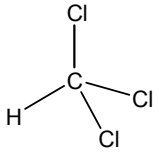
CHLOROFORM
CAS No. 67-66-3
First Listed in the *Second Annual Report on Carcinogens*



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 U.S. 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 U.S. 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 U.S. (Chem. Eng. News 1996). There are currently at least two manufacturers and 38 suppliers of chloroform in the U.S. (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 $\mu g/m^3$ and in indoor air at 1.0 to 20.0 $\mu g/m^3$ (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 $\mu g/m^3$ and 339 $\mu g/m^3$ 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

EPA regulates chloroform under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Food, Drug, and Cosmetic Act (FD&CA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Chloroform is a toxic pollutant of air and water. EPA has established water quality criteria for chloroform, effluent guidelines, rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of chloroform wastes. A reportable quantity (RQ) of 10 lb has been established for chloroform under CERCLA and CWA. Chloroform is exempted under FD&CA from tolerances for pesticide chemicals. Chloroform is recognized as an inert ingredient of toxicological concern under FD&CA. Chloroform is regulated as a hazardous constituent of waste under RCRA. EPA has established a maximum contaminant level (MCL) of 0.080 mg/L for total trihalomethanes, including chloroform, under the SDWA. Under the Emergency Planning and Community Right to Know Act (EPCRA), EPA identifies chloroform as an extremely hazardous substance and established a threshold planning quantity (TPQ) of 10,000 lb for chloroform.

FDA regulates chloroform as an indirect food additive for adhesive components in food packaging materials and as a component of materials that come into contact with food. The use of chloroform in food, drugs (for both humans and animals), and cosmetics for use in cough preparations, liniments, cosmetics, and toothache drops is banned under FD&CA.

NIOSH recommends a 2 ppm short-term exposure limit (STEL; 60 minutes). OSHA has established a permissible exposure limit (PEL) of 2 ppm and set a ceiling limit of 50 ppm (240 mg/m^3) for chloroform. ACGIH recommends a threshold limit value (TLV) of 10 ppm (49 mg/m^3). OSHA also regulates chloroform under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 38.

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