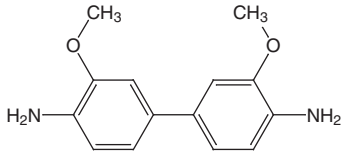
3,3′-Dimethoxybenzidine and Dyes Metabolized to 3,3′-Dimethoxybenzidine

Introduction

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

3,3′-Dimethoxybenzidine CAS No. 119-90-4

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



Carcinogenicity

3,3′-Dimethoxybenzidine 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 organ sites in rats (IARC 1974, NTP 1990, 1998). When given by stomach intubation to both male and female rats, 3,3′-dimethoxybenzidine caused tumors at various sites, including Zymbal gland tumors and cancer of the intestine (carcinoma), skin (carcinoma), and urinary bladder (papilloma). When given to rats in the diet, 3,3′-dimethoxybenzidine increased the incidence of cancer in the forestomach (papilloma). When the dihydrochloride salt of 3,3′-dimethoxybenzidine was administered in the drinking water to male and female rats, increased incidences of Zymbal gland cancer (adenoma and carcinoma), liver neoplasms and cancer (neoplastic nodules and hepatocellular carcinoma), cancer of the large intestine (adenomatous polyps and adenocarcinoma), skin cancer (basal-cell adenoma and carcinoma), and cancer of the oral cavity (squamous-cell papilloma and carcinoma) were observed. Male rats also had increased incidences of preputial gland carcinoma, cancer of the small intestine (adenocarcinoma), and mesothelioma, and female rats had increased incidences of cancer of the clitoral gland (adenoma and carcinoma), mammary gland (adenocarcinoma), and uterus or cervix (adenoma and carcinoma) (NTP 1990).

No adequate human studies of the relationship between exposure to 3,3′-dimethoxybenzidine and human cancer have been reported. No epidemiological studies have been published on cancer in workers exposed only to 3,3′-dimethoxybenzidine. Most of the workers exposed to this substance also were exposed to benzidine or other related amines, which are strongly associated with urinary bladder cancer in humans (IARC 1974, 1982, 1987).

Properties

3,3′-Dimethoxybenzidine, also known as *o*-dianisidine, occurs as colorless crystals that turn violet upon standing. It is insoluble in water and soluble in ethanol acetone, benzene, ether, and chloroform. 3,3′-Dimethoxybenzidine is available commercially as the free base (technical and 99% grades) and as its dihydrochloride salt (HSDB 2001).

Use

3,3′-Dimethoxybenzidine is used almost exclusively as a chemical intermediate for producing dyes and pigments. The Society of Dyers and Colourists reported its use in the production of 89 dyes in 1971, including Direct Blue 218, pigment orange 16, Direct Blue 1, Direct Blue 15, Direct Blue 8, Direct Blue 76, and Direct Blue 98. Some 3,3′-dimethoxybenzidine is used as a chemical intermediate to produce *o*-dianisidine diisocyanate for use in adhesives and as a component of polyurethanes. 3,3′-Dimethoxybenzidine is used as a dye for paper, plastics, rubber, and textiles, and as a test substance to detect metals, thiocyanates, and nitrites (IARC 1974, HSDB 2001).

Production

3,3′-Dimethoxybenzidine has been produced commercially since the 1920s. Data on domestic production of 3,3′-dimethoxybenzidine were last reported in 1967, when five companies produced approximately 368,000 lb (IARC 1974). Only two U.S. companies were known to produce this chemical in 1971, and only one U.S. manufacturer was listed in the Hazardous Substances Data Bank (HSDB 2001). Chem Sources (2001) listed 25 U.S. suppliers of 3,3′-dimethoxybenzidine and four suppliers of 3,3′-dimethoxybenzidine dihydrochloride. The 1979 Toxic Substances Control Act Inventory identified two companies in 1977 producing an unspecified amount of 3,3′-dimethoxybenzidine and six companies importing 55,500 lb (TSCA 1979). U.S. imports of 3,3′-dimethoxybenzidine were reported to be approximately 273,000 lb in 1971 (IARC 1974) and 106,000 lb in 1983 (USITC 1984). Imports of 3,3′-dimethoxybenzidine and its dihydrochloride salt were reported to be 655,000 lb in 1983 (USITC 1984).

Exposure

The primary routes of potential human exposure to 3,3′-dimethoxybenzidine are inhalation and dermal contact. Exposure to 3,3′-dimethoxybenzidine can occur during its use as a chemical intermediate in the production of azo dyes, *o*-dianisidine diisocyanate formulations, textile processing, and packaging processes. Human exposure could occur from trace contaminants in products that are made with 3,3′-dimethoxybenzidine (e.g., azo dyes, pigments, adhesives, resins, and polyurethane elastomers). No data were found on the quantities of 3,3′-dimethoxybenzidine in consumer products.

Workers potentially exposed to the chemical include dye makers and *o*-dianisidine diisocyanate production workers. However, present dye production processes for 3,3′-dimethoxybenzidine and its dye derivatives generally are closed systems with minimal risk to workers. The National Occupational Hazard Survey, conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that 204 workers potentially were exposed to 3,3′-dimethoxybenzidine in the workplace (NIOSH 1976). The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 estimated that 2,482 workers potentially were exposed to 3-3′-dimethoxybenzidine (NIOSH 1990). Another study estimated that approximately 1,000 workers were exposed to 3,3′-dimethoxybenzidine during dye manufacturing, but that as many as 15,000 workers potentially were exposed in the various dye application industries (HSDB 2001).

The U.S. Environmental Protection Agency′s (EPA's) Toxic Chemical Release Inventory reported low environmental releases of 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine dihydrochloride in the United States between 1988 and 1999 (TRI99 2001). Two facilities reported releases of 163 lb and 7 lb of 3,3′-dimethoxybenzidine, respectively, in 1999. One facility reported releasing 232 lb of 3,3′-dimethoxybenzidine dihydrochloride in 1999.

Regulations

EPA

Clean Air Act
NESHAP: Listed as a Hazardous Air Pollutant (HAP)
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 codes in which listing is based wholly or partly on substance - U091
Listed as a Hazardous Constituent of Waste

Guidelines

NIOSH

Listed as a potential occupational carcinogen

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Dyes Metabolized to 3,3′-Dimethoxybenzidine (3,3′-Dimethoxybenzidine Dye Class)*

Reasonably anticipated to be human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

3,3′-Dimethoxybenzidine-based dyes that are metabolized to 3,3′-dimethoxybenzidine are *reasonably anticipated to be human carcinogens* based on the fact that 3,3′-dimethoxybenzidine is carcinogenic in male and female rats (IARC 1974, NTP 1990, 1998) and that metabolism of 3,3′-dimethoxybenzidine-based dyes to release free 3,3′-dimethoxybenzidine is a generalized phenomenon that occurs in all animal species studied (Lynn *et al.* 1980, Bowman *et al.* 1983). Furthermore, a representative 3,3′-dimethoxybenzidine-based dye, C.I. direct blue 15, is carcinogenic in male and female rats (NTP 1992). The pattern of tumors observed with 3,3′-dimethoxybenzidine (NTP 1990) and C.I. direct blue 15 (NTP 1992) is similar to that observed with the structurally similar chemical 3,3′-dimethylbenzidine (NTP 1991a) and the 3,3′-dimethylbenzidine-based dye C.I. acid red 114 (NTP 1991b). Each of these four chemicals induces tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland of male rats, and clitoral gland of female rats.

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

Additional Information Relevant to Carcinogenicity

3,3′-Dimethoxybenzidine is structurally similar to benzidine, a *known human carcinogen* (IARC 1972, 1982, 1987, NTP 1998), and 3,3′-dimethylbenzidine, which is *reasonably anticipated to be a human carcinogen* (NTP 2000). Like benzidine and 3,3′-dimethylbenzidine, 3,3′-dimethoxybenzidine is used to synthesize many dyes, by linking of various chromophores to the base chemical by azo linkages. The azo bonds of 3,3′-dimethoxybenzidine-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′-dimethoxybenzidine and free chromophore. 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 and dogs (Lynn *et al.* 1980, Bowman *et al.* 1983). Lynn *et al.* (1980) provided quantitative evidence that the two 3,3′-dimethoxybenzidine-based dyes studied both were nearly completely metabolized to free 3,3′-dimethoxybenzidine. Bacteria in the animals' gastrointestinal tract are thought to be the primary agents of this metabolism (Cerniglia *et al.* 1982, Morgan *et al.* 1994). 3,3′-Dimethoxybenzidine-based dyes are mutagenic in bacteria when tested with metabolic activation and an azo-reductive preincubation protocol (NTP 1991a). It is assumed that the reductive breakdown process forms 3,3′-dimethoxybenzidine, which is 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′-Dimethoxybenzidine, also known as *o*-dianisidine, occurs as colorless crystals that turn violet upon standing. It is insoluble in water and soluble in ethanol acetone, benzene, ether, and chloroform. 3,3′-Dimethoxybenzidine is available commercially as the free base (technical and 99% grades) and as its dihydrochloride salt (HSDB 2001).

Use

3,3′-Dimethoxybenzidine is used almost exclusively as a chemical intermediate for producing dyes and pigments. The Society of Dyers and Colourists reported its use in the production of 89 dyes in 1971, including direct blue 218, pigment orange 16, direct blue 1, direct blue 15, direct blue 8, direct blue 76, and direct blue 98. Some 3,3′-dimethoxybenzidine is used as a chemical intermediate to produce *o*-dianisidine diisocyanate for use in adhesives and as a component of polyurethanes. 3,3′-Dimethoxybenzidine is used as a dye for paper, plastics, rubber, and textiles, and as a test substance to detect metals, thiocyanates, and nitrites and has been used in the past as a dye for leather (IARC 1974, HSDB 2001).

Production

The U.S. International Trade Commission (USITC 1994) reported that 3,3′-dimethoxybenzidine-based dyes were produced by three companies. Current production volumes for individual producers were not reported because they are confidential for both importers and producers. Annual U.S. production and imports of various 3,3′-dimethoxybenzidine-based dyes ranged from approximately 1,280 lb (direct blue dyes) to more than 555,000 lb (*o*-dianisidine imports) between 1978 and 1993 (USITC 1980, 1981, 1983, 1984, 1994).

Exposure

Most environmental exposures to 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine-based dyes are through contact with contaminated air, water, or soil (HSDB 2001). The general population may be exposed via contact with paper or fabric products containing these dyes and also through consumer use of these dyes.

The primary routes of potential occupational exposure to 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine-based dyes are by inhalation and dermal contact. Most occupational exposures to 3,3′-dimethoxybenzidine occur in dye manufacturing and processing plants during the production of 3,3′-dimethoxybenzidine, during the use and processing of 3,3′-dimethoxybenzidine to make 3,3′-dimethoxybenzidine-based dyes, or during the application of 3,3′-dimethoxybenzidine-based dyes. 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 production plants where powdered dyes were used to dye and print textiles. Although 3,3′-dimethoxybenzidine-based dyes were not specifically included in the survey, the results are considered representative of 3,3′-dimethoxybenzidine dye dust levels. The mean airborne concentration of total dye in the 24 plants randomly monitored was estimated to be 0.085 mg/m^3 (EPA 1990). However, current production processes using 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine-based dyes generally are closed systems that minimize worker exposure (HSDB 2001). Occupational exposure also may occur in clinical laboratories through use of 3,3′-dimethoxybenzidine in chemical tests.

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 estimated that 2,482 workers potentially were exposed to 3-3′-dimethoxybenzidine (NIOSH 1990).

Regulations and Guidelines

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

*No separate CAS registry number is assigned to dyes metabolized to 3-3′-dimethoxybenzidine.

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