3,3′-Dichlorobenzidine and Its Dihydrochloride

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

Reasonably anticipated to be human carcinogens


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, 1992). The workers were therefore not available (ATSDR 1998). In 2009, 3,3′-dichlorobenzidine was 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 (ATSDR 2009).

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 pigs 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

Physical and chemical properties of 3,3′-dichlorobenzidine are listed in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>253.1 g/mol</td>
</tr>
<tr>
<td>Melting point</td>
<td>132°C to 133°C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>402°C</td>
</tr>
<tr>
<td>Log K_a</td>
<td>3.51</td>
</tr>
<tr>
<td>Water solubility</td>
<td>0.0031 g/L at 25°C</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>2.56 × 10^{-7} mm Hg at 25°C</td>
</tr>
</tbody>
</table>


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 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).
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 in or 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