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FOR 2-CHLORO-1,3-BUTADIENE (CHLOROPRENE)

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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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 that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984b and 1986a, respectively.

EXECUTIVE SUMMARY

2-Chloro-1,3-butadiene (CAS number 126-99-8) is commonly known as chloroprene. It is a volatile, colorless liquid at room temperature with an ethereal odor, and it will polymerize spontaneously unless stablized with a polymerization inhibitor. This compound is miscible with most common organic compounds. 2-Chloro-1,3-butadiene is produced commercially by vapor phase chlorination of butadiene (Johnson, 1979). Du Pont in Laplace, LA, is the only domestic manufacturer of this compound (SRI, 1987). An estimated 284 million pounds of this compound was produced in the United States in 1981 (HSDB, 1988). 2-Chloro-1,3-butadiene is used almost exclusively, without isolation, in the production of polychloroprene, a synthetic rubber used to make such items as wire and cable covers, gaskets, automotive parts, adhesives, caulks and flame-resistant cushioning (IARC, 1979).

If released to the atmosphere, 2-chloro-1,3-butadiene is expected to exist almost entirely in the vapor phase. The dominant removal mechanisms are reaction with photochemically generated hydroxyl radicals and ozone. The overall reaction half-life has been estimated to be 7.3 hours (U.S. EPA, 1987c). Anticipated reaction products include H_2CO, $H_2C{=}CClCHO$, OHCCHO, ClCOCHO, $H_2CCHCClO$, chlorohydroxy acids and aldehydes (Cupitt, 1980). If released to water, volatilization is expected to be the dominant removal mechanism (estimated half-life from a model river is 2.8 hours). There is also potential for moderate adsorption to suspended solids and sediments. Chemical hydrolysis, reaction with singlet oxygen and bioaccumulation in aquatic organisms are not expected to be significant fate processes. Insufficient data are available to predict the significance of biodegradation in

either water or soil. If released to soil, it appears that 2-chloro-1,3-butadiene would either volatilize rapidly or percolate through soil. Chemical hydrolysis is not expected to be an important fate process.

A limited amount of monitoring data are available on 2-chloro-1,3-butadiene. 2-Chloro-1,3-butadiene was detected in 1/204 water samples collected from 14 heavily industrialized river basins found in the United States (Ewing et al., 1977) and in 2/63 industrial wastewater effluents in the United States (Perry et al., 1979). This compound was monitored in the ambient atmosphere of six cities in New Jersey throughout 1979. The average concentration at these sites was 0.097 ppb (Harkov et al., 1981). During July 1976, this compound was found in the ambient atmosphere of Houston, TX, at a concentration of 0.59 ppb (Brodzinsky and Singh, 1982). 2-Chloro-1,3-butadiene was not detected in the air samples collected above six abandoned hazardous waste sites and one active sanitary landfill in New Jersey. The detection limit in this study was 0.01 ppb (Harkov et al., 1985). During 1976, the average atmospheric concentration of the compound in 2-chloro-1,3-butadiene manufacturing plants ranged between 2 and 9 ppm (NIOSH, 1977). At one U.S. 2-chloro-1,3-butadiene polymerization plant, 8-hour TWA exposure levels in 1975 ranged from 0.51-39.18 ppm (NIOSH, 1977).

Pertinent data regarding the toxicity of 2-chloro-1,3-butadiene to aquatic organisms or aquatic plants were not located in the available literature.

There is little information regarding the pharmacokinetics of 2-chloro-1,3-butadiene. Absorption of 2-chloro-1,3-butadiene following inhalation or oral exposure is indicated only by effects seen following adminstration of the compound in toxicity and carcinogenicity studies. Data regarding the distribution of 2-chloro-1,3-butadiene following absorption were not located

in the available literature. The initial step in 2-chloro-1,3-butadiene metabolism appears to be the cytochrome P-450-catalyzed formation of an epoxide intermediate, which may then react with glutathione or form the corresponding aldehyde (Summer and Greim, 1980, 1981; Greim et al., 1981; Haley, 1978; Bartsch et al., 1979). There is both in vivo and in vitro evidence for the involvement of glutathione in the metabolism of 2-chloro-1,3-butadiene (Summer and Greim, 1980, 1981; Greim et al., 1981; Jaeger et al., 1975a). In vitro Russian studies summarized by Haley (1978) indicate that 2-chloro-1,3-butadiene is capable of taking up oxygen to form peroxides. Pertinent data regarding the excretion of 2-chloro-1,3-butadiene were not located in the available literature.

Acute, subchronic and chronic inhalation exposure to 2-chloro-1,3-butadiene has been reported to result in growth retardation (Nystrom, 1948; E.I. DuPont de Nemours and Co., 1985a,b,c; Clary et al., 1978). In addition to this decrease in body weight, changes in the relative weights of a variety of organs were noted. Significant changes were reported in the weights of the liver, kidney, adrenals and lungs of rats following inhalation exposure to 2-chloro-1,3-butadiene (E.I. DuPont de Nemours and Co., 1985a,c; Clary et al., 1978). Effects of 2-chloro-1,3-butadiene exposure on the reproductive system were reported in a Russian study that noted a gonadotropic effect of 2-chloro-1,3-butadiene exposure in male rats and mice (Sanotskii, 1976).

Some toxicity studies of 2-chloro-1,3-butadiene, particularly the early studies and the Russian studies, are difficult to interpret because the method of storage and handling of the compound are not reported. 2-Chloro-1,3-butadiene appears to be a particularly unstable compound, subject to oxidation and dimerization; Nystrom (1948) has demonstrated that these reaction products of 2-chloro-1,3-butadiene are several times more toxic than the pure compound.

Fasted rats, probably because of a reduction in liver GSH content, appear to be particularly susceptible to liver injury following acute inhalation exposure to 2-chloro-1,3-butadiene (Plugge and Jaeger, 1979; Jaeger et al., 1975b).

Long-term 2-chloro-1,3-butadiene inhalation carcinogenicity studies using rats and hamsters have been conducted. An 18-month hamster study (E.I. DuPont de Nemours and Co., 1985b) and a 2-year rat study (E.I. DuPont de Nemours and Co., 1985a) failed to show a carcinogenic effect of 2-chloro-1,3-butadiene at exposure levels $\leq$50 ppm. Two Russian studies (Khachatryan, 1972a,b) have suggested that 2-chloro-1,3-butadiene exposure produces an increased risk of skin and lung cancer in occupationally-exposed persons. These findings were not confirmed in studies done in the United States (Pell, 1978). 2-Chloro-1,3-butadiene also failed to produce a significant increase in tumor incidence in rats exposed to the compound orally over the course of a lifetime (Ponomarkov and Tomatis, 1980). Also, 2-chloro-1,3-butadiene was not carcinogenic following application to the skin (Zil'fyan et al., 1975, 1977).

2-Chloro-1,3-butadiene has been demonstrated to be mutagenic to bacteria (see Table 6-2) and caused chromosomal aberrations in humans and dominant lethal effect in rodents (Sanotskii, 1976); this apparent inconsistency between the mutagenicity of 2-chloro-1,3-butadiene and its lack of a carcinogenic effect _in vivo_ has been suggested to be due to metabolic inactivation of any carcinogenic intermediates by glutathione (Summer and Greim, 1980). The U.S. EPA (1986c), based on the limited data available, suggested that 2-chloro-1,3-butadiene is a mutagen and a clastogen.

In studies by E.I. DuPont de Nemours and Co. (1985j,k) and by Culik et al. (1978), 2-chloro-1,3-butadiene was found not to be teratogenic in rats.

There was some fetotoxicity and lowered weight gain at the two highest doses, which produced maternal toxicity. Fetotoxicity/teratogenicity has been reported in the Russian literature (Salnikova and Fomenko, 1973, 1975; Sanotskii, 1976) in rats exposed to 2-chloro-1,3-butadiene. Once again, the nature of the material used in the Russian exposures has been questioned (Culik et al., 1978). Reproductive effects in male mice and rats following exposure to 2-chloro-1,3-butadiene have been reported in the Russian literature (Sanotskii, 1976; Davtyan, 1972). These reproductive effects were not observed in studies by E.I. DuPont de Nemours and Co. (1985d,m).

A chronic inhalation RfD for 2-chloro-1,3-butadiene was calculated using data from a 2-year inhalation carcinogenicity rat study (E.I. DuPont de Nemours and Co., 1985c). A NOAEL of 4.0 mg/kg/day was determined in this study and division of this NOAEL by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive human populations) resulted in a chronic inhalation RfD for 2-chloro-1,3-butadiene of 0.04 mg/kg/day or 3 mg/day for a 70 kg human. This chronic inhalation RfD was also adopted as the subchronic inhalation RfD for this chemical. Because of a lack of pertinent oral toxicity data on 2-chloro-1,3-butadiene, subchronic and chronic oral RfDs were calculated from inhalation values using appropriate absorption factors (i.e., 50% absorption by the inhalation route and 100% absorption by the oral route). This resulted in subchronic and chronic oral RfDs for 2-chloro-1,3-butadiene of 0.02 mg/kg/day or 1.0 mg/day for a 70 kg human. An RQ of 1000 was determined for 2-chloro-1,3-butadiene; this RQ was based on the effect of decreased fetal weight observed in a developmental toxicity study using rats (E.I. DuPont de Nemours and Co., 1985k).

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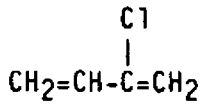
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AKT	Alanine-α-ketoglutarate transaminase
BCF	Bioconcentration factor
bw	body weight
CRD	Chronic respiratory disease
CS	Composite score
DMBA	9,10-Dimethyl-1,2-benzanthracene
GSH	Reduced glutathione
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NPSH	Non-protein sulfhydryl groups
PEL	Permissible exposure limit
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rated value
RV_e	Effect-rated value
TLV	Threshold limit value
TWA	Time-weighted average
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Chloro-1,3-butadiene is commonly known as chloroprene (Johnson, 1979). The structure, molecular weight, empirical formula and CAS Registry number for this compound are as follows:



Molecular weight: 88.54

Empirical formula: C_4H_5Cl

CAS Registry number: 126-99-8

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Chloro-1,3-butadiene is a colorless, mobile, volatile liquid at room temperature with an ethereal odor similiar to that of ethyl bromide. 2-Chloro-1,3-butadiene autooxidizes easily, polymerizes spontaneously at room temperature and forms cyclic dimers on prolonged standing in the presence of polymerization inhibitors. Many organic and inorganic compounds add to the double bonds, usually on the first and fourth carbon atoms. The chlorine atom, like that of vinyl chloride, is very unreactive. 2-Chloro-1,3-butadiene is miscible with most organic compounds (Johnson, 1979). Pertinent physical properties are as follows:

Boiling point:	59.4°C	Johnson, 1979
Melting point:	-130±2°C	Johnson, 1979
Vapor pressure (25°C):	220 mm Hg	Johnson, 1979
Log K_{ow}:	2.06 (estimated)	U.S. EPA, 1987a
Water solubilty (25°C):	2088 mg/ℓ (estimated)	U.S. EPA, 1987b

Density (20°C):	0.9585	Johnson, 1979
Refractive index, n_D^{20}:	1.4583	Johnson, 1979
Flashpoint (open cup):	-20°C	Johnson, 1979
Explosive limits in air:	4.0-20%	Johnson, 1979
Odor threshold in air:	15 ppm	Amoore and Hautala, 1983
in water:	0.024 ppm	Amoore and Hautala, 1983

1.3. PRODUCTION DATA

2-Chloro-1,3-butadiene is produced mainly from vapor phase chlorination of butadiene. The three essential steps involved in the manufacture of chloroprene by this method are as follows:

Chlorination

$$CH_2 = CH - CH = CH_2 + Cl_2 \rightarrow ClCH_2 - CH = CH - CH_2Cl + ClCH - CHCl - CH = CH_2$$

Isomerization

$$ClCH_2 - CH = CH - CH_2Cl \overset{catalyst}{\rightleftharpoons} CH_2 = CH - CHCl - CH_2Cl$$

Dehydrohalogenation

$$CH_2 = CH - CHCl - CH_2Cl + NaOH \rightarrow CH_2 = CH - CCl = CH_2 + NaCl + H_2O$$

Dimerization, bulk polymerization and the formation of autocatalytic "pop-corn" polymer, which is insoluble in the monomer, are avoided in commercial production by refrigeration at <0°C or by addition of inhibitors where higher temperatures or prolonged exposure are necessary (Johnson, 1979). 3-Chloro-1,3-butadiene is manufactured in the United States by Du Pont in Laplace, LA (SRI, 1987). It is estimated that 284 million pounds of 2-chloro-1,3-butadiene was produced in the United States during 1981 (HSDB, 1988).

1.4. USE DATA

2-Chloro-1,3-butadiene is used almost exclusively, without isolation, in the production of polychloroprene, a synthetic rubber used in wire and cable covers, gaskets, automotive parts, adhesives, caulks, flame-resistant cushioning and other applications requiring chemical, oil and weather resistance or high gum strength (Johnson, 1979). The U.S. Food and Drug Administration permits the use of 2-chloro-1,3-butadiene as a component of adhesives intended for use in food packaging (IARC, 1979).

1.5. SUMMARY

2-Chloro-1,3-butadiene (CAS number 126-99-8) is commonly known as chloroprene. It is a volatile, colorless liquid at room temperature with an ethereal odor; it will polymerize spontaneously unless stablized with a polymerization inhibitor. This compound is miscible with most common organic compounds. 2-Chloro-1,3-butadiene is produced commercially by vapor phase chlorination of butadiene (Johnson, 1979). Du Pont in Laplace, LA, is the only domestic manufacturer of this compound (SRI, 1987). An estimated 284 million pounds of this compound was produced in the United States in 1981 (HSDB, 1988). 2-Chloro-1,3-butadiene is used almost exclusively, without isolation, in the production of polychloroprene, a synthetic rubber used to make such items as wire and cable covers, gaskets, automotive parts, adhesives, caulks and flame-resistant cushioning (IARC, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Pertinent data regarding the environmental fate and transport of 2-chloro-1,3-butadiene are limited. Whenever possible, information concerning the environmental fate and transport of this compound was derived from physical property data or molecular structure.

2.1.1. **Chemical Reactions.** Using the method of Atkinson (1987), the rate constant for reaction of 2-chloro-1,3-butadiene vapor with photochemically generated hydroxyl radicals in the atmosphere has been estimated to be 2.1×10^{-11} cm^3/molecule-sec at 25°C. Based on this value and assuming an average ambient hydroxyl radical concentration of 5.0×10^5 molecules/cm^3, the half-life for this reaction has been estimated to be 18 hours. The half-life for reaction of 2-chloro-1,3-butadiene vapor with ozone in the atmosphere has been estimated to be 12 hours. This is based on an average ozone concentration of 6.0×10^{11} molecules/cm^3 and an estimated reaction rate constant of 2.6×10^{-17} cm^3/molecule-sec at 25°C (U.S. EPA, 1987c). Using these data, the overall reaction half-life of 2-chloro-1,3-butadiene in the atmosphere has been estimated to be 7.3 hours. Anticipated reaction products include H_2CO, $H_2C{=}CClCHO$, OHCCHO, ClCOCHO, $H_2CCHCClO$, chlorohydroxy acids and aldehydes (Cupitt, 1980).

2.1.2. **Photolysis.** Because of the reactivity of 2-chloro-1,3-butadiene, removal from the atmosphere by wet or dry deposition is unlikely (Cupitt, 1980).

2.2. WATER

2.2.1. **Hydrolysis.** 2-Chloro-1,3-butadiene contains no hydrolyzable functional groups; therefore, this compound is not expected to undergo chemical hydrolysis under environmental conditions (Lyman et al., 1982; Jaber et al., 1984).

2.2.2. **Oxidation.** Based on the molecular structure of 2-chloro-1,3-butadiene, it appears that this compound could potentially react with naturally occurring singlet oxygen found in surface waters. The half-life for the reaction of substituted olefins with singlet oxygen is ~8 days (Mill and Mabey, 1985). 2-Chloro-1,3-butadiene is, however, an extremely volatile compound, and compared with volatilization, this reaction is expected to be a relatively unimportant removal process (Section 2.2.5.). Pertinent data regarding reaction of 2-chloro-1,3-butadiene with other oxidants found in natural water were not located in the available literature cited in Appendix A.

2.2.3. **Bioaccumulation.** A BCF of 22 was estimated using a log K_{ow} of 2.06 (U.S. EPA, 1987a) and the following linear regression equation (Lyman et al., 1982):

$$\log BCF = 0.76 \log K_{ow} - 0.23 \qquad (2\text{-}1)$$

This BCF value suggests that bioaccumulation in aquatic organisms is not a significant environmental fate process for 2-chloro-1,3-butadiene.

2.2.4. **Adsorption.** An estimated K_{oc} value of 315 (Section 2.3.1.) suggests that 2-chloro-1,3-butadiene may adsorb moderately to suspended solids and sediments in water.

2.2.5. **Volatilization.** Henry's Law constant for 2-chloro-1,3-butadiene has been estimated to be 3.1×10^{-2} atm-m³/mol at 25°C using a method of bond contributions to intrinsic hydrophilic character (Hine and Mookerjee, 1975). This value of Henry's Law constant suggests that volatilization would be rapid from all bodies of water (Lyman et al., 1982). The half-life for 2-chloro-1,3-butadiene volatilizing from a model river 1 m deep, flowing 1 m/sec, with a wind speed of 3 m/sec has been estimated to be 2.8 hours, using Henry's Law constant and the method of Lyman et al. (1982).

2.2.6. **Biodegradation.** Pertinent data regarding biodegradation of 2-chloro-1,3-butadiene were not located in the available literature cited in Appendix A.

2.3. SOIL

2.3.1. **Hydrolysis.** This compound is not expected to undergo chemical hydrolysis under environmental conditions (Lyman et al., 1982; Jaber et al., 1984).

2.3.2. **Leaching.** A K_{oc} of 315 was estimated for 2-chloro-1,3-butadiene using a log K_{ow} of 2.06 (U.S. EPA, 1987a) and the following linear regression equation (Lyman et al., 1982):

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \qquad (2\text{-}2)$$

This K_{oc} value suggests that 2-chloro-1,3-butadiene would be moderately mobile in soil (Swann et al., 1983).

2.3.3. **Volatilization.** The relatively high vapor pressure of 2-chloro-1,3-butadiene [220 mm Hg at 25°C (Johnson, 1979)] suggests that this compound would volatilize rapidly from dry soil surfaces. It appears that volatilization from moist soil surfaces would also be rapid, as this compound does not have a strong tendency to adsorb to soil and it is expected to volatilize rapidly from water (see Sections 2.2.4. and 2.3.1.).

2.3.4. **Biodegradation.** Pertinent data regarding biodegradation of 2-chloro-1,3-butadiene were not located in the available literature cited in Appendix A.

2.4. SUMMARY

If released to the atmosphere, 2-chloro-1,3-butadiene is expected to exist almost entirely in the vapor phase. The dominant removal mechanisms are reaction with photochemically generated hydroxyl radicals and ozone.

The overall reaction half-life has been estimated to be 7.3 hours (U.S. EPA, 1987c). Anticipated reaction products include H_2CO, $H_2C{=}CClCHO$, OHCCHO, ClCOCHO, $H_2CCHCClO$, chlorohydroxy acids and aldehydes (Cupitt, 1980). If released to water, volatilization is expected to be the dominant removal mechanism (estimated half-life from a model river is 2.8 hours). There is also potential for moderate adsorption to suspended solids and sediments. Chemical hydrolysis, reaction with singlet oxygen and bioaccumulation in aquatic organisms are not expected to be signficant fate processes. Insufficient data are available to predict the significance of biodegradation in either water or soil. If released to soil, it appears that 2-chloro-1,3-butadiene would either volatilize rapidly or percolate through soil. Chemical hydrolysis is not expected to be an important fate process.

3. EXPOSURE

3.1. WATER

2-Chloro-1,3-butadiene was detected in 1 of 204 water samples collected between August 1975 and September 1976 from 14 heavily industrialized river basins in the United States (Ewing et al., 1977). The U.S. EPA STORET Data Base (U.S. EPA, 1988) indicates that 1.0 μg/ℓ 2-chloro-1,3-butadiene was found in the surface water at one monitoring station. This compound was identified in 2 of 63 industrial wastewater effluents in the United States at concentrations of <10 and 10-100 μg/ℓ (Perry et al., 1979). During 1975, chlorobutadienes were detected in the Rhine River at Basel, Koln and Duisburg at concentrations of 4.4, 0.4 and 0.3 μg/ℓ, respectively (Sontheimer et al., 1985).

3.2. FOOD

Pertinent data regarding exposure to 2-chloro-1,3-butadiene by ingestion of contaminated food were not located in the available literature cited in Appendix A.

3.3. INHALATION

2-Chloro-1,3-butadiene was detected in the ambient atmosphere of six cities in New Jersey. The sampling sites were located in Elizabeth, Camden, Newark, Rutherford, South Amboy and Batsto. Sampling in Camden was done every 6th day from May to December 1979, but sampling in the other five cities was done every 6th day for an entire year (1979). The average concentration of 2-chloro-1,3-butadiene at these sites was 0.097 ppb and the maximum concentration detected was 4.0 ppb (Harkov et al., 1981). During July 1976, 2-chloro-1,3-butadiene was found in 2 of 2 samples of ambient air from Houston, TX, with an average concentration of 0.59 ppb (Brodzinsky and Singh, 1982). During March 1977, ambient air from Baton Rouge, LA, was

DISCOVERY TOXICOLOGY:
TIERS OF MAMMALIAN HAZARD DETERMINATION

I. NEW CHEMISTRY/FIELD CANDIDATES	SPECIES	INFORMATION
ORAL ACUTE	MOUSE	SINGLE-DOSE LETHALITY, ACUTE CLINICAL SIGNS
IRRITATION - SKIN & EYE	RABBIT	ACUTE IRRITATION ON A.I. (OPTIONAL FOR SMALL-PLOT CANDIDATES)
MUTAGENICITY	BACTERIA	SURROGATE FOR GENOTOXIC CARCINOGENICITY
II. CANDIDATE SORTING/VQ		
ORAL ACUTE	RAT/MOUSE	DIFFERENTIAL SPECIES RESPONSE
DERMAL ACUTE	RABBIT	DONE IF THERE'S A CONCERN
MINIMETABOLISM (UNLABELED)	RAT	BIOACCUMULATION POTENTIAL
14-DAY FEEDING STUDY	RAT	MULTIPLE DOSE/SECOND SPECIES/TARGET ORGANS
S9 IN VITRO	RAT	INTRINSIC METABOLIC POTENTIAL
STRUCTURE/TOXICITY SCREEN	COMPUTER	PREDICTIVE MODELLING TO FLAG CONCERNS
CUSTOM ASSAYS	MISC	CLASS-SPECIFIC ENDPOINTS (E.G. PORPHYRIN ASSAY)
III. VQ/PRIOR TO STAGING		
14C-PHARMACOKINETICS	RAT	ABSORPTION/DISTRIBUTION/METABOLISM/ELIMINATION
EXTENDED FEEDING w MICRONUCLEUS	RAT/MOUSE	LONGER-TERM MULTIPLE EXPOSURE, DOSE RANGE-FINDING
DEVELOPMENTAL TOX	HYDRA?	SURROGATE FOR DEVELOPMENTAL ASSAYS
IRRITANCY	RABBIT	ON TARGET FORMULATION(S) INSTEAD OF A.I.
LLNA	MOUSE	IMMUNE RESPONSE/SENSITIZATION

THIS IS AG PROPRIETARY INFORMATION

analyzed, but 2-chloro-1,3-butadiene was not found (Brodzinsky and Singh, 1982). The air above six abandoned hazardous waste sites and one active sanitary landfill in New Jersey was analyzed, but 2-chloro-1,3-butadiene was not found. Air samples were collected at each site for 1 week during 1983-1984. The detection limit in this study was 0.01 ppb (Harkov et al., 1985).

In 1977, mean airborne concentrations of 2-chloro-1,3-butadiene of $\leq$0.72 mg/m^3 (0.2 ppm) were reported in the roll building area in a metal fabricating plant where polychloroprene was applied extensively to metal cylinders before vulcanization (IARC, 1979). Levels of airborne 2-chloro-1,3-butadiene ranging from 2-12 ppm were found in the open factory area of a floor-covering production plant; from 2-6 ppm were found in confined areas where flooring material was applied; and from 2-20 ppm were found in areas near production of dipped goods from polychloroprene latex (Nutt, 1976). During 1976, the average atmospheric concentrations of 2-chloro-1,3-butadiene in U.S. 2-chloro-1,3-butadiene manufacturing plants ranged between 2 and 9 ppm (NIOSH, 1977). During 1973, at one U.S. 2-chloro-1,3-butadiene polymerization plant, airborne concentrations of 2-chloro-1,3-butadiene were found in the range of 50-5000 mg/m^3 (14-1420 ppm) in the make-up area, 440-24,300 (130-6760 ppm) in the reactor area, 10-1500 mg/m^3 (6-440 ppm) in the monomer recovery area and 400-900 mg/m^3 (113-252 ppm) in the latex area (IARC, 1979). At the same plant, 8-hour TWA exposure levels in 1975 ranged from 0.51-39.18 ppm (NIOSH, 1977). These levels were considerably below those found in 1973 (NIOSH, 1977).

3.4. DERMAL

Pertinent data regarding exposure to 2-chloro-1,3-butadiene by dermal contact were not located in the available literature cited in Appendix A.

3.5. SUMMARY

A limited amount of monitoring data are available on 2-chloro-1,3-butadiene. 2-Chloro-1,3-butadiene was detected in 1/204 water samples collected from 14 heavily industrialized river basins (Ewing et al., 1977) and in 2/63 industrial wastewater effluents in the United States (Perry et al., 1979). This compound was monitored in the ambient atmosphere of six cities in New Jersey throughout 1979. The average concentration at these sites was 0.097 ppb (Harkov et al., 1981). During July 1976, this compound was found in the ambient atmosphere of Houston, TX at a concentration of 0.59 ppb (Brodzinsky and Singh, 1982). 2-Chloro-1,3-butadiene was not detected in the air samples collected above six abandoned hazardous waste sites and one active sanitary landfill in New Jersey. The detection limit in this study was 0.01 ppb (Harkov et al., 1985). During 1976, the average atmospheric concentration of the compound in 2-chloro-1,3-butadiene manufacturing plants ranged between 2 and 9 ppm (NIOSH, 1977). At one U.S. 2-chloro-1,3-butadiene polymerization plant, 8-hour TWA exposure levels in 1975 ranged from 0.51-39.18 ppm (NIOSH, 1977).

4. AQUATIC TOXICITY

Pertinent data regarding the toxicity of 2-chloro-1,3-butadiene to aquatic organisms or aquatic plants were not located in the available literature.

5. PHARMACOKINETICS

5.1. ABSORPTION

Although studies regarding the toxicity and carcinogenicity of 2-chloro-1,3-butadiene indicate that the compound is absorbed following oral and inhalation exposure, no studies dealing specifically with the rate or extent of absorption of 2-chloro-1,3-butadiene were located in the available literature cited in Appendix A.

5.2. DISTRIBUTION

Pertinent data regarding the distribution of 2-chloro-1,3-butadiene following inhalation or oral exposure were not located in the available literature cited in Appendix A.

5.3. METABOLISM

It has been postulated that because of structural similarities between 2-chloro-1,3-butadiene, vinyl chloride and vinylidene chloride, the metabolism of the three compounds is similar (Haley, 1978). The first step in 2-chloro-1,3-butadiene metabolism is therefore assumed to be cytochrome P-450-mediated formation of an epoxide intermediate (Summer and Greim, 1980, 1981; Greim et al., 1981; Haley, 1978). The epoxide could then combine with glutathione or give rise to the corresponding aldehyde (Haley, 1978). Evidence for epoxide formation in the metabolism of 2-chloro-1,3-butadiene comes from the study by Bartsch et al. (1979) in which a gaseous mixture of 2-chloro-1,3-butadiene was passed through a mouse-liver microsomal suspension and then through a solution of 4-(4-nitrobenzyl)pyridine in a specially designed siphon-type apparatus to trap any alkylating metabolite(s) that may have been formed. The demonstration that an alkylating intermediate was formed led Bartsch et al. (1979) to propose that epoxide formation had occurred and that one or both of the two isomeric

epoxides, 2-chloro-1,2-epoxy-butene-3 and 2-chloro-3,4-epoxy-butene-1, had been formed. In vivo studies in rats in which there was a decrease in hepatic GSH levels 3 hours after administration of a single oral dose of the compound (100-200 mg/kg) provide evidence for the involvement of glutathione in 2-chloro-1,3-butadiene metabolism (Summer and Greim, 1980, 1981). In these in vivo studies, there was also an increase in urinary thioether excretion (i.e., GSH conjugates and mercapturic acid) following oral administration of 2-chloro-1,3-butadiene (Greim et al., 1981; Summer and Greim, 1980, 1981). Experiments that demonstrate GSH depletion in isolated rat hepatocytes incubated with 2-chloro-1,3-butadiene (0.5-3.0 mM) provide in vitro evidence for the involvement of glutathione in 2-chloro-1,3-butadiene metabolism (Summer and Greim, 1980; Greim et al., 1981). Indirect evidence for the involvement of glutathione conjugation in the metabolism of 2-chloro-1,3-butadiene comes from a biochemical toxicology study by Jaeger et al. (1975a). In this study, the effects of short-term (i.e., 4 hours) inhalation exposure to 2-chloro-1,3-butadiene in rats at concentrations of $\leq$10,000 ppm (36 g/m^3) were compared for fed and fasted animals and for animals exposed at different times during their circadian rhythm. At night and in fasted animals, the content of GSH in the rat liver is greatly diminished. Exposure of fasted rats to 2-chloro-1,3-butadiene and exposure of rats to 2-chloro-1,3-butadiene at night enhanced the hepatotoxic effects of the compound compared with the effects seen in fed rats or rats exposed during the day.

Findings from in vitro Russian studies as reviewed by Haley (1978) indicate that 2-chloro-1,3-butadiene is capable of taking up oxygen in positions 1 and 2 to form peroxides.

5.4. EXCRETION

Pertinent data regarding the excretion of 2-chloro-1,3-butadiene were not located in the available literature cited in Appendix A.

5.5. SUMMARY

There is little information regarding the pharmacokinetics of 2-chloro-1,3-butadiene. Absorption of 2-chloro-1,3-butadiene following inhalation or oral exposure is indicated only by effects seen following adminstration of the compound in toxicity and carcinogenicity studies. Data regarding the distribution of 2-chloro-1,3-butadiene following absorption were not located in the available literature. The initial step in 2-chloro-1,3-butadiene metabolism appears to be the cytochrome P-450-catalyzed formation of an epoxide intermediate, which may then react with glutathione or form the corresponding aldehyde (Summer and Greim, 1980, 1981; Greim et al., 1981; Haley, 1978; Bartsch et al., 1979). There is both in vivo and in vitro evidence for the involvement of glutathione in the metabolism of 2-chloro-1,3-butadiene (Summer and Greim, 1980, 1981; Greim et al., 1981; Jaeger et al., 1975a). In vitro Russian studies summarized by Haley (1978) indicate that 2-chloro-1,3-butadiene is capable of taking up oxygen to form peroxides. Pertinent data regarding the excretion of 2-chloro-1,3-butadiene were not located in the available literature.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure.

6.1.1.1. **SUBCHRONIC** -- Toxicity studies of 2-chloro-1,3-butadiene are complicated by the fact that the compound is unstable and is subject to autooxidation and dimerization to form polyperoxides (Clary, 1977). The degradation products formed from 2-chloro-1,3-butadiene are apparently more potent than the parent compound with respect to the production of toxic effects; Nystrom (1948) demonstrated that 2-chloro-1,3-butadiene stored for several days at room temperature in the presence of air is ~4 times more toxic than the pure compound.

Nystrom (1948) exposed two groups of rats (10/group - strain and sex not specified) to 2-chloro-1,3-butadiene concentrations of 56 and 334 ppm (203 and 1210 mg/m^3). Exposure was 8 hours/day for 5 months. At the high concentration, half of the animals died by the end of week 13 of exposure. This exposure level (334 ppm) also led to significant decreases in body weight, red blood cell count and blood hemoglobin concentrations. Blood leukocyte levels increased. Statistical analyses of these changes were not given and only mean values were reported. These changes in body weight and blood were not observed in animals exposed to 56 ppm 2-chloro-1,3-butadiene, and this exposure level therefore constitutes a NOEL for this study. Data from this study (Nystrom, 1948) were obtained from a summary provided by NIOSH (1977); more detailed information pertaining to the purity of the compound, exposure schedule, the existence of a control group of animals and other parameters of toxicity evaluated was not provided.

A 26-week subchronic study on the inhalation toxicity of 2-chloro-1,3-butadiene in rats was performed by E.I. DuPont de Nemours and Co. (1985a).

Four groups of Wistar rats (40/sex/group) were exposed to atmospheres containing 2-chloro-1,3-butadiene (purity not reported) at concentrations of 0, 10, 33 and 100 ppm (0, 36, 120 and 362 mg/m³). The exposure schedule was 6 hours/day, 5 days/week. Following exposure, gross and comprehensive microscopic pathology, hematology and biochemistry were evaluated. Urinalyses were also performed. No mortality was observed and the condition of the animals and their behavior was not visibly affected by 2-chloro-1,3-butadiene exposure. At the highest exposure concentration (100 ppm), there was slight growth retardation in males; females in this exposure group produced more urine, with decreased creatinine content. There was a statistically significant increase in the relative liver and kidney weights of both males and females at the 100 ppm exposure level; females also showed a slight increase in the relative weight of the adrenal. At the lower 2-chloro-1,3-butadiene exposure levels (10 and 33 ppm), females showed a statistically significant, dose-related increase in the relative weight of the liver and also an increase in relative kidney weight at 33 ppm. At an exposure level of 33 ppm 2-chloro-1,3-butadiene, relatively low body weights were seen in males. Macroscopic and microscopic pathologic evaluation revealed no alterations that could be attributed to 2-chloro-1,3-butadiene exposure. There were also no biochemical changes attributable to exposure.

White rats (eight males/group) were exposed to 2-chloro-1,3-butadiene (purity not reported) by inhalation at concentrations of 0, 0.051, 0.15 and 1.69 mg/m³ (Sanotskii, 1976). The exposure period was 4.5 months, but the exposure schedule was not given. After 2.5 months exposure to the highest 2-chloro-1,3-butadiene level, there was an increase in the "summation threshold index" (definition of this systemic toxicity parameter was not provided). After 4.5 months exposure to the highest level, there was a

decrease in the synthesis of hippuric acid from sodium benzoate (Quick's test) and an inhibition of gas exchange. 2-Chloro-1,3-butadiene exposure at the two highest levels (0.15 and 1.69 mg/m³) had a gonadotropic effect on male rats, evidenced by functional and morphological changes in spermatogenesis (i.e., reduced number of normal spermatogonia, increased number of dead spermatozoa, an increased susceptibility of spermatozoa to acid-mediated inactivation and a decrease in their period of motility). The lowest 2-chloro-1,3-butadiene exposure level (0.051 mg/m³) had no effect on either the reproductive or systemic toxicity parameters that were measured in rats. In the same report (Sanotskii, 1976), C57BL/6 mice (eight/group) exposed for 2 months to 2-chloro-1,3-butadiene at concentrations of 0.054, 0.064, 0.13, 0.32, 1.85 and 35 mg/m³ showed no systemic signs of toxicity. Exposure for 2 months to concentrations of 2-chloro-1,3-butadiene at ≥0.32 mg/m³ affected mouse gonads, as evidenced by adverse changes in spermatogenesis. An exposure concentration of 0.064 mg 2-chloro-1,3-butadiene/m³ had no gonadotropic effect in mice.

6.1.1.2. **CHRONIC** -- Two long-term inhalation carcinogenicity studies, one using hamsters and one using rats, contained information regarding the systemic toxicity of 2-chloro-1,3-butadiene following chronic inhalation exposure. In both studies, the test compound was vaporized into atmospheres of pure nitrogen to prevent autooxidation and dimerization; exposure atmospheres were analyzed for content of 2-chloro-1,3-butadiene. In the first carcinogenicity study using Syrian Golden hamsters exposed to 0, 10 or 50 ppm (0, 36 or 181 mg/m³) 6 hours/day, 5 days/week for 18 months (E.I. DuPont de Nemours and Co., 1985b), a number of toxicity parameters (including observation of condition and behavior, determination of body and organ weights and extensive pathologic examination) were evaluated. Growth

retardation and a slight reduction in amygloidosis were observed in hamsters exposed to the highest concentration. No effects were observed at 10 ppm, the other concentration tested. In the second carcinogenicity study (E.I. DuPont de Nemours and Co., 1985c), Wistar rats were exposed to 0, 10 or 50 ppm (0, 36 or 181 mg/m³) 2-chloro-1,3-butadiene 6 hours/day, 5 days/week, for 2 years. Rats exposed to 50 ppm 2-chloro-1,3-butadiene (181 mg/m³) showed growth retardation and an increased incidence of alopecia without histopathologic lesions of the skin. Rats exposed to 10 and 50 ppm 2-chloro-1,3-butadiene (36 and 181 mg/m³) showed a decrease in relative lung weight, which was not dose-related. The toxicological significance of this decrease in relative lung weight in 2-chloro-1,3-butadiene-exposed rats is difficult to interpret in view of the fact that exposed animals had a lower incidence of CRD than did control animals. The investigators suggested that 2-chloro-1,3-butadiene exposure might have prevented, in some way, the development of CRD, which in turn led to decreased relative lung weights in the exposed animals compared with controls. Some liver effects (i.e., a nondose-related increase in relative liver weight in females at 10 and 50 ppm and the presence of foci of mild cellular alteration in both sexes at 50 ppm) were also observed in rats exposed to 2-chloro-1,3-butadiene. The increase in relative liver weight in female rats, however, was thought by the investigators to be a fortuitous finding without toxicological significance. Because the foci of cellular alteration in the liver at 50 ppm resembled lesions commonly related to the process of aging, the investigators stated that "it cannot be ruled out" that they represent a chance effect rather than the result of 2-chloro-1,3-butadiene exposure. The lower (10 ppm) exposure level is considered to be a NOAEL in this study. These

studies (E.I. DuPont de Nemours and Co., 1985b,c) are further summarized in Section 6.2.1. and are contained in the toxicity summary table for 2-chloro-1,3-butadiene presented in Chapter 9.

6.1.2. Oral Exposure. Pertinent data regarding the systemic toxicity of 2-chloro-1,3-butadiene following subchronic or chronic oral administration of the compound were not located in the available literature cited in Appendix A.

6.1.3. Other Relevant Information. One of the first studies of the systemic toxicity of 2-chloro-1,3-butadiene (von Oettingen et al., 1936) included information on the lethality of 2-chloro-1,3-butadiene to mice, rabbits and cats following 8 hours of inhalation exposure to various concentrations of the compound. It is difficult to determine LC_{50}s for the various species from these data because of the inconsistencies of effect with increasing concentration (i.e., the percentage of mortality did not strictly increase with increasing 2-chloro-1,3-butadiene concentration). Clary (1977) suggested that the inconsistencies in the data of von Oettingen et al. (1936) may have been due to improper handling and storage of the 2-chloro-1,3-butadiene used, so that the experimental animals were not uniformly exposed to pure 2-chloro-1,3-butadiene, but were instead exposed to unknown mixtures of reaction products of 2-chloro-1,3-butadiene. Despite the difficulty of determining LC_{50}s for the various species in the study by von Oettingen et al. (1936), Sanotskii (1976) has published LC_{50} values from the von Oettingen et al. (1936) study; these values, along with several other acute toxicity values for 2-chloro-1,3-butadiene, are listed in Table 6-1.

Acute inhalation exposure to 2-chloro-1,3-butadiene appears to be capable of causing liver injury in rats. Fasted adult male Sprague-Dawley

TABLE 6-1

Acute Toxicity of 2-Chloro-1,3-butadiene

Species	Route	Parameter	Concentration or Dose	Exposure Duration	Reference
Rats	inhalation	LC_{50}	8200 mg/m³	4 hours	Clary et al., 1978
Mice	inhalation	LC_{50}	600 mg/m³	8 hours	Sanotskii, 1976
Rabbits	inhalation	LC_{50}	3400 mg/m³	8 hours	Sanotskii, 1976
Cats	inhalation	LC_{50}	1300 mg/m³	8 hours	Sanotskii, 1976
Rats	oral	LD_{50}	900 mg/kg bw	NA	Ponomarkov and Tomatis, 1980
Rats	oral	LD_{50}	251 mg/kg bw	NA	Asmangulyan and Badalyan, 1971
Mice	oral	LD_{50}	260 mg/kg bw	NA	Asmangulyan and Badalyan, 1971

NA = Not applicable

rats exposed for 4 hours to 100, 150, 225 or 300 ppm 2-chloro-1,3-butadiene (362, 543, 815 and 1086 mg/m³) and killed at 24 hours showed signs of acute hepatotoxicity (Plugge and Jaeger, 1979). At all exposure concentrations, the total amount of liver nonprotein sulfhydryl groups (mostly GSH) was significantly increased >2-fold after exposure to 300 ppm, and exposure to 2-chloro-1,3-butadiene concentrations of 225 and 300 ppm resulted in increased serum sorbitol dehydrogenase activity. Serum lactate dehydrogenase activity was also increased in rats exposed to 300 ppm 2-chloro-1,3-butadiene. The increase in liver NPSH is at first difficult to reconcile with previous studies that have shown 2-chloro-1,3-butadiene exposure to result in decreased hepatic GSH levels (Summer and Greim, 1980, 1981). Plugge and Jaeger (1979) postulated that the increase in liver NPSH represents an overshoot in the amount of liver GSH caused by an increased rate of GSH synthesis to replace the amounts that were initially depleted following 2-chloro-1,3-butadiene exposure.

The effects of single short-term exposures (i.e., 4 hours) to relatively high concentrations of 2-chloro-1,3-butadiene [500, 1000, 2000 and 4600 ppm (1811, 3621, 7243 and 16,658 mg/m³)] were studied by Jaeger et al. (1975b). Fed or fasted adult male Holtzman rats (five/group) were exposed to the above concentrations of 2-chloro-1,3-butadiene, and lethality and serum AKT were measured. Fasted rats exposed to all concentrations of 2-chloro-1,3-butadiene had elevated serum AKT levels and up to three animals in each exposed group died within 24 hours. Concentrations of 2-chloro-1,3-butadiene ≤2000 ppm did not produce a change in serum AKT activity in fed rats, and there was no mortality observed at these concentrations. At an exposure concentration of 4600 ppm, elevated serum AKT and mortality were observed in fed rats.

An acute (i.e., 4-week) 2-chloro-1,3-butadiene inhalation toxicity study was conducted using rats and hamsters as part of a range-finding study before starting a 2-year inhalation study (Clary et al., 1978). Wistar rats (10/sex/group) and Syrian golden hamsters (10/sex/group) were exposed 6 hours/day, 5 days/ week to 2-chloro-1,3-butadiene at approximate concentrations of 0, 39, 162 and 630 ppm (0, 141, 587, 2281 mg/m³). At the end of the study, hematological examination (including measurements of hemoglobin and hematocrit, and erythrocyte and leukocyte counts) showed no effects of 2-chloro-1,3-butadiene exposure at any level on either rats or hamsters. In rats there was evidence of concentration-related growth retardation and statistically significant changes in the relative weights of the kidneys, liver and lungs. At the highest exposure level (630 ppm), all of the males and 8/10 of the females showed a slight to severe degree of centrilobular liver degeneration and necrosis. This effect was not observed in rats at the two lower exposure levels. The kidneys of rats exposed to the highest level of 2-chloro-1,3-butadiene showed slightly enlarged tubular epithelial cells, whereas no renal effects were seen at the lower 2-chloro-1,3-butadiene exposure levels. In hamsters, the highest 2-chloro-1,3-butadiene exposure level (630 ppm) was lethal to all of the animals. At the mid-exposure level (162 ppm), necrosis and degeneration of the hepatocytes were found, and at the lowest exposure level (39 ppm), there was some irritation of the mucous membrane of the nasal cavity.

An acute inhalation study on the systemic toxicity of 2-chloro-1,3-butadiene in rats was conducted by E.I. DuPont de Nemours and Co. (1985d). ChR-CD male rats (15) were exposed to 25 ppm 2-chloro-1,3-butadiene (91 mg/m³) 4 hours/day for 22 days; there were 10 control animals. Animal body weights were recorded, and the animals were watched for signs of

toxicity. At autopsy, various organs (i.e., lung, heart, liver, kidney, testis and thymus) were weighed, and an extensive histological examination involving >20 organs was performed. There were no clinical signs of toxicity observed during the test, and weight gain patterns in test animals were similar to controls. Gross and histopathologic examination revealed no changes attributable to the test compound.

6.2. CARCINOGENICITY

6.2.1. Inhalation. An 18-month inhalation carcinogenicity study of 2-chloro-1,3-butadiene using Syrian golden hamsters was conducted by E.I. DuPont de Nemours and Co. (1985b). Three groups of hamsters (100/sex/group) were exposed to 0, 10 or 50 ppm 2-chloro-1,3-butadiene (0, 36 or 181 mg/m^3) for 6 hours/day, 5 days/week. Systemic toxicity was discussed in Section 6.1.1.2. Pathologic evaluation including microscopic examination was performed on >30 different organs. At the highest exposure level (50 ppm), growth retardation was observed, along with a slight reduction in amyloidosis. There were no indications of carcinogenicity resulting from 2-chloro-1,3-butadiene exposure at either of the concentrations used in this study.

A 2-year inhalation carcinogenicity study was conducted by E.I. DuPont de Nemours and Co. (1985c), where Wistar rats (100/sex/group) were exposed to 2-chloro-1,3-butadiene at concentrations of 0, 10 or 50 ppm (0, 36 or 181 mg/m^3) for 6 hours/day, 5 days/week. At week 72 of the study, an equipment failure resulted in the suffocation deaths of 87 males and 73 females in the low level exposure group. Growth retardation was observed in the high exposure group. There was no action of 2-chloro-1,3-butadiene in rats up to an exposure level of 50 ppm. At the 50 ppm dose level, both male

and female rats showed an increased incidence of foci of cellular alteration in the livers (males, 14/97 in control and 30/96 in 50 ppm group; females, 13/98 in control and 27/99 in 50 ppm group).

Several epidemiological studies have examined whether 2-chloro-1,3-butadiene is capable of causing cancer in workers exposed to the compound and its reaction products. Two Russian articles (Khachatryan, 1972a,b) indicate that 2-chloro-1,3-butadiene exposure produces an increased risk of skin and lung cancer. In the first (Khachatryan, 1972a), 137 cases of skin cancer were observed during examination of 24,989 industrial workers from 1956-1970 in the Yerevan region of Russia; the population was divided into five subgroups according to the nature of employment. A subgroup composed of 684 persons with extended work experience in 2-chloro-1,3-butadiene production (i.e., production of chloroprene and polychloroprene latex and rubber) had a significantly increased incidence of skin cancer compared with three other subgroups composed of unexposed persons. A subgroup composed of 2250 workers exposed only to 2-chloro-1,3-butadiene derivatives (i.e., workers from shoe factories with exposure to polychloroprene cement) also showed an increased incidence of skin cancer. The other three subgroups (termed control populations) were composed of chemical workers (4780 persons) not exposed to 2-chloro-1,3-butadiene but with prolonged exposure to lacquers, acetone, benzene, gasoline and acids; nonchemical workers (8755 persons); and nonindustrial workers (8520 persons). The concentrations of 2-chloro-1,3-butadiene and any other toxic chemicals to which the workers may have been exposed were not reported. Khachatryan (1972a) concluded that 2-chloro-1,3-butadiene was a carcinogen or cocarcinogen for human skin and that 2-chloro-1,3-butadiene-induced skin cancer is preceded by chronic dystrophic and inflammatory skin ailments, which are caused by binding of the compound to free sulfhydryl groups in the skin. This study did not

report the skin cancer incidence by sex, provided no information regarding prior work history and made no mention of other chemicals to which the workers were concurrently exposed.

In the second study (Khachatryan, 1972b), the incidence of lung cancer was investigated among 19,979 workers in the same region of Russia during the period 1956-1970. The population was subdivided into four subgroups according to the nature of employment, but there was no distinction made in this study as had been made in the previous study (Khachatryan, 1972a) between workers exposed only to 2-chloro-1,3-butadiene and those exposed to 2-chloro-1,3-butadiene derivatives. The four subgroups were composed of workers with some occupational exposure to 2-chloro-1,3-butadiene or its derivatives (2934 persons), chemical workers with no exposure to 2-chloro-1,3-butadiene (4780 persons), nonindustrial (i.e., professional) workers (6045 persons) and nonchemical workers (6220 persons). A total of 71 cases of lung cancer were identified, but detailed information regarding the specific types of lung cancer, the individual's work experience, concentrations of 2-chloro-1,3-butadiene and its derivatives to which the workers were exposed, and smoking habits were not provided. The incidence of lung cancer in workers exposed to 2-chloro-1,3-butadiene and its derivatives (1.24%) was significantly higher than the lung cancer incidences reported in chemical workers, nonchemical workers and nonindustrial workers (0.46, 0.8 and 0.06%, respectively). Khachatryan (1972b) concluded that exposure to 2-chloro-1,3-butadiene and its derivatives led to significant increases in the incidence of lung cancer. In their evaluation of this study, NIOSH (1977) reported that work history, carrier progression, age at beginning of employment, smoking habit and contagious lung diseases have been considered, but detailed information has not been provided. The methods for diagnosing

lung cancer and the specific type of cancer diagnosis were not described; furthermore, there were inconsistencies between tables and the text regarding cancer incidence.

The finding of an increased incidence of lung cancer in workers exposed to 2-chloro-1,3-butadiene (Khachatryan, 1972b) was not confirmed in a study by E.I. DuPont de Nemours and Co. (Pell, 1978). In this study (Pell, 1978), historical prospective mortality studies were made of two cohorts of workers potentially exposed to 2-chloro-1,3-butadiene in the manufacture of neoprene. One cohort consisted of 1576 male production workers at the Louisville works in 1957; the other cohort comprised 270 men (both production workers and maintenance mechanics) who had exposure to 2-chloro-1,3-butadiene at the Chambers works in New Jersey between 1931 and 1948. Control populations consisted of DuPont Company employees and retirees, and U.S. males. Mortality was analyzed for all cohorts during the period 1957 through 1974. With the exception of maintenance mechanics in the Louisville study, the incidence of lung cancer in the 2-chloro-1,3-butadiene-exposed cohorts from both the Louisville and the Chambers works was not significantly different from that observed in the control cohorts. Maintenance mechanics in the Louisville study appeared to have an excess risk of lung cancer, but Pell (1978) felt that this excess risk may be due to the presence of another chemical carcinogen in the plant, cigarette smoking or a fortuitously high incidence of cancer cases in this group. Pell (1978) concluded that 2-chloro-1,3-butadiene exposure does not increase the risk of lung cancer. The incidence of skin cancer was not considered in this study.

The assessment of carcinogenic risk for humans exposed to 2-chloro-1,3-butadiene is difficult because of limitations in the epidemiological studies reported by Pell (1978) and Khachatryan (1972a,b). None of these epidemiological studies adequately considered the intensity or duration of exposure,

environmental concentrations or the latency period (NIOSH, 1977). In addition, neither Pell (1978) nor Khachatryan (1972a,b) attempted to analyze the data separately for workers involved in 2-chloro-1,3-butadiene polymerization and workers involved in monomer production work only, even though this distinction has been found to be important in workers in the vinyl chloride industry (NIOSH, 1977). The investigators in these epidemiological studies (Pell, 1978; Khachatryan, 1972a,b) did not mention the criteria for diagnoses of the various cancers, and the cell types for the various skin and lung cancers reported were not indicated. Also, Pell (1978) used a control population that consisted of industrial workers exposed to agents known or suspected to be carcinogenic. The use of such a control population would tend to underestimate the true carcinogenic risk from exposure to 2-chloro-1,3-butadiene (NIOSH, 1977).

6.2.2. Oral. A long-term oral carcinogenicity study of 2-chloro-1,3-butadiene using rats was conducted by Ponomarkov and Tomatis (1980). Seventeen pregnant female BD IV rats were given 100 mg 2-chloro-1,3-butadiene/kg bw as a single oral dose on day 17 of gestation. Their progeny (81 males and 64 females) were given an oral dose of 50 mg 2-chloro-1,3-butadiene/kg bw in olive oil, once/week, for their entire life span beginning from the time of weaning. Controls were 14 pregnant female BD IV rats, which received 0.3 mℓ olive oil on day 17 of pregnancy, and their offspring, which were given 0.3 mℓ olive oil weekly for life beginning at weaning. After 120 weeks, all survivors were killed and autopsied. Major internal organs were examined histologically. Several tumors were observed in 2-chloro-1,3-butadiene-treated males that were not seen in controls, and subcutaneous fibromas were more numerous in 2-chloro-1,3-butadiene-treated males than in controls. Ponomarkov and

Tomatis (1980) concluded, however, that the total incidence of tumors was similar in 2-chloro-1,3-butadiene-treated and control animals.

Zil'fyan et al. (1975, 1977) administered 2-chloro-1,3-butadiene (200 mg/kg bw) in sunflower oil by gavage to 100 random-bred albino rats. Administration of the compound was twice weekly for 25 weeks. No tumors were observed in the 40 rats that survived 2 years.

6.2.3. Other Relevant Information. 1,3-Butadiene, a nonchlorinated analog of chloroprene, has been shown to be carcinogenic in mice and rats. This structure-activity relationship and the mutagenic and cell-transforming capability of chloroprene suggest that chloroprene could be carcinogenic and should, therefore, be tested further. In vitro treatment of an established line of hamster lung cells with 1-500 μg 2-chloro-1,3-butadiene/mℓ resulted in malignant transformation of the cells (Menezes et al., 1979). Treatment with 1.0 μg/mℓ of the compound resulted in transformation 14 weeks after treatment; higher concentrations of 2-chloro-1,3-butadiene did not accelerate the transformation process.

Zil'fyan et al. (1975, 1977) applied a 50% solution of 2-chloro-1,3-butadiene in benzene to the skin of 100 random bred albino mice. Skin applications were twice weekly for 25 weeks. A positive control group of mice received 50 skin applications (2/week for 25 weeks) of a 0.1% solution of DMBA in benzene. No tumors of the skin or other organs were reported in the mice treated with 2-chloro-1,3-butadiene, whereas 92% of the DMBA-treated mice that survived to the time of appearance of the first skin tumor developed skin carcinomas.

Intratracheal administration of 2-chloro-1,3-butadiene to rats (200 mg/kg bw 5 times at 20-day intervals) produced no tumors in the lungs of

animals that died or were killed 6 or 14 months after 2-chloro-1,3-butadiene administration (Zil'fyan et al., 1977).

6.3. MUTAGENICITY

2-Chloro-1,3-butadiene has been shown overall to be mutagenic in a variety of bacterial strains by a number of investigators (Table 6-2). 2-Chloro-1,3-butadiene fed to male Drosophila melanogaster (5.7-34.3 mM for 3 days) induced recessive lethal mutations (Vogel, 1979). Mutagenicity was not detected in 8-azaguanine and ouabain-resistant V79 Chinese hamster cells exposed to vapors of 2-chloro-1,3-butadiene ($\leq$10% v/v) for 5 hours in the presence of rat liver microsomes (Drevon and Kuroki, 1979). However, this negative result should be confirmed or refuted by additional testing, since this test was performed in the presence of 10% serum, which can act as a sink in absorbing reactive chemical species. Reports from the Russian literature (Katosova and Pavlenko, 1985; Katosova, 1973) indicate the presence of chromosomal aberrations in the lymphocytes and somatic cells of occupationally exposed humans. Another Russian study (Sanotskii, 1976) indicated that rats and mice exposed by inhalation to various concentrations of chloroprene showed chromosomal aberrations and dominant lethal effects at $\geq$0.32 and $\geq$1.85 mg/m^3, respectively. The author suggested 0.15 mg/m^3 as the threshold for embryotoxic and mutagenic effects. 2-Chloro-1,3-butadiene was not mutagenic in a micronucleus test conducted by E.I. DuPont de Nemours and Co. (1985e). In this study, two groups of rats (five/sex/group) were exposed to atmospheres containing 0 or 100 ppm 2-chloro-1,3-butadiene (0 or 361.8 mg/m^3). Exposure was 6 hours/day for 4 consecutive days. Following exposure, the animals were killed and bone marrow preparations were made. The ratio of poly- and normochromatic erythrocytes, and the incidence of micronucleated cells/2000 erythrocytes were then recorded. The above

Mutagenicity Testing of 2-Chloro-1,3-Butadiene

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538	NR	plate incorporation	0.63% (v/v)	±S-9	-	S-9 prepared from liver, lung and testes of mouse, rat and monkey	E.I. DuPont de Nemours and Co., Inc., 1985f
	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	NR	plate incorporation	0.1, 1.0, 10 and 100 µl/plate	none or +S-9	- + (TA1535 at 10 and 100 µl/plate	liver S-9 prepared from Sprague-Dawley rats pre-treated with Aroclor 1254	E.I. DuPont de Nemours and Co., Inc., 1985g
	S. typhimurium TA1535, TA1537, TA98, TA100	NR	atmospheric exposure to chloroprene	0.035-1.12% in atmosphere	none or +S-9	slight activity in TA1535 and TA100 + (TA1535 and TA100)	NC	E.I. DuPont de Nemours and Co., Inc., 1985h
	S. typhimurium TA1535, TA100, TA1537, TA1538, TA98	NR	plate incorporation	150-3000 µg/plate	none or +S-9	slight activity in TA1535 and TA100 + (TA1535 and TA100)	NC	E.I. DuPont de Nemours and Co., Inc., 1985i
	S. typhimurium TA1535, TA100	NR	atmospheric exposure to chloroprene	4.3 µmol/plate	S-9	+	NC	Bartsch et al., 1980
	S. typhimurium TA100	NR	atmospheric exposure to chloroprene	0.5-8% of chloroprene vapor in air	none or +S-9	+ +	exposure to 20% vapor concentration caused strong toxicity in bacteria; 3-fold increase in mutagenic response with metabolic activation	Bartsch et al., 1975
Recessive lethal test	Drosophila melanogaster	>99%	standard feeding technique	5.7-34.3 mM	NA	+	NC	Vogel, 1979
8-Azaguanine and ouabain resistance	V79 Chinese hamster cells	99%	atmospheric exposure of plated cells to chloroprene	0.2, 1.0, 2.0 and 10% (v/v) chloroprene vapor	rat liver S-15	-	dose-related toxicity but no mutagenicity	Drevon and Kuroki, 1979

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TABLE [illegible]-2 (cont.)

Assay	Indicator Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Chromosomal aberrations	human peripheral lymphocytes	NR	occupational	1.0-45 mg/m³	NA	+	exposure to 0.05 mg/m³ did not produce chromosomal aberrations	Katosova and Pavlenko, 1985
	human peripheral lymphocytes	NR	occupational	18 mg/m³	NA	+	NC	Katosova, 1973

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

mentioned ratio and incidence were not significantly different between 2-chloro-1,3-butadiene-treated and control animals.

6.4. TERATOGENICITY

A teratogenicity and fetotoxicity study using rats was conducted at the Haskell Laboratory for Toxicology and Industrial Medicine (E.I. DuPont de Nemours and Co., 1985j; Culik et al., 1978). In both studies, the concentration of 2-chloro-1,3-butadiene in the test atmosphere was closely monitored. In the teratology study, pregnant female ChR-CD rats were exposed by inhalation to four concentrations of 2-chloro-1,3-butadiene [0, 1, 10 and 25 ppm (0, 3.6, 36 91 mg/m^3)]. There were 25 rats/dose level and exposure was 4 hours/day from day 2 or 3 of pregnancy to day 20 of gestation. After exposure, autopsies were performed on dams and fetuses were examined for abnormalities. In the fetotoxicity study, pregnant female ChR-CD rats were exposed to the same concentrations of 2-chloro-1,3-butadiene vapors that were used in the teratology study, but there were 50 rats/dose level. Exposure was 4 hours/day on days 1-12 of gestation. The dams were sacrificed on day 17 of gestation and gross autopsies were performed. There were no clinical signs of 2-chloro-1,3-butadiene-induced toxicity in the dams either during or postexposure at any inhaled level of 2-chloro-1,3-butadiene in either study. Gross pathological changes were not observed in any organ system, and 2-chloro-1,3-butadiene exposure did not affect maternal body weight. 2-Chloro-1,3-butadiene was not fetotoxic in this study. Pre- and postimplantation losses of fertilized ova, the number of live fetuses/litter and the weight and size of the fetuses were not significantly different between exposed and control groups. No major external, skeletal or soft tissue malformations were found.

Another 2-chloro-1,3-butadiene fetotoxicity/teratogenicity study that used exposure levels high enough to produce signs of maternal and fetotoxicity was conducted by E.I. DuPont de Nemours and Co. (1985k). Pregnant rats (36/dose level) were exposed by inhalation to chloroprene levels of 0, 10, 25, 75 and 175 ppm (0, 36, 91, 272 and 634 mg/m³). Exposure was 6 hours/day on days 4-16 of gestation. The highest exposure level (175 ppm) produced focal alopecia in the mothers and decreased fetal weight and slight retardation in bone development. A lower empty uterus weight and lower fetal weights were seen at the two highest dose levels (75 and 175 ppm); at the three highest exposure levels (25, 75 and 175 ppm), there was diminished maternal food consumption and weight gain. The NOEL for maternal toxicity was 10 ppm. Despite signs of fetotoxicity at 75 and 175 ppm, there were no signs of teratogenicity at any 2-chloro-1,3-butadiene exposure level, and the NOAEL for developmental toxicity in this study appears to be 25 ppm.

Comparing the Russian literature with other reports reveals some discrepancy concerning the teratogenicity/fetotoxicity of 2-chloro-1,3-butadiene. Briefly reported Russian studies (Salnikova and Fomenko, 1973, 1975; Sanotskii, 1976) indicated that 2-chloro-1,3-butadiene is fetotoxic and teratogenic in rats at an exposure level of ~1 ppm (4 mg/m³). Subsequent studies summarized above (E.I. DuPont de Nemours and Co. 1985j,k; Culik et al., 1978) indicated that 2-chloro-1,3-butadiene is not fetotoxic/teratogenic at exposure levels ~100-200 times higher than the levels used in the Russian studies. In a conference between Soviet scientists and scientists from DuPont, no resolution was reached as to the cause of this discrepancy (E.I. DuPont de Nemours and Co., 1985l), but it has been suggested that because of the chemical instability of 2-chloro-1,3-butadiene, the Russian investigators may have inadvertently exposed their animals to oxidation reaction products of 2-chloro-1,3-butadiene (Culik et al., 1978).

6.5. OTHER REPRODUCTIVE EFFECTS

Male ChR-CD rats (five) were exposed to 25 ppm 2-chloro-1,3-butadiene (91 mg/m³) 4 hours/day for 22 days (E.I. DuPont de Nemours and Co., 1985d; Culik et al., 1978); there were five control animals. After the last inhalation exposure, each male was caged with three untreated virgin females for 7 days. Following mating, the males were autopsied and the reproductive organs were examined histologically. The litters were examined for the number of pups/litter and the average body weight at weaning. There was no effect of 2-chloro-1,3-butadiene exposure on any of the reproductive parameters examined.

A 2-generation inhalation study on the effects of 2-chloro-1,3-butadiene exposure in rats was conducted by E.I. DuPont de Nemours and Co. (1985m). The vapor of test compound was generated in nitrogen, and concentrations in the test atmosphere were monitored closely as described above. F_0 generation males and females (25/sex/group) were exposed to atmospheres containing 0, 10, 33 or 100 ppm 2-chloro-1,3-butadiene (0, 36, 120 or 362 mg/m³). The exposure schedule was 6 hours/day, 5 days/week for 13 weeks. Following exposure, the chloroprene-exposed animals were mated with untreated males and females. From the progeny of this mating (F_1 generation), 320 were selected randomly, divided into four groups (40/sex/group) and exposed by inhalation to the same concentrations of 2-chloro-1,3-butadiene that were used for the F_0 generation. The F_1 generation rats were exposed 6 hours/day, 5 days/week for 10 weeks. Parameters evaluated in the F_0 generation included general condition and behavior, body weight, reproductive performance, hematology and organ pathology. F_1 generation animals were evaluated for the same parameters with the exception of reproductive performance. At the highest concentration, growth retardation was observed in members of the F_0 generation. There was, however, no effect of

2-chloro-1,3-butadiene exposure at any level on the reproductive performance of this generation. In the F_1 generation, the mid- and high concentrations of 2-chloro-1,3-butadiene produced growth retardation in both sexes compared with controls, but there was no effect of 2-chloro-1,3-butadiene exposure on any of the other parameters measured. The investigators suggested that the growth retardation observed at 100 ppm but not at 33 ppm in the F_0 generation and at both 33 and 100 ppm in the F_1 generation may have resulted from different diets fed to the different generations.

Reproductive effects following 2-chloro-1,3-butadiene exposure in male rats have been reported in the Russian literature. Sanotskii (1976) exposed C57Bl/6 mice (number not reported) to 0.017, 0.1 or 1 ppm 2-chloro-1,3-butadiene (0.062, 0.36 or 3.6 mg/m^3) for 2 months. At the two highest dose levels, adverse effects on spermatogenesis were noted consisting of an increase in the number of tubules with desquamating germinal epithelium. No effect was noted at the 0.017 ppm exposure level. In a study by Davtyan (1972), 100 male rats were exposed to 0, 0.014, 0.042 or 0.47 ppm 2-chloro-1,3-butadiene (0, 0.051, 0.15 or 1.7 mg/m^3) 4 hours/day for 5.5 months. At the two highest dose levels, there were significant reductions in sperm motility, viability and acid resistance. There was also testicular atrophy and a reduction in the number of spermatogonia in some males. No effects were reported at 0.014 ppm 2-chloro-1,3-butadiene. These findings by Davtyan (1972) and Sanotskii (1976) are questionable in that they do not appear to be reproducible. The results were not reproduced in a second paper by Davtyan et al. (1973) and in a reproduction study by E.I. DuPont de Nemours and Co. (1985e), although both of these studies used higher exposure levels of 2-chloro-1,3-butadiene. The method of handling 2-chloro-1,3-butadiene and the purity of the compound were not reported in the Russian studies (E.I. DuPont de Nemours and Co., 1985d), and this again raises the

possibility that 2-chloro-1,3-butadiene oxidation and dimerization products may have been present in the Russian exposure mixture.

6.6. SUMMARY

Acute, subchronic and chronic inhalation exposure to 2-chloro-1,3-butadiene has been reported to result in growth retardation (Nystrom, 1948; E.I. DuPont de Nemours and Co., 1985a,b,c; Clary et al., 1978). In addition to this decrease in body weight, changes in the relative weights of a variety of organs were noted. Significant changes were reported in the weights of the liver, kidney, adrenals and lungs of rats following inhalation exposure to 2-chloro-1,3-butadiene (E.I. DuPont de Nemours and Co., 1985a,c; Clary et al., 1978). Effects of 2-chloro-1,3-butadiene exposure on the reproductive system were reported in a Russian study that noted a gonadotropic effect of 2-chloro-1,3-butadiene exposure in male rats and mice (Sanotskii, 1976).

Some toxicity studies of 2-chloro-1,3-butadiene, particularly the early studies and the Russian studies, are difficult to interpret because the method of storage and handling of the compound are not reported. 2-Chloro-1,3-butadiene appears to be a particularly unstable compound, subject to oxidation and dimerization, and Nystrom (1948) has demonstrated that these reaction products of 2-chloro-1,3-butadiene are several times more toxic than the pure compound.

Fasted rats, probably because of a reduction in liver GSH content, appear to be particularly susceptible to liver injury following acute inhalation exposure to 2-chloro-1,3-butadiene (Plugge and Jaeger, 1979; Jaeger et al., 1975b).

Long-term 2-chloro-1,3-butadiene inhalation carcinogenicity studies using rats and hamsters have been conducted. An 18-month hamster study (E.I. DuPont de Nemours and Co., 1985b) and a 2-year rat study (E.I. DuPont de Nemours and Co., 1985a) failed to show a carcinogenic effect of 2-chloro-

1,3-butadiene at exposure levels ≤50 ppm. Two Russian studies (Khachatryan, 1972a,b) have suggested that 2-chloro-1,3-butadiene exposure produces an increased risk of skin and lung cancer in occupationally-exposed persons. These findings were not confirmed in studies done in the United States (Pell, 1978). 2-Chloro-1,3-butadiene also failed to produce a significant increase in tumor incidence in rats exposed to the compound orally over the course of a lifetime (Ponomarkov and Tomatis, 1980). Also, 2-chloro-1,3-butadiene was not carcinogenic following application to the skin (Zil'fyan et al., 1975, 1977).

2-Chloro-1,3-butadiene has been demonstrated to be mutagenic to bacteria (see Table 6-2) and caused dominant lethal effects in rodents and chromosomal aberrations in humans (Sanotskii, 1976); and this apparent inconsistency between the mutagenicity of 2-chloro-1,3-butadiene and its lack of a carcinogenic effect in vivo has been suggested to be due to metabolic inactivation of any carcinogenic intermediates by glutathione (Summer and Greim, 1980). The U.S. EPA (1986c) study, based on the limited data available, suggested 2-chloro-1,3-butadiene is a mutagen and a clastogen.

In studies by E.I. DuPont de Nemours and Co. (1985j,k) and by Culik et al. (1978), 2-chloro-1,3-butadiene was found not to be fetotoxic or teratogenic in rats. Fetotoxicity/teratogenicity has been reported in the Russian literature (Salnikova and Fomenko, 1973, 1975; Sanotskii, 1976) in rats exposed to 2-chloro-1,3-butadiene. Once again, the nature of the material used in the Russian exposures has been questioned (Culik et al., 1978). Reproductive effects in male mice and rats following exposure to 2-chloro-1,3-butadiene have been reported in the Russian literature (Sanotskii, 1976; Davtyan, 1972). These reproductive effects were not confirmed in studies by E.I. DuPont de Nemours and Co. (1985d,m).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The TLV-TWA for 2-chloro-1,3-butadiene is 10 ppm (35 mg/m³) (ACGIH, 1987). This value represents a reduction from the previous TLV of 25 ppm, and this reduction stems in part from minimal systemic toxicity effects seen in rats and hamsters exposed repeatedly to 39 ppm 2-chloro-1,3-butadiene over the course of 4 weeks (ACGIH, 1986; Clary et al., 1978). The PEL for 2-chloro-1,3-butadiene is 25 ppm (90 mg/m³) (OSHA, 1985). NIOSH (1977) recommends a 15-minute ceiling concentration of 1 ppm (3.6 mg/m³) as a workplace standard. An ADI of 0.13 mg/day for a 70 kg man has been derived in an earlier U.S. EPA (1984a) analysis.

7.2. AQUATIC

Data regarding guidelines and standards for 2-chloro-1,3-butadiene in aquatic organisms were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Studies regarding the carcinogenicity of 2-chloro-1,3-butadiene by inhalation exposure in hamster and rats were conducted by E.I. DuPont de Nemours and Co. (1985b,c). An 18-month inhalation study using Syrian Golden Hamsters (E.I. DuPont de Nemours and Co., 1985b) and a 2-year inhalation study using Wistar rats (E.I. DuPont de Nemours and Co., 1985c) at 2-chloro-1,3-butadiene exposure levels of $\leq$50 ppm (181 mg/m^3) failed to produce any evidence of carcinogenicity associated with exposure to the compound. Two Russian studies (Khachatryan, 1972a,b) reported an increased incidence of lung and skin cancer in persons occupationally-exposed to 2-chloro-1,3-butadiene. These findings have not been confirmed in epidemiological studies conducted in the United States (Pell, 1978).

8.1.2. Oral. Male and female BD IV rats given a weekly oral dose of 50 mg 2-chloro-1,3-butadiene/kg bw over the course of a lifetime starting at the time of weaning did not have a significantly increased incidence of cancer over that observed in rats given only the corn oil vehicle (Ponomarkov and Tomatis, 1980). Oral administration of 2-chloro-1,3-butadiene (200 mg/kg bw) twice/week for 25 weeks failed to produce tumors in rats (Zil'fyan et al., 1975, 1977).

8.1.3. Other Routes. A 50% solution of 2-chloro-1,3-butadiene in benzene applied to the skin of mice (twice/week for 25 weeks) failed to induce tumors of the skin or any other organs (Zil'fyan et al., 1975, 1977). Intratracheal administration of 2-chloro-1,3-butadiene (200 mg/kg bw) 5 times at 20-day intervals did not produce tumors in the lungs of rats (Zil'fyan et al., 1977).

8.1.4. Weight of Evidence. The epidemiological data concerning the possible carcinogenicity of 2-chloro-1,3-butadiene in humans (Khachatryan, 1972a,b; Pell, 1978) yielded results suggestive of lung cancer. Because of gross inadequacies in all three studies, collectively the human data is, however, appropriately classified as "inadequate" using the criteria described by the U.S. EPA (1986b). The animal bioassay data, which shows both negative and suggestive positive responses (liver foci in both sexes of rat by inhalation with dose response), is judged inadequate albeit suggestive. The mutagenic data, mammalian cell transforming capability and structural relationship to 1,3-butadiene suggests that chloroprene has a potential to be carcinogenic. The metabolism of chloroprene is likewise thought to include an epoxide at least in one pathway. Nevertheless, with some negative studies, the reasons for concern are not quite strong enough to give a Group C classification and thus the compound is considered to be in Group D with a note of concern that unnecessary exposure should be avoided until additional research is conducted.

8.1.5. Quantitative Risk Estimates. Because the animal and human studies are judges inadequate to assess the carcinogenicity, no inhalation or oral q_1* is derived.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Nystrom (1948) exposed rats to 2-chloro-1,3-butadiene at two exposure levels [56 and 334 ppm (203 and 1210 mg/m^3)] 8 hours/day for 5 months. The higher exposure level produced death in half of the rats by the end of the week 13, and decreases in body weight and blood changes in the surviving animals. This study (Nystrom, 1948) was not considered further for risk assessment because

of quality factors. Details of the study were obtained from a secondary source (NIOSH, 1977), and information regarding the existence and nature of a control group of animals, and whether other parameters of toxicity were evaluated (including histopathological examination) were not provided.

The second study considered for RfD development is a subchronic (i.e., 26-week) 2-chloro-1,3-butadiene inhalation study by E.I. DuPont de Nemours and Co. (1985a) where rats were exposed to 2-chloro-1,3-butadiene at three exposure levels [10, 33 or 100 ppm (36, 120, 362 mg/m^3)] 6 hours/day for 5 days/week. Effects were noted at all exposure levels; the lowest exposure level (i.e., 36 mg/m^3) was associated only with an increase in relative liver weight in females. This exposure level corresponds to a transformed animal dose of 5.0 mg/kg/day [i.e., 36 mg/m^3 x 0.152 m^3/day (rat inhalation rate) [U.S. EPA, 1980] x 1/0.196 (one/rat body weight) x 6 hours/24 hours x 5 days/7days]. Because there were no lesions associated with the increase in relative liver weight, elevated liver weight was considered an adaptive rather than adverse effect and this exposure level (10 ppm) was considered a NOAEL for this study.

The third study considered for subchronic RfD development is a reproduction study by E.I. DuPont de Nemours and Co. (1985m) (see Section 6.5.). In this study, male rats of the F_0 generation exposed to 100 ppm and both sexes of rats in the F_1 generation exposed to 33 ppm 2-chloro-1,3-butadiene 6 hours/day, 5 days/week for 13 weeks showed signs of growth retardation. There were no effects on reproduction at any exposure level. The lowest exposure level [10 ppm (36 mg/m^3)] constitutes a NOEL for this study and corresponds to a transformed animal dose of 4.6 mg/kg/day [36 mg/m^3 x 0.176 m^3/day (rat inhalation rate) x 1/0.245 kg (one/rat body weight) x 6 hours/24 hours x 5 days/7 days].

The Russian subchronic inhalation study by Sanotskii (1976) was not considered for RfD development because the exposure schedule was not given and because gonadotropic effects were reported in mice and rats at levels (0.15-1.69 mg 2-chloro-1,3-butadiene/m³) that were well below the exposure levels (36.2-90.4 mg 2-chloro-1,3-butadiene/m³) at which no gonadotropic effects were reported in reproduction rat studies by E.I. DuPont de Nemours and Co. (1985d,m).

The appropriate choice of the study for subchronic inhalation RfD development is that by E.I. DuPont de Nemours and Co. (1985a), in which a transformed animal dose of 5.0 mg/kg/day was associated with increased liver weight in female rats. This value constitutes the highest NOAEL in all of the subchronic inhalation studies summarized, below which there is no LOAEL. A subchronic inhalation RfD derived from this NOAEL, however, would be only slightly larger than the chronic inhalation RfD of 0.04 mg/kg/day [3 mg/day (0.1 mg/m³)] derived in Section 8.2.1.2. Because, in general, more confidence is placed in a chronic toxicity study and because the data base for 2-chloro-1,3-butadiene strongly indicates little difference in toxic potency or effects between subchronic and chronic exposure, it seems appropriate to adopt the chronic RfD as the subchronic RfD for this chemical.

Confidence in the subchronic inhalation RfD is high (Section 8.2.1.2.).

8.2.1.2. CHRONIC EXPOSURE -- Chronic inhalation toxicity information was found in two carcinogenicity studies by E.I. DuPont de Nemours and Co. (1985b,c) (see Sections 6.1.1.2. and 6.2.1.) and in a fetotoxicity/teratogenicity study by E.I. DuPont de Nemours and Co. (1985k) (see Section 6.4.).

Exposure of hamsters to 50 ppm 2-chloro-1,3-butadiene (181 mg/m³) 6 hours/day, 5 days/week for 18 months resulted in growth retardation (E.I. DuPont de Nemours and Co., 1985b). This exposure level represents a LOAEL, associated with a transformed animal dose of 30.7 mg/kg/day [i.e., 181

mg/m³ x 0.093 m³/day (hamster inhalation rate [U.S. EPA, 1986d]) x 1/0.098 kg (one/hamster body weight) x 6 hours/24 hours x 5 days/7 days]. There were no effects observed at the lowest exposure level used in this study [10 ppm (36 mg/m³)], and this therefore constitutes a NOAEL. This NOAEL corresponds to an animal transformed dose of 6.0 mg/kg/day [36 mg/m³ x 0.102 m³/day (hamster inhalation rate [U.S. EPA, 1986d]) x 1/0.109 kg (one/hamster body weight) x 6 hours/24 hours x 5 days/7 days].

In the second long-term carcinogenicity study (E.I. DuPont de Nemours and Co., 1985c) considered for chronic inhalation RfD development, rats were exposed to 2-chloro-1,3-butadiene [10 and 50 ppm (36 and 181 mg/m³)] 6 hours/day, 5 days/week for 2 years. The higher concentration (50 ppm) was associated with alopecia, retarded growth and mild hepatocellular lesions of uncertain biological significance. Decreased relative lung weight in both sexes and elevated relative liver weight in females were observed at both exposure concentrations. In the absence of histopathologic lesions at 10 ppm, however, these observations are considered nonadverse and 10 ppm is considered a NOAEL. This concentration is associated with a transformed animal dose of 4.0 mg/kg/day [average of male and female rats; i.e., 36 mg/m³ x 0.229 m³/day (average rat male/female inhalation rate [U.S. EPA, 1986d]) x 1/0.364 kg (one/average rat male/female body weight) x 6 hours/24 hours x 5 days/7 days].

A fetotoxicity/teratogenicity study by E.I. DuPont de Nemours and Co. (1985k) was considered, along with other chronic inhalation toxicity data, in the development of a chronic inhalation RfD for 2-chloro-1,3-butadiene. In this study, there were indications of fetotoxicity (i.e., decrease in fetal weight) in pregnant rats exposed to 75 ppm 2-chloro-1,3-butadiene (272 mg/m³) 6 hours/day on days 4-16 of gestation. This exposure corresponds to a transformed animal dose of 53.2 mg/kg/day [i.e., 272 mg/m³ x 0.147

m^3/day (rat inhalation rate [U.S. EPA, 1986d]) x 1/0.188 (one/rat body weight) x 6 hours/24 hours]. The next lower 2-chloro-1,3-butadiene exposure level (i.e., 25 ppm or 90.5 mg/m^3) represents a NOAEL for the fetus and corresponds to a transformed animal dose of 17.5 mg/kg/day [90.5 mg/m^3 x 0.152 m^3/day (rat inhalation rate [U.S. EPA, 1986d)]) x 1/0.197 kg (one/rat body weight) x 6 hours/24 hours].

Two chronic NOAELS, 6.0 mg/kg/day in hamsters and 4.0 mg/kg/day in rats, are available from studies of equal quality for consideration in deriving a chronic inhalation RfD (selection of either value over the other). In this case, the NOAEL of 4.0 mg/kg/day in rats is chosen as the basis for the RfD because rats may be slightly more sensitive than hamsters and there is no assurance that a LOAEL for rats may not occur below the NOAEL for hamsters. Division of this transformed dose by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive human populations) results in a chronic inhalation RfD for 2-chloro-1,3-butadiene of 0.04 mg/kg/day, or 3 mg/day for a 70 kg human. Dividing this RfD by a human 24-hour ventilatory volume of 20 m^3/day (U.S. EPA, 1986d) results in a chronic inhalation RfD of 0.1 mg/m^3.

Confidence in the chronic inhalation RfD is high. Data in hamsters and rats indicate that the compound is not carcinogenic. The key study was a well-designed and executed investigation that involved comprehensive gross and microscopic examination of sufficient numbers of rats of both sexes. Developmental toxicity, reproduction and chronic and subchronic toxicity studies using rats and hamsters support the NOAEL in rats.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Pertinent data regarding the systemic toxicity of 2-chloro-1,3-butadiene following subchronic oral administration were not located in the available literature

cited in Appendix A. It is possible, however, to calculate a subchronic oral RfD for 2-chloro-1,3-butadiene based on the subchronic inhalation RfD for the compound and using appropriate absorption factors for the various exposure routes. Assuming 50% absorption of 2-chloro-1,3-butadiene by the inhalation route and 100% absorption of the compound by the oral route the subchronic inhalation RfD of 0.04 mg/kg/day is multiplied by 0.5 to give a subchronic oral RfD of 0.02 mg/kg/day. Multiplication by the reference human body weight [70 kg (U.S. EPA, 1986d)] gives a subchronic oral RfD of 1.0 mg/day.

Confidence in the subchronic oral RfD for 2-chloro-1,3-butadiene is low. Although confidence in the inhalation toxicity data base is high, there is considerable uncertainty associated with route-to-route extrapolation.

8.2.2.2. **CHRONIC EXPOSURE** -- Pertinent data regarding the systemic toxicity of 2-chloro-1,3-butadiene following chronic oral exposure were not located in the available literature cited in Appendix A. A chronic oral RfD can be derived for 2-chloro-1,3-butadiene using the same approach as was used for deriving a subchronic oral RfD. Multiplying the chronic inhalation RfD (0.04 mg/kg/day) by an inhalation absorption factor of 0.5 gives a chronic oral RfD of 0.02 mg/kg/day. Multiplying the chronic oral RfD by the reference human body weight [70 kg (U.S. EPA, 1986d)] gives a chronic oral RfD of 1 mg/day. Confidence in the chronic oral RfD is low (see Section 8.2.2.1.). The above systemic toxicity risk assessment is based on results obtained from studies using pure 2-chloro-1,3-butadiene. This may not reflect the "real world" risk of exposure to 2-chloro-1,3-butadiene in the sense that oxidation products (which may be more toxic than the parent compound) may be a factor in actual exposures to 2-chloro-1,3-butadiene.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The systemic toxicity of 2-chloro-1,3-butadiene was discussed in Chapter 6 and is summarized in Table 9-1. Several chronic toxicity studies on 2-chloro-1,3-butadiene were found in the available literature that were considered adequate for RQ development.

The most severe effect in Table 9-1 is fetotoxicity (i.e., decrease in fetal weight) observed in the fetotoxicity/teratogenicity study by E.I. DuPont de Nemours and Co. (1985k). This effect occurred at an equivalent human dose of 7.4 mg/kg/day. Multiplication of this dose by the reference human body weight (70 kg) gives a MED of 518 mg/day, which corresponds to an RV_d of 1.4. The RV_e associated with the effect of decreased fetal weight is 8 and multiplication of this RV_e by the RV_d yields a CS of 11.2 (Table 9-2). This CS is associated with an RQ of 1000.

The next most severe effect observed was growth retardation, which occurred in rats exposed to 100 ppm for 26 weeks (E.I. DuPont de Nemours and Co., 1985a), hamsters and rats exposed to 50 ppm for 18 months and 2 years, respectively (E.I. DuPont de Nemours and Co., 1985b,c), and in the second (F_1) generation of rats exposed to 33 ppm for 10 weeks (E.I. DuPont de Nemours and Co., 1985m). Growth retardation rates an RV_e of 4. An RV_d of 2.2 was estimated from the human equivalent dosage of 2.3 mg/kg/day (MED = 161 mg/day) for rats exposed for 10 weeks in the reproduction study. No uncertainty factor was applied to expand from subchronic to chronic exposure because the toxic potency of 2-chloro-1,3-butadiene does not appear to increase in chronic exposure. A CS of 8.8 results (see Table 9-2).

TABLE 9-1

Inhalation Toxicity Summary for 2-Chloro-1,3-butadiene[a]

Species/Strain	Sex	No. at Start	Average Weight[b] (kg)	Exposure	Transformed Animal Dose[c] (mg/kg/day)	Transformed Human Dose[d] (mg/kg/day)	Response	Reference
Rat/Wistar	M/F	80	0.309 (M) 0.196 (F)	100 ppm (362 mg/m³) 6 hours/day, 5 days/week for 26 weeks	42.8 (M) 50.1 (F)	7.0 (M) 7.1 (F)	Increased relative kidney and liver weights (M/F), growth retardation (M), increased urine production (F), increased adrenal to body weight ratio (F)	E.I. DuPont de Nemours and Co., Inc., 1985a
	M/F	80	0.331 (M) 0.190 (F)	33 ppm (120 mg/m³) 6 hours/day, 5 days/week for 26 weeks	14 (M) 17 (F)	2.3 (M) 2.4 (F)	Increase in relative liver and kidney weight (F), body weight decrease (M)	E.I. DuPont de Nemours and Co., Inc., 1985a
	F	40	0.196	10 ppm (36 mg/m³) 6 hours/day, 5 days/for 26 weeks	5.0	0.7	Increase in relative liver weight	E.I. DuPont de Nemours and Co., Inc., 1985a
Hamster/Syrian golden	M/F	200	0.098	50 ppm (181 (mg/m³) 6 hours/day, 5 days/week for 18 months	31	3.5	Growth retardation	E.I. DuPont de Nemours and Co., Inc., 1985b
Rat/Wistar	M/F	200	0.419 (M) 0.239 (F)	50 ppm (181 mg/m³) 6 hours/day, 5 days/week for 2 years	19 (M) 23 (F)	3.4 (M) 3.5 (F)	Growth retardation, alopecia, foci of mild liver lesions, decrease in relative lung weight	E.I. DuPont de Nemours and Co., Inc., 1985c
	M/F	200	0.461 (M) 0.266 (F)	10 ppm (36 mg/m³) 6 hours/day, 5 days/week for 2 years	3.7 (M) 4.5 (F)	0.69 (M) 0.70 (F)	Decrease in relative lung weight (M/F), slightly increased relative liver weight (F)	E.I. DuPont de Nemours and Co., Inc., 1985c
Rats/NR	F	36	0.182	175 ppm (634 mg/m³) 6 hours/day on days 4-16 of gestation	125	17.2	Decreased fetal weight, retardation in bone development	E.I. DuPont de Nemours and Co., Inc., 1985k
	F	36	0.188	75 ppm (272 mg/m³) 6 hours/day on days 4-16 of gestation	53	7.4	Decreased fetal weight	E.I. DuPont de Nemours and Co., Inc., 1985k

TABLE [illegible]-1 (cont.)

Species/Strain	Sex	No. at Start	Average Weight[b] (kg)	Exposure	Transformed Animal Dose[c] (mg/kg/day)	Transformed Human Dose[d] (mg/kg/day)	Response	Reference
Rats/Wistar	M/F	50	0.237 (F_0 M) 0.150 (F_0 F)	100 ppm (362 mg/m³) 6 hours/day, 5 days/week for 13 weeks	46.9 (M) 54.7 (F)	7.0 (M) 7.1 (F)	Growth retardation	E.I. DuPont de Nemours and Co., Inc., 1985m
		80	0.255 (F_1 M) 0.167 (F_1 F)	33 ppm (120 mg/m³) 6 hours/day, 5 days/week for 10 weeks	15.2 (M) 17.5 (F)	2.3 (M) 2.3 (F)	Growth retardation	E.I. DuPont de Nemours and Co., Inc., 1985m

[a]Purity not reported

[b]Body weight estimated from data provided by investigators

[c]Calculated by multiplying the concentration in air by the animal inhalation rate [calculated from body weight according to methods of U.S. EPA (1980) and by the number of hours/day and days/week during which exposure took place. The result was then divided by the animal body weight].

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

NR = Not reported

TABLE 9-2

Inhalation Composite Scores for 2-Chloro-1,3-butadiene Using the Rat

Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
53	518	1.4	decreased fetal weight	8	11.2	1000	E.I. Dupont de Nemours and Co., Inc., 1985k
15.2 (male)	161	2.2	growth retardation	4	8.8	1000	E.I. DuPont de Nemours and Co., Inc., 1985m

Other effects summarized in Table 9-1, altered organ weights, mild histopathologic lesions in the liver and alopecia, were not more severe than those for which CSs have been calculated; hence, CSs are not calculated for these effects.

The effect chosen for RQ determination for 2-chloro-1,3-butadiene is decreased fetal weight observed in the developmental toxicity rat study by E.I. DuPont de Nemours and Co. (1985k). This effect yielded the highest CS (11.2) of the two considered for RQ determination, and this CS is associated with an RQ of 1000 (Table 9-3).

9.2. BASED ON CARCINOGENICITY

Data from several studies (E.I. DuPont de Nemours and Co., 1985b,c; Ponomarkov and Tomatis, 1980; Zil'fyan et al., 1975, 1977) indicated that 2-chloro-1,3-butadiene was not carcinogenic in animals following exposure either by the oral or inhalation route. Data from human epidemiological studies have been ambiguous in the sense that a significantly increased incidence of skin and lung cancer was reported in workers exposed to 2-chloro-1,3-butadiene in Russian studies (Khachatryan, 1972a,b), but the finding of increased lung cancer was not confirmed in a study of occupationally-exposed individuals by Pell (1978). In addition, these epidemiological studies, for reasons pointed out in Section 6.2.1., were not considered adequate to determine whether 2-chloro-1,3-butadiene exposure is associated with an increased risk of cancer in humans. Because there is evidence that 2-chloro-1,3-butadiene is not carcinogenic in animals, and inadequate evidence for carcinogenicity in humans, neither an inhalation nor an oral q_1* was derived for the compound. The lack of either an inhalation or oral q_1* for 2-chloro-1,3-butadiene and an inability to assign the

TABLE 9-3

2-Chloro-1,3-butadiene

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

Route:	inhalation
Dose*:	518 mg/day
Effect:	decreased fetal body weight
Reference:	E.I. DuPont de Nemours Co., Inc., 1985k
RV_d:	1.4
RV_e:	8
Composite Score:	11.2
RQ:	1000

*Equivalent human dose

compound to any potency group precludes a hazard ranking for 2-chloro-1,3-butadiene. Because a hazard ranking is not available, it is not possible to derive an RQ based on carcinogenicity for 2-chloro-1,3-butadiene.

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U.S. EPA 1984b. Methodology and Guidelines for Ranking Chemicals Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

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

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U.S. EPA. 1986c. Summary Overview of Health Effects Associated with Chloroprene: Health Issue Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC for the Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA/600-8-85/011F. NTIS PB86-197662.

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U.S. EPA. 1988. STORET Water Quality Database. On-line: January 1988.

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Zil'fyan, V.N., B.S. Fichidzhyan and A.M. Pogosova. 1975. Results of testing chloroprene for carcinogenicity. Zh. Eksp. Klin. Med. 15: 54-57. (Rus.) (Cited in IARC, 1979)

Zil'fyan, V.N., B.S. Fichidzhyan, D.K. Garibyan and A.M. Pogosova. 1977. Experimental study of chloroprene for carcinogenicity. Vop. Onkol. 23: 61-65. (Rus.) (Cited in IARC, 1979)

APPENDIX A

LITERATURE SEARCHED

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

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

These searches were conducted in October 1987, and the following secondary sources were reviewed:

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

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

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

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

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

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

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

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

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

NTP (National Toxicology Program). 1987. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX B

Summary Table for 2-Chloro-1,3-butadiene

	Species	Exposure[a] (mg/kg/day)	Effect	RfD (mg/kg/day)	Reference
Inhalation Exposure					
Subchronic	rat	4.0	retarded growth and mild hepatocellular lesions at next higher exposure level	0.04	E.I. DuPont de Nemours and Co., Inc.,1985c
Chronic	rat	4.0	retarded growth and mild hepatocellular lesions at next higher exposure level	0.04	E.I. DuPont de Nemours and Co., Inc.,1985c
Carcinogenicity	ID	ID	ID	ID	NA
Oral Exposure					
Subchronic	rat	ID	ID	0.02[b]	E.I. DuPont de Nemours and Co., Inc.,1985c
Chronic	rat	ID	ID	0.02[b]	E.I. DuPont de Nemours and Co., Inc., 1985c
Carcinogenicity	ID	ID	ID	ID	NA

REPORTABLE QUANTITIES		
Based on chronic toxicity:	1000	E.I. DuPont de Nemours and Co., Inc., 1985k
Based on carcinogenicity:	ID	NA

[a]Transformed animal dose

[b]Estimated from inhalation data

ID = Insufficient data; NA = not applicable