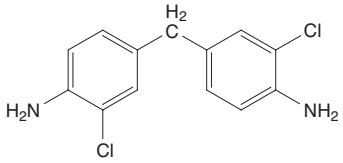
4,4′-Methylenebis(2-chloroaniline)

CAS No. 101-14-4

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as methylene-bis-*ortho*-chloroaniline, MBOCA, or MOCA



Carcinogenicity

4,4′-Methylenebis(2-chloroaniline) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4,4′-Methylenebis(2-chloroaniline) caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary administration of 4,4′-methylenebis(2-chloroaniline) caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats of both sexes and in female mice (IARC 1974). Dietary exposure also caused malignant blood-vessel tumors (hemangiosarcoma) in mice of both sexes, benign and malignant lung tumors (adenoma and adenocarcinoma) in rats of both sexes, and mammary-gland cancer (adenocarcinoma) in female rats. Cancer of the liver (hepatocellular carcinoma) and lung (carcinoma) also were observed in rats (sex not specified) administered 4,4′-methylenebis-(2-chloroaniline) by subcutaneous injection.

Since 4,4′-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens,* additional studies in experimental animals have been identified. Dietary administration of 4,4′-methylenebis(2-chloroaniline) to male rats caused cancer of the Zymbal gland (carcinoma) and mammary gland (adenocarcinoma), in addition to liver and lung tumors as reported in earlier studies (Kommineni *et al.* 1979). In female dogs, administration of 4,4′-methylenebis(2-chloroaniline) in capsule form caused cancer of the urinary bladder (transitional-cell carcinoma) and urethra (mixed transitional-cell carcinoma and adenocarcinoma) (Stula *et al.* 1978).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 4,4′-methylenebis(2-chloroaniline). Since 4,4′-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens,* additional studies in humans have been identified. In studies of workers exposed to 4,4′-methylenebis(2-chloroaniline) in the United States and Taiwan, cases of urinary-bladder cancer were detected in a screening program; however, expected rates of asymptomatic urinary-bladder cancer were not available for comparison (IARC 1993, Chen *et al.* 2005). In a small U.K. cohort of male 4,4′-methylenebis(2-chloroaniline) production workers, one urinary-bladder cancer death was reported, yielding a statistically nonsignificant fivefold increase in mortality and threefold increase in incidence, compared with national rates (Dost *et al.* 2009).

Properties

4,4′-Methylenebis(2-chloroaniline) is a chlorinated aromatic amine that exists at room temperature as a tan to colorless crystalline solid with a faint amine odor (IARC 1993, Akron 2009, HSDB 2010). It is practically insoluble in water; soluble in oxygenated solvents, trichloroethylene, toluene, ethoxyethyl acetate, methyl ethyl ketone, tetrahydrofuran, acetone, esters, aromatic hydrocarbons, dimethyl sulfoxide, dimethyl formamide, dilute acids, and carbon tetrachloride; and very soluble in benzene, diethyl ether, and ethanol. When heated to over 200°C, 4,4′-methylenebis(2-chloroaniline) undergoes an exothermic and self-sustaining decomposition reaction, which in a closed container can cause an explosion (Akron 2009). Physical and chemical properties of 4,4′-methylenebis(2-chloroaniline) are listed in the following table.

Property	Information
Molecular weight	267.0[a]
Specific gravity	1.44[a]
Melting point	110°C[a]
Boiling point	378.9°C[b]
Log K_{ow}	3.91[a]
Water solubility	13.9 mg/L at 24°C[b]
Vapor pressure	2.86×10^{-7} mm Hg at 25°C[a]

Sources: [a]HSDB 2010, [b]ChemID Plus 2009.

Use

4,4′-Methylenebis(2-chloroaniline) has been used primarily as a curing agent for isocyanate polymers and polyurethane prepolymers in the manufacture of castable urethane rubber products such as industrial tires and rollers, shock-absorption pads, and conveyor belting (IARC 1993, HSDB 2010). It is also used as a curing agent for epoxy. The cured polymers have many uses, including the manufacture of gun mounts, jet engine turbine blades, radar systems, and components in home appliances. In the laboratory, 4,4′-methylenebis(2-chloroaniline) has been used as a positive control for studying mutagens and carcinogens (HSDB 2010).

Production

Production of 4,4′-methylenebis(2-chloroaniline) was first reported in the United States in 1956 (IARC 1974). In 2010, 4,4′-methylenebis-(2-chloroaniline) was produced by three manufacturers in east Asia, one manufacturer each in China and Europe, and none in the United States (SRI 2010) and was available from 24 suppliers, including 12 U.S. suppliers (ChemSources 2010). U.S. imports of 4,4′-methylenebis(2-chloroaniline) totaled over 1.9 million pounds in 1989 (HSDB 2010) and almost 2.0 million pounds in 1991 (ATSDR 1994). 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 4,4′-methylenebis(2-chloroaniline) totaled between 1 million to 10 million pounds from 1986 to 1998, falling to between 500,000 and 1 million pounds in 2002 and 2006 (EPA 2004, 2009).

Exposure

The primary route of potential human exposure to 4,4′-methylenebis-(2-chloroaniline) is dermal contact; other potential routes are inhalation and ingestion (IARC 1993). According to EPA's Toxics Release Inventory, environmental releases of 4,4′-methylenebis(2-chloroaniline) since 1988 have ranged from lows of 19 lb in 1992 and 26 lb in 1998 to highs of 14,933 lb in 1993 and 26,185 lb in 2000. Releases fell to 14,719 lb in 2001 and 1,708 lb in 2002, remaining around 2,000 lb from 2002 to 2004. Most releases before 1999 were to air; since then, most releases have been to land. In 2005, 5,000 lb of 4,4′-methylenebis(2-chloroaniline) was released to air and to off-site landfills. The release total and pattern remained similar through 2007, when five facilities released a total of 6,233 lb (TRI 2010). 4,4′-Methylenebis-

(2-chloroaniline) has been identified in at least four hazardous-waste sites on the National Priorities List (ATSDR 1994).

When released to air, 4,4′-methylenebis(2-chloroaniline) will exist mainly as a particulate that is removed by dry and wet deposition; the portion that remains in the vapor phase will react with hydroxyl radicals, with a half-life of 5 hours. If released to surface water, 4,4′-methylenebis(2-chloroaniline) is likely to be strongly adsorbed to organic matter or may be photodegraded in surface water, but is not easily hydrolyzed. If released to soil, it will bind to soil particles and will have slight mobility in the subsurface environment; however, it may be subject to aerobic biodegradation. It may bioaccumulate in food plants but is not readily translocated through the plant (ATSDR 1994, HSDB 2010).

In 1979, 4,4′-methylenebis(2-chloroaniline) was detected in soil samples obtained within a 1-km (0.6-mi) radius of a chemical plant in Michigan; concentrations in soil samples from along public roads in the area were as high as 590 ppm. Concentrations of 4,4′-methylenebis(2-chloroaniline) were as high as 18 ppm in sludge from the wastewater-treatment plant in the area and over 1,600 ppm in sediment from an on-site industrial lagoon (ATSDR 1994).

The risk of exposure to 4,4′-methylenebis(2-chloroaniline) is greatest for workers involved in the manufacture of polyurethane and plastic products where 4,4′-methylenebis(2-chloroaniline) is used as a curing agent (ATSDR 1994). When used for this purpose, 4,4′-methylenebis(2-chloroaniline) is melted before being mixed into an elastomer formulation; it potentially could volatilize and be emitted into waste gases and wastewater (IARC 1993, ATSDR 1994, TRI 2010). Urine from workers at polyurethane plastics manufacturing facilities in the United Kingdom, France, and Australia contained 4,4′-methylenebis(2-chloroaniline) at concentrations as high as 1.3 mg/L of urine (IARC 1993, ATSDR 1994, Vaughan and Kenyon 1996, Robert *et al.* 1999a,b). In 2006, the U.S. Occupational Safety and Health Administration conducted an occupational exposure investigation of a small U.S. company that manufactured pliable polyurethane parts. Surface wipe samples collected from the top of the metal scale table were reported to have concentrations of 4,4′-methylenebis(2-chloroaniline) as high as 209 μg/m^2, and total 4,4′-methylenebis(2-chloroaniline) was measured in the urine of one worker at a concentration of 15 μg/L (Fairfax and Porter 2006). In a manufacturing facility in Taiwan, 4,4′-methylenebis(2-chloroaniline) was found in the air at concentrations of up to 0.41 mg/m^3 (410 μg/m^3) (Chen *et al.* 2005), and concentrations in the urine of 10 workers ranged from 267.9 to 15,701.1 μg/g of creatinine (mean = 5,544 μg/g) (Liu *et al.* 2005).

Regulations

Department of Transportation (DOT)

4,4′-Methylenebis(2-chloroaniline) is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

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

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.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 4,4′-methylenebis(2-chloroaniline) = U158.
Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA, an HHS agency)

4,4′-Methylenebis(2-chloroaniline) is prohibited from indirect addition to human food through food-contact surfaces; food containing any added or detectable level of this substance is prohibited.

Mine Safety and Health Administration (MSHA, Dept. of Labor)

To control airborne exposure, 4,4′-methylenebis(2-chloroaniline) shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm.
Potential for dermal absorption.

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

Recommended exposure limit (REL) = 0.003 mg/m^3.
Potential for dermal absorption.
Listed as a potential occupational carcinogen.

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