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 dye 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.

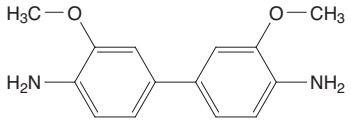
3,3′-Dimethoxybenzidine

CAS No. 119-90-4

Reasonably anticipated to be a human carcinogen

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

Also known as *o*-dianisidine



Carcinogenicity

3,3′-Dimethoxybenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 3,3′-dimethoxybenzidine caused tumors in two rodent species and at several different tissue sites. Administration of 3,3′-dimethoxybenzidine by stomach tube caused cancer (carcinoma) of the Zymbal gland, skin, and intestine and benign urinary-bladder tumors (papilloma) in rats of both sexes, and dietary exposure to 3,3′-dimethoxybenzidine caused benign forestomach tumors (papilloma) in hamsters (IARC 1974, 1982).

Since 3,3′-dimethoxybenzidine was listed in the *Third Annual Report on Carcinogens*, an additional study in rats has been identified. Administration of the dihydrochloride salt of 3,3′-dimethoxybenzidine in the drinking water increased the combined incidence of benign and malignant tumors of the Zymbal gland (adenoma and carcinoma), liver (hepatocellular adenoma and carcinoma), large intestine (adenomatous polyps and adenocarcinoma), skin (basal-cell or sebaceous-gland adenoma and carcinoma), and oral cavity (squamous-cell papilloma and carcinoma) in both sexes. In males, it also caused cancer of the preputial gland (carcinoma), small intestine (adenocarcinoma), and mesothelium of the testes (metastatic mesothelioma), and in females, it also caused cancer of the clitoral gland (carcinoma) and mammary gland (adenocarcinoma) and increased the combined incidence of benign and malignant tumors of the uterus and cervix (adenoma and carcinoma) (NTP 1990).

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′-dimethoxybenzidine. No epidemiological studies have been identified on cancer in workers exposed only to 3,3′-dimethoxybenzidine. Most of the workers exposed to 3,3′-dimethoxybenzidine were also 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 is an aromatic amine that is initially a colorless crystal but turns violet upon standing at room temperature (HSDB 2009). It is practically insoluble in water, but is soluble in alcohol, benzene, ether, chloroform, acetone, and probably most other organic solvents. It is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 3,3′-dimethoxybenzidine are listed in the following table.

Property	Information
Molecular weight	244.3[a]
Melting point	137°C[a]
Boiling point	356°C[b]
Log K_{ow}	1.81[a]
Water solubility	0.060 g/L at 25°C[a]
Vapor pressure	1.25×10^{-7} mm Hg at 25°C[b]
Vapor density relative to air	8.43[a]
Dissociation constant (pK_a)	4.2 at 25°C[c]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009, [c]SRC 2010.

Use

3,3′-Dimethoxybenzidine is used almost exclusively as a chemical intermediate for producing dyes and pigments. In 1971, the Society of Dyers and Colourists reported its use in the production of 89 dyes (see Dyes Metabolized to 3,3′-Dimethoxybenzidine, below). 3,3′-Dimethoxybenzidine is also used as a chemical intermediate to produce *o*-dianisidine diisocyanate for use in adhesives and as a component of polyurethanes. Other uses are as a dye for paper, plastics, rubber, and textiles and as a test substance for detection of metals, thiocyanates, and nitrites (IARC 1974, HSDB 2009).

Production

3,3′-Dimethoxybenzidine has been produced commercially since the 1920s. Data on U.S. production of 3,3′-dimethoxybenzidine were last reported in 1967, when five U.S. companies produced about 367,000 lb. In 1971, only two U.S. companies were known to produce 3,3′-dimethoxybenzidine, and U.S. imports of 3,3′-dimethoxybenzidine were about 273,000 lb (IARC 1974). In 2009, no U.S. manufacturers of 3,3′-dimethoxybenzidine were identified (SRI 2009), but 3,3′-dimethoxybenzidine was available from 25 U.S. suppliers, and 3,3′-dimethoxybenzidine dihydrochloride from 13 U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to 3,3′-dimethoxybenzidine are inhalation and dermal contact (HSDB 2009). The general population could be exposed to 3,3′-dimethoxybenzidine as a trace contaminant in products 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. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, only small amounts of 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine dihydrochloride were released to the environment between 1988 and 2008. In 2008, one facility released 255 lb of 3,3′-dimethoxybenzidine dihydrochloride (TRI 2010).

Exposure to 3,3′-dimethoxybenzidine can occur during its use as a chemical intermediate in the production of azo dyes and *o*-dianisidine diisocyanate formulations, in textile processing, and in packaging processes. Workers potentially exposed include dye makers and

o-dianisidine diisocyanate production workers (HSDB 2009). However, present dye production processes for 3,3′-dimethoxybenzidine and its dye derivatives generally are closed systems that minimize worker exposure. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,481 workers potentially were exposed to 3,3′-dimethoxybenzidine (NIOSH 1990). Another study (cited by the National Toxicology Program in 1986) estimated that about 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 2009).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

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) = 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 code for which the listing is based wholly or partly on the presence of 3,3′-dimethoxybenzidine = U091.

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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

CAS No.: none assigned

Reasonably anticipated to be human carcinogens

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 studies on mechanisms of carcinogenesis and cancer studies in experimental animals, which have provided the following evidence:

- Dyes in this class released free 3,3′-dimethoxybenzidine in studies on metabolism in experimental animals (Lynn *et al.* 1980, Bowman *et al.* 1983).
- 3,3′-Dimethoxybenzidine is carcinogenic in experimental animals (see 3,3′-Dimethoxybenzidine, above).
- A representative 3,3′-dimethoxybenzidine-based dye, C.I. direct blue 15, is carcinogenic in experimental animals.
- The profile of tumors caused by 3,3′-dimethoxybenzidine and direct blue 15 is similar to that caused by structurally related chemicals.

Studies on Mechanisms of Carcinogenesis

3,3′-Dimethoxybenzidine is structurally similar to both benzidine, which is listed in the Report on Carcinogens as *known to be a human carcinogen*, and 3,3′-dimethylbenzidine, which is listed as *reasonably anticipated to be a human carcinogen*. The pattern of tumors observed for direct blue 15 (NTP 1992) and 3,3′-dimethoxybenzidine (NTP 1990) in rats is similar to that observed for the structurally similar chemical 3,3′-dimethylbenzidine (NTP 1991a) and the 3,3′-dimethylbenzidine-based dye C.I. acid red 114 (NTP 1991b). In rats, these four chemicals caused tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland, and clitoral gland, as well as at other tissue sites.

Like benzidine and 3,3′-dimethylbenzidine, 3,3′-dimethoxybenzidine is used to synthesize many dyes, through azo linking of various chromophores to the base chemical. The azo bonds of 3,3′-dimethoxybenzidine-based dyes are chemically similar regardless of the chromophore used, and they are easily broken by azo-reductase enzymes to form free 3,3′-dimethoxybenzidine and free chromophore(s), a process that was observed in rats and dogs (Lynn *et al.* 1980, Bowman *et al.* 1983). Quantitative evidence demonstrated that both of the 3,3′-dimethoxybenzidine-based dyes studied (direct blue 1 and direct blue 15) were nearly completely metabolized to free 3,3′-dimethoxybenzidine (Lynn *et al.* 1980). Bacteria in the animals' gastrointestinal tract are thought to be the primary agents forming free 3,3′-dimethoxybenzidine, which is absorbed by the intestine, metabolized, and excreted in the urine and feces (Cerniglia *et al.* 1982, Morgan *et al.* 1994). Species differences in metabolism of 3,3′-dimethoxybenzidine in the liver or target tissues probably account for species differences in tissue sites of tumors (Morgan *et al.* 1994). 3,3′-Dimethoxybenzidine-based dyes are mutagenic in bacteria when tested with mammalian 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). 3,3′-Dimethoxybenzidine has been found in urine from workers exposed to 3,3′-dimethoxybenzidine-

based dyes; however, contamination of the dye with 3,3′-dimethoxybenzidine could not be ruled out (Lowry *et al.* 1980, NIOSH 1980).

There is no evidence to suggest that mechanisms by which these substances cause tumors in experimental animals would not also operate in humans.

Cancer Studies in Experimental Animals

A representative 3,3′-dimethoxybenzidine-based dye, direct blue 15, is carcinogenic in rats (NTP 1992). Exposure to direct blue 15 in the drinking water caused benign and/or malignant tumors of the skin, Zymbal gland, liver, oral cavity, and small and large intestines in both sexes, the preputial gland in males, and the clitoral gland and uterus in females. It also caused mononuclear-cell leukemia in females, and increased incidences of mononuclear-cell leukemia and brain tumors observed in males may also have been related to exposure to direct blue 15.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3,3′-dimethoxybenzidine-based dyes.

Properties

All dimethoxybenzidine-based dyes have the characteristic diazotized dimethoxybenzidine nucleus, but differ with respect to the chemical groups attached at the diazo linkages. Most of the dyes in this class contain two or three azo groups, but they can contain more. They all exist at room temperature as colored powders (in a wide range of hues) and have negligible vapor pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. There are no rigid chemical specifications for dyes, including dimethoxybenzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer (IARC 1982). Also, because various dyes are mixed together to produce particular colors, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

The Society of Dyers and Colourists reported the production of 89 3,3′-dimethoxybenzidine-based dyes in 1971, including pigment orange 16, direct blue 1, direct blue 15, direct blue 8, direct blue 76, direct blue 98, and direct blue 218. 3,3′-Dimethoxybenzidine-based dyes are used to color paper, plastics, rubber, and textiles, and in the past were used to dye leather (IARC 1974, HSDB 2009).

Production

In 2009, no information on production of dyes previously identified as derived from 3,3′-dimethoxybenzidine was found; however, the dyes were available from numerous suppliers worldwide, including at least six U.S. suppliers (ChemSources 2010). All synthetic organic dyes and dye intermediates are included in a single category for reporting of U.S. imports and exports; no data were available on imports or exports of specific dye products.

Exposure

Most environmental exposure to 3,3′-dimethoxybenzidine and 3,3′-dimethoxybenzidine-based dyes is through contact with contaminated air, water, or soil (HSDB 2009). The general population may also be exposed via contact with paper or fabric products containing these dyes or through consumer use of the dyes.

Occupational exposure to 3,3′-dimethoxybenzidine-based dyes may occur by inhalation of dust or mists, accidental ingestion, or dermal contact. Most occupational exposure is to workers in in dye-manufacturing and -processing plants. In 1986–87, the U.S. Environmental Protection Agency, 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/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 2009). Occupational exposure may also occur in clinical laboratories where 3,3′-dimethoxybenzidine is used in chemical tests. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,481 workers potentially were exposed to 3,3′-dimethoxybenzidine (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Direct blue 218 is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

3,3′-Dimethoxybenzidine-based dyes are listed as potential occupational carcinogens.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

3,3′-Dimethoxybenzidine-based dyes are listed as potential occupational carcinogens.

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