

1,4-Dioxane

CAS No. 123-91-1

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

1,4-Dioxane 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 1,4-dioxane caused tumors in several species of experimental animals and at several different tissue sites. Administration of 1,4-dioxane in drinking water caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes, female rats, and male guinea pigs. It also caused cancer of the nasal cavity (squamous-cell carcinoma) in rats of both sexes and gallbladder cancer (carcinoma) in male guinea pigs (IARC 1976, NCI 1978). In an initiation-promotion study, dermal exposure to 1,4-dioxane promoted the induction of skin tumors (squamous-cell carcinoma, sarcoma, and papilloma) by 7,12-dimethylbenzanthracene in mice of both sexes (IARC 1976).

Since 1,4-dioxane was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. 1,4-Dioxane administered in the drinking water increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats and mice of both sexes. In rats, it also caused nasal cancer (primarily squamous-cell carcinoma) and benign mammary-gland tumors (adenoma) in females and abdominal-cavity tumors (mesothelioma of the peritoneum) in males. Nasal tumors observed in male rats (squamous-cell carcinoma, esthesioneuroepithelioma, rhabdomyosarcoma, and unspecified sarcoma) were considered to be exposure-related because of the rarity of these tumors (IARC 1999, Kano *et al.* 2009). As in the drinking-water studies, inhalation exposure of male rats to 1,4-dioxane caused benign liver tumors (hepatocellular adenoma), nasal cancer (squamous-cell carcinoma), and mesothelioma of the peritoneum. In addition, significant exposure-related trends were observed for tumors of the mammary gland (fibroadenoma), kidney (renal-cell carcinoma), and Zymbal gland (adenoma) (Kasai *et al.* 2009), although the incidences at the highest dose were not significantly higher than in the control group. In male strain A/J mice (a strain with a high spontaneous incidence of lung tumors), intraperitoneal injection of 1,4-dioxane increased the number of benign lung tumors (adenoma) per animal (Maronpot *et al.* 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dioxane. A small prospective study of 165 U.S. workers exposed intermittently to low levels of 1,4-dioxane found no excess of death from cancer; however, the study was limited by the small number of cancer deaths (3) among the exposed workers (Buffler *et al.* 1978).

Properties

1,4-Dioxane (a dimer of ethylene oxide) is a cyclic ether that exists at room temperature as a colorless liquid with a faint, pleasant ethereal odor. It is miscible with water, oils, and most organic solvents, including aromatic hydrocarbons. 1,4-Dioxane is highly flammable and may form dangerous peroxides with prolonged exposure to air and sunlight, especially in the presence of moisture (IARC 1976, Akron 2009). Physical and chemical properties of 1,4-dioxane are listed in the following table.

Property	Information
Molecular weight	88.1 ^a
Specific gravity	1.03 at 20°C/4°C ^a
Melting point	12°C ^a
Boiling point	101°C ^a
Log K_{ow}	-0.27 ^b
Water solubility	1,000 g/L at 20°C ^b
Vapor pressure	37 mm Hg at 25°C ^a
Vapor density relative to air	3.03 ^a
Dissociation constant (pK _a)	-2.92 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

1,4-Dioxane is used as a solvent for cellulose acetate, ethyl cellulose, benzyl cellulose, resins, oils, waxes, and fats; in spectroscopic and photometric measurements; and in the pulping of wood. It is also used as a wetting and dispersing agent in textile processing, a degreasing agent, a polymerization catalyst, and a component of polishing compositions, dye baths, lacquers, paints, varnishes, stains, printing compositions, and paint and varnish removers (IARC 1976, 1999, ATSDR 2007, HSDB 2009). Other uses of 1,4-dioxane include the manufacture of adhesives, cements, deodorant fumigants, cosmetics, drugs, cleaning preparations, magnetic tape, plastic, rubber, insecticides, and herbicides, and as a chemical intermediate, as a polymerization catalyst, in the purification of drugs, and in the extraction of animal and vegetable oils. In the laboratory, it is used in the preparation of histological sections for microscopic examination and as a liquid scintillation counting medium. Historically, 90% of 1,4-dioxane was used as a stabilizer for 1,1,1-trichloroethane, typically at a concentration of 3.5% (ATSDR 2007). Because use of 1,1,1-trichloroethane has been limited under the Montreal Protocol on Substances that Deplete the Ozone Layer, this use is not expected to be significant.

Production

Commercial production of 1,4-dioxane in the United States was first reported in 1951, but semi-commercial quantities were available in 1929 (IARC 1976, ATSDR 2007). Estimated U.S. production of 1,4-dioxane was 12 million pounds in 1977 and 15 million pounds in 1982 (ATSDR 2007). In 2009, 1,4-dioxane was produced by one manufacturer each in the United States, Europe, and India and three manufacturers in East Asia (SRI 2009) and was available from 48 suppliers, including 26 U.S. suppliers (ChemSources 2009). From 1989 to 1995, U.S. imports of 1,4-dioxane fell from a high of 2.4 million pounds in 1989 to zero in 1995, while U.S. exports fluctuated between 11.9 million and 6.8 million pounds (USITC 2009). No more recent data on imports or exports were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,4-dioxane totaled 10 million to 50 million pounds in 1986 and 1990, decreasing to between 1 million and 10 million pounds between 1994 and 2006 (EPA 2004, 2009).

1,4-Dioxane may also be formed as a by-product during the manufacture of certain cosmetic ingredients, although it is not used as a cosmetic ingredient (FDA 2007).

Exposure

The routes of potential human exposure to 1,4-dioxane are inhalation, ingestion, and dermal contact. 1,4-Dioxane may be formed as a by-product of reactions based on condensing ethylene oxide or ethylene glycol during manufacture of detergents, shampoos, surfactants, some food additives (polysorbate 60 and polysorbate 80), and certain pharmaceuticals. The general population could be exposed to 1,4-dioxane through contact with residues contained in these products. Based on an analysis of the ingredients in 15,000 cosmetic and other personal-care products, 22% of all such products potentially contain 1,4-dioxane (EWG 2007). 1,4-Dioxane has also been reported to be present in other consumer products, such as adhesives and antifreeze products. Small amounts may be present in foods (such as meats and tomato juice), which may indicate that it is a natural constituent of some foods. It is also present in tap water, which means that exposure through the ingestion of drinking water, bathing, showering, and other household water uses are possible (ATSDR 2007).

Total environmental releases of 1,4-dioxane reported by EPA's Toxics Release Inventory from 1988 to 2009 ranged from 0.3 million to 1.3 million pounds (in 1993). In 2003, 53 facilities released 309,000 lb of 1,4-dioxane, of which 46% was released to air, 27% to surface water, and most of the remainder (26%) to off-site underground injection wells (TRI 2009). In air, 1,4-dioxane is expected to be subject to photooxidation, with a half-life of 1 to 3 days. It is expected to volatilize from water and soil. It adsorbs weakly to soil and sediment and will leach readily to groundwater. Because it does not undergo biodegradation, it will move rapidly through the subsurface with no significant change in concentration over time (Lesage *et al.* 1990). In groundwater, 1,4-dioxane forms the leading edge of a contaminant plume and travels much faster, farther, and more widely than other volatile organic compounds. However, it has a low potential for bioaccumulation. In 1984, the concentration of 1,4-dioxane in ambient air in the United States ranged from 0.1 to 0.4 $\mu\text{g}/\text{m}^3$, and the mean concentration in indoor air was 3.7 $\mu\text{g}/\text{m}^3$. In a 1990 study in California, the average indoor concentration of 1,4-dioxane was below the limit of quantitation (0.11 $\mu\text{g}/\text{m}^3$). In the United States, 1,4-dioxane was found in groundwater at concentrations ranging from less than 1 $\mu\text{g}/\text{L}$ to 109 $\mu\text{g}/\text{L}$ and in surface water at 1 $\mu\text{g}/\text{L}$ (ATSDR 2005).

Occupational exposure to 1,4-dioxane could occur during its production or its use as a solvent (IARC 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 430,000 workers, including 149,697 women, potentially were exposed to 1,4-dioxane (NIOSH 1990). In 1968, the air concentration of 1,4-dioxane in the vicinity of storage tanks at three U.S. manufacturing facilities was as high as 800 ppm (2,883 mg/m^3). When these facilities were monitored in the mid 1970s, the concentrations of 1,4-dioxane measured in workplace air ranged from 0.2 to 22 ppm (0.7 to 79.3 mg/m^3). The maximum time-weighted-average occupational exposure concentrations were 16 ppm (57.6 mg/m^3) in production areas, 22 ppm (79.3 mg/m^3) in loading areas, 11 ppm (39.6 mg/m^3) around storage tanks, and 108.9 ppm (392.4 mg/m^3) for point-source emissions. Maximum personal monitoring samples ranged from 32 ppm (115.3 mg/m^3) for loading and control operators to 16.8 ppm (60.5 mg/m^3) for tank-car unloaders. Maximum concentrations in grab samples at measurement stations in the work area under normal operations ranged from 0.64 ppm (2.3 mg/m^3) to 1.5 ppm (5.4 mg/m^3); in one drum-filling and production area, the maximum concentration was 51 ppm (183.8 mg/m^3), and in another produc-

tion area the maximum concentration was 36.7 ppm (132.2 mg/m^3) (NIOSH 1977, Santodonato 1985). Through 2005, five requests had been made to the National Institute for Occupational Safety and Health for health hazard evaluations of workplaces for exposure to 1,4-dioxane (Lewis 1979, Belanger 1980, Salisbury and Arnold 1984, Daniels 1987, Krake and Herrera-Moreno 1995). Two of these evaluations indicated excessive levels of 1,4-dioxane that contributed to adverse health effects in the workers, and changes in the work environment were recommended.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,4-dioxane on ships and barges.

Department of Transportation (DOT)

1,4-Dioxane 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 or use is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,4-dioxane = U108.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

1,4-Dioxane levels shall not exceed 10 mg/kg in glycerides and polyglycides of hydrogenated vegetable oils when used as a food additive.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 100 ppm (360 mg/m^3).

Potential for dermal absorption.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 20 ppm.

Potential for dermal absorption.

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 1 ppm (3.6 mg/m^3) (30-min exposure).

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

Listed as a potential occupational carcinogen.

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