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# Research and Development

## HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 1,3-DICHLOROPROPENE

## Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

## Prepared by

**Environmental Criteria and Assessment Office**
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NOTICE

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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 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 which would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval which 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, 1980a) 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

1,3-Dichloropropene is a colorless liquid with the odor of chloroform (Windholz, 1983). It occurs in cis- and trans-isomeric forms. The cis-isomer has a slightly higher vapor pressure than the trans-isomer (43 versus 34 mm Hg), but the water solubilities are similar (2700-2800 ppm at 20°C) (Dilling, 1977). Current production figures for 1,3-dichloropropene are not available. According to the public portion of the U.S. EPA TSCA Production File for 1977, two U.S. manufacturers (Dow and Shell Chemical) produced a combined total of 10-60 million pounds in 1977 (U.S. EPA, 1977). 1,3-Dichloropropene has been produced as a by-product of allyl chloride production in conjunction with other by-products, such as 3,3-dichloropropene and 1,2-dichloropropene (Krijgsheld and van der Gen, 1986; DeBenedictis, 1979). By-product mixtures of 1,3-dichloropropene and 1,2-dichloropropane have been marketed as a fumigant under the trade name D-D by Shell Chemical Co. (Worthing and Walker, 1987; Yang, 1986). 1,3-Dichloropropene is used as a soil fumigant and nematicide (Worthing and Walker, 1987). Several different commercial formulations containing 1,3-dichloropropene have been marketed as a fumigant. Telone II® (currently marketed by Dow Chemical) is widely used in agriculture as a soil fumigant for parasitic plant nematodes (Yang, 1986; SRI, 1986). Current Telone II® formulations contain 98% 1,3-dichloropropene (Albrecht, 1987a), although original formulations contained only 92% (Yang, 1986).

Degradation of 1,3-dichloropropene in the ambient atmosphere results primarily by reaction with photochemically generated HO• (Tuazon et al., 1984). Based upon experimentally determined rate constants (Tuazon et al., 1984), the half-lives for the reaction of cis- and trans-1,3-dichloropropene

with HO• in air are ~2.1 and 1.2 days, respectively. 1,3-Dichloropropene has been detected in rainwater (Mazurek and Simonetti, 1986), indicating that physical removal by wet deposition can occur. Hydrolysis and volatilization are important environmental fate processes in water. The rate of hydrolysis has been found to be independent of pH at pHs 5, 7 and 9 and to be essentially identical for the cis- and trans-isomers. The measured hydrolysis half-lives at 10, 20 and 30°C were 51, 11.3 and 3.1 days, respectively, with 3-chloroallyl alcohol identified as a hydrolysis product (McCall, 1987). Volatilization half-lives of 3.8-4.2 and 46-50 hours have been estimated for a model river (1 m deep) and a model environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986b). The fate of 1,3-dichloropropene in soil has been studied extensively. It hydrolyzes in wet soil to yield cis- and trans-3-chloroallyl alcohol (Castro and Belser, 1966; Roberts and Stoydin, 1976). Since the rate of hydrolysis is strongly dependent upon temperature, the importance of hydrolysis in soil will depend upon moisture content and temperature. In warm, moist soil, hydrolysis may be one of the dominant degradation processes. 1,3-Dichloropropene is susceptible to degradation by soil microorganisms (Krijgsheld and van der Gen, 1986). Adapted microbes appear capable of degrading 1,3-dichloropropene at significant rates (Tabak et al., 1981; van der Pas and Leistra, 1987). Volatilization is an important physical removal process for 1,3-dichloropropene in soil. The volatilization rate of 1,3-dichloropropene that is applied to soil as a fumigant can vary greatly with application methods, temperature, moisture content, soil porosity and soil organic content (Albrecht and Chenchin, 1985). Volatilization losses from soil may exceed 50% of the amount applied (Roberts and Stoydin, 1976) or range from only 5-10%

(Munnecke and Van Gundy, 1979). Dissolved 1,3-dichloropropene is susceptible to significant leaching in soil (Kenaga, 1980). Although leaching in wet soil can occur, concurrent hydrolysis and biodegradation should attenuate the amounts of 1,3-dichloropropene that may reach groundwaters. Vapor phase 1,3-dichloropropene is more strongly adsorbed to soil than the dissolved chemical (Munnecke and Van Gundy, 1979). The overall half-lives of 1,3-dichloroprolene in soil have been observed to vary from 3-69 days (van der Pas and Leistra, 1987; Leistra, 1970; Albrecht; 1987a).

1,3-Dichloropropene has been identified in a very limited number of drinking waters. It has been qualitatively detected in New Orleans, LA drinking water collected in August 1974 (Dowty et al., 1975; Shackelford and Keith, 1976). Monitoring studies conducted in Denver, CO and in nine municipalities along the Great Lakes failed to detect any trace of 1,3-dichloropropene (Rogers et al., 1987; Otson, 1987). Extensive groundwater monitoring for agricultural chemicals in California (including areas where Telone and D-D had been applied for years) has detected 1,3-dichloropropene in only three of thousands of samples analyzed (Cohen, 1986; Maddy et al., 1982). 1,3-Dichloropropene has been detected in leachate from municipal waste landfills and sewage treatment plants (Sabel and Clark, 1984; Lao et al., 1982). It has been suggested that chlorination of water can lead to the formation of 1,3-dichloropropene and that the identification of 1,3-dichloropropene in various water samples may be due to chlorination treatment (Krijgsheld and van der Gen, 1986). Examination of 231 different ready-to-eat foods (collected during the U.S. Food and Drug Administration's Market Basket Survey) for 22 fumigants and industrial residues failed to detect any 1,3-dichloropropene at a detection limit of ~1 ppb (Daft, 1988).

The major source of 1,3-dichloropropene release to the atmosphere is probably volatile losses from soil following soil application as a fumigant (Krijgsheld and van der Gen, 1986). Albrecht (1987b) studied the inhalation exposure of 1,3-dichloropropene in workers involved in applying Telone II® to pineapple fields in Hawaii and found exposures to be predominantly <1 ppm.

Data are available on the acute toxicity of 1,3-dichloropropene to several species of invertebrates and vertebrates. As shown in Table 4-1, 96-hour $LC_{50}$ values reveal a similar range of sensitivity among six freshwater fish species native to U.S. waters (Applegate et al., 1957; Buccafusco et al., 1981; Hermens et al., 1985; Johnson and Finley, 1980; LeBlanc, 1984; Schneider, 1979; U.S. EPA, 1978). A seventh species, the walleye, S. vitreum vitreum, showed markedly greater sensitivity, with a 96-hour $LC_{50}$ of 1.08 ppm. The water flea, D. magna, (Leblanc, 1980, 1984; U.S. EPA, 1978) showed a sensitivity comparable with that of the bluegill sunfish, L. macrochirus, the least sensitive of the freshwater fish species tested (Buccafusco et al., 1981; LeBlanc, 1984; U.S. EPA, 1978). 1,3-dichloropropene is more acutely toxic to the saltwater invertebrate, M. bahia (LeBlanc, 1984; U.S. EPA, 1978), than to the freshwater species, D. magna. The sheepshead minnow, C. variegatus, a saltwater fish, is highly sensitive to 1,3-dichloropropene (mean 96-hour $LC_{50}$ = 1.76 ppm) (LeBlanc, 1984).

Chronic toxicity tests of 1,3-dichloropropene to the fathead minnow, P. promelas, and mysid shrimp, M. bahia, revealed NOECs of 0.18 ppm and 4.2 ppm, respectively (U.S. EPA, 1978).

Data regarding the toxicity of 1,3-dichloropropene to aquatic flora follow a similar pattern to that for aquatic fauna. The saltwater alga, S. costatum, has a mean 96-hour $EC_{50}$ of 1.01 ppm (LeBlanc, 1984; U.S. EPA, 1978); the freshwater alga, S. capricornutum, has a mean 96-hour $EC_{50}$ of

4.95 ppm (LeBlanc, 1984; U.S. EPA, 1978). Data on effects of 1,3-dichloropropene on bacteria indicate that Aerobacter sp. and Pseudomonas sp. are more resistant to the compound than are higher aquatic species reported above.

Studies on the bioconcentration/bioaccumulation potential of 1,3-dichloropropene in aquatic fauna and flora were not located in the available literature, but BCFs of 7 (based on water solubility) and 1 (based on $K_{ow}$) were predicted for this compound by Kenaga (1980).

Data support 1,3-dichloropropene's effectiveness as a nematocide (Abivardi, 1970; Blackmon and Musen, 1974; Costante et al., 1987; Kotcon and Loria, 1987) and its toxicity to the earthworm, Lumbricus terrestris, and to Dipter and Coleopter larvae (Edwards and Reichle, 1969).

Data regarding the effectiveness of 1,3-dichloropropene for control of soil microorganisms are equivocal. Mathur et al. (1980) noted increased numbers of fungi, bacteria and actinomycetes after treating field plots with the chemical, but Cook et al. (1987) noted 95-100% elimination of a population of Pythium spp. with 1,3-dichloropropene.

The lack of pertinent data regarding effects of exposure of aquatic fauna and flora to 1,3-dichloropropene prevented the development of freshwater or saltwater criteria.

Approximately 80% of the administered dose of 1,3-dichloropropene was absorbed into the body following inhalation or oral exposure (Stott and Kastl, 1986; Hutson et al., 1971). As the inhaled concentration of 1,3-dichloropropene increased, the absorption did not increase linearly because of an exposure level-related decrease in respiratory ventilatory frequency and to saturation of the metabolism of 1,3-dichloropropene (see Section 5.1.).

1,3-Dichloropropene was rapidly eliminated from the body, primarily in the urine as N-acetyl-S-(3-chloroprop-2-enyl) cysteine, following inhalation or oral exposure (Hutson et al., 1971; Climie et al., 1979; Dietz et al., 1985; Stott and Kastl, 1986; Fisher and Kilgore, 1988b). 1,3-Dichloropropene elimination is due to an efficient glutathione-dependent biotransformation: 1,3-dichloropropene conjugates with glutathione, enters the mercapturic acid pathway and is excreted in the urine as N-acetyl-S-(3-chloroprop-2-enyl) cysteine (Climie et al., 1979; Fisher and Kilgore, 1988a).

Differences in disposition exist between the cis- and the trans-isomers. Greater concentrations of the trans-isomer were found in the blood of rats after inhalation exposure to approximately equal concentrations of the two isomers (Stott and Kastl, 1986), and greater amounts of the cis- than the trans-isomer were found in the urine, while much greater amounts of the trans-isomer were excreted as $CO_2$ in the expired breath (Hutson et al., 1971).

Distinct differences exist in the elimination of 1,3-dichloropropene between rats and mice. Following oral dosing with $^{14}C$-1,3-dichloropropene, more of the administered dose of radioactivity was excreted in the urine and expired air of mice than of rats (Dietz et al., 1985). The rate of urinary excretion of the mercapturic acid of 1,3-dichloropropene was comparable between rats (Fisher and Kilgore, 1988b) and humans (Osterloh et al., 1984).

The $LC_{50}$ for 1,3-dichloropropene in rats and mice was 4530 mg/m$^3$ (Hine et al., 1953). Information regarding subchronic and chronic inhalation of 1,3-dichloropropene suggests that damage to the nasal mucosa of rats and mice and damage to the urinary bladders of mice may result from exposure (Stott et al., 1988; Torkelson and Rowe, 1981; Lomax et al., 1989).

Evidence of damage to the liver and kidneys was also found (Parker et al., 1982; Torkelson and Rowe, 1981).

Oral $LD_{50}$ values in rats ranged from 140-740 mg/kg and, in mice, from 300-640 mg/kg (Torkelson and Rowe, 1981; Hine et al., 1953; Toyoshima et al., 1978a,b). Subchronic studies suggested increases in the relative weight of the kidneys in rats treated orally with 1,3-dichloropropene (Torkelson and Rowe, 1981). Chronic oral studies suggest that hyperplasia of the forestomach and of the urinary-bladders of rats and mice resulted from exposure (NTP, 1985).

The only data available regarding the carcinogenicity of 1,3-dichloropropene in humans are three reported cases of hematologic malignancies that may have been the result of acute exposure to 1,3-dichloropropene (Markovitz and Crosby, 1984). There is sufficient evidence that 1,3-dichloropropene is a carcinogen in orally exposed animals. NTP (1985) found increased incidences of squamous-cell papillomas and carcinomas of the forestomach and neoplastic nodules or carcinomas of the liver in male rats treated chronically with 1,3-dichloropropene by gavage. Mice similarly treated showed increased incidences of forestomach tumors, lung adenomas or carcinomas and transitional cell carcinomas of the urinary bladder. There is weak evidence that 1,3-dichloropropene is carcinogenic in animals exposed by inhalation. Lomax et al. (1989) found an increase in the incidence of benign lung tumors (bronchioloalveolar adenomas) in male mice treated chronically with 1,3-dichloropropene, but no evidence of any increase in neoplasms in either male or female rats or in female mice following inhalation. 1,3-Dichloropropene has been found to be mutagenic in various strains of S. typhimurium (NTP, 1985; Stolzenberg and Hine, 1980; Haworth et al., 1983). 1,3-Dichloropropene has also been found to be positive for sex-linked lethal

mutations, but negative for reciprocal translocations in D. melanogaster (NTP, 1985). 1,3-Dichloropropene does not appear to be a reproductive or a developmental toxicant.

The only available data regarding the carcinogenicity of 1,3-dichloropropene in humans are three reported cases of hematologic malignancies that may have resulted from acute exposure to 1,3-dichloropropene (Markowitz and Crosby, 1984). The available animal data indicate evidence that 1,3-dichloropropene is carcinogenic by the oral route of exposure (NTP, 1985) and may be carcinogenic following inhalation exposure (Lomax et al., 1989). Mutagenicity studies indicate that 1,3-dichloropropene is mutagenic to various strains of S. typhimurium (NTP, 1985; Haworth et al., 1983; Stolzenberg and Hine, 1980). According to U.S. EPA (1986c) guidance, 1,3-dichloropropene can be placed in Group B2 - probable human carcinogen. An inhalation $q_1^*$ of $1.3 \times 10^{-1}$ $(mg/kg/day)^{-1}$ is derived based on an increased incidence of bronchioloalveolar adenomas in male mice exposed to 60 ppm for 2 years (Lomax et al., 1989).

An oral $q_1^*$ of $1.8 \times 10^{-1}$ $(mg/kg/day)^{-1}$ is derived based on the combined incidences of tumors in the forestomach and liver and pheochromocytoma in the adrenals of male rats (NTP, 1985).

A subchronic inhalation RfD of 0.01 $mg/m^3$ is calculated by adjusting a NOEL of 10 ppm from the Stott et al. (1988) study for intermittent exposure, multiplying by the RGDR and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individual).

The subchronic inhalation RfD of 0.01 $mg/m^3$ is adopted as the chronic inhalation RfD because the chronic LOAEL in mice (20 ppm) is higher than the NOEL of 10 ppm in rats in the subchronic study used as the basis for the subchronic RfD.

A subchronic oral RfD of $3x10^{-3}$ mg/kg/day is calculated taking the NOEL of 3 mg/kg/day from the Til et al. (1973) study, adjusting for intermittent exposure to 2.6 mg/kg/day and dividing by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals and an additional modifying factor of 10 for the deficient data base). A chronic oral RfD of $3x10^{-4}$ mg/kg/day is calculated by adjusting the NOEL of 3 mg/kg/day from the Til et al. (1973) study for intermittent exposure and dividing by an uncertainty factor of 10,000 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals, 10 for the use of a subchronic study and an additional modifying factor of 10 for the deficient data base). This oral RfD of $3x10^{-4}$ mg/kg/day has been verified (U.S. EPA, 1987b). An RQ of 100 is calculated on the basis of chronic toxicity and an RQ of 100 is calculated based on carcinogenicity.

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

TABLE OF CONTENTS (cont.)

LIST OF TABLES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AEL | Adverse effects level |
| ALB | Albumia |
| BCF | Bioconcentration factor |
| BOD | Biological oxygen demand |
| BUN | Blood urea nitrogen |
| CBI | Confidential Business Information |
| cc | Cubic centimeter |
| CNS | Central nervous system |
| CS | Composite score |
| $EC_{50}$ | Concentration effective to 50% of recipients |
| $ED_{50}$ | Effective dose to 50% of recipients |
| F | Potency factor |
| F344 | Fischer 344 |
| GEMS | Graphical Exposure Modeling System |
| GLU | Glutamyl |
| GMAV | Genus mean acute value |
| GMCV | Genus mean chronic value |
| GPT | Glutamic pyruvic transaminase |
| HCT | Hematocrit |
| HEC | Human equivalent concentration |
| HGB | Hemoblobin |
| $K_{oc}$ | 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 |

## LIST OF ABBREVIATIONS (cont.)

| | |
|---|---|
| LOAEL | Lowest-observed-adverse-effect level |
| LOEC | Lowest-observed-effect concentration |
| NOEC | No-observed-effect concentration |
| NOEL | No-observed-effect level |
| NPS | Non-protein sulfhydryl |
| ppb | Parts per billion |
| ppm | Parts per million |
| RBC | Red blood cell |
| RfD | Reference dose |
| RGDR | Regional gas dose ratio |
| RQ | Reportable quantity |
| $RV_d$ | Dose rating value |
| $RV_e$ | Effect rating value |
| TLV | Threshold limit value |
| TWA | Time-weighted average |
| WBC | White blood cell |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

The structures, CAS Registry numbers, synonyms, molecular weights and empirical formulas of cis- and trans-1,3-dichloropropene are presented in Table 1-1 with the cis- and trans-isomer mixture. Mixtures of the cis- and trans-isomers are known by Dow Chemical Company trade names Telone, Telone C, Telone II® and Dorlone II (Yang, 1986; Worthing and Walker, 1987). The Shell Chemical Co. trade name for this mixture is D-D92 (Worthing and Walker, 1987). The trade-named products are not pure 1,3-dichloropropene but contain other chlorinated compounds (Section 1.4).

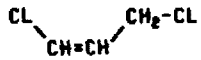
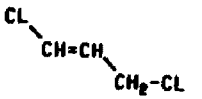
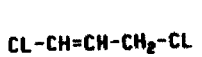
## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,3-Dichloropropene is a colorless liquid with the odor of chloroform (Windholz, 1983). The technical product (92% pure) is a colorless to amber-colored liquid with a pungent odor (Worthing and Walker, 1987). 1,3-Dichloropropene is soluble in chloroform, ether, benzene, acetone, carbon tetrachloride, heptane and methanol (Dean, 1985; Worthing and Walker, 1987). Selected physical properties of cis- and trans-1,3-dichloropropene are as follows:

| | | |
|---|---|---|
| Melting point: | no data | |
| Boiling point: | 104.3°C (cis-) | Yang, 1986 |
| | 112°C (trans-) | Yang, 1986 |
| Specific gravity: (20/4°C) | 1.224 (cis-) | Yang, 1986 |
| | 1.217 (trans-) | Yang, 1986 |
| Water solubility: at 20°C | 2700 ppm (cis-) | Dilling, 1977 |
| | 2800 ppm (trans-) | Dilling, 1977 |
| Vapor pressure: at 25°C | 43 mm Hg (cis-) | Dilling, 1977 |
| | 34 mm Hg (trans-) | Dilling, 1977 |

TABLE 1-1

Synonyms, CAS Numbers, Molecular Weight, Empirical Formula and Structure of 1,3-Dichloropropene

| Chemical (Synonyms)[a] | CAS Number | Molecular Weight | Empirical Formula | Structure |
|---|---|---|---|---|
| cis-1,3-Dichloropropene<br>1-propene, 1,3-dichloro-, (Z)-<br>cis-1,3-dichloropropylene | 10061-01-5 | 110.98 | $C_3H_4Cl_2$ |  |
| trans-1,3-Dichloropropene<br>1-propene, 1,3-dichloro-, (E)-<br>trans-1,3-dichloropropylene | 10061-02-6 | 110.98 | $C_3H_4Cl_2$ |  |
| 1,3-Dichloropropene (mixture)<br>1-propene, 1,3-dichloro-<br>1,3-dichloropropylene<br>1,3-dichloropropene, E,Z<br>alpha-chloroallyl chloride<br>gamma-chloroallyl chloride<br>alpha, gamma-chloroallyl chloride | 542-75-6 | 110.98 | $C_3H_4Cl_2$ |  |

[a]SANSS, 1989

| | | |
|---|---|---|
| Log $K_{ow}$: | 1.603 (estimated by GEMS) | U.S. EPA, 1987a |
| Conversion factor: (air at 20°C) | 1 mg/m³ = 0.217 ppm<br>1 ppm = 4.614 mg/m³ | |

1,3-Dichloropropene hydrolyzes in water to form 3-chloroallyl alcohol. The hydrolysis half-life is independent of pH and is ≃11.3 days at 20°C (McCall, 1987).

1.3. PRODUCTION DATA

Current production figures for 1,3-dichloropropene are not available. According to the public portion of the U.S. EPA TSCA Production File for 1977 (U.S. EPA, 1977), Dow Chemical Co. (Freeport, TX) manufactured 10-50 million pounds, Shell Chemical Co. manufactured 1-10 million pounds and Columbia Organic Chemicals manufactured <1000 pounds in 1977. Dow Chemical (Freeport, TX) is listed as the sole current producer of 1,3-dichloropropene (SRI, 1988).

1,3-Dichloropropene has been produced as a by-product of allyl chloride production (Krijgsheld and van der Gen, 1986), which is accomplished by the direct chlorination of propylene (DeBenedictis, 1979). Other by-products formed include 3,3-dichloropropene and 1,2-dichloropropane (DeBenedictis, 1979). By-product mixtures of 1,3-dichloropropene and 1,2-dichloropropane have been marketed as a fumigant under the trade name D-D by Shell Chemical Co. (Worthing and Walker, 1987; Yang, 1986).

1.4. USE DATA

1,3-Dichloropropene is used as a soil fumigant and nematicide (Worthing and Walker, 1987). Several different commercial formulations containing 1,3-dichloropropene have been marketed as a fumigant. Telone II® (marketed by Dow Chemical) is widely used in agriculture as a soil fumigant

for parasitic plant nematodes (Yang, 1986). Originally, Telone II® contained ≈92% 1,3-dichloropropene, 2% 1,2-dichloropropane and 5% other chlorinated propenes and hexenes with a 1% addition of epichlorohydrin as stabilizer (Yang, 1986). Currently, Telone II® is marketed as 98% 1,3-dichloropropene with no epichlorohydrin addition (Albrecht, 1987a). The fumigant D-D (marketed by Shell Chemical) contained roughly 50-80% 1,3-dichloropropene and 20-40% 1,2-dichloropropane with several percent of other chlorinated compounds (Krijgsheld and van der Gen, 1986; Yang, 1986). Fumigants marketed under trade names Telone C, Terr-O-Cide and Terr-O-Gas contained either Telone II® or D-D with additions of the pesticide chloropicrin (Yang, 1986).

## 1.5. SUMMARY

1,3-Dichloropropene is a colorless liquid with the odor of chloroform (Windholz, 1983). It occurs in cis- and trans-isomeric forms. The cis-isomer has a slightly higher vapor pressure than the trans-isomer (43 versus 34 mm Hg), but the water solubilities are similar (2700-2800 ppm at 20°C) (Dilling, 1977). Current production figures for 1,3-dichloropropene are not available. According to the public portion of the U.S. EPA TSCA Production File for 1977, two U.S. manufacturers (Dow and Shell Chemical) produced a combined total of 10-60 million pounds in 1977 (U.S. EPA, 1977). 1,3-Dichloropropene has been produced as a by-product of allyl chloride production in conjunction with other by-products, such as 3,3-dichloropropene and 1,2-dichloropropane (Krijgsheld and van der Gen, 1986; DeBenedictis, 1979). By-product mixtures of 1,3-dichloropropene and 1,2-dichloropropane have been marketed as a fumigant under the trade name D-D by Shell Chemical Co. (Worthing and Walker, 1987; Yang, 1986).

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# 2. ENVIRONMENTAL FATE AND TRANSPORT

## 2.1. AIR

1,3-Dichloropropene is degraded in the atmosphere primarily by reaction with photochemically generated HO•. Reaction with ozone will contribute to its destruction at a much slower rate than reaction with HO•. Rate constants for the reaction of cis- and trans-1,3-dichloropropene with HO• have been experimentally determined to be $7.7 \times 10^{-12}$ and $13.0 \times 10^{-12}$ $cm^3$/molecule-sec, respectively, at 22°C. Assuming an average atmospheric HO• concentration of $5 \times 10^5$ molecules/$cm^3$, the respective cis- and trans- half-lives can be calculated to be 2.1 days and 1.2 days. Rate constants for the reaction of cis- and trans-1,3-dichloropropene with ozone have been experimentally determined to be $1.5 \times 10^{-19}$ and $6.7 \times 10^{-19}$ $cm^3$/molecule-sec, respectively, at 22°C. Assuming an average atmospheric ozone concentration of $7 \times 10^{11}$ molecules/$cm^3$, the respective cis- and trans- half-lives can be calculated to be 67.4 days and 17.1 days. Formyl chloride and chloroacetaldehyde have been identified as reaction products of 1,3-dichloropropene with both HO• and ozone (Tuazon et al., 1984). Reaction with ozone also yields chloroacetic acid formic acid, hydrogen chloride, carbon dioxide and carbon monoxide.

Concentrations of 10 and 2 ng/ℓ of cis- and trans-1,3-dichloropropene, respectively, were detected in rainwater collected in Portland, OR in 1982 (Mazurek and Simonetti, 1986). This indicates that physical removal of 1,3-dichloropropene from the atmosphere by wet deposition can occur.

## 2.2. WATER

2.2.1. Hydrolysis. McCall (1987) studied the hydrolysis of $^{14}C$-radiolabeled 1,3-dichloropropene in sterile buffered water at 10, 20 and 30°C. The rate of hydrolysis was independent of pH at pHs 5, 7 and 9 and was

essentially identical for the cis- and trans-isomers. The measured hydrolysis half-lives at 10, 20 and 30°C were 51, 11.3 and 3.1 days, respectively. 3-Chloroallyl alcohol was identified as a hydrolysis product.

2.2.2. Photolysis. Direct photolysis is not an important environmental fate process with respect to 1,3-dichloropropene (Mabey et al., 1981).

2.2.3. Microbial Degradation. Tabak et al. (1981) used a static-culture flask-screening procedure utilizing BOD dilution water and settled domestic wastewater as microbial inoculum to determine that 1,3-dichloropropene is significantly biodegradable with gradual microbial adaptation. After a 28-day incubation period, 81-89% of input 1,3-dichloropropene (5-10 mg/ℓ) was biodegraded.

2.2.4. Volatilization. The Henry's Law constant for cis- and trans-1,3-dichloropropene have been measured experimentally to be 0.0012 and 0.0008 atm-$m^3$/mol at 20°C, respectively (Leistra, 1970). Henry's Law constants of this magnitude indicate that volatilization from environmental waters is probably significant (Thomas, 1982). Using a model river estimation method (Thomas, 1982), the volatilization half-lives of cis- and trans-1,3-dichloropropene from a river 1 meter deep flowing 1 m/sec with a wind velocity of 3 m/sec can be estimated to be ≈3.8 and 4.2 hours, respectively. The volatilization half-lives from a model environmental pond can be estimated to be ≈46 and 50 hours (U.S. EPA, 1986b). Based upon these estimates, volatilization from water is expected to be a major process for the removal of 1,3-dichloropropene from the aquatic environment.

2.2.5. Adsorption. Experimental data pertaining to the adsorption of 1,3-dichloropropene to aquatic sediments were not located; however, the water solubilities of 2700-2800 ppm (Dilling, 1977) suggest that partitioning from the water column to sediment may not be important.

## 2.3. SOIL

The fate of 1,3-dichloropropene in soil has been extensively studied. The important fate processes in soil are briefly discussed below.

2.3.1. Chemical Degradation. The cis- and trans-isomers of 1,3-dichloropropene have been observed to hydrolyze in wet soil to form corresponding cis- and trans-3-chloroallyl alcohol under laboratory conditions (Castro and Belser, 1966). The rate of hydrolysis was observed to increase as the soil content of aqueous solutions was increased. Other studies conducted under laboratory and outdoor conditions have found the 3-chloroallyl alcohol to be the major degradation product of 1,3-dichloropropene (Roberts and Stoydin, 1976). Degradation of 3-chloroallyl alcohol in soil occurs primarily by microbial transformation (McCall, 1987). As noted in Section 2.2.1, the hydrolysis rate of 1,3-dichloropropene is strongly dependent upon temperature. Therefore, the importance of hydrolysis in soil will depend upon moisture content and temperature. In warm moist soils, hydrolysis should be relatively rapid and a dominant removal process; however, in dry or cold soils, the importance of hydrolysis will be diminished.

2.3.2. Microbial Degradation. Although 1,3-dichloropropene is susceptible to degradation by soil microorganisms (Krijgsheld and van der Gen, 1986), the relative importance of biodegradation in soil has not been determined with certainty. Experiments specific to 1,3-dichloropropene involving degradation in nonsterile soil versus control experiments in sterilized soil are not available. Results of 1,3-dichloropropene transformation experiments in flower-bulb fields have suggested that microbes in fields previously exposed to the compound become adapted to 1,3-dichloropropene and are able to rapidly degrade it at low input concentrations (12 ppm). Half of the compound degraded in <5 days (van der Pas and Leistra, 1987).

2.3.3. Volatilization. Volatilization is an important physical removal process for 1,3-dichloropropene in soil. The amount of 1,3-dichloropropene applied to soil as a fumigant that volatilizes can vary greatly with application methods, temperature, moisture content, soil porosity and soil organic content (Albrecht and Chenchin, 1985). In experiments performed in jars to trap escaping vapor, a major portion of the 1,3-dichloropropene applied to a soil was observed to evaporate unchanged from the soil and some degradation of 1,3-dichloropropene in soil was detected (Roberts and Stoydin, 1976). It has also been reported that commercial applications at a depth of 0.3 m in a warm, moist, sandy loam soil result in evaporative losses of only 5-10 percent (Munnecke and Van Gundy, 1979; Thomas and McKenry, 1974).

2.3.4. Adsorption/Leaching. 1,3-Dichloropropene can occur in soil as a gas and as an aqueous solution. The adsorption characteristics of each of these phases is different. Experimental $K_{oc}$ values for the cis- and trans-isomers of 1,3-dichloropropene in aqueous solution are reported to be 23-26 (Kenaga, 1980). These $K_{oc}$ values indicate high mobility in soil (Swann et al., 1983) and a significant potential for leaching. Although leaching in wet soil can occur, concurrent hydrolysis and biodegradation should attenuate the amounts of 1,3-dichloropropene that may reach groundwaters. Extensive groundwater monitoring conducted in California have demonstrated that field-applied 1,3-dichloropropene is not significantly contaminating well waters (Maddy et al., 1982; Cohen, 1986).

Vapor-phase 1,3-dichloropropene is more strongly adsorbed to soil than the dissolved chemical (Munnecke and Van Gundy, 1979). Vapor-phase adsorption has been found to depend partially upon organic content of the soil and temperature. Adsorption isotherms indicate increasing adsorption with increasing organic content. Adsorption at 2°C is ≈3 times higher

than adsorption at 20°C. Adsorption isotherms measured for humous sand, peaty sand and peat indicate vapor-phase $K_{oc}$ values of ≈450-750 (Leistra, 1970).

2.3.5. Persistence. The persistence of 1,3-dichloropropene in soil has been measured by a number of investigators. van der Pas and Leistra (1987) observed half-lives of 3-4 days in fields used for planting flower-bulbs with only very small amounts remaining after periods ≤49 days. Leistra (1970) reported slower degradation rates of 0.035/day (half-life of 19.8 days) in a loam soil and 0.01/day (half-life of 69 days) in sandy and peat soils. Albrecht (1987a) reported half-lives of 3-25 days at 20°C for cis- and trans-1,3-dichloropropene. Twelve weeks after radiolabeled cis- and trans-1,3-dichloropropene was applied to soils and stored in sealed jars, 19% of the cis-isomer and 18% of the trans-isomer remained in a sandy loam soil while 10% of the cis-isomer and 22% of the trans-isomer remained in a medium loam soil (Roberts and Stoydin, 1976).

As noted previously, the removal of 1,3-dichloropropene from soil can occur from hydrolysis, microbial degradation and volatilization. Since the rate of these processes can vary significantly with soil conditions, the wide range of reported persistence half-lives demonstrates that the persistence of 1,3-dichloropropene in soil depends upon local conditions.

## 2.4. SUMMARY

Degradation of 1,3-dichloropropene in the ambient atmosphere results primarily by reaction with photochemically generated HO• (Tuazon et al., 1984). Based upon experimentally determined rate constants (Tuazon et al., 1984), the half-lives for the reaction of cis- and trans-1,3-dichloropropene with HO• in air are ≈2.1 and 1.2 days, respectively. 1,3-Dichloropropene has been detected in rainwater (Mazurek and Simonetti, 1986),

indicating that physical removal by wet deposition can occur. Hydrolysis and volatilization are important environmental fate processes in water. The rate of hydrolysis has been found to be independent of pH at pHs 5, 7 and 9 and to be essentially identical for the cis- and trans-isomers. The measured hydrolysis half-lives at 10, 20 and 30°C were 51, 11.3 and 3.1 days, respectively, with 3-chloroallyl alcohol identified as a hydrolysis product (McCall, 1987). Volatilization half-lives of 3.8-4.2 and 46-50 hours have been estimated for a model river (1 m deep) and a model environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986b). The fate of 1,3-dichloropropene in soil has been studied extensively. It hydrolyzes in wet soil to yield cis- and trans-3-chloroallyl alcohol (Castro and Belser, 1966; Roberts and Stoydin, 1976). Since the rate of hydrolysis is strongly dependent upon temperature, the importance of hydrolysis in soil will depend upon moisture content and temperature. In warm, moist soil, hydrolysis may be one of the dominant degradation processes. 1,3-Dichloropropene is susceptible to degradation by soil microorganisms (Krijgsheld and van der Gen, 1986). Adapted microbes appear capable of degrading 1,3-dichloropropene at significant rates (Tabak et al., 1981; van der Pas and Leistra, 1987). Volatilization is an important physical removal process for 1,3-dichloropropene in soil. The volatilization rate of 1,3-dichloropropene that is applied to soil as a fumigant can vary greatly with application methods, temperature, moisture content, soil porosity and soil organic content (Albrecht and Chenchin, 1985). Volatilization losses from soil may exceed 50% of the amount applied (Roberts and Stoydin, 1976) or range from only 5-10% (Munnecke and Van Gundy, 1979). Dissolved 1,3-dichloropropene is susceptible to significant leaching in soil (Kenaga, 1980). Although leaching in wet soil can occur, concurrent hydrolysis and biodegradation

should attenuate the amounts of 1,3-dichloropropene that may reach groundwaters. Vapor phase 1,3-dichloropropene is more strongly adsorbed to soil than the dissolved chemical (Munnecke and Van Gundy, 1979). The overall half-lives of 1,3-dichloroprolene in soil have been observed to vary from 3-69 days (van der Pas, 1987; Leistra, 1970; Albrecht, 1987a).

# 3. EXPOSURE

## 3.1. WATER

1,3-Dichloropropene has been identified in a very limited number of drinking waters. It has been qualitatively detected in New Orleans, LA drinking water collected in August 1974 (Dowty et al., 1975; Shackelford and Keith, 1976). Analysis of 15 drinking water samples from Denver collected between October 1, 1985 and March 31, 1986 did not detect any cis- or trans-1,3-dichloropropene at or above detection limits of 0.13 ppb (Rogers et al., 1987). 1,3-Dichloropropene was not detected (detection limit 0.1 ppb) in 42 raw and 42 finished drinking water samples collected between July 1982 and May 1983 from nine municipalities along the Great Lakes (Otson, 1987).

Trans-1,3-dichloropropene has been qualitatively identified in river water from the Genesee River and Wine Creek, which flow into Lake Ontario (Great Lakes Water Quality Board, 1983). Extensive groundwater monitoring for agricultural chemicals in California has detected cis-1,3-dichloropropene in only two groundwater samples and trans-1,3-dichloropropene in only one groundwater sample (Cohen, 1986). By comparison, dibromochloropropane (another soil fumigant) was detected in 2522 groundwater samples. In municipal wells in areas of California where Telone or D-D was applied for >15 years (54 wells, 65-1200 ft deep), 1,3-dichloropropene was not detectable in any sample at the quantification limit of 0.1 ppb (Maddy et al., 1982). cis-1,3-Dichloropropene has been detected in municipal solid waste leachate from Wisconsin (18 ppb) and in a contaminated ground water adjacent to a municiple landfill in Minnesota (Sabel and Clark, 1984). The preliminary findings of the U.S. EPA Nationwide Urban Runoff Program reported the detection of 1,3-dichloropropene (1-2 ppb) in stormwater runoff

from Eugene, OR (Cole et al., 1984). Concentrations of 1-8 ppb trans-dichloropropene have been identified in raw sewage and effluents from sewage treatment plants (Lao et al., 1982).

It has been suggested that chlorination of water can lead to the formation of 1,3-dichloropropene and that the observed presence of 1,3-dichloropropene in some drinking water samples after treatment may be due to chlorination. As an example, the effluent from municipal wastewater treatment plants was found to contain higher amounts of 1,3-dichloropropene than the influent wastewater (Krijgsheld and Van der Gen, 1986).

3.2. FOOD

Daft (1988) examined 231 different ready-to-eat foods (collected during the U.S. Food and Drug Administration's Market Basket Survey) for 22 fumigants and industrial residues. 1,3-Dichloropropene was not detected in concentrations $\geq$1 ppb in any of the food samples.

3.3. INHALATION

Atmospheric monitoring data for 1,3-dichloropropene are limited. 1,3-Dichloropropene was detected in 2 of 11 air samples collected in the Baton Rouge, LA area at levels of a trace to 10 ng/m$^3$ (0.0022 ppb) (Pellizzari et al., 1979). A mean dichloropropene level (isomers not specified) of 0.071 ppb was detected in 14 air samples collected at source dominated areas in Texas and Louisiana; source dominated areas are areas where the compound is produced or used. Dichloropropene was not detected (detection limit not reported) in seven remote air samples from the Grand Canyon (Brodzinsky and Singh, 1982).

Albrecht (1987b) studied the inhalation exposure of 1,3-dichloropropene in workers involved in applying Telone II® to pineapple fields in Hawaii. Exposures were predominantly found to be <1 ppm.

1,3-Dichloropropene is a volatile compound and after soil application as a fumigant, a fraction of the compound will volatilize and escape into the atmosphere (Krijgsheld and van der Gen, 1986). This is probably the major source of release to the atmosphere.

## 3.4. DERMAL

Pertinent monitoring data regarding the dermal exposure of 1,3-dichloropropene were not located in the available literature cited in Appendix A. Dermal exposure is possible to workers involved in fumigant applications of 1,3-dichloropropene.

## 3.5. SUMMARY

1,3-Dichloropropene has been identified in a very limited number of drinking waters. It has been qualitatively detected in New Orleans, LA drinking water collected in August 1974 (Dowty et al., 1975; Shackelford and Keith, 1976). Monitoring studies conducted in Denver, CO, and in nine municipalities along the Great Lakes failed to detect any trace of 1,3-dichloropropene (Rogers et al., 1987; Otson, 1987). Extensive groundwater monitoring for agricultural chemicals in California (including areas where Telone and D-D had been applied for years) has detected 1,3-dichloropropene in only 3 of thousands of samples analyzed (Cohen, 1986; Maddy et al., 1982). 1,3-Dichloropropene has been detected in leachate from municipal waste landfills and sewage treatment plants (Sabel and Clark, 1984; Lao et al., 1982). It has been suggested that chlorination of water can lead to the formation of 1,3-dichloropropene and that the identification of 1,3-dichloropropene in various water samples may be due to chlorination treatment (Krijgsheld and van der Gen, 1986). Examination of 231 different ready-to-eat foods (collected during the United States Food and Drug Administration's Market Basket Survey) for 22 fumigants and industrial

residues failed to detect any 1,3-dichloropropene at a detection limit of ≈1 ppb (Daft, 1988). The major source of 1,3-dichloropropene release to the atmosphere is probably volatile losses from soil following soil application as a fumigant (Krijgsheld and van der Gen, 1986). Albrecht (1987b) studied the inhalation exposure of 1,3-dichloropropene in workers involved in applying Telone II® to pineapple fields in Hawaii and found exposures to be predominantly <1 ppm.

# 4. ENVIRONMENTAL TOXICOLOGY

## 4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Toxic effects from acute exposure to 1,3-dichloropropene are summarized in Table 4-1 for several freshwater and saltwater species of invertebrates and vertebrates. Most of the acute toxicity data show similar sensitivity between the bluegill, Lepomis macrochirus, and the water flea, Daphnia magna, with $LC_{50}$s of 6.15 mg/ℓ (U.S. EPA, 1978) and 6.20 mg/ℓ (LeBlanc, 1980, 1984; Buccafusco et al., 1981). The one exception is a very low value ($LC_{50}$ = 0.09 mg/ℓ in D. magna) reported by Johnson and Finley (1980). The most sensitive resident species of fish was the walleye, Stizostedion vitreum ($LC_{50}$ = 1.08 mg/ℓ (Johnson and Finley, 1980). Comparable data on the guppy, Poecilla reticulata, were not located, but the 14-day $LC_{50}$ value of 4.57 mg/ℓ (Hermens et al., 1985) was, as would be expected, lower than the shorter-term acute values for species stated above. It appears that 1,3-dichloropropene is more toxic to saltwater than to freshwater invertebrates, and that mysid shrimp, Mysidopsis bahia, with an $LC_{50}$ of 0.79 mg/ℓ, (U.S.EPA, 1978; LeBlanc, 1984), are affected by lower concentrations of 1,3-dichloropropene than are sheepshead minnows, Cyprinodon variegatus (1.77-1.80 mg/ℓ, U.S. EPA, 1978; Heitmuller et al., 1981).

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Chronic toxicity data have been reported for the fathead minnow, Pimephales promelas, and mysid shrimp, Mysidopsis bahia (U.S. EPA, 1978). An embryolarval test of the toxicity of 1,3-dichloropropene to fathead minnows revealed a NOEC of 180 µg/ℓ and a LOEC of 330 µg/ℓ. Chronic toxicity data on saltwater fauna are limited to a life-cycle study

Acute Toxicity of 1,3-Dichloropropene to Aquatic Fauna

| Species | Common Name | Test Type | Duration/Endpoint | Concentration, (95% Confidence Limits) (mg/ℓ) | Temperature (°C) | No Effect Level (mg/ℓ) | Reference |
|---|---|---|---|---|---|---|---|
| Freshwater fauna | | | | | | | |
| Daphnia magna | water flea | NR | 48-hour $EC_{50}$ | 6.15 (4.33-8.99) | NR | 0.41 | U.S. EPA, 1978; LeBlanc, 1984 |
| D. magna | water flea | static acute | 48-hour $EC_{50}$ | 6.20 (4.3-9.0) | 22±1 | 0.41 | LeBlanc, 1980 |
| D. magna | water flea | static acute | 48-hour $EC_{50}$ | 0.09 (0.063-0.13) | NR | NR | Johnson and Finley, 1980 |
| Pimephales promelas | fathead minnow | static acute | 96-hour $LC_{50}$ | 4.10 (3.29-4.47) | NR | NR | Johnson and Finley, 1980 |
| Lepomis macrochirus | bluegill | NR | 96-hour $LC_{50}$ | 6.06 (5.14-6.82) | NR | <3.6 | U.S. EPA, 1978; LeBlanc, 1984 |
| L. macrochirus | bluegill | static acute | 96-hour $LC_{50}$ | 6.10 (5.1-6.8) | 22±1 | NR | Buccafusco et al., 1981 |
| Petromyzon marinus | lamprey (larvae) | NR | 24 hours | NR | NR | 5.0 | Applegate et al., 1957 |
| Salmo gairdneri | rainbow trout | static acute | 96-hour $LC_{50}$ | 5.90 | NR | NR | Schneider, 1979 |
| Micropterus salmoides | largemouth bass | static acute | 96-hour $LC_{50}$ | 3.65 (3.52-3.78) | NR | NR | Johnson and Finley, 1980 |
| Stizostedion vitreum vitreum | walleye | static acute | 96-hour $LC_{50}$ | 1.08 (0.99-1.18) | NR | NR | Johnson and Finley, 1980 |
| Poecilla reticulata | guppy | static, renewal | 14-day $LC_{50}$ | 4.57 (NR) | NR | NR | Hermens et al., 1985 |
| Idus idus melanotus[a] | golden orfe | static acute | 96-hour $LC_{50}$ | 0.9 (0.8-1.1) | 20 | 0.63 | Reiff, 1978 |

TABLE 4-1 (cont.)

| Species | Common Name | Test Type | Duration/Endpoint | Concentration (95% Confidence Limits) (mg/ℓ) | Temperature (°C) | No Effect Level (mg/ℓ) | Reference |
|---|---|---|---|---|---|---|---|
| Mixed group of *Notropis atherinoides* and | emerald shiner | NR | 3-day 100% lethality<br>3-day 0% lethality | NR | NR | NR | Scott and Wolf, 1962 |
| *P. promelas* | fathead minnow | NR | | | | | |
| Saltwater fauna | | | | | | | |
| *Mysidopsis bahia* | mysid shrimp | static acute | 96-hour $LC_{50}$ | 0.79 (0.62-0.98) | NR | 0.37 | U.S. EPA, 1978; LeBlanc, 1984 |
| *Cyprinodon variegatus* | sheepshead minnow | static acute | 96-hour $LC_{50}$ | 1.77 (0.71-4.49) | NR | <1.22 | U.S. EPA, 1978; LeBlanc, 1984 |
| *C. Variegatus* | sheepshead minnow | static acute | 96-hour $LC_{50}$ | 1.80 (0.7-4.5) | 25-31 | 1.2 | Heitmuller et al., 1981 |

*Not a resident of U.S. waters

NR = Not reported

mysid shrimp, Mysidopsis bahia, in which a NOEC of 2200 µg/ℓ and a LOEC of 4200 µg/ℓ were reported (U.S. EPA, 1978).

The effects of the pesticide, Shell-DD, on rhythmic adductor muscle activity of the freshwater mussel, Anodonta cygnea, were investigated by Varanka (1979). Shell-DD, which contains two active ingredients (1,3-dichloropropene and 1,2-dichloropropane), caused 50% inhibition of the tryptamine-induced activity at a concentration of $2 \times 10^{-2}$ mℓ test compound/ℓ water. The concentration of 1,3-dichloropropene was not reported.

4.1.2.2. Bioaccumulation/Bioconcentration -- Pertinent data regarding the bioaccumulation/bioconcentration potential of 1,3-dichloropropene in aquatic fauna were not located in the available literature cited in Appendix A. Predicted bioconcentration factors of 7 (based on water solubility) and 1 (based on octanol/water partition coefficients) calculated for 1,3-dichloropropene by Kenaga (1980) suggest that this compound will not be accumulated by aquatic organisms.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Toxicity of 1,3-dichloropropene to aquatic plants has been reported for one freshwater alga and one saltwater alga. A 96-hour $EC_{50}$ of 4950 µg/ℓ was determined for Selenastrum capricornutum (U.S. EPA, 1978; LeBlanc, 1984). In this same species, a 96-hour $EC_{50}$ (reduced cell division) of 4960 µg/ℓ was reported in the same study.

The saltwater alga, Skeletonema costatum, has a 96-hour $EC_{50}$ of 1000 µg/ℓ when treated with 1,3-dichloropropene (U.S. EPA, 1978; LeBlanc, 1984). The 96-hour $EC_{50}$ for cell division in this same species was reported as 1040 µg/ℓ by the U.S. EPA (1978).

4.1.3.2. BIOCONCENTRATION -- Pertinent data on the bioconcentration potential of 1,3-dichloropropene in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. Scott and Wolf (1962) examined the antibacterial activity of 1,3-dichloropropene in dilute aqueous solutions and found that 40% aqueous solutions lost much of their antimicrobial activity when stored at room temperature for 90 days. The same products in the solid state were stable at storage temperatures of $\leq$40°C for $\geq$90 days. Concentrations of 0.50% 1,3-dichloropropene killed samples of Aerobacter sp. in 21 hours, and 1.0% concentrations killed Pseudomonas sp. in 21 hours. These lethal concentrations are considerably higher than those that are lethal to higher aquatic species.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Abivardi (1970) tested the nematocidal effects of solutions of two commercial nematicides, 1,3-D and Telone (content of 1,3-dichloropropene not reported) under controlled laboratory conditions. Half-cc samples of 400, 800 and 1200 ppm active material in water and containing 50 active larvae of Pratylenchus hamatus and Tylenchulus semipenetrans were added to spot plates covered for 24 hours and then examined. Mortality was 100%.

4.2.2. Effects on Flora. Toxicity of the commercial product, 1,3-D (98% 1,3-dichloropropene) to microsclerotia of the fungus, Verticillium dahliae, was tested by Ben-Yephet et al. (1981) in sealed containers of air and soil. A concentration of 20 µg/mℓ 1,3-D in air killed 100% of the microsclerotia after 30 hours incubation, and 100 µg/g 1,3-D induced total lethality of the organism in soil incubated for 3 days.

## 4.3. FIELD STUDIES

Edwards and Reichle (1969) applied the soil fumigant, dichloropropene, D-D (concentration of dichloropropene not reported) in an *in situ* field experiment on soil systems. Approximately 170 cc/m² of D-D was applied to a plot of soil with an injection gun; the soil was then covered with plastic sheeting for 2 weeks. D-D fumigation eliminated the earthworm, *Lumbricus terrestris*, and reduced the microarthropod population (Dipter and Coleopter larvae) by 98.3%. Costante et al. (1987) injected Telone C-17 (74% 1,3-dichloropropene and 16.5% chloropicrin) into soil at 374 ℓ/hectare and noted significantly reduced populations of *Pratylenchus penetrans* after 50 and 156 days posttreatment. Another report describing the nematicidal activity of DD, a commercial pesticide containing 1,3-dichloropropene, was located, but the percentage of active ingredient was not quantified (Blackmon and Musen, 1974).

Kotcon and Loria (1987) applied a fumigant containing 94% 1,3-dichloropropene at 0, 94, 117 or 140 ℓ of formulated compound/hectare to plots in two commercial potato fields and noted significant reduction of nematodes, *Pratylenchus crenatus*, within 2 weeks at all levels of treatment. Mortality was ≤96% with application of 140 ℓ/ha.

Mathur et al. (1980) tested two commercial products that contain 1,3-dichloropropene, Telone II® and Telone C17, on organic field plots of carrots and noted increased numbers of fungi, bacteria and actinomycetes between 0 and 28 days. The concentration of 1,3-dichloropropene applied to these plots was not reported, however.

Cook et al. (1987) tested the fungicidal properties of 1,3-dichloropropene combined with 17% chloropicrin in wheat field plots and noted 95-100%

elimination of inoculum (population of Pythium spp. at start of test was >300 propagules/gram of soil).

## 4.4. AQUATIC RISK ASSESSMENT

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to 1,3-dichloropropene precluded the development of a freshwater criterion (U.S. EPA/OWRS, 1986) (Figure 4-1). Available data indicate that acute toxic effects can occur at concentrations ≥1.08 mg/ℓ in freshwater, and that chronic effects can occur at concentrations ≥0.33 mg/ℓ. Additional data required for the development of a freshwater criterion includes the results of acute assays with benthic crustaceans, an insect, a nonarthropod and nonchordate species and an insect or species from a phylum not previously represented. The development of a freshwater criterion also requires data from chronic toxicity tests with two species of fauna and at least one bioconcentration study.

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to 1,3-dichloropropene precluded the development of a saltwater criterion (U.S. EPA/OWRS, 1986) (Figure 4-2). Available data indicate that acute toxic effects can occur at concentrations ≥0.79 mg/ℓ, and chronic toxic effects at concentrations ≥4.20 mg/ℓ. Additional data required for the development of a saltwater criterion include the results of acute assays with one chordate species a nonarthropod and nonchordate species, two additional nonchordate species, and one other species of marine fauna. The development of a saltwater criterion also requires data from chronic toxicity tests with two species of fauna and at least one bioconcentration study.

| Family | TEST TYPE | | |
|---|---|---|---|
| | GMAV[a] (mg/L) | GMCV[a] (mg/L) | BCF[a] |
| #1 Chordate (Salmonid-fish) | 5.9[b] | NA | NA |
| #2 Chordate (warmwater fish) | 6.08[c] | NA | NA |
| #3 Chordate (fish or amphibian) | 1.08[d] | NA | NA |
| #4 Crustacean (planktonic) | 6.17[e] | NA | NA |
| #5 Crustacean (benthic) | NA | NA | NA |
| #6 Insectan | NA | NA | NA |
| #7 non-Arthropod/-Chordate | NA | NA | NA |
| #8 New Insectan or phylum representative | NA | NA | NA |
| #9 algae | XXXXXXXXXXXX XXXXXXXXXXXX | 4.95[f] | NA |
| #10 Vascular plant | XXXXXXXXXXXX XXXXXXXXXXXX | NA | NA |

[a]NA=Not available; [b]96-hour $LC_{50}$ for rainbow trout, Salmo gairdneri; [c]mean 96-hour $LC_{50}$ for bluegill sunfish, Lepomis macrochirus; [d]96-hour $LC_{50}$ for walleye, Stizostedion vitreum vitreum; [e]mean 48-hour $EC_{50}$ for the water flea, Daphnia magna; [f] 96-hour $EC_{50}$ for the alga, Selenastrum capricornutum, based on chlorophyl a content.

FIGURE 4-1

Organization Chart For Listing GMAVs, GMCVs And BCFs Required To Derive Numerical Water Quality Criteria By The Method Of U.S. EPA/OWRS (1986) To Protect Freshwater Aquatic Life From Exposure To 1,3-Dichloropropene

| Family | TEST TYPE | | |
|---|---|---|---|
| | GMAV[a] | GMCV[a] | BCF[a] |
| #1 Chordate | 1.76[b] | NA | NA |
| #2 Chordate | NA | NA | NA |
| #3 non-Arthropod/-Chordate | NA | NA | NA |
| #4 Crustacean (Mysid/Panaeid) | 0.79[c] | 2.20[d] | NA |
| #5 non-Chordate | NA | NA | NA |
| #6 non-Chordate | NA | NA | NA |
| #7 non-Chordate | NA | NA | NA |
| #8 other | NA | NA | NA |
| #9 algae | XXXXXXXXXXX XXXXXXXXXXX | 1.0[e] | NA |
| #10 Vascular plant | XXXXXXXXXXX XXXXXXXXXXX | NA | NA |

[a]NA=Not available; [b]mean 96-hour $LC_{50}$ for sheepshead minnow, Cyprinodon variegatus; [c]96-hour $LC_{50}$ for mysid shrimp, Mysidopsis bahia; [d]Life-cycle NOEC for mysid shrimp, M. bahia; [e]96-hour $EC_{50}$ for the alga, Skeletonema costatum, based on chlorophyl a content.

FIGURE 4-2.

Organization Chart For Listing GMAVs, GMCVs And BCFs Required To Derive Numerical Water Quality Criteria By The Method Of U.S. EPA/OWRS (1986) To Protect Saltwater Aquatic Life From Exposure To 1,3-Dichloropropene

## 4.5. SUMMARY

Data are available on the acute toxicity of 1,3-dichloropropene to several species of invertebrates and vertebrates. As shown in Table 4-1, 96-hour $LC_{50}$ values reveal a similar range of sensitivity among six freshwater fish species native to U.S. waters (Applegate et al., 1957; Buccafusco et al., 1981; Hermens et al., 1985; Johnson and Finley, 1980; LeBlanc, 1984; Schneider, 1979; U.S. EPA, 1978). A seventh species, the walleye, S. vitreum vitreum, showed markedly greater sensitivity, with a 96-hour $LC_{50}$ of 1.08 ppm. The water flea, D. magna, (Leblanc, 1980, 1984; U.S. EPA, 1978) showed a sensitivity comparable with that of the bluegill sunfish, L. macrochirus, the least sensitive of the freshwater fish species tested (Buccafusco, 1981; LeBlanc, 1984; U.S. EPA, 1978). 1,3-dichloropropene is more acutely toxic to the saltwater invertebrate, M. bahia (LeBlanc, 1984; U.S. EPA, 1978), than to the freshwater species, D. magna. The sheepshead minnow, C. variegatus, a saltwater fish, is highly sensitive to 1,3-dichloropropene (mean 96-hour $LC_{50}$ = 1.76 ppm) (LeBlanc, 1984).

Chronic toxicity tests of 1,3-dichloropropene to the fathead minnow, P. promelas, and mysid shrimp, M. bahia, revealed NOECs of 0.18 ppm and 4.2 ppm, respectively (U.S. EPA, 1978).

Data regarding the toxicity of 1,3-dichloropropene to aquatic flora follow a similar pattern to that for aquatic fauna. The saltwater alga, S. costatum, has a mean 96-hour $EC_{50}$ of 1.01 ppm (LeBlanc, 1984; U.S. EPA, 1978); the freshwater alga, S. capricornutum, has a mean 96-hour $EC_{50}$ of 4.95 ppm (LeBlanc, 1984; U.S. EPA, 1978). Data on effects of 1,3-dichloropropene on bacteria indicate that Aerobacter sp. and Pseudomonas sp. are more resistant to the compound than are higher aquatic species reported above.

Studies on the bioconcentration/bioaccumulation potential of 1,3-dichloropropene in aquatic fauna and flora were not located in the available literature, but BCFs of 7 (based on water solubility) and 1 (based on $K_{ow}$) were predicted for this compound by Kenaga (1980).

Data support 1,3-dichloropropene's effectiveness as a nematocide (Abivardi, 1970; Blackmon and Musen, 1974; Costante et al., 1987, Kotcon and Loria, 1987) and its toxicity to the earthworm, Lumbricus terrestris, and to Dipter and Coleopter larvae (Edwards and Reichle, 1969).

Data regarding the effectiveness of 1,3-dichloropropene for control of soil microorganisms are equivocal. Mathur et al. (1980) noted increased numbers of fungi, bacteria and actinomycetes after treating field plots with the chemical, but Cook et al. (1987) noted 95-100% elimination of a population of Pythium spp. with 1,3-dichloropropene.

The lack of pertinent data regarding effects of exposure of aquatic fauna and flora to 1,3-dichloropropene prevented the development of freshwater or saltwater criteria.

# 5. PHARMACOKINETICS

## 5.1. ABSORPTION

The absorption of 1,3-dichloropropene during head-only inhalation exposure to 30, 90, 300 or 900 ppm (49.3% cis- and 42.8% trans-1,3-dichloropropene and ≈8 minor contaminants) for 3 hours was determined in male F344 rats (Stott and Kastl, 1986). The average amounts of 1,3-dichloropropene absorbed by the rats exposed to 30, 90, 300 and 900 ppm were ≈14 mg/kg (82% of the available vapors absorbed), 29 mg/kg (65% absorbed), 85 mg/kg (66% absorbed) and 171 mg/kg (62% absorbed), respectively. The rate of absorption is calculated to be 144, 307, 880 and 1810 nmol/min for the 30, 90, 300 and 900 ppm exposure levels, respectively. The nonlinearity in absorption rate and absorbed dose with increasing concentration may have been due to a concentration-related decrease in the respiratory ventilatory frequency in rats exposed to ≥90 ppm and to the saturation of metabolism of the compound in rats exposed to ≥300 ppm. As determined in isolated upper and lower respiratory tracts from rats exposed to 90 or 150 ppm, absorption occurred mainly through the lower respiratory tract (calculated to be ≈73 and 79% of the total amount absorbed at 90 and 150 ppm, respectively). A small amount was also absorbed by the nasal mucosa. Blood levels of 1,3-dichloropropene suggested that 1,3-dichloropropene in the blood reached a steady state with both the cis- and trans-isomers within 60 minutes of exposure at 30 and 90 ppm and within 2 hours at 300 ppm and within ≈3 hours at 900 ppm.

Hutson et al. (1971) treated Carworth Farm E rats by gavage with cis- or trans-1,3-dichloro(2-$^{14}$C)propene in arachis oil at doses of ≈11.2 or 12 mg/kg, respectively. After 24 hours, ≈80-84% of the administered radioactivity from either isomer was excreted in the urine or as $^{14}CO_2$, indicating that ≥80% of the dose was absorbed by the gastrointestinal tract.

Similar results were obtained by Climie et al. (1979) in rats and by Dietz et al. (1985) (Sections 5.3 and 5.4). Absorption through the skin of rabbits occurred when 1,3-dichloropropene was applied in propylene glycol solution or when evaporation was retarded with a cuff (Torkelson and Oyen, 1977; Torkelson and Rowe, 1981).

## 5.2. DISTRIBUTION

The relationship between inhaled 1,3-dichloropropene and the tissue levels of reduced glutathione, which indicates 1,3-dichloropropene metabolism, was assessed (Fisher and Kilgore, 1988a; Fisher, 1988). The glutathione content was measured in the heart, kidney, liver, lung, nasal mucosa and testes of male Sprague-Dawley rats exposed to 0, 1.8, 4.5, 33, 306.1, 771.8, 954.6 or 1716 ppm Telone II® (94% 1,3-dichloropropene with approximately equal concentrations of the cis- and trans-isomers and epoxidized soybean oil as the stabilizing agent) for 1 hour. The decrease in glutathione was exposure-related. At the 4.5 ppm level, a decrease was observed in the nasal mucosa. Liver glutathione was depleted in an exposure-related manner at levels $\geq$306 ppm. At exposures $\leq$955 ppm, the content of lung glutathione remained relatively constant at ≈75% of control levels. Only at 1716 ppm did the glutathione content significantly decrease in the heart, liver and testes. No 1,3-dichloropropene was detected in the blood of animals 2 hours after exposure to $\leq$955 ppm. These data indicate that a substantial portion of the inhaled 1,3-dichloropropene is metabolized to a glutathione conjugate in the nasal mucosa and is subsequently transported to the blood.

Dietz et al. (1985) measured the NPS (the majority of which is glutathione) content of tissues and covalent binding to macromolecules of the forestomach, glandular stomach, liver, kidney and urinary bladder of rodents

treated with 1,3-dichloropropene. Male F344 rats and male B6C3F1 mice were fed a single oral dose of $^{14}$C-1,3-dichloropropene. For the NPS studies, the doses were 0, 1, 5, 25, 50 or 100 mg/kg; for binding studies, doses were 0, 1, 50 or 100 mg/kg. Significant depletion of NPS levels occurred in the forestomach of rats and mice at $\geq$25 mg/kg, with a depletion range of 17-51% of control values. NPS levels in the glandular stomach and liver were also depleted in a dose-dependent manner but at a less severe level. Limited macromolecular binding was noted in the liver, kidneys and urinary bladder, and was greatest at doses that caused the most depletion of tissue NPS in the forestomach and glandular stomach. These results also indicate that a substantial conjugation occurs in the stomach after oral dosing and before distribution to other tissues.

Dietz et al. (1985) fed a single oral dose of 1 or 50 mg/kg $^{14}$C-cis,trans-1,3-dichloropropene to male F344 rats and 1 or 100 mg/kg to male B6C3F1 mice. Urine, feces and expired air were collected for 48 hours after dosing, and the rats were then sacrificed. The tissues and the carcass were analyzed for remaining radioactivity. Only 2-6% of the administered dose remained in the carcasses of both species 48 hours after dosing. Most of the radioactivity was excreted in the urine, feces and expired air (Section 5.4). Similarly, Hutson et al. (1971) found <5% of the administered oral dose of 11.2 or 12 mg/kg 1,3-dichloro(2-$^{14}$C)propene in the gut, feces and skin and carcass 4 days after dosing.

## 5.3. METABOLISM

Hutson et al. (1971) administered $\approx$11.2 or 12 mg/kg of cis- or trans-1,3-dichloro(2-$^{14}$C)propene, respectively, to rats by gavage and found differences in metabolism between the isomers (see Section 5.1). In the first 24 hours, 80-90% of the radioactivity dose was eliminated. Most of the

radioactivity was excreted in the urine; 80.7% of the radioactivity from cis-1,3-dichloropropene and 56.5% from trans-1,3-dichloropropene was recovered from urine within the first 24 hours. The amount of $^{14}CO_2$ excreted was different for the two isomers; 3.9 and 23.6% of the dose from the $^{14}$C-cis- and trans-isomers, respectively, were excreted as $^{14}CO_2$ within 4 days. A small amount of 1,3-dichloropropene was exhaled unchanged (1-4%).

When rates of degradation of the trans-isomer and the cis-isomer were compared in vitro, the cis-isomer degraded 4-5 times faster than the trans-isomer, with absolute rates of 4.9 and 1.0 nmol/minute/mg cytosol for cis- and trans-isomers, respectively (Climie et al., 1979).

Two female Wistar rats were given a single oral dose of cis-1,3-dichloro(2$^{14}$C)propene of 20 mg/kg body weight in corn oil (Climie et al., 1979). Eighty-two to 84% of the radioactivity appeared in the urine within 24 hours after treatment. Most of the urinary radioactivity (92%) was present as N-acetyl-S-[cis-3-chloroprop-2-enyl] cysteine (cis- dichloropropene mercapturic acid or 3C-NAC), as determined by comparative chromatography procedures.

When cis-dichloropropene (0.1mM) was incubated at 37°C in vitro with rat liver supernatant (3.55 mg protein/ml) containing glutathione S-alkyl transferase and added glutathione (5 mM), no substrate remained after 10 minutes (Climie et al., 1979). When glutathione was omitted, 72% of the substrate was recovered. Therefore, it appears that the rapid urinary elimination of radioactivity from rats given cis-1,3-dichloro($^{14}$C)propene is due to an efficient glutathione-dependent biotransformation. The compound conjugates with glutathione, enters the mercapturic acid pathway and is excreted in the urine as N-acetyl-S-(3-chloroprop-2-enyl) cysteine, 3C-NAC.

Studies done by Fisher (Fisher, 1988; Fisher and Kilgore, 1988a) (see Section 5.2) indicated that, following inhalation exposure, a substantial amount of 1,3-dichloropropene was metabolized to the less toxic glutathione conjugate in the nasal mucosa, was transported to the bloodstream and was subsequently degraded to the mercapturic acid form and excreted in the urine.

## 5.4. EXCRETION

In a previously described study (see Section 5.1), Stott and Kastl (1986) determined that, following inhalation in rats of 30, 90, 300 or 900 ppm 1,3-dichloropropene, both the cis- and trans-isomers were rapidly eliminated from the blood in a biphasic manner in rats exposed to ≤300 ppm. The rapid elimination phase had a half-life of 3-6 minutes, and the slower elimination phase had a half-life of 33-43 minutes. In rats exposed to 900 ppm, 1,3-dichloropropene was also eliminated biphasically, but the initial phase was longer, with a half-life of 14-27 minutes.

Fisher and Kilgore (1988b) determined the relationship between the concentration of inhaled 1,3-dichloropropene (Telone II® - 94% 1,3-dichloropropene in approximately equal concentrations of the cis- and trans-isomers, stabilized by epoxidized soybean oil) and the urinary excretion of the mercapturic acid of cis-1,3-dichloropropene in male Sprague-Dawley rats. The rats were exposed for ≤1 hour to 0, 284, 398 or 789 ppm and urine was collected for ≤24 hours after exposure. The quantity of the mercapturic acid found in the urine was concentration-dependent from 0-284 ppm, but the amount did not increase at the 398 or 789 ppm exposure levels. It was postulated that the nonlinearity at the higher concentrations may be a result of changes in the absorption of 1,3-dichloropropene, which are due to altered respiration rates at the higher levels. Stott and Kastl (1986) found that absorption of 1,3-dichloropropene was not linear with increasing exposure

concentrations because of decrease in the respiratory ventilation frequency that are exposure-related, and to the saturation of metabolism of 1,3-dichloropropene (see Section 5.1). Osterloh et al. (1984) monitored the quantity of the mercapturic acid found in the 24-hour urine collections of agricultural workers exposed to 1,3-dichloropropene (≈0.4 ppm for 3 hours). A linear relationship was found between exposure to 1,3-dichloropropene (the product of airborne concentrations and duration of exposure) and excretion of the metabolite, 3C-NAC (see Section 5.3.). The amount of the metabolite excreted in the urine by the rats (exposed to a high concentration for a short period of time) in the Fisher and Kilgore (1988b) study (2-59 μmol 3C-NAC/24 hours) was similar to the amount excreted by agricultural workers (exposed to a low concentration for a longer period of time) in the Osterloh et al. (1984) study (4-36 μmol 3C-NAC/24 hours).

In the previously described study by Hutson et al. (1971) (see Section 5.1), the excretion by rats of radioactivity as a percentage of the administered oral dose of 11.2 mg/kg or 12 mg/kg of cis- or trans-1,3-dichloro(2$^{14}$C)propene, respectively, was determined for urine, feces and expired air. Measurements were taken at 24-hour intervals over a 4-day period. The animals were sacrificed after the fourth day following the administration of the labeled compounds, and radioactivity remaining in the carcasses was measured. Excretion data are summarized in Tables 5-1 and 5-2. As seen from Table 5-1, most of the radioactivity was excreted in the urine; ≈80% and 55% of administered dose of cis- and trans-1,3-dichloropropene, respectively, was eliminated during the first 24 hours.

When oral doses of $^{14}$C-cis or trans-1,3-dichloropropene were given to male F344 rats (1 or 50 mg/kg) and to male B6C3F1 mice (1 or 100 mg/kg), urinary excretion was the major route of elimination after 48 hours (Dietz et

TABLE 5-1

Rates of Excretion of Radioactivity After Oral Administration of 1,3-Dichloropropene

| Compound | Sex | Excretion of Radioactivity (% of administered dose) in 24-Hour Periods (hour after administration)[b] | | | | |
|---|---|---|---|---|---|---|
| | | 0-24 | 24-48 | 48-72 | 72-96 | Total (0- to 96-hour) |
| | | | Urine | | | |
| cis-1,3-Dichloropropene | M | 81.3±2.76 | 1.9±0.21 | 0.6±0.14 | 0.3±0.06 | 84.1±2.94 |
| | F | 80.3±5.34 | 1.2±0.29 | 0.4±0.23 | 0.4±0.23 | 82.3±5.18 |
| trans-1,3-Dichloropropene | M | 54.6±1.92 | 0.6±0.06 | 0.3±0.04 | 0.1±0.02 | 55.6±1.90 |
| | F | 58.7±1.08 | 1.1±0.16 | 0.5±0.13 | 0.2±0.09 | 60.5±1.00 |
| | | | Feces | | | |
| cis-1,3-Dichloropropene | M | 2.0±0.38 | 0.8±0.28 | 0.3±0.14 | 0.2±0.08 | 3.3±0.53 |
| | F | 1.4±0.43 | 0.2±0.04 | 0.1±0.03 | 0.1±0.05 | 1.8±0.42 |
| trans-1,3-Dichloropropene | M | 1.3±0.37 | 0.2±0.11 | 0.4±0.15 | 0.1±0.05 | 2.0±0.28 |
| | F | 1.9±0.24 | 0.2±0.10 | 0.2±0.10 | 0.1±0.02 | 2.4±0.26 |

[a]Source: Hutson et al., 1971

[b]The values given are the means ± SEM for groups of six rats.

TABLE 5-2

Recoveries of Radioactivity from Rats in the 4 Days Following Oral Administration of 1,3-Dichloropropene

| Compound | Sex | Recovery of Radioactivity (% of Administered Dose in 4 Days)[b] | | | | | Exhaled Air | | Total Radioactivity Recovered (% of Administered Dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Urine | Feces | Gut | Skin | Carcass | Carbon Dioxide[c] | Other Volatile Radioactivity[c] | Less Volatile Radioactivity | Including Volatile Radioactivity |
| cis-1,3-Dichloropropene | M | 84.0±2.94 | 3.3±0.53 | 0.1±0.01 | 0.5±0.09 | 0.8±0.06 | 5.3 (3) | NR | 88.7±4.27 | NR |
| | F | 82.3±5.18 | 1.8±0.42 | 0.1±0.02 | 0.5±0.07 | 0.5±0.02 | 2.4 (3) | 1.4 (2) | 85.2±4.27 | 89.0 |
| trans-1,3-Dichloropropene | M | 55.6±1.90 | 2.1±0.28 | 0.2±0.10 | 0.6±0.07 | 1.1±0.11 | 22.7 (3) | NR | 59.6±2.57 | NR |
| | F | 60.4±1.00 | 2.3±0.26 | 0.1±0.01 | 0.5±0.13 | 0.9±0.11 | 24.4 (3) | 13.5 (2) | 64.2±1.01 | 92.1 |

[a]Source: Hutson et al., 1971

[b]Except where indicated otherwise, values given are the means ± SEM for groups of six rats.

[c]Values given are means for the numbers of animals indicated in parentheses.

NR = Not reported

al., 1985). In rats, 51-61% of the dose was excreted in the urine; in mice, 63-79%. Approximately 18 and 6%, respectively, of the administered radioactivity was excreted in feces and as expired $^{14}CO_2$ in rats, and 15 and 14%, respectively, in mice. After 48 hours, only 2-6% of the original dose remained in the carcasses. Major metabolites were the mercapturic acid conjugate and the sulfoxide or sulfone derivative of N-acetyl-S-(3-chloroprop-2-enyl) cysteine.

5.5. SUMMARY

Approximately 80% of the administered dose of 1,3-dichloropropene was absorbed into the body following inhalation or oral exposure (Stott and Kastl, 1986; Hutson et al., 1971). As the inhaled concentration of 1,3-dichloropropene increased, the absorption did not increase linearly because of exposure level-related decreases in respiratory ventilatory frequency and to saturation of the metabolism of 1,3-dichloropropene (see Section 5.1). 1,3-Dichloropropene was rapidly eliminated from the body, primarily in the urine as N-acetyl-S-(3-chloroprop-2-enyl) cysteine, following inhalation or oral exposure (Hutson et al., 1971; Climie et al., 1979; Dietz et al., 1985;

1988b . 1,3-Dichloropropene
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ater amounts of the

trans-isomer were excreted as $CO_2$ in the expired breath (Hutson et al., 1971).

Distinct differences exist in the elimination of 1,3-dichloropropene between rats and mice. Following oral dosing with $^{14}C$-1,3-dichloropropene, more of the administered dose of radioactivity was excreted in the urine and expired air of mice than of rats (Dietz et al., 1985). The rate of urinary excretion of the mercapturic acid of 1,3-dichloropropene was comparable between rats (Fisher and Kilgore, 1988b) and humans (Osterloh et al., 1984).

# 6. EFFECTS

## 6.1. SYSTEMIC TOXICITY

### 6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Stott et al. (1988) exposed male and female F344 rats and B6C3F1 mice (10/sex/exposure level) to 0, 10, 30, 90 or 150 ppm of technical grade 1,3-dichloropropene (48.6% cis-1,3-dichloropropene, 42.3% 1,3-dichloropropene, 2.4% 1,2-dichloropropane and 1.2% epichlorohydrin and mixed isomers of chlorohexane, chlorohexene and trichloropropene) for 6 hours/day, 5 days/week for 13 weeks. The animals were observed for clinical signs of toxicity and body weight changes. Hematological, clinical chemistry and urinalysis determinations were conducted at the end of the study. All surviving animals underwent gross necropsy. Comprehensive histological examination was limited to high-dose and control animals and those animals that died before scheduled sacrifice. Selected tissues were examined histologically in the other groups. Significantly decreased body weight gain was observed in both sexes of rats and mice treated at $\geq$90 ppm. Degenerative changes or hyperplasia in the nasal mucosa were observed in almost all animals of both sexes of rats and mice exposed to $\geq$90 ppm and in 2/10 male rats exposed to 30 ppm. Respiratory metaplasia of the damaged portions of the olfactory region of the mucosa was found in both sexes of mice in the high exposure group. This effect involved the replacement of the damaged sensory olfactory epithelium with normal-appearing, ciliated, respiratory-type epithelium. Hyperplasia of the urinary bladder transitional epithelium was found in most female mice exposed to 90 or 150 ppm of the vapor, but not in male mice or in rats. No treatment-related effects were observed in male rats exposed to 10 ppm 1,3-dichloropropene and in female rats or male and female mice exposed to 30 ppm of the vapor.

Coate et al. (1979) exposed groups of 10 male and 10 female F344 rats and 10 male and 10 female CD-1 mice to 0, 12, 32 or 93 ppm of Telone II® (47% cis- and 45% trans-1,3-dichloropropene, 8% related compounds) for 7 hours/day, 5 days/week for 13 weeks. Both sexes of rats and female mice exposed to the highest concentration (93 ppm) had reduced body weight gain. No treatment-related histopathological effects were noted in the lungs, kidneys, liver, heart, brain, gonads or nasal turbinates of rats or mice. Other tissues were not examined microscopically.

Parker et al. (1982) exposed groups of 28 male and 28 female CD-1 mice and F344 rats to 0, 5, 15 or 50 ppm of the D-D mixture (25% cis-1,3-dichloropropene, 27% trans-dichloropropene, 29% 1,2-dichloropropane) for 6 hours/day, 5 days/week for 6 or 12 weeks. No clinical signs of toxicity or effects on body weight changes, hematology (HGB, HCT, RBC, WBC and differential leukocyte count), serum chemistry (BUN, GLU, ALB, and GPT), urinalysis, gross pathology, histopathology, organ weights and organ-to-body weight ratios of brain, heart, testes or ovaries and adrenals were observed following 12 weeks of exposure. Increased mean liver-to-body weight ratios of male rats and increased mean kidney-to-body weight ratios of female rats were seen at the 50 ppm exposure level at 12 weeks. In male and female mice exposed to the highest concentration for 12 weeks, a slight to moderate diffuse hepatocytic enlargement was seen in 12/21 treated males, 4/18 control males, 6/18 treated females and 1/18 control females. No compound-related effects were seen at lower concentration levels.

Torkelson and Oyen (1977) described a preliminary Dow Chemical Company study that exposed rats (5/sex/group) and guinea pigs (3-5/sex/group) to 50 ppm 1,3-dichloropropene (composition not specified) for 19 seven-hour exposures over a period of 28 days or to 11 ppm for 27 seven-hour exposures

over a period of 39 days. In both experiments, marked liver and kidney changes, including necrosis, were observed.

Torkelson and Oyen (1977) repeatedly exposed rats (9-11 animals/sex/exposure level), guinea pigs (7-12 animals/sex/group), rabbits (1-4 animals/sex/group) and dogs (1-2 animals/sex/group) by inhalation to 1 or 3 ppm 1,3-dichloropropene (46% cis- and 53% trans-1,3-dichloropropene, 1% epichlorohydrin) for 7 hours/day, 5 days/week for 6 months. In addition to the rats exposed for 7 hours/day, groups of five male rats were exposed at 3 ppm for 4, 2, 1 or 0.5 hours/day, 5 days/week for 6 months. Controls consisted of animals exposed to normal laboratory environments and animals exposed in sealed chambers to air only. Following the last exposure, the animals were sacrificed and the following tissues and organs were histologically examined: lung, heart, liver, kidney, spleen, testes, ovaries, adrenals, pancreas, lymph nodes, intestines, stomachs, brains, thyroids, thymus, peripheral nerves, skeletal muscles, bladders and gall bladders. Hematological tests were also performed (hemocrit, hemoglobin and differential WBC counts). Additional groups of rats were allowed a 3-month recovery period before sacrifice. No effects on any organs were found in any species at either concentration except for a slight, cloudy swelling in the renal epithelium of male rats exposed to 3 ppm 1,3-dichloropropene for 4 or 7 hours/day. Following the 3-month recovery period, the cloudy swelling was no longer apparent.

Reduced body weights and degeneration and hyperplasia of respiratory epithelium were reported in male and female F344 rats exposed to Telone II® (94% 1,3-dichloropropene, nearly equally divided between the two isomers) at 90 ppm, 6 hours/day, 5 or 6 days/week in a multigeneration

reproduction study (Breslin et al., 1987), discussed more fully in Section 6.5.

6.1.1.2. CHRONIC -- The chronic toxicity of inhaled technical grade 1,3-dichloropropene was determined in F344 rats and B6C3F1 mice (Lomax et al., 1989). Groups of 50 male and 50 female rats were exposed to 0, 5, 20 or 60 ppm (0, 22.7, 90.8 or 272 mg/m$^3$) 1,3-dichloropropene (49.5% cis- and 42.6% trans-1,3-dichloropropene, 0.7% 1,2-dichloropropane and 2% epoxidized soybean oil) 6 hours/day, 5 days/week for $\leq$2 years. Ancillary groups of 10 rats and mice/sex/exposure level were similarly exposed for 6 and 12 months. Clinical laboratory determinations (hematological and clinical chemistry parameters), along with extensive gross and histological examinations, were determined at the scheduled sacrifice intervals of 6, 12 or 24 months. No clinical signs of toxicity and no significant differences in survival were observed. Mean body weights of both male and female rats exposed to 60 ppm 1,3-dichloropropene were significantly decreased (5%) as compared with controls on test days 6-425 in males and 6-327 in females ($\alpha$ = 0.05 by Dunnett's test). The terminal weights of the treated rats, however, were similar to those of control animals. The mean body weights of both male and female mice exposed to 60 ppm 1,3-dichloropropene were lower in some instances than those of controls during the study (3-9% in males and 2-11% in females). The terminal weights of the male mice exposed to 60 ppm were significantly lower than those of the control mice ($\alpha$ = 0.05 by Dunnett's test). No statistical differences were found between the terminal body weights of treated female mice and those of controls. No treatment-related effects were observed in hematological, biochemical or urinalysis parameters.

Gross pathological examination of all rats in the study showed no apparent exposure-related effects following exposure to 1,3- dichloropropene.

Histopathological examination, however, revealed exposure-related effects in the nasal tissues of male and female rats exposed to 60 ppm 1,3-dichloropropene for 24 months. These changes were characterized by unilateral or bilateral decreased thickness of the olfactory epithelium that is due to degenerative changes, erosions of the olfactory epithelium and fibrosis beneath the olfactory epithelium. No lesions were observed at the 6- or 12-month sacrifices.

Histopathological examination of the mice revealed exposure-related morphological changes in the urinary bladder and nasal tissue. Urinary bladder hyperplasia, characterized by diffuse, uniform thickening of the transitional epithelium, was observed in both sexes of mice with duration- and concentration-related increased frequency and severity. The incidence of this lesion was significantly increased in males at 60 ppm and in females at 20 and 60 ppm at 24, but not at 6 or 12 months of exposure. The effect was much more pronounced in the female mice than in male mice. Both the male and female mice also had compound-related microscopic changes in the nasal tissues characterized by hypertrophy and hyperplasia of the respiratory epithelium or degeneration of the olfactory epithelium. Significant increases in the incidence of hyperplasia of the respiratory epithelium were found in female mice exposed to 20 and 60 ppm for 24 months and in male mice exposed to 60 ppm for 24 months. The incidence of degeneration of the olfactory epithelium was measured significantly in mice of both sexes at 60 ppm after 24 months. An additional exposure-related change was the hyperplasia and hyperkeratinization in the forestomach of 8/50 male mice following exposure to 60 ppm for 24 months.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- Solutions of Telone II® (78.5% 1,3-dichloropropene) in propylene glycol were administered by gavage at doses of 0, 1, 3, 10 or 30 mg/kg/day to 10 rats (strain unspecified)/sex/dose level for 6 days/week for 13 weeks (Til et al., 1973). No significant effects on body weight, food consumption, hematology, clinical chemistry, urinalysis or histopathology were noted at any dose level. A statistically significant higher relative kidney weight, however, was found in males treated with 10 or 30 mg/kg/day and in females at 30 mg/kg/day.

As reported in abstracts of Russian studies, the effects of 1,3-dichloropropene on trypsin, trypsin inhibitor, amylase and lipase activities in the serum of albino rats was investigated by Strusevich and Ekshtat (1974) and Strusevich and Sadovnik (1975). The rats were fed daily doses of 0.1, 0.5 or 2.5 mg/kg/day 1,3-dichloropropene for 6 months. Trypsin activity increased and trypsin inhibitor activity of the blood decreased during the 6 months of treatment. Blood lipase activity increased and amylase activity was unaffected. No additional details of the studies were reported in the abstracts.

6.1.2.2. CHRONIC -- Groups of 52 male and 52 female F344 rats were given doses of 0, 25 or 50 mg/kg/day Telone II® (89% cis- and trans-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% trichloropropene and 1.0% epichlorohydrin) in corn oil by gavage 3 days/week for 104 weeks (NTP, 1985). In the same bioassay, groups of 50 male and 50 female B6C3F1 mice were given doses of 0, 50 or 100 mg/kg/day by gavage 3 days/week for 104 weeks. In ancillary studies, groups of 28 male and 28 female rats and mice were given Telone II® at the above doses, and interim kills of five animals/sex/group were performed at 9, 16, 21, 24 or 27 months.

No differences in survival were found among the groups of rats in the 2-year study; 35-42 rats/sex/group survived until the end of the study. In mice, survival of the control males was significantly lower than either the low or high dose groups. Only 8/50 control male mice survived until the end of the experiment, compared with 28/50 animals in the low-dose group and 31/50 animals in the high-dose group. Twenty-five of the deaths among the male control mice occurred at weeks 48-51 and were attributed to myocarditis, which was not treatment-related. Survival of the high-dose female mice was significantly less than that of the controls; 36/40 high-dose females and 46/50 female controls survived. Survival in the low-dose group of female mice was 45/50.

The mean body weights of male rats in the high-dose group (50 mg/kg/day) were ≈5% lower than those of the control group after 28 weeks, while body weights in the low-dose male group (25 mg/kg/day) and in both groups of treated females were comparable with controls. There were no significant differences in hematologic and clinical chemistry indices among all groups of rats. Basal cell hyperplasia of the forestomach was observed in increased incidences in treated male and female rats, but these lesions were considered preneoplastic, since rats also had increased incidences of papillomas and carcinomas of the forestomach. The incidences of edema of the submucosa of the urinary bladder was 9/52 and 3/52 for high-dose males and females, respectively, compared with 0/52 for the control and low-dose groups. Increased incidences of nephropathy were observed in treated female rats (15/52, control; 24/52, low dose and 22/52, high dose), but not in male rats, as compared with controls.

The mean body weights of treated mice were initially lower than those of the vehicle controls and remained lower throughout the study (5-9%). This difference was due to lack of randomization at the beginning of the experiment. No significant differences in hematologic or clinical chemistry parameters were observed. Dose-related increased incidences of epithelial hyperplasia of the urinary bladder were observed in male and female treated mice. The incidences were as follows: 0/50 for male controls, 9/50 for low-dose males and 18/50 for high-dose males; 2/50 for female controls, 15/50 for low-dose females and 19/48 for female high-dose groups. Increased incidences of transitional cell carcinomas of the urinary bladder were also observed in the treated groups (Section 6.2.2). High-dose female mice also had increased incidences of epithelial hyperplasia of the forestomach. A dose-related increased incidence of hydronephrosis occurred in female, but not male, mice. The incidences were 0/50 for controls, 2/50 for low-dose and 14/50 for the high-dose groups.

6.1.3. Other Relevant Information. Torkelson and Oyen (1977) tested human volunteers for their ability to detect the odor of 1,3-dichloropropene. At each concentration of 4.5 or 13.6 mg/m$^3$ for 1-3 minutes, 7/10 individuals detected the odor, which was stronger at the higher concentration.

Dermatosis was reported in three men dermally exposed to D-D (53% 1,3-dichloropropene, 27.1% 1,2-dichloropropane, 1% epichlorohydrin and the remainder, dichloropropene isomers) while spraying the fumigant on their crops (Nater and Gooskens, 1976). An itchy erythematous rash was found at the site of exposure. Patch tests revealed that, in one case, an allergic contact sensitivity to D-D existed.

Irritation to eyes and upper respiratory mucosa of humans occurs after exposure to vapors of dichloropropene. Inhalation of vapor in concentrations

>1500 ppm produces headache, irritation to the mucous membranes, dizziness, nausea, vomiting, gasping, coughing, substernal pain and respiratory distress, with slight elevation of serum enzyme levels. At concentrations <1500 ppm, CNS depression and moderate irritation of the respiratory system occur (Gosselin et al., 1976). Ingestion of 1,3-dichloropropene produces acute gastrointestinal distress, pulmonary congestion and edema, and CNS depression in humans. Dermal exposure causes severe skin irritation with a marked inflammatory response.

$LD_{50}$ and $LC_{50}$ values for rats, mice and rabbits are listed in Table 6-1. Torkelson and Oyen (1977) found that 2700 ppm (≈12,000 mg/m³) 1,3-dichloropropene was extremely irritating to the respiratory tract and caused lung, nasal, liver and kidney injury in rats. Rats survived a 1-hour exposure to 1000 ppm (≈4500 mg/m³), but death occurred when exposure was increased to 2 hours. Guinea pigs died following a single 7-hour exposure to 400 ppm (≈1800 mg/m³); rats survived the same exposure, but severe injury and weight loss was evident. Weight loss was recovered after 8 days but lung injury was still present.

Torkelson and Rowe (1981) reported that direct application of two drops of 1,3-dichloropropene to the eyes of rabbits caused moderate to severe injury; vapors of 1,3-dichloropropene caused irritation and lacrimation. Application of 1,3-dichloropropene to the skin of rabbits, accompanied by the prevention of evaporation, caused necrosis and edema. Carreon and Wall (1983) reported that 4/10 guinea pigs exhibited signs of sensitization to Telone II®, and Jeffrey et al. (1987) reported edema, erythema and dermal necrosis at the site of administration of 200 mg/kg Telone II®.

Torkelson and Oyen (1977) reported that Telone II®, in a 12.5% solution in propylene glycol, was applied under a cuff to rabbits that were

$LD_{50}/LC_{50}$ Values for Dichloropropene

| Route | Species | $LD_{50}/LC_{50}$ Value (95% Confidence Limit) (mg/kg) | Comments | Reference |
|---|---|---|---|---|
| Oral | rat (M)<br>rat (F) | 710<br>470 | Liver and kidneys grossly affected, lung injury in survivors | Torkelson and Rowe, 1981 |
| | rat (M)<br>rat (F) | 560 (452-695)<br>510 (480-726) | Animals died 1-3 days after dosing. | Toyoshima et al., 1987a |
| | rat | 140±25 | NC | Hine et al., 1953 |
| | rat | 150 (130-170) | $LD_{50}$ for all rats was 150 mg/kg; $LD_{50}$ for males was 130 mg/kg; $LD_{50}$ for females was between 110 and 250 mg/kg. | Jones and Collier, 1986 |
| | mouse | 300±37 | NC | Hine et al, 1953 |
| | mouse (M)<br>mouse (F) | 640 (582-704)<br>640 (547-749) | Animals died 1-2 days after dosing. | Toyoshima et al., 1978b |
| Inhalation | rat<br>mouse | 4530* | Cumulative high acute toxicity | Hine et al., 1953 |
| Dermal | rat<br>mouse | >1211 | NC | Toyoshima et al., 1978a,b |
| | rabbit | 2100±260 | Single dose skin penetration | Hine et al., 1953 |
| | rabbit | 333 (102-610) | Dose was administered and the area was covered for 24 hours. | Jeffrey et al, 1987 |

*mg/m³

NC = No comment

then left undisturbed for 24 hours. Absorption occurred by this route, resulting in deaths with doses of 0.125 and 0.25 g/kg. When undiluted Telone II® was applied in the same manner to a group of both species of rabbits, a dermal $LD_{50}$ value of 504 mg/kg was obtained. When applied to the eyes of six rabbits, four of the rabbits had severe conjunctival irritation and two exhibited slight to moderate corneal injury after 24 hours of observation. The effects disappeared after 8 days.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Markovitz and Crosby (1984) described three reported cases of hematologic malignancies in humans that may have been the result of acute exposure to 1,3-dichloropropene. Two of the cases involved two firemen exposed to 1,3-dichloropropene after a spill from a tank truck. In nine firemen exposed to the vapors, symptoms included headache, neck pain, nausea and breathing difficulty. Eight years following the spill, two of the firemen developed malignant histiocytic lymphomas and died. In the third case, a farmer was exposed to 1,3-dichloropropene in the field for 30 days and developed redness and pain in the right ear, the nasal mucosa and the pharynx. The farmer returned to the field 1 year later and was exposed again to 1,3-dichloropropene; the symptoms worsened. The farmer was diagnosed with acute myelomonocytic leukemia and died of pneumonia 5 weeks after admission to the hospital.

The chronic toxicity and oncogenicity of technical grade 1,3-dichloropropene was determined in rats and mice (see Section 6.1.1.2) (Lomax et al., 1989). Groups of 50 male and 50 female F344 rats and B6C3F1 mice were exposed to 0, 5, 20 or 60 ppm (0, 22.7, 90.8 or 272 mg/m³) 1,3-dichloropropene (49.5% cis- and 42.6% trans-1,3-dichloropropene, 0.7% 1,2-dichloropropane and 2% epoxidized soybean oil) 6 hours/day, 5 days/week for $\leq$2 years.

Ancillary groups of 10 rats and mice/sex/exposure level were similarly exposed for 6 and 12 months.

No statistically significant increases in primary, benign or malignant tumor incidence was found in male or female rats when compared with the controls. The incidence of bronchioloalveolar adenomas (a benign lung tumor) was significantly increased in male mice exposed to 60 ppm 1,3-dichloropropene for 24 months (Table 6-2). No increase in incidence was found in the male mice exposed to 5 or 20 ppm. No increase in primary, benign or malignant tumors was found in the treated female mice. A hyperplastic response was found in the urinary bladders of both male and female treated mice (see Section 6.1.1.2.), but no dose-related tumorigenic response was found. A dose-related, statistically significant decrease was found in the incidence of liver and lymphoreticular tissue tumors in the mice.

6.2.2. Oral. In the previously reported chronic oral bioassay (NTP, 1985), rats and mice were treated by gavage with Telone II®, a commercial product containing 89% cis- and trans-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% trichloropropene and 1.0% epichlorohydrin. Details regarding the dosing schedule, numbers of animals and survival were presented in Section 6.1.2.2.

Significantly increased incidences of neoplastic lesions were observed in the forestomach and liver of rats and in the forestomach, urinary bladder and lungs of mice. Tumor incidences and the results of Fischer Exact Tests and Cochran-Armitage Tests for dose-related trends are presented in Table 6-3. In addition, the incidence of adrenal gland pheochromocytoma were significantly ($p=0.029$ by life table and incidental tumor tests) increased in male rats treated at 25 mg/kg. The incidence of thyroid follicular cell adenomas

TABLE 6-2

Incidence of Bronchioloalveolar Adenomas in B6C3F1 Mice Exposed to 1,3-Dichloropropene for 24 Months[a]

| Sex | Dose (ppm) | Tumor Incidence |
|---|---|---|
| Male | 0 | 9/50 |
| | 5 | 6/50 |
| | 20 | 13/50 |
| | 60 | 22/50[b] |
| Female | 0 | 4/50 |
| | 5 | 3/50 |
| | 20 | 5/50 |
| | 60 | 3/50 |

QUALITY OF EVIDENCE

Strengths of study: Compound was administered by a relevant route of exposure at three concentrations. Adequate numbers of animals/group survived to be at risk for late-developing tumors. Adequate duration of exposure. Two species (rats and mice) and both sexes were used.

Overall adequacy: Adequate

[a]Source: Lomax et al., 1989

[b]Statistical difference from control mean by Yate's $x^2$ pairwise test, $\alpha$=0.05 and linear trend by Cochran-Armitage linear trend test, $\alpha$=0.02, two-sided.

Chronic Oral Exposure to Telone II[a,b,c] for 2 Years

| Species/Strain | Sex (No.) | Dose (mg/kg/day) | Target Organ | Tumor Type | Tumor Incidence (p value) | |
|---|---|---|---|---|---|---|
| Rat/F344 | M (52) | 0 | forestomach | squamous-cell | 1/52 | 0.002[d] |
| | | 25 | | papilloma | 1/52 | 0.752[e] |
| | | 50 | | | 9/52 | 0.008[e] |
| Rat/F344 | M (52) | 0 | forestomach | squamous-cell | 0/52 | 0.015[d] |
| | | 25 | | carcinoma | 0/52[f] | |
| | | 50 | | | 4/52 | 0.059[e] |
| Rat/F344 | F (52) | 0 | liver | neoplastic | 1/52 | 0.015[d] |
| | | 25 | | nodule or | 6/52 | 0.056[e] |
| | | 50 | | carcinoma | 8/52 | 0.016[e] |
| Rat/F334 | M (52) | 0 | forestomach | squamous-cell | 1/52 | <0.001[d] |
| | | 25 | | papilloma or | 1/52 | 0.752[e] |
| | | 50 | | carcinoma | 13/52 | <0.001[e] |
| Rat/F334 | M (52) | 0 | liver | neoplastic | 1/52 | 0.030[d] |
| | | 25 | | nodules | 6/52 | 0.056[e] |
| | | 50 | | | 7/52 | 0.030[e] |
| Rat/F344 | F (52) | 0 | forestomach | squamous-cell | 0/52 | 0.082[d] |
| | | 25 | | papilloma | 2/52 | 0.248[e] |
| | | 50 | | | 3/52 | 0.121[e] |
| Mice/B6C3F1 | F (50) | 0 | forestomach | squamous-cell | 0/50 | 0.026[d] |
| | | 25 | | papilloma or | 1/50 | 0.500[e] |
| | | 50 | | carcinoma | 4/50 | 0.059[e] |
| Mice/B6C3F1 | F (50) | 0 | urinary bladder | transitional | 0/50 | <0.001[d] |
| | | 50 | | cell carcinoma | 8/50 | 0.003[e] |
| | | 100 | | | 21/48 | <0.001[e] |

TABLE 6-3 (cont.)

| Species/Strain | Sex (No.) | Dose (mg/kg/day) | Target Organ | Tumor Type | Tumor Incidence (p value) | |
|---|---|---|---|---|---|---|
| Mice/B6C3F1 | F (50) | 0 | lung | alveolar/ | 0/50 | 0.002[d] |
| | | 50 | | bronchiolar | 2/50 | 0.121[e] |
| | | 100 | | ademona | 8/50 | 0.003[e] |
| Mice/B6C3F1 | M (50) | 0 | lung | alveolar/ | 2/50 | 0.029[d] |
| | | 50 | | bronchiolar | 4/50 | 0.339[e] |
| | | 100 | | adenoma or carcinoma | 8/50 | 0.046[e] |

QUALITY OF EVIDENCE

Strenghts of study: Two-year study; sufficient number of animals, both sexes, two dose levels, two species were used; ancillary studies were included (see text).

Weakness of study: Male mouse vehicle control had many early deaths from myocarditis.

Overall adequacy: Adequate

[a]Source: NTP, 1985

[b]Corn oil vehicle in all studies

[c]Purity of compound: 89% cis- and trans-isomers of 1,3 dichloropropene with 1.0% epichlorohydrin

[d]Cochran-Armitage Trent Test

[e]Fischer Exact Test

[f]No p value is presented because no tumors were observed in the 25 mg/kg and vehicle control groups.

or carcinomas in female rats showed a marginally significant ($p<0.05$) positive dose-related trend. NTP (1985) reported that, under the conditions of the study, there was clear evidence of carcinogenicity for male F344/N rats and for female B6C3F1 mice, and there was some evidence in female F344/N rats. The study was deemed an inadequate study of carcinogenicity in male B6C3F1 mice because of high mortality in the control group. Although the early deaths of the control male mice confounded the results, a carcinogenic effect of Telone II® was suggested by the tumor incidences of transitional cell carcinomas of the urinary bladder, alveolar/bronchiolar neoplasms and squamous cell papillomas of the forestomach in male mice.

Results of the ancillary studies indicated that the development of forestomach lesions was time-dependent. Pooling of the tumor incidences from the ancillary studies and the 2-year study (not shown in Table 6-3) enhanced the statistical significance.

The Telone II® used in the bioassay contained 1.0% epichlorohydrin, a known carcinogen, which may have influenced the development of forestomach lesions.

6.2.3. Other Relevant Information. A group of 30 female Ha:ICR mice was given weekly subcutaneous injections of cis-1,3-dichloropropene in trioctanoin at a dose of 3 mg/mouse/week (Van Duuren et al., 1979). After 538 days, six mice had local sarcomas (fibrosarcomas) (6/30; $p<0.0005$) and no distant tumors were observed. No tumors developed in untreated and vehicle-treated animals.

Van Duuren et al. (1979) also studied cis-1,3-dichloropropene as a tumor-initiator and as a whole carcinogen when applied to the skin of mice. A group of 30 female Ha:ICR mice received a single dermal application of 122 mg

1,3-dichloropropene in 0.2 mℓ acetone followed by phorbol myristate acetate in acetone at 5 μg, 3 times/week for 428-576 days. Controls consisted of 100 untreated mice, 90 mice treated with 0.0025 mg/application and 120 mice treated with 0.005 mg/application of the tumor promoter. No significant differences were observed between the dichloropropene-initiated mice and those treated with the promoter alone, with respect to local or distant tumors. When 1,3-dichloropropene was tested as a whole carcinogen, three papillomas developed in 3/30 female mice treated with 122 mg/application 3 days/week for ≤589 days. Two of the mice had carcinomas. Although no local tumors were observed in mice treated at 41 mg/application, or in acetone-treated or untreated controls, the incidence in high-dose mice was not significantly different. The number of mice with distant tumors was also not different from that in controls.

6.3. MUTAGENICITY

Studies on the mutagenicity of 1,3-dichloropropene are summarized in Table 6-4. 1,3-Dichloropropene was positive for reverse mutation in Salmonella typhimurium strains TA100 and TA1535 both with and without metabolic activation (NTP, 1985; Stolzenberg and Hine, 1980; Haworth et al., 1983). In S. typhimurium strain TA98, a positive reaction was obtained without metabolic activation (NTP, 1985; Haworth et al. 1983; Vithayathil et al. 1983). Although Talcott and King (1984) and Watson et al. (1987) demonstrated that the mutagenicity to strain TA100 of mixtures of cis- and trans-1,3-dichloropropene was abolished following removal of polar impurities, other investigators (Creedy et al., 1984; Neudecker et al., 1977; DeLorenzo et al., 1977) found that both the cis-isomer and the trans-isomer (both relatively pure) were mutagenic in strains TA100, TA1538, TA1537,

TABLE 6-4

Mutagenicity of 1,3-Dichloropropene

| Assay | Indicator Organism | Compound/ Purity | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA 100 TA 1535 TA 1537 TA 98 | 95.6% | plate incorporation | 0.3333 µg/ plate | ± S-9 | +/+ +/+ -/- -/+ | S-9 mixtures from both rats and hamsters were used. No difference was found between species. Where a positive response was found, the chemical was cytotoxic at >333 µg/plate. | NTP, 1985; Haworth et al., 1983 |
| Reverse mutation | S. typhimurium TA 98 | NR | liquid incubation | 100 µg/plate | none | + | NC | Vithayathie et al., 1983 |
| Reverse mutation | S. typhimurium TA 100 | NR | plate incorporation | 10, 1, $10^{-1}$ µmol/plate | ± S-9 | +/+ | NC | Stolzenberg and Hine, 1980 |
| Reverse mutation | S. typhimurium TA 1978 TA 1535 TA 100 | cis- and trans- isomers/NR | plate incorporation | 20, 50, 100 µg/plate | ± S-9 | +/+ | NC | Delorenzo et al., 1977 |
| Reverse mutation | S. typhimurium TA 100 | cis- and trans- isomers/98% | plate incorporation | 10-200µg/plate | ± S-9 | +/+ | addition of glutathione protected against mutagenicity. | Creedy et al., 1984 |
| Reverse mutation | S. typhimurium TA 1538 TA 1537 TA 1535 | cis-isomer/ 99.97%; trans- isomer/97.46% | plate incorporation | 0, 0.1, 0.5, 1.0 µg/mL | ± S-9 | +/+ | NC | Neudecker et al., 1977 |
| Reverse mutation | S. typhimurium TA 100 | mix of cis- and trans-/ 77-95% pure | plate incorporation | ≤1 mg/plate | none | + | impurities in the DCP preparation were removed and the mutagenic response was no longer found. The impurities themselves were mutagenic. | Talcott and King, 1984 |

TABLE 6-4 (cont.)

| Assay | Indicator Organism | Compound/ Purity | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA 100 | cis- isomer/ 99.7% | plate incorporation | 25-2000 µg/ plate | ± S-9 | + | the study showed that previously shown intrinsic mutagenicity was probably due to impurities and not 1,3 DCP. | Watson et al., 1987 |
| Reverse mutation | S. typhimurium TA 100 | cis- and transisomers/ >99.5% | plate incorporation | NR | ± S-9 | +/+ | activation was increased by greater amounts of and longer incubation with S-9. | Neudecker and Henschler, 1986 |
| Sister chromatid *exchange* | Chinese hamster *V79 cell* | 98% | cell culture | 3.3, 6.6, 10.0 mm | ± S-9 | -/+ | 1,3 DCP was inactivated by the S-9 mixture in the V79/SCE assay. | von der Hude et al., 1987 |
| Sex-linked recessive lethal | Drosophila melanogaster | 95.5% | feeding | 0.5750 ppm | NA | + | NC | NTP, 1985; Valencia et al., 1985 |
| Reciprocol trans-locations | D. melanogaster | 95.5% | feeding/injection | 0.5750 ppm | NA | - | NC | NTP, 1985; Valencia et al., 1985 |

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

TA1535 and TA1978. Neudecker and Henschler (1986) found that the mutagenicity of 1,3-dichloropropene in S. typhimurium increased with increasing levels of the S-9 mixture and with longer incubation periods. Creedy et al. (1984) also demonstrated that, if glutathione was added to the assay system, the mutagenicity of either isomer was reduced.

1,3-Dichloropropene was positive for sex-linked recessive lethal mutations, but negative for reciprocal translocations in Drosophila melanogaster (NTP, 1985; Valencia et al., 1985).

6.4. DEVELOPMENTAL TOXICITY

Hanley et al. (1987) studied the effects of inhalation exposure to 0, 20, 60 or 120 ppm 1,3-dichloropropene (47.7% cis- and 42.4% trans-1,3-dichloropropene) for 6 hours/day during gestation days 6-15 in 30 F344 rats and on days 6-18 in 25-31 New Zealand White rabbits. Maternal toxicity (body weight gain, liver weight, kidney weight, mortality, food and water consumption and reproductive parameters) and developmental toxicity (fetal body weight, number of resorptions, external and skeletal examination and visceral examination) were assessed. No evidence of developmental toxicity was observed in rats or rabbits, but significant maternal toxicity was seen in both species of animals. Signs of maternal toxicity increased with increasing exposure concentrations in both species. Maternal toxicity was evidenced in the rabbits by a decrease in weight gain at the highest two exposure levels. Decreases in maternal weight gain were observed at all exposure levels in rats. In rats, maternal toxicity was also evidenced at all exposure levels by decreases in food and water consumption and statistically significant decreases in absolute liver weights, and, at the highest level, by statistically significant increases in relative kidney weights. A statistically significant increase in the incidence of one minor skeletal variant (delayed

ossification of the vertebral centra) was observed among fetuses of dams exposed to 120 ppm 1,3-dichloropropene, but this was considered secondary to the maternal toxicity. No adverse effects on other ossification sites were found in the fetal rats.

6.5. OTHER REPRODUCTIVE EFFECTS

Venable et al. (1980) reported a fertility study of 79 male workers engaged in the manufacture of 1,3-dichloropropene. Results from this study indicated no significant effect on fertility from exposure to 1,3-dichloropropene at levels occurring in the work environment.

Linnett et al. (1988) exposed 30 male and 24 female Wistar rats to 0, 10, 30 or 90 ppm D-D (28.1% cis-1,3-dichloropropene, 25.6% trans-1,3-dichloropropene, 25.6% 1,2-dichloropropane and the remainder, primarily dichloropropene isomers) for 6 hours/day, 5 days/week for 10 weeks. Treated males were mated with untreated females, and treated females were mated with untreated males. Libido, fertility and morphology of the reproductive tract of either sex were not affected and no treatment-related dominant lethal effect was observed in male rats. Body weight gain decreased slightly and liver and kidney weights increased slightly in both sexes at the highest exposure concentration.

In a U.S. EPA (1988) review of an unpublished experiment (Breslin et al., 1987), groups of 30 male and 40 female F344 rats were exposed by inhalation to Telone II® (94% 1,3-dichloropropane, nearly equally divided between cis and trans isomers) at concentrations of 0, 10, 30 or 90 ppm, 6 hours/day, 5 days/week in a multigeneration reproduction study. Exposure began 10 weeks before mating and was increased to 7 days/week during a 2-week breeding period. Exposure of the $F_1$ generation began after weaning on the 6 hours/day, 5 days/week schedule and continued for 12 weeks. The highest concentration tested was considered by U.S. EPA (1988) to be a NOAEL for

reproductive effects associated with a slight decrease in the conception indices in $F_1$ and $F_2$ females. Nonreproductive effects reported in the 90 ppm groups included hyperplasia of the respiratory epithelium, degeneration of olfactory tissue and decreased body weight gain in rats of both sexes.

In a mouse sperm morphology assay (Osterloh et al., 1983), male mice (C57BL/6XC3H, four mice/dose level) were injected intraperitoneally for 5 consecutive days with 1,3-dichloropropene (Telone II®) in 0.25 mL corn oil at doses of 10, 19, 38, 75, 150, 300 and 600 mg/kg/day. A negative control group received only corn oil, and 90 mg/kg/day methyl methanesulfonate was injected as a positive control. The morphology of 200 sperm/mouse was assessed 35 days following the first injection. Testicular weights, total epididymal sperm counts and percentage of abnormally-shaped sperm were averaged and compared with controls after 35 days. Methyl methanesulfonate produced a high percentage of abnormally-shaped sperm (16.4-22.9%). At the three highest dose levels (150, 300 and 600 mg/kg/day), all mice died before day 35. Most of the animals injected with the lower doses survived and exhibited no significant changes in testes weight, total sperm count or percent of abnormal sperm compared to vehicle controls. Data are presented in Table 6-5. Ten pesticides, including four known testicular toxins and three known mutagens, were tested in this study. None of the pesticides tested positive. The authors concluded that the mouse sperm morphology assay only tested for damage at the spermatid stage of sperm development and was not a suitable test for testicular toxins.

6.6. SUMMARY

The $LC_{50}$ for 1,3-dichloropropene in rats and mice was 4530 mg/m³ (Hine et al., 1953). Information regarding subchronic and chronic inhalation of 1,3-dichloropropene suggests that damage to the nasal mucosa of rats and

TABLE 6-5

Testicular Weights, Sperm Counts and Percent Abnormal Sperm After Intraperitoneal Injection of 1,3-Dichloropropene[a]

| | Control | 75 mg/kg | 38 mg/kg[b] | 19 mg/kg | 10 mg/kg[c] |
|---|---|---|---|---|---|
| Testes weight (mg) | 203±40 | 229±14 | 211±7 | 218±9 | 218±9 |
| Total sperm count (million/mℓ) | 25.9±8.9 | 32.0±3.0 | 32.3±4.5 | 29.1±6.1 | 25.8±0.6 |
| Percent abnormal sperm | 1.0±0.4 | 0.9±0.9 | 0.8±1.0 | 1.1±0.3 | 1.8±1.1 |
| Methyl methanesulfonate (positive control) percent abnormal sperm | 16.4±22.9 | NA | NA | NA | NA |

[a]Source: Osterloh et al., 1983

[b]Three of four survived 35 days.

[c]Two of four survived 35 days.

NA = Not applicable

mice and damage to the urinary bladders of mice may result from exposure (Stott et al., 1988; Torkelson and Rowe, 1981; Lomax et al., 1989). Evidence of damage to the liver and kidneys was also found (Parker et al., 1982; Torkelson and Rowe, 1981).

Oral $LD_{50}$ values in rats ranged from 140-740 mg/kg and, in mice, from 300-640 mg/kg (Torkelson and Rowe, 1981; Hine et al., 1953; Toyoshima et al., 1978a,b). Subchronic studies suggested increases in the relative weight of the kidneys in rats treated orally with 1,3-dichloropropene (Torkelson and Rowe, 1981). Chronic oral studies suggest that hyperplasia of the forestomach and of the urinary bladders of rats and mice resulted from exposure (NTP, 1985).

The only data available regarding the carcinogenicity of 1,3-dichloropropene in humans are three reported cases of hematologic malignancies that may have been the result of acute inhalation exposure to 1,3-dichloropropene (Markovitz and Crosby, 1984). There is sufficient evidence that 1,3-dichloropropene is a carcinogen in orally exposed animals. NTP (1985) found increased incidences of squamous-cell papillomas and carcinomas of the forestomach and neoplastic nodules or carcinomas of the liver in rats treated chronically with 1,3-dichloropropene by gavage. Mice similarly treated showed increased incidences of forestomach tumors, lung adenomas or carcinomas and transitional cell carcinomas of the urinary bladder. There is weak evidence that 1,3-dichloropropene is carcinogenic in animals exposed by inhalation. Lomax et al. (1989) found an increase in the incidence of benign lung tumors (bronchioloalveolar adenomas) in male mice treated chronically with 1,3-dichloropropene. 1,3-Dichloropropene has been found to be mutagenic in various strains of S. typhimurium (NTP, 1985; Stolzenberg and Hine, 1980; Haworth et al., 1983). 1,3-Dichloropropene has also been found to be

positive for sex-linked lethal mutations,. but negative for reciprocal translocations in D. melanogaster (NTP, 1985). 1,3-Dichloropropene does not appear to be a reproductive or a developmental toxicant.

# 7. EXISTING GUIDELINES AND STANDARDS

## 7.1. HUMAN

The ACGIH (1986, 1988) has recommended and adopted a TWA-TLV of 1 ppm (5 $mg/m^3$) for 1,3-dichloropropene. This value is based on the findings of Torkelson and Oyen (1977) that exposure to 1 ppm, 7 hours/day for 6 months resulted in no injury to four species and that 3 ppm resulted in slight, reversible injury in one species (see Section 6.1.1.2). A skin notation is also listed by the ACGIH (1988), which means that appreciable exposure may occur through skin contact with the vapors. OSHA (1989) has also recommended and adopted a TWA of 1 ppm (5 $mg/m^3$) with a skin designation for 1,3-dichloropropene. The U.S. EPA (1987b) verified a chronic oral RfD of $3x10^{-4}$ mg/kg/day, based on increased organ weights in rats fed 1,3-dichloropropene for 90 days (Til et al., 1973). The U.S. EPA (1987b) reported an oral slope factor for carcinogenicity of $1.8x10^{-1}$/mg/kg/day and a carcinogenicity classification of B2 (probable human carcinogen); based on tumors in rats and mice in the NTP (1985) study (see Section 6.2.2), positive mutagenic activity, and structural similarity to known oncogens that produce similar types of tumors in rodents. IARC (1987) classified 1,3-dichloropropene as a class 2B carcinogen (probable human carcinogen).

## 7.2. AQUATIC

Pertinent data regarding guidelines for exposure of aquatic organisms to 1,3-dichloropropene were not located in the available literature cited in Appendix A.

# 8. RISK ASSESSMENT

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential business information (CBI), which this document could not address, does not exist. However, it was determined that existing CBI data would not alter the approach to risk assessment or the risk assessment values presented herein.

## 8.1. CARCINOGENICITY

8.1.1. Inhalation. The chronic toxicity and oncogenicity of technical grade 1,3-dichloropropene were determined in rats and mice (see Sections 6.1.1.2. and 6.2.1.) (Lomax et al., 1989). Groups of rats and mice were exposed to 0, 5, 20 or 60 ppm (0, 22.7, 90.8 or 272 mg/m$^3$) 1,3-dichloropropene (49.5% cis- and 42.6% trans-1,3-dichloropropene, 0.7% 1,2-dichloropropane and 2% epoxidized soybean oil) 6 hours/day, 5 days/week for $\leq$2 years. Clinical signs of toxicity were not observed, and no significant differences in survival were found in any group of exposed animals.

No statistically significant increases in primary, benign or malignant tumor incidence were found in male or female rats when compared with the controls. The incidence of bronchioloalveolar adenomas (benign lung tumors) was significantly increased in male mice exposed to 60 ppm 1,3-dichloropropene for 24 months (22/50 treated, 9/50 controls). No increase in incidence was found in male mice exposed to 5 or 20 ppm (see Table 6-2). No increase in primary, benign or malignant tumors was found in the treated female mice. In contrast to these results, NTP (1985) found significantly increased incidences of neoplastic lesions in the forestomach and liver of rats and in the forestomach, urinary bladder and lungs of mice in a chronic gavage

study. In both studies, a tumorigenic response was found in the tissues through which the 1,3-dichloropropene was absorbed, i.e., the forestomach in the gavage study and the lungs in the inhalation study. In the gavage study, however, tumors were also induced at sites distant from the point of entry. Hyperplasia of the urinary bladder, however, was found in animals exposed by both inhalation and ingestion. Lomax et al. (1989) determined that, when the concentration of 1,3-dichloropropene administered by inhalation was converted to mg/kg, the dose given in the inhalation study was 2-3 times higher than the dose given in the oral study. A major difference between the studies was the compound used to stabilize the 1,3-dichloropropene mixture. In the oral study, 1% epichlorohydrin, a compound that reportedly causes nasal and forestomach tumors in rats following chronic inhalation and oral exposure, respectively, was used as a stabilizer; in the inhalation study, a relatively nontoxic epoxidized soybean oil stabilizer was used. The levels of epichlorohydrin used in the gavage study, however, were about 30-fold lower than the doses shown to be tumorigenic by ingestion. The differing results, therefore, are most likely due to the differences in administration: repeated bolus doses administered by gavage vs. repeated 7-hour inhalation exposures. Another reason for differing results can be differences in metabolic pathways following oral vs. inhalation exposures. Results from pharmacokinetic studies (Fisher, 1988; Fisher and Kilgore, 1988a) (see Section 5.3.) have indicated that, following inhalation exposure, a substantial amount of 1,3-dichloropropene is metabolized to the less toxic glutathione conjugate, transported to the bloodstream and is subsequently degraded to the mercapturic acid form and excreted in the urine.

8.1.2. Oral. In the NTP (1985) chronic gavage study, increased incidences of squamous-cell papillomas and carcinomas of the forestomach and neoplastic

nodules or carcinomas of the liver were observed in rats treated with Telone II® (89% 1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% trichloropropene and 1% epichlorohydrin) at doses of 25 and 50 mg/kg/day, 3 days/week for 2 years. In addition, the incidence of adrenal gland pheochromocytoma increased significantly in male rats treated at 25 mg/kg, and the incidence of thyroid follicular cell adenoma or carcinoma in female rats showed a significant ($p<0.05$) positive dose-related trend. Mice similarly treated at 50 and 100 mg/kg/day had increased incidences of forestomach tumors, lung adenomas or carcinomas and transitional cell carcinomas of the urinary bladder (see Table 6-3). NTP (1985) noted that epichlorohydrin may have influenced the development of forestomach lesions, but it was concluded that there was clear evidence for the carcinogenicity of Telone II® in male rats and female mice, some evidence in female rats and inadequate evidence in male mice, due to high mortality in the male control group.

8.1.3. Other Routes. Weekly subcutaneous injection of cis-1,3-dichloropropene in mice at 3 mg/mouse/week resulted in significantly increased incidences of injection-site fibrosarcomas. No significant differences between treated mice and control mice were observed when cis-1,3-dichloropropene was tested as a tumor initiator or as a whole carcinogen on the skin (Van Duuren et al., 1979).

8.1.4. Weight of Evidence. The only available data regarding the carcinogenicity of 1,3-dichloropropene in humans are three reported cases of hematologic malignancies that may have resulted from acute exposure to 1,3-dichloropropene (Markovitz and Crosby, 1984). The available animal data indicate evidence that 1,3-dichloropropene is carcinogenic by the oral route of exposure and may be carcinogenic following inhalation exposure (NTP, 1985; Lomax et al., 1989). Mutagenicity studies indicate that 1,3-dichloropropene

is mutagenic to various strains of S. typhimurium (NTP, 1985; Haworth et al., 1983; Stolzenberg and Hine, 1980). According to U.S. EPA (1986c) guidelines, 1,3-dichloropropene can be placed in Group B2: probable human carcinogen.

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- The only long-term inhalation study available that assesses the carcinogenicity of 1,3-dichloropropene indicates that exposure is associated with an increased incidence of bronchioloalveolar adenomas (benign tumors) in male mice exposed to 60 ppm (272 mg/m$^3$) for 2 years (Lomax et al., 1989). (Data used to calculate the $q_1^*$ value are presented in Appendix B.) Only benign tumors were observed in this study and quantitative risk estimate based solely on benign tumor alone is not routinely performed; however, incidences of lung adenomas as well as other types of tumors were also increased following oral exposure. Therefore, the results from the inhalation study by Lomax et al. (1980) are considered relevant and a quantitative risk estimate is derived. The value for $q_1^*$ was calculated using the linearized multistage model developed by Kenneth Crump and adopted by U.S. EPA. The conversion factor used to adjust for species-to-species extrapolation was the cube root of the ratio of the average body weight of a man (assumed to be 70 kg) to the body weight of the experimental animal (Appendix B). The value for the $q_1^*$ in humans is calculated to be $1.3 \times 10^{-1}$ (mg/kg/day)$^{-1}$. Assuming a reference human body weight of 70 kg and a respiratory rate of 20 m$^3$/day, ambient air concentrations of $2.7 \times 10^{-4}$, $2.7 \times 10^{-5}$ and $2.7 \times 10^{-6}$ mg/m$^3$ are associated with increased cancer risks of $1 \times 10^{-5}$, $1 \times 10^{-6}$ and $1 \times 10^{-7}$, respectively.

8.1.5.2. ORAL -- The only long-term study available that assesses the carcinogenicity of 1,3-dichloropropene following chronic oral exposure is

that by NTP (1985). This study indicates that chronic exposure is associated with increased incidences of squamous-cell papillomas and carcinomas of the forestomach, neoplastic nodules or carcinomas of the liver, possibly adrenal and thyroid tumors in rats, and increased incidences of forestomach tumors, lung adenomas or carcinomas and transitional cell carcinomas of the urinary bladder in mice. Because of the demonstrated carcinogenicity of Telone II®, it is appropriate to derive a $q_1^*$ for 1,3-dichloropropene. The value for $q_1^*$ was calculated using the linearized multistage model developed by Kenneth Crump and adopted by U.S. EPA. The conversion factor used to adjust for species-to-species extrapolation was the cube root of the ratio of the average body weight of a man (assumed to be 70 kg) to the body weight of the experimental animal (Appendix B). A $q_1^*$ of $1.8 \times 10^{-1}$/mg/kg/day is calculated based on the combined incidences of tumors in the forestomach and liver and pheochromocytoma in the adrenals of male rats. The concentrations of 1,3-dichloropropene in drinking water associated with risk levels of $10^{-5}$, $10^{-6}$ and $10^{-7}$ are $2 \times 10^{-3}$, $2 \times 10^{-4}$ and $2 \times 10^{-5}$ mg/ℓ, respectively.

## 8.2. SYSTEMIC TOXICITY

### 8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Stott et al. (1988) exposed F344 rats and B6C3F1 mice to 0, 10, 30, 90 or 150 ppm of technical-grade 1,3-dichloropropene (90% 1,3-dichloropropene) 6 hours/day, 5 days/week for 13 weeks. Degenerative or hyperplastic changes in the nasal mucosa were observed in both sexes of rats and mice exposed to $\geq$90 ppm and in 2/10 male rats exposed to 30 ppm. Hyperplasia of the urinary bladder transitional epithelium was found in female mice exposed to 90 or 150 ppm of the vapor. No treatment-related effects were observed in rats or mice

exposed to 10 ppm 1,3-dichloropropene. A NOEL of 10 ppm (45.4 mg/m³) (rec #2) and a LOAEL of 30 ppm (136.2 mg/m³) (rec #13) for respiratory effects in rats were identified. This study will be used as the basis for the subchronic RfD, since a higher percentage of the vapor administered in this study consisted of 1,3-dichloropropene compared with the Parker et al. (1982) study below.

Parker et al. (1982) exposed mice and rats to 0, 5, 15 or 50 ppm of a mixture of D-D (52% cis-and trans-1,3-dichloropropene and 29% 1,2-dichloro propane) 6 hours/day, 5 days/week for 6 or 12 weeks. Slight to moderate diffuse hepatocytic enlargement was found in male and female mice exposed to 50 ppm for 12 weeks. Increased mean liver-to-body weight ratios of male rats and increased mean kidney-to-body weight ratios of female rats were seen at the 50 ppm level. No compound-related effects were found at lower levels, so 15 ppm (68 mg/m³) can be defined as the NOAEL (rec #25) and 50 ppm (227 mg/m³) can be defined as the LOAEL (rec #26) for liver effects in rats and mice. Although a higher LOEL value is identified in the Parker et al. (1982) study than in the Stott et al. (1988) study (15 ppm vs. 10 ppm), the Stott et al. (1988) study will be used as the basis for the inhalation RfD, since the vapor used in this study was 90% 1,3-dichloropropene, while the vapor used in the Parker et al. (1982) study was only 52%.

Coate et al. (1979) reported that rats and mice exposed to 93 ppm Telone II® for 13 weeks had reduced body weight gain (rec #20-24). Torkelson and Oyen (1977) reported a Dow Chemical study in which liver and kidney necrosis was found in rats and guinea pigs exposed to $\geq$11 ppm (rec #33, 34). Neither of these studies will be used as the basis for the subchronic inhalation RfD, since the former study reports a NOAEL higher than the LOAEL in the Stott et al. (1988) study and the latter study was a pilot consisting

of very few animals. Torkelson and Oyen (1977) reported a slight, apparently reversible cloudy swelling of the renal epithelium in male rats exposed to 3 ppm, but not to 1 ppm, of 1,3-dichloropropene (99% 1,3-dichloropropene) for 4 or 7 hours/day, 5 days/week for 6 months. The renal effect was not substantiated in a study in which 50 rats/sex/group were exposed to $\leq$60 ppm for 2 years, or 10 rats/sex/group were exposed to $\leq$60 ppm for 6 or 12 months. No compound-related effects were found following exposure of rabbits, guinea pigs or dogs to 1 or 3 ppm 1,3-dichloropropene for 6 months. It is reasonable, therefore, to consider the 3 ppm level in the study by Torkelson and Oyen (1977) as a NOAEL (rec #5).

The subchronic inhalation RfD is calculated by adjusting 10 ppm (45.4 $mg/m^3$) from the Stott et al. (1988) study for intermittent exposure, multiplying by the RGDR and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individual). The RGDR is the ratio of (rat ventilation rate/the extrathoracic surface area of the rat) to (human ventilation rate/extrathoracic surface area of the human) [(0.223 $m^3$/day/11.6 $m^2$)/(20 $m^3$/day/177 $m^2$)] (Jarabek, 1988). Therefore, the calculated subchronic inhalation RfD is 0.01 $mg/m^3$. Confidence in the key study used to derive the RfD is high; the study was well conducted and extensive histopathological examinations of the animals were done. Confidence in the data base is medium, since several studies were conducted, two of which were of high quality, but effects seen in a lower quality study were not substantiated. Therefore, confidence in the subchronic inhalation RfD is medium.

8.2.1.2. CHRONIC EXPOSURE -- Lomax et al. (1989) determined the chronic toxicity of inhaled 1,3-dichloropropene (93% 1,3-dichloropropene) in rats and mice exposed to 5, 20 or 60 ppm for 6 hours/day, 5 days/week for $\leq$2 years.

Examinations of hematological, biochemical and urinalysis data in treated animals did not indicate toxicity from 1,3-dichloropropene exposure. Histopathological examination of rats revealed exposure-related effects in the nasal tissue of male and female rats exposed to 60 ppm for 24 months, but not after exposure for 6 or 12 months. Histopathological examination of mice revealed exposure-related morphological changes in the urinary bladder and lung of both sexes. Significant increases in the incidence of hyperplasia and inflammation of the transitional epithelium of the urinary bladder was found in male mice exposed to 60 ppm for 24 months and in female mice exposed to 20 and 60 ppm for 24 months. Significant increases in the incidence of hyperplasia of the respiratory and olfactory epithelium were found in male mice exposed to 60 ppm for 24 months and in female mice exposed to 20 and 60 ppm for 24 months. Therefore, a NOEL of 5 ppm (22.7 $mg/m^3$) (rec #5) and a LOAEL of 20 ppm (90.8 $mg/m^3$) (rec #6) is defined for the respiratory and bladder effects of 1,3-dichloropropene in mice. A NOEL of 20 ppm (90.8 $mg/m^3$) (rec #3) and a LOAEL of 60 ppm (272 $mg/m^3$) (rec #4) are defined for the respiratory effects in rats. Although the exposure level of 5 ppm in mice is a NOEL for respiratory and bladder effects, the respiratory effects cannot be considered in the derivation of the RfD because values for respiratory tract surface areas are not yet available for B6C3F1 mice. The bladder effects, however, are systemic effects for which methodology exists. A chronic inhalation RfD of 0.04 $mg/m^3$ could be calculated by adjusting 22.7 $mg/m^3$ (5 ppm) for intermittent exposure to 4.1 $mg/m^3$, multiplying by the ratio of the blood/gas partition coefficient for animals/humans (no information available, so the default value of 1 is used), and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect the most sensitive individual). The pharmacokinetic study by Stott

and Kastl (1986) suggests that a steady state of 1,3-dichloropropene was reached in the blood within the duration period of the daily exposures. This RfD, however, is greater than the subchronic inhalation RfD of 0.01 mg/m³, based on a NOEL of 10 ppm for respiratory effects in rats. The LOAEL in the subchronic study was 30 ppm, at which 2/10 rats had degenerative changes in the nasal mucosa. Only 2/50 rats exposed to 20 ppm in the chronic study had nasal tissue lesions; the increased incidence is not statistically significant when compared with the incidence (0/50) in the controls. Furthermore, 20 ppm is a chronic LOAEL in mice and is higher than the NOEL of 10 ppm in rats in the subchronic study used as the basis for the subchronic RfD. Therefore, the inhalation RfD of 0.01 mg/m³ is adopted as the chronic inhalation RfD. As discussed in Section 8.2.1.1., confidence in the key study is high and in the data base, medium. Overall confidence in the chronic inhalation RfD is medium because it protects for the critical effect of respiratory effects in rats, but it may not be protective for the respiratory effects in mice.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Til et al. (1973) administered 1,3-dichloropropene (Telone II®) in propylene glycol to 10 Albino rats/sex/dose to 0, 1, 3, 10 or 30 mg/kg/day, 6 days/week for 90 days. No significant differences between the groups were found in the means of body weight and food consumption. No biologically significant differences in hematology or clinical chemistry parameters were found, and no compound-related abnormalities were seen upon gross autopsy. Increased relative kidney weights, however, were found in male rats at 10 and 30 mg/kg/day and in female rats at 30 mg/kg/day. Therefore, a NOEL for kidney effects of 3 mg/kg/day (rec #1) and a LOAEL of 10 mg/kg/day (rec #7) were identified.

This study will be used as the basis for the subchronic oral RfD, since the only other subchronic oral studies are abstracts of Russian studies which lack experimental details (Strusevich and Ekshtat, 1974; Strusevich and Sadovnik, 1975).

The subchronic oral RfD is calculated by taking the NOEL of 3 mg/kg/day from the Til et al. (1973) study, adjusting for intermittent exposure to 2.6 mg/kg/day and dividing by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals and an additional modifying factor of 10 for the deficient data base). An RfD of $3 \times 10^{-3}$ mg/kg/day is calculated. Confidence in the key study that is the basis for the subchronic RfD is low because the study is of poor quality. Confidence in the data base is low since few subchronic oral studies exist. Overall confidence in the subchronic oral RfD is low.

8.2.2.2. CHRONIC EXPOSURES -- NTP (1985) determined the chronic toxicity of 1,3-dichloropropene in rats given 0, 25 or 50 mg/kg/day and mice given 0, 50 or 100 mg/kg/day Telone II® (89% 1,3-dichloropropene) by gavage in corn oil 3 days/week for 104 weeks. No effects on survival were found in male and female rats. Basal cell hyperplasia of the forestomach was observed in increased incidences in both sexes of treated rats in the high dose group; edema of the submucosa of the urinary bladder increased in high dose male and female rats. Increased incidences of nephropathy were found in both the high and low dose female rats. In mice, the survival of the control male mice was significantly reduced due to myocarditis (not treatment-related). Survival of the high dose female mice was significantly less than controls. Increased incidences of epithelial hyperplasia of the urinary bladder were found in both dose groups of both sexes of mice. High-dose female mice also had increased incidences of epithelial hyperplasia of the

forestomach and of hydronephrosis. An AEL of 25 mg/kg was defined for kidney neuropathy in female rats (rec #2) and hyperplasia of the forestomach in male rats (rec #4); an AEL of 50 mg/kg was defined for hyperplasia of the urinary bladder in both male and female mice (rec #5, 6). Consequently, the Til et al. (1973) study described in Section 8.2.2.1., which was the basis for the subchronic oral RfD, is used as the basis for the chronic oral RfD. In the 90-day gavage study by Til et al. (1973), kidney weights increased in male rats given 10 mg/kg/day and in female rats given 30 mg/kg/day. The RfD is calculated by adjusting the NOEL of 3 mg/kg/day for intermittent exposure and dividing by an uncertainty factor of 10,000 (10 for interspecies extrapolation, 10 to protect the most sensitive individuals, 10 for the use of a subchronic study and an additional modifying factor of 10 for the deficient data base). A chronic oral RfD of $3 \times 10^{-4}$ mg/kg/day is calculated and this value has been verified (U.S. EPA, 1987b). As discussed in Section 8.2.2.1., confidence in the key study used as the basis for the chronic oral RfD is low because of its poor quality and its short duration. Confidence in the data base is low, as the chronic NTP (1985) study was not designed to study chronic toxicity and does not define a NOAEL. Overall confidence in the chronic oral RfD is low.

# 9. REPORTABLE QUANTITIES

## 9.1. BASED ON SYSTEMIC TOXICITY

The available data on the effects of long-term administration of 1,3-dichloropropene in animals were discussed in detail in Chapter 6. Studies that provide dose-response data are summarized in Table 9-1. Subchronic studies are included in Table 9-1 because effects of subchronic exposure are similar to those of chronic exposure and occur at doses and exposure concentrations not appreciably different than those given in the chronic studies. For this reason, no uncertainty factors were applied to doses in subchronic studies.

Several studies discussed in Chapter 6 are not included in Table 9-1. Torkelson and Oyen (1977) reported that, at exposures of 50 ppm (227 $mg/m^3$) 1,3-dichloropropene (19 exposures in 28 days) or 11 ppm (50 $mg/m^3$) 1,3-dichloropropene (27 exposures in 39 days), liver and kidney necrosis was found in rats. The only effect observed among rats, guinea pigs, dogs or rabbits exposed by inhalation to 1,3-dichloropropene $\leq$7 hours/day, 5 days/week for 6 months was cloudy swelling of the renal tubule epithelium of male rats (13.6 $mg/m^3$, 4 or 7 hours/day). These studies were not included in Table 9-1 because the composition of the 1,3-dichloropropene was not specified and the reported effects have not been substantiated in other studies using higher exposure levels of 1,3-dichloropropene of $\geq$89% for longer durations.

Parker et al. (1982) found increased relative liver and kidney weights in rats and hepatocellular hypertrophy in mice exposed by inhalation to 50 ppm of the D-D mixture (52% 1,3-dichloropropene, 29% 1,2-dichloropropane). This study is not included in Table 9-1 since the concentration of 1,2-dichloropropane in the D-D mixture was very high. Similarly, Linnett et al. (1988)

TABLE 9-1

Toxicity Summary for 1,3-Dichloropropene

| Route | Species/ Strain | Sex | Number at Start | Average Body Weight (kg) | Vehicle/ Physical State | Purity | Exposure | Transformed Animal Dose (mg/kg/day) | Equivalent Human Dose[a] (mg/kg/day) | Response | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhalation | rat/F344 | M | 10 | 0.26[b] | air | 90.9% | 30 ppm (136 mg/$m^3$) 6 hours/day, 5 days/week for 13 weeks | 17.1[c] | 2.6 | degenerative changes in nasal nucosa | Stott et al., 1988 |
| Inhalation | rat/F344 | M<br>F | 10<br>10 | 0.235[b]<br>0.160 | air | 92% | 93 ppm (422 mg/$m^3$) 7 hours/day, 5 days/week for 13 weeks | 64.0[c]<br>72.5[c] | 9.6 | reduced body weight gain | Coate et al., 1979 |
| Inhalation | rat/F344 | M<br>F | 50<br>50 | 0.380[b]<br>0.230 | air | 92.1% | 60 ppm (272 mg/$m^3$) 6 hours/day, 5 days/week for 2 years | 30.2[c]<br>35.7 | 5.3 | decreased body weight gain; degeneration of nasal mucosa | Lomax et al., 1989 |
| Inhalation | mouse/ B6C3F1 | M<br>F | 10<br>10 | 0.027[b]<br>0.022 | air | 90.9% | 90 ppm (409 mg/$m^3$) 6 hours/day, 5 days/week for 13 weeks | 97.4[c]<br>106.2 | 7.1 | degenerative changes in nasal mucosa (both sexes); hyperplasia of urinary bladder epithelium (females) | Stott et al., 1988 |
| Inhalation | mouse/ CD-1 | F | 10 | 0.031[b] | air | 92% | 93 ppm (422 mg/$m^3$) 7 hours/day, 5 days/week for 13 weeks | 113[3] | 8.6 | reduced body weight gain | Coate et al., 1979 |
| Inhalation | mouse/ B6C3F1 | F | 50 | 0.03[d] | air | 92.1% | 20 ppm (90.8 mg/$m^3$) 6 hours/day, 5 days/week for 2 years | 21.1[c] | 1.6 | hyperplasia of respiratory mucosa and urinary bladder epithelium | Lomax et al., 1989 |

TABLE 9-1 (cont.)

| Route | Species/ Strain | Sex | Number at Start | Average Body Weight (kg) | Vehicle/ Physical State | Purity | Exposure | Transformed Animal Dose (mg/kg/day) | Equivalent Human Dose[a] (mg/kg/day) | Response | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Oral | rat/ albino | M | 10 | 0.221[b] | propylene glycol | 78.5% | 10 mg/kg/day, 6 days/week for 13 weeks | 8.6[c] | 1.3 | increased relative kidney weight | Til et al., 1973 |
| Oral | rat/F344 | F | 50 | 0.25[b] | corn oil | 89% | 25 mg/kg/day 3 days/week for 104 weeks | 10.7[c] | 1.6 | increased incidence of nephropathy | NTP, 1985 |
| Oral | rat/F334 | M<br>F | 50<br>50 | 0.425[b]<br>0.25 | corn oil | 89% | 50 mg/kg/day 3 days/week for 104 weeks | 21.4[c] | 3.9<br>3.3 | edema of submucosa of urinary bladder | NTP, 1985 |
| Oral | mouse/ B6C3F1 | F | 50 | 0.028 | corn oil | 89% | 100 mg/kg/day, 3 days/week for 104 weeks | 42.9[c] | 3.2 | reduced survival | NTP, 1985 |

[a]Calculated by multiplying the transformed animal dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg)

[b]Estimated from data in the study

[c]Calculated by expanding exposure concentration in $mg/m^3$ from intermittent to continuous, multiplying by the animal inhalation rate (U.S. EPA, 1980a) and dividing by the animal body weight

[d]Reference body weight (U.S. EPA, 1980a)

[e]Calculated by expanding dose over a 7-day week

found a decrease in body weight and an increase in liver and kidney weights in male and female rats exposed to 90 ppm D-D in a reproduction study. This also will not be used as a basis for an RQ value because of the composition of the D-D mixture (53.7% 1,3-dichloropropene).

The effects of exposure to 1,3-dichloropropene include degenerative changes in the nasal mucosa, hyperplastic changes in the urinary bladder, reduced body weight gain, increased kidney weights, nephropathy and reduced survival. The lowest doses resulting in each of these effects were used to calculate CSs (Table 9-2). The highest CS (20) was obtained in the chronic oral study by NTP (1985) in which mice treated with 10 mg/kg/day had reduced survival. The corresponding RQ is 100 pounds and is recommended as the basis for the RQ for chronic toxicity to 1,3-dichloropropene (Table 9-3).

9.2. BASED ON CARCINOGENICITY

The NTP (1985) reports clear evidence of carcinogenicity in rats and mice following oral exposure to Telone II® (1,3-dichloropropene) (Table 6-3). Squamous cell papillomas and carcinomas of the forestomach and increased incidence of neoplastic nodules of the liver were observed in male F344 rats. Squamous-cell papillomas were found in female F344 rats. In addition, the incidence of adrenal gland pheochromocytoma were significantly increased in male rats treated at 25 mg/kg, and the incidence of thyroid follicular cell adenoma or carcinoma in female rats showed a marginally significant ($p<0.05$) positive dose-related trend. In female B6C3F1 mice, increased incidences of transitional-cell carcinomas of the urinary bladder were found as well as alveolar/bronchiolar adenomas of the lung and squamous-cell papillomas or carcinomas of the forestomach. Results in male B6C3F1 mice were not clear because of high mortality in the control group. Dose-related increased incidences of transitional-cell carcinomas of the urinary bladder,

TABLE 9-2

Oral Composite Scores for 1,3-Dichloropropene

| Route | Species | Animal Dose (mg/kg/day) | Chronic Human MED (mg/day) | $RV_d$ | Effect | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Inhalation | rat | 17.1 | 182 | 2.1 | degenerative changes in nasal mucosa | 6 | 12.6 | 1000 | Stott et al., 1988 |
| Inhalation | rat | 30.2 | 371 | 1.6 | reduced body weight gain | 4 | 6.4 | 1000 | Lomax et al., 1989 |
| Inhalation | mouse | 21.1 | 112 | 2.4 | hyperplasia of respiratory mucosa and urinary bladder epithleum | 4 | 9.6 | 1000 | Lomax et al., 1989 |
| Oral | rat | 8.6 | 91 | 2.6 | increased kidney weight | 4 | 10.4 | 1000 | Til et al., 1973 |
| Oral | rat | 10.7 | 112 | 2.4 | increased incidence of nephropathy | 7 | 16.8 | 1000 | NTP, 1985 |
| Oral | rat | 21.4 | 231 | 2.0 | edema of urinary bladder | 5 | 10.0 | 1000 | NTP, 1985 |
| Oral | mouse | 42.9 | 224 | 2.0 | reduced survival | 10 | 20.0 | 100 | NTP, 1985 |

TABLE 9-3

1,3-Dichloropropene

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

| | |
|---|---|
| Route: | oral |
| Species/sex: | mouse/female |
| Dose[a]: | 224 mg/day |
| Duration: | 104 weeks |
| Effect: | reduced survival |
| $RV_d$: | 2.0 |
| $RV_e$: | 10 |
| CS: | 20 |
| RQ: | 100 |
| Reference: | NTP, 1985 |

[a]Equivalent human dose

squamous-cell papillomas of the forestomach and alveolar/bronchiolar adenomas and carcinomas of the lung, however, were found in the male mice. Lomax et al. (1989) found no statistically significant increase in tumor incidence in F344 rats treated with 1,3-dichloropropene by inhalation. In B6C3F1 mice, an increased incidence of a benign lung tumors (bronchioloalveolar adenomas) was found in male mice exposed to 60 ppm 1,3-dichloropropene. Van Duuren et al. (1979) also observed sarcomas in Swiss mice injected with 1,3-dichloropropene. Markovitz and Crosby (1984) found some evidence for a causal relationship between acute exposure of humans to 1,3-dichloropropene and the development of hematologic malignancies.

1,3-Dichloropropene is given a cancer classification of B2, a probable human carcinogen, by U.S. EPA (1987b) and 2B, as a chemical or group of chemicals that is probably carcinogenic for humans, by IARC (1987).

Data used to calculate the potency factors (F or $1/ED_{10}$) for inhalation and oral exposure are summarized in Table 9-4 and Table 9-5. Fs were derived using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA. For the inhalation data, the unadjusted $1/ED_{10}$ obtained from the animal data ($4.8 \times 10^{-2}$/mg/kg/day) was corrected for interspecies extrapolation by multiplying the cube root of the weight of a human (70 kg) by the weight of the animal, and the resultant F is $6.4 \times 10^{-1}$/mg/kg/day (Table 9-4) (Lomax et al., 1989). For the oral data, equivalent human doses and combined incidences of forestomach and liver tumors and adrenal pheochromocytoma in male rats (U.S. EPA, 1987b) were used (Table 9-5). The resultant F for oral data is $9.6 \times 10^{-1}$/mg/kg/day. Since the F for oral exposure is <1, 1,3-dichloropropene is placed in Potency Group 3; since the chemical is in group B2, 1,3-dichloropropene has a Low Hazard Ranking, according to the Hazard Ranking Scheme for Reportable Quantities under CERCLA. The RQ associated with Medium Hazard ranking is 100.

TABLE 9-4

Derivation of Potency Factor (F) for Inhalation Exposure to 1,3 Dichloropropene (Telone II®)

| | | | | |
|---|---|---|---|---|
| Exposure route: | inhalation | | | |
| Species: | mouse | | | |
| Strain: | $B6C3F_1$ | | | |
| Sex: | male | | | |
| Vehicle or physical state: | vapor | | | |
| Body weight: | 0.030[a] | | | |
| Duration of treatment: | 2 years | | | |
| Duration of study: | 2 years | | | |
| Lifespan of animal: | 2 years[b] | | | |
| Target organ: | lung | | | |
| Tumor type: | benign adenoma | | | |
| Experimental doses/ exposure: ($mg/m^3$, 6 hours/ day, 5 days/week) | 0 | 22.7 | 90.8 | 272.0 |
| Transformed doses (mg/kg/day): | 0 | 5.3 | 21.2 | 63.1 |
| Tumor incidence: | 9/50 | 6/50 | 13/50 | 22/50 |
| Unadjusted $1/ED_{10}$ (F) | $4.8 \times 10^{-2}$/mg/kg/day | | | |
| Adjusted $1/ED_{10}$ (F) | $6.4 \times 10^{-1}$/mg/kg/day | | | |
| Reference: | Lomax et al., 1989 | | | |

[a]Reported

[b]Estimated

TABLE 9-5

Derivation of Potency Factor (F) for Oral Exposure to
1,3 Dichloropropene (Telone II®)

| | | | |
|---|---|---|---|
| Exposure route: | oral, gavage | | |
| Species: | rat | | |
| Strain: | F344 | | |
| Sex: | male | | |
| Vehicle or physical state: | corn oil | | |
| Body weight: | 0.42 kg[b] | | |
| Duration of treatment: | 104 weeks | | |
| Duration of study: | 104 weeks | | |
| Lifespan of animal: | 104 weeks[a] | | |
| Target organ: | forestomach, liver | | |
| Tumor type: | papillomas, carcinomas, neoplastic nodules, pheochromocytomas, follicular cell adenoma/ carcinoma | | |
| Experimental doses/ exposure: (mg/kg/day, 3 days/week) | 0 | 50 | 100 |
| Transformed doses(human) (mg/kg/day): | 0 | 2 | 4 |
| Tumor incidence: | 4/52 | 13/52 | 23/52 |
| $^1/ED_{10}$ (F factor) | $9.6 \times 10^{-1}$/mg/kg/day | | |
| Reference: | NTP, 1985 | | |

[a]Estimated

[b]Reported

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# APPENDIX A

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

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
SCISEARCH
Federal Research in Progress

These searches were conducted in March, 1989, 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.

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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. 2879-3816 p.

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. 3817-5112 p.

Grayson, M. and D. Eckroth, Ed. 1978-84. 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 edition. Publishing Sciences Group, Inc., MA. 575 p.

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USITC (United States International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publication 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. United States 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 Sheet for Derivation of $q_1^*$ for Inhalation Exposure

Compound: 1,3-dichloropropene

Reference: Lomax et al., 1989

Species/strain/sex: mouse, B6C3F1, male

Body weight = 0.030 kg (measured)

Length of exposure (le) = 24 months

Length of experiment (Le) = 24 months

Lifespan of animal (L) = 24 months

Tumor site and type: lung, benign adenoma

| Experimental Doses or Exposures ($mg/m^3$, 6 hours/ day, 5 days/week) | Transformed Dose (mg/kg/day) | Incidence Number responding/number tested |
|---|---|---|
| 0 | 0 | 9/50 |
| 22.7 | 5.3 | 6/50 |
| 90.8 | 21.2 | 13/50 |
| 272 | 63.1 | 22/50 |

---

Unadjusted $q_1^* = 9.97 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 1.32 \times 10^{-1}$ $(mg/kg/day)^{-1}$

APPENDIX C

Summary Table for 1,3-Dichloropropene

| | Species | Exposure | Effect | RfD or $q_1^*$ | Reference |
|---|---|---|---|---|---|
| Inhalation exposure | | | | | |
| Subchronic | rat | 10 ppm (45.4 mg/m³) 6 hours/day, 5 days/week for 13 weeks (HEC, 1.4 mg/m³) | degenerative changes in nasal mucosa at higher doses | 0.01 mg/m³ | Stott et al., 1982 |
| Chronic | rat | 10 ppm (45.4 mg/m³) 6 hours/day, 5 days/week for 13 weeks (HEC, 1.4 mg/m³) | degenerative changes in nasal mucosa at higher doses | 0.01 mg/m³ | Stott et al., 1988 |
| Carcinogenicity | mouse | 5, 20, 60 ppm (22.7, 90.8, 272 mg/m³) 6 hours/day, 5 days/week for 2 years | benign lung tumors | $1.3 \times 10^{-1}$ $(mg/kg/day)^{-1}$ | Lomax et al., 1989 |
| Oral exposure | | | | | |
| Subchronic | rat | 3 mg/kg/day, 6 days/week for 90 days | increased kidney weight at higher doses | $3 \times 10^{-3}$ (mg/kg/day) | Till et al., 1973 |
| Chronic | rat | 3 mg/kg/day, 6 days/week for 90 days | increased kidney weight at higher doses | $3 \times 10^{-4}$ (mg/kg/day) | Till et al., 1973 |
| Carcinogenicity | rat | 0, 25, 50 mg/kg/day, 3 days/week for 104 weeks | forestomach, liver | $1.8 \times 10^{-1}$ $(mg/kg/day)^{-1}$ | NTP, 1985 |

REPORTABLE QUANTITIES

Based on chronic toxicity: 100

Based on carcinogenicity: 100

# APPENDIX D

# DOSE-DURATION RESPONSE GRAPHS FOR EXPOSURE TO 1,3-DICHLOROPROPENE

## D.1. DISCUSSION

Dose-duration response graphs for inhalation and oral exposure to 1,3-dichloropropene generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) developed under contract to ECAO-Cincinnati are presented in Figures D-1 to D-6. Data used to generate these graphs are presented in Section D.2. In generation of these figures, all responses are classified as adverse (FEL, AEL or LOAEL) or non-adverse (NOEL or NOAEL) for plotting. For inhalation exposure, the ordinate expresses concentration in either of two ways. In Figures D-1 and D-2, the experimental concentration expressed as $mg/m^3$ was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration ($mg/m^3$). In Figures D-3 and D-4, the expanded experimental concentration was multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975) to estimate an equivalent human or scaled concentration ($mg/m^3$). For oral exposure, the ordinate expresses dosage as human equivalent dose (Figures D-5 and D-6). The animal dosage in mg/kg/day is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1976). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human.

The Boundary for Adverse Effects (solid line) is drawn to identify the lowest adverse effect dose or concentration at the shortest duration of

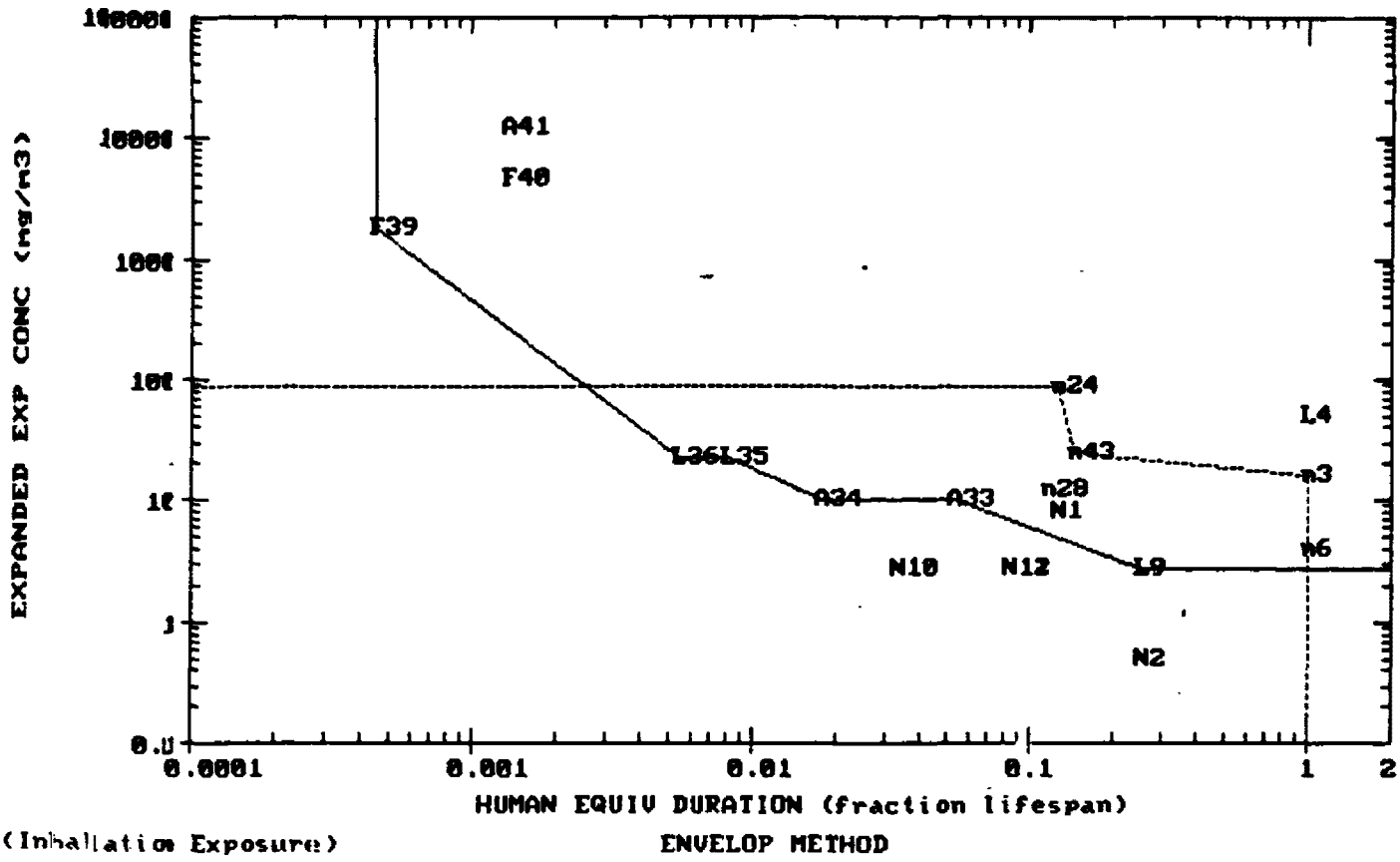


Figure D-1

Dose/Duration - Response Graph for Inhalation Exposure to 1,3-Dichloropropene: Expanded Experimental Concentration, Envelop Method

Key:
- N = NOEL
- n = NOAEL
- L = LOAEL
- A = AEL
- F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

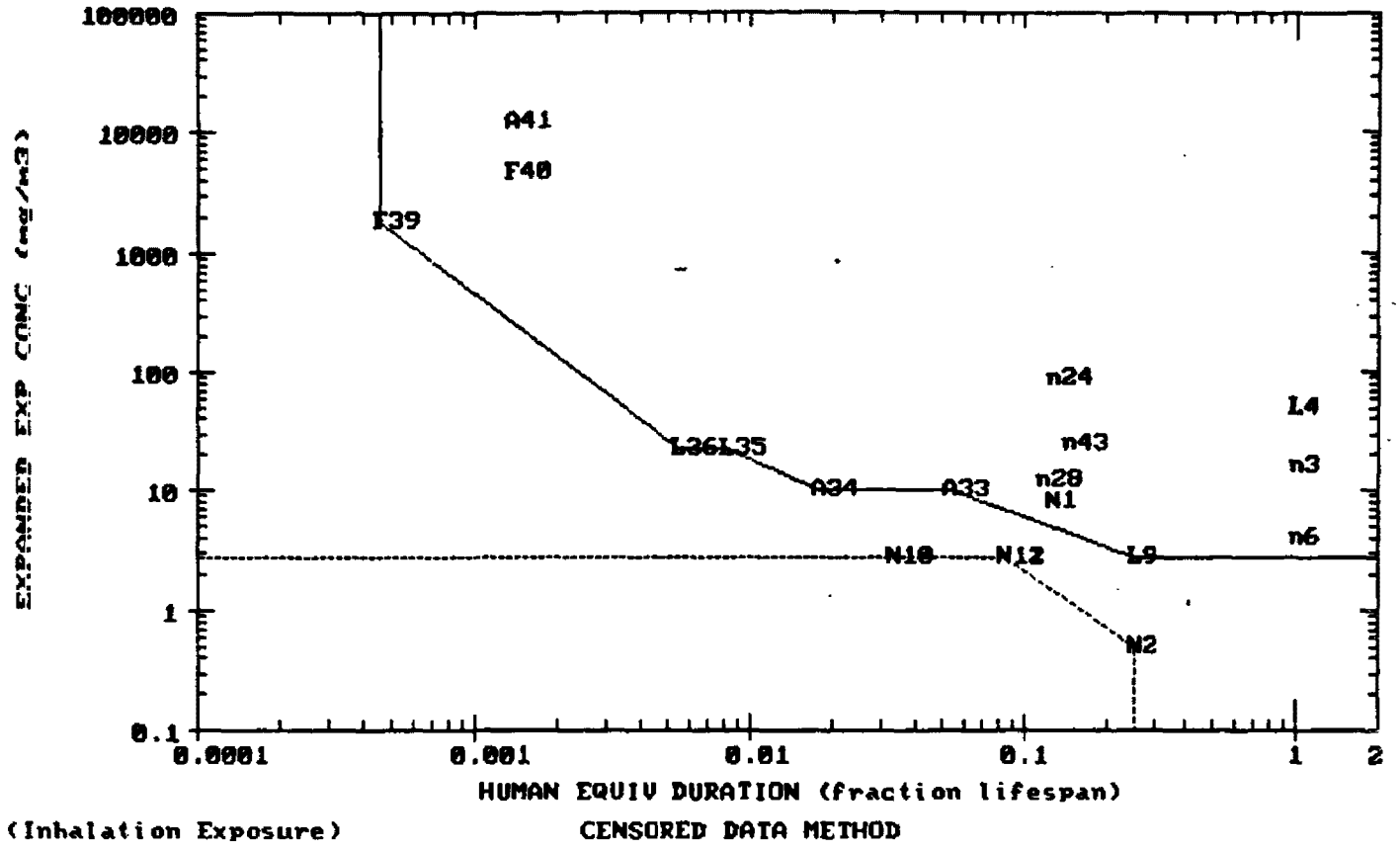


Figure D-2

Dose/Duration - Response Graph for Inhalation Exposure to 1,3 Dichloropropene: Expanded Experimental Concentration, Censored Data Method

Key:
- N = NOEL
- n = NOAEL
- L = LOAEL
- A = AEL
- F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

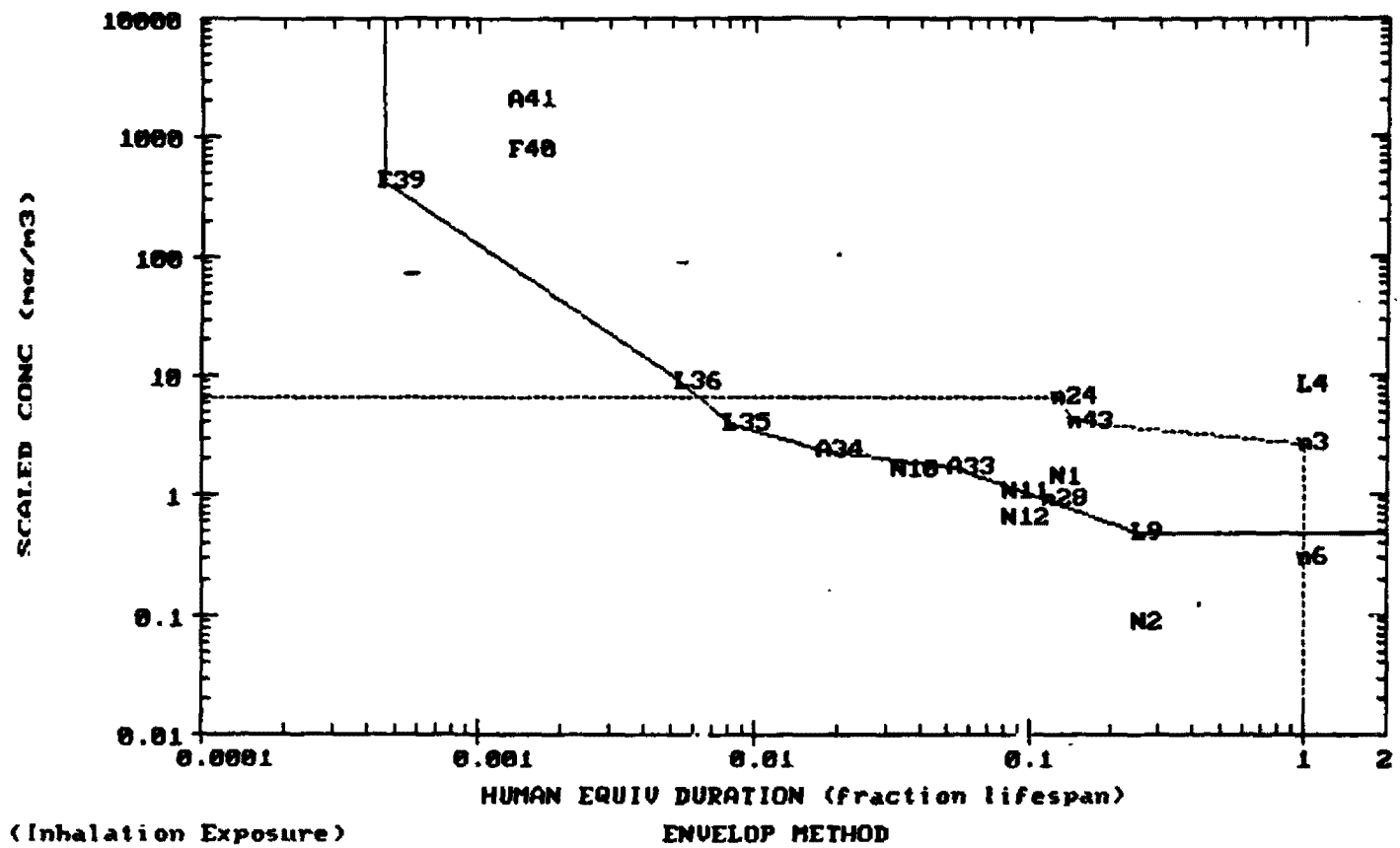


Figure D-3

Dose/Duration - Response Graph for Inhalation Exposure to 1,3 Dichloropropene: Scaled Concentration, Envelop Method

Key:
- N = NOEL
- n = NOAEL
- L = LOAEL
- A = AEL
- F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

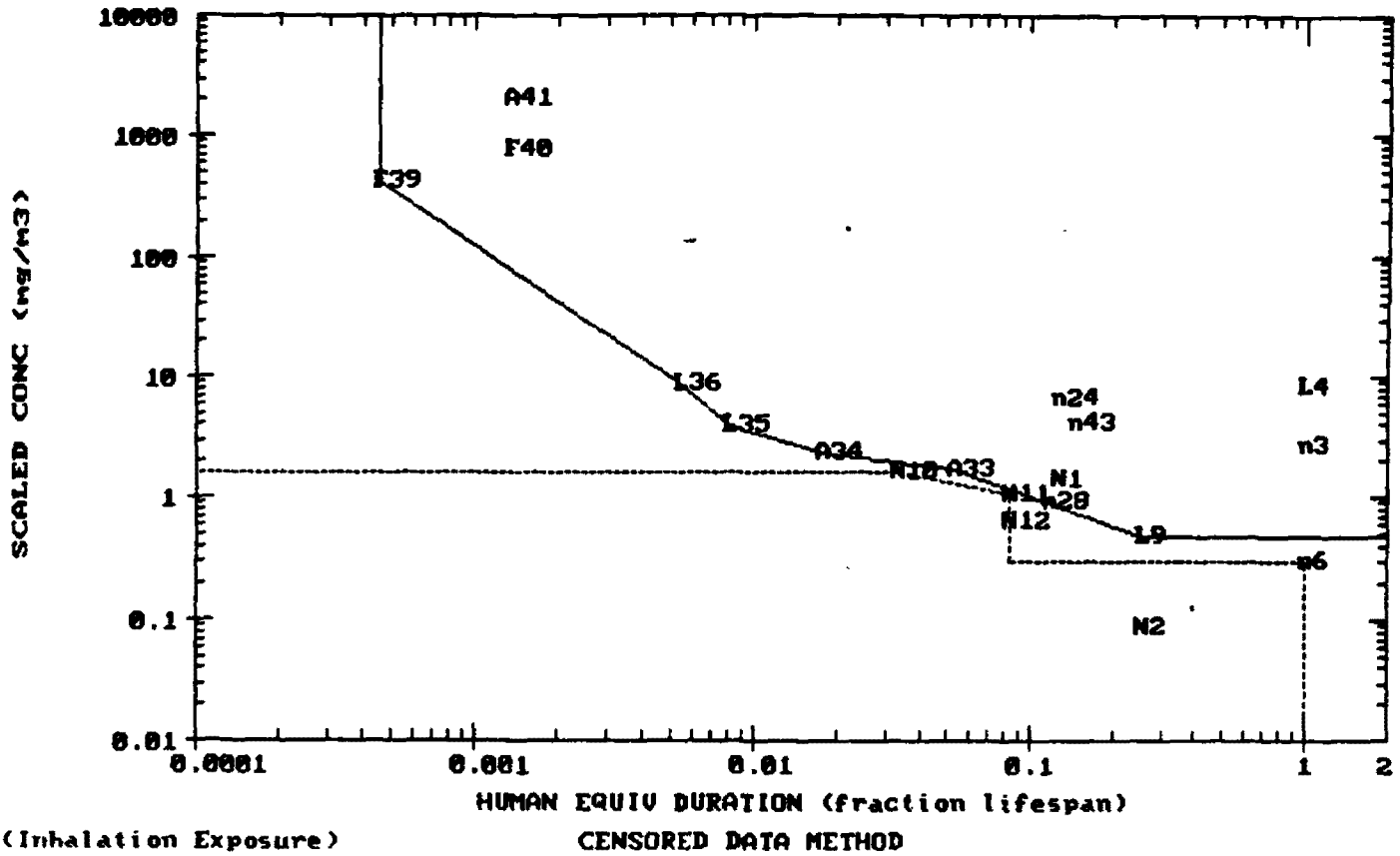


Figure D-4

Dose/Duration - Response Graph for Inhalation Exposure to
1,3 Dichloropropene: Scaled Concentration, Censored Data Method

Key:
N = NOEL
n = NOAEL
L = LOAEL
A = AEL
F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

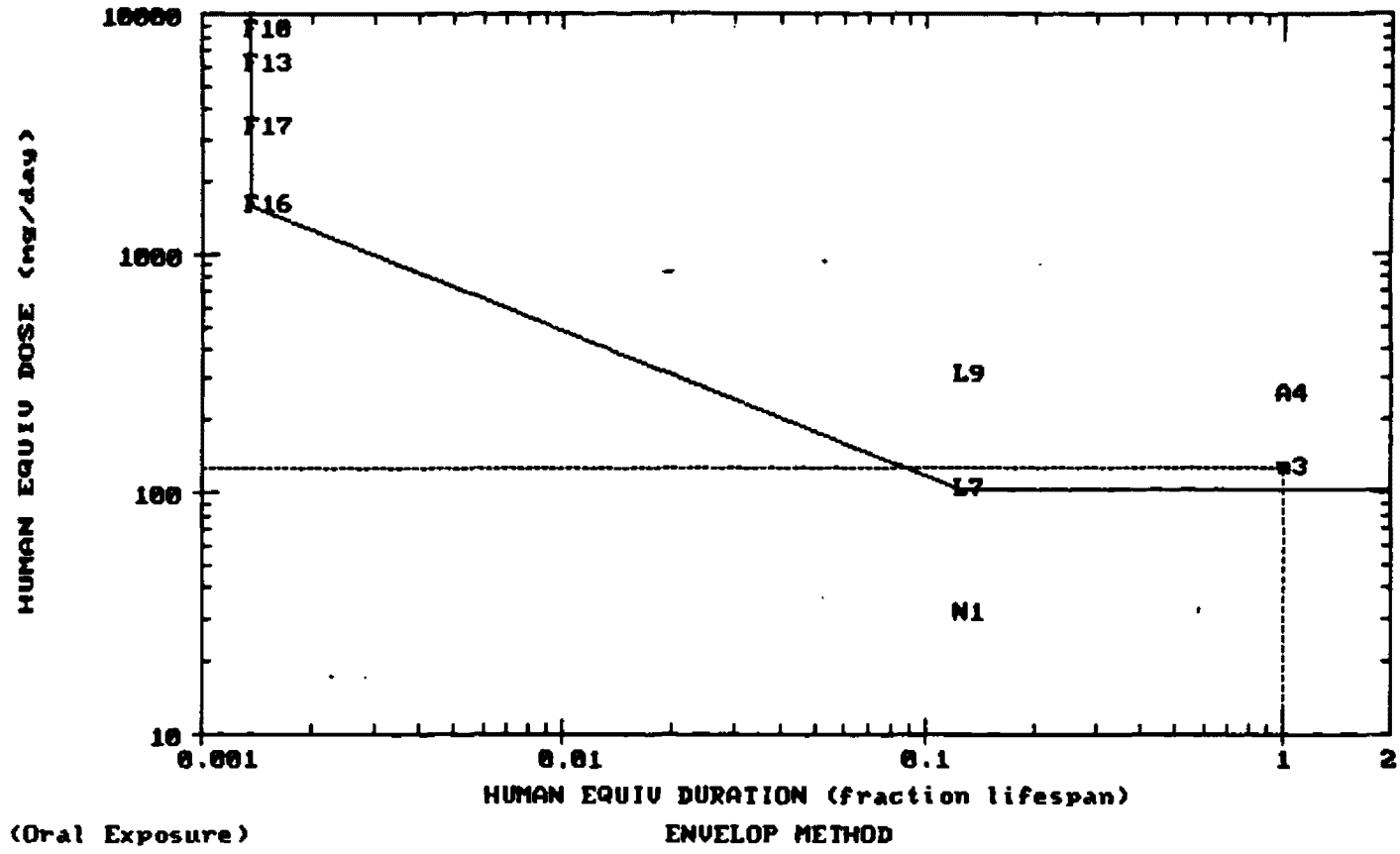


Figure D-5

Dose/Duration - Response Graph for Oral Exposure to
1,3 Dichloropropene: Human Equivalent Dose, Envelop Method

Key:
N = NOEL
L = LOAEL
A = AEL
F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

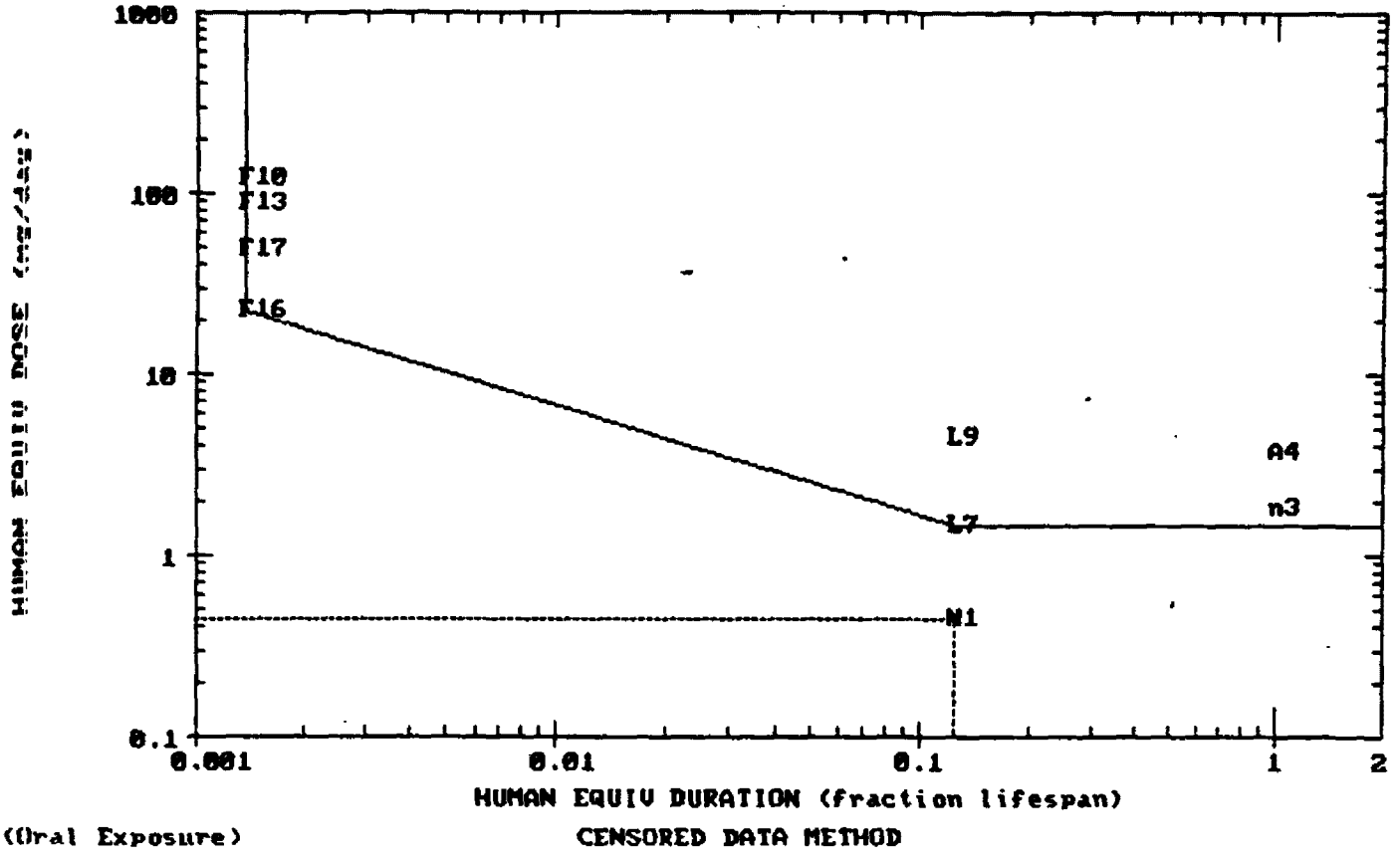


Figure D-6

Dose/Duration - Response Graph for Oral Exposure to
1,3 Dichloropropene: Human Equivalent Dose, Censored Data Method

Key:
N = NOEL
L = LOAEL
A = AEL
F = FEL

Solid Line = Adverse Effects Boundary

Dotted Line = No Adverse Effects Boundary

exposure at which an adverse effect occurred. From this point, an infinite line is extended upward, parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point, a line is extended to the right, parallel to the duration axis. This Region of Adverse Effects lies above the Adverse Effects Boundary.

Using the envelope method, the Boundary for No Adverse Effects (dashed line) is drawn by identifying the highest no adverse effects dose or concentration. From this point, a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next lower or equal no adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The Region of No Adverse Effects lies below the No Adverse Effects Boundary. At either ends of the graph between the Adverse Effects and No Adverse Effects Boundaries are Regions of Ambiguity. The area (if any) resulting from intersection of the Adverse Effects and No Adverse Effects Boundaries is defined as the Region of Contradiction.

In the censored data method, all no adverse effect points located in the Region of Contradiction are dropped from consideration and the No Adverse Effect Boundary is redrawn so that it does not intersect the Adverse Effects Boundary and no Region of Contradiction is generated. This method results in the most conservative definition of the No Adverse Effects Region.

In the graphs depicting the inhalation data (Figures D-1 to D-4), no one species, effect or study figures predominantly in defining the Adverse Effects Boundary. The LOAELs for the primary inflection of the Adverse Effects Boundary (rec #35 and 36), ≈0.004-0.007 lifespan of the human equivalent durations, reflect toxic maternal effects (decreased body weight gain) in rats and rabbits in a teratogenicity study (Hanley et al. 1987). The AELs (rec #33 and 34) found at ≈0.02-0.05 lifespan of the human equivalent durations reflect kidney and liver necrosis in rats and guinea pigs (Torkelson and Oyen, 1977). The Region of Contradiction is quite large and is contained within the 0.003-1.0 lifespan region of the human equivalent duration. This region is not characterized by any one species, effect or study, and probably reflects differences in study protocol and quality. The chronic and subchronic inhalation RfD of 0.01 $mg/m^3$ is based on a NOEL for degenerative changes in the nasal mucosa of rats (rec #1) (Stott et al. 1988). The inhalation RfDs are well below the Boundary for No Adverse Effects.

In the graphs depicting the oral data (Figure D-5 and D-6), the data points concentrated at ≈0.0015 lifespan of the human equivalent duration reflect oral $LD_{50}$s for rats and mice (rec #10, 13, 16, 17). The LOAEL for the primary inflection point (rec #7, ≈0.15 lifespan of the human equivalent duration, in the Adverse Effect Boundary reflects an increase in kidney weights in male rats (Til et al., 1973). The Adverse Effect Boundary is nearly without slope at human equivalent durations ≈0.1 lifespan, suggesting little difference between the subchronic and chronic toxicity of 1,3-dichloropropene. This conclusion, however, cannot be drawn due to the small number of oral studies available. The Region of Contradiction is quite small, reflecting the small number of oral studies available. The

chronic and subchronic oral RfDs of $3 \times 10^{-4}$ and $3 \times 10^{-3}$, respectively, are based on a NOEL for kidney effects in the Til et al. study (rec #1) and are well below the boundary for No Adverse Effects.

## D.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

### D.2.1. INHALATION EXPOSURE

Chemical Name: 1,3-dichloropropene
CAS Number: 542-75-6
Document Title: Health and Environmental Effects Document on 1,3-Dichloropropene
Document Number: FO110-106
Document Date: 5/16/89
Document Type: HEED

==========

RECORD #1:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 8.100 |
| Sex: | Male | Duration Exposure: 13.0 Weeks |
| Effect: | NOEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 10 |
| Number Responses: | 0 |
| Type of Effect: | DEGEN |
| Site of Effect: | NASAL |
| Severity Effect: | 6 |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm, 6 hours/day, 5 days/week. Basis of subchronic and chronic RfD. Degeneration of the nasal mucosa seen in all rats at 90 and 150 ppm and in male rats at 30 ppm.

Citation: Stott et al., 1988

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RECORD #2:

Species: Rats
Sex: Male
Effect: NOEL
Route: Inhalation

Dose: 0.500
Duration Exposure: 6.0 Months
Duration Observation: 6.0 Months

Number Exposed: 11
Number Responses: 0
Type of Effect: HYPRT
Site of Effect: KIDNY
Severity Effect: 3

Comment: Concentrations given: 1, 3 ppm 4 or 7 hours/day, 5 days/week. Slight reversible cloudy swelling of the renal epithelium at 3 ppm. Composition of test material not specified.

Citation: Torkelson and Oyen, 1977

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RECORD #3:

Species: Rats
Sex: Both
Effect: NOAEL
Route: Inhalation

Dose: 16.200
Duration Exposure: 24.0 Months
Duration Observation: 24.0 Months

Number Exposed: 100
Number Responses: 1
Type of Effect: DEGEN
Site of Effect: NASAL
Severity Effect: 6

Comment: Concentrations given: 0, 5, 20, 60 ppm. Degeneration of the nasal tissues seen at high incidence in one male and females at 60 ppm and in one male at 20 ppm at 24, but not at 6 or 12 months.

Citation: Lomax et al., 1989

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RECORD #4:

Species: Rats
Sex: Both
Effect: LOAEL
Route: Inhalation

Dose: 48.600
Duration Exposure: 24.0 Months
Duration Observation: 24.0 Months

Number Exposed: 100
Number Responses: 35
Type of Effect: DEGEN
Site of Effect: NASAL
Severity Effect: 6

Comment: Concentrations given: 0, 5, 20, 60 ppm 6 hours/day, 5 days/week. Degeneration of the nasal tissues seen at high incidence in male and female at 60 ppm at 24, but not at 6 or 12 months.

Citation: Lomax et al., 1989

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RECORD #5:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 16.200 | |
| Sex: | Female | Duration Exposure: 24.0 Months | |
| Effect: | LOAEL | Duration Observation: 24.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 0 | 50 |
| Number Responses: | | 21 | 28 |
| Type of Effect: | | HYPRP | HYPRP |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 3 |

Comment: Concentrations given: 0, 5, 20, 60 ppm 6 hours/day, 5 days/week. Hyperplasia of the urinary bladder and the nasal epithelium were found at 20 and 60 ppm.

Citation: Lomax et al. 1989

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RECORD #6:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 4.000 | |
| Sex: | Female | Duration Exposure: 24.0 Months | |
| Effect: | NOAEL | Duration Observation: 24.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 46 | 50 |
| Number Responses: | | 4 | 4 |
| Type of Effect: | | HYPRP | HYPRP |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 3 |

Comment: Concentrations given: 0, 5, 20, 60 ppm. Hyperplasia of the urinary bladder and nasal epithelium were found at 20 ppm and greater.

Citation: Lomax et al., 1989

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RECORD #7:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 16.200 | |
| Sex: | Male | Duration Exposure: 24.0 Months | |
| Effect: | NOAEL | Duration Observation: 24.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 48 | 50 |
| Number Responses: | | 11 | 4 |
| Type of Effect: | | HYPRP | HYPRP |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 3 |

Comment: Concentrations given: 0, 5, 20, 60 ppm. Hyperplasia of the urinary bladder and nasal epithelium were found at 60 ppm.

Citation: Lomax et al., 1989

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RECORD #8:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 48.600 | |
| Sex: | Male | Duration Exposure: 24.0 Months | |
| Effect: | AEL | Duration Observation: 24.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 47 | 50 |
| Number Responses: | | 37 | 48 |
| Type of Effect: | | HYPRP | HYPRP |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 3 |

Comment: Concentrations given: 0, 5, 20, 60 ppm. Hyperplasia of the urinary bladder and nasal epithelium were found at 60 ppm.

Citation: Lomax et al., 1989

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RECORD #9:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 2.800 | |
| Sex: | Male | Duration Exposure: 6.0 Months | |
| Effect: | LOAEL | Duration Observation: 6.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 9 | |
| Number Responses: | | NR | |
| Type of Effect: | | HYPRT | |
| Site of Effect: | | KIDNY | |
| Severity Effect: | | 3 | |

Comment: Concentrations given: 1, 3 ppm. Slight, reversible cloudy swelling of the renal epithelium at 3 ppm. Composition of test material not specified.

Citation: Torkelson and Oyen, 1977

---

RECORD #10:

| | | | |
|---|---|---|---|
| Species: | Dogs | Dose: 2.800 | |
| Sex: | Both | Duration Exposure: 6.0 Months | |
| Effect: | NOEL | Duration Observation: 6.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 2 | |
| Number Responses: | | 0 | |
| Type of Effect: | | TOXSL | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 2 | |

Comment: Concentrations given: 1, 3 ppm. No histological effects found.

Citation: Torkelson and Oyen, 1977

---

RECORD #11:

| | | | |
|---|---|---|---|
| Species: | Rabbits | Dose: 2.800 | |
| Sex: | Both | Duration Exposure: 6.0 Months | |
| Effect: | NOEL | Duration Observation: 6.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 5 | |
| Number Responses: | | 0 | |
| Type of Effect: | | TOXSL | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 2 | |

Comment: Concentrations given: 1, 3 ppm. No histological effects seen.

Citation: Torkelson and Oyen, 1977

---

RECORD #12:

| | | | |
|---|---|---|---|
| Species: | Guinea Pigs | Dose: 2.800 | |
| Sex: | Both | Duration Exposure: 6.0 Months | |
| Effect: | NOEL | Duration Observation: 6.0 Months | |
| Route: | Inhalation | | |
| Number Exposed: | | 18 | |
| Number Responses: | | 0 | |
| Type of Effect: | | TOXSL | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 2 | |

Comment: Concentrations given: 1, 3 ppm. No histological effects seen.

Citation: Torkelson and Oyen, 1977

---

RECORD #13:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 24.300 | |
| Sex: | Male | Duration Exposure: 13.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 10 | |
| Number Responses: | | 2 | |
| Type of Effect: | | DEGEN | |
| Site of Effect: | | NASAL | |
| Severity Effect: | | 6 | |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm 6 hours/day, 5 days/week. Degeneration of nasal epithelium seen at 30 ppm.

Citation: Stott et al., 1988

---

RECORD #14:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 24.300 | |
| Sex: | Female | Duration Exposure: 13.0 Weeks | |
| Effect: | NOEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 10 | |
| Number Responses: | | 0 | |
| Type of Effect: | | DEGEN | |
| Site of Effect: | | NASAL | |
| Severity Effect: | | 6 | |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Degeneration of nasal epithelium seen at ≥90.

Citation: Stott et al., 1988

---

RECORD #15:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 73.000 | |
| Sex: | Female | Duration Exposure: 13.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 10 | |
| Number Responses: | | 10 | |
| Type of Effect: | | DEGEN | |
| Site of Effect: | | NASAL | |
| Severity Effect: | | 6 | |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Degeneration of the nasal epithelium seen at ≥90 ppm.

Citation: Stott et al., 1988

---

RECORD #16:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 24.300 | |
| Sex: | Female | Duration Exposure: 13.0 Weeks | |
| Effect: | NOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 9 | 9 |
| Number Responses: | | 0 | 0 |
| Type of Effect: | | HYPRP | DEGEN |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 6 |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Hyperplasia of the urinary bladder and nasal degeneration seen at ≥90 ppm.

Citation: Stott et al., 1988

---

RECORD #17:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 73.000 | |
| Sex: | Female | Duration Exposure: 13.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 9 | 9 |
| Number Responses: | | 7 | 9 |
| Type of Effect: | | HYPRP | DEGEN |
| Site of Effect: | | OTHER | NASAL |
| Severity Effect: | | 3 | 6 |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Degeneration of the urinary bladder and nasal degeneration seen at ≥90 ppm.

Citation: Stott et al., 1988

---

RECORD #18:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 24.300 | |
| Sex: | Male | Duration Exposure: 13.0 Weeks | |
| Effect: | NOEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 10 | |
| Number Responses: | | 0 | |
| Type of Effect: | | DEGEN | |
| Site of Effect: | | NASAL | |
| Severity Effect: | | 6 | |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Nasal degeneration found at ≥90 ppm.

Citation: Stott et al., 1988

---

RECORD #19:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 73.000 | |
| Sex: | Male | Duration Exposure: 13.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 10 | |
| Number Responses: | | 10 | |
| Type of Effect: | | DEGEN | |
| Site of Effect: | | NASAL | |
| Severity Effect: | | 6 | |

Comment: Concentrations given: 0, 10, 30, 90, 150 ppm. Nasal degeneration seen at ≥90 ppm.

Citation: Stott et al., 1988

---

RECORD #20:

| | | |
|---|---|---|
| Species: | Rats | Dose: 30.300 |
| Sex: | Both | Duration Exposure: 13.0 Weeks |
| Effect: | NOAEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 12, 32, 93 ppm.
Decreased body weight gain at 93 ppm.

Citation: Coate et al., 1979

---

RECORD #21:

| | | |
|---|---|---|
| Species: | Rats | Dose: 88.000 |
| Sex: | Both | Duration Exposure: 13.0 Weeks |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 12, 32, 93 ppm.
Decreased body weight gain at 93 ppm.

Citation: Coate et al., 1979

---

RECORD #22:

| | | |
|---|---|---|
| Species: | Mice | Dose: 30.300 |
| Sex: | Female | Duration Exposure: 13.0 Weeks |
| Effect: | NOAEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 12, 32, 93 ppm.
Decreased body weight gain at 93 ppm.

Citation: Coate et al., 1979

---

RECORD #23:

| | | |
|---|---|---|
| Species: | Mice | Dose: 88.000 |
| Sex: | Female | Duration Exposure: 13.0 Weeks |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 12, 32, 93 ppm. Decreased body weight gain at 93 ppm.

Citation: Coate et al., 1979

---

RECORD #24:

| | | |
|---|---|---|
| Species: | Mice | Dose: 88.000 |
| Sex: | Male | Duration Exposure: 13.0 Weeks |
| Effect: | NOAEL | Duration Observation: 13.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 12, 32, 93 ppm. Decreased body weight gain at 93 ppm.

Citation: Coate et al., 1979

---

RECORD #25:

| | | |
|---|---|---|
| Species: | Rats | Dose: 12.200 |
| Sex: | Both | Duration Exposure: 12.0 Weeks |
| Effect: | NOAEL | Duration Observation: 12.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 18 |
| Number Responses: | NR |
| Type of Effect: | WGTIN |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Increased liver-to-body weight seen in males and increased kidney-to-body weight seen in females at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #26:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 40.500 | |
| Sex: | Both | Duration Exposure: 12.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 12.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 18 | |
| Number Responses: | | NR | |
| Type of Effect: | | WGTIN | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 4 | |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Increased liver-to-body weight in males and increased kidney-to-body weight in females at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #27:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 40.500 | |
| Sex: | Male | Duration Exposure: 12.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 12.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | 21 | |
| Number Responses: | | 12 | |
| Type of Effect: | | HYPRT | |
| Site of Effect: | | LIVER | |
| Severity Effect: | | 3 | |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Hepatocytic enlargement seen at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #28:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 12.200 | |
| Sex: | Male | Duration Exposure: 12.0 Weeks | |
| Effect: | NOAEL | Duration Observation: 12.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | HYPRT | |
| Site of Effect: | | LIVER | |
| Severity Effect: | | 3 | |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Hepatocytic enlargement seen at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #29:

| | | |
|---|---|---|
| Species: | Mice | Dose: 12.200 |
| Sex: | Female | Duration Exposure: 12.0 Weeks |
| Effect: | NOAEL | Duration Observation: 12.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 18 |
| Number Responses: | NR |
| Type of Effect: | HYPRT |
| Site of Effect: | LIVER |
| Severity Effect: | 3 |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Hepatocytic enlargement seen at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #30:

| | | |
|---|---|---|
| Species: | Mice | Dose: 40.500 |
| Sex: | Female | Duration Exposure: 12.0 Weeks |
| Effect: | LOAEL | Duration Observation: 12.0 Weeks |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 18 |
| Number Responses: | 6 |
| Type of Effect: | HYPRT |
| Site of Effect: | LIVER |
| Severity Effect: | 3 |

Comment: Concentrations given: 0, 5, 15, 50 ppm. Hepatocytic enlargement seen at 50 ppm.

Citation: Parker et al., 1982

---

RECORD #31:

| | | |
|---|---|---|
| Species: | Rats | Dose: 24.300 |
| Sex: | Both | Duration Exposure: 10.0 Weeks |
| Effect: | NOEL | Duration Observation: 10.0 Weeks |
| Route: | Inhalation | |

| | | | |
|---|---|---|---|
| Number Exposed: | 30 | 30 | 30 |
| Number Responses: | NR | NR | NR |
| Type of Effect: | WGTDC | WGTIN | WGTIN |
| Site of Effect: | BODY | KIDNY | LIVER |
| Severity Effect: | 3 | 4 | 4 |

Comment: Concentrations given: 0, 10, 30, 90 ppm. Small decrease in body weight gain and slight increases in liver and kidney weights were found at 90 ppm in this reproduction study.

Citation: Linnett et al., 1988

---

RECORD #32:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 73.000 | |
| Sex: | Both | Duration Exposure: 10.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 10.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | 30 | 30 | 30 |
| Number Responses: | NR | NR | NR |
| Type of Effect: | WGTDC | WGTIN | WGTIN |
| Site of Effect: | BODY | KIDNY | LIVER |
| Severity Effect: | 3 | 4 | 4 |

Comment: Concentrations given: 0, 10, 30, 90 ppm. Small decrease in body weight gain and slight increase in liver and kidney weights at 90 ppm in this reproduction study.

Citation: Linnett et al., 1988

---

RECORD #33:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 10.100 | |
| Sex: | N.S. | Duration Exposure: 39.0 Days | |
| Effect: | AEL | Duration Observation: 39.0 Days | |
| Route: | Inhalation | | |
| Number Exposed: | NR | | NR |
| Number Responses: | NR | | NR |
| Type of Effect: | NECRO | | NECRO |
| Site of Effect: | KIDNY | | LIVER |
| Severity Effect: | 6 | | 6 |

Comment: Concentrations given: 11, 50 ppm.

Citation: Torkelson and Oyen, 1977

---

RECORD #34:

| | | | |
|---|---|---|---|
| Species: | Guinea Pigs | Dose: 10.100 | |
| Sex: | N.S. | Duration Exposure: 39.0 Days | |
| Effect: | AEL | Duration Observation: 39.0 Days | |
| Route: | Inhalation | | |
| Number Exposed: | NR | | NR |
| Number Responses: | NR | | NR |
| Type of Effect: | NECRO | | NECRO |
| Site of Effect: | KIDNY | | LIVER |
| Severity Effect: | 6 | | 6 |

Comment: Concentrations given: 11, 50 ppm.

Citation: Torkelson and Oyen, 1977

---

RECORD #35:

| | | |
|---|---|---|
| Species: | Rats | Dose: 22.700 |
| Sex: | Female | Duration Exposure: 6.0 Days |
| Effect: | LOAEL | Duration Observation: 15.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 30 |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 20, 60, 120 ppm. No teratogenicity found but maternal toxicity seen at $\geq$20 ppm.

Citation: Hanley et al., 1987

---

RECORD #36:

| | | |
|---|---|---|
| Species: | Rabbits | Dose: 22.700 |
| Sex: | Female | Duration Exposure: 12.0 Days |
| Effect: | LOAEL | Duration Observation: 23.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | 25 |
| Number Responses: | NR |
| Type of Effect: | WGTDC |
| Site of Effect: | BODY |
| Severity Effect: | 4 |

Comment: Concentrations given: 0, 20, 60, 120 ppm. No teratogenicity seen but maternal toxicity found at $\geq$20 ppm.

Citation: Hanley et al., 1987

---

RECORD #37:

| | | |
|---|---|---|
| Species: | Rats | Dose: 4530.000 |
| Sex: | N.S. | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: 4530 $mg/m^3$ was an $LC_{50}$.

Citation: Hine et al., 1953

---

RECORD #38:

| | | |
|---|---|---|
| Species: | Mice | Dose: 4530.000 |
| Sex: | N.S. | Duration-Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: 4530 $mg/m^3$ was the $LC_{50}$.

Citation: Hine et al., 1953

---

RECORD #39:

| | | |
|---|---|---|
| Species: | Guinea Pigs | Dose: 1800.000 |
| Sex: | N.S. | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: Concentration given: 400 ppm. Death seen after 7-hour exposure.

Citation: Torkelson and Oyen, 1977

---

RECORD #40:

| | | |
|---|---|---|
| Species: | Rats | Dose: 4500.000 |
| Sex: | N.S. | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Inhalation | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: 1000 ppm was the $LC_{50}$.

Citation: Torkelson and Oyen, 1977

---

RECORD #41:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 12000.000 | |
| Sex: | N.S. | Duration Exposure: 1.0 Days | |
| Effect: | AEL | Duration Observation: 1.0 Days | |
| Route: | Inhalation | | |
| Number Exposed: | NR | NR | NR |
| Number Responses: | NR | NR | NR |
| Type of Effect: | IRRIT | TOXDF | TOXDF |
| Site of Effect: | MMBRN | KIDNY | LIVER |
| Severity Effect: | 3 | 6 | 6 |

Comment: Concentration given: 2700 ppm 1,3-DCP was a mucous membrane irritant and caused injury to lung, kidney, liver and nasal area.

Citation: Torkelson and Oyen, 1977

---

RECORD #42:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 72.900 | |
| Sex: | Both | Duration Exposure: 15.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 15.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | 70 | | 70 |
| Number Responses: | NR | | NR |
| Type of Effect: | DEGEN | | WGTDC |
| Site of Effect: | LUNG | | BODY |
| Severity Effect: | 6 | | 4 |

Comment: 90 ppm (range 0, 10, 30, 90 ppm) 6 hours/day, 5 days/week in multigeneration repro study. NOAEL for repro (slight reduction in female conception indices); respiratory epithelial lesions, body weight loss.

Citation: Breslin et al., 1987

---

RECORD #43:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 24.300 | |
| Sex: | Both | Duration Exposure: 15.0 Weeks | |
| Effect: | NOAEL | Duration Observation: 15.0 Weeks | |
| Route: | Inhalation | | |
| Number Exposed: | 70 | | 70 |
| Number Responses: | NR | | NR |
| Type of Effect: | DEGEN | | WGTDC |
| Site of Effect: | LUNG | | BODY |
| Severity Effect: | 6 | | 4 |

Comment: 30 ppm (see previous record).

Citation: Breslin et al., 1987

---

D.2.2. ORAL EXPOSURE

Chemical Name: 1,3-dichloropropene
CAS Number: 542-75-6
Document Title: Health and Environmental Effects Document on 1,3-Dichloropropene
Document Number: FO110-106
Document Date: 5/16/89
Document Type: HEED

---

RECORD #1:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 2.600 |
| Sex: | Male | Duration Exposure: 13.0 Weeks |
| Effect: | NOEL | Duration Observation: 13.0 Weeks |
| Route: | Gavage- | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTIN |
| Site of Effect: | KIDNY |
| Severity Effect: | 4 |

Comment: Doses given: 0, 1, 3, 10, 30 mg/kg. Used as the basis for the chronic and subchronic oral RfD. A higher relative kidney weight was seen in male rats at ≥10 mg/kg.

Citation: Til et al., 1973

---

RECORD #2:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 10.700 |
| Sex: | Female | Duration Exposure: 2.0 Years |
| Effect: | AEL | Duration Observation: 2.0 Years |
| Route: | Gavage | |

| | |
|---|---|
| Number Exposed: | 52 |
| Number Responses: | 24 |
| Type of Effect: | NEURP |
| Site of Effect: | KIDNY |
| Severity Effect: | 6 |

Comment: Doses given: 0, 25, 50 mg/kg 15/52 control, 24/52 low dose and 22/52 high dose.

Citation: NTP, 1985

---

RECORD #3:

| | | |
|---|---|---|
| Species: | Rats | Dose: 10.700 |
| Sex: | Male | Duration Exposure: 2.0 Years |
| Effect: | NOAEL | Duration Observation: 2.0 Years |
| Route: | Gavage | |
| Number Exposed: | | 52 |
| Number Responses: | | 5 |
| Type of Effect: | | HYPRP |
| Site of Effect: | | OTHER |
| Severity Effect: | | 3 |

Comment: Doses given: 0, 25, 50 mg/kg. Hyperplasia of the forestomach seen at 50 mg/kg.

Citation: NTP, 1985

---

RECORD #4:

| | | |
|---|---|---|
| Species: | Rats | Dose: 21.400 |
| Sex: | Male | Duration Exposure: 2.0 Years |
| Effect: | AEL | Duration Observation: 2.0 Years |
| Route: | Gavage | |
| Number Exposed: | | 52 |
| Number Responses: | | 13 |
| Type of Effect: | | HYPRP |
| Site of Effect: | | OTHER |
| Severity Effect: | | 3 |

Comment: Doses given: 0, 25, 50 mg/kg. Hyperplasia of the forestomach seen at 50 mg/kg.

Citation: NTP, 1985

---

RECORD #5:

| | | |
|---|---|---|
| Species: | Mice | Dose: 21.400 |
| Sex: | Female | Duration Exposure: 2.0 Years |
| Effect: | AEL | Duration Observation: 2.0 Years |
| Route: | Gavage | |
| Number Exposed: | | 50 |
| Number Responses: | | 15 |
| Type of Effect: | | HYPRP |
| Site of Effect: | | OTHER |
| Severity Effect: | | 3 |

Comment: Doses given: 0, 25, 50 mg/kg. Hyperplasia of the urinary bladder was found at 50 mg/kg.

Citation: NTP, 1985

---

RECORD #6:

| | | |
|---|---|---|
| Species: | Mice | Dose: 21.400 |
| Sex: | Male | Duration Exposure: 2.0 Years |
| Effect: | AEL | Duration Observation: 2.0 Years |
| Route: | Gavage | |

| | |
|---|---|
| Number Exposed: | 50 |
| Number Responses: | 9 |
| Type of Effect: | HYPRP |
| Site of Effect: | OTHER |
| Severity Effect: | 3 |

Comment: Doses given: 0, 50, 100 mg/kg. Hyperplasia of the urinary bladder found at 50 mg/kg.

Citation: NTP,-1985

---

RECORD #7:

| | | |
|---|---|---|
| Species: | Rats | Dose: 8.600 |
| Sex: | Male | Duration Exposure: 13.0 Weeks |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks |
| Route: | Gavage | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTIN |
| Site of Effect: | KIDNY |
| Severity Effect: | 4 |

Comment: Doses given: 0, 1, 3, 10, 30 mg/kg. Increase in kidney weight was found in male rats treated with $\geq$10 mg/kg. The NOAEL 2.6 mg/kg is basis for chronic and subchronic RfD.

Citation: Til et al., 1973

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RECORD #8:

| | | |
|---|---|---|
| Species: | Rats | Dose: 8.600 |
| Sex: | Female | Duration Exposure: 13.0 Weeks |
| Effect: | NOEL | Duration Observation: 13.0 Weeks |
| Route: | Gavage | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | WGTIN |
| Site of Effect: | KIDNY |
| Severity Effect: | 4 |

Comment: Doses given: 0, 1, 3, 10, 30 mg/kg.

Citation: Til et al., 1973

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RECORD #9:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 25.700 | |
| Sex: | Female | Duration Exposure: 13.0 Weeks | |
| Effect: | LOAEL | Duration Observation: 13.0 Weeks | |
| Route: | Gavage | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | WGTIN | |
| Site of Effect: | | KIDNY | |
| Severity Effect: | | 4 | |

Comment: Doses given: 0, 1, 3, 10, 30 mg/kg.

Citation: Til et al., 1973

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RECORD #10:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 710.000 | |
| Sex: | Male | Duration Exposure: 1.0 Days | |
| Effect: | FEL | Duration Observation: 1.0 Days | |
| Route: | Oral, NOS | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | DEATH | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 10 | |

Comment: $LD_{50}$ was 710 mg/kg.

Citation: Torkelson and Rowe, 1981

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RECORD #11:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 470.000 | |
| Sex: | Female | Duration Exposure: 1.0 Days | |
| Effect: | FEL | Duration Observation: 1.0 Days | |
| Route: | Oral, NOS | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | DEATH | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 10 | |

Comment: $LD_{50}$ was 470 mg/kg.

Citation: Torkelson and Rowe, 1981

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RECORD #12:

| | | |
|---|---|---|
| Species: | Rats | Dose: 560.000 |
| Sex: | Male | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Oral, NOS | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: $LD_{50}$ was 560 mg/kg (95% confidence limits were 452-695).

Citation: Toyoshima et al., 1978a

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RECORD #13:

| | | |
|---|---|---|
| Species: | Rats | Dose: 510.000 |
| Sex: | Female | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Oral, NOS | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: $LD_{50}$ was 510 mg/kg (95% confidence limits were 480-726)

Citation: Toyoshima et al., 1978a

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RECORD #14:

| | | |
|---|---|---|
| Species: | Rats | Dose: 140.000 |
| Sex: | N.S. | Duration Exposure: 1.0 Days |
| Effect: | FEL | Duration Observation: 1.0 Days |
| Route: | Oral, NOS | |

| | |
|---|---|
| Number Exposed: | NR |
| Number Responses: | NR |
| Type of Effect: | DEATH |
| Site of Effect: | BODY |
| Severity Effect: | 10 |

Comment: $LD_{50}$ was 140 +/- 25 mg/kg.

Citation: Hine et al., 1953

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RECORD #15:

| | | | |
|---|---|---|---|
| Species: | Rats | Dose: 150.000 | |
| Sex: | N.S. | Duration Exposure: 1.0 Days | |
| Effect: | FEL | Duration Observation: 1.0 Days | |
| Route: | Oral, NOS | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | DEATH | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 10 | |

Comment: $LD_{50}$ was 150 mg/kg (95% confidence limits were 130-170) $LD_{50}$ for males was 130 mg/kg and the $LD_{50}$ for females was between 110 and 250 mg/kg.

Citation: Jones and Collier, 1986

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RECORD #16:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 300.000 | |
| Sex: | N.S. | Duration Exposure: 1.0 Days | |
| Effect: | FEL | Duration Observation: 1.0 Days | |
| Route: | Oral, NOS | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | DEATH | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 10 | |

Comment: $LD_{50}$ was 300 +/- 37 mg/kg.

Citation: Hine et al., 1953

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RECORD #17:

| | | | |
|---|---|---|---|
| Species: | Mice | Dose: 640.000 | |
| Sex: | Both | Duration Exposure: 1.0 Days | |
| Effect: | FEL | Duration Observation: 1.0 Days | |
| Route: | Oral, NOS | | |
| Number Exposed: | | NR | |
| Number Responses: | | NR | |
| Type of Effect: | | DEATH | |
| Site of Effect: | | BODY | |
| Severity Effect: | | 10 | |

Comment: $LD_{50}$ for both males and females was 640 mg/kg.

Citation: Toyoshima et al., 1978b

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