13th Report on Carcinogens

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U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program

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Benzidine and Dyes Metabolized to Benzidine

Introduction

Benzidine was first listed in the *First Annual Report on Carcinogens* (1980), and dyes metabolized to benzidine were first listed as a class in the *Ninth Report on Carcinogens* (2000). The profiles for benzidine and dyes metabolized to benzidine, which are listed (separately) as *known to be human carcinogens*, follow this introduction.

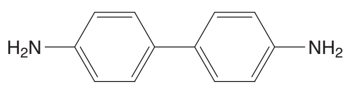
Benzidine

CAS No. 92-87-5

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as 4,4′-diaminobiphenyl



Carcinogenicity

Benzidine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous epidemiological studies (case reports and cohort studies) of workers in various geographical locations have reported a strong association between occupational exposure to benzidine and urinary-bladder cancer. Moreover, epidemiological data suggest that urinary-bladder cancer incidence has decreased since measures to limit benzidine exposure were instituted. A few studies have evaluated exposure to benzidine alone; however, in many studies, workers were co-exposed to other chemicals. Some studies have suggested that the risk of urinary-bladder cancer increases with increasing length of exposure to benzidine (IARC 1972, 1982, 1987). Since benzidine was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, some, but not all, studies have reported an association between benzidine exposure and cancer at other tissue sites (i.e., liver, kidney, central nervous system, oral cavity, larynx, esophagus, bile duct, gallbladder, stomach, and pancreas); the evidence for an association with benzidine is more limited for cancer at these tissue sites than for urinary-bladder cancer (Choudhary 1996).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of benzidine from studies in experimental animals. Oral exposure to benzidine caused mammary-gland cancer in female rats, liver cancer in mice and hamsters, and urinary-bladder cancer in dogs. When administered by subcutaneous injection, benzidine caused Zymbal-gland tumors in rats and liver tumors in mice, and when administered by intraperitoneal injection, it caused Zymbal-gland and mammary-gland tumors in rats (IARC 1982, 1987).

Studies on Mechanisms of Carcinogenesis

Benzidine is metabolized by cytochrome P450 enzymes (via N-oxidation) to form electrophilic compounds that can bind covalently to DNA (Choudhary 1996). Benzidine caused mutations in bacteria and plants, but gave conflicting results in cultured rodent cells. It also caused many other types of genetic damage in various test systems, including yeast, cultured human and other mammalian cells, and rodents exposed *in vivo*. The damage included mitotic gene conversion (in yeast), micronucleus formation, DNA strand breaks, unscheduled DNA synthesis, cell transformation, chromosomal aberrations, sister chromatid exchange, and aneuploidy (IARC 1987). Workers exposed to benzidine and or benzidine-based dyes had higher levels of chromosomal aberrations in their white bloods cells than did unexposed workers (Choudhary 1996).

Properties

Benzidine is a biphenyl amine that exists at room temperature as a white to slightly reddish crystalline powder (ATSDR 2001). It is slightly soluble in cold water, more soluble in hot water, and readily soluble in less-polar solvents, such as diethyl ether and ethanol. It darkens on exposure to air and light (Akron 2009). Physical and chemical properties of benzidine are listed in the following table.

Property	Information
Molecular weight	184.2[a]
Specific gravity	1.250 at 20°C/4°C[a]
Melting point	120°C[a]
Boiling point	401°C[a]
Log K_{ow}	1.34[a]
Water solubility	0.322 g/L at 25°C[a]
Vapor pressure	8.98×10^{-7} mm Hg at 25°C[b]
Vapor density relative to air	6.36[a]
Dissociation constant (pK_a)	4.3[a]

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

Use

Benzidine has been used for over a century as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds (IARC 1982). In the past, benzidine also was used in clinical laboratories for detection of blood, as a rubber compounding agent, in the manufacture of plastic films, for detection of hydrogen peroxide in milk, and for quantitative determination of nicotine. Most of these uses have been discontinued because of concerns about benzidine's potential carcinogenicity. Some dyes that may contain benzidine as an impurity are still used as stains for microscopy and similar laboratory applications (ATSDR 2001).

Production

Benzidine is no longer manufactured for commercial sale in the United States (ATSDR 2001). All large-scale production was discontinued in 1976, and only relatively small quantities remain available for use in diagnostic testing. All benzidine production must be for captive consumption (in-house use) and take place in closed systems under stringent workplace controls. Estimated U.S. benzidine production in 1983 was only 500 lb (possibly excluding some captive production), compared with 10 million pounds in 1972 (ATSDR 2001). In 2009, no U.S. manufacturers of benzidine were identified (SRI 2009), but it was available from 13 U.S. suppliers (ChemSources 2009). Benzidine has not been imported into the United States in recent years. In 1980, the last year for which an estimate was found, U.S. imports of benzidine totaled 8,900 lb (ATSDR 2001). No data on U.S. exports of benzidine were found.

Exposure

Because benzidine may be produced only for captive consumption, its direct release into the environment is expected to be low. However, accidental releases from closed systems potentially could result in exposure of the general populaton through inhalation, ingestion, or dermal contact (ATSDR 2001). According to EPA's Toxics Release Inventory, environmental releases of benzidine were 16 lb in 1993, 250 lb in 1994, and 2 lb in 1999. Releases peaked in 2001, when 532 lb was released (300 lb to surface water and most of the rest to an off-site landfill). In 2007, two facilities released a total of 16 lb of benzidine (6 lb to air and 10 lb to a hazardous-waste landfill) (TRI 2009). In the past, benzidine might have been released into wastewaters and sludges. Because benzidine is moderately persistent in the environment, exposure of populations living near former benzidine or benzidine-dye manufacturing or waste-disposal sites may still be of concern. Benzidine has been identified in 28 of 1,585 hazardous-waste sites proposed for inclusion on the U.S. Environmental Protection Agency's National Priorities List; however, it is not known how many sites were evaluated for benzidine. In 1990, benzidine was detected in groundwater at a hazardous-waste site (the former location of a large dye manufacturer) at concentrations of 240 μg/L on site and 19 μg/L off site (ATSDR 2001).

Benzidine-based dyes may still be imported into the United States, and microbial degradation of these dyes may release free benzidine into the environment (ATSDR 2001). The U.S. Food and Drug Administration limits the benzidine content in food colorants to 1 ppb; however, other impurities in synthetic coloring agents may be metabolized to benzidine after ingestion.

Before Occupational Safety and Health Administration regulations were adopted to limit occupational exposure to benzidine (starting in 1974), benzidine and its derivatives were manufactured and used in open systems that permitted release of benzidine into workplace air. Air concentrations of benzidine measured in a benzidine manufacturing plant ranged from 0.007 to 17.6 mg/m^3, and levels in the urine of exposed workers ranged from 1 to 112 μg/L (ATSDR 2001). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,554 workers, including 426 women, potentially were exposed to benzidine (NIOSH 1990). Benzidine is available in limited quantities for use as a research chemical and may be present as a trace impurity in stains used by medical or laboratory technicians. Others potentially exposed to benzidine include workers involved in its production in closed systems and workers at hazardous-waste sites where benzidine is present (ATSDR 2001).

Regulations

Department of Transportation (DOT)

Benzidine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.000086 μg/L; based on fish or shellfish consumption only = 0.00020 μg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 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 benzidine = U021.
Benzidine is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

The color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 may contain benzidine at maximum levels that range from 1 to 20 ppb.
The color additive Ext. D&C yellow no. 1 is banned, because there is no assurance that it will not produce benzidine from the decomposition of a subsidiary reaction product.

Mine Safety and Health Administration

To control airborne exposure, benzidine 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)

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 by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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Dyes Metabolized to Benzidine (Benzidine Dye Class)

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Dyes that are metabolized to benzidine are *known to be human carcinogens* based on the following evidence: (1) benzidine is known to be a human carcinogen, (2) metabolism of benzidine-based dyes results in the release of free benzidine in humans and in all experimental animal species studied, and (3) benzidine exposure from exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine.

Studies on Mechanisms of Carcinogenesis

Benzidine was one of the first chemicals for which an association between occupational exposure and increased cancer risk was recognized. Industrial exposure to benzidine was first associated with urinary-bladder cancer in the early 1920s. Benzidine was listed as *known to be a human carcinogen* in the *First Annual Report on Carcinogens* (1980). The evidence supporting its listing is summarized in the profile for benzidine, above.

Benzidine was first synthesized in 1845, and the first benzidine-based dye, Congo red, was prepared in 1884. A wide spectrum of colors can be achieved by varying the dye molecules' chromophores, which are linked to benzidine by an azo linkage (–N=N–). Similar or different chromophores may be linked at each amino (NH_2) group of the benzidine molecule to form various bisazobiphenyl dyes. Regardless of the chromophore(s) involved, the azo linkages of all benzidine-based dyes are essentially chemically equivalent; easily formed, they also are easily broken by chemical or enzymatic reduction to form free benzidine and free chromophore(s). Benzidine-based dyes were shown to be metabolized to free benzidine in rats, dogs (Lynn *et al*. 1980), hamsters (Nony *et al*. 1980), and rhesus monkeys, probably by bacteria in the gastrointestinal tract (Rinde and Troll 1975). Lowry *et al*. (1980) concluded that the amount of benzidine and its metabolites detected in urine of exposed workers could not be accounted for by the minute amounts of free benzidine in the dyes to which they were exposed, and therefore that humans also metabolize benzidine-based dyes to free benzidine. Lynn *et al*. (1980) found that in rats and dogs, each benzidine-based dye studied was reduced to yield an amount of free benzidine equal to that observed following an equimolar dose of benzidine.

Cancer Studies in Experimental Animals

All three benzidine-based dyes that have been tested caused cancer in rodents after oral exposure for 13 weeks (NCI 1978, IARC 1982). C.I. direct black 38 caused liver cancer in rats and mice, mammary-gland cancer in mice, and colon and urinary-bladder cancer in rats. C.I. direct blue 6 caused liver cancer in rats, and C.I. direct brown 95 caused hepatocellular adenoma in the liver and one malignant liver tumor in rats. Based on these data, the International Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of technical-grade C.I. direct black 38, technical-grade C.I. direct blue 6, and technical-grade C.I. direct brown 95 in experimental animals.

Cancer Studies in Humans

Because benzidine workers exposed to benzidine-based dyes typically have been co-exposed to benzidine, it has been difficult to clearly establish the carcinogenicity of benzidine-based dyes in epidemiological studies. In studies of Chinese workers who remained in the same jobs for many years, the incidence of urinary-bladder cancer was elevated in workers who had been exposed almost exclusively to benzidine-based dyes (You *et al*. 1990) and in workers exposed to both benzidine and benzidine-based dyes (Bi *et al*. 1992). However, neither report adequately documented levels of exposure to either benzidine or the dyes. IARC (1982) concluded that the epidemiological data were inadequate to evaluate the carcinogenicity of individual benzidine dyes to humans, but that taken together with the presence of benzidine in the urine of exposed workers, they provided sufficient evidence that occupational exposure to benzidine-based dyes increased the risk of cancer in humans.

Properties

All benzidine-based dyes have the characteristic diazotized benzidine nucleus (the structure of benzidine is shown in the profile above) 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 as colored powders (in a wide range of hues) at room temperature and have negligible vapor pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. Benzidine-based dyes are relatively stable in air and in solution at ambient temperatures but degrade in aqueous solution at high temperatures, particularly in the presence of iron. Impurities, such as benzidine, 4-aminobiphenyl, and 2,4-diaminoazobenzene, may be present in these dyes as a result of thermal or enzymatic decomposition (NIOSH 1980). There are no rigid chemical specifications for benzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer (IARC 1982). Various dyes are also mixed together to produce particular colors; therefore, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

Benzidine-based dyes were used primarily to color textiles, leather, and paper products and also in the petroleum, rubber, plastics, wood, soap, fur, and hair-dye industries. About 40% was used to color paper, 25% to color textiles, 15% to color leather, and 20% for diverse applications. By the mid 1970s, most manufacturers started phasing out the use of benzidine-based dyes and replacing them with other types of dyes (NIOSH 1980). More than 300 benzidine-based dyes are listed in the *Colour Index,* including 18 commercially available in the United States. Access to these dyes for home use is no longer permitted in the United States; however, some dyes (particularly direct browns, greens, and blacks) were available as consumer products in the 1970s (ATSDR 2001).

Production

Commercial quantities of benzidine-based dyes were produced in the United States starting no later than 1914, and total U.S. production reached 14 million kilograms (31 million pounds) in 1948 (IARC 1982). In 1974, nine U.S. manufacturers produced benzidine-based dyes, but by 1979, only one manufacturer remained, producing 17 benzidine-based dyes. Domestic production was about 2.9 million kilograms (6.4 million pounds) in 1976, but dropped to about 780,000 kg (1.7 million pounds) in 1978. Direct black 38 accounted for about 48% of U.S. production in 1978, followed by direct blue 2 (12.8%) and direct green 6 (6.4%) (NIOSH 1980). As of 2009, several benzidine-based dyes still had U.S. suppliers, including direct red 28 (28 suppliers), direct black 38 (12 suppliers), direct blue 6 (5 suppliers), direct green 6 (3 suppliers), direct brown 95 (3 suppliers), direct brown 2 (1 supplier), and direct blue 2 (1 supplier) (ChemSources 2009). However, these dyes are no longer used or marketed in significant quantities in the United States (ATSDR 2001). U.S. imports of benzidine-based dyes increased from 272,000 kg (600,000 lb) in 1976 to 730,000 kg (1.6 million pounds) in 1978 (NIOSH 1980) and declined to 213,000 kg (469,000 lb) in 1979. Benzidine-based dyes may still be imported into the United States, but no data on the amounts were found (ATSDR 2001).

Exposure

The primary routes of potential exposure to benzidine-based dyes are inhalation and accidental ingestion; however, dermal absorption also can occur. The potential for exposure has declined since the late 1970s, as benzidine-based dyes were removed from both industrial and consumer markets and replaced with other types of dyes. Since 1980, use of mixtures containing benzidine at concentrations of 0.1% or more is permitted only in closed systems; all workers must observe special precautions to reduce exposure, and strict procedures must be followed to transport such materials. Nevertheless, accidental releases of these dyes could lead to some occupational and environmental exposure (IARC 1982, ATSDR 2001).

In the past, environmental exposure to benzidine-based dyes potentially occurred in the vicinity of dye and pigment plants or waste-disposal sites. According to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009), no environmental releases of benzidine-based dyes have been reported since 1989, when 750 lb of direct black 38 was released. The National Occupational Hazard Survey (NOHS, conducted from 1972 to 1974) estimated that 79,200 workers in 63 occupations (primarily the Dye Manufacturing, Textile Dyeing, Printing, Paper, and Leather industries) potentially were exposed to benzidine-based dyes (NIOSH 1976). In a Special Occupational Hazard Review for benzidine-based dyes, the National Institute for Occupational Safety and Health identified 236 benzidine-based dyes and stated that occupational exposure to such dyes had decreased since the NOHS. Of the benzidine-based dyes specifically mentioned in this profile, four (direct blue 6 tetrasodium salt and the disodium salts of direct black 38, direct brown 95, and direct red 28) were included in the National Occupational Exposure Survey (conducted from 1981 to 1983); the estimated numbers of potentially exposed workers ranged from 830 for direct brown 95 disodium salt to 11,374 for direct black 38 disodium salt (NIOSH 1990). Although no current estimate of occupational exposure to benzidine-based dyes was found, the number of potentially exposed workers is expected to be much lower than in the past.

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: C.I. direct blue 6, C.I. direct blue 218, C.I. direct black 38, and C.I. direct brown 95 are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

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