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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR TRICHLOROANILINES

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

Prepared by

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under 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 for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval, for example, one that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. A carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided instead. 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 the 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). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer-based RQs are defined in U.S. EPA, 1984a and 1986a, respectively.

EXECUTIVE SUMMARY

2,3,4-Trichloroaniline, 2,4,5- and 2,4,6-trichloroaniline exist in the solid phase at room temperature (Dean, 1985). Aromatic amines are usually weaker bases than aliphatic amines but undergo many similar reactions (Northcott, 1978). CMR (1986) lists four suppliers for 2,4,5-trichloroaniline and two suppliers each for 2,3,4- and 2,4,6-trichloroaniline. The U.S EPA TSCA Production File (U.S. EPA, 1977) contains production data on 2,4,5- and 2,4,6-trichloroaniline, but contains no information on 2,3,4-trichloroaniline. Domestic production volume data for recent years could not be located in the available literature as cited in Appendix A. During 1983, 807 pounds of 2,4,5-trichloroaniline was imported through principal U.S. customs districts (USITC, 1984). 2,4,6-Trichloroaniline is used as an intermediate in the manufacture of benzene derivatives, including 1,3,5-trichlorobenzene, in the formulation of a fungicide and in the preparation of hexachlorodiphenyl urea (Mitchell et al., 1984). It may also be used as a dye and pigment intermediate (Society of Dyers and Colorist, 1971).

Trichloroanilines are weak bases and as such, may be protonated under acidic conditions and form salts that are more water soluble than the parent compound. Variations in the behavior of trichloroanilines may result from protonation. In air, these compounds are expected to exist almost entirely in the vapor phase (Eisenreich et al., 1981). The estimated half-life for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline vapor reacting with photochemically generated hydroxyl radicals in the atmosphere is ~3 weeks at 25°C (U.S. EPA, 1987). Trichloroanilines also have the potential to undergo direct photolysis in the atmosphere. Small amounts of these compounds may be removed from the atmosphere by wet deposition. Reaction with ozone is

not likely to be environmentally relevant (U.S. EPA, 1987). In water, trichloroanilines are not expected to hydrolyze, oxidize or bioaccumulate significantly in aquatic organisms. Photolysis, physical adsorption to suspended solids and sediments, and volatilization should be important removal processes. The photolysis half-life of 2,4,6-trichloroaniline in a surface water exposed to mid-June sunlight was <1 day (Dennis et al., 1983). The half-life for 2,4,6-trichloroaniline volatilization from water 1 m deep, flowing at a speed of 1 m/sec, with a wind speed of 3 m/sec has been estimated to be ~19 days at 20°C (see Section 2.2.7.). Results of a few biodegradation screening studies indicate that trichloroanilines may not be readily susceptible to biodegradation and that the acclimation period before biodegradation may be 20-27 days (Mitchell et al., 1984; Freitag et al., 1985; Janicke and Hilge, 1980). In soil, it appears that trichloroanilines may be immobilized by both physical adsorption and covalent binding, although some mobilization may occur in acidic soils from protonation. Lack of data precludes the possibility of predicting the importance of chemical and microbial degradation processes in the environment. Volatilization from wet and dry soil surfaces is not expected to be significant.

Trichloroanilines may be released to the environment in the effluent from user facilities (Ellis et al., 1982). They may be formed as a result of chlorinating wastewaters that contain aniline (Mitchell et al., 1984) or as a metabolite of microbial degradation of various phenylurea and phenylcarbamate herbicides (Hwang et al., 1985). 2,4,5-Trichloroaniline and 2,4,6-trichloroaniline were identified in drinking water and in effluents from advanced wastewater treatment plants in several cities in the United States (Lucas, 1984); however, there were no quantitative data in the literature from which to estimate daily human exposure to the compounds through the consumption of drinking water.

There was little information available concerning toxicity of trichloroanilines to aquatic organisms. The lowest reported toxic concentration was 0.8 mg/ℓ 2,3,4-trichloroaniline, a 96-hour LC_{50} for sand shrimp, Crangon septimspinosa (McLeese et al., 1979). A study in which Photobacterium phosphoreum was exposed to four trichloroaniline isomers indicated that 2,4,5-trichloroaniline was most toxic, followed by 2,3,4-trichloroaniline, 3,4,5-trichloroaniline and 2,4,6-trichloroaniline, which was least toxic (Devillers et al., 1986).

Pertinent data regarding the absorption, distribution, metabolism or excretion of 2,3,4-, 2,4,5- of 2,4,6-trichloroaniline could not be located in the available literature as cited in Appendix A.

Administration of 2,4,6-trichloroaniline to rats by gavage at doses of 160 or 800 mg/kg/day for 45 days, or 4 or 40 mg/kg, 5 days/week for 6 months, produced a variety of effects, which include methemoglobinemia, gross hemorrhagic/degenerative alterations in the circulatory system and altered liver enzyme activities (Sapegin et al., 1985). Also, embryotoxicity was reported at 4 mg/kg, and histological alterations in the testes were reported at 800 mg/kg. The validity of these findings is uncertain, however, because of inadequate reporting and discrepancies.

2,4,6-Trichloroaniline hydrochloride was administered to male rats in the diet at TWA concentrations of 1917 and 3833 ppm for 18 months followed by 6 months observation without histopathological effects (Weisburger et al., 1978). Dietary administration of 6000 or 12,000 ppm 2,4,6-trichloroaniline hydrochloride to mice for 18 months followed by 3 months observation produced a dose-related, statistically significant increase in the incidence of vascular tumors in male mice (Weisburger et al., 1978); histopathological effects did not occur in similarly treated females.

Equivocal results were reported for 2,4,6-trichloroaniline in mutagenicity assays with bacteria (Zimmer et al., 1980; Shimizu and Takemura, 1984). Chromosomal aberrations occurred in the bone marrow cells of rats exposed by gavage to 40 mg/kg 2,4,6-trichloroaniline, 5 days/week for 6 months (Sapegin et al., 1985).

Information regarding the toxic or carcinogenic effects of 2,3,4- or 2,4,5-trichloroaniline could not be located in the available literature as cited in Appendix A.

Because 2,4,6-trichloroaniline hydrochloride induced tumors in one sex of one species (limited evidence) in the Weisburger et al. (1978) study, 2,4,6-trichloroaniline and its hydrochloride are classified in the EPA's Group C weight of evidence category for carcinogenicity.

Values for q_1*s for oral exposure of 2.9×10^{-2} $(mg/kg/day)^{-1}$ 2,4,6-trichloroaniline hydrochloride and 3.4×10^{-2} $(mg/kg/day)^{-1}$ 2,4,6-trichloroaniline were calculated based on the dose-response data for vascular tumors in male mice. Increased lifetime risk of cancer at risk levels of 10^{-5}, 10^{-6} and 10^{-7} are associated with drinking water levels of 1.2×10^{-2}, 1.2×10^{-3} and 1.2×10^{-4} mg/ℓ for 2,4,6-trichloroaniline hydrochloride and 1.0×10^{-2}, 1.0×10^{-3} and 1.0×10^{-4} mg/ℓ for 2,4,6-trichloroaniline. F factors of 1.82×10^{-1} $(mg/kg/day)^{-1}$ for 2,4,6-trichloroaniline hydrochloride and 2.16×10^{-1} $(mg/kg/day)^{-1}$ for 2,4,6-trichloroaniline were also calculated, placing these chemicals in Potency Group 3, which combined with an EPA Group C classification gives these chemicals a LOW Hazard Ranking under CERCLA. The RQ based on carcinogenicity is, therefore, 100 pounds.

Data were inadequate to derive chronic toxicity RQs for 2,4,6-trichloroaniline and its hydrochloride and to derive any q_1*s, RfDs or RQs for the other isomers.

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF TABLES

LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
EC_{50}	Concentration effective to 50% of recipients
FEL	Frank effect level
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

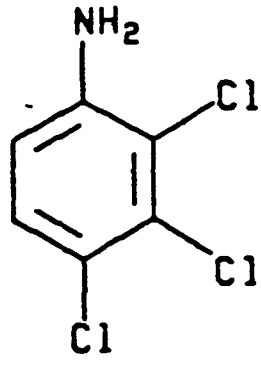
The synonyms, structures and CAS Registry numbers for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline are as follows:

2,3,4-Trichloroaniline

CAS Registry number: 634-67-3

Synonyms: 2,3,4-trichlorobenzenamine; 2,3,5-trichlorophenylamine; 1-amino-2,3,4-trichlorobenzene

Structure:

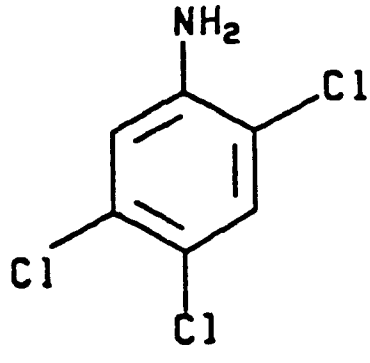


2,4,5-Trichloroaniline

CAS Registry number: 636-30-6

Synonyms: 2,4,5-trichlorobenzenamine; 2,4,5-trichlorophenylamine; 1-amino-2,4,5-trichlorobenzene

Structure:

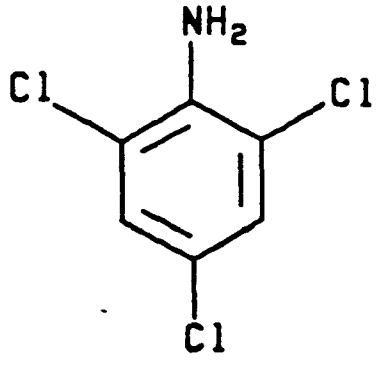


2,4,6-Trichloroaniline

CAS Registry number: 634-93-5

Synonyms: sym-trichloroaniline; 2,4,6-trichlorobenzenamine; 2,4,6-trichlorophenylamine; 1-amino-2,4,6-trichlorobenzene

Structure:



All of the trichloroaniline isomers have a molecular weight of 196.46 and the empirical formula $C_6H_4Cl_3N$.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The selected trichloroaniline isomers are solids at room temperature (Dean, 1985). 2,3,4-Trichloroaniline is soluble in alcohol and 2,4,5-trichloroaniline is soluble in alcohol and ether (Weast, 1985). Aromatic amines are usually weaker bases than aliphatic amines but undergo many similar reactions (Northcott, 1978). Amines can be readily converted to their salts by aqueous mineral acids or carboxylic acids, and aqueous hydroxyl ions can readily convert these salts back to the free amine (Morrison and Boyd, 1973). When heated to decomposition, trichloroanilines are expected to emit toxic chlorine and NO_x fumes (Sax, 1984). Physical properties for the selected trichloroaniline isomers are listed in Table 1-1.

TABLE 1-1

Physical Properties of Selected Trichloroaniline Isomers

Isomer	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Log K_{ow}	Water Solubility (mg/ℓ)
2,3,4-Trichloroaniline	67.5[a]	291[a]	1.7×10^{-3} (25°C)[b]	3.33[d]	207 (25°C)[e]
2,4,5-Trichloroaniline	93-95[a]	270[a]	3.55×10^{-3} (25°C)[b]	3.45[d]	157 (25°C)[e]
2,4,6-Trichloroaniline	73-75[a]	262[a]	9.3×10^{-3} (25°C)[b] 3.2×10^{-4} (20.5°C)[c]	3.52[d]	134 (25°C)[e] 32 (19°C)[c]

[a]Dean, 1985

[b]Estimated by the method of Neely and Blau (1985)

[c]Dennis et al., 1983

[d]Hansch and Leo, 1985

[e]Estimated using the equation, $\log 1/S = 0.996 \log K_{ow} - 0.339$ (Lyman et al., 1982), where S is in mol/ℓ

1.3. PRODUCTION DATA

Halogenated anilines are usually produced by the reduction of the corresponding nitro compounds with iron and hydrochloric acid (Kouris and Northcott, 1963). 2,4,6-Trichloroaniline can be produced from aniline vapor and chlorine in the presence of hydrogen chloride in an anhydrous organic solvent (Northcott, 1978). The U.S. EPA TSCA Production File (U.S. EPA, 1977) contains no production data on 2,3,4-trichloroaniline; data for the other two trichloroaniline isomers are given in Table 1-2.

CMR (1986) lists four suppliers for 2,4,5-trichloroaniline and two suppliers each for 2,3,4- and 2,4,6-trichloroaniline. Domestic production volume data for recent years could not be located in the available literature as cited in Appendix A. During 1983, 807 pounds of 2,4,5-trichloroaniline was imported through principal U.S. customs districts (USITC, 1984).

1.4. USE DATA

2,4,6-Trichloroaniline is used as an intermediate in the manufacture of benzene derivatives, including 1,3,5-trichlorobenzene, in the formulation of a fungicide and in the preparation of hexachlorodiphenyl urea (Mitchell et al., 1984). Trichloroanilines may also be used as dye and pigment intermediates (Society of Dyers and Colourists, 1971; Dao et al., 1986).

1.5. SUMMARY

2,3,4-Trichloroaniline, 2,4,5- and 2,4,6-trichloroaniline exist in the solid phase at room temperature (Dean, 1985). Aromatic amines are usually weaker bases than aliphatic amines but undergo many similar reactions (Northcott, 1978). CMR (1986) lists four suppliers for 2,4,6-trichloroaniline and two suppliers each for 2,3,4- and 2,4,6-trichloroaniline. The U.S. EPA TSCA Production File (U.S. EPA, 1977) contains production data on

TABLE 1-2

1977 Production Data for 2,4,5- and 2,4,6-Trichloroaniline[a]

Isomer	Company/Location	Production/Import Volume (million pounds)
2,4,5-Trichloroaniline	American Hoecht Corp. (Importer) Bridgewater, NJ	confidental
	Confidential (Importer)	0.001-0.010
2,4,6-Trichloroaniline	Tennessee Eastman Co. Kingsport, TN	0.200-2.000 (half of the total for site limited use)
	Columbia Organic Chemicals Co. Columbia, SC	<0.001
	The Upjohn Co. North Haven, CT	confidential
	Aceto Chemical Co. Flushing, NY	<0.001 (site limited use)
	Fike Chemicals Inc. Nitro, WV	none[b]
	Plastifax, Inc. Gulfport, MI	confidential
	Carroll Products, Inc. (Importer) Wood River Junction, RI	none[b]
	Chemical Systems Division Santa Clara, CA	0.010-0.100 (site limited use)

TABLE 1-2 (cont.)

Isomer	Company/Location	Production/Import Volume (million pounds)
2,4,6-Trichloroaniline	Drake Chemicals Inc. Lock Haven, PA	confidential
	ICC Industries, Inc. (Importer) New York, NY	<0.001
	Confidential	0.001-0.01

[a]Source: U.S. EPA, 1977

[b]This company has the potential to produce/import this compound.

2,4,5- and 2,4,6-trichloroaniline, but contains no information on 2,3,4-trichloroaniline. Domestic production volume data for recent years could not be located in the available literature as cited in Appendix A. During 1983, 807 pounds of 2,4,5-trichloroaniline was imported through principal U.S. customs districts (USITC, 1984). 2,4,6-Trichloroaniline is used as an intermediate in the manufacture of benzene derivatives, including 1,3,5-trichlorobenzene, in the formulation of a fungicide and in the preparation of hexachlorodiphenyl urea (Mitchell et al., 1984). It may also be used as a dye and pigment intermediate (Society of Dyers and Colourists, 1971).

2. ENVIRONMENTAL FATE AND TRANSPORT

Trichloroanilines are weak bases that may be protonated under acidic conditions to form salts at pH values related to their pKa values. These salts are much more water soluble than the parent compound. Protonation can alter the behavior of a compound in water and soil, for example, by decreasing volatilization as well as increasing or decreasing adsorption to soil, sediments or suspended solids in water.

2.1. AIR

Based on the vapor pressures listed in Table 1-1, trichloroanilines are expected to exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al., 1981).

2.1.1. Reaction with Hydroxyl Radicals. The estimated half-life for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline vapor reacting with photochemically generated hydroxyl radicals in the atmosphere is ~3 weeks using an estimated reaction rate constant of 8.98×10^{-12} cm^3/molecule-sec at 25°C and an ambient hydroxyl radical concentration of 8.0×10^5 molecules/cm^3 (U.S. EPA, 1987).

2.1.2. Reaction with Ozone. Trichloroanilines are not susceptible to oxidation by ozone (U.S. EPA, 1987).

2.1.3. Photolysis. 2,4,6-Trichloroaniline that was adsorbed to silica gel underwent 39.5% degradation (based on % CO_2 evolved) when irradiated with light wavelengths >290 nm for 17 hours (Freitag et al., 1985). 2,3,4-Trichloroaniline, 2,4,5- and 2,4,6-trichloroaniline in methanol strongly absorb UV light in the environmentally significant wavelength range of >290 nm (Sadtler, 1965, 1970, 1976). These data indicate that trichloroanilines may undergo direct photolysis in the troposphere.

2.1.4. Physical Removal Processes. Based on the water solubilities listed in Table 1-1, it appears that small amounts of trichloroanilines may be removed from the atmosphere by wet deposition.

2.2. WATER

2.2.1. Hydrolysis. Since halogenated aromatics and aromatic amines are generally resistant to chemical hydrolysis (Lyman et al., 1982), trichloroanilines are also expected to be resistant to hydrolysis. 2,4,6-Trichloroaniline in distilled water under ambient conditions at pH 5, 7 and 9 remained stable to chemical hydrolysis over a 2-week period (Dennis et al., 1983).

2.2.2. Oxidation. 2,4,6-Trichloroaniline in distilled water under ambient conditions at pH 5, 7 and 9 remained stable to chemical oxidation over a 2-week period (Dennis et al., 1983).

2.2.3. Photolysis. 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline strongly absorb UV light in the environmentally significant range (wavelengths >290 nm) (Sadtler, 1965, 1970, 1976), indicating that potential exists for direct photolysis in aqueous solution for these compounds. When 78 µg/ℓ 2,4,5-trichloroaniline was added to fresh lake water samples and irradiated with 12 hours of sunlight followed by 12 hours of darkness, 28% degradation was observed in both treated and untreated water samples. No degradation was observed when samples were kept in the dark. Therefore, the estimated photolytic half-life of 2,4,5-trichloroaniline is ~2 days. Photochemical degradation products were presumed to be chloroaminophenol and catechols (Hwang et al., 1985). When a 30 mg/ℓ aqueous solution of 2,4,6-trichloroaniline was irradiated with a pyrex-filtered mercury vapor lamp, the photolysis half-life was ~7.5 hours. Exposure of the aqueous solution to bright mid-June sunlight resulted in a disappearance half-life of ~20 hours (Dennis et al., 1983). Therefore, photolysis is an important fate process for trichloroaniline.

2.2.4. Microbial Degradation. In short-term degradation studies (<3 days) with moderately eutrophic lake water, no degradation of 2,4,6-trichloroaniline was observed when the solution was kept in the dark, but 28% of the compound degraded when the solution was exposed to 12 hours of sunlight and 12 hours of darkness (Hwang et al., 1985). Based on experimental results, it was speculated that photolysis initiates transformation of 2,4,6-trichloroaniline, followed by further degradation to CO_2 by microbes and sunlight. In this study, 19% of the mineralization of the photoproducts was attributed to microbial processes (Hwang et al., 1985). Therefore, the authors concluded that 2,4,6-trichloroaniline would not biodegrade in natural water in 3 days, but it would slowly biodegrade the photodegradation products of photolysis. With contaminated surface water Mitchell et al. (1984) demonstrated that 2,4,6-trichloroaniline required an approximate 20- to 27-day lag period before degradation would be observed. A 0.4% degradation (based on % CO_2 evolved) of 0.05 mg/ℓ 2,4,6-trichloroaniline was observed after 5 days incubation in activated sludge (Freitag et al., 1985). 2,4,6-Trichloroaniline was found to be resistant to biodegradation by activated sludge (Janicke and Hilge, 1980).

2.2.5. Bioaccumulation. BCFs of 260 in algae, Chlorella fusca, and 330 in the golden ide, Leuciscus idus melanotus, have been measured for 2,4,6-trichloroaniline (Freitag et al., 1985). Based on the log K_{ow} values listed in Table 1-1, BCFs of 200, 247 and 279 were estimated for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline, respectively, using the equation log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982). These BCF values suggest that bioaccumulation of trichloroanilines in aquatic organisms would be insignificant.

2.2.6. Adsorption. In treated and untreated freshwater samples that were irradiated with sunlight, the amount of 2,4,6-trichloroaniline and its photoproducts on particles was 8.6 and 16.9%, respectively (Hwang et al., 1985). Substituted and unsubstituted aromatic amines have been found to undergo irreversible covalent binding with humic substances in aqueous solution. Although the presence of chlorine in the ortho- position to the aniline will reduce the probability of this covalent binding (Parris, 1980), a small fraction of trichloroaniline in natural water may undergo irreversible covalent binding with humic substances in these waters. Based on these observations and the estimated K_{oc} of 1540-1960 (Section 2.3.3.) physical adsorption and covalent binding to suspended solids and sediments should be significant.

2.2.7. Volatilization. Loss of 2,4,6-trichloroaniline from freshwater samples during a biodegradation screening study was attributed to volatilization. A 50% loss was observed after ~20 days (Mitchell et al., 1984). Henry's Law constant for 2,4,6-trichloroaniline has been estimated to be 2.7×10^{-6} atm-m³/mol when a vapor pressure of 3.3 mm Hg at 20.5°C and a water solubility of 32 mg/ℓ at 19°C was used (Dennis et al., 1983). Based on this value of Henry's Law constant the volatilization half-life of 2,4,6-trichloroaniline volatilizing from water 1 m deep, flowing at a speed of 1 m/sec, with a wind speed of 3 m/sec has been estimated to be ~19 days, using the method of Lyman et al. (1982). Protonation of trichloroanilines under acidic conditions would cause a decrease in the volatility of these compounds; however, it is not certain whether protonation would be significant under environmental conditions.

2.3. SOIL

2.3.1. Chemical Degradation. Pertinent data regarding the chemical degradation of trichloroanilines in soil could not be located in the available literature as cited in Appendix A.

2.3.2. Microbial Degradation. Limited data are available regarding the biodegradation of trichloroanilines in soil. 2,3,4-Trichloroaniline was transformed by purified peroxidase from an isolated soil fungus, Geotrichum candidum; however, no detectable transformation of 2,4,5- or 2,4,6-trichloroaniline was observed after 14 days. None of these compounds were transformed by purified aniline oxidase extracted from G. candidum (Bartha, 1975; Bordeleau and Bartha, 1972).

2.3.3. Adsorption. The K_{oc} values for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline were calculated to be 1540, 1790 and 1960, respectively, using the log K_{ow} values listed in Table 1-1 and the linear regression equation, $\log K_{oc} = 0.544 \log K_{ow} + 1.377$ (Lyman et al., 1982). These K_{oc} values indicate that trichloroanilines should have low mobility in soil (Swann et al., 1983). Thus, it appears that these compounds would be immobilized in soil by physical adsorption and partly by covalent binding as observed with other substituted amines (Parris, 1980).

2.3.4. Volatilization. Pertinent data regarding volatilization of trichloroanilines from soil could not be located in the available literature as cited in Appendix A. Based on the expected adsorption and covalent binding of trichloroanilines to soils (see Section 2.3.3.) and possible protonation of these compounds in acidic soils, volatilization from wet and dry soil surfaces is not expected to be significant.

2.4. SUMMARY

Trichloroanilines are weak bases and, therefore, may be protonated under acidic conditions and form salts that are more water soluble than the parent compound. Variations in the behavior of trichloroanilines may result from protonation. In air, these compounds are expected to exist almost entirely in the vapor phase (Eisenreich et al., 1981). The estimated half-life for 2,3,4-, 2,4,5- and 2,4,6-trichloroaniline vapor reacting with photochemically generated hydroxyl radicals in the atmosphere is ~3 weeks at 25°C (U.S. EPA, 1987). Trichloroanilines also have the potential to undergo direct photolysis in the atmosphere. Small amounts of these compounds may be removed from the atmosphere by wet deposition. Reaction with ozone is not likely to be environmentally relevant (U.S. EPA, 1987). In water, trichloroanilines are not expected to hydrolyze, oxidize or bioaccumulate significantly in aquatic organisms. Photolysis, physical adsorption to suspended solids and sediments, and volatilization should be important removal processes. The photolysis half-life of 2,4,6-trichloroaniline in a surface water exposed to mid-June sunlight was <1 day (Dennis et al., 1983). The half-life for 2,4,6-trichloroaniline volatilization from water 1 m deep, flowing at a speed of 1 m/sec, with a wind speed of 3 m/sec has been estimated to be ~19 days at 20°C (see Section 2.2.7.). Results of a few biodegradation screening studies indicate that trichloroanilines may not be readily susceptible to biodegradation and that the acclimation period before biodegradation may be 20-27 days (Mitchell et al., 1984; Freitag et al., 1985; Janicke and Hilge, 1980). In soil, it appears that trichloroanilines may be immobilized by both physical adsorption and covalent binding, although some mobilization may occur in acidic soils because of protonation.

Lack of data precludes the possibility of predicting the importance of chemical and microbial degradation processes in the environment. Volatilization from wet and dry soil surfaces is not expected to be significant.

3. EXPOSURE

Pertinent data regarding human exposure to trichloroanilines by inhalation, ingestion of food or dermal contact could not be located in the available literature as cited in Appendix A. Trichloroanilines may be released to the environment in the effluent from use facilities (Ellis et al., 1982). Trichloroanilines may be formed as a result of chlorinating wastewaters that contain aniline (Mitchell et al., 1984) or as a metabolite of microbial degradation of various phenylurea and phenylcarbamate herbicides (Hwang et al., 1985).

3.1. WATER

2,4,5-Trichloroaniline was identified in drinking water collected from Cincinnati, OH (Oct. 1978) and Seattle, WA (Nov. 1976). 2,4,6-Trichloroaniline was identified in drinking water collected from Poplarville, MS (Mar. 1979); Cincinnati, OH (Oct. 1978 and Jan. 1980); New Orleans, LA (Jan. 1976); Philadelphia, PA (Feb. 1976) and Seattle, WA (Nov. 1976) (Lucas, 1984). 2,4,5-Trichloroaniline was detected in treated wastewaters obtained from Orange County, CA (Jan. 1976), and 2,4,6-trichloroaniline was positively identified in treated wastewaters obtained from Lake Tahoe, CA (Oct. 1974); Pomona, CA (Sept. 1974); Orange County, CA (Feb. 1976) and Washington, DC (May 1975) (Lucas, 1984). Trichloroaniline (isomer not specified) was qualitatively identified in the effluent from a publicly-owned treatment works in Sauget, IL (Ellis et al., 1982).

3.2. SUMMARY

Trichloroanilines may be released to the environment in the effluent from user facilities (Ellis et al., 1982). They may be formed as a result of chlorinating wastewaters that contain aniline (Mitchell et al., 1984) or

as a metabolite of microbial degradation of various phenylurea and phenylcarbamate herbicides (Hwang et al., 1985). 2,4,5- and 2,4,6-Trichloroaniline were identified in drinking water and in effluents from advanced wastewater treatment plants in several cities in the United States (Lucas, 1984); however, there were no quantitative data in the literature from which to estimate daily human exposure to the compounds through the consumption of drinking water.

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

Available aquatic toxicity data for the trichloroanilines are presented in Table 4-1. For marine species, the lowest reported toxic concentration was 0.8 mg/ℓ 2,3,4-trichloroaniline, a 96-hour LC_{50} for sand shrimp, Crangon septimspinosa (McLeese et al., 1979). Among freshwater species, the lowest reported toxic concentration was 1.96 mg/ℓ 2,4,5-trichloroaniline, a 14-day LC_{50} for guppies, Poecilia reticulata (Hermens et al., 1985). Available information was too limited to generalize about the relative toxicities of the trichloroaniline isomers.

4.2. CHRONIC EFFECTS

Pertinent data regarding chronic toxicity of trichloroanilines to aquatic organisms could not be located in the available literature as cited in Appendix A.

4.3. PLANT EFFECTS

The only toxicity data available for aquatic plants were that of Knie et al. (1983), who reported that the EC_{10} for inhibition of photosynthesis in Haematococcus pluvialis was >12 mg/ℓ 2,4,6-trichloroaniline. Devillers et al. (1986) conducted tests for inhibition of luminescence in Photobacterium phosphoreum exposed to four trichloroaniline isomers. The most toxic isomer was 2,4,5-trichloroaniline and the least toxic was 2,4,6-trichloroaniline (see Table 4-1).

4.4. SUMMARY

Limited information was available concerning toxicity of trichloroanilines to aquatic organisms. The lowest reported toxic concentration was 0.8 mg/ℓ 2,3,4-trichloroaniline, a 96-hour LC_{50} for sand shrimp, Crangon septimspinosa (McLeese et al., 1979). A study in which Photobacterium

TABLE 4-1

Acute Toxicity of Trichloroanilines to Aquatic Organisms

Species	Compound	Concentration (mg/L)	Effect	Reference
		FRESHWATER		
FISH				
Fathead minnow *Pimephales promelas*	2,3,4-trichloroaniline	3.56 2.27	96-hour LC_{50} 96-hour EC_{50}, immobilization	Brooke et al., 1984
Golden orfe *Leuciscus idus*	2,4,6-trichloroaniline	1.7 2.3	LC_0 LC_{50}	Knie et al., 1983
Guppy *Poecilia reticulata*	2,3,4-trichloroaniline 2,4,5-trichloroaniline	7.08 1.96	14-day LC_{50} 14-day LC_{50}	Hermens et al., 1985
INVERTEBRATES				
Water flea *Daphnia magna*	2,4,6-trichloroaniline	2 6	EC_0, immobilization EC_{50}, immobilization	Knie et al., 1983
PLANTS				
Green alga *Haematococcus pluvialis*	2,4,6-trichloroaniline	>12	EC_{10}, inhibition of photosynthesis	Knie et al., 1983
BACTERIA				
Photobacterium phosphoreum	2,3,4-trichloroaniline 2,4,5-trichloroaniline 2,4,6-trichloroaniline 3,4,5-trichloroaniline	2.36 1.49 4.60 3.34	30-minute EC_{50}, inhibition of luminescence 30-minute EC_{50}, inhibition of luminescence 30-minute EC_{50}, inhibition of luminescence 30-minute EC_{50}, inhibition of luminescence	Devillers et al., 1986
Pseudomonas putida	2,4,6-trichloroaniline	>21	EC_{10}, inhibition of cell multiplication	Knie et al., 1983
		SALTWATER		
INVERTEBRATES				
Sand shrimp *Crangon septemspinosa*	2,3,4-trichloroaniline	0.800	96-hour LC_{50}	McLeese et al., 1979

phosphoreum was exposed to four trichloroaniline isomers indicated that 2,4,5-trichloroaniline was most toxic, followed by 2,3,4-trichloroaniline, 3,4,5-trichloroaniline and 2,4,6-trichloroaniline, which was least toxic (Devillers et al., 1986).

5. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism or excretion of 2,3,4-, 2,4,5- of 2,4,6-trichloroaniline could not be located in the available literature as cited in Appendix A.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure. Pertinent data regarding the effects of inhalation exposure to the trichloroanilines could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- Subchronic oral studies were conducted in which white rats were exposed to 2,4,6-trichloroaniline at doses of 80, 160 or 800 mg/kg/day for 45 days or 0.4, 4 or 40 mg/kg, 5 days/week for 6 months (Sapegin et al., 1985). The compound was administered by gavage in 8% (45-day study) or 0.04, 0.4 and 4% (low-, middle- and high-dose groups, respectively; 6-month study) oil (type unspecified) solutions and doses >8% were added in the diet. The 45-day study used 128 male and female rats (number/sex not indicated) and the 6-month study used 180 rats (120 females, 60 males), but treatment and control group sizes, and sex distribution were not specified. The endpoints assessed in these studies were incompletely specified, but the results (Tables 6-1 and 6-2) indicate that the emphasis was primarily on determination of hematologic, clinical chemical and gross pathologic effects. Histological examinations appear to have been limited to the testicles and ovaries (Section 6.5.).

Confidence in the Sapegin et al. (1985) study is limited by inadequate reporting and discrepant results. The findings tabulated in Tables 6-1 and 6-2 suggest that hemoglobin, the vascular system (hemorrhagic/degenerative effects) and liver (enzymatic alterations) were affected at 160 and 800 mg/kg in the 45-day study and 4 and 40 mg/kg in the 6-month study. The extent of significant treatment-related effects is unclear, however, as p

TABLE 6-1

Effects of Daily Gavage Exposure to 2,4,6-Trichloroaniline for 45 Days in Rats[a]

Dose (mg/kg/day)	Response
800	Depression (unspecified); hair loss; cyanosis; hematuria; decreased mean hemoglobin concentration ($p<0.02$)[b]; increased number of red blood cells (hypochromic and polychromatophilic); anisocytosis and poikilocytosis; leukopenia (tendency); increased serum alanine aminotransferase ($p<0.001$)[b]; increased serum aspartate aminotransferase ($p<0.02$)[b]; decreased SGPT/SGOT ratio; increased serum residual nitrogen ($p<0.001$)[b]; increased serum pyruvic acid ($p<0.001$)[b]; decreased serum catalase ($p<0.001$)[b]; decreased oxygen consumption ($p<0.01$)[b]; decreased weight gain; increased relative weights of heart, liver, kidneys and spleen; unspecified degenerative alterations; hemorrhagic areas in myocardium, liver, kidneys, brain and spleen; decreased lactate and succinic dehydrogenase activities in liver and kidneys
160	Effects similar to 800 mg/kg/day but less pronounced (not elaborated)
80	No significant effects

[a]Source: Sapegin et al., 1985

[b]Significant change when compared with an unspecified control group; data reported, statistical method not reported

TABLE 6-2

Effects of Daily Gavage Exposure to 2,4,6-Trichloroaniline, 5 Days/Week for 6 Months in Rats[a]

Dose (mg/kg/day)	Response
40	Increased methemoglobin concentration ($p<0.02$)[b]; increased number of red blood cells (hypochromic); anisocytosis and poikilocytosis; reticulocytosis; hypochromia; Heinz bodies in erythrocytes; decreased oxygen consumption ($p<0.05$)[b]; impaired aquisition of conditioned reflexes ($p<0.001$)[b]; decreased weight gain in males; increased relative brain weight; decreased relative weight of liver; decreased succinic dehydrogenase activity in liver; decreased lactate dehydrogenase activity in liver and kidneys; unspecified degenerative alterations in blood vessels in the brain, liver and kidneys
4	Effects similar to 40 mg/kg but less pronounced (not elaborated)
0.4	No significant effects

[a]Source: Sapegin et al., 1985

[b]Significant change when compared with an unspecified control group; data reported, statistical method not reported

values were reported for only some of the effects at the highest dose in each study and results at the middle doses were reported to be similar but less pronounced.

6.1.2.2. CHRONIC -- A study of 2,4,6-trichloroaniline hydrochloride was conducted in which male Charles River rats were treated at concentrations of 3000 or 6000 ppm in the diet for 5 months followed by 1500 or 3000 ppm, respectively, for 13 months (Weisburger et al., 1978). The TWA concentrations were 1917 and 3833 ppm, respectively. Male and female CD-1 mice were treated similarly at levels of 6000 or 12,000 ppm for 18 months. Mice were observed for an additional 3 months and rats for an additional 6 months. This study was primarily designed to assess carcinogenicity (Section 6.2.2.). Nonneoplastic pathological effects of treatment did not occur in either species. The dosage reduction in the rat experiment was due to a $\geq$10% decrease in weight gain below control weight gain and to increased mortality (effect not specified).

6.1.3. Other Relevant Information. Oral administration of single doses of 0.25 mmol/kg (49.1 mg/kg) 2,4,6-trichloroaniline in an unspecified vehicle to five cats produced mean methemoglobin percentages of 35.9-43.7% after 1-5 hours (McLean et al., 1969). The overall mean of the five post-treatment hourly mean methemoglobin percentages was 38.8%, which is somewhat less than that determined for the same molar dose of aniline (48.1%). Adult cats were used in this study because they are particularly sensitive to methemoglobin formation. Eastman Kodak Company (1970) reported that 2,4,6-trichloroaniline is not a methemoglobin inducer in rats, but additional information was not provided. Aniline and many of the substituted anilines (including the monochloroanilines and 2,4- and 3,4-dichloroaniline) produced methemoglobin in cats (McLean et al., 1969). U.S. EPA (1984b) considers all aniline compounds as potential methemoglobin inducers.

The acute oral LD_{50} of 2,4,6-trichloroaniline for rats was determined to be between 1600 and 3200 mg/kg (Eastman Kodak Company, 1970).

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 2,3,4-, 2,4,5- or 2,4,6-trichloroaniline could not be located in the available literature as cited in Appendix A.

6.2.2. Oral. The carcinogenicity of 2,4,6-trichloroaniline hydrochloride was evaluated by dietary administration in groups of 25, six- to 8-week-old male Charles River rats, male CD-1 mice and female CD-1 mice (Weisburger et al., 1978). The purity of the test chemical was determined by thin-layer chromatography and infrared spectra, and was inferred to be 97-99%. Both species were treated at two levels that were intended to represent the MTD and 1/2 MTD. The rats were maintained on diets containing compound concentrations of 3000 or 6000 ppm for 5 months followed by 1500 or 3000 ppm, respectively, for 13 months (see Section 6.1.2.2.). Male and female mice were treated at concentrations of 6000 or 12,000 ppm for 18 months. Groups of 25 untreated male rats and mice of each sex served as controls. Mice were observed for an additional 3 months and rats for an additional 6 months. Necropsies, which included histological examinations of grossly abnormal organs and lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestine, reproductive organs and rat pituitary tissues, were conducted on all animals that died after $\geq$6 months of treatment and at termination of the study. The emphasis of the study, however, was on determination of carcinogenicity; growth and survival data were not reported, which precludes determining if a MTD was achieved.

2,4,6-Trichloroaniline hydrochloride induced a dose-related, statistically significant increase in the incidence of unspecified vascular tumors in male mice (Weisburger et al., 1978). As detailed in Table 6-3, increased incidences of tumors in treated groups were statistically significant by the Fischer Exact test if $p<0.05$ for both matched and pooled control groups. Incidences of hepatocellular carcinomas were also increased in treated male mice, but only in the low-dose group when compared with pooled controls (see Table 6-3). 2,4,6-Trichloroaniline did not produce statistically significant increases in tumor incidences in the female mice or male rats (according to authors).

6.2.3. Other Relevant Information. The induction of both tumors and methemoglobinemia by aniline and substituted aniline compounds is attributed to the formation of N-oxidized metabolites (Clayson and Garner, 1976; U.S. EPA, 1984b). Evidence for the carcinogenicity of aniline (U.S. EPA, 1985), 4-chloroaniline (NCI, 1979) and other aromatic amines (Clayson and Garner, 1976), and methemoglobin induction by 2,4,6-trichloroaniline (McLean et al., 1969), therefore, provides an additional indication of the potential carcinogenicity of 2,4,6-trichloroaniline.

6.3. MUTAGENICITY

2,4,6-Trichloroaniline was not mutagenic for Salmonella typhimurium strains TA100, TA98 or TA1537 when tested in plate incorporation assays with and without Aroclor 1254-induced rat liver S-9 metabolic activation preparation (Zimmer et al., 1980). Compound purity was between ~97 and 99%, but the doses were not specified. Liquid-suspension assays conducted with the same strains of S. typhimurium and metabolic activation preparations were also negative (Zimmer et al., 1980).

TABLE 6-3

Tumor Incidence in Male CD-1 Mice Treated with Dietary 2,4,6-Trichloroaniline Hydrochloride for 18 Months and Observed for an Additional 3 Months[a,b]

Dose (ppm)	Target Organ	Tumor Type	Tumor Incidence (p value)
0[c]	vascular system	NR	5/99
0[d]	vascular system	NR	2/16
6,000	vascular system	NR	10/18 ($p<0.025$)[e]
12,000	vascular system	NR	12/16 ($p<0.025$)[e]
0[f]	liver	hepatocellular carcinoma	7/99
0[g]	liver	hepatocellular carcinoma	1/16
6,000	liver	hepatocellular carcinoma	5/18 ($p<0.025$)[h]
12,000	liver	hepatocellular carcinoma	1/16 (NS)

TABLE 6-3 (cont.)

QUALITY OF EVIDENCE	
Strengths of study:	The compound was administered by a relevant route of exposure at two dose levels for a significant portion of the lifespan with an additional observation period. Female CD-1 mice and male Charles River rats were similarly tested, but data were not reported because of negative results. The extent of histopathological examination was adequate. Appropriate statistical analyses were performed.
Weaknesses of study:	Small number of animals were evaluated. The type(s) of vascular tumors were not specified.
Overall adequacy:	Adequate

[a]Source: Weisburger et al., 1978

[b]Purity (97-99%); not reported specifically for 2,4,5-trichloroaniline hydrochloride

[c]Pooled controls from untreated diet control groups of similarly designed 18-month experiments with other aromatic amines or derivatives in the same study.

[d]Matched controls

[e]Significantly different from matched and pooled control groups, Fisher Exact test

[f]Pooled controls

[g]Simultaneous controls

[h]Significantly different from pooled control group only, Fisher Exact test

NR = Not reported; NS = not specified

In a study in which the mutagenicity of 2,4,6-trichloroaniline was evaluated with S. typhimurium strains TA98, TA100 and TA1538 and Escherichia coli strains WP2uvrA and WP2uvra/pKm by the pre-incubation (liquid suspension) method (Shimizu and Takemukra, 1984), mutagenicity was reported in S. typhimurium or E. coli, but the species and strain(s) other than S. typhimurium TA98 were not specified. Mutagenicity of 2,4,6-trichloroaniline was also demonstrated in a fluctuation test conducted with S. typhimurium TA98.

Rats exposed to 2,4,6-trichloroaniline by gavage at 40 mg/kg, 5 days/week for 6 months showed a statistically significant increase in the number of bone marrow cells containing lacunae and chromosomal aberrations (1.6 vs. 0.4% in unspecified controls) (Sapegin et al., 1985). Treatment-related clastogenic effects did not occur in rats similarly treated with 4 or 0.4 mg/kg. Limited additional information was available regarding the design of this inadequately reported study (see Section 6.1.2.1.).

6.4. TERATOGENICITY

Rats were exposed to 2,4,6-trichloroaniline by gavage at doses of 0.4, 4 and 40 mg/kg, 5 days/week for 6 months (Sapegin et al., 1985) (see Section 6.1.2.1.). A teratogenicity study was conducted at "the end of the 6-month experiment." Additional information regarding the design of the teratology study was not reported, but it may be inferred that mating and gestation occurred during the 6-month exposure period since the 4 mg/kg dose was reported to be embryotoxic; evidenced by an increase in pre- and postimplantation fetal mortality, massive hematomas in the abdominal cavity and a decrease in the number of fetuses/female. The significance of these effects is difficult to ascertain since further details (incidences of embryotoxic effects at 4 mg/kg dose, effects on the dam, and effects on at the 40 mg/kg dose) were not reported. Teratogenicity was not reported.

6.5. OTHER REPRODUCTIVE EFFECTS

A subchronic toxicity study was conducted in which rats were exposed daily by gavage to 2,4,6-trichloroaniline at concentrations of 80, 160 or 800 mg/kg for 45 days (Sapegin et al., 1985). Histological examination of the testes showed a decrease in the weight "coefficients" and volume of the testicles, and an increase in the number of tubules with desquamated spermatogenic epithelium at 800 mg/kg. These effects were attributed to a general toxic effect and did not occur at 160 or 80 mg/kg. Histological or functional alterations in the ovaries did not occur at any dose. In another experiment that was summarized in the same report, rats were exposed to 2,4,6-trichloroaniline by gavage at doses of 0.4, 4 and 40 mg/kg, 5 days/week for 6 months. Treatment at any dose in this study had no significant effect on "the morphofunctional indices" in the testes or ovaries; this appears to refer to histology, spermatogenesis and ovogenesis. Limited additional information regarding the design of the studies is presented in Section 6.1.2.1.

6.6. SUMMARY

Administration of 2,4,6-trichloroaniline to rats by gavage at doses of 160 or 800 mg/kg/day for 45 days, or 4 or 40 mg/kg, 5 days/week for 6 months produced a variety of effects, including methemoglobinemia, gross hemorrhagic/degenerative alterations in the circulatory system and altered liver enzyme activities (Sapegin et al., 1985). Also, embryotoxicity was reported at 4 mg/kg and histological alterations in the testes were reported at 800 mg/kg. However, because of inadequate reporting and discrepancies the validity of these findings is uncertain,.

2,4,6-Trichloroaniline hydrochloride was administered to male rats in the diet at TWA concentrations of 1917 and 3833 ppm for 18 months followed by 6 months observation without histopathological effects (Weisburger et al., 1978). Dietary administration of 6000 or 12,000 ppm 2,4,6-trichloroaniline hydrochloride to mice for 18 months followed by 3 months observation produced a dose-related, statistically significant increase in the incidence of vascular tumors in male mice (Weisburger et al., 1978); histopathological alterations did not occur in similarly treated females.

Equivocal results were reported for 2,4,6-trichloroaniline in mutagenicity assays with bacteria (Zimmer et al., 1980; Shimizu and Takemura, 1984). Chromosomal aberrations occurred in the bone marrow cells of rats exposed by gavage to 40 mg/kg 2,4,6-trichloroaniline, 5 days/week for 6 months (Sapegin et al., 1985).

Information regarding the toxic or carcinogenic effects of 2,3,4- or 2,4,5-trichloroaniline could not be located in the available literature as cited in Appendix A.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in Appendix A.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the effects of trichloroanilines could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 2,3,4-, 2,4,5- or 2,4,6-trichloroaniline could not be located in the available literature as cited in Appendix A.

8.1.2. Oral. The carcinogenicity of 2,4,6-trichloroaniline hydrochloride was evaluated by dietary administration to groups of 25 six- to 8-week-old male Charles River rats, male CD-1 mice and female CD-1 mice (Weisburger et al., 1978). The rats were maintained on diets containing compound concentrations of 3000 or 6000 ppm for 5 months followed by 1500 or 3000 ppm for 13 months (TWA 1917 or 3833 ppm). The rats were observed for an additional 6 months. Both sexes of mice were treated at concentrations of 6000 or 12,000 ppm for 18 months and observed for an additional 3 months. Groups of 25 untreated male rats and mice of each sex served as controls. As detailed in Section 6.2.2. and Table 6-3, 2,4,6-trichloroaniline hydrochloride induced a dose-related, statistically significant increase in the incidence of unspecified vascular tumors in the male mice. Incidences of hepatocellular carcinomas were also increased in treated male mice but only in the low-dose group when compared with pooled controls. Statistically significant increases in tumor incidences in the female mice or male rats did not occur.

8.1.3. Other Routes. Pertinent data regarding the carcinogenicity of inhaled 2,3,4-, 2,4,5- or 2,4,6-trichloroaniline by routes other than oral could not be located in the available literature as cited in Appendix A.

8.1.4. Weight of Evidence. 2,4,6-Trichloroaniline hydrochloride produced vascular tumors and an equivocal increase in hepatocellular carcinomas in male CD-1 mice, but no increase in the incidence of tumors in female CD-1 mice or male Charles River rats (Weisburger et al., 1978). Since tumors

occurred in one species and sex in a single study, and because the study is limited by small group sizes, these data are interpreted as limited evidence of carcinogenicity. Thus, 2,4,6-trichloroaniline and its hydrochloride are classified as EPA Group C (U.S. EPA, 1986b).

The induction of both carcinogenicity and methemoglobinemia by aniline and substituted aniline compounds are attributed to the formation of N-oxidized metabolites (Clayson and Garner, 1976; U.S. EPA, 1984b). Evidence for the carcinogenicity of aniline (U.S. EPA, 1985), 4-chloroaniline (NCI, 1979) and other aromatic amines (Clayson and Garner, 1976), and methemoglobin induction by 2,4,6-trichloroaniline (McLean et al., 1969), therefore, provides an additional indication of the potential carcinogenicity of 2,4,6-trichloroaniline and the hydrochloride, but not enough to raise the EPA classification.

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- Lack of pertinent inhalation data precludes derivation of a q_1^* for inhalation exposure.

8.1.5.2. ORAL -- A q_1^* for oral exposure to 2,4,6-trichloroaniline hydrochloride can be calculated by using the incidences of vascular tumors in the male mice from the Weisburger et al. (1978) study. The mice were exposed to 2,4,6-trichloroaniline hydrochloride at dietary concentrations of 6000 and 12,000 ppm for 18 months followed by an observation period of 3 months. Expanding the exposures over a 21-month period by multiplying the dietary levels by 18 months/21 months yields TWA exposure levels of 5143 and 10,286 ppm. Using the TWA dietary concentrations and the standard mouse food consumption estimate of 0.13 kg food/kg bw/day, the daily doses for the low- and high-dose groups are calculated to be 669 and 1337 mg/kg/day, respectively. Using these doses with the corresponding vascular tumor incidences and the computerized multistage model developed by Howe and Crump

(1982), the unadjusted q_1^* is calculated to be 1.4625×10^{-3} $(mg/kg/day)^{-1}$ (Appendix B). This q_1^* may be conservative as the numbers of animals used in the multistage calculation were relatively small. The human q_1^*, calculated by multiplying the unadjusted q_1^* by the cube root of the ratio of assumed human body weight (70 kg) to assumed animal body weight (0.03 kg) and by the cube of the ratio of assumed mouse lifespan (24 months) to experiment duration (21 months) is 2.9×10^{-2} $(mg/kg/day)^{-1}$. Assuming that a 70 kg human consumes 2 ℓ/day, the concentrations of 2,4,6-trichloroaniline hydrochloride in drinking water associated with increased lifetime risk of cancer at risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.2×10^{-2}, 1.2×10^{-3} and 1.2×10^{-4} mg/ℓ, respectively.

A q_1^* for 2,4,6-trichloroaniline of 3.4×10^{-2} $(mg/kg/day)^{-1}$ is calculated by multiplying the q_1^* for the hydrochloride by the ratio of the molecular weight of the hydrochloride (232.92) to the molecular weight of 2,4,6-trichloroaniline (196.46). The concentrations of 2,4,6-trichloroaniline in drinking water associated with increased lifetime risk of cancer at risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.0×10^{-2}, 1.0×10^{-3} and 1.0×10^{-4} mg/ℓ.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. Pertinent data regarding the effects of inhalation exposure to the trichloroanilines could not be located in the available literature as cited in Appendix A.

8.2.2. Oral Exposures.

8.2.1.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Administration of 2,4,6-trichloroaniline to rats by gavage at 160 or 800 mg/kg/day for 45 days or 4 or 40 mg/kg, 5 days/week for 6 months produced methemoglobinemia, gross hemorrhagic/degenerative alterations in the circulatory system and

altered liver enzyme activities (Sapegin et al., 1985). Also, embryotoxicity was reported at 4 mg/kg administered 5 days/week for 6 months and testicular effects were reported at 800 mg/kg/day. There were no effects at 80 mg/kg/day for 45 days or 0.4 mg/kg/day, 5 days/week for 6 months.

Because effects at 4 mg/kg, 5 days/week for 6 months and 160 mg/kg/day for 45 days were reported to be similar but less pronounced than those at the high doses, these doses appear to be LOAELs. The lack of specific information, however, precludes evaluation of these dose effects or dose-response relationships. Assessment of the results is further complicated by a lack of survival data, the occurrence of an 80 mg/kg/day NOAEL in the 45-day study, a 40 mg/kg, 5 days/week FEL in the 6-month study and the fact that pathological effects were not observed in rats treated with TWA dietary concentrations of 1917 and 3833 ppm [~96 or 192 mg/kg/day 2,4,6-trichloroaniline hydrochloride (~81 or 162 mg/kg/day 2,4,6-trichloroaniline) assuming 5% body weight daily food consumption] for 18 months (Weisburger et al., 1978) (see Section 6.1.2.2.). Thus, a subchronic oral RfD cannot be calculated for 2,4,6-trichloroaniline. Calculation of RfDs for 2,3,4- or 2,4,5-trichloroaniline is precluded by a lack of toxicity data.

8.2.2.2. CHRONIC EXPOSURES -- The only chronic study of 2,4,6-trichloroaniline was the dietary study using rats and mice by Weisburger et al. (1978) (see Section 8.1.2.). Nonneoplastic pathological effects did not occur in either species. The dosage reduction in the rat experiment was due to a >10% decrease in weight gain and increased mortality. Because of the positive carcinogenicity results in mice, however, it is not appropriate to derive a chronic oral RfD for 2,4,6-trichloroaniline. Calculation of RfDs for the other isomers is precluded by lack of data.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

Chronic (Weisburger et al., 1978), subchronic and reproductive (Sapegin et al., 1985) studies are available for 2,4,6-trichloroaniline, but inadequacies preclude use of these data for the calculation of an RQ (Table 9-1).

Weisburger et al. (1978) administered 2,4,6-trichloroaniline hydrochloride in the diet to groups of 25 male Charles River rats at TWA concentrations of 1917 or 3833 ppm for 18 months followed by 6 months observation or to groups of 25 male and 25 female CD-1 mice at 6000 or 12,000 ppm for 18 months followed by 3 months observation (see Section 6.2.2.). Nonneoplastic pathological effects of exposure were not observed, but the reduction in dosage in the rat groups was due to a >10% weight gain reduction and mortality. The effect pertinent to the dose reductions was not specified further, thus precluding calculation of an RQ.

Gavage studies were conducted in which white rats were treated with 2,4,6-trichloroaniline at concentrations of 80, 160 or 800 mg/kg/day for 45 days or 0.4, 4 or 40 mg/kg, 5 days/week for 6 months (Sapegin et al., 1985). Various effects were attributed to treatment, including methemoglobinemia, apparent hepatic damage and widespread gross hemorrhagic and degenerative alterations at the highest or middle doses or both in each experiment (see Section 6.1.2.1.). Additionally, embryotoxicity was reported at 4 mg/kg, 5 days/week in the 6-month study and testicular effects (apparent atrophy and spermatogenic epithelium desquammation) at 800 mg/kg/day in the 45-day study. The significance of these effects cannot be established, however, because of low confidence in the study resulting from inadequate reporting of experimental design and results, and apparent discrepancies within the study (Sapegin et al., 1985) and with the Weisburger et al. (1978) study.

TABLE 9-1

2,4,6-Trichloroaniline and 2,4,6-Trichloroaniline Hydrochloride

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

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are insufficient for deriving an RQ.

Interpretation of the Sapegin et al. (1985) study is complicated by unexplained proximity of the 80 mg/kg/day NOAEL in the 45-day study to the 40 mg/kg, 5 days/week FEL in the 6-month study, by uncertainty regarding the MED for an effect since effects at the middle doses were inadequately documented (similar to but less pronounced than the high doses), by a lack of hemorrhagic/degenerative and testicular alterations in rats that were maintained on diets that provided 96 or 192 mg/kg/day 2,4,6-trichloroaniline hydrochloride (81 or 162 mg/kg/day 2,4,6-trichloroaniline) for 18 months (Weisburger et al., 1978) (see Section 6.1.2.2.), and by the unexplained indication that the testicular effects were due to a general rather than specific toxic effect. The embryotoxicity reported at 4 mg/kg has uncertain significance because it was not reported at 40 mg/kg and additional information regarding experimental design or the results was not reported. Calculation of an RQ from the effects reported by Sapegin et al. (1985), therefore, is precluded by low confidence in the study.

9.2. BASED ON CARCINOGENICITY

The carcinogenicity of 2,4,6-trichloroaniline hydrochloride was evaluated by dietary administration to groups of 25, six- to 8-week-old male Charles River rats, male CD-1 mice and female CD-1 mice (Weisburger et al., 1978). The rats were maintained on diets containing TWA concentrations of 1917 or 3833 ppm for 18 months followed by a 6-month observation period. Both sexes of mice were treated at concentrations of 6000 or 12,000 ppm for 18 months and observed for an additional 3 months. Groups of 25 untreated male rats and mice of each sex served as controls. As detailed in Section 6.2.2. and Table 6-3, 2,4,6-trichloroaniline hydrochloride induced a dose-related, statistically significant increase in the incidence of unspecified vascular tumors in the male mice. Incidences of hepatocellular carcinomas

were also increased in treated male mice, but only in the low-dose group when compared with pooled controls. Statistically significant increases in tumor incidences in the female mice or male rats did not occur. Since tumors occurred in one species and sex in a single study, these data are interpreted as limited evidence of carcinogenicity and are consistent with an EPA Group C classification (U.S. EPA, 1986b).

An F factor for oral exposure to 2,4,6-trichloroaniline hydrochloride can be calculated using the incidences of vascular tumors in the male mice from the Weisburger et al. (1978) study. Multiplying the exposure of 6000 and 12,000 ppm by 18 months/21 months and by the standard mouse food consumption estimate of 0.13 kg food/kg bw/day, the daily doses for the low- and high-dose groups are calculated to be 669 and 1337 mg/kg/day, respectively (Table 9-2). Using these doses, the corresponding vascular tumor incidences and the computerized multistage model developed by Howe and Crump (1982), the unadjusted $1/ED_{10}$ is calculated to be 9.1754×10^{-3} $(mg/kg/day)^{-1}$. The adjusted $1/ED_{10}$ (F factor) for humans, calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of assumed human body weight (70 kg) to assumed mouse body weight (0.03 kg) and by the cube of the ratio of mouse lifespan (24 months) to experiment duration (21 months), is 1.82×10^{-1} $(mg/kg/day)^{-1}$. An F factor of 2.16×10^{-1} $(mg/kg/day)^{-1}$ for 2,4,6-trichloroaniline is calculated by multiplying the F factor for the hydrochloride by the ratio of the molecular weight of the hydrochloride to the molecular weight of 2,4,6-trichloroaniline (232.92/196.46). These F factors place 2,4,6-trichloroaniline and the hydrochloride in Potency Group 3. An EPA Group C chemical that is in Potency Group 3 ranks LOW in the Hazard Ranking Scheme under CERCLA. A LOW hazard ranking is assigned an RQ of 100.

TABLE 9-2

Derivation of Potency Factor (F)
for 2,4,6-Trichloroaniline Hydrochloride

Reference:	Weisburger et al., 1978
Exposure route:	oral
Species:	mouse
Strain:	CD-1
Sex:	male
Vehicle or physical state:	diet
Body weight:	0.03 kg (assumed)
Duration of treatment:	18 months
Duration of study:	21 months
Lifespan of animal:	24 months (assumed)
Target organ:	vascular system
Tumor type:	not specified
Experimental doses/exposures:	0, 6000, 12,000 ppm
Transformed doses: (mg/kg/day)	0, 669, 1337
Tumor incidence:	2/16, 10/18, 12/16
Unadjusted $1/ED_{10}$:	9.1754×10^{-3} $(mg/kg/day)^{-1}$
Adjusted $1/ED_{10}$: (F Factor)	1.82×10^{-1} $(mg/kg/day)^{-1}$

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U.S. EPA. 1984b. Aniline and Chloro-, Bromo- and/or Nitroanilines; Response to the Interagency Testing Committee. Federal Register. 49: 108-126.

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APPENDIX A

LITERATURE SEARCHED

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

TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
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 January, 1987. In addition, hand searches were made of Chemical Abstracts (Collective Indices 5-9), and the following secondary sources should be 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). 1986-1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1986-1987. Cincinnati, OH. 111 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. 1978-1984. 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.

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

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Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

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USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984, 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.

APPENDIX B

Cancer Data Sheets for Derivation of q_1^*

Compound: 2,4,6-Trichloroaniline hydrochloride

Reference: Weisburger et al., 1978

Species/strain/sex: mouse, CD-1, male

Route/vehicle: oral, diet

Length of exposure (le) = 18 months

Length of experiment (Le) = 21 months

Lifespan of animal (L) = 24 months

Body weight = 0.03 kg (assumed)

Tumor site and type: vascular system (not specified)

Exposure ppm (TWA)[a]	Transformed Dose[b] (mg/kg/day)	Incidence No. Responding/No. Tested
0	0	2/16
5,143	669	10/18
10,286	1337	12/16

Unadjusted $q_1^* = 1.46251 \times 10^{-3}$ $(mg/kg/day)^{-1}$
Human $q_1^* = 2.895567 \times 10^{-2}$ $(mg/kg/day)^{-1}$

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[a]6000 or 12,000 ppm x 18 months/21 months

[b]It is assumed that mice consume 0.13 kg food/kg bw/day

APPENDIX C

Summary Table for 2,4,6-Trichloroaniline and 2,4,6-Trichloroaniline Hydrochloride[a]

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	NA	NA	NA	RfD: NA	NA
Chronic	NA	NA	NA	RfD: NA	NA
Carcinogenicity	NA	NA	NA	q_1^*: 1.46×10^{-2} $(mg/kg/day)^{-1}$[b] for TCA·HCl and 1.7×10^{-2} $(mg/kg/day)^{-1}$[b] for TCA	NA
Oral Exposure					
Subchronic	NA	NA	NA	RfD: NA	NA
Chronic	NA	NA	NA	RfD: NA	NA
Carcinogenicity	mouse	6000 and 12,000 ppm in diet for 18 months	vascular system tumors	q_1^*: 2.9×10^{-2} $(mg/kg/day)^{-1}$ for TCA·HCl and 3.4×10^{-2} $(mg/kg/day)^{-1}$ for TCA	Weisburger et al., 1978

		Reference
REPORTABLE QUANTITIES		
Based on Chronic Toxicity:	ID	NA
Based on Carcinogenicity:	100 pounds	Weisburger et al., 1978

[a]Pertinent data for 2,3,4- or 2,4,5-trichloroaniline were not available

[b]Calculated from the oral q_1^*s

NA = Not applicable; ID = Insufficient data; TCA = trichloroaniline