, D.C.: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

Gordon, S. M., L. A. Wallace, P. J. Callahan, D. V. Kenny and M. C. Brinkman. 1998. Effect of water temperature on dermal exposure to chloroform. Environ Health Perspect 106(6): 337-45.

HSDB. 2001. Hazardous Substances Data Base. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IARC. 1972. Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds and Natural Products. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 1. Lyon, France: International Agency for Research on Cancer. 184 pp.

IARC. 1979. Some Halogenated Hydrocarbons. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. 609 pp.

IARC. 1982. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 4. Lyon, France: International Agency for Research on Cancer. 292 pp.

IARC. 1987. Overall Evaluations of Carcinogenicity. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, France: International Agency for Research on Cancer. 440 pp.

IARC. 1999. Some Chemicals That Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 73. Lyon, France: International Agency for Research on Cancer. 338 pp.

ITA. 2001. Subheading 290313: Chloroform. International Trade Administration. U.S. Department of Commerce. http://www.ita.doc.gov/td/industry/otea/Trade-Detail/.

Jorgenson, T. A., E. F. Meierhenry, C. J. Rushbrook, R. J. Bull and M. Robinson. 1985. Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1 mice. Fundam Appl Toxicol 5(4): 760-9.

Kirk-Othmer. 1979. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., vol. 5. New York, NY: Jon Wiley and Sons.

Lindstrom, A. B., J. D. Pleil and D. C. Berkoff. 1997. Alveolar breath sampling and analysis to assess trihalomethane exposures during competitive swimming training. Environ Health Perspect 105(6): 636-42.

NCI. 1976. Report on Carcinogens Bioassay of Chloroform (CAS No. 67-66-3). Gavage Studies. Bethesda, MD: National Institute of Health, Carcinogenesis Program, Division of Cancer and Prevention.

NIOSH. 1976. National Occupational Hazard Survey (1972-74). Cincinnati, OH: Department of Health, Education and Welfare.

NIOSH. 1984. National Occupational Exposure Survey (1981-83). Cincinnati, OH: U. S. Department of Health and Human Services. http://www.cdc.gov/noes/noes3/empl0003.html.

Roe, F. J., A. K. Palmer, A. N. Worden and N. J. Van Abbe. 1979. Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. J Environ Pathol Toxicol 2(3): 799-819.

TRI99. 2001. Toxic Chemical Release Inventory 1999. Data contained in the Toxic Chemical Release Inventory (TRI). National Library of Medicine. http://www.epa.gov/triexplorer/.

Tumasonis, C. F., D. N. McMartin and B. Bush. 1987. Toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. J Environ Pathol Toxicol Oncol 7(4): 55-63.

USDOCImports. 1990. U.S. Imports for Consumption, Harmonized TSUSA Commodity by Country of Origin. Washington, D.C.: U.S. Government Printing Office.

WHO. 1994. Chloroform. Environmental Health Criteria 163. Geneva: World Health Organization. 174 pp.