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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT
FOR 1,3-BUTADIENE

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

Prepared by

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

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

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

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

EXECUTIVE SUMMARY

1,3-Butadiene is a colorless gas with a mild aromatic odor at ambient temperatures (Hawley, 1981). It is soluble in most common organic solvents, but is almost insoluble in water (Kirshenbaum, 1978; McAuliffe, 1966). In 1985, 10 U.S. manufacturers produced 2.3 billion pounds of rubber-grade 1,3-butadiene (USITC, 1986). U.S. production of all grades of butadiene in both 1985 and 1986 was estimated to be ~2.5 billion pounds (C&E News, 1986). 1,3-Butadiene is used predominantly in the production of synthetic rubbers and elastomers (CMR, 1985).

1,3-Butadiene is not expected to be a persistent environmental compound. When released to the atmosphere, it will oxidize rapidly with several oxidant species. The dominant atmospheric removal process will be reaction with hydroxyl radicals, which has an estimated half-life of 2.6 hours in a normal atmosphere. If released to the aquatic environment, volatilization and oxidation (by singlet oxygen) are expected to be the significant environmental fate processes. The estimated volatilization half-life of 1,3-butadiene from a river 1 m deep flowing 1 m/sec is ~2.2 hours. The estimated half-life of the reaction with singlet oxygen in sunlit natural water is ~1 day. Aquatic hydrolysis, direct photolysis, adsorption to sediment and bioconcentration are not expected to be significant; if released to soil, significant evaporation is likely to occur. Based on estimated K_{oc} values (116-288), any residual 1,3-butadiene in soil is susceptible to significant leaching.

Atmospheric emission sources of 1,3-butadiene include industrial effluent and fugitive emissions, forest fires and exhausts from automobiles, diesel engines and jet turbines (Graedel, 1978; Hayano et al., 1985; Hughes

et al., 1979; Katzman and Libby, 1975). Based on available monitoring data (see Table 3-1), a typical ambient air concentration of 1,3-butadiene in a U.S. urban/suburban area is ~1-2 ppb. Assuming an ambient air concentration of 1.5 ppb, an average daily inhalation intake of 66 μg has been estimated for the U.S. urban/suburban population. An NIOHS conducted between 1972 and 1974 estimated that ~65,000 U.S. workers are potentially exposed to 1,3-butadiene (NIOSH, 1984).

The only available information concerning the toxicity of 1,3-butadiene to aquatic biota was a 24-hour LC_{50} of 71.5 mg/ℓ for pinperch, Lagodon rhomboides (Daugherty and Garret, 1951).

1,3-Butadiene is absorbed after inhalation by B6C3F1 mice and Sprague-Dawley rats (Bond et al., 1986). Estimates of absorption were ≥4-20% of inhaled dose for mice and >1.5-17% for rats exposed to very high concentrations.

Following inhalation, 1,3-butadiene is distributed to the brain, liver, kidney and spleen of rats at nearly equivalent levels, and very high levels are found in the perinephric fat (Shugaev, 1969). 1,3-Butadiene was also found to distribute to the mouse brain and the central nervous system of the cat following inhalation exposure (Shugaev, 1969).

The primary in vivo metabolites of 1,3-butadiene in the blood of rats and mice following inhalation exposure appear to be 1,2-epoxy-3-butene and butadiene diepoxide (Bond et al., 1986). Saturation of the metabolic elimination mechanism for 1,3-butadiene was approached at inhalation exposure levels >1000 ppm (2200 mg/m³) in both Sprague-Dawley rats and B6C3F1 mice (Kreiling et al., 1986a,b; Filser and Bolt, 1984). The maximal metabolic rate of elimination of 1,3-butadiene (V_{max}), however, was found to be approximately twice as high in mice as in rats. Exhalation of 1,3-butadiene

monoxide and acetone has been demonstrated in rats exposed to 1,3-butadiene by inhalation (Filser and Bolt, 1984). The primary in vitro metabolites of 1,3-butadiene(using rat liver microsomes) are 1,3-epoxybutene-3, 3-butene-1,2-diol, diepoxybutene and 3,4-epoxy-1,2-butanediol (Malvoisin and Roberfroid, 1982).

Excretion of radioactivity derived from inhaled radiolabeled 1,3-butadiene was determined to be primarily in the urine and exhaled air of 1,3-butadiene-exposed Sprague-Dawley rats and B6C3F1 mice (Bond et al., 1986). These routes of elimination accounted for ~75-85% of the total ^{14}C eliminated.

The toxicity of 1,3-butadiene following inhalation exposure appears to depend on the species of animal. Adverse effects attributable to 1,3-butadiene exposure were practically nonexistent except for increased salivation observed in female Sprague-Dawley rats exposed to 8000 ppm (17,698 mg/m^3); 6 hours/day, 5 days/week for 13 weeks (Crouch and Pullinger, 1978; Crouch et al., 1979) and in rabbits and dogs exposed to 6700 mg/m^3, 7.5 hours/day, 6 days/week for 8 months (Carpenter et al., 1944). The bone marrow appears to be a target site for 1,3-butadiene toxicity in B6C3F1 and NIH mice (Irons et al., 1986a,b; Leiderman et al., 1986). A 1,3-butadiene-induced macrocytic-megaloblastic anemia was observed in B6C3F1 and NIH mice exposed to 1250 ppm (2765 mg/m^3), 6 hours/day, 5-6 days/week for as few as 6 weeks (Irons et al, 1986a,b; Leiderman et al., 1986). Chronic inhalation exposure to 1,3-butadiene at $\geq$625 ppm (1383 mg/m^3), 6 hours/day, 5 days/week for 60 weeks caused gonadal atrophy in both sexes of B6C3F1 mice (NTP, 1984). Nonneoplastic lesions of the nasal cavity of male mice occurred at 1250 ppm (2765 mg/m^3) (NTP, 1984).

Several epidemiological studies (McMichael et al., 1974; Andjelkovich et al., 1976; Matanoski et al., 1982) associate work in the SBR industry with excess risk of cancers of the hematopoietic and lymphatic systems, but concurrent exposure to potential carcinogens other than 1,3-butadiene also occurred. Long-term inhalation carcinogenicity studies performed with B6C3F1 mice (NTP, 1984) and Sprague-Dawley rats (Hazleton Laboratories, 1981a) confirmed that 1,3-butadiene is carcinogenic in these species. Rats exhibited an increased incidence of the following tumors: Leydig cell adenomas, exocrine adenomas of the pancreas, multiple mammary gland tumors, follicular cell adenomas and carcinomas of the thyroid, and stromal sarcomas of the uterus-cervix. The most prevalent tumor types in B6C3F1 mice were malignant lymphomas associated with the hematopoietic system, and hemangiosarcomas. This mouse strain is not only much more sensitive in terms of a carcinogenic response than is the Sprague-Dawley rat, but the tumor sites also differ in the two species. Several hypotheses for these differences have been postulated, including a faster rate of 1,3-butadiene metabolism by the mouse (Kreiling et al., 1986a,b); limited detoxification by the mouse leading to greater accumulation of the primary reactive metabolite, 1,2-epoxybutene-3 (Kreiling et al., 1987); a lower absorption rate in the rat vs. the mouse (Bond et al., 1986); and the presence of an endogenous virus (MuLV) in the B6C3F1 mouse strain, which may act in combination with butadiene to yield increased luekemia-lymphoma response (Irons et al., 1986a).

1,3-Butadiene is mutagenic in bacteria with activation (DeMeester et al., 1980) and induces chromosomal aberrations and SCE in mice (Tice et al., 1987). Data from Hazleton Laboratories (1981b) indicate that 1,3-butadiene is a teratogen when pregnant female rats are exposed by inhalation at 8000 ppm (17,698 mg/m^3), 6 hours/day during organogenesis.

1,3-Butadiene has been classified as an EPA Group B2 compound, probable human carcinogen. A q_1^* of 2.4×10^{-1} $(ppm)^{-1}$ or 1.8 $(mg/kg/day)^{-1}$ expressed as internal dosage [or 9.0 $(mg/kg/day)^{-1}$ assuming 20% absorption via inhalation and 100% absorption from the gut] was derived as the geometric mean of q_1^*s developed from the data in male and female mice in the NTP (1984) inhalation study. An RQ of 1000 was derived for systemic toxicity from a chronic inhalation rat study (Hazleton Laboratories, 1981a). An RQ of 10 was based on carcinogenicity in male mice (NTP, 1984).

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

TABLE OF CONTENTS (cont.)

LIST OF TABLES

LIST OF ABBREVIATIONS

ADP	Adenosine 5'-diphosphate
ATP	Adenosine 5'-triphosphate
BCF	Bioconcentration factor
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NOAEL	No-observed-adverse-effect level
NOHS	National Occupational Hazard Survey
PEL	Permissible exposure level
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SBR	Styrene-butadiene rubber
SCE	Sister-chromatid exchange
TLV	Threshold limit value
UDS	Unscheduled DNA synthesis
v/v	Volume per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1,3,-Butadiene is the common name for the chemical also known as butadiene, biethylene, bivinyl, divinyl, trans-butadiene, erythrene, pyrrolylene, vinylethylene and buta-1,1-diene (SANSS, 1987). The structure, molecular weight, empirical formula and CAS Registry number for 1,3-butadiene are as follows:

$$CH_2=CH-CH=CH_2$$

Molecular weight: 54.09

Empirical formula: C_4H_6

CAS Registry Number: 106-99-0

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,3-Butadiene is a colorless gas with a mild aromatic odor at ambient temperatures (Hawley, 1981). It is soluble in ethanol and methanol and readily soluble in most other common organic solvents (Kirshenbaum, 1978). Selected physical properties of 1,3-butadiene are listed below:

Melting point:	-108.9°C	Kirshenbaum, 1978
Boiling point:	-4.41°C	Kirshenbaum, 1978
Specific gravity: (liquid at 20°C)	0.6211	Hawley, 1981
Vapor pressure, atm:		
at -4.5°C	1	Perry and Green, 1984
at 14.5°C	2	Perry and Green, 1984
at 47.0°C	5	Perry and Green, 1984
Water solubility:		
at 25°C	735 ppm	McAuliffe, 1966
Log K_{ow}:	1.99	Hansch and Leo, 1981
Air odor threshold:	1.6 ppm	Amoore and Hautala, 1983

Flash point:	-76°C	Hawley, 1981
Air conversion factors at 20°C:	1 mg/m³ = 0.445 1 ppm = 2.212 mg/m³	

Although 1,3-butadiene is a gas at normal temperatures and pressures, it is easily liquified (Hawley, 1981). The liquid material polymerizes readily, particularly in the presence of oxygen, and the commercial material usually contains an inhibitor to prevent spontaneous polymerizaton during shipping and handling (Hawley, 1981; Kirshenbaum, 1978). Butadiene undergoes addition, substitution, oxidation and Diels-Alder reactions and can be hydrogenated to butene and butane (Kirshenbaum, 1978).

1.3. PRODUCTION DATA

In 1985, 10 U.S. manufacturers produced 2.3 billion pounds of rubber-grade 1,3-butadiene (USITC, 1986). U.S. production of all grades of butadiene in both 1985 and 1986 was estimated to be ~2.5 billion pounds (C&E News, 1986). 1,3-Butadiene is produced by the following manufacturers, with a combined annual capacity of 3.755 billion pounds (SRI, 1986):

Company	Location
Amoco Corp.	Chocolate Bayou, TX
Atlantic Richfield	Channelview, TX
Dow Chemical	Freeport, TX
DuPont	Chocolate Bayou, TX
El Paso Products	Corpus Christi, TX
Exxon Corp.	Baton Rouge, LA
Exxon Corp.	Baytown, TX
Mobil Corp.	Beaumont, TX
Shell Oil	Deer Park, TX
Shell Oil	Norco, LA
Texaco	Port Neches, TX
Texas Olefins	Houston, TX

Current exports of 1,3-butadiene total ~125 million pounds/year, with imports totaling ~500 million pounds/year (C&E News, 1986).

1,3-Butadiene is manufactured by steam cracking of naphtha and gas oil fractions, which produce butadiene and ethylene as co-products, or by the catalytic dehydrogenation of n-butene and n-butane (Kirshenbaum, 1978). The steam cracking process is the predominant U.S. production process (SRI, 1986). The isomeric 1,2-butadiene is sometimes found as a contaminant of 1,3-butadiene (Kirshenbaum, 1978).

1.4. USE DATA

The use pattern for 1,3-butadiene was estimated in CMR (1985) as follows: styrene-butadiene rubber, 37%; polybutadiene rubber, 22%; adiponitrile/HMDA (hexamethylenediamine), 11%; styrene-butadiene latexes, 9%; neoprene, 7%; ABS resins, 5%; exports, 4%; nitrile rubber, 3% and other, 2%. The dominant use is the production of synthetic rubbers and elastomers; the miscellaneous uses include use as a chemical intermediate for the production of 1,4-hexadiene and 1,5,9-cyclodecatriene (Kirshenbaum, 1978).

1.5. SUMMARY

1,3-Butadiene is a colorless gas with a mild aromatic odor at ambient temperatures (Hawley, 1981). It is soluble in most common organic solvents, but is almost insoluble in water (Kirshenbaum, 1978; McAuliffe, 1966). In 1985, 10 U.S. manufacturers produced 2.3 billion pounds of rubber-grade 1,3-butadiene (USITC, 1986). U.S. production of all grades of butadiene in both 1985 and 1986 was estimated to be ~2.5 billion pounds (C&E News, 1986). 1,3-Butadiene is used predominantly in the production of synthetic rubbers and elastomers (CMR, 1985).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Because of its very high vapor pressure, 1,3-butadiene will exist entirely in the vapor phase in the atmosphere. It is extremely reactive with various atmospheric oxidants and, therefore, does not persist in the atmosphere. Although 1,3-butadiene is transformed rapidly in the atmosphere, it has been detected as a commonly occurring atmospheric contaminant (Section 3.3.), probably because of its continual emission to the atmosphere from automobile exhaust, diesel exhaust and other sources.

2.1.1. Reaction with Hydroxyl Radicals. The recommended rate constant for the vapor-phase reaction of 1,3-butadiene with photochemically produced hydroxyl radicals in the atmosphere is 6.68×10^{-11} cm³/molecule-sec at 25°C (Atkinson, 1985). Assuming an average atmospheric hydroxyl radical concentration of 8×10^{5} molecules/cm³ (U.S. EPA, 1987), the estimated half-life is 3.6 hours, which indicates that reaction with hydroxyl radicals will be the dominant atmospheric removal process.

2.1.2. Reaction with Ozone. The recommended rate constant for the vapor-phase reaction of 1,3-butadiene with ozone in the atmosphere is 8.1×10^{-18} cm³/molecule-sec at 25°C (Atkinson and Carter, 1984). Assuming an average atmospheric ozone concentration of 6×10^{11} molecules/cm³ (U.S. EPA, 1987), the estimated half-life is ~40 hours. Acrolein has been identified as one of the products of the reaction of 1,3-butadiene with ozone (Niki et al., 1983).

2.1.3. Reaction with Atomic Oxygen. The rate constant for the vapor-phase reaction of 1,3-butadiene with atomic oxygen (O^3P) in the atmosphere is 19.4×10^{-12} cm³/molecule-sec at 24°C (Atkinson and Pitts, 1977). Assuming an average atmospheric atomic oxygen concentration of 2.5×10^{4} molecules/cm³ (Graedel, 1978), the estimated half-life is ~16.5 days.

2.1.4. **Reaction with Nitrate Radical.** The reaction with nitrate radicals has been recognized as a potentially important night-time environmental sink for some chemicals. The rate constant for the vapor-phase reaction of 1,3-butadiene in the atmosphere is 5.34×10^{-14} cm^3/molecule-sec at 22°C (Atkinson et al., 1984). Assuming an average atmospheric nitrate radical concentration of 2.4×10^4 molecules/cm^3 (Atkinson et al., 1984), the estimated half-life is ~15 hours.

2.2. **WATER**

2.2.1. **Hydrolysis.** 1,3-Butadiene does not contain hydrolyzable functional groups; therefore, it is considered inert to environmental hydrolysis (Jaber et al., 1984).

2.2.2. **Photolysis/Photooxidation.** Direct photolysis is not environmentally significant with respect to 1,3-butadiene (Jaber et al., 1984).

Jaber et al. (1984) estimated the aquatic oxidation rate constants for the reaction of 1,3-butadiene with peroxy radicals and singlet oxygen to be 2/M-sec and 1×10^7 M-sec, respectively. Assuming that the concentrations of peroxy radicals and singlet oxygen in sunlit natural water are 10^{-9} M and 10^{-12} M, respectively (Mabey et al., 1981), the corresponding half-lives for 1,3-butadiene are 11 years and 1 day. Therefore, reaction with singlet oxygen is a potentially significant removal mechanism.

2.2.3. **Microbial Degradation.** Limited data are available pertaining to the environmental biodegradation of 1,3-butadiene. Thom and Agg (1975) listed 1,3-butadiene as biodegradable under typical biological sewage treatment conditions as long as suitable acclimation is achieved. A Nocardia species isolated from soil has been found to use 1,3-butadiene as a sole carbon and energy source (Watkinson and Sommerville, 1976).

2.2.4. **Volatilization.** Based on measured water-to-air equilibria data (Hine and Mookerjee, 1975), the Henry's Law constant for 1,3-butadiene at 25°C is 0.0617 atm-m³/mole. This value of Henry's Law constant indicates that volatilization from water will be rapid. Using the method outlined in Lyman et al. (1982), the estimated volatilization half-life of 1,3-butadiene from a river 1 m deep flowing at 1 m/sec with a wind velocity of 3 m/sec is ~2.2 hours. The volatilization rate from deeper or less rapidly moving bodies of water will be slower.

2.2.5. **Adsorption.** Based on the estimated K_{oc} values from Section 2.3., 1,3-butadiene is not expected to partition significantly from the water column to sediment or suspended particulate matter.

2.2.6. **Bioconcentration.** The BCF values of an organic chemical can be estimated from the following regression equations (Lyman et al., 1982):

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

$$\log BCF = 2.791 - 0.564 \log WS \text{ (in ppm)} \quad (2\text{-}2)$$

For 1,3-butadiene, the BCF values calculated from Equations 2-1 and 2-2 are ~19 and 17, respectively, based on a log K_{ow} of 1.99 and a water solubility of 735 ppm. These BCF values indicate that 1,3-butadiene is not expected to bioconcentrate significantly in aquatic organisms.

2.3. SOIL

Pertinent data regarding the chemical or microbial degradation of 1,3-butadiene in soil could not be located in the available literature as cited in Appendix A.

2.3.1. **Adsorption.** The K_{oc} of an organic chemical can be estimated from the following regression equations (Lyman et al., 1982):

$$\log K_{oc} = 3.64 - 0.55 \log WS \text{ (in ppm)} \quad (2\text{-}3)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \quad (2\text{-}4)$$

For 1,3-butadiene, the K_{oc} values calculated from Equations 2-3 and 2-4 are 116 and 288, respectively, based on a water solubility of 735 ppm and a log K_{ow} of 1.99. These K_{oc} values indicate high to medium soil mobility (Swann et al., 1983); 1,3-butadiene is susceptible to significant leaching in most soils.

2.3.2. Volatilization. Because 1,3-butadiene is a gas at normal temperatures and pressures, rapid evaporation from dry surfaces can be expected. In addition, 1,3-butadiene volatilizes rapidly from water (see Section 2.2.4.), which suggests significant evaporation from moist soil surfaces.

2.4. SUMMARY

1,3-Butadiene is not expected to be a persistent environmental compound. When released to the atmosphere, it will oxidize rapidly with several oxidant species. The dominant atmospheric removal process will be reaction with hydroxyl radicals, which has an estimated half-life of 2.6 hours in a normal atmosphere. If released to the aquatic environment, volatilization and oxidation (by singlet oxygen) are expected to be the significant environmental fate processes. The estimated volatilization half-life of 1,3-butadiene from a river 1 m deep flowing 1 m/sec is ~2.2 hours. The estimated half-life of the reaction with singlet oxygen in sunlit natural water is ~1 day. Aquatic hydrolysis, direct photolysis, adsorption to sediment and bioconcentration are not expected to be significant; if released to soil, significant evaporation is likely. Based on estimated K_{oc} values (116-288), any residual 1,3-butadiene in soil is susceptible to significant leaching.

3. EXPOSURE

An NOHS conducted between 1972 and 1974 estimated that ~65,000 U.S. workers may be exposed to 1,3-butadiene (NIOSH, 1984). Surveys conducted by NIOSH at six user facilities found worker exposure levels of 0.06-39 ppm (0.13-86 mg/m^3), significantly below the OSHA standard of 1000 ppm (2200 mg/m^3) (OSHA, 1985).

3.1. WATER

Ewing et al. (1977) collected surface water samples from 204 sites near heavily industrialized areas across the United States and analyzed the samples for a wide variety of contaminants. 1,3-Butadiene was identified in only one sample. The U.S. EPA STORET data base contained only one reporting station for 1,3-butadiene; the reported level of 1,3-butadiene was 3 ppb.

3.2. FOOD

Pertinent food monitoring data could not be located in the available literature as cited in Appendix A.

3.3. INHALATION

Ambient air monitoring data for 1,3-butadiene are presented in Table 3-1. These data indicate that the general population in urban/suburban areas is typically exposed to an ambient air concentration of 1.5 ppb (3.3 μg/m^3) and an average intake of 20 m^3 of air/day, resulting in an average daily inhalation intake of ~66 μg.

1,3-Butadiene is emitted to the atmosphere in automobile and diesel exhaust, in incomplete combustion products from forest fires, from effluents and fugitive emissions from industrial manufacturing processes and in jet turbine exhausts (Graedel, 1978; Hayano et al., 1985; Hughes et al., 1979; Katzman and Libby, 1975). It has also been identified in tobacco smoke (Graedel, 1978).

TABLE 3-1

Ambient Air Monitoring Data for 1,3-Butadiene

Location	Sampling Dates	Concentration (ppb)	Comments	Reference
Houston, TX	Sept. 1973 - April 1974	0-33.3 (24.8 average)	Sampling locations included industrial areas and tunnels; average concentration reflects 16/20 samples with detectable levels of the compound	Lonnemen et al., 1979
Texas (five cities) and Denver, CO	Sept. 1973 - April 1974	1.7 (mean) from urban/suburban areas and 4.2 (mean) for source-dominated areas	Only data considered acceptable by the authors were used	Brodzinsky and Singh, 1982
Riverside, CA	1965-1966	<0.1-9	A total of nine stations monitored	Stephens and Burleson, 1967
Los Angeles, CA	August - November 1960	0-9 (~3 average)	Sampling done in central business district	Neligan, 1962
Lake Michigan	August 1976	0-1	Concentration reflects a maximum value since cis-2-butene could not be separated from 1,3-butadiene	Miller and Alkezweeny, 1980
Rio Blanco, CO Great Smokey Mountains, TN	July - September 1978	0-3.5 0-0.6	Concentration reflects a maximum value since cis-2-butene could not be separated from 1,3-butadiene	Arnts and Meeks, 1981
Jones State Forest, TX (38 miles north of Houston)	January 1978	0.1-4.9 ppm (carbon)	Concentration reflects a maximum value since cis-2-butene could not be separated from 1,3-butadiene	Sella, 1979
Rural Northwest, NC	Sept. 1981 - Oct. 1982	0.0-4.4 (carbon)	A total of six locations monitored	Sella et al., 1984
St. Petersburg/Tampa, FL Everglades, FL	May 1976	0-0.9	NC	Lonneman et al., 1978

NC = No comment

3.4. DERMAL

Pertinent dermal monitoring data could not be located in the available literature as cited in Appendix A.

3.5. SUMMARY

Atmospheric emission sources of 1,3-butadiene include industrial effluent and fugitive emissions, forest fires and exhausts from automobiles, diesel engines and jet turbines (Graedel, 1978; Hayano et al., 1985; Hughes et al., 1979; Katzman and Libby, 1975). Based on available monitoring data (see Table 3-1), a typical ambient air concentration of 1,3-butadiene in a U.S. urban/suburban area is ~1-2 ppb. Assuming an ambient air concentration of 1.5 ppb, an average daily inhalation intake of 66 μg has been estimated for the U.S. urban/suburban population. An NOHS conducted between 1972 and 1974 estimated that ~65,000 U.S. workers are potentially exposed to 1,3-butadiene (NIOSH, 1984).

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

The only available information regarding the toxicity of 1,3-butadiene to aquatic biota was a 24-hour LC_{50} of 71.5 mg/ℓ for pin perch, Lagodon rhomboides, a marine fish species (Daugherty and Garrett, 1951).

4.2. CHRONIC EFFECTS

Pertinent data regarding the chronic toxicity of 1,3-butadiene to aquatic organisms could not be located in the available literature as cited in Appendix A.

4.3. PLANT EFFECTS

Pertinent data regarding the effects of 1,3-butadiene on aquatic plants could not be located in the available literature as cited in Appendix A.

4.4. SUMMARY

The only available information concerning the toxicity of 1,3-butadiene to aquatic biota was a 24-hour LC_{50} of 71.5 mg/ℓ for pinperch, Lagodon rhomboides (Daugherty and Garret, 1951).

5. PHARMACOKINETICS

5.1. ABSORPTION

In preliminary experiments, NTP (1985a) investigated the inhalation absorption of ^{14}C-1,3-butadiene in rats and mice exposed nose-only to concentrations of 7-7100 ppm (15.45-15,675 mg/m^3) for 6 hours. Following exposure the animals were placed in metabolism cages for measurement of excreted radioactivity. Based on the excretion of radioactivity and plethysmographic data obtained from other animals similarly exposed, the investigators estimated respiratory retention of 7.1, 3.1 and 1.5% of the inhaled dosage in rats exposed to 70, 930 and 7100 ppm (154.5, 2053 and 15,675 mg/m^3) and 54, 9.6 and 4.7% in mice exposed to 7, 80 and 1040 ppm (15.45, 176.6 and 2296 mg/m^3), respectively.

In a published version of these and additional inhalation absorption studies, Bond et al. (1986) exposed Sprague-Dawley rats and B6C3F1 mice for 6 hours to various concentrations of ^{14}C-1,3-butadiene (four to six animals at each concentration) by nose only inhalation. The concentrations of 1,3-butadiene for rats were 0.14, 1.4, 12.1, 134, 1720 and 12,700 mg/m^3. Exposure concentrations for mice were 0.14, 1.4, 12.1, 145 and 1870 mg/m^3. At the end of the exposure period, the rats and mice were sacrificed and placed individually in a desiccator containing enough tetraethyl ammonium hydroxide to digest the carcass. Volatile radioactivity liberated during the digestion process was measured in the atmosphere of the desiccator, and samples of the digest were taken to measure radioactivity remaining in the carcass. Total ^{14}C retained in the animals at the end of the 6-hour exposure period was estimated as the sum of the volatile radioactivity and the radioactivity in the digest. This method [of measuring the absorption and retention of ^{14}C-labeled 1,3-butadiene and unidentified

metabolites] indicated that the percentage of inhaled 1,3-butadiene retained in the animals as [^{14}C]-1,3-butadiene equivalents [at the end of the 6-hour exposure] ranged from 4-20% in mice and from 1.5-17% in rats. These figures are measurements of radioactivity retained by the animal at the end of the 6-hour exposure period and do not include any 1,3-butadiene or metabolites absorbed and exhaled during the exposure period. When these data were normalized to body weight for each species, the amount of 1,3-butadiene and metabolites accumulated at the end of the 6-hour exposure period (in terms of μmol [^{14}C]-1,3-butadiene equivalent/kg) was significantly larger in mice (0.2-650 μmol/kg) than in rats (0.08-160 μmol/kg) over the range of 1,3-butadiene concentrations used (0.14-1800 mg/m^3).

Data were not located regarding the absorption of 1,3-butadiene from the gastrointestinal tract. In the absence of data to the contrary it is prudently conservative to assume 100% absorption for purposes of risk assessment.

5.2. DISTRIBUTION

The distribution of 1,3-butadiene in various organs of the rat, in the brain of the mouse and in the central nervous system of the cat was studied by Shugaev (1969). Animals were exposed for 2 or 4 hours to concentrations approximating the 2- or 4-hour LC_{50}. Animals that died were not used to determine 1,3-butadiene in organs. Following inhalation exposure to 1,3-butadiene, the organs were removed and homogenized, and extracted with ether, benzene or iso-octane. The extracts were then analyzed for butadiene in the brain, liver, kidney and spleen of the rat at essentially equivalent levels (36.3-51.4 mg %), and higher levels of butadiene were found in the perinephric fat (152 mg %). 1,3-Butadiene was found in the brain of the

mouse following inhalation exposure and was fairly evenly distributed throughout the central nervous system of the cat. In this study (Shugaev, 1969), the elimination of butadiene from the brain and liver of the rat was examined by exposing animals to butadiene by inhalation for 1 hour, and then sacrificing the animals and determining the tissue concentrations of butadiene at various times (0.1, 15, 30, 60 and 90 minutes) after termination of exposure. Butadiene concentrations decreased steadily in the brain and liver; in rats sacrificed 90 minutes after termination of exposure, only trace amounts of butadiene were found in the liver and brain.

5.3. METABOLISM

In a study by Bond et al. (1986) (see Section 5.1.), B6C3F1 mice and Sprague-Dawley rats were exposed by nose only inhalation to ^{14}C-1,3-butadiene, labeled in the number 1 carbon atom. Concentrations of 1,3-butadiene used for rats were 134 and 1720 mg/m^3 for rats, and 14.2, 145 and 1870 mg/m^3 for mice. After 2, 4 or 6 hours of exposure, groups of three animals were withdrawn from the inhalation chamber and blood samples were immediately taken and analyzed for 1,3-butadiene and metabolites. Ninety percent of the total ^{14}C measured in the blood consisted of volatile butadiene metabolites (1,2-epoxy-3-butene and butadiene diepoxide) and nonvolatile metabolites (unidentified). The parent compound 1,3-butadiene and radioactive $^{14}CO_2$, derived from 1,3-butadiene, were also found. Species differences in metabolism were found at inhaled 1,3-butadiene concentrations of ~130 and 1800 mg/m^3. Mice had significantly higher blood concentrations of 1,2-epoxy-3-butene than did rats, and rats had significantly higher concentrations of $^{14}CO_2$ in the blood than did mice. 1,3-Butadiene and diepoxybutene concentrations were similar.

A study of the rate of metabolism of 1,3-butadiene in male B6C3F1 mice was performed by Kreiling et al. (1986a,b) using a gas uptake method. This method involved placing a group of mice (usually eight) in a desiccator containing initial butadiene concentrations of between 10 ppm (22 mg/m^3) and 5000 ppm (11,061 mg/m^3) and following the disappearance of 1,3-butadiene (by gas chromatography) from the desiccator atmosphere over time. That disappearance of 1,3-butadiene from the desiccator atmosphere is a measure of the metabolic elimination rate of butadiene in the mice is supported by the observation that pretreatment with dithiocarb, a metabolic inhibitor, decreases the rate of disappearance of 1,3-butadiene. The metabolic elimination rate constants determined for mice were compared with those determined for rats using a similar gas uptake technique (Bolt et al., 1984). At all exposure concentrations, mice metabolized 1,3-butadiene faster than did rats. The metabolic elimination rate for butadiene in mice was proportional to exposure concentrations up to 1000 ppm (2212 mg/m^3). At exposure concentrations >1000 ppm, metabolic elimination of 1,3-butadiene in mice approached saturation, and a V_{max} for the 1,3-butadiene elimination rate was calculated to be 400 $\mu mol \cdot h^{-1} kg^{-1}$. In rats (Bolt et al., 1984), the metabolic elimination rate was also proportional to exposure concentrations up to ~1000 ppm (2212 mg/m^3). Above 1000 ppm, the metabolic elimination of 1,3-butadiene in rats approached saturation, but the calculated V_{max} for rats (220 $\mu mol \cdot h^{-1} kg^{-1}$) was well below that calculated for mice. Bolt et al. (1984) also observed that pretreatment of rats with Aroclor 1254 to induce the 1,3-butadiene metabolizing enzyme (presumably cytochrome P-450) increased the V_{max} of the 1,3-butadiene elimination mechanism. In the Aroclor-pretreated rats, saturation of this elimination mechanism was not observed up to exposure concentrations of 12,000 (26,547 mg/m^3) 1,3-butadiene.

When Sprague-Dawley rats were exposed in an inhalation chamber (desiccator) to concentrations of 1,3-butadiene (>2000 ppm or 4425 mg/m^3), which are much larger than those required to achieve saturation of the 1,3-butadiene metabolism mechanism, the exhalation of butadiene monoxide by the rats was demonstrated (Filser and Bolt, 1984).

In vitro experiments using liver microsomal preparations from rats and an NADPH-generating system demonstrated that 1,3-butadiene is metabolized to 1,2-epoxybutene-3 (Malvoisin et al., 1979). Pretreatment of rats with phenobarbital before preparation of liver microsomes increased the rate of oxidation of 1,3-butadiene to 1,2-epoxybutene-3 by the microsomal preparation, and treatment of microsomal preparation with SkF 525A inhibited the butadiene epoxidase activity and strengthened the case for the involvement of cytochrome P-450 in the microsomal epoxidation of 1,3-butadiene. 1,3-Epoxybutene-3 undergoes further metabolism in vitro and reacts with microsomal epoxide hydratase to form 3-butene-1,2-diol (Malvoisin and Roberfroid, 1982; Malvoisin et al., 1982) or 1,2-epoxybutene-3 may undergo a second oxidation reaction to form diepoxybutene (Malvoisin and Roberfroid, 1982). 3-Butene-1,2-diol may also undergo a second oxidation reaction to form 3,4-epoxy-1,2-butanediol. The metabolic pathway of 1,3-butadiene is shown in Figure 5-1.

Species differences were also noted in the ability of liver homogenates to produce butadiene monoxide when incubated with 1,3-butadiene (Schmidt and Loeser, 1985, 1986). B6C3F1 mouse liver preparations were found to have a much greater butadiene monoxide-producing activity when incubated with 1,3-butadiene than did human liver preparations, which suggests that the mouse may not be a good model for studying the metabolism of 1,3-butadiene (Schmidt and Loeser, 1986).

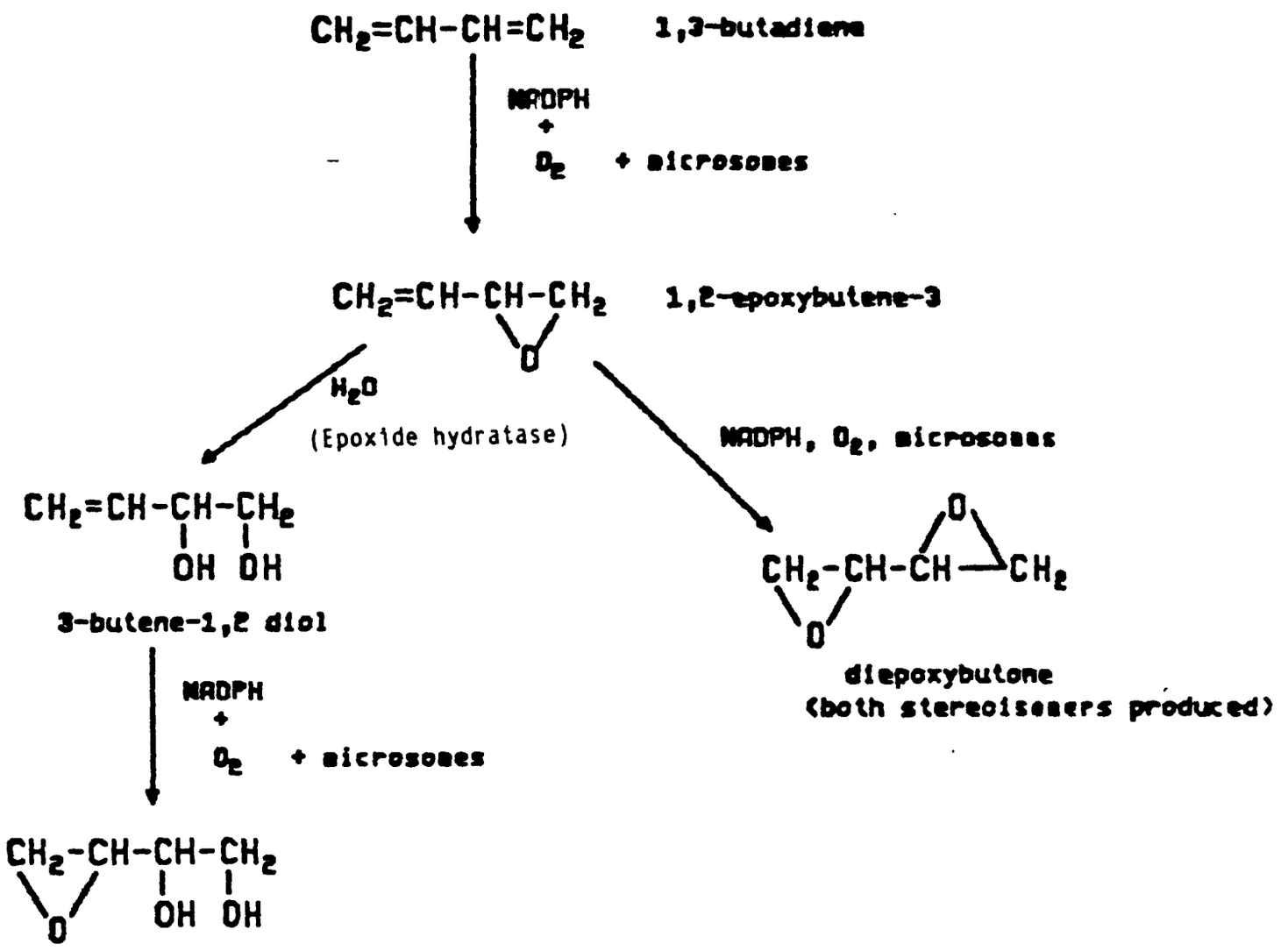

FIGURE 5-1

Microsomal Metabolic Pathway of 1,3-Butadiene

Source: Malvoisin and Roberfroid, 1982

5.4. EXCRETION

The excretion of an inhaled dose of radiolabeled 1,3-butadiene was measured in Sprague-Dawley rats and B6C3F1 mice by Bond et al. (1986). Groups of mice were exposed to 1,3-butadiene concentrations of 14.2, 145 and 1870 mg/m^3 (four animals at each concentration), and rats (four animals at each concentration level) were exposed to 1,3-butadiene concentrations of 134, 1720 and 12,700 mg/m^3. At the end of the exposure period, the animals were placed in metabolism cages. Urine and feces samples (collected separately) were taken at various times after the end of exposure and expired air was collected in a series of traps designed to collect 1,3-butadiene and its volatile metabolites. The traps for expired air were sampled for radioactivity at the same time that urine and fecal samples were taken, and this sampling was continued for 65 hours following the termination of exposure. At all concentrations of 1,3-butadiene tested, urine and exhaled air were the major routes of excretion of ^{14}C for both rats and mice, and these routes accounted for ~75-85% of the total ^{14}C eliminated. The relative importance of the different pathways for the excretion of 1,3-butadiene and its metabolites varied with the concentration of 1,3-butadiene to which the animals were exposed. At higher concentrations of inhaled 1,3-butadiene, exhalation of $^{14}CO_2$ became a major pathway for urinary excretion of ^{14}C. In mice, the half-time for urinary excretion of ^{14}C was 4.6 hours and the half-time for fecal excretion of ^{14}C was 8.6 hours. In rats, the half-time for excretion of ^{14}C in feces and urine were 22 and 5.6 hours, respectively.

5.5. SUMMARY

1,3-Butadiene is absorbed after inhalation by B6C3F1 mice and Sprague-Dawley rats (Bond et al., 1986). Estimates of absorption were ≥4-20% of inhaled dose for mice and >1.5-17% for rats exposed to very high concentrations.

Following inhalation, 1,3-butadiene is distributed to the brain, liver, kidney and spleen of rats at nearly equivalent levels, and very high levels are found in the perinephric fat (Shugaev, 1969). 1,3-Butadiene was also found to distribute to the mouse brain and the central nervous system of the cat following inhalation exposure (Shugaev, 1969).

The primary *in vivo* metabolites of 1,3-butadiene in the blood of rats and mice following inhalation exposure appear to be 1,2-epoxy-3-butene and butadiene diepoxide (Bond et al., 1986). Saturation of the metabolic elimination mechanism for 1,3-butadiene was approached at inhalation exposure levels >1000 ppm (2200 mg/m^3) in both Sprague-Dawley rats and B6C3F1 mice (Kreiling et al., 1986a,b; Filser and Bolt, 1984). The maximal metabolic rate of elimination of 1,3-butadiene (V_{max}), however, was found to be approximately twice as high in mice as in rats. Exhalation of 1,3-butadiene monoxide and acetone has been demonstrated in rats exposed to 1,3-butadiene by inhalation (Filser and Bolt, 1984). The primary *in vitro* metabolites of 1,3-butadiene (using rat liver microsomes) are 1,3-epoxybutene-3, 3-butene-1,2-diol, diepoxybutene and 3,4-epoxy-1,2-butanediol (Malvoisin and Roberfroid, 1982).

Excretion of radioactivity that is derived from inhaled radiolabeled 1,3-butadiene was determined to be primarily in the urine and exhaled air of 1,3-butadiene-exposed Sprague-Dawley rats and B6C3F1 mice (Bond et al., 1986). These routes of elimination accounted for ~75-85% of the total ^{14}C eliminated.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures.

6.1.1.1. **SUBCHRONIC** -- A 3-month inhalation toxicity study of 1,3-butadiene was conducted by Crouch and Pullinger (1978) and Crouch et al. (1979). Five groups of Sprague-Dawley rats (40 male and 40 female animals in each group) were exposed to 0, 1000 ppm (2212 mg/m^3), 2000 ppm (4425 mg/m^3), 4000 ppm (8849 mg/m^3) and 8000 ppm (17,698 mg/m^3) (concentrations in mg/m^3 as reported by authors), 6 hours/day, 5 days/week for 13 weeks. The parameters examined in the exposed rats included growth rate, food consumption, hematology and blood biochemistry, urine analysis, erythrocyte and brain cholinesterase activity, erythrocyte osmotic fragility, neuromuscular function and neutrophil phagocytosis. Macroscopic and histopathologic examinations were also conducted. No effects attributable to 1,3-butadiene exposure were observed in any of these parameters and the only adverse affect reported was increased salivation in female animals that were exposed to higher concentrations of 1,3-butadiene.

Carpenter et al. (1944) exposed groups of 24 albino rats, 12 guinea pigs, 4 rabbits and 1 dog to 1,3-butadiene by inhalation. Animals were equally distributed by sex except for the dogs, which were all females. The concentrations used were 600 ppm (1327 mg/m^3), 2300 ppm (5088 mg/m^3) and 6700 ppm (14,822 mg/m^3). Exposure was for 7 1/2 hours/day, 6 days/week for 8 months. Chamber-exposed controls were maintained. Biological parameters examined were body weight, blood cytology, fertility (rats, rabbits and guinea pigs), blood and urine chemistry, kidney and liver weights (rats only), ocular examination of rabbits and dogs, and general organ gross and microscopic pathology. The only adverse effect noted was a decrease in body

weight gain in exposed rats and male guinea pigs. Body weight gain in rats was <90% of controls only at ≥2300 ppm. Quantitative data were not provided for guinea pigs. Carpenter et al. (1944) concluded that 1,3-butadiene is a relatively innocuous substance.

Several studies have indicated that stem cells in the bone marrow of mice are a target site for 1,3-butadiene-induced toxicity. Irons et al. (1986a) exposed male B6C3F1 mice to 1,3-butadiene by inhalation to 1250 ppm (2765 mg/m³), 6 hours/day, 6 days/week for 6-24 weeks. Blood and bone marrow were examined, and treated mice were found to have a 1,3-butadiene-induced macrocytic-megaloblastic anemia. Leiderman et al. (1986) also exposed male B6C3F1 mice to 1,3-butadiene by inhalation to 1250 ppm (2765 mg/m³). The exposure schedule used was 6 hours/day, 5 days/week for 6 or 30-31 weeks. In vivo and in vitro assays were used to investigate the proliferation and differentiation of bone marrow cells. After 6 weeks of exposure to 1,3-butadiene, Leiderman et al. (1986) concluded that there were alterations in bone marrow stem cell development.

Studies of 1,3-butadiene toxicity using B6C3F1 mice are complicated by the presence of an endogenous type C retrovirus (MuLV) present in this strain. Irons et al. (1986b) exposed eight male NIH Swiss mice, which do not possess this virus, to 1,3-butadiene by inhalation at a concentration of 1250 ppm (2763 mg/m³), 6 hours/day, 5 days/week for 6 weeks. At the end of the exposure period, peripheral blood was drawn and analyzed and the cellularity of bone marrow from the femur was determined. Irons et al. (1986b) concluded that 1,3-butadiene exposure caused alterations in bone marrow precursor cell activity and that the changes in the bone marrow and peripheral blood were indicative of a 1,3-butadiene-induced macrocytic-

megaloblastic anemia. It was also concluded from this study that the bone marrow toxicity induced by exposure to 1,3-butadiene is independent of the presence of the murine MuLV virus.

The effects of inhalation exposure to 1,3-butadiene on the immune system were examined by Thurmond et al. (1986). B6C3F1 mice were exposed to a 1,3-butadiene concentration of 1250 ppm (2765 mg/m³), 6 hours/day, 5 days/week for 6 or 12 weeks. Lymphoid organ histopathology was examined and immune function assays were performed to evaluate specific humoral and cell-mediated immunity; no significant immunological defects were detected in the 1,3-butadiene-exposed mice.

A number of Russian studies, available only as brief abstracts, have been performed on the subchronic inhalation toxicity of 1,3-butadiene. Rats exposed for 81 days (exposure schedule unknown) to 1,3-butadiene (30 mg/m³) developed dystrophic processes in the tissue structures of the kidneys and heart (Nikiforova et al., 1969) and structural changes in the spleen (Molodyuk et al., 1969). Rats exposed for 81 days to 1,3-butadiene (30 mg/m³ and 300 mg/m³) developed erythrocytosis and leukocytosis (Ripp and Lyutikova, 1966), and rabbits exposed to 1,3-butadiene (200 mg/ℓ; exposure schedule not given) showed an increased ratio of erythroblasts to granulocytes (Pokrovskii and Volchkova, 1968). Experimental animals (species not reported) exposed to 1,3-butadiene by inhalation (1.0, 3.0 and 30 mg/m³) had morphological changes in the liver and kidneys, disturbances of the central nervous system, and changes in the immune system (Ripp, 1969). Rats exposed by inhalation to 1,3-butadiene (100 mg/ℓ), 6 hours/day, 6 days/week for 4.5 months had alterations in the bronchial epithelium of the lung and a hypersecretory state in the connective tissue structures of the lungs (Kuz'min, 1969). These studies were not available in sufficient detail to assess their reliability.

6.1.1.2. **CHRONIC** -- In an inhalation study of the toxicity of 1,3-butadiene in male and female B6C3F1 mice (NTP, 1984), exposure to 1,3-butadiene, 6 hours/day, 5 days/week for 60-61 weeks at concentrations of 0, 625 ppm (1383 mg/m^3) or 1250 ppm (2765 mg/m^3) caused gonadal atrophy in both sexes at both concentrations. Male B6C3F1 mice exposed to 2765 mg/m^3 had nonneoplastic lesions of the nasal cavity; the details of this study are presented in Section 6.2.1.

Chronic toxicity data were obtained from the 105- to 111-week cancer study by Hazleton Laboratories (1981a) (also reported in Owen et al., 1987) (Section 6.2.1.). In this experiment, Sprague-Dawley rats of both sexes were exposed to 1000 or 8000 ppm (2212 or 17,698 mg/m^3), 6 hours/day, 5 days/week. There were no effects on overall body weight gain, hematology, blood biochemistry, urinalysis, neuromuscular tests or gross pathology. Survival was significantly reduced in both sexes at 8000 ppm, and rats at this level exhibited ataxia and ocular and nasal discharge. Increased absolute and relative liver weights were observed in 8000 ppm rats of both sexes and in 1000 ppm females, but histopathologic changes in the liver were not observed at either concentration, and the elevated liver weights were attributed to enzyme induction, an adaptative rather than a toxic response. Increased absolute and relative heart, lung and kidney weights were observed in 8000 ppm males. Males at 8000 ppm had an increased incidence of nephropathy that was considered partially responsible for the decreased survival observed in this group.

6.1.2. **Oral Exposures.**

6.1.2.1. **SUBCHRONIC** -- Rats (strain not specified) were given 1,3-butadiene orally at 100 mg/kg/day for 2.5 months (Donetskaya and Schvartsapel, 1970). Granular and hydropic dystrophy, cytolysis and disturbances of permeability were found in the cells of the brain, sympathetic

ganglia, heart, liver and kidneys. Lymphohistiocytic infiltration was found in the lungs, heart, liver, kidneys and gastrointestinal tract. A thickening of the interalveolar septa was also found in the lungs.

6.1.2.2. CHRONIC -- Pertinent data regarding chronic oral exposure to 1,3-butadiene could not be located in the available literature as cited in Appendix A.

6.1.3. Other Relevant Information. The oral LD_{50} for 1,3-butadiene is 5480 mg/kg in the rat and 3210 mg/kg in the mouse (Sax, 1984). Humans exposed to 2000 ppm (4425 mg/m^3), 4000 ppm (8849 mg/m^3) or 8000 ppm (17,698 mg/m^3) 1,3-butadiene for 6-8 hours experienced a slight irritation of the eyes (Carpenter et al., 1944). Inhalation of 1,3-butadiene (exposure schedule and concentration not reported) by mice increased liver content of ATP and increased the ratio of ATP to ADP (Oura et al., 1967). Direct dermal contact with 1,3-butadiene caused burns and frostbite (Sandmeyer, 1981).

6.2. CARCINOGENICITY

6.2.1. Inhalation. Human epidemiologic data regarding the carcinogenicity of 1,3-butadiene are restricted to several studies of workers exposed in the production of SBR. SBR usually is made up of 26% 1,3-butadiene and 9% styrene (U.S. EPA, 1985). Exposure to many other chemicals including toluene and benzene also occurred; exposures usually were not quantified and the effects of 1,3-butadiene independent from other chemicals could not be evaluated. Some of these epidemiologic studies (McMichael et al., 1974; Andjelkovich et al., 1976; Meinhardt et al., 1982) suggested a correlation between SBR production and excess cancer risk; others (Checkoway and Williams, 1982; Matanoski et al., 1982) did not. The strengths and weaknesses of these studies have been reviewed extensively by the U.S. EPA (1985). [It is beyond the scope of this task to repeat that effort here].

Two long-term inhalation carcinogenicity studies, one using B6C3F1 mice (NTP, 1984) and one using Sprague-Dawley rats (Hazleton Laboratories, 1981a; Owen et al., 1987) established 1,3-butadiene as a carcinogen in both species. NTP (1984) exposed groups of 50 male and 50 female mice to 0, 625 or 1250 ppm (0, 1383 or 2765 mg/m^3), 6 hours/day, 5 days/week for 60 weeks (males) or 61 weeks (females). The experiment was designed with a 103- to 104-week exposure period, which was shortened because of high mortality primarily associated with neoplasia. Incidences of statistically significant tumors are summarized in Table 6-1. The tumor type with the highest overall incidence in both sexes was a lymphoma associated with the hematopoietic system. Other tumors with statistically increased incidences in both sexes included alveolar or bronchiolar adenomas or carcinomas, hemangiosarcoma of the heart and squamous cell neoplasm of the forestomach. The increased incidence of hemangiosarcoma of the heart following 1,3-butadiene exposure is significant because this is a rare tumor type in this strain of mouse (Wooder, 1986). 1,3-Butadiene-exposed female B6C3F1 mice also had increased incidences of hepatocellular adenoma and carcinoma, acinar cell carcinoma of the mammary gland and granulosa cell neoplasm of the ovary.

In the Hazleton Laboratory (1981a) study, groups of 110 male and 110 female Sprague-Dawley rats were exposed to 1,3-butadiene at concentrations of 1000 ppm (2212 mg/m^3) or 8000 ppm (17,698 mg/m^3) for 111 weeks (males) or 105 weeks (females). Ten rats/sex/group were sacrificed at 52 weeks for gross and histopathological examination. Male rats had an increased incidence of Leydig cell adenomas and carcinomas of the testes and an increased incidence of exocrine adenoma of the pancreas (Table 6-2). Female rats had an increased incidence of multiple mammary gland tumors, follicular cell adenomas and carcinomas of the thyroid, and stromal sarcomas of the uterus-cervix.

TABLE 6-1

Inhalation Carcinogenicity of Butadiene (98.9-100% purity)
After 60-61 Weeks of Exposure (6 hours/day, 5 days/week) in B6C3F1 Mice[a]

Dose (ppm)	Sex	Target Organ	Tumor Type	Tumor Incidence	Statistical Significance[b]
0	M	lung	alveolar/bronchiolar adenoma or carcinoma	2/50	p<0.001
		hematopoietic system	lymphoma	0/50	p<0.001
		heart	hemangiosarcoma	0/50	p=0.032
		forestomach	all papillomas or carcinomas	0/49	p=0.363
625 (1381 mg/m³)	M	lung	alveolar/bronchiolar adenoma or carcinoma	14/49	p<0.001
		hematopoietic system	lymphoma	23/50	p<0.001
		heart	hemangiosarcoma	16/49	p<0.001
		forestomach	all papillomas or carcinomas	7/40	p=0.003
1250 (2763 mg/m³)	M	lung	alveolar/bronchiolar adenoma or carcinoma	15/49	p<0.001
		hematopoietic system	lymphoma	29/50	p<0.001
		heart	hemangiosarcoma	7/49	p=0.006

Dose (ppm)	Sex	Target Organ	Tumor Type	Tumor Incidence	Statistical Significance[b]
1250 (2763 mg/m³)	M	forestomach	all papillomas or carcinomas	1/44	p=0.473
0	F	lung	alveolar/bronchiolar adenoma or carcinoma	3/49	p<0.001
		hematopoietic system	lymphoma	1/50	p=0.006
		heart	hemangiosarcoma	0/50	p<0.001
		forestomach	all papillomas or carcinomas	0/49[c]	p<0.001
		liver adenoma or carcinoma	hepatocellular	0/50	p=0.016
		mammary gland	acinar cell carcinoma	0/50	p=0.007
		ovary	granulosa cell neoplasm	0/49	p<0.001
625 (1381 mg/m³)	F	lung	alveolar/bronchiolar adenoma or carcinoma	12/48	p=0.01
		hematopoietic system	lymphoma	10/49	p=0.003
		heart	hemangiosarcoma	11/48	p<0.001

TABLE 6-1 (cont.)

Dose (ppm)	Sex	Target Organ	Tumor Type	Tumor Incidence	Statistical Significance[b]
625 (1381 mg/m³)	F	forestomach	all papillomas or carcinomas	5/42	p=0.018
		liver	hepatocellular adenoma or carcinoma	2/47	p=0.232
		mammary gland	acinar cell carcinoma	2/49	p=0.242
		ovary	granulosa cell neoplasm	6/45	p=0.010
1250 (2763 mg/m³)	F	lung	alveolar/bronchiolar adenoma or carcinoma	23/49	p<0.001
		hematopoietic system	lymphoma	10/49	p=0.003
		heart	hemangiosarcoma	18/49	p<0.001
		forestomach	all papillomas or carcinomas	10/49	p<0.001
		liver	hepatocellular adenoma or carcinoma	5/49	p=0.027
		mammary gland	acinar cell carcinoma	6/49	p=0.012
		ovary	granulosa cell neoplasm	13/48[c]	p<0.001

Quality of Evidence

Strengths of Study: The compound was administered to both sexes at two dose levels; adequate number of animals/group; natural route of exposure; chemical of high purity.

Weakness of Study: The study was terminated at 60-61 weeks because of the large number of deaths.

Overall Adequacy: Adequate

[a]Source: NTP, 1984

[b]The p-value for control incidences is the result of the Cochran-Armitage Test for the linear trend; p-value for incidences in treated groups is the result of the Fisher Exact Test.

[c]These values differ from those provided in the summary analysis in NTP (1984) but agree with the incidences reported in the Appendices and compiled by U.S. EPA (1986b).

NR = Not reported

TABLE 6-2

Inhalation Carcinogenicity of Butadiene (unknown purity) in Sprague-Dawley Rats Exposed 6 hours/day, 5 days/week[a,b]

Dose (ppm)	Sex	Target Organ	Tumor Type	Tumor Incidence[c]	Statistical Significance[d]
0	M	testes	Leydig cell adenoma and carcinoma	0/100	p<0.003
		pancreas	exocrine adenoma	3/100	p=0.019
1000 (2,212 mg/m³)		testes	Leydig cell adenoma and carcinoma	3/100	p=0.12
		pancreas	exocrine adenoma	1/100	p=0.879
8000 (17,698 mg/m³)	M	testes	Leydig cell adenoma and carcinoma	8/100	p<0.001
		pancreas	exocrine adenoma	10/100	p=0.041
0	F	mammary glands	multiple mammary gland tumors	50/100	p<0.001
		thyroid	follicular cell adenomas and carcinomas	0/100	p<0.001
		uterus-cervix	stromal sarcoma	1/100	p=0.115
1000 (2,212 mg/m³)	F	mammary glands	multiple mammary gland tumors	79/100	p<0.001
		thyroid	follicular cell adenomas and carcinomas	4/100	p=0.06

TABLE 6-2 (cont.)

Dose (ppm)	Sex	Target Organ	Tumor Type	Tumor Incidence[c]	Statistical Significance[d]
1000 (2,212 mg/m³)	F	uterus-cervix	stromal sarcoma	4/100	p=0.184
8000 (17,698 mg/m³)	F	mammary glands gland tumors	multiple mammary	84/100	p<0.001
		thyroid	follicular cell adenomas and carcinomas	11/100	p<0.001
		uterus-cervix	stromal sarcoma	5/100	p=0.106

Quality of Evidence

Strengths of Study: The compound was administered to both sexes at two dose levels; adequate number of animals/group; natural route of exposure.

Weakness of Study: The study has not been published and the unpublished report does not include detailed individual histopathological evaluations. The MTD may not have been reached.

Overall Adequacy: Adequate

[a]Source: U.S. EPA, 1985

[b]Male Sprague-Dawley rats were exposed for 111 weeks. Females were exposed for 105 weeks.

[c]The denominator reflects the assumption that 100 rats/sex/group survived for >52 weeks and were examined histologically.

[d]The p-value for control incidences is the result of the Cochron-Armitage Test for linear trend. The p-value for incidences in treated groups is the result of the Fisher Exact Test.

6.2.2. Oral. Pertinent data regarding the carcinogenicity of 1,3-butadiene by the oral route of exposure could not be located in the available literature as cited in Appendix A.

6.2.3. Other Relevant Information. The positive carcinogenicity studies in Sprague-Dawley rats (Hazleton Laboratories, 1981a) and in B6C3F1 mice (Haseman et al., 1984; Huff et al., 1985; NTP, 1984) reveal that mice were more sensitive than rats regarding carcinogenic response to butadiene. Several investigators (Kreiling et al., 1986a,b; Bond et al., 1986) raised the question of whether differences in species metabolism of 1,3-butadiene might be responsible for differences in species susceptibility to the carcinogenic properties of 1,3-butadiene. Mice do metabolize 1,3-butadiene faster than rats (Kreiling et al., 1986a,b) and higher blood levels of the primary reactive metabolite, 1,2-epoxy-3-butene, have been found in butadiene-exposed mice when compared with similarly exposed rats (Bond et al., 1986; Kreiling et al., 1987).

Differences in species metabolism of 1,3-butadiene between Sprague-Dawley rats and B6C3F1 mice may only partially explain the greater sensitivity of B6C3F1 mice to the carcinogenic properties of 1,3-butadiene following inhalation exposure. Another possibility is that an endogenous virus (MuLV) present in the B6C3F1 mouse strain acted in combination with 1,3-butadiene to produce the high incidence of lymphoma present in this strain of mouse after 1,3-butadiene exposure. Studies are in progress using a mouse strain (NIH) which is free from the MuLV virus to elucidate what role, if any, this virus plays in the development of lymphomas in 1,3-butadiene-exposed B6C3F1 mice (Irons et al., 1986b).

The toxic response to 1,3-butadiene consisting of a butadiene-induced macrocytic-megaloblastic anemia in mice (Irons et al., 1986a,b) may be

considered a preneoplastic response. This 1,3-butadiene-induced anemia in mice is considered to be similar to human preleukemic syndrome and may play a role in butadiene-induced murine thymus lymphoma/leukemia (Irons et al., 1986a).

6.3. MUTAGENICITY

Mutagenicity data are summarized in Table 6-3. Apparently metabolism of 1,3-butadiene to a reactive metabolite is required for butadiene to exert its mutagenic effect in certain strains of Salmonella typhimurium (Poncelet et al., 1980; DeMeester et al., 1980; Wooder, 1986), although positive results without S-9 activation were obtained in an earlier study in S. typhimurium strain TA1535 at higher concentrations. Similarly, positive results in a forward mutation test in mouse lymphoma cells were obtained in the presence but not the absence of S-9 from rats (Sernau et al., 1986). Positive results were also obtained in in vivo micronucleus (Choy et al., 1986) and SCE tests (Cunningham et al., 1986), in mouse and rat bone marrow cells and in the SCE test in rat bone marrow cells (Cunningham et al., 1986). Results were negative in in vivo tests for unscheduled DNA synthesis in liver cells from rats and mice (Vincent et al., 1986) and in the micronucleus test in rat bone marrow cells (Choy et al., 1986; Cunningham et al., 1986). Recently, Tice et al. (1987) reported increases in chromosome aberrations and SCE (with depressed mitotic activity) in bone marrow and increased micronuclei formation in peripheral blood.

6.4. TERATOGENICITY

An inhalation teratogenicity study of 1,3-butadiene was performed by Hazleton Laboratories (1981b). Female Sprague-Dawley rats were exposed to 200, 1000 or 8000 ppm (442, 2212 or 17,698 mg/m^3) 6 hours/day on days 6-15 (inclusive) of gestation. Maternal toxicity in the form of reduced body

TABLE 6-3

Mutagenicity Testing of 1,3-Butadiene

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1530	99.5%	gaseous in desiccator	2-32% v/v in desiccator atmosphere	-S-9	-	For butadiene to exert mutagenic activity, S-9 mix must be prepared from livers of rats pretreated with phenobarbitone or Aroclor 1254.	DeMeester et al., 1980
					+S-9 (from liver of Aroclor 1254 pretreated rat)	+		
				16% v/v in desiccator atmosphere	+S-9 (from liver of phenobarbitone pretreated rat)	+	S-9 mix from untreated rats was ineffective.	
					+S-9 (from liver of untreated rat)	-	Exposure of bacteria to butadiene was by placing plates in desiccator with butadiene air mixture.	
Reverse mutation	S. typhimurium TA1530	99.5%	gaseous in desiccator	70% v/v concentration of butadiene in atmosphere of desiccator	-S-9	+	NC	DeMeester et al., 1978
					+S-9 (from liver of Aroclor 1254 pretreated rat)	+		
	TA1535	99.5%	gaseous in desiccator	same as above	-S-9	+	NC	
					+S-9 (from liver of Aroclor 1254 pretreated rat)	+		
	TA1537	99.5%	gaseous in desiccator	same as above	-S-9	-	NC	
					+S-9 (Aroclor 1254 pretreated rat)	-		
	TA1538	99.5%	gaseous in desiccator	same as above	-S-9	-	NC	
					+S-9 (Aroclor 1254 pretreated rat)	-		

TABLE 6-3 (cont.)

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	TA98	99.5%	gaseous in desiccator	70% v/v concentration of butadiene in atmosphere of desiccator	-S-9	-	NC	DeMeester et al., 1978
					+S-9 (Aroclor 1254 pretreated rat)	-		
	TA100	99.5%	gaseous in desiccator	same as above	-S-9	-	NC	
					+S-9 (Aroclor 1254 pretreated rat)	-		
Reverse mutation	S. typhimurium TA1530	99.5%	gaseous in desiccator	16% v/v concentration of butadiene in atmosphere	+S-9 (from liver of Arachlor 1254 pretreated rat)	+	NC	Poncelet et al., 1980
Forward mutation	L5178Y mouse lymphoma cell	NR	cell culture	20, 40, 60 or 80% v/v gaseous exposure to butadiene	-S-9	-	NC	Sernau et al., 1986
				same as above	+S-9	+	Dose-related response was observed with respect to mutation frequency.	
UDS	liver cells from male B6C3F1 mice	NR	in vivo	animals exposed to 10,000 ppm (22,100 mg/m³) butadiene for 2 days	NA	-	NC	Vincent et al., 1986
	liver cells from Sprague-Dawley rats	NR	animals exposed total of 9 or 12 hours over 2 days	10,000 ppm (22,100 mg/m³)	NA	-	NC	Vincent et al., 1986
Micronucleus test	B6C3F1 mouse bone marrow cells	NR	animals exposed 6 hours/day for 2 days	100-10,000 ppm (221-22,100 mg/m³)	NA	+	Dose-dependent increase in micronucleus induction	Cunningham et al., 1986

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Micronucleus test	B6C3F1 mouse peripheral blood	>99%	animals exposed 6 hours + T_{90}/day for 10 days	6.25, 62.5, 625 ppm	NA	+	Dose response	Tice et al., 1987
SCE and chromosomal aberrations	B6C3F1 mouse bone marrow	>99%	animals exposed 6 hours + T_{90}/day for 10 days	6.25, 62.5, 625 ppm	NA	+	Dose response	Tice et al., 1987

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

weight gain was observed at 442 and 2212 mg/m³ and loss of maternal body weight was observed at 17,698 mg/m³. A teratogenic effect in the form of major skeletal and cardiovascular-thoracic anomalies was noted in fetuses of dams exposed to 8000 ppm (17,698 mg/m³).

An abstract of a Russian study (Serebrennikov and Ogleznev, 1978) indicated that a 4-month inhalation of 1,3-butadiene (concentration not reported) by female rats (strain not specified) caused embryonal mortality and teratogenesis.

6.5. OTHER REPRODUCTIVE EFFECTS

NTP (1984) performed a cancer study in which groups of 50 B6C3F1 mice/sex were exposed to 0, 625 or 1250 ppm (0, 1383 or 2765 mg/m³), 6 hours/day, 5 days/week. The study had to be terminated after 60-61 weeks because of high cancer-related mortality. Gonadal atrophy was observed in both sexes in both treated groups.

6.6. SUMMARY

The toxicity of 1,3-butadiene following inhalation exposure appears to depend on the species of animal. Adverse acute effects attributable to 1,3-butadiene exposure were practically nonexistent except for increased salivation in females in Sprague-Dawley rats exposed to 8000 ppm (17,698 mg/m³), 6 hours/day, 5 days/week for 13 weeks (Crouch and Pullinger, 1978; Crouch et al., 1979) and in rabbits and dogs exposed to 6700 mg/m³, 7.5 hours/day, 6 days/week for 8 months (Carpenter et al., 1944). Reduced body weight in rats and male guinea pigs was observed at this level. The bone marrow appears to be a target site for 1,3-butadiene toxicity in B6C3F1 and NIH mice (Irons et al., 1986a,b; Leiderman et al., 1986). A 1,3-butadiene-induced macrocytic-megaloblastic anemia was observed in B6C3F1 and NIH mice exposed to 1250 ppm (2765 mg/m³), 6 hours/day, 5-6 days/week for as few as

6 weeks (Irons et al., 1986a,b; Leiderman et al., 1986). Chronic inhalation exposure to 1,3-butadiene at ≥625 ppm (1383 mg/m³), 6 hours/day, 5 days/week for 60 weeks caused gonadal atrophy in both sexes of B6C3F1 mice (NTP, 1984). Nonneoplastic lesions of the nasal cavity of male mice occurred at 1250 ppm (2765 mg/m³) (NTP, 1984).

Several epidemiological studies (McMichael et al., 1974; Andjelkovich et al., 1976; Matanoski et al., 1982) associate work in the SBR industry with excess risk of cancers of the hemotopoietic and lymphatic systems, but concurrent exposure to potential carcinogens other than 1,3-butadiene also occurred. Long-term inhalation carcinogenicity studies performed with B6C3F1 mice (NTP, 1984) and Sprague-Dawley rats (Hazleton Laboratories, 1981a; Owen et al., 1987) confirm that 1,3-butadiene is carcinogenic in these species. Statistically significant ($p \leq 0.05$) increased incidences of primary tumors at multiple sites were observed including lymphomas, hemangiosarcomas, alveolar/bronchiolar adenomas, acinar cell carcinomas, granulosa cell tumors or carcinomas, forestomach papillomas and carcinomas, and hepatocellular adenomas and carcinomas. The most prevalent tumor types in B6C3F1 mice were lymphomas associated with the hematopoietic system and hemangiosarcomas. Five other tumor sites also had statistically significant increases ($p \leq 0.05$) in this study, which had to be terminated after 60-61 weeks because of high cancer mortality. This mouse strain was found to be far more sensitive in terms of a carcinogenic response than was the Sprague-Dawley rat.

Butadiene is mutagenic in bacteria only with activation (DeMeester et al., 1980) and induces chromosomal aberrations and SCE in mice (Tice et al., 1987; Wooder, 1986). Data from Hazleton Laboratories (1981b) indicate that 1,3-butadiene is a teratogen when pregnant female rats are exposed by inhalation at 8000 ppm (17,698 mg/m³), 6 hours/day during organogenesis.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

A TLV of 10 ppm (22 mg/m^3) has been adopted for 1,3-butadiene (ACGIH, 1986a), and this compound has been listed in Appendix A2, Industrial Substances Suspect of Carcinogenic Potential for Man. This TLV has been adopted on the basis of positive inhalation carcinogenicity studies with rats and mice and observed teratogenic effects in rats (ACGIH, 1986b). The OSHA (1985) PEL is 1000 ppm (2200 mg/m^3).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the effects of 1,3-butadiene could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Two long-term inhalation carcinogenicity studies of 1,3-butadiene have been conducted. In the NTP (1984) study, mice were exposed to 1,3-butadiene at concentrations of 625 (1381 mg/m^3) or 1250 ppm (2763 mg/m^3). The exposure schedule was 6 hours/day, 5 days/week. The study was scheduled for 2 years but had to be terminated after 60-61 weeks because of high cancer mortality. Several tumor types in various organs were observed, but the two most significant were lymphoma arising from the hematopoietic system and hemangiosarcomas. In general, cancer response was both massive and rapid. Male and female Sprague-Dawley rats exposed to 1000 ppm (2212 mg/m^3) and 8000 ppm (17,698 mg/m^3) 1,3-butadiene by inhalation for 6 hours/day, 5 days/week for 105 or 111 weeks (Hazleton Laboratories, 1981a, subsequently published as Owen et al., 1987) also developed tumors of various organs (testes, pancreas, mammary gland, thyroid and uterus-cervix).

8.1.2. Ingestion. Pertinent data regarding the carcinogenicity of 1,3-butadiene via ingestion could not be located in the available literature as cited in Appendix A. However, because of the high volatility of 1,3-butadiene and its low solubility in water, this route is not considered nearly as important as the inhalation route.

8.1.3. Other Routes. Pertinent data regarding the carcinogenicity of 1,3-butadiene following exposure by other than the inhalation or ingestion routes could not be located in the available literature as cited in Appendix A.

8.1.4. Weight of Evidence. Based on the positive results from two long-term inhalation carcinogenicity studies (NTP, 1984; Hazleton Laboratories, 1981a) in two species (rats and mice) that caused multiple tumor types,

together with supporting information about metabolites having genotoxic and carcinogenic properties, and inadequate epidemiological evidence for 1,3-butadiene carcinogenicity in humans, 1,3-butadiene is classified by EPA as Group B2, probable human carcinogen.

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- U.S. EPA (1985) derived q_1*s for 1,3-butadiene based on the incidence of tumors in the NTP (1984) mouse study and Hazleton Laboratories (1981a) rat study using the multistage model. Separate q_1*s were developed for males and females of both species. From the NTP (1984) study, tumor incidences of 2/50, 43/49 and 40/45 were used for male mice at 0, 625 and 1250 ppm (0, 1383 and 2765 mg/m^3) and tumor incidences of 4/48, 31/48 and 45/49 were used for female mice exposed to the same concentrations. These numerators are the numbers of animals observed at time of death with tumor types that both occurred at a statistically increased incidence (hemangiosarcomas, lymphomas, lung and forestomach tumors in both sexes, plus mammary, ovarian and liver tumors in female mice) and also tumor types considered unusual in this strain of mouse at 60-61 weeks (preputial gland squamous-cell carcinomas, brain gliomas and Zymbal gland carcinomas in male mice). The transformed doses were calculated as internal or retained doses, based on an evaluation of then unpublished NTP (1985) mouse absorption data, which showed a substantial reduction, in the percent of the inhaled dose that was retained, as the exposure concentration increased. Retained dose in the NTP (1984) study was estimated from plots of log μg/kg butadiene retained in animals vs. log ppm exposure concentration in the NTP (1985) study (U.S. EPA, 1985). Potency estimates were then calculated using a correction term to account for the shortened experiment time of 60-61 weeks. Adjusting to lifetime exposure resulted in a q_1* of 6.1×10^{-1} $(mg/kg/day)^{-1}$ (internal dose) or 9.2×10^{-1}

$(ppm)^{-1}$ (air concentration) based on data from male mice, and $3.0x10^{-1}$ $(mg/kg/day)^{-1}$ (internal dose) or $4.5x10^{-1}$ $(ppm)^{-1}$ based on data from female mice. Since the male and female mouse response was so similar, the results were combined by taking as the final potency estimate the geometric mean of $6.4x10^{-1}$ $(ppm)^{-1}$. Assuming humans breathe 20 m^3/day, weigh 70 kg and absorb 54% of inhaled 1,3-butadiene (at low exposure concentrations), this q_1^* was expressed as 1.8 $(mg/kg/day)^{-1}$ in terms of internal dose (U.S. EPA, 1985). The potency estimates from mouse studies were considered to be consistent with the human responses; however, there were too many uncertainties and gaps in the human data base to make more definitive statement (U.S. EPA, 1985).

Subsequent to the NTP (1985) unpublished report, the final data were published (Bond et al., 1986) and these published data contained differences in the low exposure absorption in the mouse (but not in the rat) compared with the unpublished report. The main difference is that low exposure inhalation absorption of butadiene in the mouse (and, by extrapolation, humans) is now estimated to be 20% instead of 54% (see Section 5.1.). These new figures lead to a decrease in the estimated potency from $q_1^* = 6.4x10^{-1}$ $(ppm)^{-1}$ to $q_1^* = 2.4x10^{-1}$ $(ppm)^{-1}$. The details have recently been presented (Bayard, 1988; Cote and Bayard, 1988). These estimates supersede those of the U.S. EPA (1985) document. The estimate based on internal dose remains the same, $q_1^* = 1.8$ $(mg/kg/day)^{-1}$, since the low exposure absorption fraction is assumed the same for mice and humans.

U.S. EPA (1985) also derived q_1^*s of $7.0x10^{-3}$ $(mg/kg/day)^{-1}$ internal dose or $4.2x10^{-3}$ $(ppm)^{-1}$ from the data on male rats, and $9.4x10^{-2}$ $(mg/kg/day)^{-1}$ internal dose or $5.6x10^{-2}$ $(ppm)^{-1}$ from the data on female rats from the Hazleton Laboratories (1981a) studies. U.S. EPA (1985) noted that these data were unpublished and had not been audited.

In addition, a major concern was that the individual animal data were not included in the report. Subsequently, the data have been published (Owen et al., 1987). The published data in general support the unpublished report. However, small differences in some incidence rates are apparent. Because the primary data are still not available for evaluation and because the U.S. EPA (1985) analysis demonstrates that a more conservative approach to carcinogenic risk assessment is based on the NTP (1984) mouse data, this document shall adopt the q_1^* of 2.4×10^{-1} $(ppm)^{-1}$ from the U.S. EPA (1985) analysis of the NTP (1984) mouse data as the upper limit estimate of incremental carcinogenic potency.

The concentration of butadiene in the air associated with an upper limit increased lifetime risk of cancer at a risk level of 10^{-5} was calculated by dividing 10^{-5} by the q_1^* of 2.4×10^{-1} $(ppm)^{-1}$ to give a lower limit concentration of 4.2×10^{-5} ppm or 9.3×10^{-5} mg/m^3. This lower limit concentration (9.3×10^{-5} mg/m^3) is associated with a risk level of 10^{-5}. The lower limit concentration associated with a risk level of 10^{-6} is 4.2×10^{-6} ppm or 9.3×10^{-6} mg/m^3 and the concentration associated with a risk level 10^{-7} is 4.2×10^{-7} ppm or 9.3×10^{-7} mg/m^3.

8.1.5.2. ORAL -- Based on the NTP (1984) inhalation study which showed 1,3-butadiene to be a potent carcinogen at multiple sites, the assumption is made that 1,3-butadiene can also cause cancer via the ingestion route. Assuming 100% absorption from the gut (see Section 5.1.) and an inhalation absorption at low exposures of 20%, an upper limit incremental risk estimate of $q_1^* = 9.0$ $(mg/kg/day)^{-1}$ is used. This value supersedes that of U.S. EPA (1985).

8.2. SYSTEMIC TOXICITY

Two animal studies, one using mice (NTP, 1984) and one using rats (Hazleton Laboratories, 1981a; Owen et al., 1987), demonstrated that 1,3-butadiene is a carcinogen following exposure by inhalation. Data regarding the carcinogenicity of 1,3-butadiene following exposure by the oral route could not be located in the available literature as cited in Appendix A. In the absence of evidence to the contrary, it was assumed that 1,3-butadiene is potentially carcinogenic by both routes of exposure (oral and inhalation); in addition, insufficient data for RfD derivation precludes such a quantitative derivation for systemic toxicity (RfD).

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of 1,3-butadiene was discussed in Chapter 6 and dose-response data relevant for consideration in derivation of CSs are summarized in Table 9-1. The studies of Irons et al. (1986a,b) and Leiderman et al. (1986) were not considered suitable for RQ determination because the responses in these studies (macrocytic-megaloblastic anemia and alterations in stem cell development) were considered to be preneoplastic responses in 1,3-butadiene-exposed mice.

The most severe effect in Table 9-1 is mortality in rats at an equivalent human dosage of 340 mg/kg/day. Another severe effect is teratogenicity with maternal toxicity (Hazleton Laboratories, 1981b). This effect occurred at an equivalent human dose of 483 mg/kg/day.

The next most severe effect was gonadal atrophy in mice (NTP, 1984). The effect on reproductive dysfunction associated with this atrophy was not studied. Gonodal atrophy occurred at an equivalent human dose of 24 mg/kg/day in females. Multiplication of this dose by 70 kg gives an MED of 1666 mg/day.

The least severe response, reduced body weight in rats (Carpenter et al., 1944), occurred at an equivalent human dose of 148 mg/kg/day. CSs for these effects are calculated and presented in Table 9-2.

The highest CS, 10, corresponding to the lowest RQ (1000) is associated with mortality in chronically exposed rats in the study by Hazleton Laboratories (1981a). This is the RQ of choice and it is presented in Table 9-3.

TABLE 9-1

Inhalation Toxicity Summary for 1,3-Butadiene

Species/ Strain	Sex/ Number	Average Body Weight (kg)	Purity/Vehicle	Exposure	Transformed Animal Dose[a] (mg/kg/day)	Equivalent Human Dose[b] (mg/kg/day)	Response	Reference
Rats/ albino	M,F/24	0.35[c]	NR/air	2300 ppm (5088 mg/m³), 7.5 hours/day, 6 days/ week for 8 months	868	148	Reduced body weight (86.3% of controls)	Carpenter et al., 1944
Rats/ Sprague-Dawley	M/100, F/100	0.35[c]	NR/air	8000 ppm (17,698 mg/m³), 6 hours/day, 5 days/week for 105-111 weeks	2014	344	Mortality	Hazleton Laboratories, 1981a; Owen et al., 1987
Rats/ Sprague-Dawley	F/24	0.272[d]	NR/air	8000 ppm (17,698 mg/m³), 6 hours/day, days 6-15 of gestation inclusive	3074[e]	483	Maternal toxicity, body weight loss, teratogenic effect, major skeletal anomalies in fetuses, cardiovascular thoracic abnormalities in fetuses	Hazleton Laboratories, 1981b
Mice/ B6C3F1	M/50	0.037[f]	98.9-100%/air	625 ppm (1383 mg/m³), 6 hours/day, 5 days/week for 60 weeks	300[e]	24.3	Gonadal atrophy	NTP, 1984
Mice/ B6C3F1	F/50	0.028[f]	98.9-100%/air	625 ppm (1383 mg/m³), 6 hours/day, 5 days/week for 61 weeks	326[e]	24	Gonadal atrophy	NTP, 1984

[a]Calculated by multiplying the exposure concentration (mg/m³) by the daily exposure (hours/24 hours) and by the weekly exposure (days/7 days) and by the inhalation rate (m³/day) and dividing by the animal body weight (kg). Reference inhalation rates are from U.S. EPA (1986a).

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

[c]Reference body weights from U.S. EPA (1986a)

[d]Weight at day 12 of gestation

[e]Calculated using an inhalation rate given by the formula in U.S. EPA (1980).

[f]Taken from growth curves

NR = Not reported

TABLE 9-2

Inhalation Composite Scores for 1,3-Butadiene

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	2014	24,080	1	Mortality	10	10	1000	Hazleton Laboratories, 1981a; Owen et al., 1987
Rat	3074	33,810	1	Teratogenic effect maternal toxicity	9	9	1000	Hazleton Laboratories, 1981a
Mouse	326	1,680	1	Gonadal atrophy	8	8	1000	NTP, 1984
Rat	868	1,036*	1	Reduced body weight	4	4	5000	Carpenter et al., 1944

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-3

1,3-BUTADIENE

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

Route:	inhalation
Dose*:	24,080 mg/day
Effect:	mortality
Reference:	Hazleton Labortories, 1981a; Owen et al., 1987
RV_d:	1
RV_e:	10
Composite Score:	10
RQ:	1000

*Equivalent human dose

9.2. BASED ON CARCINOGENICITY

Two long-term inhalation carcinogenicity studies of 1,3-butadiene have been performed (Hazleton Laboratories, 1981a; NTP, 1984). These studies were summarized in Section 6.2. and Tables 6-1 and 6-2. There is sufficient evidence from these two studies to conclude that 1,3-butadiene is a carcinogen in animals. There is, however, inadequate evidence to demonstrate or refute the carcinogenic potential in humans. Butadiene is therefore classified as an EPA Group B2, probable human carcinogen. The available animal data provide a basis to derive an RQ based on carcinogenicity. An F Factor was calculated from the geometric mean of the tumor incidence in male and female mice. The data and derivation of the F factor are presented in Table 9-4. Because the F factor is between 1 and 100, 1,3-butadiene is placed in Potency Group 2. An EPA Group B2 chemical in Potency Group 2 has a MEDIUM hazard ranking under CERCLA. Therefore, the RQ based on carcinogenicity is 10.

TABLE 9-4

Derivation of Potency Factor (F)
Agent: Butadiene

Reference:	NTP, 1984	NTP, 1984
Exposure route:	inhalation	inhalation
Species:	mouse	mouse
Strain:	B6C3F1	B6C3F1
Sex:	male	female
Vehicle or physical state:	air	air
Body weight (average):	0.035 kg	0.035 kg
Duration of treatment:	60 weeks	61 weeks
Duration of study:	60 weeks	61 weeks
Planned duration of study:	104 weeks	104 weeks
Target organ and tumor type:	Lung-adenoma/carcinoma Hematopoietic system-malignant lymphoma Heart-hemangiosarcoma Forestomach-squamous cell neoplasm Preputial gland-squamous cell carcinomas Zymbal gland-carcinomas Brain - glioma	Lung-adenoma/carcinoma Hematopoietic system-malignant lymphoma Heart-hemangiosarcoma Forestomach-squamous cell neoplasms liver.. Mammary gland aciner cell carcinoma. Ovary-granulosa cell tumors Liver-Hepatocellular tumors
Experimental doses/ exposure:	0, 625, 1250 ppm 6 hours/day, 5 days/week	0, 625, 1250 ppm, 6 hours/day, 5 days/week
Transformed doses (mg/kg/day) internal:	0, 17.6, 28.5	0, 17.6, 28.5
Tumor incidence:	2/50, 43/49, 40/45	4/48, 31/48, 45/49
Unadjusted $1/ED_{10}$: (mouse)	0.8955 $(mg/kg/day)^{-1}$	0.1853 $(mg/kg/day)^{-1}$

TABLE 9-4 (cont.)

Species extrapolation factor:	12.6	12.6
Adjusted factor for early sacrifice:	5.21	4.96
Internal to external dose:	0.20	0.20
Adjusted $1/ED_{10}$ (external) (F factor):	11.8 $(mg/kg/day)^{-1}$	2.3 $(mg/kg/day)^{-1}$
Geometric mean:	5.2 $(mg/kg/day)^{-1}$	

10. REFERENCES

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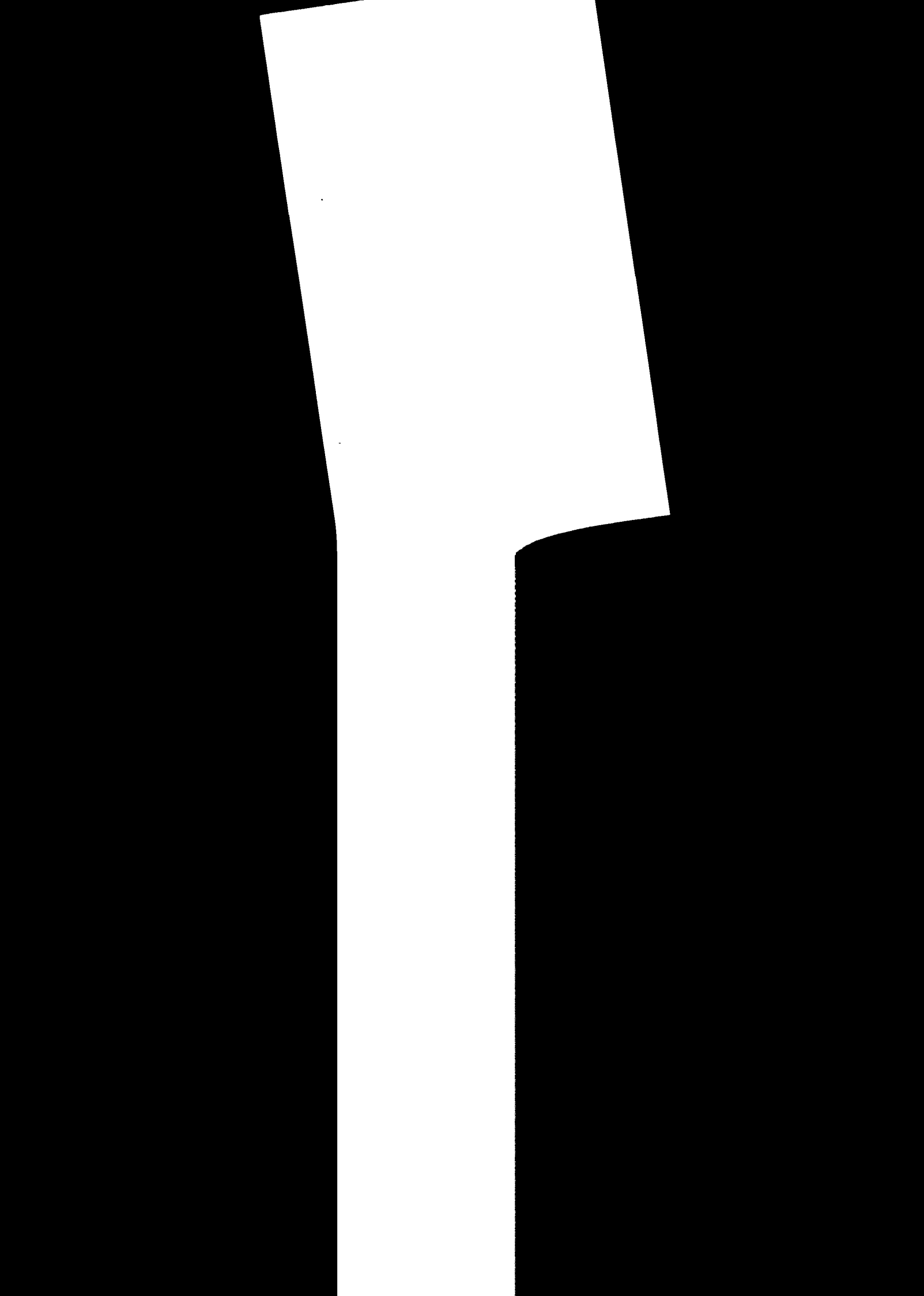

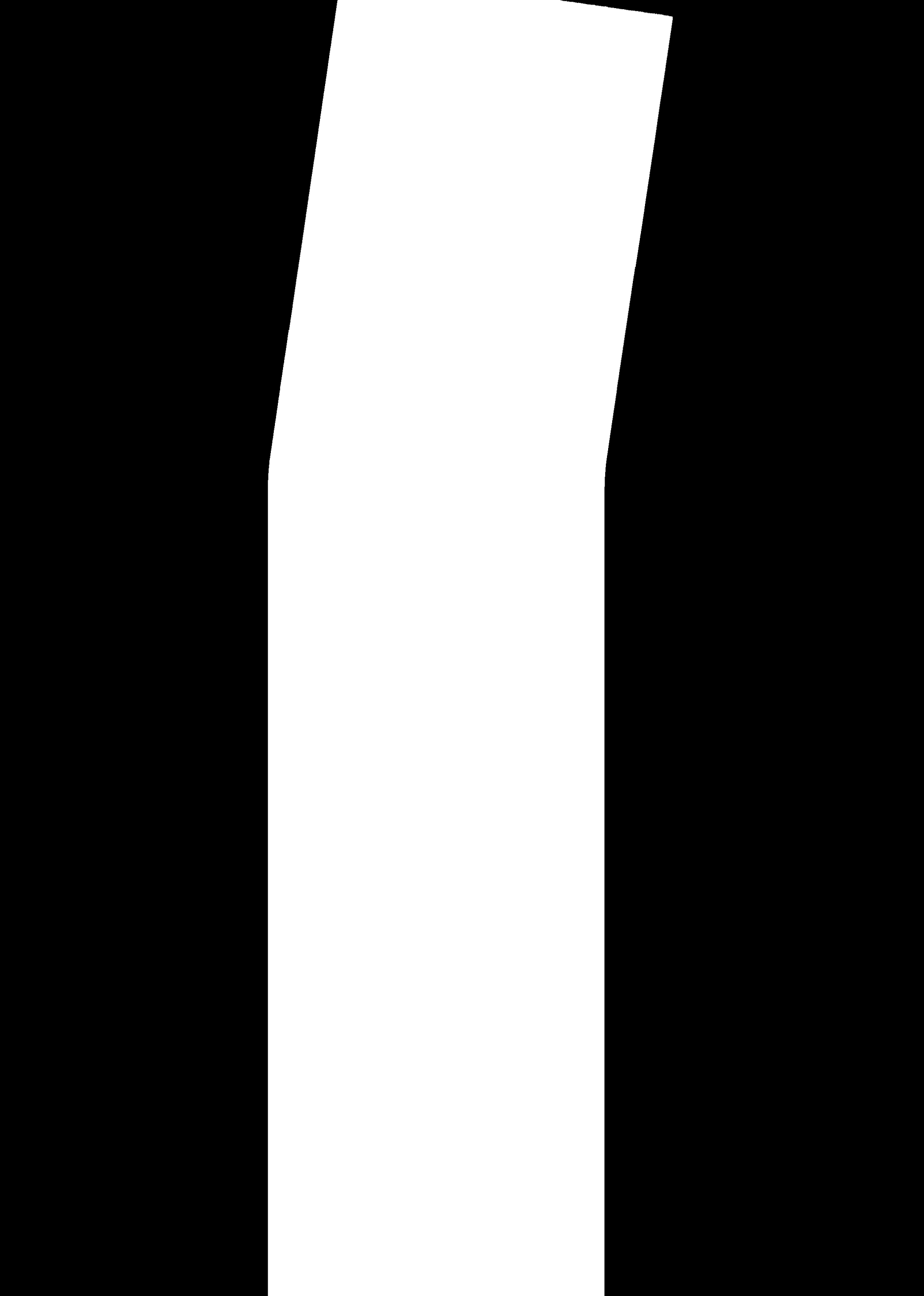

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APPENDIX A

LITERATURE SEARCHED

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

TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in February, 1987. In addition, hand searches were made of Chemical Abstracts (Collective Indices 5-9), and the following secondary sources should be reviewed:

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

ACGIH (American Conference of Governmental Industrial Hygienists). 1986-1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1986-1987. Cincinnati, OH. 111 p.

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

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

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

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

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

USITC (U.S. International Trade Commission). 1985. Synthetic Organic Chemicals. U.S. Production and Sales, 1984, USITC Publ. 1422, Washington, DC.

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

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

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

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

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

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

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

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

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

In addition, the following documents were consulted:

Santodonato, J. 1985. Monograph on human exposure to chemicals in the workplace: 1,3-butadiene. National Cancer Inst. p. 53.

U.S. EPA. 1976. Biological effects and environmental aspects of 1,3-butadiene. Office of Toxic Substances, Washington, DC. p. 58.

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APPENDIX B

Summary Table for 1,3-Butadiene

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	mouse (both sexes)	0, 1381 or 2763 mg/m³, 6 hours/day, 5 days/week for 60-61 weeks	various tumors at multiple sites	$q_1^* = 2.4 \times 10^{-3}$ (ppm)$^{-1}$[a] or 9.0 (mg/kg/day)$^{-1}$[b,c]	NTP, 1984
Oral Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	mouse (both sexes)	0, 1381 or 2763 mg/m³, 6 hours/day, 5 days/week for 60-61 weeks	various tumors at multiple sites	$q_1^* = 9.0$ (mg/kg/day)$^{-1}$[b,c] F = 5.2 (mg/kg/day)$^{-1}$[b,c]	NTP, 1984
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		1000			Hazleton Laboratories, 1981a
Based on Carcinogenicity:		10			NTP, 1984

[a]Derived as the geometric mean of q_1^*s calculated for male and female mice.

[b]Expressed in terms of administered dose.

[c]Derived from inhalation data assuming 100% gastrointestinal absorption and 20% absorption via inhalation at low concentrations.

ID = Insufficient data