

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 is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chloroform caused tumors in two rodent species and at two different tissue sites. Administration of chloroform by stomach tube caused liver cancer (hepatocellular carcinoma) in mice of both sexes (NCI 1976) and kidney tumors (epithelial tumors) in male mice and rats (IARC 1979, Roe *et al.* 1979).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified, which reported that chloroform caused liver and kidney tumors by additional routes of exposure. Benign liver tumors (adenoma) were observed in female rats administered chloroform in the drinking water (IARC 1987, 1999) and female mice exposed by inhalation (Yamamoto *et al.* 2002). Benign and malignant kidney tumors (tubular-cell adenoma, carcinoma, or adenocarcinoma) were observed in male rats exposed via the drinking water (IARC 1987, 1999), male mice exposed by inhalation (Yamamoto *et al.* 2002), and male rats following combined exposure via inhalation and the drinking water (Nagano *et al.* 2006).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chloroform. Two community-based studies of exposure to chlorinated water found excesses of cancer at several tissue sites, particularly the urinary bladder (Cantor *et al.* 1978, Hogan *et al.* 1979), but a causal relationship could not be inferred (IARC 1982).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified, mostly involving exposure to chlorinated water, which may contain chloroform and other chlorinated hydrocarbons, via drinking, bathing, showering, or swimming. The International Agency for Research on Cancer (IARC 1999) concluded that a causal relationship between cancer and chloroform could not be inferred, because of the use of indirect methods of assessing exposure, incomplete control for confounding by exposure to other water impurities or other risk factors, and differing results for men and women. Overall, cohort and case-control studies found a relationship between exposure to chlorinated water and the risk of some types of cancer, particularly of the urinary bladder and rectum and possibly of the colon (IARC 1982, 1987, 1999).

Since the last IARC review, additional community-based studies have been identified, which have examined cancer risks associated with estimated exposure to chlorinated drinking water. Several studies, including a pooled analysis of six case-control studies, reported associations of urinary-bladder cancer with overall trihalomethane exposure (Villanueva *et al.* 2004, 2007, Chang *et al.* 2007, Michaud *et al.* 2007); two studies found an exposure-response relationship for men but not women (Villanueva *et al.* 2004, 2007). One study also found an association in men between urinary-bladder cancer and ex-

posure to trihalomethanes via bathing, showering, or swimming in pools (Villanueva *et al.* 2007). Some studies also reported associations between colorectal cancer and overall trihalomethane exposure (King *et al.* 2000, Kuo *et al.* 2009, 2010). Few studies of drinking-water exposure attempted to distinguish the risk associated specifically with exposure to chloroform, and none controlled adequately for exposure to other trihalomethanes or other risk factors. However, one study found a significantly elevated risk of urinary-bladder cancer associated with high levels of chloroform in drinking water (Bove *et al.* 2007).

Properties

Chloroform is a trihalomethane that exists at room temperature as a clear, colorless, highly refractive heavy liquid with a pleasant ethereal odor (Akron 2009, HSDB 2009). It is slightly soluble in water, soluble in carbon disulfide, and miscible with alcohol, ether, benzene, carbon tetrachloride, and fixed and volatile oils (HSDB 2009). Chloroform is stable under normal temperatures and pressures in a closed container (Akron 2009). It is light sensitive and may decompose slowly in the presence of sunlight and in the dark in the presence of air (IARC 1979). Physical and chemical properties of chloroform are listed in the following table.

| Property | Information |
|-------------------------------|----------------------------------|
| Molecular weight | 119.4 ^a |
| Specific gravity | 1.4888 at 25°C/25°C ^a |
| Melting point | -63.41°C ^a |
| Boiling point | 61.2°C ^a |
| Log K_{ow} | 1.97 ^a |
| Water solubility | 7.950 g/L at 25°C ^b |
| Vapor pressure | 197 mm Hg at 25°C ^a |
| Vapor density relative to air | 4.12 ^a |

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

In 2007, about 95% of the chloroform produced in the United States was used to make chlorodifluoromethane (HCFC-22, also known as R-22); 62% of HCFC-22 was used as a refrigerant, and 33% was used in the production of fluoropolymers (HSDB 2009). However, the use of HCFC-22 is being phased out under the 1987 Montreal Protocol, and as of January 1, 2010, manufacturers were not allowed to produce new air conditioners or heat pumps containing HCFC-22 (EPA 2010). The remaining chloroform produced has miscellaneous uses, including as a solvent or an extraction solvent for lacquers, floor polishes, adhesives in artificial silk manufacturing, resins, fats, greases, gums, waxes, oils, alkaloids, penicillin, vitamins, flavors, and rubber; as a drycleaning spot remover; in fire extinguishers; as an intermediate in the preparation of dyes and pesticides; and as a fumigant for stored grain crops (IARC 1979, ATSDR 1997, HSDB 2009). It may also be used as a local anesthetic in certain dental endodontic surgeries and in aspirin-chloroform mixtures applied topically to relieve pain from severe cases of herpes or post-therapeutic neuralgia (ATSDR 1997, HSDB 2009).

Before 1976, chloroform was used in a wide variety of drug products, including cough syrups, antihistamines, and decongestants (IARC 1979). In the 1970s, the U.S. Food and Drug Administration banned drugs containing chloroform and also banned its use in cosmetics because of its carcinogenicity. However, it did not ban drug products that contain chloroform in residual amounts resulting from its use as a solvent in manufacturing or its presence as a by-product from the synthesis of drug ingredients (IARC 1979, ATSDR 1997). An approved new drug application is required for marketing any drug product containing chloroform (FDA 1999).

Production

One U.S. manufacturer began chloroform production in 1903, but commercial production was not reported until 1922 (IARC 1979). From the early 1980s to the mid 1990s, the annual production of chloroform increased by 20% to 25%, primarily because of the great demand for the refrigerant HCFC-22 (ATSDR 1997). The U.S. Environmental Protection Agency (EPA 2016) estimated that in 2015, combined U.S. production plus imports fell in the range of 1 to 5 billion pounds. In 2009, chloroform was available from 105 suppliers, including 42 U.S. suppliers (ChemSources 2009). In the late 1980s, U.S. imports of chloroform were as high as 38 million pounds and exports as low as 33.5 million pounds. Since then, both imports and exports have fluctuated considerably, with exports greatly exceeding imports. More recent volumes of U.S. chloroform production, imports, and exports are shown in the following table.

| Category | Year | Quantity (lb) |
|-----------------------------------|------|------------------------|
| Production + imports ^a | 2015 | 1 billion to 5 billion |
| U.S. imports ^b | 2017 | 2.5 million |
| U.S. exports ^b | 2017 | 74.3 million |

Sources: ^aEPA 2016. ^bUSITC 2018.

Exposure

Evidence that people in the United States are exposed to chloroform is provided by the 2013–2014 National Health and Nutrition Examination Survey, which found that the 95th-percentile concentration of chloroform in whole blood for the U.S. general population was 40.0 pg/mL, based on samples from 3,136 individuals of all ages, both genders, and all race and ethnicity groups (CDC 2018). Exposure to chlorinated water is expected to be a primary source of human exposure to chloroform, because many public water supplies and swimming pools contain trihalomethanes as by-products of chlorination for disinfection purposes. Chloroform is the most prevalent trihalomethane in treated water. Most exposure of the general population occurs during the use of chlorine-treated water for showering, swimming, cleaning, drinking, or cooking (IARC 1979, 1999, ATSDR 1997, HSDB 2009).

Chloroform's concentration in water systems is not constant over time or location, because trihalomethane concentrations increase with the length of time the water remains in the distribution system (Ashley *et al.* 2005). Typical daily levels of adult exposure to chloroform from drinking water are estimated to range from 0.199 to 1.89 µg/kg of body weight (WHO 2004). Foods such as dairy products, oils and fats, vegetables, bread, and beverages may also contain small amounts of chloroform (IARC 1999, HSDB 2009), resulting in an estimated average daily intake of 0.043 to 0.478 µg/kg of body weight for adults aged 20 to 59 years (IPCS 2004).

Chloroform is also present in the ambient air, surface water, ground water, and soil. According to EPA's Toxics Release Inventory, environmental releases of chloroform declined steadily from about 28 million pounds in 1988 to 706,555 lb in 2007, when it was released from 67 facilities (TRI 2009). Chloroform has been detected in the atmosphere at concentrations ranging from 0.10 to 10.0 µg/m³ in urban areas in the United States and in indoor air at 0.17 to 43.9 µg/m³ (IPCS 2004). It has also been measured in surface water in rivers, lakes, and oceans, and in precipitation. The highest concentration recently measured in a U.S. river was 2.1 µg/L (McCulloch 2003). In open oceans and estuaries, the highest reported concentration was 70 µg/L in the estuary of the Mersey River, in England (Zok *et al.* 1998). Chloroform has also been measured in snowpack in the Antarctic, Italy, and Germany, at a maximum concentration of 380 ng/kg (0.00038 mg/kg) in

Antarctic snow (Zoccolillo *et al.* 2007). Contamination of ground-water by chloroform was found at the site of a plutonium processing facility near Knoxville, Tennessee, at a mean concentration of 0.108 mg/L (Datskou and North 1996). Chloroform was measured at 1.1 mg/kg in soil samples taken from a small garden in Spain irrigated with chlorine-treated tap water (Campillo *et al.* 2004).

If exposure to chloroform through inhalation of ambient air and indoor air and through ingestion of food are added to exposure through ingestion of drinking water, daily adult exposure is estimated to range from 0.70 µg/kg to over 3.0 µg/kg of body weight. Exposure due to daily showering (inhalation and dermal) alone is estimated to add 0.36 to 3.4 µg/kg. Two studies reported changes in chloroform concentrations in the blood as a result of household water use, including showering, bathing, and hand washing of dishes (Ashley *et al.* 2005, Nuckols *et al.* 2005). The concentration of chloroform in the blood increased 2- to 7-fold after showering; at two study sites, the median water concentrations of chloroform were 8 and 85 ppb, and the median blood concentrations after showering were 57 and 280 ppt (ng/L) (Nuckols *et al.* 2005). Ingestion of drinking water caused little elevation in blood levels of chloroform; however, the use of hot water during showering, bathing, and hand washing of dishes caused significant peaks in chloroform blood concentrations. Dermal absorption of chloroform is affected by water temperature during bathing. Among 10 subjects, the mean amount of chloroform exhaled was 0.2 µg at the lowest bath-water temperature (30°C) and 7 µg at the highest temperature (40°C), for a 35-fold increase (Gordon *et al.* 1998).

Several studies have shown that inhalation and dermal exposure to chloroform are important during swimming. Lindstrom *et al.* (1997) measured dermal and inhalation exposure to chloroform from swimming in a chlorinated pool; two college students (one male and one female) were monitored during a typical two-hour workout. The mean concentration of chloroform in their breath was as high as 371 µg/m³ and 339 µg/m³, over twice the maximum possible concentration from inhalation exposure only. Furthermore, the maximum alveolar breath concentrations ultimately reached over twice the ambient indoor chloroform concentration, suggesting that dermal absorption was more important than inhalation. The dermal contribution was estimated at over 90% of total exposure. Other studies found that inhalation exposure to chloroform resulted in 80% absorption. Placental transfer of chloroform also has been demonstrated (IPCS 2004).

Occupational exposure may occur during the manufacture or use of chloroform (ATSDR 1997). Workers at wastewater and other treatment plants can be exposed to significant levels of chloroform. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 95,772 workers, including 41,394 women, in 20 industrial categories potentially were exposed to chloroform (NIOSH 1990).

Regulations

Department of Transportation (DOT)

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

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

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

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

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 60 µg/L; based on fish or shellfish consumption only = 2,000 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 and substance subject to reporting requirements.
Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 6.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chloroform = U044, F024, F025, 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 for the sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform.

Food and Drug Administration (FDA, an HHS agency)

All drug products containing chloroform have been removed from the market, and a new drug application is required for approval.

Chloroform may not be used as an ingredient in cosmetic products.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.

Ceiling concentration = 50 ppm (240 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Short-term exposure limit (STEL) = 2 ppm (9.78 mg/m³) (60-min exposure).

Immediately dangerous to life and health (IDLH) limit = 500 ppm.

Listed as a potential occupational carcinogen.

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