United States
Environmental Protection
Agency

ECAO-CIN-G036
June, 1988

Research and Development

HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 4-CHLOROBENZOTRIFLUORIDE

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

DRAFT: DO NOT CITE OR QUOTE

NOTICE

DISCLAIMER

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

PREFACE

Health and Environmental Effects 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 for 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 i.e., for an interval 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. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), 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 the Comprehensive Environmental Response, Compensation and Liability Act (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, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

4-Chlorobenzotrifluoride is a colorless liquid at ambient temperatures, with an aromatic odor (Hawley, 1981; Boudakian, 1980). It is practically insoluble in water (Elanco Products Company, 1984). This compound undergoes easy nitration and nucleophilic substitution reactions (Boudakian, 1980). Currently, Occidental Petroleum Corp. of Niagara Falls, NY, is the only major manufacturer of this chemical in the United States (SRI, 1987; USITC, 1987). Data regarding the current U.S. production volume are not available, although ~10-50 million pounds was produced in 1977 (U.S. EPA, 1977). It is produced from the reaction of 4-chlorobenzotrichloride and anhydrous hydrogen fluoride. This chemical is used primarily as an intermediate in the manufacture of certain dyes, drugs and herbicides (Boudakian, 1980).

Of the three likely chemical processes that may lead to the loss of 4-chlorobenzotrifluoride in the atmosphere, neither direct photolysis nor its reaction with atmospheric O_3 is significant (Atkinson et al., 1985). Its reaction with photochemically produced HO radical has a rate constant of 2.3×10^{-13} cm^3/molecule-sec (Atkinson et al., 1985). Assuming the atmospheric concentration of HO radical as 10^6 radicals/cm^3, the lifetime of this compound in the air has been estimated to be ~50 days (Atkinson et al., 1985). Therefore, the compound is expected to persist in the atmosphere. In water, photolysis of the chemical is not important (Elanco Products Co., 1983a). Although the rates of aerobic and anaerobic biodegradation of the compound in water could not be determined, these rates are slower than the volatilization rate (Elanco Products Co., 1983b,c,d). From the value of the ratio of the volatilization rate of the compound to the oxygen reaeration rate determined experimentally (Elanco Products Co.,

1983d) and the values of oxygen reaeration rates in a few natural waters (Thomas, 1982), the half-life for volatilization of the compound from water has been estimated to be 1-6 days. The K_{oc} value of 420-490 in sediments (Elanco Products Co., 1983e) indicates that the compound will sorb moderately to suspended solids and sediments in natural waters. Based on the experimentally determined BCF of 122-202 in bluegill sunfish, Lepomis macrochirus (Elanco Products Co., 1984), the compound is not expected to bioconcentrate significantly in aquatic organisms. From the data available in aquatic studies, it can be predicted that photolysis in soil will be unimportant, and some loss of the compound will occur from the soil surface because of volatilization, although the volatilization process will become less important as the soil depth increases. The K_{oc} value of 510-530 in soil (Elanco Products Co., 1983e) indicates that the compound may leach through some soils, particularly soil from improper disposal sites. No data regarding the biodegradability of the compound in soil are available.

There is a paucity of data on the levels of 4-chlorobenzotrifluoride in environmental media. This compound was qualitatively detected in water from Lake Ontario at Niagara River (Great Lakes Water Quality Board, 1983). The source of the compound in the water was possibly the nearby manufacturer of the chemical. Hauser and Bromberg (1982) reported the qualitative detection of this compound in the sediment/soil/water samples collected from contaminated areas of Love Canal, Niagara Falls. Bass and yellow perch collected from Niagara River and analyzed in 1978 contained 4-chlorobenzotrifluoride in the concentration range 0.17-2.0 ppm. The compound was not detected at a later date (1980), however, at a detection limit of 0.01 ppm in various samples of fish (walleye, brown trout and sucker) from Lake Erie and Lake Ontario near the suspected contaminated areas (Occidental Chem. Corp.,

1980b). Cacco and Ferrari (1982) reported the detection of this compound at a level of 1 ppm in groundwater near an improper disposal site near Vicenza, Italy.

Exposure of rainbow trout and bluegill sunfish to 4-chlorobenzotrifluoride generated 96-hour LC_{50} values of 13.5 and 12.0 (10.3-13.9) mg/ℓ, respectively (Union Carbide Environmental Services, 1979b). Exposure of D. magna to 4-chlorobenzotrifluoride generated a 48-hour LC_{50} of 12.4 (10.7-14.5) mg/ℓ (Union Carbide Environmental Services, 1979c).

The concentration of 4-chlorobenzotrifluoride that produced chronic effects in aquatic organisms was ~1-2 orders of magnitude lower than that produced for acute effects. The MATC for fathead minnow eggs was >0.54 but <1.4 mg/ℓ 4-chlorobenzotrifluoride. The MATC for D. magna was ≥0.03 and <0.05 mg/ℓ 4-chlorobenzotrifluoride (Union Carbide Environmental Services, 1979d).

The single study of [^{14}C]-4-chlorobenzotrifluoride metabolism using rats (Quistad and Mulholland, 1983) indicated that the compound is absorbed and excreted readily, predominantly as the parent compound. The major route of excretion was through expired air, which accounted for 62-82% of the dose. Urinary metabolites identified were the glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, which accounted for ≤2.7 and 4.4% of the dose, respectively. A minor urinary metabolite, the mercapturic acid conjugate of 4-chlorobenzotrifluoride accounted for 0.1-0.2% of the dose.

Minimal to moderate renal tubular degeneration was observed in male rats treated by gavage with 4-chlorobenzotrifluoride at doses >40 mg/kg/day for 3 months (Arthur and Probst, 1983). Centrilobular hypertrophy of the liver was observed in male rats at 4-chlorobenzotrifluoride doses >150 mg/kg/day

and in female rats at 500 mg/kg/day. No significant effects were observed in rats treated for 3 months by gavage with 4-chlorobenzotrifluoride at 10 mg/kg/day.

In contrast to the Arthur and Probst (1983) study, histological kidney and liver effects were not observed in a 2-generation study in which Sprague-Dawley rats were treated by gavage with 4-chlorobenzotrifluoride at doses $\leq$45 mg/kg/day for $\geq$90 days (Hooker Chemical Corp., 1981). 4-Chlorobenzotrifluoride treatment did not have any effect on reproductive parameters.

A Russian study (Rapoport et al., 1986) reported that inhalation exposure of rats to 4-chlorobenzotrifluoride at concentrations >20.5 mg/m^3 for 120 hours resulted in changes in blood analyses, motor activity and muscle strength. Significant changes were not observed in rats exposed at 5.5 mg/m^3 for 120 hours.

Hooker Chemical Corp. (1979a) reported a 4-hour LC_{50} for 4-chlorobenzotrifluoride in Sprague-Dawley rats of 33 mg/m^3. The oral LD_{50} for 4-chlorobenzotrifluoride in Sprague-Dawley rats was reported as >5.0 mℓ/kg (6.7 g/kg) (Hooker Chemical Corp., 1985a), while the dermal LD_{50} in rabbits was reported to be >2.0 mℓ/kg (2.7 g/kg) (Hooker Chemical Corp., 1985b).

Except for positive results in assays of unscheduled DNA synthesis (Benigni and Dogliotti, 1980) and sister chromatid exchange (Hooker Chemical Corp., 1979c), results of mutagenicity assays of 4-chlorobenzotrifluoride have been negative.

4-Chlorobenzotrifluoride has not been tested for carcinogenicity or teratogenicity.

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 were not located in the available literature cited in Appendix A.

Because of the lack of data concerning carcinogenicity in humans and animals, 4-chlorobenzotrifluoride can be classified as an EPA Group D chemical. The derivation of carcinogenic potency factors and a cancer-based RQ is precluded by the lack of carcinogenicity data. Based on the Hooker Chemical Corp. (1981) 2-generation study using rats, subchronic and chronic oral RfDs for 4-chlorobenzotrifluoride of 0.2 mg/kg/day (11 mg/day) and 0.02 mg/kg/day (1 mg/kg) were calculated. Because of the lack of supporting studies, confidence in the oral RfDs is low. A chronic toxicity RQ for 4-chlorobenzotrifluoride of 1000 was calculated from the Arthur and Probst (1983) 90-day rat study.

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF TABLES

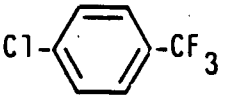
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
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
MATC	Maximum allowable toxicant concentration
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rated value
RV_e	Effect-rated value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

4-Chlorobenzotrifluoride is also known as 1-chloro-4-(trifluoromethyl) benzene; (p-chlorophenyl)trifluoromethane; 4-chloro-α-α-α-trifluoro-toluene; p-chlorobenzotrifluoride; and p-chlorotrifluoromethylbenzene (HSDB, 1988). The structure, molecular formula, molecular weight and CAS Registry number for this compound are as follows:



Molecular formula: $C_7H_4ClF_3$

Molecular weight: 180.56

CAS Registry number: 98-56-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

4-Chlorobenzotrifluoride is a colorless liquid at ambient temperatures (Boudakian, 1980), with an aromatic odor (Hawley, 1981). It is not soluble in water but is soluble in n-hexane (Elanco Products Company, 1984). Selected physical properties of this compound are as follows:

Melting point:	-36.0°C	Hawley, 1981
Boiling point:	138.6°C	Hooker Chems. and Plastics Corp., 1980
Density:	1.338 g/cm³ at 25°C	Boudakian, 1980
Vapor pressure:	7.86 mm Hg at 25°C	Hooker Chems. and Plastics Corp., 1980
Water solubility:	29.1 mg/ℓ at 23°C	Hooker Chems. and Plastics Corp., 1980
Odor threshold:	50% panel members at 0.63 mg/m³ and 100% at 0.8 mg/m³	Occidental Chems. Corp., 1980a

Log K_{ow}:	3.52	Elanco Products Company, 1984
Conversion factor in air:	1 ppm = 7.51 mg/m³ at 20°C and 760 mm Hg	

4-Chlorobenzotrifluoride undergoes several chemical reactions. Nitration of this compound yields nitro-substituted products that are used as intermediates in the production of dyes, germicides and herbicides. Because of the strong electron-withdrawing effect, this compound also undergoes nucleophilic substitution reactions (Boudakian, 1980).

1.3. PRODUCTION DATA

According to EPA's TSCA production file (U.S. EPA, 1977), the major producer of 4-chlorobenzotrifluoride in the United States in 1977 was Hooker Chems. and Plastics Corp. of Niagara Falls, NY. This company produced between 10 and 50 million pounds of the compound in 1977. At least three companies imported this chemical in the United States during the same year (U.S. EPA, 1977). More recent data (USITC, 1987; SRI, 1987) indicate that Occidental Petroleum Corp. at Niagara Falls, NY, the parent company of Hooker Chems. and Plastics Corp., is the only current major manufacturer of the chemical in the United States. It is produced from the reaction of 4-chlorobenzotrichloride and anhydrous hydrogen flouride under high or atmospheric pressure conditions (Boudakian, 1980) or the reaction of 4-chlorotoluene with hydrogen fluoride (HSDB, 1988).

1.4. USE DATA

4-Chlorobenzotrifluoride is used as an intermediate in the manufacture of certain dyes, drugs, herbicides and germicides (Boudakian, 1980). It is also used as a solvent and a dielectric fluid (Hawley, 1981).

1.5. SUMMARY

4-Chlorobenzotrifluoride is a colorless liquid at ambient temperatures, with an aromatic odor (Hawley, 1981; Boudakian, 1980). It is practically insoluble in water (Elanco Products Company, 1984). This compound undergoes easy nitration and nucleophilic substitution reactions (Boudakian, 1980). Currently, Occidental Petroleum Corp. of Niagara Falls, NY, is the only major manufacturer of this chemical in the United States (SRI, 1987; USITC, 1987). Data regarding the current U.S. production volume are not available, although ~10-50 million pounds was produced in 1977 (U.S. EPA, 1977). It is produced from the reaction of 4-chlorobenzotrichloride and anhydrous hydrogen fluoride. This chemical is used primarily as an intermediate in the manufacture of certain dyes, drugs and herbicides (Boudakian, 1980).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

The fate of 4-chlorobenzotrifluoride in the gas phase was studied by Atkinson et al. (1985) and the results were applied to assess its fate under atmospheric conditions (Occidental Chem. Corp., 1984). Later, the same study was published in the open literature (Atkinson et al., 1985). Although the study did not directly determine the photolytic fate of the compound, the upper limit for photolytic rate was indirectly determined to be 2.7×10^{-6}/ sec at a light intensity ~1.5 times higher than solar radiation. Therefore, the lower limit for photolytic lifetime (lifetime = $1/R_1$) under atmospheric conditions was estimated to be 6.5 days. Since the compound exhibits its first absorption band in the wavelength region 230-280 nm and shows no detectable absorption at wavelengths >280 nm, Atkinson et al. (1985) concluded that atmospheric photolysis is probably unimportant compared with other loss processes. The same conclusion regarding the significance of photolysis can be reached from the aquatic photolysis study (Section 2.2.).

The rate constants for the vapor phase reaction of HO radical and O_3 with 4-chlorobenzotrifluoride at 23°C are 2.3×10^{-13} cm³/molecule-sec and $<5 \times 10^{-21}$ cm³/molecule-sec, respectively (Atkinson et al., 1985). If the daily average atmospheric concentrations of HO radical and O_3 are assumed to be 10^6 radicals/cm³ and 7.2×10^{11} molecules/cm³, respectively, the corresponding lifetimes will be 50 days and >8.8 years (Atkinson et al., 1985). Therefore, in the absence of any other faster loss process, the lifetime of this compound in the atmosphere will be close to 50 days and it will be very persistent in the ambient atmosphere.

2.2. WATER

There is a paucity of data in the open literature regarding the fate and transport of 4-chlorobenzotrifluoride in water. The data reported here were obtained from the public files section of the reports of the major manufacturer as submitted to EPA's Office of Toxic Substances (OTS) under 8D submission rules.

The photolytic fate of this chemical in water was reported by Elanco Products Co. (1983a). When a 10 ppm aqueous solution of the chemical in sealed and sterilized glass tubes was exposed to natural light for $\leq$28 days, no degradation was observed and almost 100% of the compound remained unaltered. Therefore, it was concluded that the compound is not photolabile. The aerobic and anaerobic biodegradation of 4-chlorobenzotrifluoride in water was also reported by Elanco Products Co. (1983b,c). When microorganisms from soil and raw domestic sewage acclimatized to 4-chlorobenzotrifluoride were used as microbial inoculum for aerobic biodegradation study in flasks with attached CO_2 traps, only 13% of the initial theoretical compound could be accounted for on day 0, presumably because of volatilization. By the fifth day, only 2% of the compound remained. The report concluded that the high volatility of the compound precluded the determination of its aerobic biodegradative fate. Similarly, when the compound was inoculated with anaerobic digestor sludge under anaerobic conditions for >59 days, it was determined that the compound might be inhibitory to anaerobic microorganisms for a period of 17 days at an initial concentration of 50 mg C/ℓ. No conclusion regarding anaerobic biodegradation of 4-chlorobenzotrifluoride could be drawn from these experiments, however, because the control experiments showed unexplained high losses of the compound (77%), possibly resulting from undefined abiotic reactions.

The loss of 4-chlorobenzotrifluoride from water because of volatilization was reported by Elanco Products Co. (1983d). With a 10 ppm aqueous solution of the compound, the average ratio of compound volatilization rate to oxygen reaeration rate was determined to be 0.64 at ambient temperature. If it is assumed that the oxygen reaeration rates from a pond, a river and a lake are 0.19/day, 0.96/day and 0.24/day, respectively (Thomas, 1982), the estimated volatilization half-lives from these water bodies would be ~1-6 days. Therefore, it can be concluded that volatilization of the compound from water is an important process. The sorption of the compound by soil and sediment was also reported by Elanco Products Co. (1983e). With sandy loam soil of 1.2% organic matter content and clay loam soil of 3.1% organic matter content, the authors of this report estimated the soil K_{oc} value to range between 510 and 530. The K_{oc} value in sediments of 3.0-3.2% organic matter content was ~420-490. Therefore, the compound is expected to remain moderately sorbed to most soils and sediments.

Bioconcentration by Bluegill sunfish, Lepomis macrochirus, was tested in a static nonaerated system in the presence of 0.025-0.25 ppm 4-chlorobenzotrifluoride for $\leq$48 hours (Elanco Products Co., 1984). A steady-state BCF of 122-202 was estimated, indicating that the compound will not bioconcentrate significantly in aquatic organisms.

2.3. SOIL

Data regarding the fate of 4-chlorobenzotriflouride in soil are extremely limited. As discussed in Section 2.2., the K_{oc} value for this compound in soil has been experimentally determined to be 510-530 (Elanco Products Co., 1983e). From this moderate K_{oc} value, it can be predicted that 4-chlorobenzotrifluoride may leach significantly from some soils if the biodegradation rate in the soil is slower than the infiltration rate. Since

the compound was detected in a groundwater in Italy near an improper disposal site (Cacco and Ferrari, 1982), it is likely that biodegradation, at least in soils that contain high concentrations of the compound, will not be fast. Based on data provided in Section 2.2., photolysis on soil surfaces will probably be unimportant, and some loss of the compound will occur from soil surfaces as a result of volatilization. Volatilization loss from soil will become increasingly less important, however, as the soil depth increases. Based on the data available regarding its fate in water, it is likely that the compound will be persistent in most soils. The absorption of the compound from soil and the subsequent possibility of translocation to upper parts of plants were studied by Cacco and Ferrari (1982), who demonstrated that the translocation of the compound from root to leaves of grass and legumes is rapid; however, the compound is metabolized rapidly in legumes but not in grass.

2.4. SUMMARY

Of the three likely chemical processes that may lead to the loss of 4-chlorobenzotrifluoride in the atmosphere, neither direct photolysis nor its reaction with atmospheric O_3 is significant (Atkinson et al., 1985). Its reaction with photochemically produced HO radical has a rate constant of 2.3×10^{-13} cm^3/molecule-sec (Atkinson et al., 1985). Assuming the atmospheric concentration of HO radical as 10^6 radicals/cm^3, the lifetime of this compound in the air has been estimated to be ~50 days (Atkinson et al., 1985). Therefore, the compound is expected to persist in the atmosphere. In water, photolysis of the chemical is not important (Elanco Products Co., 1983a). Although the rates of aerobic and anaerobic biodegradation of the compound in water could not be determined, these rates are slower than the volatilization rate (Elanco Products Co., 1983b,c,d). From

the value of the ratio of the volatilization rate of the compound to the oxygen reaeration rate determined experimentally (Elanco Products Co., 1983d) and the values of oxygen reaeration rates in a few natural waters (Thomas, 1982), the half-life for volatilization of the compound from water has been estimated to be 1-6 days. The K_{oc} value of 420-490 in sediments (Elanco Products Co., 1983e) indicates that the compound will sorb moderately to suspended solids and sediments in natural waters. Based on the experimentally determined BCF of 122-202 in Bluegill sunfish, Lepomis macrochirus, (Elanco Products Co., 1984), the compound is not expected to bioconcentrate significantly in aquatic organisms. From the data available in aquatic studies, it can be predicted that photolysis in soil will be unimportant, and some loss of the compound will occur from the soil surface because of volatilization, although the volatilization process will become less important as the soil depth increases. The K_{oc} value of 510-530 in soil (Elanco Products Co., 1983e) indicates that the compound may leach through some soils, particularly soil from improper disposal sites. No data regarding the biodegradability of the compound in soil are available.

3. EXPOSURE

There is a paucity of data on the levels of 4-chlorobenzotrifluoride in environmental media. This compound was qualitatively detected in water from Lake Ontario at Niagara River (Great Lakes Water Quality Board, 1983). The source of the compound in the water was possibly the nearby manufacturer of the chemical. Hauser and Bromberg (1982) reported the qualitative detection of this compound in the sediment/soil/water samples collected from contaminated areas of Love Canal, Niagara Falls. Bass and yellow perch collected from Niagara River and analyzed in 1978 contained 4-chlorobenzotrifluoride in the concentration range 0.17-2.0 ppm. The compound was not detected at a later date (1980), however, at a detection limit of 0.01 ppm in various samples of fish (walleye, brown trout and sucker) from Lake Erie and Lake Ontario near the suspected contaminated areas (Occidental Chem. Corp., 1980b). Cacco and Ferrari (1982) reported the detection of this compound at a level of 1 ppm in groundwater near an improper disposal site near Vicenza, Italy.

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

The acute toxicity of 4-chlorobenzotrifluoride to aquatic organisms was assessed for two species of fish (rainbow trout, Salmo gairdneri, and bluegill sunfish, Lepomis macrochirus) and a macroinvertebrate (the crustacean, Daphnia magna). Exposure of rainbow trout to 4-chlorobenzotrifluoride in static acute toxicity tests produced nominal 24-, 48-, 72- and 96-hour LC_{50} estimates of 13.5 mg/ℓ (Union Carbide Environmental Services, 1979a). Confidence limits were not generated because of a lack of intermediate levels of mortality. No deaths were observed at 10 mg/ℓ 4-chlorobenzotrifluoride, and 100% mortality was observed at 18 mg/ℓ for each observation period. The test was conducted in reconstituted water at 12°C.

Exposure of bluegill sunfish to 4-chlorobenzotrifluoride in static acute toxicity tests produced nominal 24-, 48-, 72- and 96-hour LC_{50} values with 95% confidence limits of 19.1 (15.9-22.9), 13.5 (11.5-15.8), 12.7 (11.4-14.1) and 12.0 (10.3-13.9) mg/ℓ, respectively (Union Carbide Environmental Services, 1979b). No deaths were observed at 5.6 mg/ℓ 4-chlorobenzotrifluoride after 96 hours. The test was conducted in reconstituted water at 22°C.

Exposure of D. magna to 4-chlorobenzotrifluoride in static acute toxicity tests produced nominal 24- and 48-hour LC_{50} estimates with 95% confidence limits of 13.2 (11.4-15.2) and 12.4 (10.7-14.5) mg/ℓ, respectively (Union Carbide Environmental Services, 1979c). No deaths were observed at 5.6 mg/ℓ 4-chlorobenzotrifluoride after either 24 or 48 hours of exposure. The test was conducted in well water at 21°C.

4.2. CHRONIC EFFECTS

The chronic toxicity of 4-chlorobenzotrifluoride to aquatic organisms was assessed for a single species of fish (fathead minnow, Pimephales promelas) and the macroinvertebrate, D. magna. Percentage hatch and survival of fathead minnow embryos exposed to 4-chlorobenzotrifluoride were used to estimate a 31-day MATC of >0.54 but <1.4 mg/ℓ (EG&G Bionomics, 1981). Fathead minnow eggs were exposed to 4-chlorobenzotrifluoride in a flowthrough system using well water at a temperature of 25°C. Measured concentrations of 4-chlorobenzotrifluoride were used to calculate the MATC value.

The chronic effects of exposure of D. magna to 4-chlorobenzotrifluoride were assessed by generating 4-, 7-, 14- and 21-day LC_{50} estimates with 95% confidence limits of 0.163 (0.120-0.222), 0.150 (0.105-0.214), 0.073 (0.05-0.107) and 0.071 (0.047-0.107) mg/ℓ, respectively (Union Carbide Environmental Services, 1979d). In addition, brood size of actively reproducing D. magna adults exposed to 4-chlorobenzotrifluoride was used to estimate a 21-day MATC of ≥0.03 but <0.05 mg/ℓ 4-chlorobenzotrifluoride. The test was conducted in well water under flowthrough conditions at a mean temperature of 20.8°C. Measured concentrations of 4-chlorobenzotrifluoride were used to calculate the MATC and LC_{50} values.

4.3. PLANT EFFECTS

There were no studies identified that addressed the effects of exposure of aquatic plants to 4-chlorobenzotrifluoride.

4.4. SUMMARY

Exposure of rainbow trout and bluegill sunfish to 4-chlorobenzotrifluoride generated 96-hour LC_{50} values of 13.5 and 12.0 (10.3-13.9) mg/ℓ, respectively (Union Carbide Environmental Services, 1979b). Exposure of D.

magna to 4-chlorobenzotrifluoride generated a 48-hour LC_{50} of 12.4 (10.7-14.5) mg/ℓ (Union Carbide Environmental Services, 1979c).

The concentration of 4-chlorobenzotrifluoride that produced chronic effects in aquatic organisms was ~1-2 orders of magnitude lower than that produced for acute effects. The MATC for fathead minnow eggs was >0.54 but <1.4 mg/ℓ 4-chlorobenzotrifluoride. The MATC for D. magna was ≥0.03 and <0.05 mg/ℓ 4-chlorobenzotrifluoride (Union Carbide Environmental Services, 1979d).

5. PHARMACOKINETICS

5.1. ABSORPTION

A metabolism study of [CF_3-^{14}C]-4-chlorobenzotrifluoride, which found radioactivity in the expired air and urine of male and female Sprague-Dawley rats treated at doses of 1 or 104 mg/kg (in corn oil), indicated that the compound is absorbed from the gastrointestinal tract (Quistad and Mulholland, 1983). Within 4 days of dosing, radioactivity in the expired air and urine of treated rats accounted for 68-82% and 6-15% of the dose, respectively, with the total by both routes ranging from 76-88%. Only 2-4% of the dose was found in the feces. Analysis of blood for radioactivity identified a peak concentration of ~0.05 ppm, 1 hour after dosing, suggest- ing that absorption from the gastrointestinal tract was rapid.

5.2. DISTRIBUTION

Four days after rats of both sexes were given a gavage dose of [CF_3-^{14}C]-4-chlorobenzotrifluoride in corn oil (1 or 104 mg/kg), ~1% of the radioactivity remained in the carcass, except for selected tissues (see below) (Quistad and Mulholland, 1983). Analysis of organs and tissues, including the spleen, fallopian tubes and ovaries, testes, pancreas, lungs, kidney, brain, heart, muscles, fat, liver, hide, stomach and intestines, revealed slightly higher levels of radioactivity in tissues from female rats compared with male rats. The radioactivity in the tissues was identified as 4-chlorobenzotrifluoride, and tissue concentrations ranged from <1-16 µg/kg following a 1 mg/kg dose, and <40-371 µg/kg following a 104 mg/kg dose. The only exception was abdominal fat from female, but not male, rats, which contained higher levels of radioactivity: 104 µg/kg following a 1

mg/kg dose and 1420 μg/kg following a 104 mg/kg dose. Approximately 90% of the radioactivity in the abdominal fat was identified as 4-chlorobenzotrifluoride.

5.3. METABOLISM

In a metabolism study of [CF_3-^{14}C] 4-chlorobenzotrifluoride where rats were treated orally, Quistad and Mulholland (1983) found that the compound was not metabolized extensively. At a dose of 1 mg/kg, ~15% of the dose was metabolized. Analysis of radioactivity in the expired air revealed that unmetabolized [^{14}C]-4-chlorobenzotrifluoride accounted for a majority of the 62-82% of the dose recovered, with negligible amounts recovered as $^{14}CO_2$. At least 56% of the radioactivity found in the feces was unmetabolized 4-chlorobenzotrifluoride; the remaining radioactivity was not identified. The major urinary metabolites identified were the glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, which accounted for $\leq$2.7 and 4.4% of the total dose, respectively. A minor metabolite, the mercapturic acid conjugate of 4-chlorobenzotrifluoride, accounted for 0.1-0.2% of the total dose, respectively. Because 4-chlorobenzoic acid and its conjugates were not detected in the urine, the investigators concluded that the CF_3 moiety was stable to hydrolysis. Little difference in qualitative or quantitative metabolism between male and female rats was observed.

5.4. EXCRETION

Four days after rats were given a single oral dose of [CF_3-^{14}C]-4-chlorobenzotrifluoride in corn oil at 1 (four females, two males) or 104 mg/kg (two females), 62-82% of the dose was recovered in the expired air (Quistad and Mulholland, 1983). Analysis of air resulted in recovery of 35% of the radioactivity before the rats defecated; this suggested that pulmonary excretion was rapid, and confirmed that the radioactivity had been

expired and had not volatilized from the feces. Radioactivity recovered in the feces accounted for 2.6-3.5% of the dose, while urinary radioactivity accounted for 13.6-14.9% of the dose following treatment at 1 mg/kg, and 5.9% of the dose at 104 mg/kg. Total recoveries ranged from 79-90%. The investigators stated that the relatively low recoveries were a reflection of difficulties in the radioassay of volatile [^{14}C]-4-chlorobenzotrifluoride.

5.5. SUMMARY

The single study of [^{14}C]-4-chlorobenzotrifluoride metabolism using rats (Quistad and Mulholland, 1983) indicated that the compound is absorbed and excreted readily, predominantly as the parent compound. The major route of excretion was through expired air, which accounted for 62-82% of the dose. Urinary metabolites identified were the glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, which accounted for $\leq$2.7 and 4.4% of the dose, respectively. A minor urinary metabolite, the mercapturic acid conjugate of 4-chlorobenzotrifluoride, accounted for 0.1-0.2% of the dose.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure. Pertinent data regarding the toxicity of 4-chlorobenzotrifluoride following subchronic and chronic inhalation exposure were not located in the available literature cited in Appendix A.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- In a 3-month study, groups of 15 F344 rats/sex (5-6 weeks old) were treated daily by gavage with 4-chlorobenzotrifluoride (97.7% pure) in corn oil at doses of 0, 10, 40, 150 or 500 mg/kg/day (Arthur and Probst, 1983). One male rat at 10 mg/kg/day and two male rats at 500 mg/kg/day died. No significant dose-related physical or behavioral signs or ophthalmic changes were noted. Transiently significant reductions in body weight gain were observed in all dose groups, with body weight gain in males at 500 mg/kg/day consistently below controls. Food intake of all 4-chlorobenzotrifluoride-treated rats was depressed throughout the study, the largest decrease being observed in males at 500 mg/kg/day. The only significant hematology changes noted were in high-dose male rats, which had a statistically significant ($p<0.05$) decrease in total erythrocytes and a shift toward an increase in neutrophils and a decrease in lymphocytes. Results of clinical chemistry analyses revealed slightly elevated levels of serum urea nitrogen in male rats treated at 150 and 500 mg/kg. Total bilirubin was increased in both male and female rats at 500 mg/kg. Urinalysis indicated mild proteinuria in both sexes at 150 and 500 mg/kg. Determinations of hepatic p-nitroanisole O-demethylase activity showed significantly ($p<0.05$) greater levels in males at 40, 150 and 500 mg/kg/day, and in females at 500 mg/kg/day. At necropsy, relative liver and kidney weights were significantly ($p<0.05$) increased "at the higher doses"

(presumably 150 and 500 mg/kg). Thyroid weights were slightly increased in treated rats, with significant increases ($p<0.05$) in females at 40 and 500 mg/kg. Slightly increased adrenal weights were observed in males at 150 and 500 mg/kg/day and in females at 500 mg/kg/day. Histological examinations revealed renal tubular degeneration in one low-dose male rat (10 mg/kg/day) and in all male rats treated at doses >40 mg/kg/day. The severity of the renal lesions was dose-related, ranging from minimal (decreased cellular height, increased cytoplasmic basophilia, increased hyaline droplet formation) to moderate (increased number of necrotic cortical epithelial cells, and prominent hyaline casts in tubules of the outer zone medulla and occasionally in the cortex). Tubular degeneration was not observed in female rats or in any male controls. Centrilobular hypertrophy was observed in the livers of all males and one female rat treated at 150 mg/kg/day and in all rats treated at 500 mg/kg/day. Centrilobular hypertrophy was not observed in control rats. Among high-dose rats, the effect on the liver was slightly more prominent in males than in females. The investigators concluded that rats tolerated the 10 mg/kg dose for 90 days without significant toxicity.

6.1.2.2. CHRONIC -- Pertinent data regarding the toxicity of 4-chlorobenzotrifluoride following chronic oral exposure were not located in the available literature cited in Appendix A.

6.1.3. Other Relevant Information. Hooker Chemical Corp. (1979a) reported a 4-hour LC_{50} of 33.0 mg/m³ for 4-chlorobenzotrifluoride in Sprague-Dawley rats (male and female). No mortality occurred at 6.03 or 20.8 mg/m³. According to the investigators, signs of irritation during the exposure (redness around the eyes, excessive lacrimation, nasal discharge) occurred at concentrations >20.8 mg/m³, and lung discoloration on necropsy was observed in all exposure groups. These results suggest that

pulmonary irritation may be an important component in the toxicity of 4-chlorobenzotrifluoride following inhalation exposure.

In a Russian study (Rapoport et al., 1986), male nonpurebred albino male rats (numbers unspecified) were exposed to 4-chlorobenzotrifluoride at 5.5, 20.5, 71.6 or 440 mg/m^3, continuously for 120 hours. The rats were observed for at least 115 days following exposure. Examinations included body weight, muscular strength (grasping reflex), blood analyses (RBC and leukocyte counts, hematocrit, content of hemoglobin in one erythrocyte, liver function, cholinesterase and lactate dehydrogenase) and studies of the nervous system ("summation-threshold index," motor activity). Exposure at 440 and 71.6 mg/m^3 resulted in a change in "practically all of the parameters studied." The 20.5 mg/m^3 concentration was considered the "minimally effective" concentration, while 5.5 mg/m^3 was considered the "subthreshold." The results, which are difficult to interpret, are presented as time of onset of significant changes in parameters. In general, time of onset of significant effects increased with decreasing exposure concentration. The study does not relate exposure concentration to incidence or severity of effects.

The oral LD_{50} for 4-chlorobenzotrifluoride in Sprague-Dawley rats (male and female) was reported as >5.0 mℓ/kg (6.7 g/kg) (Hooker Chemical Corp., 1985a). At a dose of 5 mℓ/kg (6.7 g/kg), 2/8 male and 0/8 female rats died during the 14-day observation period.

The dermal LD_{50} in New Zealand White rabbits was reported to be >2.0 mℓ/kg (2.7 g/kg) (Hooker Chemical Corp., 1985b). 4-Chlorobenzotrifluoride was applied to shaved abraded skin (back) and the test area was occluded. Only one dose was studied; at 2 mℓ/kg (2.7 g/kg), 0/5 male and 1/5 female rabbits died during the 14-day observation period.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of 4-chlorobenzotrifluoride following inhalation exposure were not located in the available literature cited in Appendix A.

6.2.2. Oral. Pertinent data regarding the carcinogenicity of 4-chlorobenzotrifluoride following oral exposure were not located in the available literature cited in Appendix A.

6.2.3. Other Relevant Data. Hooker Chemical Corp. (1980) reported that 4-chlorobenzotrifluoride tested negative for cell transformation in Balb/C3T3 cells. The compound (purity unspecified) was added to the culture medium at concentrations of 0.1-40 nℓ/mℓ, which allowed 80 to 50% of the cells to survive. The study did not report whether an activating system was used. Lilly Research Laboratories (1983a) also found that 4-chlorobenzotrifluoride (97% pure) tested negative for cell transformation in Balb/C3T3 cells. This study was conducted in the presence of S-9, with the compound added to the culture medium at concentrations of 10-300 µg/ℓ. Reduced survival was observed at 300 µg/mℓ, a concentration at which the compound was not completely miscible with the culture medium.

6.3. MUTAGENICITY

Data regarding the mutagenicity of 4-chlorobenzotrifluoride are presented in Table 6-1. 4-Chlorobenzotrifluoride tested negative in assays for reverse mutation in Salmonella typhimurium (Haworth et al., 1983; Hooker Chemical Corp., 1978a). Urine from mice treated with 4-chlorobenzotrifluoride also tested negative in assays for reverse mutation in S. typhimurium (Hooker Chemical Corp., 1979b). Negative results have been reported for 4-chlorobenzotrifluoride in assays for reverse mutation in Saccharomyces cerevisiae, DNA repair in Escherichia coli (Hooker Chemical

TABLE 6-1

Mutagenicity Testing of 4-Chlorobenzotrifluoride

Assay	Indicator Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA98, TA100	96%	preincubation	10-1000 µg/plate	±S-9	-	NC	Haworth et al., 1983
Reverse mutation	S. typhimurium TA1535, TA1537, TA98, TA100	NR	plate incorporation	0.01-10 µl/plate	±S-9	-	NC	Hooker Chemical Corp., 1978a
Reverse mutation (urine assay)	S. typhimurium TA1535, TA1537, TA98, TA100	NR	male CD-1 mice treated by gavage for 2 days at 50, 167 or 500 mg/kg/day; urine tested for mutagenicity by plate incorporation	0.1, 0.2 or 0.3 ml urine/plate	± deconjugating enzyme, β-glucuronidase, before urine was added to plate	-	Urine was collected overnight (16 hours); the time between dosing and urine collection was not stated.	Hooker Chemical Corp., 1979b
Reverse mutation	Saccharomyces cerevisiae D4	NR	plate incorporation	0.1-10 µl/plate	± S-9	-	NC	Hooker Chemical Corp., 1978a
DNA repair test	Escherichia coli W3HO/polA+, P3478/polA-	NR	spot test (check)	0.01-10 µl/plate (check)	±S-9	-	NC	Hooker Chemical Corp., 1978a
Forward mutation	L5178Y mouse lymphoma	NR	added to culture medium	3.13-50 nl/ml	±S-9	-	Concentrations of ≥78 nl/ml were highly toxic to mouse lymphoma cells.	Hooker Chemical Corp., 1978b
Unscheduled DNA synthesis	EUE cells	NR	NR	NR	NR	+	Study was available only as an abstract, which did not further describe the cells used or the study protocol.	Benigni and Dogliotti, 1980
Chromosome aberrations	Chinese hamster ovary cells	NR	added to cultures	29.99-130 nl/ml	±S-9	-	Cells treated for 12 hours collected at 14 or 24 hours, cytotoxicity at 90 nl/ml.	Lilly Research Laboratories, 1983b

TABLE [redacted] (cont.)

Assay	Indicator Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Sister chromatid exchange	L5178 mouse lymphoma cells	NR	added to culture medium	0.0025, 0.0050, 0.0100, 0.0200, 0.0400 µl/ml	±S-9	‡	Without activation, results were significant at all concentrations. With activation, results were significant at 0.0025, 0.0100 and 0.0200 µl/ml (not dose-related)	Hooker Chemical Corp., 1979c
Chromosome aberrations	bone marrow cells of rats	NR	gavage dose	0.5, 1.7 or 5.0 ml/kg	NA	-	Analyses were completed 6, 24 and 48 hours after a single gavage dose.	Lilly Research Laboratories, 1983c

NA = Not applicable; NC = no comment; NR = not reported

Corp., 1978a), forward mutation in mouse lymphoma cells (Hooker Chemical Corp., 1978b), and chromosome aberrations in Chinese hamster ovary cells (Lilly Research Laboratories, 1983b) and rat bone marrow cells (Lilly Research Laboratories, 1983c). The only positive results for 4-chlorobenzotrifluoride were in an assay for unscheduled DNA synthesis in EUE cells (cells were not further described) (Benigni and Dogliotti, 1980), and in an assay for sister chromatid exchange in mouse lymphoma cells (Hooker Chemical Corp., 1979c).

6.4. TERATOGENICITY

Pertinent data regarding the teratogenicity of 4-chlorobenzotrifluoride were not located in the available literature cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Hooker Chemical Corp. (1981) reported results of a 2-generation reproductive study in which groups of 20 Sprague-Dawley rats/sex were treated by gavage with 4-chlorobenzotrifluoride (97% pure) in corn oil at doses of 0, 5, 15 or 45 mg/kg/day. The parental generation was treated for 4 weeks before mating, throughout reproduction, and through the weaning of the F_1 generation. The F_1 generation was culled to 10 pups/litter on day 14, and was treated for 90 days postweaning. Offspring were not examined for malformations. No treatment-related mortalities, behavior changes or consistent treatment-related changes in weight gain and food consumption were observed in the F_0 or F_1 rats. No significant treatment-related changes in hematology and clinical chemistry were noted in F_0 or F_1 rats. Treatment of rats with 4-chlorobenzotrifluoride had no effect on the number of pups/litter, pup survivability or length of gestation period. Body weight of female pups from rats treated at 45 mg/kg/day was significantly ($p<0.05$) decreased compared with controls on day 1 after birth. On day 4, body weights of offspring (males and females) were significantly

($p<0.05$) increased compared with controls in all treatment groups. At necropsy, no dose-related gross lesions were observed in the F_0 rats. Histological examinations were not completed. In the F_1 generation, determination of organ weights revealed a nonsignificant dose-related increase in mean liver weights and mean liver-to-body weight ratios in both sexes. Histological examinations of major tissues and organs completed on F_1 controls and on rats treated at 45 mg/kg/day did not reveal any treatment-related effects.

6.6. SUMMARY

Minimal to moderate renal tubular degeneration was observed in male rats treated by gavage with 4-chlorobenzotrifluoride at doses >40 mg/kg/day for 3 months (Arthur and Probst, 1983). Centrilobular hypertrophy of the liver was observed in male rats treated with 4-chlorobenzotrifluoride doses at >150 mg/kg/day and in female rats at 500 mg/kg/day. No significant effects were observed in rats treated for 3 months by gavage with 4-chlorobenzotrifluoride at 10 mg/kg/day.

In contrast to the Arthur and Probst (1983) study, histological kidney and liver effects were not observed in a 2-generation study in which Sprague-Dawley rats were treated by gavage with 4-chlorobenzotrifluoride at doses $\leq$45 mg/kg/day for $\geq$90 days (Hooker Chemical Corp., 1981). 4-Chlorobenzotrifluoride treatment did not have any effect on reproductive parameters.

A Russian study (Rapoport et al., 1986) reported that inhalation exposure of rats to 4-chlorobenzotrifluoride at concentrations >20.5 mg/m^3 for 120 hours resulted in changes in blood analyses, motor activity and muscle strength. Significant changes were not observed in rats exposed at 5.5 mg/m^3 for 120 hours.

Hooker Chemical Corp. (1979a) reported a 4-hour LC_{50} for 4-chlorobenzotrifluoride in Sprague-Dawley rats of 33 mg/m³. The oral LD_{50} for 4-chlorobenzotrifluoride in Sprague-Dawley rats was reported as >5.0 mℓ/kg (6.7 g/kg) (Hooker Chemical Corp., 1985a), while the dermal LD_{50} in rabbits was reported to be >2.0 mℓ/kg (2.7 g/kg) (Hooker Chemical Corp., 1985b).

Except for positive results in assays of unscheduled DNA synthesis (Benigni and Dogliotti, 1980) and sister chromatid exchange (Hooker Chemical Corp., 1979c), results of mutagenicity assays of 4-chlorobenzotrifluoride have been negative.

4-Chlorobenzotrifluoride has not been tested for carcinogenicity or teratogenicity.

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 were not located in the available literature cited in Appendix A.

7.2. AQUATIC

Pertinent guidelines and standards for the protection of aquatic life from exposure to 4-chlorobenzotrifluoride were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 4-chlorobenzotrifluoride were not located in the available literature cited in Appendix A.

8.1.1. Weight of Evidence. As a result of a lack of data concerning carcinogenicity in humans and animals, 4-chlorobenzotrifluoride can be classified as an EPA Group D chemical (U.S. EPA, 1986b), not classifiable as to human carcinogenicity.

8.1.2. Quantitative Risk Estimates. The derivation of carcinogenic potency factors for 4-chlorobenzotrifluoride is precluded by the lack of carcinogenicity data.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. The derivation of inhalation risk assessment values for 4-chlorobenzotrifluoride is precluded by the lack of subchronic and chronic inhalation studies.

An LC_{50} study using rats (Hooker Chemical Corp., 1979a) suggested that pulmonary irritation may be an important component in the toxicity of 4-chlorobenzotrifluoride following inhalation exposure. The only other inhalation study, a Russian study (Rapoport et al., 1986), reported changes in blood analyses, motor activity and muscular strength in rats exposed to 4-chlorobenzotrifluoride continuously at >20.5 mg/m^3 for 120 hours. Significant effects were not observed in rats exposed to 4-chlorobenzotrifluoride at 5.5 mg/m^3 for 120 hours.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES -- In the 90-day study by Arthur and Probst (1983), F344 rats were treated by gavage with 4-chlorobenzotrifluoride in corn oil at 0, 10, 40, 150 or 400 mg/kg/day. No

significant treatment-related effects were observed at 10 mg/kg/day. In male rats treated at >40 mg/kg/day, renal tubular degeneration was observed, with severity increasing from minimal effects at 40 mg/kg/day to moderate effects at 150 mg/kg/day. Centrilobular hypertrophy in the liver was observed in all male rats and in one female rat at 150 mg/kg/day, and in all rats at 400 mg/kg/day.

The only other study of sufficient duration for risk assessment is the 2-generation study using Sprague-Dawley rats (Hooker Chemical Corp., 1981). In this study, no significant treatment-related effects on reproduction or histological changes were noted in rats treated by gavage with 4-chlorobenzotrifluoride in corn oil at 0, 5, 15 or 45 mg/kg/day. The F_0 rats were treated for 4 weeks before mating, through mating and weaning, and the F_1 were treated for 90 days after weaning. A nonsignificant dose-related increase in liver weights was noted in F_1 rats.

A 3-month rat study (Arthur and Probst, 1983) indicated that the kidney and liver are the target organs of 4-chlorobenzotrifluoride toxicity. The LOAEL found in this study was 40 mg/kg/day, a dose at which minimal renal tubular degeneration in male rats was observed. The highest NOAEL below the 40 mg/kg/day LOAEL is the 15 mg/kg/day dose from the 2-generation rat study (Hooker Chemical Corp., 1981). A subchronic oral RfD of 0.2 mg/kg/day, or 11 mg/day for a 70 kg human, is calculated from the NOAEL of 15 mg/kg/day by dividing the NOAEL by an uncertainty factor of 100, 10 to extrapolate from animals to humans, and 10 to protect sensitive individuals.

Confidence in this RfD is low. The studies useful for risk assessment are limited to two rat studies. These studies indicate a possible strain difference; one study reported renal tubular degeneration in male F344 rats treated with 4-chlorobenzotrifluoride at 40 mg/kg/day (Arthur and Probst,

1983), but no treatment-related effects were observed in Sprague-Dawley rats in a 2-generation study at 45 mg/kg/day (Hooker Chemical Corp., 1981). Low confidence in the subchronic RfD is also indicated because of the lack of teratogenicity studies.

8.2.2.2. CHRONIC EXPOSURES -- Chronic oral studies of 4-chlorobenzotrifluoride were not available. A chronic oral RfD of 0.02 mg/kg/day or 1 mg/day for a 70 kg human can be derived by dividing the subchronic oral RfD by an additional uncertainty factor of 10 to extrapolate from subchronic exposure.

Confidence in this RfD is low. There are only two rat studies available concerning the toxicity of 4-chlorobenzotrifluoride, and they indicate a possible strain difference in the development of renal tubular degeneration.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The only study reporting effects following subchronic exposure to 4-chlorobenzotrifluoride is the 3-month study by Arthur and Probst (1983). As discussed in Section 6.1.2.1. and summarized in Table 9-1, male rats treated by gavage with 4-chlorobenzotrifluoride in corn oil at a dose of 40 mg/kg/day developed minimal renal tubular degeneration, while rats treated at 150 mg/kg/day developed proteinuria, mild to moderate renal tubular degeneration and centrilobular hypertrophy of the liver. As indicated in Table 9-1, the animal doses of 40 and 150 mg/kg/day correspond to human MEDs of 43 and 149 mg/day, and RV_ds of 3.0 and 2.2, respectively. The most appropriate RV_e for minimal renal tubular degeneration observed at the lower dose is 3, and the RV_e for renal tubular degeneration associated with mild proteinuria is 7. Multiplication of the RV_ds by the RV_es yields CSs of 9.0 and 15.4 for minimal renal tubular degeneration and tubular degeneration associated with proteinuria, respectively. The highest CS, 15.4, is the most appropriate basis for the RQ of 1000 (Table 9-2).

9.2. BASED ON CARCINOGENICITY

Pertinent data concerning the carcinogenicity of 4-chlorobenzotrifluoride were not located. Except for an assay for sister chromatid exchange (Hooker Chemical Corp., 1979c) and an assay for unscheduled DNA synthesis (Benigni and Dogliotti, 1980), mutagenicity assays have reported negative results (see Section 6.3.). The lack of data concerning the carcinogenicity of 4-chlorobenzotrifluoride in either humans or animals indicates that the compound should be classified as an EPA Group D chemical (U.S. EPA, 1986b), not classifiable as to human carcinogenicity. Hazard ranking based on carcinogenicity is not possible.

TABLE 9-1

Composite Scores for the Oral Toxicity of 4-Chlorobenzotrifluoride (97% Pure) in Corn Oil Using Male F344 Rats[a]

No. at Start	Average Body Weight[b] (kg)	Dose/Exposure	Animal Dose (mg/kg/day)	Equivalent Human MED[c] (mg/day)	RV_d	Effect	RV_e	CS	RQ
15	0.25	40 mg/kg/day by gavage for 3 months	40	43	3.0	Minimal renal tubular degeneration	3	9	1000
15	0.2	150 mg/kg/day by gavage for 3 months	150	149	2.2	Mild proteinuria, renal tubular degeneration and centrilobular hypertrophy of the liver	7	15.4	1000

[a]Source: Arthur and Probst, 1983

[b]Estimated from graphs

[c]Animal dose multiplied by the cube root of the ratio of animal to reference human body weight (70 kg) and by 70 kg to express human MED in mg/day, and divided by an uncertainty factor of 10 to expand from subchronic to chronic exposure.

TABLE 9-2

4-Chlorobenzotrifluoride
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	149
Effect:	mild proteinuria, renal tubular degeneration, centrilobular hypertrophy of the liver
Reference:	Arthur and Probst, 1983
RV_d:	2.2
RV_e:	7
Composite Score:	15.4
RQ:	1000

*Equivalent human dose

10. REFERENCES

Arthur, B.H. and K.S. Probst. 1983. A subchronic study in Fischer 344 rats given daily gavage doses of 4-chlorobenzotrifluoride (PCBTF). Toxicology Division, Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, IN. U.S. EPA/OPTS Public Files. Microfiche #OTS0507306.

Atkinson, R., S. Aschmann, A. Winer and J. Pitts, Jr. 1985. Atmospheric gas phase loss processes for chlorobenzene, benzotrifluoride, and 4-chlorobenzotrifluoride, and generalization of predictive techniques for atmospheric lifetimes of aromatic compounds. Arch. Environ. Contam. Toxicol. 14(4): 417-425.

Benigni, R. and E. Dogliotti. 1980. UDS studies on selected environmental chemicals. Mutat. Res. 74: 217.

Boudakian, M.M. 1980. Fluorinated aromatic compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 10, M. Grayson, Ed. John Wiley and Sons, New York, NY. p. 901; 912, 921-925, 936.

Cacco, G. and G. Ferrari. 1982. Absorption and translocation of 4-(trifluoromethyl)chlorobenzene in soil and crops. J. Agric. Food Chem. 30: 196-197.

EG&G Bionomics. 1981. The toxicity of parachlorobenzotrigluoride (PCBTF) to fathead minnow (Pimephales promelas) embryos and larvae. Report #BW-81-3-838 (OTS0508145).

Elanco Products Company. 1983a. Photolysis of p-chlorobenzotrifluoride in water. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507306.

Elanco Products Company. 1983b. Aerobic aquatic biodegradation of 4-chlorobenzotrifluoride. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507306.

Elanco Products Company. 1983c. Anaerobic biodegradation of 4-chlorobenzotrifluoride. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507306.

Elanco Products Company. 1983d. Volatilization rate of p-chlorobenzotrifluoride from water. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507306.

Elanco Products Company. 1983e. Absorption of p-chlorobenzotrifluoride on soil and sediment. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507306.

Elanco Products Company. 1984. Bioconcentration of ^{14}C-p-chlorobenzotrifluoride by bluegill in a static test system. Prepared by Lilly Res. Labs., Greenfield, IN. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507307.

Great Lakes Water Quality Board. 1983. An inventory of chemical substances identified in the Great Lakes ecosystem. Vol. 1 - Summary. Report to the Great Lakes Water Quality Board. Windsor Ontario, Canada. p. 12, 59, 90.

Hauser, T.R. and S.M. Bromberg. 1982. EPA's monitoring program at Love Canal 1980. Environ. Monit. Assess. 2: 249-271.

Hawley, G.G., Ed. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., New York, NY. p. 235.

Haworth, S., T. Lawlor, K. Mortlemans, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1: 3-5, 8-9, 16-21, 41, 51, 78.

Hooker Chemical Corp. 1978a. Mutagenicity evaluation of parachlorobenzotrifluoride (PCBTF) in the Ames Salmonella/microsome plate test. Final Report. Submitted by Litton Bionetics, Inc., Kensington, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0508133.

Hooker Chemical Corp. 1978b. Mutagenicity evaluation of parachlorobenzotrifluoride in the mouse lymphoma forward mutation assay. Final report. Submitted by Litton Bionetics, Inc., Kensington, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0508135.

Hooker Chemical Corp. 1979a. An acute inhalation toxicity study of parachlorobenzotrifluoride in the rat. Prepared by Bio/dynamic Inc. U.S. EPA/OPTS Public Files. Microfiche #OTS0508137.

Hooker Chemical Corp. 1979b. Mutagenicity evaluation of parachlorobenzotrifluoride in a in vivo/in vitro urine assay. Final Report. Submitted by Litton Bionetics, Inc., Kensington, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0508139.

Hooker Chemical Corp. 1979c. Mutagenicity evaluation of parachlorobenzotrifluoride (PCBTF) in the sister chromatid exchange assay in L5178Y mouse lymphoma cells. Final report. Submitted by Litton Bionetics, Inc., Kensington, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0508136.

Hooker Chemical Corp. 1980. Evaluation of p-chlorobenzotrifluoride in the in vitro transformation of BALB/3T3 cells assay. Submitted by Litton Bionetics, Inc., Kensington, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0508144.

Hooker Chemical Corp. 1981. Modified 90-day gavage and reproduction study in rats PCBTF. Conducted by Elars Bioresearch Laboratories, Inc., Fort Collins, CO. U.S. EPA/OPTS Public Files. Microfiche #OTS0508148.

Hooker Chemical Corp. 1985a. Acute oral toxicity (LD_{50}) in albino rats. Prepared by Raltech Scientific Services, Inc., Madison, WI. U.S. EPA/OPTS Public Files. Microfiche #OTS508138.

Hooker Chemical Corp. 1985b. Acute dermal toxicity (LD_{50}) in albino rabbits. Prepared by Raltech Scientific Services, Inc., Madison, WI. U.S. EPA/OPTS Public Files. Microfiche #OTS508134.

Hooker Chems. and Plastics Corp. 1980. Solubility of p-chlorobenzotrifluoride in water. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0508143.

HSDB (Hazardous Substances Data Bank). 1988. Office of Toxic Substances, U.S. EPA, Washington, DC. Online retrieval January 21, 1988.

Lilly Research Laboratories. 1983a. Evaluation of compound #38502 in the BALB/c-3T3 Neoplastic transformation assay with an Aroclor-induced rat liver microsomal (S9) metabolic activating system. Submitted by Arthur D. Little, Incorporated, Cambridge, MA. U.S. EPA/OPTS Public Files. Microfiche #OTS0507306.

Lilly Research Laboratories. 1983b. Chromosome aberrations in Chinese hamster ovary cells: Test article compound 38502, Lot No. 633F02. Prepared by Microbiological Associates, Bethesda, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0507306.

Lilly Research Laboratories. 1983c. Activity of compound 38502 (T2025) in the acute in vivo cytogenetic assay in male and female rats. Prepared by Microbiological Associates, Bethesda, MD. U.S. EPA/OPTS Public Files. Microfiche #OTS0507306.

Occidental Chem. Corp. 1980a. Odor threshold studies on eleven chemicals. Prepared by Arthur D. Little, Inc., Cambridge, MA. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0205957.

Occidental Chem. Corp. 1980b. Analysis of fish samples from Lakes Erie and Ontario for chlorinated benzotrifluorides as contaminants. Analyzed by FDA, Washington, DC. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507284.

Occidental Chem. Corp. 1984. Loss processes for 4-chlorobenzotrifluoride under atmospheric conditions. Prepared by R. Atkinson et al., Univ. of Calif., Riverside, CA. USEPA/OPTS Public Files, 8D Submission. Microfiche #OTS 0507309.

Quistad, G.B. and K.M. Mulholland. 1983. Metabolism of p-chlorobenzotrifluoride by rats. J. Agric. Food Chem. 31(3): 585-589.

Rapoport, K.A., L.A. Tepikina, Y.G. Fel'dman, et al. 1986. Setting the limits for parachlorobenzotrifluoride in atmospheric air. Gig. Sanit. 10: 82-83. (Russian translation)

SRI (Stanford Research Institute). 1987. 1987 Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 533.

Thomas, R.G. 1982. Volatilization from water. In: Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds, W.J. Lyman et al., Ed. McGraw Hill Publishers, New York, NY. p. 15-20.

Union Carbide Environmental Services. 1979a. The acute toxicity of parachlorobenzotrifluoride to the rainbow trout, Salmo gairdneri Richardson. UCES Project No. 11506-81-08 (OTS 0508140).

Union Carbide Environmental Services. 1979b. The acute toxicity of parachlorobenzotrifluoride to the bluegill sunfish, Lepomis macrochirus Rafinesque. UCES Project No. 11506-81-07 (OTS 0508149).

Union Carbide Environmental Services. 1979c. The acute toxicity of parachlorobenzotrifluoride to the water flea, Daphnia magna Straus. UCES Project No. 11506-81-06 (OTS 0508141).

Union Carbide Environmental Services. 1979d. Daphnia magna chronic study testing parachlorotrifluoride (97% active ingredient). UCES Project No. 11507-18 (OTS 0508142).

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. 1980. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapter of the Consent Decree Water Criteria Documents. Federal Register. 45(31): 49347-49357.

U.S. EPA 1984. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Methodology for Evaluating Carcinogenicity in Support of Reportable Quantity Adjustment Pursuant to CERCLA Section 102. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid and Emergency Response, Washington, DC.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

USITC (U.S. International Trade Commission). 1987. Synthetic Organic Chemicals. United States Production and Sales, 1986. USITC Publ. 1892, Washington, DC. p. 31, 41.

APPENDIX A

LITERATURE SEARCHED

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

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB

These searches were conducted in October 1987, 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). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. 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. 1978-1984. 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. IARC, WHO, 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. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1987. 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, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

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

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

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

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.

Summary Table for 4-Chlorobenzotrifluoride

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic				ID	
Chronic				ID	
Carcinogenicity				ID	
Oral Exposure					
Subchronic	rat	15 mg/kg for ≥90 days	NOAEL	0.2 mg/kg/day or 11 mg/day for a 70 kg human	Hooker Chemical Corp., 1981
Chronic	rat	15 mg/kg for ≥90 days	NOAEL	0.02 mg/kg/day or 1 mg/day for a 70 kg human	Hooker Chemical Corp., 1981
Carcinogenicity				ID	
REPORTABLE QUANTITIES					
Based on chronic toxicity:		1000			Arthur and Probst, 1983
Based on carcinogenicity:		ID			

ID = Insufficient data