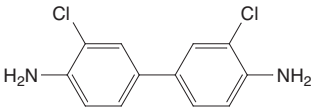
3,3′-Dichlorobenzidine and Its Dihydrochloride

CAS Nos. 91-94-1 and 612-83-9

Reasonably anticipated to be human carcinogens

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



Carcinogenicity

3,3′-Dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The names 3,3′-dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride are used interchangeably in the published literature. Although only the dihydrochloride salt is believed to be available commercially, it is not always clear whether the salt or the free base was the compound studied.

Cancer Studies in Experimental Animals

3,3′-Dichlorobenzidine or its dihydrochloride caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Dietary administration of 3,3′-dichlorobenzidine caused mammary-gland cancer (adenocarcinoma) in rats of both sexes, granulocytic leukemia and Zymbal-gland cancer (carcinoma) in male rats, urinary-bladder cancer (transitional-cell or papillary transitional-cell carcinoma) in hamsters and in female dogs, and liver cancer (hepatocellular carcinoma) in female dogs (IARC 1974, Stula *et al.* 1975, 1978). Subcutaneous injection of 3,3′-dichlorobenzidine caused skin and mammary-gland tumors in rats (IARC 1974). Since 3,3′-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens,* additional studies in mice have been identified. Prenatal exposure to 3,3′-dichlorobenzidine caused lymphoid leukemia (IARC 1982), and dietary exposure caused liver cancer (hepatocellular carcinoma) in males (IARC 1982, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 3,3′-dichlorobenzidine or 3,3′-dichlorobenzidine dihydrochloride. In three retrospective epidemiological studies, no urinary-bladder tumors were reported in men occupationally exposed to 3,3′-dichlorobenzidine (Gerarde and Gerarde 1974, Gadian 1975, MacIntyre 1975). These studies were limited by low statistical power and short follow-up time (less than 15 years for most workers).

Since 3,3′-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens,* additional epidemiological studies have been identified. Three cohort studies reported an excess of bladder cancer among paperboard-printing workers (Sinks *et al.* 1992), chemical-manufacturing workers (Ouellet-Hellstrom and Rench 1996), and dye-manufacturing workers (Rosenman and Reilly 2004) who were potentially exposed to 3,3′-dichlorobenzidine; however, the workers potentially were also exposed to other substances associated with urinary-bladder cancer, such as *o*-toluidine or benzidine. One of the cohort studies (Ouellet-Hellstrom and Rench 1996) found a significant increase in the standardized incidence ratio for urinary-bladder cancer among chemical manufacturing plant workers potentially exposed to 3,3′-dichlorobenzidine who were first employed after benzidine manufacture had ended. Although pigments containing 3,3′-dichlorobenzidine were reported to have been used at the plant employing the paperboard-printing workers, exposure to 3,3′-dichlorobenzidine could not be verified by environmental measurements; this study also found an increased risk of kidney-cancer incidence and mortality (Sinks *et al.* 1992). A significant increase in cancer of the blood cells (mostly leukemia) was found among dye-manufacturing workers exposed only to 3,3′-dichlorobenzidine (Rosenman and Reilly 2004).

Properties

3,3′-Dichlorobenzidine is a chlorinated aromatic amine derived from benzidine (IARC 1974). It exists at room temperature as gray to purple needle-like crystals. It is slightly soluble in water and dilute hydrochloric acid, but readily soluble in benzene, diethyl ether, ethanol, and glacial acetic acid. Physical and chemical properties of 3,3′-dichlorobenzidine are listed in the following table.

Property	Information
Molecular weight	253.1[a]
Melting point	132°C to 133°C[a]
Boiling point	402°C[a]
Log K_{ow}	3.51[a]
Water solubility	0.0031 g/L at 25°C[a]
Vapor pressure	2.56×10^{-7} mm Hg at 25°C[b]
Dissociation constant (pK_a)	3.2[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

3,3′-Dichlorobenzidine is used in the United States primarily in the manufacture of pigments for printing ink, textiles, paper, paint, rubber, and plastics and as a curing agent for isocyanate-containing polymers and solid urethane plastics (IARC 1974, ATSDR 1998). As of 1983, at least seven synthetic organic pigments, toners, and lakes were produced with 3,3′-dichlorobenzidine. The yellow pigments derived from the chemical and its salts, including benzidine yellow, can be used as substitutes for the lead chromate pigments (ATSDR 1998, HSDB 2009). Use of 3,3′-dichlorobenzidine to synthesize dyes ceased in 1986 with the introduction of better dyes from other sources; however, its use in the manufacture of pigments has continued (ATSDR 1998). Both 3,3′-dichlorobenzidine and its dihydrochloride also are used in a color test for the detection of gold (IARC 1982). In addition, 3,3′-dichlorobenzidine is used in the production of tetraaminobiphenyl, which is used to produce polybenzimidazole, a thermally stable polymer used in protective clothing such as firefighters' apparel and high-temperature gloves. 3,3′-Dichlorobenzidine has also been used as a compounding ingredient for rubber and plastics (ATSDR 1998).

Production

Commercial production of 3,3′-dichlorobenzidine in the United States began in 1938 (IARC 1974). Production volumes of 3,3′-dichlorobenzidine were considered confidential by individual companies and therefore were not available (ATSDR 1998). In 2009, 3,3′-dichlorobenzidine was produced by one manufacturer, in Europe, and the hydrochloride was produced by 10 manufacturers, including 1 each in Europe and China, 2 in East Asia, and 6 in India (SRI 2009). 3,3′-Dichlorobenzidine was available from 14 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009). The dihydrochloride is imported; imports peaked in 2000 at 8.7 million pounds, falling to 5.4 million pounds by 2008 (USITC 2009). The quantity of pigments derived from 3,3′-dichlorobenzidine totaled 129,000 lb in 1983 (ATSDR 1998). 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 3,3′-dichlorobenzidine dihydrochloride totaled 1 million to 10 million pounds in

1986 and 1990 and 10 million to 50 million pounds between 1994 and 2006 (EPA 2004, 2009).

Exposure

The routes of potential human exposure to 3,3′-dichlorobenzidine are inhalation of airborne dust, ingestion of contaminated well water by those living near hazardous waste sites, and dermal contact, primarily during industrial operations. For the general population, the likelihood of exposure to 3,3′-dichlorobenzidine probably is low. Exposure via air, soil, or water is expected to be negligible, and the greatest likelihood of exposure to 3,3′-dichlorobenzidine is from improper land disposal. No current uses of 3,3′-dichlorobenzidine in commonly used consumer products were identified. In the past, exposure might have occurred during the use of pressurized spray containers of paints, lacquers, and enamels containing traces of benzidine yellow, a pigment derived from 3,3′-dichlorobenzidine (ATSDR 1998).

3,3′-Dichlorobenzidine may be released as atmospheric emissions or in wastewater during production or use as a dye intermediate. Atmospheric emissions most likely have been reduced by the adoption of closed-system operations. According to EPA's Toxics Release Inventory, environmental releases of 3,3′-dichlorobenzidine totaled 32 lb in 1999 (on-site releases), 1,000 lb in 2007, and 1,565 lb in 2008 (to off-site landfills) (TRI 2009). If released to air, 3,3′-dichlorobenzidine is expected to adsorb to particulate matter and photodegrade. If released to water, the free base will rapidly adsorb to sediment and particulate matter, where it will be bound. 3,3′-Dichlorobenzidine may undergo photolysis in water exposed to sunlight. If released to soil, it will bind to soil and possibly react with soil components. 3,3′-Dichlorobenzidine's strong tendency to partition to soils and sediments reduces the potential for human exposure (ATSDR 1998).

EPA reported in 1980 that data on the presence of 3,3′-dichlorobenzidine in the environment were limited; one survey detected 3,3′-dichlorobenzidine at concentrations of 0.13 to 3.0 mg/L at one 3,3′-dichlorobenzidine production waste-disposal site (IARC 1982). Between 1993 and 2003, 36 samples of surface water and sediment were taken from Lake Macatawa, in Holland, Michigan (Harden *et al.* 2005). Early samples contained 3,3′-dichlorobenzidine at concentrations exceeding the water-quality criteria by factors of up to 1,300; however, 3,3′-dichlorobenzidine was not detected in samples taken in 2003. Maximum concentrations of 3,3′-dichlorobenzidine in wastewater were estimated to be 10 ppb from metal finishing, 2 ppb (average = 0.3 ppb) from nonferrous metals manufacture, 10 ppb from paint and ink manufacture, and 3 ppb from coal mining (HSDB 2009).

Occupational exposure to the dihydrochloride probably continues to occur during its manufacture and conversion to derived pigments (HSDB 2009). No data were found on the number of workers potentially exposed to 3,3′-dichlorobenzidine dihydrochloride.

Regulations

Department of Transportation (DOT)

3,3′-Dichlorobenzidine 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: 3,3′-Dichlorobenzidine is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: 3,3′-Dichlorobenzidine is listed as a toxic pollutant.

Water Quality Criteria: For 3,3′-dichlorobenzidine, based on fish or shellfish and water consumption = 0.049 µg/L; based on fish or shellfish consumption only = 0.15 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for 3,3′-dichlorobenzidine.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substances 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 3,3′-dichlorobenzidine = U073.

3,3′-Dichlorobenzidine is listed as a hazardous constituent of waste.

Mine Safety and Health Administration

To control airborne exposure, 3,3′-dichlorobenzidine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

3,3′-Dichlorobenzidine is listed as a potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure to 3,3′-dichlorobenzidine by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

3,3′-Dichlorobenzidine and its salts are listed as potential occupational carcinogens.

References

ATSDR. 1998. *Toxicological Profile for 3,3-Dichlorobenzidine*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp108.pdf.

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp and select Registry Number and search on CAS number. Last accessed: 8/13/09.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on dichlorobenzidine. Last accessed: 8/13/09.

EPA. 2004. *Non-confidential IUR Production Volume Information.* U.S. Environmental Protection Agency. http://www.epa.gov/oppt/iur/tools/data/2002-vol.html and search on CAS number. Last accessed: 8/13/09.

EPA. 2009. *Inventory Update Rule 2006*. U.S. Environmental Protection Agency. http://cfpub.epa.gov/iursearch/2006_iur_natlcheminfo.cfm?id=4061. Last accessed: 8/13/09.

Gadian T. 1975. Carcinogens in industry, with special reference to dichlorobenzidine. *Chem Ind* Oct. 4: pp. 821-831.

Gerarde HW, Gerarde DF. 1974. Industrial experience with 3,3′-dichlorobenzidine: an epidemiological study of a chemical manufacturing plant. *J Occup Med* 16(5): 322-335.

Harden J, Donaldson FP, Nyman MC. 2005. Concentrations and distribution of 3,3′-dichlorobenzidine and its congeners in environmental samples from Lake Macatawa. *Chemosphere* 58(6): 767-777.

HSDB. 2009. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 8/13/09.

IARC. 1974. 3,3′-Dichlorobenzidine. In *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 4. Lyon, France: International Agency for Research on Cancer. pp. 49-55.

IARC. 1982. 3,3′-Dichlorobenzidine and Its Dihydrochloride. In *Some Industrial Chemicals and Dyestuffs*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 29. Lyon, France: International Agency for Research on Cancer. pp. 239-256.

IARC. 1987. 3,3′-Dichlorobenzidine. In *Overall Evaluations of Carcinogenicity.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl 7. Lyon, France: International Agency for Research on Cancer. pp. 193-194.

MacIntyre DI. 1975. Experience of tumors in a British plant handling 3 3′ dichlorobenzidine. *J Occup Med* 17(1): 23-26.

Ouellet-Hellstrom R, Rench JD. 1996. Bladder cancer incidence in arylamine workers. *J Occup Environ Med* 38(12): 1239-1247.

Rosenman KD, Reilly MJ. 2004. Cancer mortality and incidence among a cohort of benzidine and dichlorobenzidine dye manufacturing workers. *Am J Ind Med* 46(5): 505-512.

Sinks T, Lushniak B, Haussler BJ, Sniezek J, Deng JF, Roper P, Dill P, Coates R. 1992. Renal cell cancer among paperboard printing workers. *Epidemiology* 3(6): 483-489.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 11/25/09.

Stula EF, Sherman H, Zapp JA Jr, Clayton JW Jr. 1975. Experimental neoplasia in rats from oral administration of 3,3′-dichlorobenzidine, 4,4′-methylene-bis-bis(2-chloroaniline), and 4,4′-methylene-bis(2-methylaniline). *Toxicol Appl Pharmacol* 31(1): 159-176.

Stula EF, Barnes JR, Sherman H, Reinhardt CF, Zapp JA Jr. 1978. Liver and urinary bladder tumors in dogs from 3,3′-dichlorobenzidine. *J Environ Pathol Toxicol* 1(4): 475-490.

TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select 3,3′-Dichlorobenzidine. Last accessed: 5/09.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2921598010. Last accessed: 10/20/09