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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DIRECT SKY BLUE 6B

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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NOTICE

DISCLAIMER

This report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

EXECUTIVE SUMMARY

Direct Sky Blue 6B is a common name for the commercial azo dye Direct Blue 1, which is produced by the diazotization of o-dianisidine with 4-amino-5-hydroxy-1,3-naphthalenedisulfonic acid under alkaline conditions (Society of Dyers and Colourists, 1971a). It is very soluble in water but insoluble in most organic solvents. It can be used to dye, stain or print cellulose, nylon, leather, paper, silk, wool, cotton or biological materials and to produce writing inks and pigments (Society of Dyers and Colourists, 1971a). In 1980, four U.S. manufacturers produced 0.115 million pounds of Direct Sky Blue 6B (USITC, 1981), but only one U.S. manufacturer reported production in 1984 (USITC, 1985). Four U.S. companies currently market Direct Sky Blue 6B under various tradenames (AATCC, 1985). In 1983, ~40,000 pounds of the dye was imported into the United States through principal customs districts (USITC, 1984).

The only available data specifically regarding the environmental fate of Direct Sky Blue 6B is a report that sorption to activated sludge is effective in removing it from dye wastewaters (Lebiedowski and Przybinski, 1980). If released to water, Direct Sky Blue 6B may be susceptible to significant adsorption because dyestuffs by their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers) are likely to be adsorbed onto both sewage works sludge and silts and sediment of rivers and lakes (Brown and Laboureur, 1983). Removal of adsorbed Direct Blue 6B may occur by biodegradation since a number or azo dyes have been found to be substantially biodegraded under anaerobic and aerobic conditions (Brown and Laboureur, 1983; Lebiedowski and Przybinski, 1980). In general, direct dyes are expected to be relatively stable to direct photolysis in natural waters

(Porter, 1973), although humic materials present in natural water may indirectly accelerate the photodecomposition of azo dyes (Haag and Mill, 1985). In reducing environments, like natural water, reduction of the azo dyes to the corresponding amines is possible (Takemura et al., 1965). Hydrolysis, volatilization and bioconcentration are not expected to be significant. Therefore, indirect photolysis, microbial degradation and adsorption are the most important processes determining dye fate in water.

If released to the atmosphere, Direct Sky Blue 6B will probably be associated with particulate matter and dusts that are subject to wet and dry deposition. Based on its reactivity with other aromatic amines (Atkinson, 1985), it is speculated that oxidation of this dye by HO radical in the atmosphere may be a significant process. If released to soil, Direct Sky Blue 6B may not leach significantly since it is significantly adsorbed by soil. Microbial degradation or transformation within soil may occur. Photodegradation beyond the surface layer of soil is not likely.

Occupational exposure to Direct Sky Blue 6B occurs during its production and its use in dyeing. Wastewater effluents are probably the major source of release to the environment. Ambient monitoring data could not be located in the available literature as cited in the Appendix.

EN CAS Analytical Labs (1977a,b) reported 96-hour LC_{50} values of 240 and 290 mg/ℓ for two batches of Diphenyl Brill Blue FF Supra for bluegills. On the basis of CAS number, this is the same compound as Direct Sky Blue 6B. EN CAS Analytical Labs (1977c) also reported that waste treatment plant bacteria were unaffected by concentrations of $\leq$300 mg/ℓ. Konishi and Hidaka (1969) found that Direct Sky Blue 6B stimulated carp chemoreceptors in vitro.

Oral absorption of Direct Sky Blue 6B can be inferred from toxicity data (Section 5.6.). Data concerning the distribution of Direct Sky Blue 6B after oral or inhalation exposure could not be located in the available literature. Beaudoin and Pickering (1960) gave pregnant rats intraperitoneal injections of Direct Sky Blue 6B and observed staining of nuclei of macrophages of maternal tissue. The yolk sac also contained a small amount of the dye. Lynn et al. (1980) orally dosed rats and dogs with Direct Sky Blue 6B and observed 3,3'-dimethoxybenzidine in the urine of both these species, and the rat urine also contained N-acetyl-3,3'-dimethoxybenzidine. The rats and dogs excreted small amounts of 3,3'-dimethoxybenzidine after 72 and 48 hours, respectively.

Pertinent data regarding the carcinogenicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. However, 3,3'-dimethoxybenzidine (o-dianisidine) is found in urine of workers occupationally exposed to dyes derived from o-dianisidine (NIOSH, 1980; OSHA/NIOSH, 1980). Positive results were obtained for S. typhimurium strain TA98 with metabolic activation by S-9 (Prival et al., 1982, 1984; Prival and Mitchell, 1982). Mutagenic activity was enhanced when FMN was added as a reducing agent. Prival and Mitchell (1982) found uninduced hamster S-9 enhanced mutagenicity to a greater extent than did induced rat S-9. Direct Sky Blue 6B did not induce UDS in vivo or in vitro (Joachim and Decad, 1984).

No data regarding the teratogenic effects of Direct Sky Blue 6B after oral or inhalation exposure were available; a few studies by the intraperitoneal route were available. Beaudoin (1968) observed dose-related increased resorptions and malformations in rats at $\geq$140 mg/kg/day. Amels et al. (1977) observed a dose-related increase in ocular malformations in rats given intraperitoneal doses $\geq$100 mg/kg of Direct Sky Blue 6B. Maternal

toxicity was observed in mice given 250 mg/kg/day intraperitoneally (Chernoff and Kavlock, 1983). Pertinent data regarding other reproductive effects or subchronic and chronic toxicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. The oral LD_{50} is >5 mg/kg (M.B. Research Laboratories, 1978), and rats exposed by inhalation to 18.94 mg/ℓ for 4 hours were essentially unaffected by Direct Sky Blue 6B, except for hyperactivity (Southwest Foundation for Research and Education, 1979).

The lack of chronic and subchronic toxicity and carcinogenicity data precludes the derivation of an RfD, RQ, q_1^* and F factor. Although carcinogenicity data in humans and animals are inadequate, the fact that 3,3'-dimethoxybenzidine, a known EPA Group B2 carcinogen, is a metabolite of the dye warrants placing Direct Sky Blue 6B in EPA Group B2: probable human carcinogen. This category includes all agents with sufficient evidence on carcinogenicity in animals and inadequate evidence or no data of carcinogenicity in humans (U.S. EPA, 1986c).

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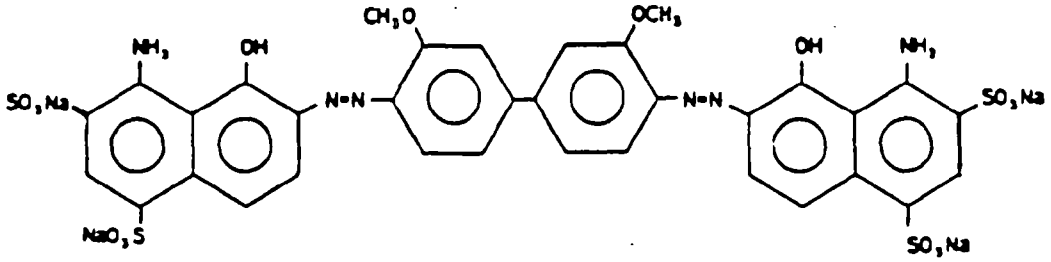
LIST OF ABBREVIATIONS

BOD	Biochemical oxygen demand
CAS	Chemical Abstract Service
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
FMN	Flavin mononucleotide
GC	Gas chromatography
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MS	Mass sectrometry
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
UDS	Unscheduled DNA synthesis

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Direct Sky Blue 6B is commonly referred to as Direct Blue 1. The Colour Index reference number is C.I. 24410 (Society of Dyers and Colourists, 1971a,b). The current CAS designation for Direct Sky Blue 6B is 1,3-naphthalenedisulfonic acid, 6,6'-[3,3'-dimethoxy[1,1'-biphenyl]-4,4'-diyl)bis-azo]-bis[4-amino-5-hydroxy-]tetrasodium salt. It is a 3,3'-dimethoxybenzidine (o-dianisidine) based dye. Direct Blue 1 is currently marketed in the United States under the tradenames Atlantic Direct Sky Blue 6B Ex. 300% (Atlantic Indust.), Cylcofast Sky Blue (C. Lever Co. Inc.), Direct Brilliant Sky Blue 6B Concentrate (Crompton and Knowles Corp.) and Elcomine Sky Blue 6B (International Dyestuffs Corp.) (AATCC, 1985). Various synonyms and trade names for this compound are Direct Blue 6B, Direct Blue 6BS, Direct Sky Blue 6B, Direct Sky Blue 6BS and Niagara Sky Blue 6B (RTECS, 1981-1982). The structure, empirical formula and CAS Registry number for Direct Sky Blue 6B are as follows:



Molecular weight: 992.8

Empirical formula: $C_{34}H_{24}N_6O_{16}S_4Na_4$

CAS Registry number: 2610-05-1

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Direct Sky Blue 6B is very soluble in water where it forms a bright blue solution, slightly soluble in ethylene glycol monoethyl ether and insoluble in most other organic solvents (Society of Dyers and Colourists, 1971a). All direct dyes are water soluble and form anions by dissociation (Kuehni et

al., 1979). In aqueous solution, the molecules of direct dyestuffs are linked by hydrogen bonds forming larger agglomerates or colloidal solutions, which reduces their solubility and promotes disposition on cellulosic fibers. The structure of these agglomerates allows firm linkage to the cellulose molecule by multiple hydrogen bonds (Kuehni et al., 1979).

Physical properties such as melting point, boiling point, vapor pressure, density and log K_{ow} could not be located in the available literature. Lack of appropriate parameter values precluded the computer calculation of log K_{ow} (U.S. EPA, 1986a). The air conversion factor for Direct Sky Blue 6B is 1 ppm = 41 mg/m^3.

The manufacture and testing of Direct Sky Blue 6B probably do not conform to rigid chemical specifications, and its composition may vary in order to meet shade and intensity requirements.

1.3. PRODUCTION DATA

Direct Sky Blue 6B is produced by coupling o-dianisidine to 2 mol of Chicago acid (4-amino-5-hydroxy-1,3-naphthalenedisulfonic acid) under alkaline conditions (Society of Dyers and Colourists, 1971a).

In 1980, four U.S. manufacturers produced 0.115 million pounds of Direct Sky Blue 6B (USITC, 1981), the most recent production figure available; in 1984, Atlantic Industries was the only manufacturer listed (USITC, 1985). Four U.S. companies currently market Direct Sky Blue 6B under various tradenames (AATCC, 1985). The production data available from the public portion of the U.S. EPA TSCA production file for 1977 are listed in Table 1-1.

TABLE 1-1

Direct Sky Blue 6B Production Data for 1977*

Producer/Location	Manfacturer or Importer	Production Range (thousands of pounds)
Fabricolor Inc. Paterson, NJ	manufacturer	none
Mobay Chemical Bayonne, NJ	manufacturer	confidential
Atlantic Chemical Nutley, NJ	manufacturer	10-100
American Research Products South Euclid, OH	manufacturer	confidential
Toms River Chemical Toms River, NJ	manufacturer	confidential
Hilton-Davis Chemical Cincinnati, OH	manufacturer	none
Harshaw Lowell, NC	manufacturer	1-10
GAF Corp. Rensselaer, NY	manufacturer	10-100
DuPont Deepwater, NJ	manufacturer	none
Marubeni American Corp. New York, NY	importer	confidential
Ugine Kuhlmann of America Paramus, NJ	importer	confidential
American Hoechst Bridgewater, NJ	importer	confidential

*Source: U.S. EPA, 1977

Importation of Direct Sky Blue 6B through principal U.S. customs districts in recent years was reported as follows (USITC, 1982, 1983, 1984):

Year	Import Volume (pounds)
1983	39,991
1982	13,229
1981	14,189

1.4. USE DATA

Direct Sky Blue 6B is a dye that can be used to dye cellulose, nylon, leather and paper; print cellulose and nylon; stain silk, wool, cotton and biological materials; and produce writing inks and pigments (Society of Dyers and Colourists, 1971b).

1.5. SUMMARY

Direct Sky Blue 6B is a common name for the commercial azo dye Direct Blue 1, which is produced by the diazotization of o-dianisidine with 4-amino-5-hydroxy-1,3-naphthalenedisulfonic acid under alkaline conditions (Society of Dyers and Colourists, 1971a). It is very soluble in water but insoluble in most organic solvents. It can be used to dye, stain or print cellulose, nylon, leather, paper, silk, wool, cotton or biological materials and to produce writing inks and pigments (Society of Dyers and Colourists, 1971b). In 1980, four U.S. manufacturers produced 0.115 million pounds of Direct Sky Blue 6B (USITC, 1981), but only one U.S. manufacturer reported production in 1984 (USITC, 1985). Four U.S. companies currently market Direct Sky Blue 6B under various tradenames (AATCC, 1985). In 1983, ~40,000 pounds of the dye was imported into the United States through principal customs districts (USITC, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Experimental hydrolysis data could not be located in the available literature; however, Direct Sky Blue 6B does not contain functional groups that are readily susceptible to environmental hydrolysis. Therefore, hydrolysis is not expected to be environmentally relevant.

2.1.2. Oxidation/Reduction. Specific experimental data on oxidation/reduction of Direct Sky Blue 6B could not be located in the available literature. Takemura et al. (1965) reported that bubbling H_2S through a pure azo-dye solution yields aromatic amines and suggested that azo dyes in wastewater may be reduced at the azo linkage (by H_2S or SO_2 in the water) to form intermediates such as benzidine or naphthylamine from which the dye was produced. One possible source of aromatic amines detected in a polluted river water in Japan was speculated to be due to the reduction of azo dyes discharged in the river by H_2S or SO_2 in the river (Takemura et al., 1965).

2.1.3. Photolysis. Porter (1973) examined the photodegradation rate in aqueous solution of 8 direct dyes and 12 other azo dyes in artificial light and 1 direct and 1 acid dye in natural sunlight. Based on the experimental results, the author concluded that direct dyes are relatively stable to direct photolysis in natural waters. Although Direct Sky Blue 6B was not one of the dyes studied, its structure is similar to several dyes that were tested.

Haag and Mill (1985) examined the aqueous photodegradation rate of 15 azo days by simulated or natural sunlight. Significant direct photolysis was observed for some dyes; however, humic materials in natural water were

found to strongly accelerate the indirect photodecomposition rate of all the dyes. Therefore, indirect photolysis may be an important removal mechanism for azo dyes in the aquatic environment.

2.1.4. Microbial Degradation. Microbial degradation data specific to Direct Sky Blue 6B are limited. An abstract of a Polish study (Lebiedowski and Przybinski, 1980) reported that activated sludge treatment of dyeing wastewaters containing this dye reduced the BOD by 30-50% in 2-2.5 hours. Brown et al. (1981) reported that Direct Sky Blue 6B is not likely to have a significantly inhibiting effect during sewage treatment.

Brown and Laboureur (1983) reported that a number of azo dyes were substantially biodegraded under anaerobic test conditions and suggested that the breakdown of dyestuffs in the environment may be initiated under anaerobic conditions.

2.1.5. Volatilization. Experimental volatilization data could not be located in the available literature; however, since Direct Sky Blue 6B is soluble in water (Society of Dyers and Colourists, 1971a) and is expected to have a relatively low vapor pressure because of its ionization ability, a relatively small Henry's Law constant is expected. Therefore, volatilization from water is not expected to be significant in the environment.

2.1.6. Adsorption. Dyestuffs by their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers) are likely to be adsorbed onto both sewage works sludge and onto silts and sediments of rivers and lakes (Brown and Laboureur, 1983). In conventional biological waste treatment systems, soluble dye removal usually occurs when the dye is adsorbed onto sludge (Porter, 1973). It was reported that the sorption properties of activated sludge contribute to the purification of Sky Blue 6B from dyeing wastewaters (Lebiedowski and Przybinski, 1980). Sewage works sludge is usually treated by anaerobic digestion or landfilling.

Removal of dye from the sludge must therefore occur by anaerobic biodegradation. Similar anaerobic conditions exist in many lakes and rivers with respect to adsorbed material on silts and sediments and, therefore, adsorbed dyes may be subject to anaerobic biodegradation in the environment (Brown and Laboureur, 1983).

2.1.7. Bioconcentration. Experimental bioconcentration data could not be located in the available literature. Since Direct Sky Blue 6B is water soluble (Society of Dyers and Colourists, 1971a), bioconcentration in aquatic organisms is not expected to be significant.

2.2. AIR

Direct Sky Blue 6B in the atmosphere is most likely to be associated with particulate matter and dusts, especially from atmospheric effluents resulting from its production and use. These particulate matter and dusts are subject to wet and dry deposition. Aromatic amines are known to be very reactive (half-life of a few hours) with HO radical in the atmosphere (Atkinson, 1985). Therefore, since this dye also contains aromatic amine groups, it may also react with atmospheric HO radical.

2.3. SOIL

Pertinent experimental data on the fate of Direct Sky Blue 6B in soil could not be located in the available literature. Chemical degradation may not occur significantly since dyes, in general, are resistant to common oxidants such as ozone, chlorine and nitrogen oxides (Porter, 1973) and hydrolysis is not expected to be environmentally relevant. If significant removal of Direct Sky Blue 6B is to occur in soil, microbial degradation may be the environmental fate process involved. A number of azo dyes have been shown to be susceptible to anaerobic biodegradation (Brown and Laboureur, 1983). Photodegradation of Direct Sky Blue 6B beyond the surface layers may not be significant.

Since Direct Sky Blue 6B is water soluble (Society of Dyers and Colourists, 1971a), leaching in soil might be expected; however, the substantive nature of dyestuffs (Brown and Laboureur, 1983), including the direct dyes (Kuehni et al., 1979), indicates that significant adsorption to soil may occur. Therefore, significant leaching in soil may not occur.

2.4. SUMMARY

The only available data specifically regarding the environmental fate of Direct Sky Blue 6B is a report that sorption to activated sludge is effective in removing it from dye wastewaters (Lebiedowski and Przybinski, 1980). If released to water, Direct Sky Blue 6B may be susceptible to significant adsorption because dyestuffs by their substantive nature (ability to be exhaustively deposited from aqueous baths to fibers) are likely to be adsorbed onto both sewage works sludge and onto silts and sediment of rivers and lakes (Brown and Laboureur, 1983). Removal of adsorbed Direct Blue 6B may occur by biodegradation since a number of azo dyes have been found to be substantially biodegraded under anaerobic and aerobic conditions (Brown and Laboureur, 1983; Lebiedowski and Przybinski, 1980). In general, direct dyes are expected to be relatively stable to direct photolysis in natural waters (Porter, 1973), although humic materials present in natural water may indirectly accelerate the photodecomposition of azo dyes (Haag and Mill, 1985). In reducing environments, like natural water, reduction of the azo dyes to the corresponding amines is possible (Takemura et al., 1965). Hydrolysis, volatilization and bioconcentration are not expected to be significant. Therefore, indirect photolysis, microbial degradation and adsorption are the important fate processes in water.

If released to the atmosphere, Direct Sky Blue 6B will probably be associated with particulate matter and dusts that are subject to wet and dry deposition. Based on its reactivity with other aromatic amines (Atkinson, 1985), it is speculated that oxidation of this dye by HO radical in the atmosphere may be a significant process. If released to soil, Direct Sky Blue 6B may not leach significantly since dyestuffs are susceptible to significant adsorption. Microbial degradation or transformation within soil may occur. Photodegradation beyond the surface layer of soil is not likely.

3. EXPOSURE

Direct Sky Blue 6B has not been reported to occur in nature; therefore, exposure from natural sources is not expected to occur. Occupational exposure to Direct Sky Blue 6B occurs during its production and use for the dyeing of various products. Likely routes of exposure are inhalation of particulates and dermal exposure. A National Occupational Hazard Survey conducted during 1972-1974 estimated that 1141 U.S. workers are potentially exposed to Direct Sky Blue 6B in an occupational setting (NIOSH, 1984).

3.1. WATER

Pertinent monitoring data for Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. For the organic dye industry, in general, it was estimated that ~90% of the dye is taken up by the fabric, while 10% is lost to wastewater effluents during dye operations (Porter, 1973; Brown et al., 1981). Loss of dyes to wastewater effluents during manufacture were estimated to be 1-2% (Brown et al., 1981). Waste streams from dye manufacture contain dissolved inorganic salts and small amounts of dye and dye intermediates (Steadman et al., 1977). Wastewater effluents are therefore the major source of release to water; the efficiency of wastewater treatment operations will determine the amount of dye that reaches natural water.

Release of dye from textile fabrics may occur from commercial or consumer washing; however, dyes in most finished products are considered to be essentially "fast" (they do not migrate or wash out) (Jones, 1979). Various after-treatments are commonly applied to fabrics dyed with direct dyes to improve their colorfastness (Kuehni et al., 1979).

3.2. FOOD

Pertinent monitoring data regarding exposure to Direct Sky Blue 6B through food could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Ambient air or occupational monitoring data could not be located in the available literature as cited in the Appendix.

Ambient atmospheric emissions may occur from ventilation of effluents at production and use sites. In addition, air effluents from production operations, such as spray drying, may be sources of release. Particulate emissions from these sources are usually filtered at plant sites, which should reduce significantly the amount of particulate matter actually reaching the ambient atmosphere.

3.4. DERMAL

Pertinent dermal exposure data could not be located in the available literature as cited in the Appendix. The general public is exposed mainly to finished dyes after they have been applied to the product; however, according to one author there is little chance of dyes coming off in perspiration, saliva or washings if label instructions are followed (Jones, 1979).

3.5. SUMMARY

Occupational exposure to Direct Sky Blue 6B occurs during its production and its use in dyeing. Wastewater effluents are probably the major source of release to the environment. Ambient monitoring data could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. Oral absorption can be inferred from toxicity data (Section 5.6.).

4.2. DISTRIBUTION

Beaudoin and Pickering (1960) studied the distribution of Direct Sky Blue 6B in pregnant Sherman rats. Fifteen rats were injected intraperitoneally on gestation day 8 with a dose of 14 mg/100 g (140 mg/kg) in a 2% aqueous solution. Rats were sacrificed on day 20 of gestation, and maternal lungs, liver, uterus, ovary, spleen, lymph nodes, kidneys and placenta were examined for the presence of dye. Direct Sky Blue 6B was sparsely distributed in the macrophages of the tissues, often staining the nuclei, rather than being present as granules in the cytoplasm. In the kidney, all nuclei were stained including the nuclei of the glomeruli and Bowman's capsule. The yolk sac contained a small amount of Direct Sky Blue 6B.

4.3. METABOLISM

Lowry et al. (1980) observed dimethoxybenzidine in the urine of workers occupationally exposed to 3,3'-dimethoxybenzidine-based dyes. Similar results were reported by Genin (1977). Lynn et al. (1980) studied the metabolism of Direct Sky Blue 6B in rats and dogs. Four male Sprague-Dawley rats were given a single 100 mg/kg dose of Direct Sky Blue 6B by gavage. Urine was collected at 24-hour intervals and analyzed for 3,3'-dimethoxybenzidine by GC-MS. Two female mongrel dogs were given a single dose (100 mg/kg) of Direct Sky Blue 6B in the diet. Urine was collected at 24-hour intervals for 3 days and analyzed for 3,3'-dimethoxybenzidine. Control urine was collected from all rats and dogs used in the study before they

were dosed. Urine from dosed rats and dogs contained 3,3'-dimethoxybenzidine, and the rat urine was found to contain N-acetyl-3,3'-dimethoxybenzidine.

4.4. EXCRETION

After 72 hours rats excreted 0.55±0.37% (mean±SD from four animals) of the Direct Sky Blue 6B administered as 3,3'-dimethoxybenzidine (Lynn et al., 1980). In dogs, 0.08% (mean from two animals) of the administered dose was excreted as 3,3'-dimethoxybenzidine 48 hours after dosing.

4.5. SUMMARY

Oral absorption of Direct Sky Blue 6B can be inferred from toxicity data (Section 5.6.). Data concerning the distribution of Direct Sky Blue 6B after oral or inhalation exposure could not be located in the available literature. Beaudoin and Pickering (1960) gave pregnant rats intraperitoneal injections of Direct Sky Blue 6B and observed staining of nuclei of macrophages of maternal tissue. The yolk sac also contained a small amount of the dye. Lynn et al. (1980) orally dosed rats and dogs with Direct Sky Blue 6B and observed 3,3'-dimethoxybenzidine in the urine of both these species, and the rat urine also contained N-acetyl-3,3'-dimethoxybenzidine. The rats and dogs excreted small amounts of 3,3'-dimethoxybenzidine after 72 and 48 hours, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of Direct Sky Blue 6B to laboratory animals could not be located in the available literature as cited in the Appendix. Direct Sky Blue 6B was not scheduled for testing by the National Toxicology Program (NTP, 1986).

Genin (1977) found five cases of bladder tumors in an unspecified number of workers occupationally exposed to dyes with a latency period of ~18-43 years. 3,3'-Dimethoxybenzidine in quantities from trace amounts to 0.3 µg/mℓ were measured in the urine of 3/22 workers exposed to dimethoxybenzidine-based dyes. Direct Sky Blue 6B was not specifically mentioned, however.

5.2. MUTAGENICITY

Direct Sky Blue 6B has been tested for mutagenicity and genotoxicity; details of these tests are summarized in Table 5-1. Prival et al. (1982, 1984) and Prival and Mitchell (1982) found that the presence of FMN was required for Direct Sky Blue 6B to produce at least a 2-fold increase of mutants compared with the control. Prival and Mitchell (1982) found that uninduced hamster S-9 greatly enhanced the number of mutations compared with induced rat S-9.

Joachim and Decad (1984) found that Direct Sky Blue 6B was negative in a rat hepatocyte UDS assay, both after the compound was given to rats by gavage and after the compound was introduced into the cell cultures.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic effects of Direct Sky Blue 6B after oral or inhalation exposure could not be located in the available literature as cited in the Appendix.

TABLE 5-1

Mutagenicity Testing of Direct Sky Blue 6B

Assay	Indicator Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA98	commercial grade	plate incorporation	0.1-1.0 µmol/plate	+S-9, +FMN; +S-9, -FMN	+ +	FMN increased mutagenic activity	Prival et al., 1982, 1984
Reverse mutation	S. typhimurium TA98	commercial grade	plate incorporation		+S-9, +FMN	+	rat S-9 induced or hamster S-9 uninduced used; hamster S-9 enhanced mutagenic activity	Prival and Mitchell, 1982
Reverse mutation	S. typhimurium TA1538	technical grade	plate incorporation	100-1000 µg/plate	+S-9	-	no reduction system used	Joachim and Decad, 1984
UDS	rat hepatocytes	technical grade	cell culture	50-500 µg/ml	none	-	microscopic exam indicated that dye did not enter the cells	Joachim and Decad, 1984
UDS	rat hepatocytes	technical grade	gavage, in vitro	500 mg/kg	NA	-	only one dose tested	Joachim and Decad, 1984

NR = Not reported; NA = not applicable

A study by Beaudoin (1968) showed Direct Sky Blue 6B to be teratogenic in Wistar rats after intraperitoneal injection. Groups of 5-18 rats were injected intraperitoneally with a 2% aqueous solution of Direct Sky Blue 6B on gestation day 8 at doses of 70, 140 or 200 mg/kg. At the same time, 15 control rats were injected with distilled water. Dams were killed on day 20, uteri were removed and the number of resorption sites and live fetuses were counted. Fetuses were fixed in Bouin's fluid or 95% alcohol for later examination. The resorption rate of the low-dose group was similar to that of the control, while the two highest dose groups showed a dose-related increase in resorptions. No malformed survivors were found in the lowest dose group, while the 140 and 208 mg/kg groups showed dose-related increases in the number of malformations. Anomalies included anophthalmia, hydrocephalus, exencephaly, microphthalmia and megalophthalmia. Fetal weights were significantly ($p=0.01$) reduced in the 200 mg/kg dye-treated group as compared with controls. Exposure to the highest dose caused maternal death. Eleven dams receiving an unspecified dose of Direct Sky Blue 6B showed a decrease in weight gain, which was most significant during days 8-13.

Chernoff and Kavlock (1983) injected 30 pregnant CD-1 mice intraperitoneally on gestation day 8 with 250 mg/kg Direct Sky Blue 6B in distilled water. At the same time, 40 control mice received injections of distilled water. Dams were allowed to give birth naturally, but dams that did not give birth by postnatal day 3 were sacrificed, and their uteri examined for implantation sites. Mice treated with Direct Sky Blue 6B did not give birth to live offspring. The dose level used led to maternal death and a decrease in maternal weight gain.

Amels et al. (1977) injected an unspecified number of pregnant Wistar rats and Houdet rats intraperitoneally with 100, 150 or 200 mg/kg Direct Sky

Blue 6B in aqueous solution on day 9 of gestation. Rats were killed on days 12-18 and 20 of pregnancy. Fetuses were examined for abnormalities, particularly for ocular malformations. Treatment of control animals was not specified, and results were tabulated without the day of sacrifice specified. The number of ocular malformations showed a dose-related increase. Only two other unspecified structural abnormalities were noted in the 133 fetuses examined. No information concerning maternal toxicity was provided.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic and subchronic toxicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

The acute oral toxicity of Direct Sky Blue 6B was investigated by M.B. Research Laboratories (1978). Five male and five female Wistar rats received 5 g/kg Direct Sky Blue 6B by oral intubation, and were observed for 14 days after dosing. No rats died during the study, indicating that the acute oral LD_{50} in rats is >5 g/kg.

The acute inhalation toxicity of Direct Sky Blue 6B was investigated by Southwest Foundation for Research and Education (1979). Five male and five female Sprague-Dawley rats were exposed for 4 hours to the highest airborne concentration obtainable (18.94 mg/ℓ). The rats were observed for 14 days after exposure. No deaths occurred, but nine of the rats appeared hyperactive. At necropsy, no abnormalities that could be considered chemically-related were observed.

Acute dermal toxicity of Direct Sky Blue 6B was studied in New Zealand White rabbits by M. B. Research Laboratories (1978). A dose of 2.0 g/kg Direct Sky Blue 6B was placed on the clipped and abraded backs of four rabbits and covered with gauze and impervious material. After 24 hours, the dye was washed off with warm tap water; 1 hour later the sites were graded. Direct Sky Blue 6B was found to be minimally irritating. Rabbits were observed for 14 days, then necropsied. At necropsy, no abnormalities were observed.

Eye irritation of Direct Sky Blue 6B was studied in six New Zealand White rabbits (M.B. Research Laboratories, 1978). A dose of 0.1 g was placed in the lower conjunctival sac of one eye of each rabbit and the lid shut for 1 second. The eyes were graded at 1, 24, 48 and 72 hours after dosing according to accepted protocol. The results of this study classified Direct Sky Blue 6B as moderately irritating.

5.7. SUMMARY

Pertinent data regarding the carcinogenicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. Positive results were obtained for S. typhimurium strain TA98 with metabolic activation by S-9 (Prival et al., 1982, 1984; Prival and Mitchell, 1982). Mutagenic activity was enhanced when FMN was added as a reducing agent. Prival and Mitchell (1982) found uninduced hamster S-9 enhanced mutagenicity to a greater extent than did induced rat S-9. Direct Sky Blue 6B did not induce UDS in vivo or in vitro (Joachim and Decad, 1984).

No data regarding the teratogenic effects of Direct Sky Blue 6B after oral or inhalation exposure were available; a few studies by the intraperitoneal route were available. Beaudoin (1968) observed dose-related increased resorptions and malformations in rats at $\geq$140 mg/kg/day. Amels et

al. (1977) observed a dose-related increase in ocular malformations in rats given intraperitoneal doses ≥100 mg/kg of Direct Sky Blue 6B. Maternal toxicity was observed in mice given 250 mg/kg/day intraperitoneally (Chernoff and Kavlock, 1983). Pertinent data regarding other reproductive effects or subchronic and chronic toxicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. The oral LD_{50} is >5 mg/kg (M.B. Research Laboratories, 1978), and rats exposed by inhalation to 18.94 mg/ℓ for 4 hours were essentially unaffected by Direct Sky Blue 6B, except for hyperactivity (Southwest Foundation for Research and Education, 1979).

6. AQUATIC TOXICITY

6.1. ACUTE

EN CAS Analytical Labs (1977a,b) reported 96-hour LC_{50} values of 240 and 290 mg/ℓ for two different batches of Diphenyl Brill Blue FF Supra (CAS No. 2610-05-1) for bluegills, Lepomis macrochirus.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of Direct Sky Blue 6B to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effects of Direct Sky Blue 6B on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding Direct Sky Blue 6B residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Konishi and Hidaka (1969) reported that Direct Sky Blue 6B stimulated carp, Cyprinus carpio, chemoreceptors in vitro. Kiyohara et al. (1984) reported that Direct Sky Blue 6B was used as a selective stain for tastebuds in various fish species. EN CAS Analytical Labs (1977c) reported that Diphenyl Brill Blue FF Supra had no effect on waste treatment plant bacteria at concentrations $\leq$300 mg/ℓ, the highest concentration tested.

6.6. SUMMARY

EN CAS Analytical Labs (1977a,b) reported 96-hour LC_{50} values of 240 and 290 mg/ℓ for two batches of Diphenyl Brill Blue FF Supra for bluegills. On the basis of CAS number, this is the same compound as Direct Sky

Blue 6B. EN CAS Analytical Labs (1977c) also reported that waste treatment plant bacteria were unaffected by concentrations of ≤300 mg/ℓ. Konishi and Hidaka (1969) found that Direct Sky Blue 6B stimulated carp chemoreceptors *in vitro*.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

OSHA/NIOSH (1980) concluded that 3,3'-dimethoxybenzidine dyes may present a cancer risk to humans and recommend caution in handling and minimum exposure. U.S. EPA (1981) in response to ITC recommendations decided not to require testing of 3,3'-dimethoxybenzidine-based dyes.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the toxic effects of Direct Sky Blue 68 could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the carcinogenicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. Positive results were obtained for S. typhimurium strain TA98 with metabolic activation by S-9 (Prival et al., 1982, 1984; Prival and Mitchell, 1982; Joachim and Decad, 1984). Mutagenic activity was enhanced when FMN was added. Prival and Mitchell (1982) found uninduced hamster S-9 enhanced mutagenicity to a greater extent than did induced rat S-9. Direct Sky Blue 6B did not induce UDS in vivo or in vitro (Joachim and Decad, 1984).

No data regarding the teratogenic effects of Direct Sky Blue 6B after oral or inhalation exposure were available; a few studies by the intraperitoneal route were available. Beaudoin (1968) observed dose-related increased resorptions and malformations in rats at $\geq$140 mg/kg/day. Amels et al. (1977) observed a dose-related increase in ocular malformations in rats given intraperitoneal doses $\geq$100 mg/kg of Direct Sky Blue 6B. Maternal toxicity was observed in mice given 250 mg/kg/day intraperitoneally (Chernoff and Kavlock, 1983). Pertinent data regarding other reproductive effects and subchronic or chronic toxicity of Direct Sky Blue 6B could not be located in the available literature as cited in the Appendix. The oral LD_{50} is >5 mg/kg (M. B. Research Labs, 1978), and rats exposed to 18.94 mg/ℓ were essentially unaffected by Direct Sky Blue 6B except for hyperactivity. Thus, data are insufficient to derive an RfD.

Direct Sky Blue 6B is a 3-3'-dimethoxybenzidine-based dye. 3,3-Dimethoxybenzidine, a recognized animal carcinogen (IARC, 1982), is also a metabolite of the dye and was identified in workers occupationally exposed to dyes (Lowry et al., 1980). Genin (1977) found several bladder cancer

cases upon examination of plant records of workers occupationally exposed to dyes, but Direct Sky Blue B6 was not specifically mentioned. Thus, Direct Sky Blue 68 may present a carcinogenic risk to man.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) BASED ON CHRONIC TOXICITY

No subchronic or chronic oral or inhalation toxicity studies of Direct Sky Blue 6B were located; therefore, data are insufficient for deriving an RQ (Table 9-1).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Pertinent data describing the carcinogenicity of Direct Sky Blue 6B by the oral or inhalation routes were not available. Genin (1977) found five cases of bladder tumors in an unspecified number of workers occupationally exposed to dyes, but Direct SKy Blue 6B was not specifically mentioned. Lowry et al. (1980) and Genin (1977) detected 3,3'-dimethoxybenzidine in the urine of workers occupationally exposed to dyes. 3,3'-Dimethoxybenzidine is a known carcinogen with an IARC ranking of 2B and a EPA ranking of B2 (IARC, 1982; U.S. EPA, 1986b). Thus, Direct Sky Blue 6B may present a carcinogenic risk to humans; however, human and animal data are inadequate. Since there is inadequate evidence that Direct Sky Blue 6B is carcinogenic in humans or in animals, this dye could be classified in the EPA D category (U.S. EPA, 1986c), but the fact that its metabolite is a known carcinogen more appropriately places this dye in EPA Group B2.

TABLE 9-1

Direct Sky Blue 6B

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ

10. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in May, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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