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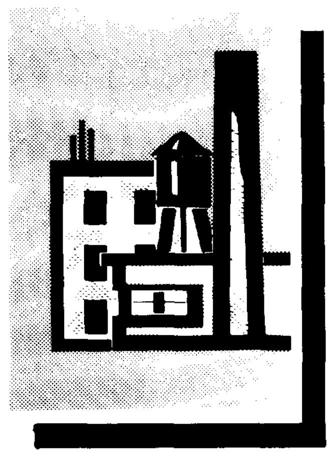
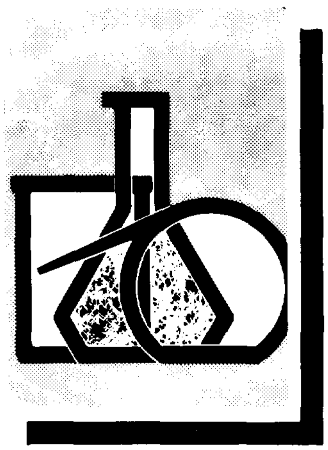
SPECIAL OCCUPATIONAL HAZARD REVIEW for





BENZIDINE-BASED DYES

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Consequently, the National Institute for Occupational Safety and Health (NIOSH) has implemented a program to evaluate the adverse health effects of widely used chemical and physical agents. This program includes the development of Special Hazard Reviews that serve to support and complement the other major health assessment activities of the Institute.

The intent of a Special Hazard Review is to analyze and document, from a health standpoint, the problems associated with a given industrial chemical, process, or physical agent. Generally, a Special Hazard Review is concerned with those hazards of a chronic nature such as cancer, mutagenicity, teratogenicity, or effects on reproduction. However, they may also deal with other effects that have been identified as being harmful to workers when these effects result from exposure to substances found in the workplace. Special Hazard Reviews also recommend control measures, work practices, or other appropriate action to assist employers in protecting the health and well-being of workers.

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SYNOPSIS

This Special Hazard Review evaluates available information concerning the carcinogenicity and metabolism of benzidine-based dyes and concludes that all these dyes should be recognized as potential human carcinogens.

This conclusion is based on evidence that four of the dyes have rapidly induced tumors in animals; that two studies of dye workers demonstrate an association between benzidine-based dye exposure and bladder cancer in workers; that all of the benzidine-based dyes thus far tested have been metabolized in animals to the carcinogen, benzidine; and that the enzyme (azoreductase) which breaks down these dyes to benzidine is found in both animals and humans. This enzyme acts upon a multitude of azo compounds to chemically reduce and break the azo linkage and, therefore, it is highly probable that the azo-linkage in the as yet untested benzidine-based dyes is also cleaved forming benzidine. In addition, two carcinogenic impurities, 4-aminobiphenyl (an OSHA regulated carcinogen) and 2,4-diaminoazobenzene (an animal carcinogen) have been identified in one commercial sampling of a benzidine-based dye and may contribute to the carcinogenic potential of these dyes.

Dyes constitute a large and diverse group of chemicals that have many applications for imparting color to diverse products. More than 1,200 chemically unique and structurally different dyes are manufactured in the United States, and an additional 800 are imported. Dyes are classified according to their chemical structure as well as by the method of application in the dyeing process.

A major class of dyes are those derived from benzidine, an aromatic amine acknowledged by both industry and government as causing bladder cancer in humans.

These recommendations include those dyes containing an unsubstituted benzidine structure in their makeup. Such dyes are largely classified as direct dyes, since they may be applied directly to fabrics or other substrates without pretreatment or subsequent processing.

Of some 200 benzidine-based dyes, about 30 are now marketed in the United States. The most recent estimate of employee exposure is about 79,000 workers in 63 occupations. Market trends show a decreased usage from over 7 million pounds in 1976 to about 3.3 million pounds in 1978. All but one US company has phased out the manufacture of these dyes, but imports have increased to 1.6 million pounds in 1978 indicating continued worker exposure. Benzidine-based dyes are used primarily to color textiles, leather, and paper. However, diverse industries consume 20% of the total.

ACKNOWLEDGEMENTS

The Division of Criteria Documentation and Standards Development (DCDSD), NIOSH, had primary responsibility for development of this Special Hazard Review on Benzidine-Based Dyes. Arthur R. Gregory, Ph.D., was responsible for compilation and technical evaluation of data in this document, and assembled it for review. Technical review was provided by Imogene Sevin, Ph.D., of DCDSD; Bryan Hardin, Larry Lowery, Ph.D., and Richard W. Niemeier, Ph.D., of the Division of Biomedical and Behavioral Science; Mark Boeniger of the Division of Surveillance, Hazard Evaluations, and Field Studies; and Charles Neumeister of the Division of Physical Sciences and Engineering. Editorial review was provided by William N. LeVee, Division of Criteria Documentation and Standards Development. Irwin P. Baumel, Ph.D. and Frank Mackison had NIOSH program responsibility and assisted in preparation of the document.

CONTENTS

I. INTRODUCTION

Dyes constitute a large and diverse group of chemicals that have diverse applications for imparting color to many types of products. They may be broadly defined as water-soluble chemical substances that contain chromophoric structures and thus may be used to color another substance by becoming attached to it by molecular bonding, adsorption, absorption, or mechanical adherence.

Pigments, in contrast to dyes, are insoluble and impart their color to another substance by being physically attached to or incorporated into it. Detailed information on dyes and pigments may be found in the Colour Index [1], a compendium of technical information on dyes and their use.

The use of dyes dates as far back as prehistoric man, but the synthetic dye industry began in 1856 when William H. Perkin first synthesized the dye mauve [2]. Since that time, the synthetic dye industry has grown extensively in the United States as well as in other countries.

More than 1,200 chemically unique and structurally different dyes are manufactured in the United States, and an additional 800 dyes are imported [3]. Dyes are classified according to their chemical structure as well as by the method of application in the dyeing process. The dyes evaluated in this review are those containing the benzidine moiety without any substitution on the diphenyl portion of the molecule, ie, those having a para diamino diphenyl grouping in their structural configuration. They are hereafter referred to as benzidine-based dyes. Benzidine-based dyes are largely classified as direct dyes, since they may be applied directly to fabrics or other substrates without pretreatment or without subsequent processes that firmly attach the dye to the substrate (mordanting) [2]. More than 200 benzidine-based dyes are listed in the Colour Index or are used commercially (see Appendix II). Over 30 benzidine-based dyes have commercial importance in the United States, according to the US International Trade Commission [3]. Seventeen are manufactured in this country, all by a single company; the remaining dyes are all imported (see Appendix III). Benzidine-based dyes are used chiefly in the leather, textile, and paper industries [1,3,4], but they are also used by beauticians, craft workers, and the general public [5].

The common starting material for the manufacture of these dyes, benzidine, is acknowledged by both industry [6] and government (Federal Register 39(20):3756-97, January 29, 1974) to cause bladder cancer. This is based on considerable evidence from studies with humans as well as with animals. The carcinogenicity of benzidine was reviewed by Clayson [7] and by Haley [8]. The evidence presented in those reviews demonstrates that both brief and prolonged exposures to benzidine have been associated with the development of bladder cancer in workers [9].

Aromatic amines, as a class of chemicals, are generally carcinogenic. Benzidine is an outstanding carcinogen within this class; it causes cancer in humans, rats, hamsters, and mice [9-22]. The structure-activity relationship between aromatic amines and carcinogenic potency has been reviewed in detail [12,23,24]. In addition, benzidine has also been used as a reference mutagen (a known positive control) for several years by the Huntingdon Research Center [25]. In light of all the extensive evidence in both humans and experimental animals, NIOSH recommended in 1973 that benzidine be regulated as a carcinogen; in 1974, the Occupational Safety and Health Administration of the Department of Labor promulgated a regulatory standard for benzidine.

Until recently there had been little concern regarding the dyes derived from and which contain benzidine as an integral portion of their chemical structure. Benzidine chemically united to other substances was not considered dangerous; in 1959, Billiard-Duchesne [26] stated there was "no danger in using the finished dyes." Only recently has there been serious consideration given to the likelihood that processes in the body could free the benzidine that was originally used in the manufacture of the dyes [27]. The process of metabolizing or converting a substance back to a starting component or to another compound is commonly referred to as biotransformation.

In April 1978, NIOSH [28] and the National Cancer Institute (NCI) jointly recommended that three widely used benzidine-based dyes (Direct Black 38, Direct Blue 6, and Direct Brown 95) be handled as if they were carcinogens. The NIOSH/NCI recommendation was based on two major findings. First, NCI had determined in a short-term animal feeding study that rats administered the above dyes developed a high incidence of hepatocarcinomas and neoplastic nodules in 5-13 weeks. No similar lesions developed in control animals [29]. Second, NIOSH field studies demonstrated that some workers who had been exposed to these dyes had benzidine in their urine [27]. The amount found in the urine was greater than could be expected from benzidine contamination in the dyes. This demonstrated that the dye itself had broken down, releasing benzidine.

Since that time, NIOSH has examined and evaluated the available literature concerning these and related dyes. This Special Hazard Review appraises the carcinogenic potential of those dyes known to contain the unsubstituted benzidine moiety.

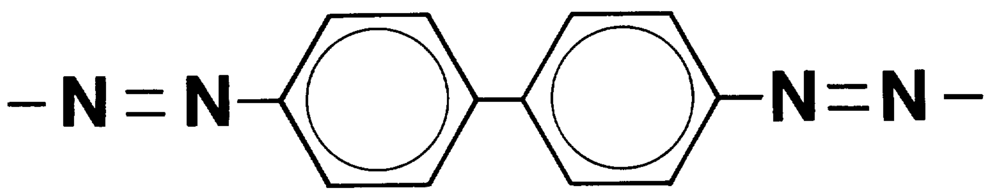
II. CHARACTERISTICS OF BENZIDINE-BASED DYES

Chemical and Physical Characteristics

At room temperature, benzidine-based dyes are all colored solids with negligible vapor pressure. The specific water solubility varies from dye to dye, but all are sufficiently water-soluble to be used for dyeing in an aqueous solution. They are all relatively stable in air or solution at ambient temperatures, and possess considerable fastness to light. Unlike some of the anthraquinone vat dyes, benzidine-based dyes do not accelerate the tendering of cellulosic type fabrics under the influence of light [30]. They exhaust onto (combine with) cellulosic fibers from a salt bath without other treatment. Based on this property, these dyes are called substantive [4]. They usually contain two or three azo groups.

Direct dyes give excellent coverage and generally do not otherwise alter the appearance or character of the material to be colored. They cover a wide hue range [1,4]. Many direct dyes now on the market do not contain the benzidine moiety and, therefore, are not considered in this review. These nonbenzidine-derived direct dyes provide industry with a wide range of colors and hues which may be considered for use as substitutes for benzidine-based dyes [1,30-32].

The chemical structures of benzidine-based dyes currently of commerical importance are shown in Appendix III; all have the characteristic diazotized benzidine nucleus as shown in Figure II-1 and differ only in the substituents attached at either diazo linkage, ie, -N=N-. This linkage is considered the most labile portion of each of these dyes, and, in each case, enzymatic [29,33-35] or thermal breakdown [2,36] results in the production of benzidine.



DIAZOTIZED BENZIDINE MOIETY

FIGURE II-1

Purity and Stability

Benzidine and other carcinogenic substances such as 4-amino biphenyl and 2,4-diaminoazobenzene may be present in benzidine-based dyes both as the result of impurities introduced in manufacturing processes or may be present in benzidine-based dyes as products of thermal or enzymatic decomposition. NIOSH has measured the amount of benzidine present in direct dyes from imported and domestic sources [27]. For 26 samples of 11 types of dyes imported from seven countries, the benzidine concentration ranged from less than 1 ppm to 224 ppm. Only six samples contained greater than 10 ppm of benzidine. Similar results were found for 26 samples from domestic sources. No single type of dye accounted for the high results. Few investigators have attempted to analyze impurities other than benzidine present in direct dyes. However, in one commercially produced lot of Direct Black 38 (a benzidine-based dye), 150 ppm of 4-amino biphenyl and 9,200 ppm of 2,4-diaminoazobenzene (Basic Orange 2) were found even though only 0.1 ppm of benzidine was detected [37].

The concentration of impurities such as benzidine can be increased by decomposition of dyes containing benzidine as a portion of the structure. A measurable increase in the concentration of benzidine and 4-amino biphenyl impurities was found when Direct Black 38 in aqueous solution was stored at 25 or 37.5 C for 48 hours [37]. In hamster urine stored at room temperature, substantial increases in the concentrations of benzidine, 4-amino biphenyl, and 2,4-diaminoazobenzene were found 48 and 96 hours after the addition of Direct Black 38 to the urine; at 5 C the dye in hamster urine was stable at least 96 hours [37].

Although all decomposition products have not been identified, benzidine-based dyes have been shown to break down in aqueous solution at elevated temperatures [36]. Mel'nikov and Kirillova [36] examined a number of technical grade direct dyes, including some that were benzidine-based. They found that the rate of decomposition of the dyes was accelerated by increased temperature and greatly accelerated in the presence of iron. For example, at 140 C after 6 hours, 17.3% of Congo Red (Direct Red 28) decomposed, and, under the same conditions in the presence of iron, 83% decomposed. When a 0.1% aqueous solution of Congo Red (Direct Red 28) was stored at 100 C for 1 hour, no decomposition was observed. The presence of textile additives such as urea, triethanolamine, and cellosolve also increased the rate of decomposition.

III. CHARACTERISTICS OF EXPOSURE

Manufacture and Uses

The synthesis of dyes is briefly described in the Colour Index [1]. Generally, the diazotized benzidine is reacted (coupled) with suitable secondary components such as hydroxylated aromatics or aromatic amines [1,2,4]. Since the manufacture of dyes is directed toward producing a particular color and not to producing a specific chemical entity, impurities such as benzidine, 4-amino biphenyl, 2,4-diaminoazobenzene, diphenyline, and semidine find their way into the final dye product. If these substances do not interfere with the dyeing process, ordinarily they are not removed [4,38]. Additional substances, including other dyes, may be required to produce the particular shade or hue desired in a product. Thus, dyes in general represent mixtures of substances rather than a particular chemical entity [4,38-40]. This is further complicated by the fact that manufacturers may use differing conditions of synthesis, starting materials of different purity, and even different methods to manufacture dyes [30,39,41]. These facts are important since each dye is depicted as a definitive chemical structure in textbooks [2] and in the Colour Index [1].

More than 30 manufacturers in the United States now produce various direct dyes. Only one of the nine US manufacturers that produced benzidine-based dyes in 1974 still does so in 1979 [3,40,42]. Some distributors import the benzidine-based dyes for resale in the United States [27]. The 1979 Buyer's Guide published by the American Association of Textile Chemists and Colorists (AATCC) lists 20 unsubstituted benzidine-based dyes for sale in the United States [43]. Not all dyes sold in the United States, however, are listed in the Buyer's Guide (W Martin, verbal communication, July 1979).

Since 1974, the eight US manufacturers that phased out the synthesis of benzidine-based dyes [3] have replaced them with phthalocyanine, o-tolidine, o-dianisidine, phenylenediamine, and dioxyazine-type dyes [40]. Nonbenzidine-based substitutes appear to be in demand; five manufacturers now sell nonbenzidine-based substitutes for Direct Black 38 [30,40,43]. A suitable substitute for Direct Blue 6 in the leather dyeing industry has been difficult to find [40]. NIOSH considers the need for appropriate toxicologic testing of all dye substitutes to be essential before they are used in the workplace.

Benzidine-based dyes are used extensively to color textiles, leather, and paper. Ease of application has been a major asset to their general availability and widespread usage. Of the total use, 40% is used to color paper, 25% to color textiles, 15% for leather, and 20% for diverse applications in the petroleum, rubber, plastics, wood, soap, fur, and hair dye industries [1,3,28,32].

Production Volume

Seventeen benzidine-based dyes are produced in the United States by one manufacturer, Fabricolor, Inc., of New Jersey. Table III-1 gives the US production figures for benzidine dyestuffs manufactured during 1978. These figures were provided to NIOSH through the courtesy of Fabricolor (E Angstadt, written communication, January 1979).

TABLE III-1

1978 US PRODUCTION FOR BENZIDINE DYESTUFFS

C.I. Generic Name	C.I. Number	kg	Pounds
Acid Red 85	22245	17,980	39,639
Direct Orange 8	22130	12,341	27,208
Direct Brown 2	22311	12,576	27,725
Direct Brown 6	30140	3,884	8,563
Direct Brown 31	35660	16,967	37,406
Direct Brown 74	36300	14,703	32,414
Direct Brown 95	30145	34,452	75,953
Direct Brown 154	30120	28,946	63,816
Direct Green 1	30280	5,745	12,666
Direct Green 6	30295	49,476	109,076
Direct Red 1	22310	11,961	26,370
Direct Red 28	22120	16,931	37,327
Direct Blue 2	22590	99,080	218,435
Direct Blue 6	22610	27,907	61,524
Direct Black 4	30245	11,995	26,444
Direct Black 38	30235	373,336	823,065
Resin F. Black WP	--	38,383	84,620
Total		776,664	1,712,251

Adapted from E. Angstadt, written communication, January 1979

Extent of Occupational Exposure

Based on a national survey conducted from 1972 to 1974 [44], NIOSH estimated that approximately 79,200 workers in 63 occupations were potentially exposed to benzidine-based dyes. These potential exposures occurred in the dye manufacturing, textile dyeing, printing, paper, and leather industries. Appendix III lists the estimated worker exposure for each commercially available benzidine-based dye. Dye use in arts and crafts was not included. An estimate of worker exposure to benzidine was given by Ferber et al in 1976 [45]. However, no estimate was made of worker exposure to the dyes derived from benzidine.

NIOSH has contacted the one US manufacturer of benzidine-based dyes as well as four previous US manufacturers. While US production has decreased from a high of 2,919 Mg (6,436,000 lbs) in 1976 to 777 Mg (1,712,251 lbs) in 1978, imports have increased from 272 Mg (600,000 lbs) in 1976 to 726 Mg (1,600,000 lbs) in 1978. The present actual worker exposure to benzidine-based dyes cannot be ascertained precisely, but appears substantial in light of the continuing production, sale, and use of these dyes [30,41,43,46].