

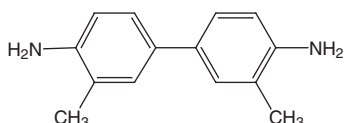
3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine

Introduction

3,3'-Dimethylbenzidine was first listed in the *Third Annual Report on Carcinogens* (1983), and 3,3'-dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine (3,3'-dimethylbenzidine dyes class) were first listed in the *Tenth Report on Carcinogens* (2002). The profiles for 3,3'-dimethylbenzidine and dyes metabolized to 3,3'-dimethylbenzidine, which are listed (separately) as *reasonably anticipated to be human carcinogens*, follow this introduction.

3,3'-Dimethylbenzidine CAS No. 119-93-7

Reasonably anticipated to be a human carcinogen
First Listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

3,3'-Dimethylbenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in rats (IARC 1972, NTP 1991). When given to rats by subcutaneous injection, commercial 3,3'-dimethylbenzidine induced cancers (carcinomas) of the Zymbal gland and ear (external auditory canal). When given to rats in their drinking water, the dihydrochloride salt of 3,3'-dimethylbenzidine increased the incidence of cancer of the Zymbal gland (adenomas and carcinomas), neoplasms and cancer of the liver (neoplastic nodules or hepatocellular carcinomas), cancer of the large intestine (adenomatous polyps or adenocarcinomas), skin cancer (basal cell adenomas and carcinomas), and cancers of the oral cavity (squamous cell papillomas and carcinomas) in both males and females; cancer of the preputial gland (carcinomas) small intestine (adenocarcinomas) and neoplasms in the lung in males; and cancer of the clitoral gland (adenomas and carcinomas) and mammary gland (adenocarcinomas) in females.

No adequate human studies of the relationship between exposure to 3,3'-dimethylbenzidine and human cancer have been reported (IARC 1972, 1987).

Properties

3,3'-Dimethylbenzidine occurs as a white to reddish crystalline powder that is slightly soluble in water and very soluble in ethanol, ethyl ether, and dilute acids. It is produced as technical-grade dry and paste formulations of various purities. When heated to decomposition, it emits toxic fumes of nitrogen oxides (HSDB 2000).

Use

More than 75% of 3,3'-dimethylbenzidine produced is used as a dye or an intermediate for producing dyestuffs and pigments. According to the Society of Dyers and Colourists, more than 95 dyes are derived from 3,3'-dimethylbenzidine. Approximately 20% of 3,3'-dimethylbenzidine is used to produce polyurethane-based high-strength elastomers, coatings, and rigid plastics. 3,3'-Dimethylbenzidine is used in small

quantities by clinical laboratories in test tapes for the detection of blood and by water companies, swimming pool owners, and others to test for chlorine in water or air (IARC 1972). 3,3'-Dimethylbenzidine is also used in a chemical test for the detection of gold (HSDB 2000).

Production

The 1997 Directory of Chemical Producers identified one producer of 3,3'-dimethylbenzidine, with no production volume reported (SRI 1997). Three U.S. producers of 3,3'-dimethylbenzidine were identified in 1986 and 1985, but no production volumes were reported (SRI 1986, USITC 1987). In 1978, the major company producing 3,3'-dimethylbenzidine in the United States ceased production; its annual production had averaged approximately 200,000 lb (HSDB 2000). Imports appear to be the major source of 3,3'-dimethylbenzidine in the United States. The 1979 Toxic Substances Control Act Inventory identified four companies importing 115,500 lb in 1977. The confidential business information aggregate was between 1 million and 100 million pounds (TSCA 1979). The U.S. International Trade Commission reported imports of 75,000 lb of 3,3'-dimethylbenzidine, and 163,700 lb of its hydrochloride salt in 1983, compared with more than 5,000 lb of 3,3'-dimethylbenzidine hydrochloride in 1980. In 1979, approximately 3.5 million pounds of 3,3'-dimethylbenzidine and 240,000 pounds of the hydrochloride were imported into the United States (USITC 1984). 3,3'-Dimethylbenzidine was imported through the principal U.S. customs districts in 1989, but the quantity was not published. Chem Sources (2001) identified 19 U.S. suppliers of 3,3'-dimethylbenzidine.

Exposure

The primary routes of potential human exposure to 3,3'-dimethylbenzidine are inhalation, dermal contact, and ingestion. Workers potentially exposed to 3,3'-dimethylbenzidine include dye makers, repackagers of 3,3'-dimethylbenzidine and dimethylbenzidine-based dyes, and personnel in clinical and analytical laboratories. Workers in a variety of occupations may be exposed to small quantities of 3,3'-dimethylbenzidine used for analytical purposes, including water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives. Swimming pool water test kits contain 0.5% to 1.0% 3,3'-dimethylbenzidine. Exposure may occur if the test solutions are emptied into the pool. In 1978, the National Institute of Occupational Safety and Health (NIOSH) estimated that fewer than 100 employees were exposed to large quantities of 3,3'-dimethylbenzidine in the United States, but as many as 200,000 may have been exposed to small quantities (NIOSH 1979). The National Occupational Exposure Survey (1981 to 1983) estimated that 8,676 workers, including 5,383 women, potentially were exposed to 3,3'-dimethylbenzidine (NIOSH 1984). This estimate was based on observations of actual use of the compound (62% of total observations) and the use of trade-name products known to contain the compound (38%). The National Occupational Hazard Survey, conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 estimated that 9,639 workers potentially were exposed to 3,3'-dimethylbenzidine (NIOSH 1990).

Dimethylbenzidine-based dyes and pigments break down to form 3,3'-dimethylbenzidine. Residual levels of 3,3'-dimethylbenzidine may be present in dimethylbenzidine-based dyes and pigments and in the final consumer products. Available data indicate that such contaminants occur in the parts-per-million range. A dimethylbenzidine-based dye was not absorbed dermally to any substantial degree when tested in rabbits.

The U.S. Environmental Protection Agency's (EPA's) Toxic Chemical Release Inventory reported that one facility produced, processed, or otherwise used 3,3'-dimethylbenzidine in the United States in 1996. The facility, reporting under the industrial classification

for manufacture of cyclic crudes and intermediates (SIC Code 2865), released a total of 6 lb to air and 25 lb to water (TRI96 1998). In 1999, three facilities reportedly produced, processed, or otherwise used 3,3'-dimethylbenzidine in the United States. Total air emissions were 17 lb, and 1 lb was released to surface water (TRI99 2001).

Regulations

EPA

Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

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 as a Hazardous Constituent of Waste

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U095

Guidelines

NIOSH

Ceiling Recommended Exposure Limit = 0.02 mg/m³ (60 minute exposure)

Listed as a potential occupational carcinogen

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Dyes Metabolized to 3,3'-Dimethylbenzidine (3,3'-Dimethylbenzidine Dye Class)*

Reasonably anticipated to be human carcinogen

First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

3,3'-Dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine are *reasonably anticipated to be human carcinogens* based on the fact that 3,3'-dimethylbenzidine is carcinogenic in male and female rats (IARC 1972, NTP 1991b, 2000) and the fact that metabolism of 3,3'-dimethylbenzidine-based dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied (Lynn *et al.* 1980, Bowman *et al.* 1982). Furthermore, a representative 3,3'-dimethylbenzidine-based dye, C.I.

Acid Red 114, is carcinogenic in male and female rats (NTP 1991a). The pattern of tumors observed with C.I. Acid Red 114 (NTP 1991a) and 3,3'-dimethylbenzidine (NTP 1991b) is similar to that observed with the structurally similar chemical 3,3'-dimethoxybenzidine (NTP 1992) and the 3,3'-dimethoxybenzidine-based dye C.I. Direct Blue 15 (NTP 1992). These four chemicals each induce tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland of male rats, and clitoral gland of female rats, and other tissue sites.

No adequate human studies of the relationship between exposure to 3,3'-dimethylbenzidine-based dyes and human cancer have been reported.

Additional Information Relevant to Carcinogenicity

3,3'-Dimethylbenzidine is structurally similar to benzidine, a *known human carcinogen* (IARC 1972, 1979, 1982, 1987, NTP 2000), and 3,3'-dimethoxybenzidine, which is *reasonably anticipated to be a human carcinogen* (IARC 1974, NTP 2000). Like benzidine and 3,3'-dimethoxybenzidine, 3,3'-dimethylbenzidine is used to synthesize many dyes, by linking of various chromophores to the base chemical by azo linkages. The azo bonds of 3,3'-dimethylbenzidine-based dyes are chemically similar regardless of the chromophore used, and they are easily broken by chemicals or enzymes via reduction to form free 3,3'-dimethylbenzidine and free chromophore(s). A number of bacteria catalyze this process, including *Escherichia coli*, found in the human gastrointestinal tract (Cerniglia *et al.* 1982, Morgan *et al.* 1994). This reductive process also has been found in rats, dogs, and hamsters (Lynn *et al.* 1980, Bowman *et al.* 1983, Nony *et al.* 1983). Bacteria in the animals' gastrointestinal tract are thought to be the primary agents of this metabolism in animals (Cerniglia *et al.* 1982, Morgan *et al.* 1994). 3,3'-Dimethylbenzidine-based dyes are mutagenic in bacteria when tested with metabolic activation and an azo-reductive preincubation protocol (NTP 1991a). It is assumed that the breakdown process results in the formation of 3,3'-dimethylbenzidine, known to cause mutations in bacteria (Haworth *et al.* 1983).

No available information suggests that mechanisms by which these substances cause cancer in laboratory animals would not also operate in humans.

Properties

3,3'-Dimethylbenzidine occurs as a white to reddish crystalline powder that is slightly soluble in water and very soluble in ethanol, ethyl ether, and dilute acids. It is produced as technical-grade dry and paste formulations of various purities. When heated to decomposition, it emits toxic fumes of nitrogen oxides (HSDB 2000).

Use

According to the Society of Dyers and Colourists, more than 95 dyes are derived from 3,3'-dimethylbenzidine. More than 75% of 3,3'-dimethylbenzidine produced is used as a dye or an intermediate for production of 3,3'-dimethylbenzidine-based dyes. These dyes and pigments are used in printing textiles, as biological stains, and in color photography.

Production

The U.S. International Trade Commission (USITC 1994) reported that 3,3'-dimethylbenzidine-based dyes were produced by three companies. Current production volumes for individual producers are not reported because they are confidential for both importers and producers. Annual U.S. production and imports of various 3,3'-dimethylbenzidine-based dyes ranged from approximately 7,500 lb to more than 180,000 lb (USITC 1980, 1981, 1984, 1994).

Exposure

Most environmental exposures to 3,3'-dimethylbenzidine occur through contact with industrially contaminated air, water, or soil

(HSDB 2001). The general population may be exposed via contact with paper or fabric products containing 3,3'-dimethylbenzidine-based dyes.

Most occupational exposures to 3,3'-dimethylbenzidine and 3,3'-dimethylbenzidine-based dyes are of workers in dye manufacturing and processing plants. Occupational exposure may occur by inhalation of dust or mist, accidental ingestion, or dermal contact. In 1986 and 1987, EPA, the American Textile Manufacturers Institute, and the Toxicological Association of the Dyestuffs Manufacturing Industry conducted a joint survey to estimate airborne concentrations of dye dust in dye-weighing rooms of facilities where powdered dyes were used to dye and print textiles. The estimated mean airborne concentration of total dye in 24 randomly monitored plants was 0.085 mg/m³ (EPA 1990).

The National Occupational Exposure Survey (NIOSH 1990) estimated that 9,639 workers potentially were exposed to 3,3'-dimethylbenzidine between 1981 to 1983 (NIOSH 1990).

Workers in other occupations may be exposed to small quantities of 3,3'-dimethylbenzidine and 3,3'-dimethylbenzidine-based dyes. These workers include water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives (NTP 1998).

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to dyes metabolized to 3,3'-dimethylbenzidine were identified.

*No separate CAS registry number is assigned to dyes metabolized to 3,3'-dimethylbenzidine.

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