EPA/600/X-87/038
January 1987

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2,4-DIMETHYLANILINE AND 2,4-DIMETHYLANILINE HYDROCHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. 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.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

2,4-Dimethylaniline, also called 2,4-xylidine, is a liquid at ambient temperature (Northcott, 1978). It is slightly soluble in water (Amoore and Hautala, 1983) and is soluble in ethanol, ethyl ether and benzene (Weast, 1980). Recent production data indicate that only one company, DuPont Co., Deepwater, NJ, manufactured this compound and a mixture of dimethylaniline isomers in the United States in 1984 (USITC, 1985; SRI, 1985). The total U.S. production volume for this chemical was not available, but 12,347 pounds of it was imported into the United States in 1983 (USITC, 1984). It is primarily used in the manufacture of a variety of dyes (U.S. EPA, 1984; Northcott, 1978). Data regarding the physical and chemical properties of 2,4-dimethylaniline hydrochloride were limited, and apparently it is not commercially produced in the United States.

Adequate information was not available in the literature to assess the fate of 2,4-dimethylaniline in different environmental media. Conclusions reached regarding the fate and transport of this compound were based on limited data and the physical and chemical properties of 2,4-dimethylaniline. Limited experimental data were available regarding the photodegradation and biodegradability of this compound. The compound is expected to undergo photochemical oxidation with molecular oxygen in natural surface water in the presence of sunlight (Meallier, 1969; Pouyet and Meallier, 1967); however, lack of experimental data precludes estimation of a half-life for this reaction. The photochemical reaction may be further enhanced by photosensitization of the reactant by certain algae present in surface water (Zepp and Schlotzhauer, 1983). The biodegradability tests conducted by Baird et al. (1977) indicate that this compound will biodegrade

significantly with activated sludge during wastewater treatment processes; however, Japanese MITI test results contradict this finding and list 2,4-dimethylaniline as degradation resistant (Kitano, 1978; Kawasaki, 1980). It is not clear whether biodegradation will play a significant role in the loss of this compound from natural waters. Based on its physical properties, the compound is not expected to volatilize significantly from surface water. The physical properties and the experimental data of Paris (1980) for other aromatic amines indicate that 2,4-dimethylaniline will be significantly sorbed onto sediments containing humic substances. In the absence of humic substances, the sorption will not be significant.

In the atmosphere, significant removal of this compound through reaction with OH radical is expected. Some removal of this compound by wet deposition will occur, but significant removal through adsorption onto aerosol particles and subsequent precipitation is not expected.

Indirect evidence indicates that 2,4-dimethylaniline will undergo some biodegradation in soil (Bollag et al., 1978). Similarly, volatility of this compound from dry soils is expected to depend on humic matter content; increasing the humic materials will decrease the volatility. In wet soils, the volatility characteristics will be similar to those in water, and significant volatilization may not occur. The leachability of 2,4-dimethylaniline depends on the nature of soil. In sandy soils, significant leaching will occur (Pereira et al., 1983), but leaching will be insignificant in soils containing humic substances.

2,4-Dimethylaniline has been detected in both the mainstream and sidestream smoke of cigarettes (Patrianakos and Hoffmann, 1979). Therefore, inhalation exposure to this compound in both active and passive smokers will

occur. Undetermined amounts of this compound may be inhaled by workers from shale oil and coal liquefaction operations (Hawthorne et al., 1985; Harris et al., 1980). The National Occupational Hazard Survey determined that ~1790 people were occupationally exposed to xylidine mixtures in 1970 (U.S. EPA, 1984). No data on the level of this compound in ambient air were located. Although this compound has been detected in the groundwater of a coal tar and wood-preserving waste disposal site in St. Louis Park, MN (Pereira et al., 1983), it has not been detected in either surface water or drinking water. Data regarding the detection of the compound in food could not be located in the available literature as cited in the Appendix.

Little information was available concerning effects of 2,4-dimethylaniline on aquatic organisms. LC_{50} values of 196 and 25 mg/ℓ were reported for the golden orfe, L. idus (Juhnke and Luedemann, 1978) and D. magna (Bringmann and Kuehn, 1978), respectively. Among the plants tested, the blue-green alga, M. aeruginosa was more sensitive than the green alga, S. quadricauda, with toxicity thresholds of 0.43 and 5.0 mg/ℓ, respectively. 2,4-Dimethylaniline will not significantly bioconcentrate in aquatic organisms (Kawasaki, 1980). Information concerning 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

Data from the Lindstrom (1961) study indicate that ingested 2,4-dimethylaniline was absorbed from the gastrointestinal tract, metabolized and excreted in the urine. A small amount of 2,4-dimethylaniline was excreted unchanged, some was conjugated and excreted as 2,4-dimethylphenyl sulfamate and some was acetylated and excreted as 2,4-dimethylacetanilide. Most of the parent compound, however, was oxidized to 3-methyl-4-aminobenzoic acid,

which is then acetylated and excreted as 3-methyl-4-acetamidobenzoic acid or conjugated with glycine and excreted as p-aminohippuric acid or excreted unchanged. The possibility of fecal or respiratory excretion was not investigated. Data from the Magnusson et al. (1979) study suggest that 2,4-dimethylaniline may be oxidized by hepatic microsomal enzymes.

Pertinent data regarding the distribution of 2,4-dimethylaniline could not be located in the available literature as cited in the Appendix.

Limited evidence is available to suggest that 2,4-dimethylaniline is carcinogenic to animals. Weisburger et al. (1978) demonstrated that dietary 2,4-dimethylaniline hydrochloride at 250 ppm caused an increased incidence of lung tumors in female CD-1 mice. No neoplastic changes of any type were observed in male CD-1 mice or CD rats of either sex exposed to dietary 2,4-dimethylaniline hydrochloride. Russfield et al. (1973) reported an increased incidence of fibrosarcomas or subcutaneous fibromas and an increase in hepatomas in male Charles River rats fed 2,4-dimethylaniline at unspecified doses for 2 years.

A number of investigators have reported that 2,4-dimethylaniline is mutagenic to S. typhimurium strain TA100, but only in the presence of S-9 (Chung et al., 1981; Zimmer et al., 1980; Nohmi et al., 1983, 1984). Negative results were obtained with S. typhimurium strains TA98 and TA1537, regardless of the presence of S-9 (Zimmer et al., 1980; Nohmi et al., 1984). Nohmi et al. (1983) identified the mutagenic metabolite of 2,4-dimethylaniline as 2,4-dimethylphenylhydroxylamine.

Pertinent data regarding the teratogenicity or reproductive effects of 2,4-dimethylaniline could not be located in the available literature as cited in the Appendix.

Only two chronic/subchronic toxicity studies with 2,4-dimethylaniline were located in the available literature. Weisburger et al. (1978) reported only neoplastic effects in Charles River rats or CD-1 mice fed diets containing 2,4-dimethylaniline hydrochloride for 18 months followed by 6 or 3 months observation, respectively. Lindstrom et al. (1963) observed a variety of adverse effects in Osborne-Mendel rats fed diets containing 375, 750, 2500, 5000 or 10,000 ppm 2,4-dimethylaniline for up to 6 months. These included dose-related, significantly decreased growth at $\geq$2500 ppm, significantly increased relative liver weight at all levels of exposure, significantly increased relative kidney weight at all levels of exposure, target cell anemia at all levels of exposure, slight hyperkeratosis of the forestomach at 10,000 ppm and histological evidence of liver damage at 5000 and 10,000 ppm and kidney damage at 10,000 ppm.

Oral studies of $\leq$4 weeks duration have also shown that 2,4-dimethylaniline caused liver damage in rats at $\geq$20 mg/kg/day and dogs at 50 mg/kg/day (Magnusson et al., 1971, 1979; Short et al., 1983). McLean et al. (1969) demonstrated that intravenous administration of 2,4-dimethylaniline (2.5 mmol/kg for 5 hours) had no significant effect on methemoglobin formation in cats. Oral LD_{50} values of 470 and 250 mg/kg 2,4-dimethylaniline have been reported for male rats and mice (sex not reported), respectively (Vernot et al., 1977).

A q_1^* of 7.5×10^{-1} $(mg/kg/day)^{-1}$ for 2,4-dimethylaniline and a q_1^* of 5.8×10^{-1} $(mg/kg/day)^{-1}$ for 2,4-dimethylaniline hydrochloride were derived based on the increased incidence of lung tumors in female mice fed 2,4-dimethylaniline in the diet in the study by Weisburger et al. (1978). The water concentrations associated with increased lifetime risk at

levels of 10^{-5}, 10^{-6} and 10^{-7} are $5x10^{-4}$, $5x10^{-5}$ and $5x10^{-6}$ mg/ℓ for 2,4-dimethylaniline and $6x10^{-4}$, $6x10^{-5}$ and $6x10^{-6}$ mg/ℓ for 2,4-dimethylaniline hydrochloride. F factors of 2.19 and 1.68 $(mg/kg/day)^{-1}$ were also derived for 2,4-dimethylaniline and the hydrochloride, respectively, placing these chemicals in Potency Group 2. Because there were no data regarding the carcinogenicity of these compounds to humans and because the data for animals are limited, these chemicals are placed in CAG Group C as possible human carcinogens. Potency Group 2 and CAG Group C chemicals have a LOW hazard ranking under CERCLA.

An RQ of 1000 was derived for 2,4-dimethylaniline and its hydrochloride based on the findings of anemia and increased liver and kidney weights in the 6-month dietary study using rats by Lindstrom et al. (1963).

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF TABLES

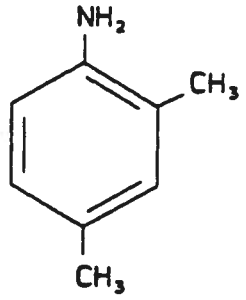
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BSP	Sulfobromophthalein
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MTD	Maximum tolerated dose
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average
v/v	Volume per volume
w/v	Weight per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1.1.1. 2,4-Dimethylaniline. The chemical known as 2,4-dimethylaniline is also called 2,4-xylidine; benzenamine, 2,4-dimethyl-; m-xylidine; m-4-xylidine; 2-methyl-p-toluidine; 4-amino-1,3-xylene; and 4-methyl-o-toluidine (U.S. EPA, 1986b). The structure, empirical formula, molecular weight and CAS Registry number for this compound are as follows:

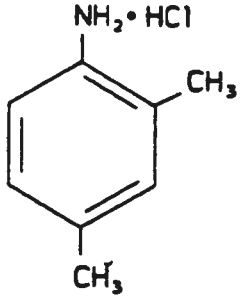


Molecular weight: 121.18

Empirical formula: $C_8H_{11}N$

CAS Registry number: 95-68-1

1.1.2. 2,4-Dimethylaniline Hydrochloride. 2,4-Dimethylaniline hydrochloride is also called 2,4-xylidine hydrochloride; 2,4-dimethylbenzenamine hydrochloride; m-4-xylidine hydrochloride; 1-amino-2,4-dimethylbenzene hydrochloride; and 4-amino-1,3-xylene hydrochloride. The structure, empirical formula, molecular weight and CAS Registry number for this compound are as follows:



Molecular weight: 157.66

Empirical formula: $C_8H_{12}NCl$

CAS Registry number: 21436-96-4

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1.2.1. 2,4-Dimethylaniline. 2,4-Dimethylaniline is a liquid at ambient temperature (Northcott, 1978). It is slightly soluble in water (Amoore and Hautala, 1983) and is soluble in ethanol, ethyl ether and benzene (Weast, 1980). Other physical properties of this compound are listed below:

Melting point:	16°C -14.3°C	 Weast, 1980
Boiling point:	214°C	Northcott, 1978
Density:	0.9723 g/cm³ at 20/4°C	Weast, 1980
Vapor pressure, mm Hg:		
at 17°C	0.068	Chao et al., 1983
at 20°C	0.075	Weber et al., 1981
at 25°C	0.154	Amoore and Hautala, 1983
Water solubility:		
at 25°C	6400 mg/ℓ	Amoore and Hautala, 1983
Log K_{ow}:	1.85 (estimated)	Verschueren, 1983
pKa:		
at 25°C	4.89	Gomez et al., 1972
Air odor threshold:	0.056 ppm (v/v)	Amoore and Hautala, 1983
Water odor threshold:	1.8 ppm (w/v)	Amoore and Hautala, 1983
Conversion factor:		
at 20°C	1 ppm = 5.037 mg/m³	

2,4-Dimethylaniline will undergo electrophilic substitution reactions. It can react with alkyl halides to form alkylamine products. Primary and secondary aromatic amines react with nitrous acid to yield N-nitroso compounds and finally diazonium salts (Gutsche and Pasto, 1975). 2,4-Dimethylaniline, like other xylidine isomers, forms complexes with copper (U.S. EPA, 1984).

1.2.2. 2,4-Dimethylaniline Hydrochloride. 2,4-Dimethylaniline hydrochloride is a solid at ambient temperature. It has a melting point of 235°C and a boiling point of 255.1°C at 1 atm (IARC, 1978). Although it is reported to be practically insoluble in cold water (IARC, 1978), the water solubility of this compound is expected to be higher than the free base (2,4-dimethylaniline). Aqueous solubility data for the salt could not be located in the available literature as cited in the Appendix.

1.3. PRODUCTION DATA

1.3.1. 2,4-Dimethylaniline. According to the TSCA Inventory of Chemical Producers, only two U.S. companies (American Cyanamid Co., Bound Brook, NJ, and DuPont Co., Deepwater, NJ) manufactured this chemical in 1977, and four companies imported it into the United States (U.S. EPA, 1977). Riches-Nelson, Inc., Greenwich, CT, imported between 100,000 and 1,000,000 pounds of the chemical in 1977 (U.S. EPA, 1977). More recent production information indicates that only one company, DuPont Co., Deepwater, NJ, manufactured this chemical in the United States in 1984 (USITC, 1985). Mixed isomers of dimethylaniline were also produced by DuPont Co., Deepwater, NJ, in 1984 (USITC, 1985; SRI, 1985). The components of the commercial mixed isomers were: 2,4-dimethylaniline, 30-50%; 2,5-dimethylaniline, 25% (max.); 2,6-dimethylaniline, 20% (max.); 3,5-, 2,3- and 3,4-dimethylaniline, 35% (max.) (U.S. EPA, 1984).

The recent U.S. production volume for 2,4-dimethylaniline is not known; however, 12,347 pounds of this chemical were imported to the United States in 1983 (USITC, 1984) and 590,986 pounds in 1981 (U.S. EPA, 1984). 2,4-Dimethylaniline is manufactured by the reduction of 4-nitro-m-xylene in the presence of iron (Sandridge and Staley, 1978).

1.3.2. 2,4-Dimethylaniline Hydrochloride. Data regarding the commercial production of 2,4-dimethylaniline hydrochloride in the United States could not be located in the available literature as cited in the Appendix.

1.4. USE DATA

2,4-Dimethylaniline and its hydrochloride salt are used in the manufacture of a large number of dyes (U.S. EPA, 1984; Northcott, 1978).

1.5. SUMMARY

2,4-Dimethylaniline, also called 2,4-xylidine, is a liquid at ambient temperature (Northcott, 1978). It is slightly soluble in water, (Amoore and Hautala, 1983) and is soluble in ethanol, ethyl ether and benzene (Weast, 1980). Recent production data indicate that only one company, DuPont Co., Deepwater, NJ, manufactured this compound and a mixture of dimethylaniline isomers in the United States in 1984 (USITC, 1985; SRI, 1985). The total U.S. production volume for this chemical was not available, but 12,347 pounds of it was imported into the United States in 1983 (USITC, 1984). It is primarily used in the manufacture of a variety of dyes (U.S. EPA, 1984; Northcott, 1978). Data regarding the physical and chemical properties of 2,4-dimethylaniline hydrochloride were limited, and apparently it is not commercially produced in the United States.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Limited information on the fate and transport of 2,4-dimethylaniline or its hydrochloride salt in the environment was located in the available literature. The conclusions regarding the fate and transport were based on the available data and the physical and chemical properties of these compounds.

2.1. WATER

Meallier (1969) and Pouyet and Meallier (1967) reported that 2,4-dimethylaniline undergoes photochemical oxidation by molecular oxygen in the presence of light from a high pressure mercury arc lamp filtered to primarily emit a wavelength maximum of 365 nm. Although these experiments demonstrated that oxidation of 2,4-dimethylaniline will occur in natural surface water in the presence of sunlight, the half-life of the compound that results from this reaction cannot be estimated because of the unavailability of the reaction rate constant. Like other unsubstituted and substituted aromatic amines, photosensitization by certain algae present in water enhances the photolysis of 2,4-dimethylaniline in natural surface water (Zepp and Schlotzhauer, 1983). Kinetic data for the photosensitization reaction of 2,4-dimethylaniline by algae have not yet been reported.

Another process that may degrade or transform 2,4-dimethylaniline is biodegradation. Lammerding et al. (1982) studied the biodegradation of 2,4-dimethylaniline by a pure culture of Escherichia coli and reported that in the presence of nitrate, 2,4-dimethylaniline was quickly converted to diazonium salts. It was shown that the organisms act only to convert nitrate to nitrite and that the actual diazotization steps occur through the

chemical process. The biodegradation of 2,4-dimethylaniline by mixed microorganisms was reported by Baird et al. (1977). With activated sludge as the microbial inoculum, 36% of 2,4-dimethylaniline (initial concentration of 20 mg/ℓ) was degraded in 6 hours. This indicates that the compound is significantly biodegradable, at least under wastewater treatment conditions. Under the Japanese MITI test conditions that consist of using activated sludge as microbial inoculum, a temperature of 25°C, and a test period of 2 weeks, an initial substrate concentration of 100 mg/ℓ 2,4-dimethylaniline was <30% degraded; therefore, the compound was considered to be nonbiodegradable (Kitano, 1978; Kawasaki, 1980). It is thus apparent that substantial uncertainty exists regarding the biodegradability of 2,4-dimethylaniline with activated sludge. It was unclear whether the nonbiodegradability of this compound under the MITI test conditions was due to the toxic effect of the compound at higher concentrations. Baird et al. (1977), however, reported that 2,4-dimethylaniline at a concentration of 20 mg/ℓ did not inhibit microorganisms present in activated sludge.

Experimental data could not be located in the available literature, as cited in the Appendix, on the loss of 2,4-dimethylaniline by volatilization from water or by sorption onto suspended particulate matter and subsequent sedimentation. From the vapor pressure and solubility data given in Section 1.2., the Henry's Law constant for this compound is estimated to be 3.84×10^{-6} atmos-$m^3 mol^{-1}$, suggesting that the compound is not expected to volatilize significantly from water (Lyman et al., 1982). The water solubility and low K_{ow} value (see Section 1.2.) of this compound indicate that theoretically significant adsorption to suspended particulate matter in water should not occur; however, Paris (1980) showed that aromatic amines covalently bind to humic materials present in soils and particulate matter

in water. Therefore, 2,4-dimethylaniline may be irreversibly bound onto them. In fact, Bollag et al. (1978) demonstrated that the irreversible binding of 2,6-dimethylaniline by soil may be >60% of the overall amount added. Therefore, the removal of 2,4-dimethylaniline through binding is expected to be significant in soils containing humic materials.

The bioconcentration of 2,4-dimethylaniline by aquatic organisms was evaluated using the Japanese MITI test, and the BCF was given as <10 (Kawasaki, 1980). The BCF can also be estimated from the equation log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982). Assuming a value of 1.85 for log K_{ow} (see Section 1.2.), the BCF value is estimated to be 15. These values both support the conclusion that 2,4-dimethylaniline will not bioconcentrate significantly in aquatic organisms.

2.2. AIR

Based on the atmospheric OH radical concentration of 10^6 molecules cm^{-3} (Cupitt, 1980), and the rate constant of 148×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} for OH radical reaction with N,N-dimethylaniline (Atkinson, 1985), the half-life of the OH radical reaction is estimated to be >1 hour. Therefore, it is expected that 2,4-dimethylaniline will react significantly with atmospheric OH radical, and this reaction may be the primary one in determining the fate of this compound in the atmosphere. The water solubility of 2,4-dimethylaniline suggests that some of this compound may be removed by wet deposition (Cupitt, 1980).

2.3. SOIL

The photodegradation of 2,4-dimethylaniline in soil is expected to be less significant than in water because more light is scattered and less

light penetrates through soil. Biodegradation, on the other hand, may be higher because of the expected higher concentration of microorganisms in soils than in most waters. In spite of its water solubility, its ability to form covalent bindings with the carbonyl groups of humic substances may result in significant sorption. When ring-labeled (^{14}C) 2,6-dimethylaniline was incubated in nonautoclaved soil for 24 hours, 66% of the applied radioactivity was bound to the soil (Bollag et al., 1978). Therefore, 2,4-dimethylaniline is expected to behave similarly in soils.

No experimental data regarding the volatility of 2,4-dimethylaniline from soils were located in the available literature. When Bollag et al. (1978) incubated nonautoclaved soil with ring-labeled (^{14}C) 2,6-dimethylaniline and aerated the soil continuously for 6 weeks, 13% of the applied radioactivity was trapped as volatile basic compounds. Because the trapped compound was basic, the authors assumed that it was 2,6-dimethylaniline without further characterization. The volatility of 2,6-dimethylaniline was almost 60% in the autoclaved soil. This may have been due to decreased binding to soil as a result of elimination of biological activity or alteration of soil property. If the increase in volatility in autoclaved soil is assumed to be due to the destruction of humic materials that are responsible for covalently binding to aromatic amines (Bollag et al., 1978), volatility in general is expected to increase with a decrease in humic materials in soils. Therefore, the volatility is expected to be significant from sandy soils.

The leachability of 2,4-dimethylaniline from soils depends on the nature of soil. In soil containing significant amounts of humic materials, significant sorption will slow down the leaching of the chemical in soil, and

biodegradation is expected to degrade most of the chemical before it reaches groundwater. On the other hand, in sandy soils where the sorption will be weaker, leaching of 2,4-dimethylaniline in groundwater will be expected because of its significant water solubility. Pereira et al. (1983) detected 2,4-dimethylaniline in groundwater from a sand aquifer inside a waste disposal site of a coal tar distillation and wood-preserving facility in Minnesota.

2.4. SUMMARY

Adequate information was not available in the literature as cited in the Appendix to assess the fate of 2,4-dimethylaniline in different environmental media. Conclusions reached regarding the fate and transport of this compound were based on limited data and the physical and chemical properties of 2,4-dimethylaniline. Limited experimental data were available regarding the photodegradation and biodegradability of this compound. The compound is expected to undergo photochemical oxidation with molecular oxygen in natural surface water in the presence of sunlight (Meallier, 1969; Pouyet and Meallier, 1967); however, the half-life for this reaction cannot be estimated because of the lack of experimental data. Photosensitization may further enhance the photochemical reaction of the reactant by certain algae present in surface water (Zepp and Schlotzhauer, 1983). The biodegradability tests conducted by Baird et al. (1977) indicate that this compound will biodegrade significantly with activated sludge during wastewater treatment processes; however, Japanese MITI test results contradict this finding and list 2,4-dimethylaniline as degradation resistant (Kitano, 1978; Kawasaki, 1980). It is not clear whether biodegradation will play a significant role in the loss of this compound from natural waters. Based on its physical properties, the compound is not expected to volatilize significantly from

surface water. The physical properties and the experimental data of Paris (1980) for other aromatic amines indicate that 2,4-dimethylaniline will be significantly sorbed onto sediments containing humic substances. In the absence of humic substances, the sorption will not be significant. 2,4-Dimethylaniline will not bioconcentrate in aquatic organisms (Kawasaki, 1980).

In the atmosphere, significant removal of this compound through reaction with OH radical is expected. Some removal of this compound by wet deposition will occur, but significant removal through adsorption onto aerosol particles and subsequent precipitation is not expected.

Indirect evidence indicates that 2,4-dimethylaniline will undergo some biodegradation in soil (Bollag et al., 1978). In soils that contain humic materials, significant sorption of this compound will occur; however, in sandy soils that contain little humic substance, sorption will not be significant. Similarly, volatility of this compound from dry soils is expected to depend on humic matter content; increasing the humic materials will decrease the volatility. In wet soils, the volatility characteristics will be similar to those in water, and significant volatilization may not occur. The leachability of 2,4-dimethylaniline depends on the nature of soil. In sandy soils, significant leaching will occur (Pereira et al., 1983), but leaching will be insignificant in soils containing humic substances.

3. EXPOSURE

3.1. AIR

Patrianakos and Hoffmann (1979) detected a mixture of 3-ethylaniline and 2,4-dimethylaniline in cigarette smoke; the compounds could not be separated by the analytical method used. The concentration of this mixture varied between 7 and 57 ng/cigarette in the mainstream smoke, and was much higher in sidestream smoke. For a cigarette that contained 57 ng of this mixture in the mainstream smoke, the sidestream smoke contained 1200 ng of the mixture, suggesting that inhalation exposure to 2,4-dimethylaniline will occur to active and passive cigarette smokers. Alkyl anilines, probably including 2,4-dimethylaniline, are emitted from shale oil wastewaters used to cool spent shale (Hawthorne et al., 1985), and from coal liquefaction processes (Harris et al., 1980); occupational exposure to 2,4-dimethylaniline may occur as a result of these two operations. According to the National Occupational Hazard Survey conducted from 1972-1974, ~1790 people were potentially exposed to xylidine mixtures in the workplace in 1970 (U.S. EPA, 1984). Data regarding the level of this compound in ambient air could not be located in the available literature as cited in the Appendix.

3.2. WATER

Pereira et al. (1983) qualitatively identified 2,4-dimethylaniline (not analytically separated from the 2,6-isomer) in the groundwater of a sand aquifer located at the waste disposal site of a former coal tar distillation and wood-preserving facility in St. Louis Park, MN. No other information about the detection of this compound in surface water or groundwater was found.

3.3. FOOD

Pertinent data regarding the presence of 2,4-dimethylaniline in food could not be located in the available literature as cited in the Appendix.

3.4. SUMMARY

2,4-Dimethylaniline has been detected in both the mainstream and sidestream smoke of cigarettes (Patrianakos and Hoffmann, 1979). Therefore, inhalation exposure to this compound in both active and passive smokers will occur. Undetermined amounts of this compound may be inhaled by workers from shale oil and coal liquefaction operations (Hawthorne et al., 1985; Harris et al., 1980). The National Occupational Hazard Survey determined that ~1790 people were occupationally exposed to xylidine mixtures in 1970 (U.S. EPA, 1984). No data on the level of this compound in ambient air were located. Although this compound has been detected in the groundwater of a coal tar and wood-preserving waste disposal site in St. Louis Park, MN (Pereira et al., 1983), it has not been detected in either surface water or drinking water. Data regarding the detection of the compound in food could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Unchanged 2,4-dimethylaniline and metabolites were found in the urine of rats, dogs and rabbits gavaged with 2,4-dimethylaniline hydrochloride, indicating the 2,4-dimethylaniline is absorbed from the gastrointestinal tract (Lindstrom, 1961). Other details regarding gastrointestinal absorption of 2,4-dimethylaniline were not reported in Lindstrom (1961) or located elsewhere in the available literature.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Lindstrom (1961) administered 200 mg/kg/day 2,4-dimethylaniline hydrochloride in water to male Osborne-Mendel rats by gavage for an unspecified period of time. Upon analysis of the urine, Lindstrom (1961) concluded that a small amount of 2,4-dimethylaniline was excreted unchanged, some was conjugated and excreted as 2,4-dimethylphenyl sulfamate and some was acetylated and excreted as 2,4-dimethylacetanilide. Most of the parent compound, however, was oxidized to 3-methyl-4-aminobenzoic acid, which was then acetylated and excreted as 3-methyl-4-acetamidobenzoic acid or conjugated with glycine and excreted as p-aminohippuric acid or excreted unchanged. No phenolic metabolites were identified. The excreted metabolites were not quantified with respect to the administered dose. Oral administration of 2,4-dimethylaniline hydrochloride ("100 mg portions") to rabbits and dogs yielded similar results. When the dose of 2,4-dimethylaniline hydrochloride given to rats was lowered progressively from 200 to 5 mg/kg/day, the amount

of unchanged 2,4-dimethylaniline and conjugated metabolites excreted in the urine ultimately became undetectable, but 3-methyl-4-aminobenzoic acid could always be identified. This indicates that, perhaps, 3-methyl-4-aminobenzoic acid is the only metabolite formed after exposure to low levels of 2,4-dimethylaniline.

Results of ultrastructural, biochemical and histochemical examinations of the livers of rats gavaged with 2,4-dimethylaniline for 4 weeks indicated that 2,4-dimethylaniline may be oxidized by hepatic microsomal enzymes and eliminated as a glucuronide conjugate (Magnusson et al., 1979). Observed results included proliferation of the smooth endoplasmic reticulum and increases in cytochrome P-450, microsomal protein, aniline hydroxylase activity and glucuronyl transferase activity.

4.4. EXCRETION

Linstrom (1961) observed the excretion of 2,4-dimethylaniline and metabolites in the urine of rats, dogs and rabbits exposed orally to 2,4-dimethylaniline hydrochloride (see Section 4.3.). The extent of excretion with respect to administered dose was not quantified, and the possibility of fecal or respiratory excretion was not investigated.

4.5. SUMMARY

Data from the Lindstrom (1961) study indicate that ingested 2,4-dimethylaniline was absorbed from the gastrointestinal tract, metabolized and excreted in the urine. A small amount of 2,4-dimethylaniline was excreted unchanged, some was conjugated and excreted as 2,4-dimethylphenyl sulfamate and some was acetylated and excreted as 2,4-dimethylacetanilide. Most of the parent compound, however, was oxidized to 3-methyl-4-aminobenzoic acid, which is then acetylated and excreted as 3-methyl-4-acetamidobenzoic acid or conjugated with glycine and excreted as p-aminohippuric acid or excreted

unchanged. The possibility of fecal or respiratory excretion was investigated. Data from the Magnusson et al. (1979) study suggest that 2,4-dimethylaniline may be oxidized by hepatic microsomal enzymes.

Pertinent data regarding the distribution of 2,4-dimethylaniline could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

Weisburger et al. (1978) fed 2,4-dimethylaniline hydrochloride to male Charles River CD rats and male and female CD-1 mice for 18 months. Groups of 25 rats were fed 2000 or 4000 ppm 2,4-dimethylaniline hydrochloride for 3 months, then 250 or 500 ppm for 2 months and, finally, 500 or 1000 ppm for 13 months. A group of 25 male rats was maintained as controls. Groups of 25 male and 25 female mice were fed 0, 125 or 250 ppm 2,4-dimethylaniline hydrochloride for 18 months. Dose levels were determined from subchronic range-finding studies; the higher dose was the MTD based on food consumption, weight gain and mortality. Rats and mice were maintained for an additional 6 and 3 months, respectively, after treatment, and then killed. Gross and microscopic examinations of major organs were performed on all animals that survived for $\geq$6 months. The only effect reported was a significantly increased incidence of lung tumors ($p<0.025$, Fisher Exact test) in high-dose female mice compared with matched and pooled controls (Table 5-1). No other neoplastic or nonneoplastic effects were reported for any other group tested.

In an earlier report from the same laboratory, Russfield et al. (1973) stated that a group of 50 male Charles River rats fed 2,4-dimethylaniline in the diet for 2 years had an increased incidence of fibrosarcomas or subcutaneous fibromas compared with controls (39% treated vs. 16% controls). Treated rats also had an excess of hepatomas. No other details were provided, and a full report of these results could not be located in the available literature. Furthermore, Weisburger et al. (1973) made no mention of their earlier report.

TABLE 5-1

Incidence of Lung Tumors in Female CD-1 Mice Fed 2,4-Dimethylaniline Hydrochloride in the Diet for 18 Months and Examined at 24 Months*

Dose (ppm)	Tumor Incidence
0	5/22 (matched controls) 32/102 (pooled controls)
125	5/18
250	11/19 (significantly increased compared with both control groups using Fisher Exact Test $p<0.025$)

QUALITY OF EVIDENCE

Strengths of study: Compound was administered to both sexes of mice and male rats by natural route of exposure over the lifespan of the animal; compound was 97-99% pure

Weaknesses of study: Small numbers of animals; animals that died $\leq$6 months into the study were not necropsied

*Source: Weisburger et al., 1978

5.2. MUTAGENICITY

Mutagenicity studies are summarized in Table 5-2. A number of investigators have demonstrated that 2,4-dimethylaniline is mutagenic to Salmonella typhimurium -strain TA100, but only in the presence of S-9 (Chung et al., 1981; Zimmer et al., 1980; Nohmi et al., 1983, 1984). Negative results were obtained with S. typhimurium strains TA98 and TA1537, regardless of the presence of S-9 (Zimmer et al., 1980; Nohmi et al., 1984). Nohmi et al. (1983) identified the mutagenic metabolite of 2,4-dimethylaniline as 2,4-dimethylphenylhydroxylamine.

Consistent with the requirement for metabolic activation, Nohmi et al. (1984) reported that 2,4-dimethylaniline did not cause reduction in the transforming activity of Bacillus subtilis DNA. Zimmer et al. (1980) observed no damage to DNA as measured by alkaline elution of DNA in V79 cells (Chinese hamster lung fibroblasts) incubated in the presence of 2,4-dimethylaniline (up to 3 mM) and mammalian S-9 for up to 4 hours. Seiler (1977) observed inhibition of the incorporation of tritiated thymidine into the testicular DNA of mice given a single oral dose (200 mg/kg) of 2,4-dimethylaniline.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic effects of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

TABLE 5-2

Mutagenicity of 2,4-Dimethylaniline and Metabolites

Test System	Exposure/Dose	Results	Reference
S. typhimurium TA98, TA100, TA1537	Plate assay with rat liver S-9 or mouse liver S-9: 5 doses from 0-1.5 µmole/plate (doses NS). Suspension test with 3 doses all <0.5 µmole/plate (doses shown for TA100 only)	Positive mutagenic response in TA100 only with either mouse or rat liver S-9 in the plate assay. Positive in the suspension test in TA100 with rat liver S-9 (mouse S-9 not tested). Negative in TA98 and TA1537.	Zimmer et al., 1980
Chinese hamster lung fibroblasts (V79). DNA breakage test (alkaline elution assay)	Cells exposed to 1 or 3 mM 2,4-dimethylaniline (+S-9) for 2 or 4 hours	Negative at all exposure levels.	Zimmer et al., 1980
S. typhimurium TA100, TA98	Plate assay, dose/plate NS tested ± rat liver S-9	Positive with S-9, negative without S-9	Nohmi et al., 1984
B. subtilis assay for loss of transforming DNA activity	Cells incubated for 2 days in 10 mM 2,4-dimethylaniline	Negative	Nohmi et al., 1984

TABLE 5-2 (cont.)

Test System	Exposure/Dose	Results	Reference
S. typhimurium TA100	A 2,4-dimethylaniline metabolite, 2,4-dimethylphenylhydroxylamine, identified by mass spectroscopy was tested at levels of 0, 25, 50 and 100 µl/plate without S-9 activation	This metabolite was positive without S-9.	Nohmi, 1983
S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	Exposure levels reported for TA100 only: 5, 10, 25, 50, 100, 250, 500, 1000 µg/plate each with and without S-9 (rat)	Mutagenic at doses ≥25 µg/plate in the presence of S-9, negative without S-9	Chung et al., 1981

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Only two chronic toxicity studies were located in the available literature with 2,4-dimethylaniline. No nonneoplastic effects were reported in the study by Weisburger et al. (1978), which was discussed in Section 5.1.

In another study, Lindstrom et al. (1963) fed 2,4-dimethylaniline (0, 375, 750, 2500, 5000 or 10,000 ppm) to groups of 10 male and 10 female weanling Osborne-Mendel rats for up to 6 months. Rats were weighed weekly and observed for clinical signs of toxicity throughout the experiment. After 3 months, four rats from each treatment level were killed and examined. Sections of the livers, kidneys, testes, adrenals (female only) and spleens (females only) taken from four rats from each treated group and six controls were examined histologically. Furthermore, sections of pancreas, stomach, small intestine, colon and adrenal were taken from eight rats exposed to 10,000 ppm and examined histologically.

There was no effect on mortality. Weight gain was significantly reduced ($p<0.001$; statistical methods were not reported) among rats of both sexes fed $\geq$2500 ppm. This effect was most severe at 10,000 ppm (a 60% reduction in comparison with controls) and was apparent at both 3 and 6 months. Gross and microscopic examinations revealed compound-related damage to the kidney and liver. Relative liver weight was dose-related and significantly greater than controls at all levels of exposure; the difference was most striking at the two highest exposure levels. Gross examination revealed small, pale, rounded foci at 5000 and 10,000 ppm. Histological examination revealed cholangiofibrosis, bile duct proliferation, hepatocellular necrosis and foci of hepatocellular hyperplasia among rats exposed to 5000 and 10,000 ppm.

These effects were more severe at 10,000 ppm than at 5000 ppm. At 2500 ppm, slight bile duct proliferation and hepatocellular hyperplasia were observed in a few rats. No effects on the liver were seen at ≤750 ppm. Relative kidney weight was significantly greater than controls at all levels of exposure; however, pathological evidence of kidney damage was observed only among rats fed 10,000 ppm 2,4-dimethylaniline. Damage (slight to moderate) was characterized by foci of cortical tubular atrophy, interstitial fibrosis, chronic inflammation and various papillary changes, including edema, cast formation, and necrosis and repair. Dose-related, significantly increased testicular weight was observed among male rats fed ≥2500 ppm, but this may have been a result of decreased body weight; no gross or histopathological effects on the testes were observed. Dose-related target cell anemia was reported to occur among rats exposed to all levels of 2,4-dimethylaniline. Slight hyperkeratosis was also observed in the forestomachs of all rats exposed to 10,000 ppm of 2,4-dimethylaniline. No other effects were observed.

Short et al. (1983) treated a group of 30 male Fischer 344 rats with 0 or 117 mg/kg/day of 98.7% pure 2,4-dimethylaniline by gavage. No vehicle was used. Groups of 10 rats were killed after 5, 10 or 20 days of treatment. The rats were evaluated for body and organ weight changes, clinical signs of toxicity and histopathological lesions in the liver, kidney, spleen, bone marrow, esophagus, trachea, thyroid, parathyroid and urinary bladder. Body weights were significantly reduced ($p<0.005$) in the treated groups at all sacrifice times. Mean absolute liver and kidney weights were signficantly increased at 10 and 20 days. Treatment-related histopathological lesions were limited to the liver and consisted of extensive cloudy swelling, diffuse hepatocellular necrosis, periacinar connective tissue proliferation, vacuolar degeneration and bile duct proliferation.

Magnussen et al. (1979) studied effects on the liver of a group of five male and five female Sprague-Dawley rats treated with 2,4-dimethylaniline in saline at a dose of 400 mg/kg/day for 1 week, followed by 500 mg/kg/day for 3 weeks (TWA = 475 mg/kg/day). A control group of five rats/sex were given saline alone. There were no treatment-related deaths. Treated rats had decreased body weights with no effects on food consumption, enlarged livers and increased absolute and relative liver weights. Histological examination of livers revealed centrilobular hepatocytomegaly, occasional necrotic cells and decreased liver glycogen and glucose-6-phosphatase levels. Electron microscopy revealed proliferation of the endoplasmic reticulum and isolated degenerative hepatocytes characterized by vacuolization, inclusion bodies and dilatation of bile canaliculi.

Magnusson et al. (1971) also investigated the effects of 2,4-dimethylaniline on the liver and kidney in rats and dogs. Groups of five male and five female Sprague-Dawley rats were treated by gavage daily at doses of 0, 20 or 100 mg/kg/day for 4 weeks. Another group of five rats/sex received 500 mg/kg/day for 2 weeks followed by 700 mg/kg/day for another 2 weeks (TWA = 600 mg/kg/day). Six rats at the high-dose level died within 6-25 days. High-dose rats had decreased body weight and decreased hemoglobin levels and hematocrit. Increased levels of ornithine carbamyltransferase, indicative of liver damage, was observed in 2/10, 1/10 and 4/10 rats at the low, medium and high doses, respectively. Relative liver weights were increased at all doses, while microscopic lesions were observed only at the high dose. The lesions consisted of scattered foci of necrosis and vacuolization of hepatocytes in all high-dose rats. No effects on the kidney were observed.

Groups of beagle dogs (one male and one female) were treated orally with capsules containing 2,4-dimethylaniline at doses of 0, 2, 10 or 50 mg/kg/day for 4 weeks. Vomiting occurred after dosing with 10 or 50 mg/kg/day, and high-dose dogs had a general unthrifty appearance and weight loss. High-dose dogs also had pale, enlarged livers and slight fatty degeneration of hepatocytes and increased BSP retention, indicative of liver damage. There were no effects on other clinical chemistry and hematological parameters or on the kidney.

5.6. OTHER RELEVANT INFORMATION

Oral LD_{50} values of 470 and 250 mg/kg 2,4-dimethylaniline have been reported for male rats and mice (sex not reported), respectively (Vernot et al., 1977).

McLean et al. (1969) demonstrated that unlike aniline, 2,4-dimethylaniline (intravenous administration of 2.5 mmol/kg for 5 hours) had no significant effects on methemoglobin formation in cats.

5.7. SUMMARY

Limited evidence is available to suggest that 2,4-dimethylaniline is carcinogenic to animals. Weisburger et al. (1978) demonstrated that dietary 2,4-dimethylaniline hydrochloride at 250 ppm caused an increased incidence of lung tumors in female CD-1 mice. No neoplastic changes of any type were observed in male CD-1 mice or CD rats of either sex exposed to dietary 2,4-dimethylaniline hydrochloride. Russfield et al. (1973) reported an increased incidence of fibrosarcomas or subcutaneous fibromas and an increase in hepatomas in male Charles River rats fed 2,4-dimethylaniline at unspecified doses for 2 years (abstract only).

A number of investigators have reported that 2,4-dimethylaniline is mutagenic to S. typhimurium strain TA100, but only in the presence of S-9 (Chung et al., 1981; Zimmer et al., 1980; Nohmi et al., 1983, 1984).

Negative results were obtained with S. typhimurium strains TA98 and TA1537, regardless of the presence of S-9 (Zimmer et al., 1980; Nohmi et al., 1984). Nohmi et al. (1983) identified the mutagenic metabolite of 2,4-dimethylaniline as 2,4-dimethylphenylhydroxylamine.

Pertinent data regarding the teratogenicity or reproductive effects of 2,4-dimethylaniline could not be located in the available literature as cited in the Appendix.

Only two chronic/subchronic toxicity studies with 2,4-dimethylaniline were located in the available literature. Weisburger et al. (1978) reported only neoplastic effects in Charles River rats or CD-1 mice fed diets containing 2,4-dimethylaniline hydrochloride for 18 months followed by 6 or 3 months observation, respectively. Lindstrom et al. (1963) observed a variety of adverse effects in Osborne-Mendel rats fed diets containing 375, 750, 2500, 5000 or 10,000 ppm 2,4-dimethylaniline for up to 6 months. These included dose-related, significantly decreased growth at $\geq$2500 ppm, significantly increased relative liver weight at all levels of exposure, significantly increased relative kidney weight at all levels of exposure, target cell anemia at all levels of exposure, slight hyperkeratosis of the forestomach at 10,000 ppm and histological evidence of liver damage at 5000 and 10,000 ppm and kidney damage at 10,000 ppm.

Oral studies of $\leq$4 weeks duration have also shown that 2,4-dimethylaniline caused liver damage in rats at $\geq$20 mg/kg/day and dogs at 50 mg/kg/day (Magnusson et al., 1971, 1979; Short et al., 1983). McLean et al. (1969) demonstrated that intravenous administration of 2,4-dimethylaniline (2.5 mmol/kg for 5 hours) had no significant effect on methemoglobin formation in cats. Oral LD_{50} values of 470 and 250 mg/kg 2,4-dimethylaniline have been reported for male rats and mice (sex not reported), respectively (Vernot et al., 1977).

6. AQUATIC TOXICITY

6.1. ACUTE

The only data available concerning toxicity of 2,4-dimethylaniline to fishes were provided by Juhnke and Luedemann (1978), who reported 48-hour LC_0, LC_{50} and LC_{100} values of 98, 196 and 294 mg/ℓ, respectively, in the golden orfe, Leuciscus idus.

Bringmann and Kuehn (1977) reported 24-hour LC_0, LC_{50} and LC_{100} values of 3, 25 and 100 mg/ℓ, respectively, for Daphnia magna. Bringmann and Kuehn (1982) reported a 24-hour EC_{50} value of 16-650 mg/ℓ for immobilization of D. magna. Bringmann and Kuehn (1982) also reported a 24-hour EC_0 and EC_{100} of 39 and 100-200 mg/ℓ, respectively, but did not explain the discrepancy between the EC_{50} and EC_{100} values. Bringmann and Kuehn (1981) determined that 9.8 mg/ℓ was the toxicity threshold for inhibition of culture growth of the flagellate protozoan, Entosiphon sulcatum. Toxicity thresholds for the ciliate, Uronema parduczi, and the flagellate, Chilomonas paramecium, were 12 and >40 mg/ℓ, respectively.

Data concerning 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Toxicity thresholds for inhibition of population growth of the green alga, Scenedesmus quadricauda, and the blue-green alga, Microcystis aeruginosa, were 5.0 and 0.43 mg/ℓ, respectively (Bringmann and Kuehn, 1978).

For the bacterium, Pseudomanas putida, the toxicity threshold was 8 mg/ℓ (Bringmann and Kuehn, 1980). In a study using the algal lawn technique, growth of the green alga, Chlorella autotrophica, was unaffected by 1-500 µg/dish, but was partially inhibited at 1000 and 2000 µg/dish and completely inhibited at 10,000 µg/dish (Winters et al., 1977). In a similar experiment, growth of the marine blue-green alga, Agmenellum quadruplicatum, was unaffected by 0.1 and 1.0 µg/dish, but was partially inhibited at 10 µg/dish and completely inhibited by 100 and 1000 µg/dish (Batterton et al., 1978).

6.4. RESIDUES

Pertinent data regarding residues of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

Little information was available concerning effects of 2,4-dimethylaniline on aquatic organisms. LC_{50} values of 196 and 25 mg/ℓ were reported for the golden orfe, L. idus (Juhnke and Luedemann, 1978) and D. magna (Bringmann and Kuehn, 1978), respectively. Among the plants tested, the blue-green alga, M. aeruginosa was more sensitive than the green alga, S. quadricauda, with toxicity thresholds of 0.43 and 5.0 mg/ℓ, respectively. Information concerning 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1985-1986) adopted a TLV of 2 ppm (~10 mg/m^3) for mixed dimethylaniline, but listed no value specifically for 2,4-dimethylaniline. The TLV was recommended because dimethylaniline has toxic properties similar to those of aniline, which has a TLV of 2 ppm (~8 mg/m^3) (ACGIH, 1986). The OSHA standard for dimethylaniline is 5 ppm (~25 mg/m^3) (OSHA, 1985).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Limited evidence is available to suggest that 2,4-dimethylaniline and its hydrochloride are carcinogenic to animals. Weisburger et al. (1978) demonstrated that dietary 2,4-dimethylaniline hydrochloride caused an increased incidence of lung tumors in female CD-1 mice. No neoplastic changes of any type were observed in male CD-1 mice or male or female CD rats exposed to dietary 2,4-dimethylaniline hydrochloride. In an earlier report by Russfield et al. (1973) (abstract only), increased incidence of fibrosarcomas or subcutaneous fibromas and an increase in hepatomas were reported in male Charles River rats fed unspecified concentrations of 2,4-dimethylaniline for 2 years. This study was reported in abstract form, and further details could not be located in the available literature.

A number of investigators have reported that 2,4-dimethylaniline is mutagenic to S. typhimurium strain TA100, but only in the presence of S-9 (Chung et al., 1981; Zimmer et al., 1980; Nohmi et al., 1983, 1984). Negative results were obtained with S. typhimurium strains TA98 and TA1537, regardless of the presence of S-9 (Zimmer et al., 1980; Nohmi et al., 1984). Nohmi et al. (1983) identified the mutagenic metabolite of 2,4-dimethylaniline as 2,4-dimethylphenylhydroxylamine.

Data pertaining to the teratogenicity or reproductive effects of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

Only two chronic/subchronic toxicity studies with either 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride were located. Weisburger et al. (1978) reported only neoplastic effects in Charles River rats or CD-1 mice fed 2,4-dimethylaniline hydrochloride for 18 months, followed by 6 or 3

months observation, respectively. Lindstrom et al. (1963) observed a variety of adverse effects in Osborne-Mendel rats fed diets containing 375, 750, 2500, 5000 or 10,000 ppm 2,4-dimethylaniline for up to 6 months. These included dose-related significantly decreased growth at all exposure levels, significantly increased relative liver weight and kidney weight at all exposure levels, target cell anemia at all exposure levels, slight hyperkeratosis of the forestomach at 10,000 ppm and histological evidence of liver damage at 5000 and 10,000 ppm and kidney damage at 10,000 ppm.

Oral studies of $\leq$4 weeks duration have also shown that 2,4-dimethylaniline caused liver damage in rats at $\geq$20 mg/kg/day and dogs at 50 mg/kg/day, (Magnusson et al. 1971, 1979; Short et al., 1983). McLean et al. (1969) demonstrated that intravenous administration of 2,4-dimethylaniline (2.5 mmol/kg for 5 hours) had no significant effect on methemoglobin formation. Oral LD_{50} values of 470 and 250 mg/kg 2,4-dimethylaniline have been reported for male rats and mice (sex not reported), respectively (Vernot et al., 1977).

No data are available that address the carcinogenicity of 2,4-dimethylaniline or its hydrochloride following human exposure and, according to IARC and EPA criteria, there is limited evidence that 2,4-dimethylaniline is carcinogenic to animals (see Chapter 9 for further discussion). A q_1^* can be derived for 2,4-dimethylaniline hydrochloride on the basis of an increased incidence of lung tumors in female CD-1 mice (Weisburger et al., 1978). Data, calculations and assumptions made in the estimation of these values are presented in Table 8-1. The animal q_1^* was calculated using the multistage model developed by Howe and Crump (1982). The human q_1^* for 2,4-dimethylaniline hydrochloride is 5.8×10^{-1} $(mg/kg/day)^{-1}$. The concentrations in water associated with increased lifetime risk at levels of

TABLE 8-1

Derivation of a q_1^* for 2,4-Dimethylaniline Hydrochloride

Reference: Weisburger et al., 1978

Species/strain/sex: mouse/CD-1/female

Route/vehicle: oral/diet

le = 18 months

Le = 21 months

L = 24 months

bw = 0.03 kg (assumed)

Tumor site and type: lung tumors (unspecified)

Exposure (ppm)	Transformed Dose† (mg/kg/day)	Incidence
0	0	5/22 (matched)
125	13.9	5/18
250	27.9	11/19

†Exposure x 0.13 x 18/21 = transformed dose, where 0.13 is the reference food factor for mice

animal $q_1^* = 3.3422795 \times 10^{-2}$ $(mg/kg/day)^{-1}$

human q_1^* = animal $q_1^* \times (70\ kg/0.03\ kg)^{1/3} \times (L/Le)^3 =$
5.7978667×10^{-1} $(mg/kg/day)^{-1}$

10^{-5}, 10^{-6} and 10^{-7} are $6x10^{-4}$, $6x10^{-5}$ and $6x10^{-5}$ mg/ℓ, assuming that a 70 kg man consumes 2 ℓ water/day. An equivalent human q_1^* for 2,4-dimethylaniline of $7.5x10^{-1}$ $(mg/kg/day)^{-1}$ can be calculated by multiplying the human q_1^* for the hydrochloride by the ratio of the molecular weight of 2,4-dimethylaniline hydrochloride to the molecular weight of 2,4-dimethylaniline [i.e., 157.66/121.18 x $5.8x10^{-1}$ $(mg/kg/day)^{-1}$ = $7.5x10^{-1}$ $(mg/kg/day)^{-1}$]. The water concentrations associated with increased risk levels of 10^{-5}, 10^{-6} and 10^{-7} are $5x10^{-4}$, $5x10^{-5}$ and $5x10^{-6}$ mg/ℓ, respectively.

9. REPORTABLE QUANTITY

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Chronic studies of the nonneoplastic toxicity of 2,4-dimethylaniline or 2,4-dimethylaniline hydrochloride could not be located in the available literature as cited in the Appendix. Subchronic and shorter-term oral studies, which were discussed in Section 5.5. and reported liver and kidney pathology and body weight changes in rats and dogs, were available and are summarized in Table 9-1. Although the studies by Short et al. (1983) and Magnussen et al. (1971, 1979) are relatively short-term, it is appropriate to consider them for RQ derivation because effects similar to those observed in the longer-term study by Lindstrom et al. (1963) were also seen at similar or lower doses in the short-term studies. As seen from Table 9-1, these effects include anemia, increased relative liver and kidney weights, decreased body weight gain and weight loss, histopathological changes in the kidney or liver, and clinical evidence of liver damage and impaired function.

Of these effects, the one that would warrant the highest RV_e is the impaired liver function, as evidenced by increased BSP retention time. This effect occurred in dogs treated with 50 mg/kg/day (equivalent human dose of 27 mg/kg/day) along with weight loss, general unthrifty appearance and fatty degeneration of the liver. The RV_e associated with such effects is 7 (Table 9-2). Multiplying the equivalent human dose by 70 kg and dividing by an uncertainty factor of 10 because the study is less than chronic, results in an MED of 189 mg/day, which corresponds to an RV_d of 2.1. Multiplying the RV_d by the RV_e results in a CS of 14.7, which corresponds to an RQ of 1000.

TABLE 9-1

Oral Toxicity Summary for 2,4-Dimethylaniline

Species/ Strain	Sex	No. at Start	Average Weight (kg)[a]	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Rat/ Osborne-Mendel	M,F	10M, 10F	0.24 (M) 0.13 (F)	diet	NR	375 ppm for 3 or 6 months	18.75[c]	2.8 (M) 2.3 (F)	Anemia, increased relative liver and kidney weights	Lindstrom et al., 1963
Rat/ Osborne-Mendel	M,F	10M, 10F	0.24 (M) 0.13 (F)	diet	NR	750 ppm for 3 or 6 months	37.5[c]	5.7 (M) 4.6 (F)	Anemia, increased relative liver and kidney weights	Lindstrom et al., 1963
Rat/ Osborne-Mendel	M,F	10M, 10F	0.19 (M) 0.11 (F)	diet	NR	2500 ppm for 3 or 6 months	125[c]	17.3 (M) 14.5 (F)	Anemia, increased relative liver and kidney weights; significantly decreased body weight	Lindstrom et al., 1963
Rat/ Osborne-Mendel	M,F	10M, 10F	0.17 (M) 0.09 (F)	diet	NR	5000 ppm for 3 or 6 months	250[c]	33.6 (M) 27.2 (F)	Anemia, increased relative liver and kidney weights; significantly decreased body weight; liver cholangiofibrosis, bile duct proliferation, hepatocellular necrosis	Lindstrom et al., 1963
Rat/ Osborne-Mendel	M,F	10M, 10F	0.10 (M) 0.07 (F)	diet	NR	10,000 ppm for 3 or 6 months	500[c]	56.3 (M) 50.0 (F)	In addition to all of the above, kidney lesions consisting of cortical atrophy, interstitial fibrosis, chronic inflammation, edema, case formation, necrosis and repair	Lindstrom et al., 1963
Rat/ Fischer-344	M	30	~0.19	gavage without vehicle	98.7%	117 mg/kg/day for 5, 10 or 20 days	117	16.3	Significantly decreased body weight; significantly increased mean absolute liver and kidney weights; liver lesions consisting of cloudy swelling, diffuse necrosis degeneration and bile duct proliferation	Short et al., 1983

TABLE 9-1 (cont.)

Species/ Strain	Sex	No. at Start	Average Weight (kg)[a]	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)[b]	Response	Reference
Rat/ Sprague-Dawley	M,F	5M, 5F	~0.3 (M) ~0.25 (M)	gavage in saline	NR	400 mg/kg/day for 1 week, 500 mg/kg/day for 3 weeks (TWA = 475 mg/kg/day)	475	77.2 (M) 72.6 (F)	Significantly decreased body weight, enlarged liver, increase absolute and relative liver weight	Magnussen et al., 1979
Rat/ Sprague-Dawley	M,F	5M, 5F/ group	~0.3	gavage, vehicle NR	NR	20, 100 or 600 mg/kg/day for 4 weeks	20, 100 or 600	3.2, 16.2 or 97.5	At 600 mg/kg/day, 6/10 deaths, decreased body weight, hemoglobin levels and hematocrit, liver lesions (necrosis and vacuolization) at ≥20 mg/kg/day, increased relative liver weight and decreased ornithine carbamyl transferase level	Magnussen et al., 1971
Dog/ beagle	M,F	1M, 1F/ group	~11	capsule	NR	2, 10 or 50 mg/kg/day for 4 weeks	2, 10 or 50	27/10	At 50 mg/kg/day, weight loss and unthriftiness, enlarged liver, fatty degeneration of hepatocytes, increased BSP retention; at ≥10 mg/kg/day, vomiting after dosing	Magnussen et al., 1971

[a]Average weight was estimated from data provided by the investigators. For the study by Lindstrom et al. (1963), weight gain at 26 weeks was added to initial weight of 45 g and divided by 2.

[b]Calculated by multiplying the animal dose by the cube root of the ratio of the animal body weight to the human body weight

[c]Calculated by assuming that a rat consumes a daily amount of food equal to 5% of its body weight

NR = Not reported

TABLE 9-2

Oral Composite Scores for 2,4-Dimethylaniline

Species	Animal Dose (mg/kg/day)	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	18.75	16	3.7	Anemia; increased kidney and liver weights; no histopathological changes in liver or kidney	4	14.8	1000	Lindstrom et al., 1963
Rat	250	190	2.1	Histopathological evidence of liver and kidney damage including necrosis; anemia; increased kidney and liver weights; decreased body weight	6	12.6	1000	Lindstrom et al., 1963
Dog	50	189	2.1	Impaired liver function, fatty degeneration of hepatocytes, enlarged liver, weight loss	7	14.7	1000	Magnussen et al., 1971

*The doses were divided by an uncertainty factor of 10 to approximate chronic exposure

The next most serious effects are the histopathological lesions in the liver and kidney, which would warrant an RV_e of 6. The lowest equivalent human dose at which liver necrosis was observed is 27.2 mg/kg/day [5000 ppm group of female rats in the study by Lindstrom et al. (1963)]. Multiplying by 70 kg and dividing by an uncertainty factor of 10 results in an MED of 190 mg/day, corresponding to an RV_d of 2.1. Although the RV_d is the same as that of impaired liver function, a more serious effect, in the study by Magnussen et al. (1971), it is appropriate to calculate a CS for liver damage in rats in the Lindstrom et al. (1963) study because it was a longer-term study and employed greater numbers of animals. Multiplying the RV_d of 2.1 by the RV_e of 6 results in a CS of 12.6, which corresponds to an RQ of 1000.

Anemia, increased liver and kidney weights, reduced body weight gain, and hepatocellular hyperplasia and bile duct proliferation all occurred in rats treated at a dietary level of 2500 ppm (equivalent human dose = 14.5 mg/kg/day). Increased relative liver weight and ornithine carbamyl transferase, which represents clinical evidence of liver damage, occurred in rats treated with 20 mg/kg/day (equivalent human dose = 3.2 mg/kg/day). These effects warrant an RV_e of 4. An RV_e, however, could also be assigned to anemia and liver and kidney weight increases alone, which occurred at 375 ppm (equivalent human dose of 2.3 mg/kg/day). Multiplying 2.3 mg/kg/day by 70 kg and dividing by an uncertainty factor of 10 results in an MED of 16 mg/day, which corresponds to an RV_d of 3.7. The CS is 14.8, which corresponds to an RQ of 1000.

As seen from Table 9-2, all the CSs correspond to RQs of 1000. The highest CS, however, was obtained using data for increased liver and kidney weights and anemia in rats in the 6-month study by Lindstrom et al. (1963) (Table 9-3).

TABLE 9-3

2,4-Dimethylaniline

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

Route:	oral
Dose*:	16 mg/day
Effect:	anemia; increased liver and kidney weights
Reference:	Lindstrom et al., 1963
RV_d:	3.7
RV_e:	4
Composite Score:	14.8
RQ:	1000

*Equivalent human dose

If it is assumed that the toxicity of 2,4-dimethylaniline hydrochloride is similar to that of 2,4-dimethylaniline at equivalent doses corrected for molecular weight differences, an RQ for 2,4-dimethylaniline hydrochloride can be derived using the same data. Multiplying the MED of 2,4-dimethylaniline of 16 mg/day by 157.66/121.18 results in an MED for the hydrochloride of 21 mg/day, which corresponds to an RV_d of 3.5. Multiplying the RV_d of 3.5 by the RV_e of 4 results in a CS of 14, which corresponds to an RQ of 1000 (Table 9-4).

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

Weisburger et al. (1978) demonstrated that dietary 2,4-dimethylaniline hydrochloride caused an increased incidence of lung tumors in female CD-1 mice. No neoplastic changes of any type were observed in male CD-1 mice or CD rats of either sex exposed to dietary 2,4-dimethylaniline hydrochloride. Details of the Weisburger et al. (1978) study were reported in Section 5.1. Tumor incidences for female mice were summarized in Table 5-1.

In an earlier report from the same laboratory, Russfield et al. (1973) stated that a group of 50 male Charles River rats fed 2,4-dimethylaniline for 2 years had an increased incidence of fibrosarcomas or subcutaneous fibromas compared with controls (39% treated vs. 16% controls). Treated rats also had excess hepatomas. No other details were provided, and a full report of these results was not located in the available literature. Furthermore, Weisburger et al. (1973) made no mention of their earlier report.

An F factor of 1.68 $(mg/kg/day)^{-1}$ can be derived for 2,4-dimethylaniline hydrochloride from the study of Weisburger et al. (1978) on the basis of increased incidence of lung tumors in female CD-1 mice. Data, calculations and assumptions made in the estimation of these values are presented

TABLE 9-4

2,4-Dimethylaniline Hydrochloride

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

Route:	oral
Dose[a]:	21 mg/day[b]
Effect:	anemia; increased liver and kidney weights
Reference::	Lindstrom et al., 1963
RV_d:	3.5
RV_e:	4
Composite Score:	14
RQ:	1000

---

[a]Equivalent human dose

[b]The compound administered was 2,4-dimethylaniline

in Table 9-5. The unadjusted $1/ED_{10}$ was derived using the multistage model developed by Howe and Crump (1982). An equivalent F factor of 2,4-dimethylaniline of 2.19 $(mg/kg/day)^{-1}$ can be calculated by multiplying the F factor for the hydrochloride by the ratio of the molecular weights 2,4-dimethylaniline hydrochloride to 2,4-dimethylaniline as follows: $157.66/121.18 \times 1.68\ (mg/kg/day)^{-1} = 2.19\ (mg/kg/day)^{-1}$.

No data arre available to determine whether 2,4-dimethylaniline or its hydrochloride are carcinogenic to humans and, according to IARC and CAG criteria, there is limited evidence that 2,4-dimethylaniline is carcinogenic to animals. Thus, 2,4-dimethylaniline and its hydrochloride can be classified in IARC Group 3 and EPA Group C. An EPA Classification of C indicates that these chemicals are possible human carcinogens (U.S. EPA, 1986a). The potency factors of 1.68 and 2.19 $(mg/kg/day)^{-1}$ fall between 1 and 100, placing these chemicals in Potency Group 2, which along with an EPA classification of Group C, place 2,4-dimethylaniline and its hydrochloride in the LOW category of the CERCLA hazard ranking scheme.

TABLE 9-5

Derivation of Potency Factor (F)
Agent: 2,4-Dimethylaniline hydrochloride

Reference:	Weisburger et al., 1978		
Exposure Route:	oral		
Species:	mouse		
Strain:	CD-1		
Sex:	female		
Vehicle or Physical State:	diet		
Body Weight:	0.03 kg		
Duration of Treatment:	18 months		
Duration of Study:	21 months		
Lifespan of Animal	24 months		
Target Organ:	lung		
Tumor Type:	lung tumors (not specified)		
Experimental Doses/Exposure (ppm):	0	125	250
Transformed Doses[a] (mg/kg/day):	0	13.9	27.9
Tumor Incidence:	5/22	5/18	11/19
Unadjusted $1/ED_{10}$:	8.4756537×10^{-2} $(mg/kg/day)^{-1}$		
$1/ED_{10}$ (F Factor)[b]:	1.68 $(mg/kg/day)^{-1}$		

[a] ppm x 0.13 x 18/21 = transformed dose (0.13 is the assumed food factor for mice)

[b] Adjusted $1/ED_{10}$ = unadjusted $1/ED_{10}$ x $(70 \text{ kg}/0.03 \text{ kg})^{1/3}$ x (lifespan of mouse/duration of study)^3

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. Threshold limit values for chemical substances in the workroom environment adopted by ACGIH with intended changes for 1985-1986. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH. p. 637.

Amoore, J.E. and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6): 272-290.

Atkinson, R. 1985. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem. Rev. 85: 69-201.

Baird, R., L. Carmona and R.L. Jenkins. 1977. Behavior of benzidine and other aromatic amines in aerobic wastewater treatment. J. Water Pollut. Control Fed. 49: 1609-1615.

Batterton, J., K. Winters and C. Van Baalen. 1978. Anilines: Selective toxicity to blue-green algae. Science. 199(4333): 1068-1070.

Bollag, J.M., P. Blattmann and T. Laanio. 1978. Adsorption and transformation of four substituted anilines in soil. J. Agric. Chem. 26: 1302-1306.

Bringmann, G. and R. Kuehn. 1977. Results of the damaging effect of water pollutants on Daphnia magna. Z. Wasser Abwasser Forsch. 10(5): 161-166. (Ger.)

Bringmann, G. and R. Kuehn. 1978. Limiting values for the noxious effects of water pollutant material to blue algae (Microcystis aeruginosa) and green algae (Scenedesmus quadricauda) in cell propagation inhibition tests. Vom Wasser. 50: 45-60. (Ger.)

Bringmann, G. and R. Kuehn. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae and protozoa in the cell multiplication inhibition test. Water Res. 14(3): 231-241.

Bringmann, G. and R. Kuehn. 1981. Comparison of the effect of harmful substances on flagellates and ciliates as well as on bacteriovorous and saprozoic protozoans. Gas-Wasserfach: Wasser/Abwasser. 122(7): 308-313. (Ger.)

Bringmann, G. and R. Kuehn. 1982. Results of toxic action of water pollutants on Daphnia magna Straus tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1): 1-6. (Ger.)

Chao, J., C.T. Lin and T.H. Chung. 1983. Vapor pressure of coal chemicals. J. Phys. Chem. Ref. Data. 12: 1033-1063.

Chung, K., G.E. Fulk and A.W. Andrews. 1981. Mutagenicity testing of some commonly used dyes. Appl. Environ. Microbiol. 42: 641-648.

Cupitt, L.T. 1980. Fate of toxic and hazardous materials in the air environment. ESRL, ORD, U.S. EPA, Research Triangle Park, NC. EPA 600/3-80-084. NTIS PB 80-221948.

Gomez, A., J. Mullens and P. Huyskens. 1972. Specific interactions of anilines with water. J. Phys. Chem. 76(26): 4011.

Gutsche, C.D. and D.J. Pasto. 1975. Fundamentals of Organic Chemistry. Prentice-Hall, Inc., Englewood Cliffs, NJ. p. 315-318.

Harris, L.R., J.A. Gideon, S. Berardinelli, et al. 1980. Coal liquefaction: Recent findings in occupational safety and health. Am. Ind. Hyg. Assoc. J. 41(8).

Hawthorne, S.B., R.E. Kievers and R.M. Barkley. 1985. Organic emissions from shale oil wastewaters and their implications for air quality. Environ. Sci. Technol. 19(10): 992-997.

Howe, R.B. and K.S. Crump. 1982. GLOBAL 82. A Computer Program to Extrapolate Quantal Animal Toxicity Data to Low Doses. Prepared for Office of Carcinogen Standards. OSHA, U.S. Dept. of Labor under Contract No. 41USC252C3.

IARC (International Agency for Research on Cancer). 1978. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some aromatic amines and related nitro compounds -- hair dyes, colouring agents and miscellaneous industrial chemicals. WHO, IARC, Lyon, France. Vol 16. p. 367-376.

Juhnke, I. and D. Luedemann. 1978. Results of the study of 200 chemical compounds on acute fish toxicity using the golden orfe test. Z. Wasser Abwasser Forsch. 11(5): 161-164. (Ger.)

Kawasaki, M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxicol. Environ. Safety. 4: 444-454.

Kitano, M. 1978. Biodegradation and bioaccumulation test on chemical substances. OECD Tokyo meeting. Reference book TSU-No. 3.

Lammerding, A.M., N.J. Bunce, R.L. Merrick and C.T. Corke. 1982. Structural effects on the microbial diazotization of anilines. J. Agric. Food Chem. 30(4): 644-647.

Lindstrom, H.V. 1961. The metabolism of FD&C Red No. 1. I. The fate of 2,4-meta-xylidine in rats. J. Pharmacol. Exp. Ther. 132: 306-310.

Lindstrom, H.V., W.H. Hansen, A.A. Nelson and O.G. Fitzhugh. 1963. The metabolism of FD&C Red No. 1. II. The fate of 2,4-para-xylidine and 2,6-meta-xylidine in rats and observations on the toxicity of xylidine isomers. J. Pharmacol. Exp. Ther. 142: 257-264.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. p. 5-5, 5-16.

MacLean, S., G.A. Starmer and J. Thomas. 1969. Methemoglobin formation by aromatic amines. J. Pharm. Pharmacol. 21(7): 441-450.

Magnusson, G., N.O. Bodin and E. Hansson. 1971. Hepatic changes in dogs and rats induced by xylidine isomers. Acta. Pathol. Microbiol. Scand. 79(6): 639-648.

Magnusson, G., S.K. Majeed, W.H. Down, R.M. Saccharin and W. Jorgeson. 1979. Hepatic effects of xylidine isomers in rats. Toxicology. 12(1): 63-74.

Meallier, P. 1969. Kinetic study of the photochemical oxidation of simple aromatic amines. Ann. Chim. 4: 15-28.

Nohmi, T., R. Miyata, K. Yoshikawa, M. Nakadate and M. Ishidate, Jr. 1983. Metabolic activation of 2,4-xylidine and its mutagenic metabolite. Biochem. Pharmacol. 32(4): 735-738.

Nohmi, T., R. Miyata, K. Yoshikawa, M. Nakadate and M. Ishidate. 1984. Mutations in Salmonella typhimurium and inactivation of Bacillus subtilis transforming DNA induced by phenylhydroxylamine derivatives. Mutat. Res. 136: 159-168.

Northcott, J. 1978. Aniline and its derivatives. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 3, 2nd ed. John Wiley and Sons, New York. p. 317.

OSHA (Occupational Safety and Health Administration). 1985. Permissible Exposure Limits. Code of Federal Regulations. 29: 1910.1000.

Paris, G.E. 1980. Covalent binding of aromatic amines to humates. 1. Reactions with carbonyls and quinones. Environ. Sci. Technol. 14: 1099-1106.

Patrianakos, C. and D. Hoffmann. 1979. Chemical studies on tobacco smoke: 64. Analysis of aromatic amines in cigarette smoke. J. Anal. Toxicol. 3(4): 150-154.

Pereira, W.E., C.E. Rostad, J.R. Garbarino and M.F. Hult. 1983. Groundwater contamination by organic bases derived from coal-tar wastes. Environ. Toxicol. Chem. 2(3): 283-294.

Pouyet, B. and P. Meallier. 1967. Kinetics of oxygen absorption by some simple aromatic amines under the action of ultraviolet rays. C.R. Acad. Sci., Paris, Ser. C. 264: 1440-1443.

Russfield, A.B., E. Boger, F. Homburger, E.K. Weisburger and J.H. Weisburger. 1973. Effect of structure on 7 methyl anilines on toxicity and on incidence of subcutaneous and liver tumors in Charles River rats. Fed. Proc. 32: 833. (Abstract No. 3467)

Sandridge, R.L. and H.B. Staley. 1978. Amines by reduction. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol: 3, 2nd ed. John Wiley and Sons, Inc., New York. p. 365.

Seiler, J.P. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. Mutat. Res. 46: 305-310.

Short, C.R., C. King, P.W. Sistrunk and K.M. Kerr. 1983. Subacute toxicity of several ring-substituted dialkylanilines in the rat. Fund. Appl. Toxicol. 3(4): 285-292.

SRI (Stanford Research Institute). 1985. 1985 Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 963.

U.S. EPA. 1977. Computer print-out of non-confidential production data from TSCA inventory. OPTS, CID, U.S. EPA, Washington, DC.

U.S. EPA. 1984. TSCA/ITC (Toxic Substances Control Act/Interagency Testing Committee) Information Review: Xylidines. IR Number 410. TSCA/ITC, Washington, DC.

U.S. EPA. 1986a. Guidelines for Carcinogenic Risk Assessment. Federal Register. 51(185): 33990-34003.

U.S. EPA. 1986b. SANSS (Structure and Nomenclature Search System). On-line: April, 1986.

USITC (U.S. International Trade Commission). 1984. Imports of Benzenoid Chemicals and Products, 1983. USITC Publ. 1548, Washington, DC. p. 30.

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. United States Production and Sales, 1984. USITC Publ. 1745, Washington, DC. p. 48.

Vernot, E.H., J.D. MacEwen, C.C. Haun and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. p. 417-424.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 3rd ed. Van Nostrand Reinhold Co., New York. p. 546.

Weast, R.C., Ed. 1980. CRC Handbook of Chemistry and Physics, 61st ed. CRC Press, Inc., Boca Raton, FL. p. C-634.

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor pressure distribution of selected organic chemicals. EPA 600/2-81-021. 39 p.

Weisburger, E.K., A.B. Russfield, F. Homburger, et al. 1978. Testing of twenty-one environmental aromatic amines of derivative for long-term toxicity or carcinogenicity. J. Environ. Pathol. Toxicol. 2(2): 325-356.

Winters, K., J.C. Batterton and C. Van Baalen. 1977. Phenalene-1-one: Occurrence in a fuel oil and toxicity to microalgae. Environ. Sci. Technol. 11(3): 270-272.

Zepp, R.G. and P.F. Schlotzhauer. 1983. Influence of algae on photolysis rates of chemicals in water. Environ. Sci. Technol. 17: 462-468.

Zimmer, D., J. Mazurek, G. Petzold and B.K. Bhuyan. 1980. Bacterial mutagenicity and mammallian cell DNA damage by several substituted anilines. Mutat. Res. 77(4): 317-326.

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

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Jaber, H.M., W.R. Mabey, S.T. Liu, T.W. Chow and H.L. Johnson. 1984. Data aquisition for environmental transport and fate screening for compounds of interest in the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

U.S. EPA. 1986. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

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

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.