TOXICOLOGICAL PROFILE FOR 1,3-BUTADIENE

Agency for Toxic Substances and Disease Registry
Public Health Service

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

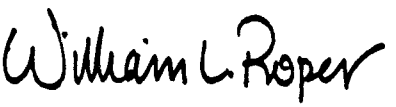
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,3-butadiene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). 1,3-Butadiene has been found at 3 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 1,3-butadiene. As EPA evaluates more sites, the number of sites at which 1,3-butadiene is found may change. The information is important for you because 1,3-butadiene may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,3-butadiene.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as 1,3-butadiene, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 1,3-BUTADIENE?

1,3-Butadiene is a colorless gas with a mild gasoline-like odor. 1,3-Butadiene is almost always found at low levels in urban air samples, but it breaks down quickly in the air. In sunny weather, half of 1,3-butadiene goes away from the air in about 2 hours. Sunlight is not necessary for the removal of 1,3-butadiene from air, but it helps. In the winter time when the days are short or if it is not sunny, about half of it would still be gone in a few days.

Because we do not have enough information, we are not sure exactly what happens to 1,3-butadiene in soil or water. We do not know how often 1,3-butadiene is found in soil or water samples because we do not have reliable methods of looking for it there. If 1,3-butadiene were spilled on water or soil, based on its properties, we expect it to evaporate quickly into the air. We do not expect 1,3-butadiene to collect in plants or fish or to be found in the sediment of rivers and lakes. We also don't expect 1,3-butadiene to be found in soil or underground water sources, but we don't know this for sure. We also don't know how long it takes for 1,3-butadiene to break down in soil or in water because these types of studies have not been done.

1. PUBLIC HEALTH STATEMENT

Very large amounts of 1,3-butadiene are produced every year from petroleum. 1,3-Butadiene is used to make man-made rubber, which is then used mostly for car and truck tires. It is also used to make other kinds of rubber and plastics. 1,3-Butadiene is also found in small amounts in gasoline. Some plastics or man-made rubbers may have very small amounts of 1,3-butadiene trapped in them. These levels are not expected to be high enough to cause health problems. Small amounts are found in the exhaust of automobiles and trucks at approximately 10 parts in 1 billion parts of air (ppb) and in gasoline vapors at 4 ppb. 1,3-Butadiene is also found in cigarette smoke, and it may also be found in the smoke of wood fires.

You will find more information on the chemical properties of 1,3-butadiene in Chapter 3. The uses of 1,3-butadiene are given in Chapter 4. More information on how 1,3-butadiene will behave in the environment is given in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO 1,3-BUTADIENE?

You can be exposed to 1,3-butadiene by breathing air, drinking water, or eating food contaminated with it. Also, people most likely to be exposed to 1,3-butadiene are workers in the production of rubber, plastics, and resins.

1,3-Butadiene has been found at three hazardous waste sites. It has been detected in gases coming from soil. We do not have enough information to know exactly how people near hazardous waste sites may be exposed to 1,3-butadiene.

Because 1,3-butadiene is a gas, you are most likely exposed to it by breathing contaminated air. Large amounts of 1,3-butadiene in the air come from leaks or intentional releases at manufacturing plants. Because it is found in the exhaust of cars and trucks, and in the smoke from wood fires and cigarettes, it is always present at very low levels in the air around cities and towns. The average amount of 1,3-butadiene in the air is 0.3 parts of 1,3-butadiene per billion parts of air (ppb) in cities and suburban areas. These levels are not expected to cause any health problems. The amount of 1,3-butadiene in the air may be much higher near polluted cities or near oil refineries, chemical manufacturing plants, and plastic and rubber factories where this chemical is made or used. The amount in the air can also be very high if 1,3-butadiene is accidentally spilled during shipment from one place to another. 1,3-Butadiene has been measured at very low levels (l-10 ppb) in the plastic or rubber of food containers, but it has not often been found in food samples. These amounts are not expected to cause any health problems. The manufacture of food containers is closely regulated by the Food and Drug Administration (FDA) of the United States. 1,3-Butadiene has been found in drinking water, but we do not know what the concentration was or where it came from.

You can find more information on how much 1,3-butadiene is in the environment and how you might be exposed to it in Chapter 5.

1.3 HOW CAN 1,3-BUTADIENE ENTER AND LEAVE MY BODY?

1,3-Butadiene can enter your body through your lungs if you breathe air contaminated with it. 1,3-Butadiene may also enter your body through the skin if you come into contact with it, but we do not know how much enters this way. We do not know if 1,3-butadiene is present in ground or surface waters near hazardous wastes sites or what happens to it after you drink water contaminated with this compound. Although 1,3-butadiene has been found at only three NPL waste sites, people at or near these waste sites may be exposed by breathing 1,3-butadiene that evaporates into the air. The amount of 1,3-butadiene that enters the body depends on the amount in the environment and the length of time a person comes into contact with it. Animal studies have shown that the breakdown products of 1,3-butadiene leave the body in the urine and in the air breathed out. We don't know what happens to 1,3-butadiene in the body if it is found in water that people drink. More information on how 1,3-butadiene enters and leaves the body can be found in Chapter 2.

1.4 HOW CAN 1,3-BUTADIENE AFFECT MY HEALTH?

Short-term exposure to high levels of 1,3-butadiene causes eye, nose, and throat irritation. Exposure to very high levels could occur during accidental release and could lead to symptoms like drunkenness and unconsciousness, or even to death. However, no such accidental releases have been reported so far. We do not know the exact levels in air that cause these effects in humans. Studies of rubber industry workers suggested possible harmful effects such as more cases of heart diseases, blood diseases, lung diseases, and even cancer from the long-term exposure to low levels of 1,3-butadiene. These rubber industry workers were also exposed to other chemicals along with 1,3-butadiene, so we do not know for sure which chemical (or a combination of them) caused these effects. In addition, the effect of harmful habits like smoking was not considered in the evaluation of health risks of occupational exposure to 1,3-butadiene. 1,3-Butadiene has a gasoline-like odor, which some people can smell at a concentration as low as 1.6 ppm. Skin contact with liquid 1,3-butadiene can cause irritation and frostbite in humans.

Laboratory animals that breathed in high levels of 1,3-butadiene for a short time died. Mice that survived exposure to 1,3-butadiene longer than 14 days had damage in the organs that make blood cells and damage to nose tissues. Pregnant mice that breathed in low amounts of 1,3-butadiene had miscarriages. Birth defects were found in offspring of rats and mice exposed to 1,3-butadiene during pregnancy. Rats that breathed in lower levels of 1,3-butadiene for more than 1 year had kidney disease and damaged lungs; some of them died. Mice that breathed in lower levels of 1,3-butadiene for more than 1 year had harmful effects in their reproductive organs and damaged livers. Rats and mice that breathed in small amounts of 1,3-butadiene for a long time period developed cancer in many organs.

There is no information on human or animal health effects from eating food or drinking water containing 1,3-butadiene.

There is no information on animal health effects from skin contact with 1,3-butadiene.

A more complete discussion of the effects of 1,3-butadiene on health can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1.3-BUTADIENE?

We have no reliable medical test to determine whether you have been exposed to 1,3-butadiene at this time, but scientists are trying to find a way to test blood to see if 1,3-butadiene attaches to certain compounds such as deoxyribonucleic acid (DNA) or proteins that are found in the blood. For further information, please read Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The Environmental Protection Agency (EPA) requires industries to report spills of 1 pound or more of 1,3-butadiene. EPA also intends to add 1,3-butadiene to the list of hazardous air pollutants (EPA 1985b).

1,3-Butadiene levels in the workplace are controlled by the Occupational Safety and Health Administration (OSHA). The previous limit in workplace air was 1,000 ppm, averaged over an 8-hour workday in a 40-hour workweek. However, the National Institute for Occupational Safety and Health (NIOSH) recommended that OSHA consider lowering this limit because 1,3-butadiene has caused cancer in animals. OSHA is in the process of lowering it.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,3-butadiene and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 1,3-butadiene based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods- -acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of 1,3-butadiene are indicated in Figure 2-l. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

2. HEALTH EFFECTS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Information on the lethality of 1,3-butadiene in humans is limited. Epidemiological studies indicate the possibility of higher than normal mortality rates from cancer and certain cardiovascular diseases among rubber workers (Downs et al. 1987; Fox et al. 1974; Matanoski et al. 1982; McMichael et al. 1974, 1975, 1976). For further information see Sections 2.2.1.8 and the discussion of cardiovascular effects in Section 2.2.1.2.

In an acute exposure situation, B6C3Fl mice were exposed to 1,3-butadiene at concentrations ranging from 625 to 8,000 ppm (NTP 1984). All animals survived, and there were no compound-related effects observed at necropsy. When rabbits were exposed to 250,000 ppm of 1,3-butadiene, the experiment resulted in death of the majority of animals within an average of 23 minutes of exposure (Carpenter et al. 1944). The LC_{50} for mice after 2 hours of exposure was 122,000 ppm and the LC_{50} for rats after 4 hours of exposure was 129,000 ppm (Shugaev 1969).

No deaths were observed in rats during 13 weeks of exposure to l,000-8,000 ppm of 1,3-butadiene (Crouch et al. 1979), or in rats, guinea pigs, rabbits, and dogs during 8 months of exposure to 6,700 ppm (Carpenter et al. 1944). In contrast, appreciable mortality occurred in mice exposed to 5,000 ppm or more for 14 weeks (NTP 1984).

During chronic exposure to 625 and 1,250 ppm of 1,3-butadiene for 61 weeks, significantly increased mortality occurred among B6C3Fl mice primarily due to cancer (NTP 1984). Similar results were obtained in another study using a much lower concentration (20 ppm) (Melnick et al. 1989, 1990). Exposure of rats to 8,000 ppm 1,3-butadiene resulted in statistically significant increased mortality from cancer when compared with controls (Owen et al. 1987). The LC_{50}s, all reliable LOAEL values, and the highest NOAEL

values in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The systemic effects of 1,3-butadiene after inhalation exposure are described below. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to 1,3-butadiene.

The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Workers exposed to 1,3-butadiene gas during the manufacture of rubber complained of irritation of the eyes, nasal passages, throat, and lungs (Wilson 1944). In some, coughing, fatigue, and drowsiness developed. All symptoms disappeared on removal from the gas. The exposure levels were not stated in the study.

No effects in respiratory tissues in rats, mice, guinea pigs, or dogs were found in intermediate-duration studies (Carpenter et al. 1944; Crouch et al. 1979; NTP 1984). The study of Carpenter et al. (1944) was limited because of poorly described methods and the use of few animals per group.

After chronic exposure to 1,250 ppm 1,3-butadiene, an increase in nonneoplastic respiratory changes was found in mice (NTP 1984), including chronic inflammation of the nasal cavity, fibrosis, cartilaginous metaplasia, osseous metaplasia, atrophy of the sensory epithelium, and hyperplasia of the respiratory epithelium (Melnick et al. 1990). No lesions of the nasal cavity were found in the controls. However, lung tumors were found in animals at 6.25, 625, and 1,250 ppm (Melnick et al. 1989; NTP 1984) (see Section 2.2.1.8). Lungs of rats exposed chronically to 8,000 ppm 1,3-butadiene revealed metaplasia (Owen et al. 1987).

Cardiovascular Effects. In a retrospective epidemiological study, excessive mortality among middle-aged workers in the rubber industry was noted for certain types of cardiovascular diseases, mainly chronic rheumatic and arteriosclerotic heart diseases (McMichael et al. 1974). Furthermore, increased mortality for arteriosclerotic heart disease was reported among black males in the rubber industry (Matanoski and Schwartz 1987). This result was confirmed in an update of the original study (Matanoski et al. 1988, 1990). However, the authors noted that the practice of categorizing the individuals of unknown race under whites may have caused a slight inflation of the results.

No cardiovascular lesions were found in mice or rats after intermediate-duration exposure to 8,000 ppm 1,3-butadiene (Crouch et al. 1979; NTP 1984).

TABLE 2-1. Levels of Significant Exposure to 1,3-Butadiene - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4 hr/d				129,000 (LC_{50})	Shugaev 1969
2	Rabbit	1 d 23 min/d				250,000	Carpenter et al. 1944
3	Mouse	2 wk 5 d/wk 6 hr/d		8,000			NTP 1984
4	Mouse	1 d 2 hr/d				122,000 (LC_{50})	Shugaev 1969
Neurological							
5	Human	1 d 6-8 hr/d		8,000			Carpenter et al. 1944
6	Rabbit	1 d 23 min/d				250,000 (anesthesia)	Carpenter et al. 1944
Developmental							
7	Rat	10 d 6 hr/d Gd 6-15		200	1,000 (wavy ribs)	8,000 (skeletal abnormalities)	Irvine 1981
8	Mouse	10 d Gd 6-15 6 hr/d			40 (decreased fetal weight)	200 (extra ribs)	Hackett et al. 1987
Reproductive							
9	Mouse	5 d 6 hr/d				1,000 (sperm head abnormalities)	Hackett et al. 1988a
10	Mouse	5 d 6 hr/d				200 (dead implantations)	Hackett et al. 1988a
INTERMEDIATE EXPOSURE							
Death							
11	Rat	13 wk 5 d/wk 6 hr/d		8,000			Crouch et al. 1979

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
12	Mouse	14 wk 5 d/wk 6 hr/d		2,500		5,000 (increased mortality)	NTP 1984
Systemic							
13	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Hemato Hepatic Renal Derm/oc	8,000 8,000 8,000 8,000 8,000 8,000			Crouch et al. 1979
14	Mouse	14 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Hepatic Renal Derm/oc	8,000 8,000 8,000 8,000 8,000 8,000 8,000			NTP 1984
15	Mouse	3-24 wk 6 d/wk 6 hr/d	Hemato			1,250 (macrocytic megaloblastic anemia)	Irons et al. 1986a
Immunological							
16	Mouse	6-24 wk 5 d/wk 6 hr/d			1,250 (lymphoid organ histopathology)		Thurmond et al. 1986
Neurological							
17	Rat	13 wk 5 d/wk 6 hr/d		8,000			Crouch et al. 1979
18	Mouse	14 wk 5 d/wk 6 hr/d		8,000			NTP 1984
Cancer							
19	Mouse	13-52 wk 5 d/wk 6 hr/d				200 (CEL)	Melnick et al. 1990

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
CHRONIC EXPOSURE							
Death							
20	Rat	105-111 wk 5 d/wk 6 hr/d		1,000		8,000 (increased mortality)	Owen et al. 1987
21	Mouse	61 wk 5 d/wk 6 hr/d				625 (increased mortality)	NTP 1984
22	Mouse	65 wk 5 d/wk 6 hr/d		6.25		20 (increased mortality)	Melnick et al. 1989, 1990
Systemic							
23	Rat	105-111 wk 5 d/wk 6 hr/d	Resp	1,000	8,000 (increased organ weight, metaplasia)		Owen et al. 1987
			Cardio	8,000			
			Gastro	8,000			
			Hemato	8,000			
			Hepatic	8,000			
			Renal	1,000		8,000 (nephrosis)	
			Derm/oc	8,000			
24	Mouse	61 wk 5 d/wk 6 hr/d	Resp			1,250 (atrophy of nasal olfactory epithelium)	NTP 1984
			Cardio		625 (endothelial hyperplasia)		
			Gastro		625 (epithelial hyperplasia		
			Hepatic		625 (necrosis)		
			Renal	1,250			
			Derm/oc	1,250			
25	Mouse	65 wk 5 d/wk 6 hr/d	Resp	20	62.5 (epithelial hyperplasia)		Melnick et al. 1989, 1990
			Cardio	20	62.5 (epithelial hyperplasia)		
			Gastro	20	62.5 (epithelial hyperplasia)		
			Hemato	20	62.5 (anemia)		
Neurological							
26	Rat	105-111 wk 5 d/wk 6 hr/d		8,000			Owen et al. 1987

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
27	Mouse	61 wk 5 d/wk 6 hr/d		1,250			NTP 1984
Reproductive							
28	Mouse	61 wk 5 d/wk 6 hr/d				625 (gonadal atrophy)	NTP 1984
29	Mouse	65 wk 5 d/wk 6 hr/d				6.25 (ovarian atrophy)	Melnick et al. 1989, 1990
Cancer							
30	Rat	105-111 wk 5 d/wk 6 hr/d				1,000 (CEL)	Owen et al. 1987
31	Mouse	61 wk 5 d/wk 6 hr/d				625 (CEL)	NTP 1984
32	Mouse	65 wk 5 d/wk 6 hr/d				6.25 CEL	Melnick et al. 1989, 1990

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk = week

FIGURE 2-1. Levels of Significant Exposure To 1,3-Butadiene - Inhalation

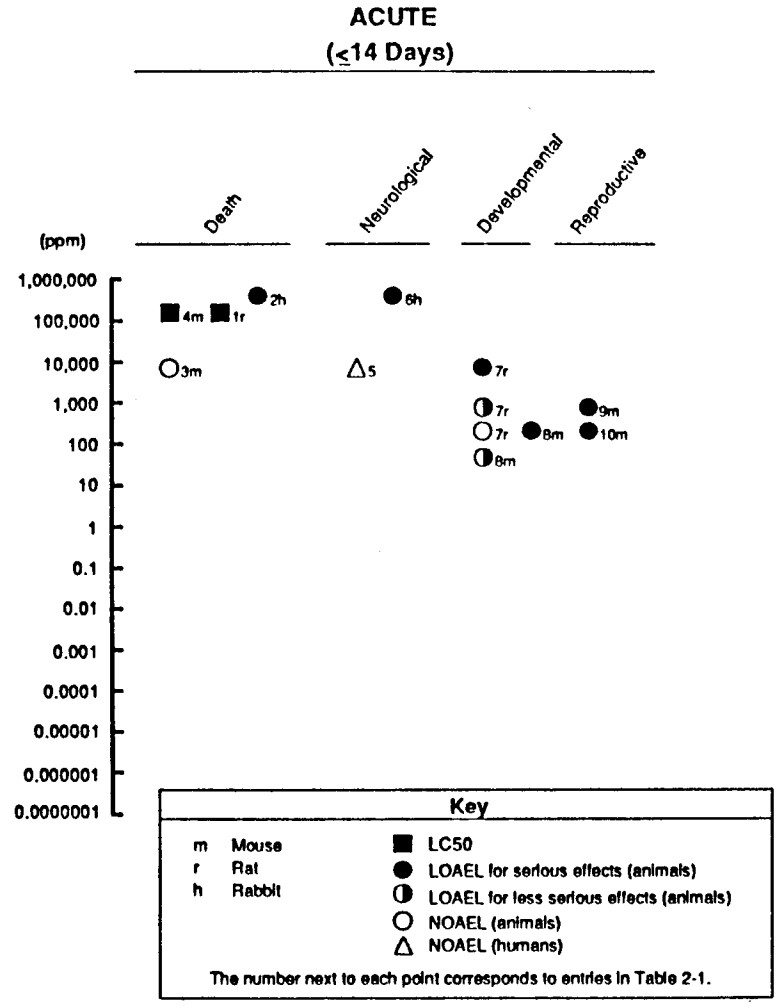


FIGURE 2-1 (Continued)

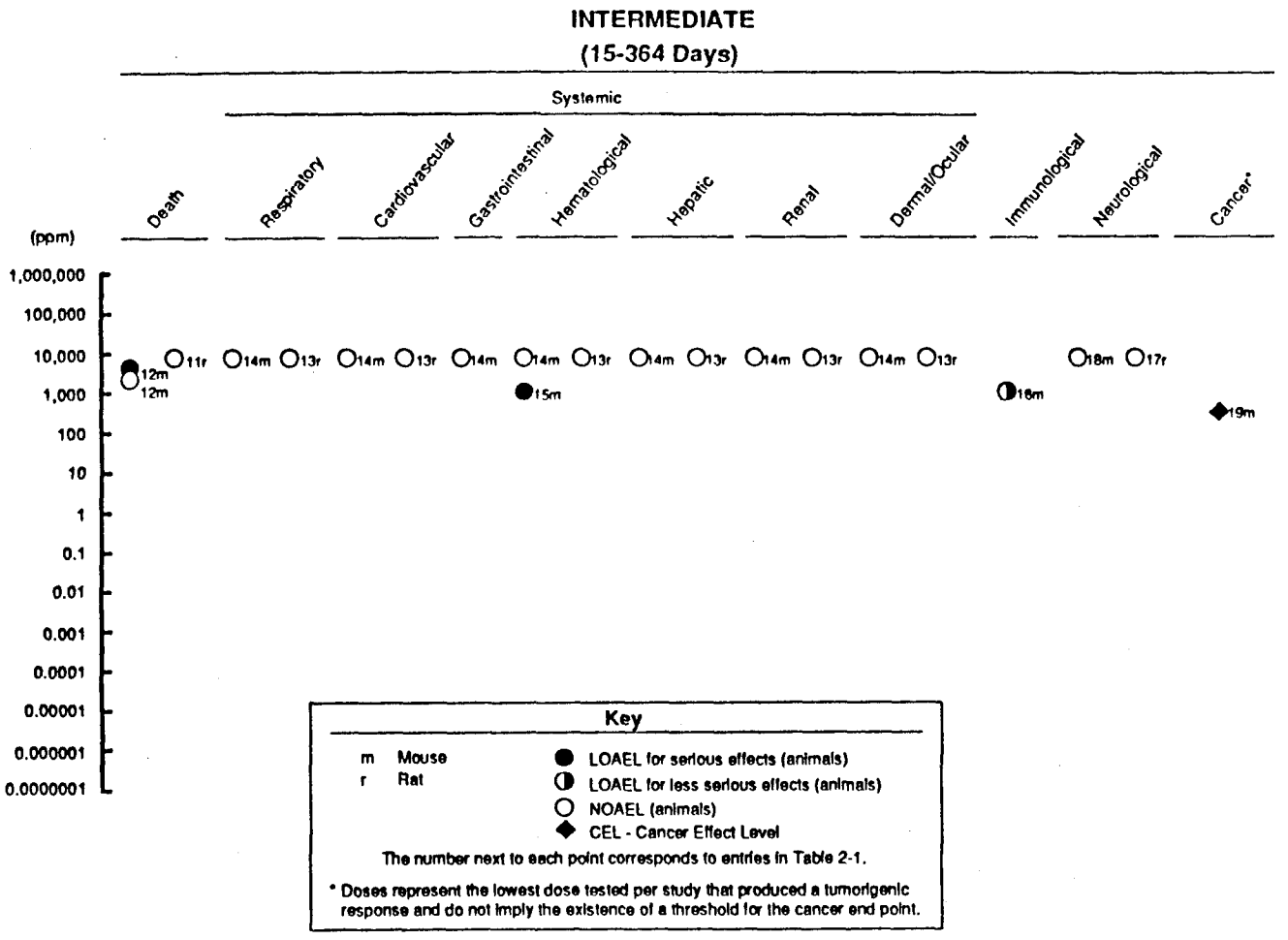
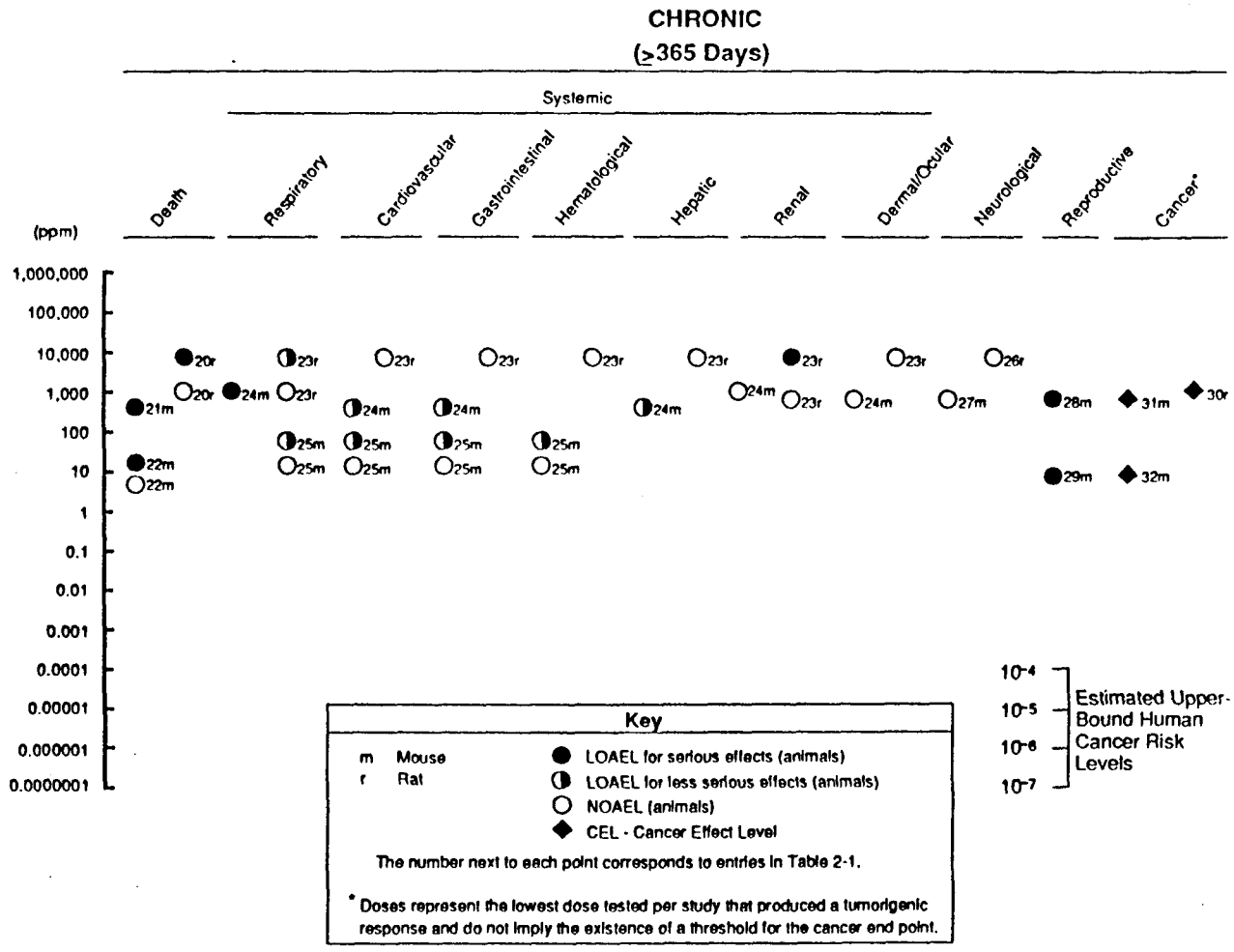


FIGURE 2-1 (Continued)



Endothelial hyperplasia in the heart (an early preneoplastic lesion) was observed in mice after 61 weeks of exposure (Melnick et al. 1990; NTP 1984). A high incidence of hemangiosarcomas of the heart was also noted in exposed animals (see Section 2.2.1.8). No exposure-related histopathological cardiac lesions were found in rats exposed chronically to up to 8,000 ppm for 2 years (Owen et al. 1987).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 1,3-butadiene.

No histopathological changes were found after examination of gastrointestinal tract tissues of mice following intermediate-duration exposure (NTP 1984). In a chronic-duration study, high incidences of epithelial hyperplasia (a possible preneoplastic lesion) and carcinoma of the forestomach were found among exposed mice (Melnick et al. 1990; NTP 1984), but no exposure-related nonneoplastic gastrointestinal lesions were found in rats exposed chronically to up to 8,000 ppm (Owen et al. 1987).

Hematological Effects. A hematological survey of workers at a styrene-butadiene rubber plant revealed little indication of bone marrow toxicity among the workers (Checkoway and Williams 1982). Styrene and 1,3-butadiene were the most significant chemicals in the atmosphere; benzene and toluene were present in much lower concentrations. A group of eight tank farm workers (workers who fill freight train shipping containers) (mean level exposure of 20 ppm) demonstrated slightly lower levels of red blood cells, hemoglobin, platelets, and neutrophils compared with other workers, but these findings were within the normal range. Other epidemiological studies, however, implicated 1,3-butadiene as the possible cause of hematopoietic malignancies among styrene-butadiene rubber workers (McMichael et al. 1975) at exposure levels that may be lower than 20 ppm.

No signs of blood dyscrasias were found among 164 animals (rats, rabbits, guinea pigs, dogs) exposed to concentrations up to 6,700 ppm of 1,3-butadiene for 8 months (Carpenter et al. 1944). The results were supported by a 3-month study, in which no effects on hematological indices were found in rats after exposure to 8,000 ppm of 1,3-butadiene (Crouch et al. 1979).

A treatment-related macrocytic-megaloblastic anemia was observed in B6C3Fl and NIH mice exposed to 1,250 ppm 1,3-butadiene for 6-24 weeks (Irons et al. 1986a, 1986b). The bone marrow damage was expressed as reduced numbers of red blood cells, decreased hemoglobin concentration and hematocrit, and increased mean corpuscular volume of circulating erythrocytes. The changes were observed in both strains, independently of the occurrence of murine leukemia viruses in the animals. No such changes were evident after 3 weeks exposure of B6C3Fl mice to the same concentration (Irons et al. 1986a). Decreases in red blood cell counts and hemoglobin concentrations were reported

in male mice after an intermediate duration exposure to 62.5 ppm or more 1,3-butadiene (Melnick et al. 1989, 1990).

In contrast to the findings in mice, no effects on hematology and blood chemistry of Sprague-Dawley rats were observed after exposure to 1,000 and 8,000 ppm of 1,3-butadiene for 105-111 weeks (Owen et al. 1987). The hematological effects in mice after chronic exposure consisted of malignancies of the hematopoietic system (Melnick et al. 1989, 1990; NTP 1984) (see Section 2.2.1.8).

Hepatic Effects. No studies were located regarding hepatic effects of 1,3-butadiene in humans after inhalation exposure.

No histopathological changes in livers of rats (Crouch et al. 1979) or mice (NTP 1984) were found after intermediate-duration exposure to 1,3-butadiene. The relative liver weights of both sexes of Sprague-Dawley rats were elevated after the chronic exposure to 1,3-butadiene (1,000 and 8,000 ppm); however, this finding was not associated with any pathological changes (Owen et al. 1987). Mice, on the other hand, in addition to the neoplastic changes (see Section 2.2.1.8), had a significant increase in liver necrosis at both exposure levels (625 and 1,250 ppm 1,3-butadiene) (NTP 1984).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,3-butadiene.

The results of urinalysis in 164 animals, including rats, guinea pigs, rabbits, and dogs were all normal after an 8-month exposure to concentrations up to 6,700 ppm of 1,3-butadiene (Carpenter et al. 1944), but the methods were poorly described. These results were supported, however, in rats after 13 weeks exposure to concentrations up to 8,000 ppm of 1,3-butadiene (Crouch et al. 1979). Furthermore, no renal pathology was found in mice after exposure to 8,000 ppm for 14 weeks or 1,250 ppm for 61 weeks (NTP 1984). Nephrosis was found among male rats after 111 weeks of exposure to 8,000 ppm, but not 1,000 ppm of 1,3-butadiene (Owen et al. 1987).

Dermal/Ocular Effects. Two men reported slight irritation of the eyes and difficulty in focusing on instrument scales during 6-7 hours exposure to 2,000 and 4,000 ppm 1,3-butadiene (Carpenter et al. 1944).

Ophthalmologic examination of the eyes of dogs and rabbits disclosed no signs of injury during the course of exposure to up to 6,700 ppm 1,3-butadiene for 8 months (Carpenter et al. 1944). After the termination of the experiment, histological examination revealed that the sclera, cornea, and ciliary body were normal. Sections of the optic nerve with adjacent retina showed no myelin sheath degeneration. Although the ophthalmological

examination was described in detail, the study was limited by the small number of animals used.

No histopathological dermal or ocular changes were found in *rats or* mice after 13-14 weeks exposure to 8,000 ppm (Crouch et al. 1979; NTP 1984) or in rats after 111 weeks exposure to 8,000 ppm 1,3-butadiene (Owen et al. 1987).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects of 1,3-butadiene in humans after inhalation exposure.

After 3-21 weeks of exposure to 1,250 ppm 1,3-butadiene, an increased expression of murine leukemia virus (MuLV) was observed in hematopoietic tissues of B6C3Fl mice, but not in NIH mice (Irons et al. 1987a). Furthermore, altered regulation of the stem cell development in B6C3Fl strain was reported after similar exposure (Leiderman et al. 1986). The significance of these results is discussed in the subsection on cancer in Section 2.4.

No severe immunological changes were detected after evaluation of specific humoral and cell-mediated immunity in B6C3Fl mice exposed to 1,250 ppm 1,3-butadiene for 6, 12, or 24 weeks (Thurmond et al. 1986). Suppression of cytotoxic T-lymphocyte generation to mastocytoma cells was observed after 6 weeks, but recovered after 12 weeks of exposure. The histological examination of lymphoid organs showed depressed spleen cellularity after 24 weeks of exposure; this value is recorded as a LOAEL for immunological effects in Table 2-l and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

Inhalation of 1,3-butadiene is mildly narcotic in humans at low concentrations (not otherwise specified) and may result in a feeling of lethargy and drowsiness (Sandmeyer 1981). At very high concentrations, 1,3-butadiene causes narcosis leading to respiratory paralysis and death. The first signs observed in humans are blurred vision, nausea, paresthesia and dryness of the mouth, throat, and nose, followed by fatigue, headache, vertigo, decreased blood pressure and pulse rate, and unconsciousness. Respiratory paralysis is likely to occur only after exposure *to* high concentrations of 1,3-butadiene such as after spills or leaks.

Psychomotor responses of *two* men inhaling 2,000, 4,000 or 8,000 ppm 1,3-butadiene for 6-8 hours/day on different days were evaluated by Carpenter et al. (1944). At the two higher concentrations, the subjects performed a steadiness test; at the highest concentration, a tapping rate test was also performed. Results after 1,3-butadiene exposure were identical to those obtained before exposure.

Rabbits exposed to 250,000 ppm of 1,3-butadiene went through all stages of anesthesia to death in the average time of 23 minutes (Carpenter et al. 1944). Less than 2 minutes of exposure was required for loss of motor and labyrinth reflexes.

No effects on erythrocyte or brain cholinesterase or on neuromuscular function tests were found in rats exposed to up to 8,000 ppm for 13 weeks (Crouch et al. 1979). In intermediate and chronic exposure studies in mice and rats, no treatment-related histopathological lesions were found in .organs and tissues of the nervous system (brain, spinal cord, sciatic nerves) (Crouch et al. 1979; NTP 1984; Owen et al. 1987). Tests for neurological functions were not performed by NTP (1984) and were unreliable as performed by Owen et al. (1987) because mammary tumors interfered with the mobility of rats. The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,3-butadiene.

When exposed to concentrations up to 8,000 ppm of 1,3-butadiene during gestation days 6-15, Sprague-Dawley rats showed signs of dose-related maternal and fetal toxicity (Irvine et al. 1981). Depressed body weight gain among dams was observed at all concentrations, and fetal growth was significantly decreased in the 8,000 ppm group. The fetotoxicity of 1,3-butadiene was expressed by a statistically significant increased incidence of skeletal abnormalities (wavy ribs, irregular rib ossification) in the 1,000 ppm group and by major abnormalities (defects of the skull, spine, sternum, long bones, and ribs) in the 8,000 ppm group. In a study in which female outbred Sprague-Dawley derived rats were exposed to 1,3-butadiene at concentrations up to 1,000 ppm during gestation days 6-15 (Hackett et al. 1987a), some skeletal abnormalities and ossification reductions were found in the fetuses, but were not statistically significant and not considered to be treatment related. In contrast, fetotoxicity expressed as decreased fetal weight was observed in male mice fetuses after exposure of dams during gestation days 6-15 to 40 ppm 1,3-butadiene, and increased incidences of extra ribs and reduced ossification of sternebrae were found in fetuses from groups exposed to 200 ppm and 1,000 ppm, respectively (Hackett et al. 1987b).

The highest NOAEL value and all reliable LOAEL values for developmental effects in rats for the acute duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 1,3-butadiene.

A concentration-related increase in the incidence of sperm-head abnormalities occurred in B6C3Fl mice after exposure to 1,000 and 5,000 ppm of 1,3-butadiene for 6 hours/day for 5 days (Hackett et al. 1988a). Dominant lethality in CD-1 mice was also observed during the first 2 postexposure weeks after the males were exposed to 200, 1,000 but not 5,000 ppm (Hackett et al. 1988b). The study was considered to be inconclusive because of the lack of dose response.

In animals exposed to 6,700 ppm or less 1,3-butadiene, no impairment of fertility was noted when groups of male and female rats, rabbits, or guinea pigs were housed together and allowed to mate freely (Carpenter et al. 1944). In intermediate duration studies, no histopathological evidence of treatment related effects in reproductive organs of rats (Crouch et al. 1979) or mice (NTP 1984) was found, but reproductive function was not assessed in these studies.

In a chronic study, exposure of mice to 6.25 ppm or more of 1,3-butadiene resulted in an increased incidence of ovarian atrophy in females (Melnick et al. 1989, 1990), while a corresponding increase in testicular atrophy was observed in males only after exposure to 625 ppm (Melnick et al. 1989, 1990; NTP 1984). The data indicated high susceptibility of female mice to 1,3-butadiene-induced effects in reproductive organs. Malignant tumors in reproductive tissues were found after chronic exposure in rats, but reproductive functions were not evaluated (Owen et al. 1987). All reliable LOAEL values for effects in the reproductive system in mice in each duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No significant differences in cytogenetic analysis (chromosome aberrations and sister chromatid exchanges in peripheral lymphocytes) were found between a group of 30 styrene-butadiene rubber workers and a group of matched controls (Zhou et al. 1986). The influence of sex, age, or smoking habits was evaluated in the study. However, the exact exposure levels to 1,3-butadiene were not measured.

Generally, no genotoxic effects were found in bone marrow of rats exposed by inhalation to 1,3-butadiene (Choy et al. 1986; Cunningham et al. 1986). B6C3Fl mice were exposed to 1,3-butadiene at concentrations up to 10,000 ppm for 6 hours/day for 2 days (Choy et al. 1986). A statistically significant dose-related increase in micronucleus induction was observed in mice beginning at 100 ppm. The frequency of micronucleated polychromatic erythrocytes was also significantly increased in B6C3Fl mice exposed 6 hours/day, 5 days/week

for 13 weeks to concentrations of 62.5 and 625 ppm of 1,3-butadiene (Jauhar et al. 1988). In B6C3Fl mice exposed to 6.25, 62.5, and 625 ppm of 1,3-butadiene for 6 hours/day for 10 days, the most sensitive indicator of genotoxic damage was the frequency of sister chromatid exchanges (statistically significant at 6.25 ppm), followed by micronucleated polychromatic erythrocyte levels (statistically significant at 62.5 ppm), and then by chromosomal aberration frequencies (statistically significant at 625 ppm) (Tice et al. 1987). A statistically significant increase in sister chromatid exchange was also observed in mice starting at 100 ppm of 1,3-butadiene, with a four-fold increase over control levels evident at 10,000 ppm (exposure 6 hours/day for 2 days) (Cunningham et al. 1986). In B6C3Fl and NIH Swiss mice, comparable increases in the frequency of chromosomal aberrations were observed following exposure to 1,250 ppm of 1,3-butadiene for 6 hours (Irons et al. 1987b). These results indicate that 1,3-butadiene-treatment in vivo produces significant increases in chromatid aberrations in both strains.

In a dominant lethal study in which male CD-1 mice were exposed to 1,3-butadiene for 5 days and mated to nonexposed females, an increased number of dead implantations per pregnancy occurred at 200 and 1,000 ppm, but not at 5,000 ppm during the first 2 weeks postexposure (Hackett et al. 1988a). These results were considered to be inconclusive because of the lack of a strict dose-response relationship.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

Epidemiological retrospective studies of mortality among workers in the rubber industry were conducted by several investigators (Case and Hosker 1954; Fox et al. 1974; Matanoski and Schwartz 1987; Matanoski et al. 1982, 1988, 1990; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982). Occupational exposure in styrene-butadiene rubber plants was linked to increased incidences in respiratory, bladder, stomach, and lymphato-hematopoietic cancers. Because workers were exposed to mixtures of various chemicals, the contribution of 1,3-butadiene exposure to the development of these effects was unclear. Therefore, an attempt has been made to link the effects to specific exposures. When the workers were grouped according to a work area and a job longest held, production workers had increased Standard Mortality Ratios (SMR) for hematolymphopoietic neoplasms (SMR was 230 for other lymphatic neoplasms in whites; SMRs were 532 for lymphosarcoma, 656 for leukemia, and 484 for other lymphatic neoplasms in blacks) and maintenance workers had increased SMRs for digestive cancers (SMRs were 144 for esophageal and 166 for stomach cancer in whites) (Matanoski et al. 1990). The Matanoski et al. (1982, 1988, 1990) studies were, however, confounded by assuming the individuals of unknown race (15% of the total) to be white. This approach may have caused a slight inflation of results on racial distribution of mortality from cancers in the cohort. A nested case-control study for hemato-lymphopoietic cancers was performed in

one of the original cohorts of styrene-butadiene rubber workers (Matanoski et al. 1989b). The leukemia cases were associated with exposure to 1,3-butadiene (odds ratio=9.4). No such an association was found for exposure to styrene. The results were supported by a study in a 1,3-butadiene-monomer manufacturing plant (Downs et al. 1987). A higher mortality rate for lymphosarcoma and reticulum cell sarcoma (SMR=235) was reported in the cohort. Observed deaths from cancer of gastrointestinal, respiratory, urinary, and skeletal systems were also statistically evaluated in this cohort and compared with the expected numbers. No increase in mortality was reported for these categories. Similar results were reported in an update of the study (SMR=229 for lymphosarcoma) (Divine 1990). However, almost half of the cohort worked less than 5 years in the industry and the workers also had an occupational history of working in other chemical industries.

The lack of historic exposure data to 1,3-butadiene and, as mentioned above, possible exposure to other chemicals are the main confounding factors of epidemiological studies in 1,3-butadiene exposed workers. In addition, though adjustments for age, calendar time, and race were done in most studies, the adjustment for smoking was lacking.

Lymphocytic lymphomas were found in B6C3Fl mice exposed to 200 ppm 1,3-butadiene for 40 weeks and observed up to 104 weeks (Melnick et al. 1990). Further experiments with various intermediate-durations and various levels of exposure indicated that tumor types other than lymphocytic lymphoma had a better chance to develop with longer survival of the animals.

When B6C3Fl mice were exposed for 61 weeks to 625 or 1,250 ppm 1,3-butadiene, multiple-site carcinomas developed (NTP 1984). The most common were hemangiosarcoma of the heart, malignant lymphoma, alveolar/bronchiolar adenoma and carcinoma, papilloma and carcinoma of the stomach, hepatocellular adenoma or carcinoma, and mammary gland and ovary carcinomas and nonmalignant granulosa cell tumors. When the chronic exposure study in mice was repeated, lymphocytic lymphomas were the major cause of death in groups exposed to 625 ppm 1,3-butadiene (Melnick et al. 1989, 1990). An increased incidence of hemangiosarcoma of the heart was found in males exposed to 62.5 ppm and higher. Furthermore, the incidence of alveolar-bronchiolar neoplasms was increased in males exposed to 62.5 ppm 1,3-butadiene and in females exposed to doses as low as 6.25 ppm (Melnick et al. 1989).

Multiple carcinomas occurred in rats after chronic exposure to 1,000 ppm and 8,000 ppm 1,3-butadiene for 105/111 weeks (Owen et al. 1987). Significantly increased incidences of Leydig cell adenoma, pancreatic exocrine adenoma, uterine sarcoma, mammary tumors, Zymbal gland carcinoma, and thyroid follicular cell tumors were observed in the higher concentration group. The cancer effect levels (CELs) are recorded in Table 2-l and plotted in Figure 2-l.

Using the tumor data from male and female mice in the NTP (1984) study, EPA derived a unit risk for inhalation exposure of $6x10^{-4}$ ppb (IRIS 1991). This unit risk corresponds to upper bound individual lifetime cancer risks at 10^{-4} to 10^{-7} risk levels of $2x10^{-4}$ to $2x10^{-7}$ ppm, which are plotted in Figure 2-l. The unit risk should not be used if the air concentration exceeds 7.2 ppb, since above this concentration, the slope factor may differ from that stated (IRIS 1991).

The EPA derivation does not take into consideration the more recent study by Melnick et al. (1989, 1990) because the data were not available at the time of the q_1* derivation. Furthermore, the latest data regarding species differences in 1,3-butadiene toxicokinetics between rodents and primates indicated that mice may be more susceptible to 1,3-butadiene-induced effects (Dahl et al. 1990; Sun et al. 1989a).

2.2.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to 1,3-butadiene.

2.2.2.1 Death
2.2.2.2 Systemic Effects
2.2.2.3 Immunological Effects
2.2.2.4 Neurological Effects
2.2.2.5 Developmental Effects
2.2.2.6 Reproductive Effects
2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to 1,3-butadiene.

2.2.3 Dermal Exposure

Dermal contact with liquid 1,3-butadiene causes a sensation of cold followed by a sensation of burning, which is the result of rapid evaporation; this may cause frostbite. High gas concentrations may cause mild skin irritation as well (MCA 1974). No other studies were located regarding the following health effects in humans or animals after dermal exposure to 1,3-butadiene.

2.2.3.1 Death
2.2.3.2 Systemic Effects
2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,3-butadiene.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption of 1,3-butadiene in humans after inhalation exposure.

The distribution coefficient for 1,3-butadiene between rabbit blood and air was 0.603 in vitro and 0.654 in vivo, suggesting simple passive diffusion of the gas from the alveoli to the blood (Carpenter et al. 1944). After 9 minutes exposure of rabbits to 250,000 ppm, the concentration of 1,3-butadiene was 0.26 mg/mL in the femoral artery and 0.18 mg/mL in the femoral vein. Pulmonary absorption, therefore, appears to be rapid. Distribution studies in rats and mice following inhalation exposure to 1,3-butadiene indicate that it is absorbed from the lungs in these species as well (see Section 2.3.2.1). When Macaca fascicularis monkeys were exposed to radioactively labeled 1,3-butadiene, the uptake was calculated as 16.40 μmol/hour/10 ppm of inhaled and 3.20 μmol/hour/10 ppm of retained 1,3-butadiene (Dahl et al. 1990).

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to 1,3-butadiene.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 1,3-butadiene.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to 1,3-butadiene.

The distribution of 1,3-butadiene in several tissues in rats was measured following a l-hour inhalation exposure to 129,000 ppm (Shugaev 1969). There was a high concentration of 1,3-butadiene in perinephric fat with lower levels in the brain, liver, septum, and kidney. These levels decreased with time; at 90 minutes following inhalation exposure, only trace levels of 1,3-butadiene could be found.

Species differences in the distribution.of inhaled 1,3-butadiene were studied in Sprague-Dawley rats and B6C3Fl mice (Bond et al. 1986, 1987). The tissues from both species contained high concentrations of ^{14}C-1,3-butadiene derived radioactivity 1 hour postexposure. The mouse tissues contained up to seven times more of 1,3-butadiene and its metabolites in their tissues as compared to rats, while up to five times more was detected in their blood.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals after oral exposure to 1,3-butadiene.

2.3.2.3 Dermal Exposure

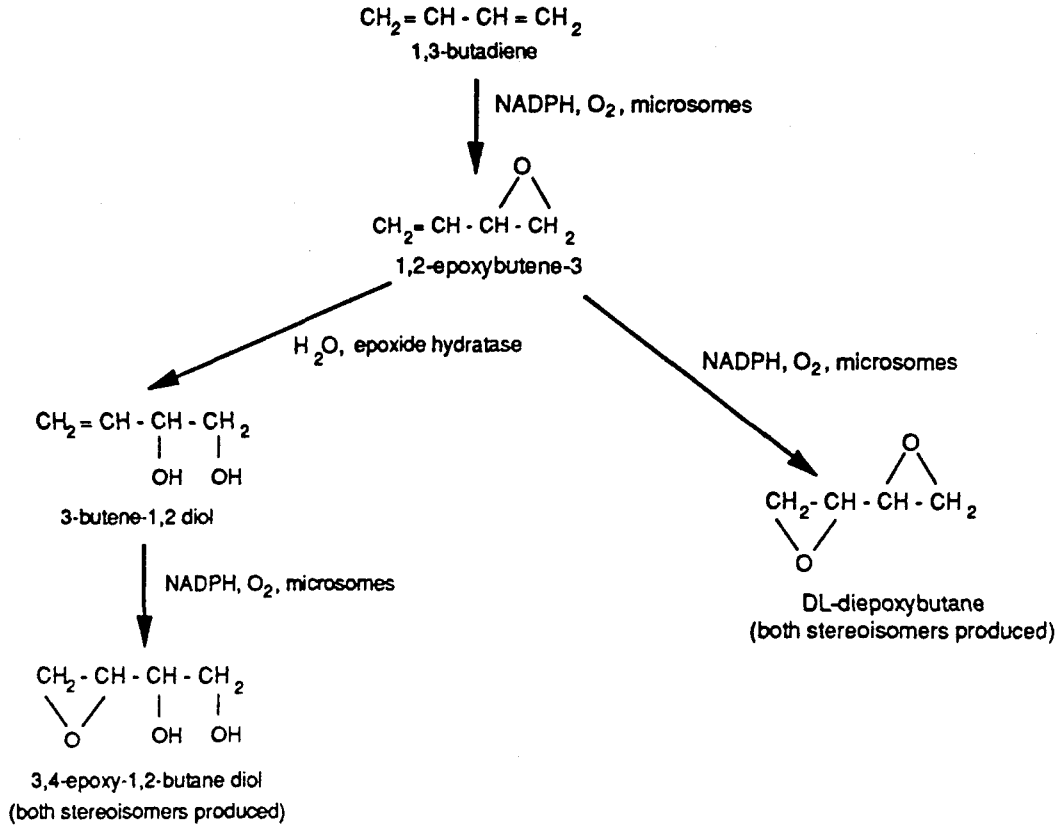
No studies were located regarding distribution in humans or animals after dermal exposure to 1,3-butadiene.

2.3.3 Metabolism

The amount of 1,2-epoxybutene-3 formed in postmitochondrial preparations from human liver was proportional to the monooxygenase activity, but lower when compared with the amount formed in postmitochondrial preparations from livers of rats and mice (Schmidt and Loeser 1985, 1986). These species differences in the metabolism of 1,3-butadiene to the epoxide suggest differences between humans and rodents in the expression of 1,3-butadiene toxicity (see Section 2.4).

The metabolism of 1,3-butadiene was studied by Malvoisin et al. (1979) in rat liver microsomes. One of the major metabolites of 1,3-butadiene was found to be 1,2-epoxybutene-3. Hepatic microsomal metabolism was further investigated (Malvoisin and Roberfroid 1982), and the hypothetical metabolic pathway shown in Figure 2-2 was proposed. 1,3-Butadiene was metabolized to 1,2-epoxybutene-3, which was then transformed into 3-butene-1,2-diol by microsomal epoxide hydrolase. In the metabolism of 1,2-epoxybutene-3 in

FIGURE 2-2. Microsomal Metabolic Pathway of 1,3-Butadiene in Rats*



*Adapted from Malvoisin and Roberfroid 1982

microsomes, two stereoisomers of DL-diepoxybutane, and two stereoisomers of 3,4-epoxy-1,2-butanediol were detected as further metabolites.

The participation of cytochrome P-450 in the metabolism of 1,3-butadiene was suggested on the basis of experimental data (Bolt et al. 1983). The amount of epoxide formed in the rat liver microsomes was dependent on incubation time, microsomal protein, and substrate concentration.

Species differences in the formation of 1,2-epoxybutene-3 from 1,3-butadiene were first studied by Schmidt and Loeser (1985, 1986). A high capability of mouse liver and especially lung postmitochondrial fractions to produce 1,2-epoxybutene-3 after incubation with 1,3-butadiene was demonstrated. In comparison, rat liver and lung produced significantly less 1,2-epoxybutene-3. Pharmacokinetic analysis revealed species differences between rats and mice after inhalation exposure to 1,2-epoxybutene-3 (Kreiling et al. 1987; Laib et al. 1990). A limited rate of 1,2-epoxybutene-3 detoxification and its subsequent accumulation was observed in mice at 500 ppm exposure, but not in rats at exposures up to 5,000 ppm. This may partially account for the differing levels of toxicity and carcinogenicity between rats and mice long-term studies. Monkey postmitochondrial liver preparations catalyzed only a slow formation of the epoxide; no epoxide was detected with lung preparations.

Species differences in the ability of 1,3-butadiene to bind covalently to nucleoproteins and DNA from the liver were found in B6C3Fl mice and Wistar rats exposed to ^{14}C-1,3-butadiene (Kreiling et al. 1986a). In correspondence with the higher metabolic rate of 1,3-butadiene in mice, the formation rate of reactive protein-binding metabolites was about twice as high in this species as noted in rats. Other experiments demonstrated protein-DNA and DNA-DNA crosslinks in the liver tissues in B6C3Fl mice, but not in Wistar rats following exposure to ^{14}C-1,3-butadiene (Jellito et al, 1989). The crosslinking was due to the reaction of 1,3-butadiene metabolites (1,2-epoxybutene-3 and diepoxybutane) with guanine. Further differences between mouse and rat metabolism were observed in the ability of 1,3-butadiene to deplete nonprotein sulfhydryl (NPSH) (Deutschmann and Laib 1989; Kreiling et al. 1988). The depletion of NPSH content was greater in mice than in rats after 1,3-butadiene exposure, suggesting that detoxification of active metabolites proceeds mainly via glutathione-S-transferase mediated pathways in mice. Further differences were noted between 1,3-butadiene metabolism in rodents and in monkeys (Dahl et al. 1990; Sun et al. 1989a). At low exposure levels, blood levels of toxic metabolites were lower in monkeys than in rodents. The difference was not so great at higher 1,3-butadiene exposures (Sun et al. 1989a). Similar exposures to lower 1,3-butadiene levels, however, resulted in blood concentrations of total 1,3-butadiene metabolites in monkeys that were about 5-50 times lower than in mice and about 4-14 times lower than in rats (Dahl et al. 1991). The results indicated possible lower susceptibility to toxic effects of low levels of 1,3-butadiene in monkeys.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of 1,3-butadiene in humans following inhalation exposure to 1,3-butadiene.

In rats exposed to 1,3-butadiene, 1,2-epoxybutene-3 and acetone were exhaled as suspected metabolites of the administered compound (Bolt et al. 1983). The pharmacokinetic profile of inhaled 1,3-butadiene was studied in mice (Kreiling et al. 1986b) and in rats (Bolt et al. 1984; Filser and Bolt 1984). Following exposure of mice and rats to ^{14}C-1,3-butadiene, the elimination of radioactivity was rapid, and 77%-99% of the initial tissue amount was eliminated with half-times of between 2 and 10 hours (Bond et al. 1987). At concentrations of approximately 1,000 ppm or less, the elimination of 1,3-butadiene followed first-order kinetics in both species. The first order metabolic clearance of inhaled 1,3-butadiene per kg body weight was 4,500 ml/hour for rats (Laib et al. 1988) and 7,300 ml/hour for mice (Kreiling et al. 1986b). The maximal metabolic elimination rate was calculated as 220 μmol/hour/kg for rats (Laib et al. 1988) and 400 μmol/hour/kg for mice (Kreiling et al. 1986b). With increasing concentrations of ^{14}C-1,3-butadiene, exhalation of radiolabeled carbon was a major pathway for elimination of ^{14}C in mice and rats (Bond et al. 1986).

About 2% of the total inhaled amount of 1,3-butadiene was excreted as its metabolites in Cynomolgus monkeys (Sun et al. 1989a). Carbon dioxide was the major exhalatory product at low exposure levels, while epoxy-metabolites were exhaled at higher levels. Urinary excretion of total metabolites was not influenced by exposure levels. In Macaca fascicularis monkeys, about 39% of metabolites was eliminated in the urine, 0.8% in feces, and 56% was exhaled as carbon dioxide during the first 70 hours postexposure (Dahl et al. 1990).

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to 1,3-butadiene.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to 1,3-butadiene.

2.4 RELEVANCE TO PUBLIC HEALTH

Epidemiological studies have suggested a possible risk of harmful effects associated with occupational exposure to 1,3-butadiene by finding a higher incidence of cardiovascular and hematopoietic diseases, respiratory diseases, and cancer among exposed workers, but exposures were not to 1,3-butadiene

exclusively. Narcosis and death from respiratory paralysis may occur in humans and animals after inhalation exposure to very high concentrations of 1,3-butadiene. In animals, effects include increased mortality, anemia, respiratory lesions, liver necrosis, nephrosis, and cancer. Fetotoxic and reproductive effects have been observed in mice after exposure to 1,3-butadiene.

Data regarding exposure levels and their correlation with observed effects from studies in humans exposed by the inhalation route were insufficient to derive MBL values.

The toxicity of 1,3-butadiene has been studied in animals by the inhalation route. A few acute-duration toxicity studies were conducted that did not, however, evaluate many of the systemic end points (Carpenter et al. 1984; Shugaev 1969). Developmental effects were observed in the offspring of rats and mice exposed to 1,3-butadiene during gestation (Hackett et al. 1987b; Irvine 1981). Fetotoxicity in mice was observed in the lowest 1,3-butadiene concentration tested from all acute studies. Therefore, no acute-duration inhalation MBL was derived.

Intermediate-duration studies showed that 1,3-butadiene induces anemia in mice at low exposure levels by interfering with normal bone marrow development (Irons et al. 1986a). The changes resembled those found in human preleukemic syndrome (Biemer 1983). Toxicity studies in mice provided evidence that the mouse is highly susceptible to 1,3-butadiene-induced effects. Toxicokinetic studies indicated that the susceptibility may be due to the differences in metabolism of 1,3-butadiene between mice and other species (Deutschmann and Laib 1989; Jellito et al. 1989; Kreiling et al. 1986a, 1987, 1988; Schmidt and Loeser 1985, 1986). These included variations in the formation rate of toxic metabolites, in the extent of covalent binding of metabolites to proteins and DNA, and in the ability to deplete nonprotein sulfhydryl content. It was demonstrated that blood levels of toxic metabolites were much lower in 1,3-butadiene-exposed monkeys than in mice (Dahl et al. 1990; Sun et al. 1989a). The difference was not, however, so distinct at higher exposure levels. Humans are more likely to be exposed to low 1,3-butadiene concentrations at which the greatest interspecies differences were observed. Therefore, the high susceptibility of the mouse to toxic effects of low 1,3-butadiene levels makes its use in the derivation of health hazard risk assessment for humans questionable. The only other species tested in inhalation studies was the rat (Crouch et al. 1979). However, the study did not identify target organs. Therefore, no intermediate-duration inhalation MBL was derived.

Chronic-duration studies were conducted in rats (Owen et al..1987) and in mice (NTP 1984). The study in mice was repeated with lower exposure levels (Melnick et al. 1989, 1990). Multiple-site neoplasms developed in exposed animals of both species. The low exposure study in mice provided NOAEL and LOAEL levels for hematological, respiratory, cardiovascular, and

gastrointestinal effects. However, increased mortality and reproductive effects were reported in the study at the same exposure level as these systemic NOAELs. Therefore, the results were not suitable for the derivation of a chronic-duration inhalation MRL.

No studies were located regarding effects in humans or animals after oral exposure. Therefore, no acute-, intermediate-, and chronic-duration oral MRLs could be derived.

Acute-, intermediate-, and chronic-duration dermal MRLs were not derived for 1,3-butadiene due to the lack of data and an appropriate methodology for the development of dermal MRLs.

Death. No case reports were located regarding acute lethality of 1,3-butadiene in humans. Evidence of an anesthetic effect of 1,3-butadiene leading to death in animals after very high exposures (greater than 120,000 ppm) was given by Carpenter et al. (1944) and Shugaev (1969). Retrospective mortality studies among workers in the rubber industry have revealed an increased incidence of death from cancer, cardiovascular diseases, and diabetes (Case and Hoskar 1954; Fox et al. 1974; Matanoski and Schwartz 1987; Matanoski et al. 1982; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982). These findings are supported by chronic exposure studies on mice (Melnick et al. 1989, 1990; NTP 1984) and rats (Owen et al. 1987) where deaths from cancer were increased among exposed animals. It is also ***not*** known whether long-term exposure of humans to low levels of 1,3-butadiene at waste sites or in the environment would lead to diseases that could shorten the lifespan.

Systemic Effects

Respiratory Effects. The data regarding respiratory effects due to acute exposure to 1,3-butadiene in humans are limited to reports on irritation of respiratory passages after inhalation exposure (Wilson 1944). The irritation might cause even more serious health problems with chronic exposure. The findings of nonneoplastic changes in the nasal cavity in mice after chronic exposure to 1,3-butadiene (NTP 1984) support these data.

Cardiovascular Effects. The only cardiovascular effects found in humans were those reported by McMichael et al. (1974) regarding excessive deaths from arteriosclerotic and chronic rheumatic heart disease. Endothelial hyperplasia of the heart was found in mice after chronic exposure (Melnick et al. 1990). The potential for cardiovascular effects in humans exposed to 1,3-butadiene at or near hazardous waste sites is not known,

Hematological Effects. Slightly lower levels of red blood cells, hemoglobin, platelets, and neutrophils among tank car workers (workers who fill freight train shipping containers) as compared to other workers in the

rubber industry were reported by Checkoway and Williams (1982). These results correspond to results observed in exposed mice (Irons et al. 1986a; Melnick et al. 1989, 1990). 1,3-Butadiene treatment-related changes during intermediate-duration inhalation exposure included a decrease in circulating erythrocytes, total hemoglobin, hematocrit and a leukopenia, due to a decrease in segmented neutrophils. However, no effects on hematology or blood chemistry of rats were found during a chronic exposure study (Owen et al. 1987). Because hematological effects have been observed in animals after inhalation exposure to 1,3-butadiene and may occur in humans exposed occupationally, hematological effects in people who live at or near hazardous waste sites containing 1,3-butadiene may be possible.

Hepatic Effects. No reports were located regarding hepatic effects of 1,3-butadiene in humans. The only adverse effect of 1,3-butadiene in animals, other than cancer, was reported by NTP (1984) in mice, in which chronic inhalation exposure resulted in a higher incidence of liver necrosis. No such changes were found after chronic exposure in rats (Owen et al. 1987).

The metabolism via liver microsomes is of great importance in detoxification of 1,3-butadiene in animals (Bolt et al. 1983; Malvoisin et al. 1979). One of the major metabolites of 1,3-butadiene in the liver was 1,2-epoxybutene-3 (Malvoisin and Roberfroid 1982), which was subsequently transformed into 3-butene-1,2-diol by microsomal epoxide hydrolase. The metabolites were mutagenic in in vitro tests (De Meester et al. 1988). The differences in the formation of 1,2-epoxybutene-3 in the postmitochondrial fractions of mice and rats were examined by Schmidt and Loeser (1985, 1986). A higher rate of production of 1,2-epoxybutene-3 was found in mice than rats. In addition to the higher production rate of 1,2-epoxybutene-3 from 1,3-butadiene, accumulation of the reactive epoxide intermediates, the low capacity for further metabolism, and their detoxification mainly via glutathione-S-transferase-mediated pathways are responsible for the drastic depletion of hepatic NPSH contents in mice (Bond et al. 1988; Deutschmann and Laib 1989; Kreiling et al. 1988). These results partially explain the differing levels of toxicity and carcinogenicity in long-term studies found between mice and rats. Human and monkey postmitochondrial liver fractions catalyzed only a slow formation of the epoxide, and with lung fractions, no epoxide was detected (Schmidt and Loeser 1985, 1986), suggesting that different metabolic rates operate in primates than in rodents. Therefore, the relevance to humans of the liver necrosis observed in mice is not clear.

Renal Effects. No studies were located regarding renal effects of 1,3-butadiene in humans. No effects were reported in rats, guinea pigs, rabbits, dogs (Carpenter et al. 1944), rats (Crouch et al. 1979), or mice (NTP 1984) except for the more frequent occurrence of nephrosis in male rats after chronic inhalation exposure to 8,000 ppm 1,3-butadiene (Owen et al. 1987). The relevance of this information to humans is unclear.

Immunological Effects. No data were located regarding immunological effects in humans. The effect of 1,3-butadiene exposure on the immune system of mice was investigated by Thurmond et a1.(1986), who found a reversible suppression of cytotoxic T-lymphocyte generation to mastocytoma cells and a depression of spleen cellularity. The regulation of stem cell development was altered in B6C3Fl mice after intermediate duration inhalation exposure to 1,3-butadiene (Leiderman et al. 1986). The changes in proliferation and differentiation of hematopoietic cells were similar to those usually preceding the onset of the expression of lymphoma in B6C3Fl mice after chronic exposure to 1,3-butadiene (NTP 1984) (see discussion of Cancer in Section 2.4). No information was found regarding immunological effects and lymphoma in humans after exposure to 1,3-butadiene. However, based upon these studies in laboratory animals where stem cell development was affected, it would be prudent to consider that potentially adverse immunological effects from exposure to 1,3-butadiene could occur in humans.

Neurological Effects. Inhalation of high concentrations of 1,3-butadiene is narcotic in humans (Sandmeyer et al. 1981) and animals (Carpenter et al. 1944) and can lead to death from respiratory paralysis (Carpenter et al. 1944; Shugaev 1969). Although the exact concentration leading to narcosis in humans is not known, exposure to 250,000 ppm produced anesthesia in rabbits. Nausea, dryness of the mouth and nose, headache, and decreased blood pressure and pulse rate are the first signs observed in humans (Sandmeyer 1981). These data become relevant for humans only during exposure following industrial accidents resulting in significant leaks or spills of 1,3-butadiene.

Developmental Effects. No data were available regarding developmental effects of 1,3-butadiene in humans. Fetotoxic effects (skeletal abnormalities and lens opacity) of 1,3-butadiene exposure were observed in rats (Irvine et al. 1981) and in mice (Hackett et al. 1987) after 1,3-butadiene treatment of pregnant rats during days 6-15 of gestation. Based upon these experimental data in laboratory animals, it would be prudent to consider the potential for adverse health effects from exposure to 1,3-butadiene in humans. The low molecular weight and high lipid solubility of 1,3-butadiene suggest that it may cross the placenta.

Reproductive Effects. No studies were located regarding reproductive effects in humans after exposure to 1,3-butadiene. Increased incidence of gonadal atrophy in mice occurred after chronic inhalation exposure to 1,3-butadiene (Melnick et al. 1989, 1990; NTP 1984). Inhalation exposure of male mice to 1,3-butadiene resulted in dominant lethal mutations and sperm head abnormalities (Hackett et al. 1988a, 1988b). Laboratory investigations in animals suggest that 1,3-butadiene affects the more mature cells of the reproductive system. Based upon this information in laboratory animals, the potential for human reproductive effects upon exposure to 1,3-butadiene should be considered.

Genotoxic Effects. 1,3-Butadiene has been tested for genotoxicity in a number of in vitro and in vivo studies (Tables 2-2 and 2-3). Positive results have been found in the reverse mutation assay in Salmonella typhimurium TA1530 and TA1535 in the absence or in the presence of metabolic activation system (De Meester et al. 1978). However, the interpretation of these results was confounded by the fact that the Petri dishes not containing S-9 mix *were* contaminated by volatile active metabolites (De Meester et al. 1988). It was concluded that S-9 mix was necessary to activate 1,3-butadiene into mutagen(s). TA1530 was the most sensitive strain, but 1,3-butadiene mutagenicity was detectable only with metabolic activation in the subsequent study (De Meester et al. 1980). No significant mutagenic effect on S. tynhimurium strain TA100 with metabolic activation was observed (Victorin and Stahlberg 1988). A weak genotoxic activity was detected in strain TA1535 with rat S-9 (Arce et al. 1989). On the basis of these data, 1,3-butadiene appears to require metabolic activation to produce genotoxicity.

Several recent studies dealt with the mutagenic effect of 1,3-butadiene in vivo. Details of the in vivo studies were discussed in Section 2.2.1.7. A significant dose-related increase in induction of micronuclei was found in mice, but not rats, after intermediate-duration exposure to up to 625 ppm 1,3-butadiene (Jauhar et al. 1988). Also, an increase in the frequency of chromosomal aberrations and sister chromatid exchanges was found in mice (Cunningham et al. 1986; Sharief et al. 1986; Tice et al. 1987). No genotoxic effects were found in rats exposed by inhalation to 1,3-butadiene (Cunningham et al. 1986), as demonstrated by using cytogenetic analysis of their bone marrow.

Although cytogenetic monitoring of 1,3-butadiene rubber workers for chromosomal aberrations revealed no significant differences between exposed and control groups (Zhou et al. 1986), 1,3-butadiene is clearly genotoxic in mice. As discussed in Section 2.3.3, species differences exist in the metabolism of 1,3-butadiene, and data suggest that humans may metabolize this compound at different metabolic rates than do rodents. If the genotoxic and clastogenic response of 1,3-butadiene requires activation to an active metabolite that is formed more slowly or deactivated more rapidly in humans than in rats and mice, the genotoxicity observed in animals may only be observed after much higher exposures in humans. The data in humans are too limited, however, to rule out the possibility of a genotoxic potential in humans exposed to 1,3-butadiene.

Cancer. An increased incidence of bronchial carcinoma was reported in rubber industry workers (Fox et al. 1974). Although information on smoking was not available in the cohort, no excesses were found in other smokingrelated diseases. However, the possible influence of smoking, occupational coexposure to other chemicals, and/or urban effects could not be ruled out in the study.

TABLE 2-2. Genotoxicity of 1,3-Butadiene In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium:	Gene mutation			
TA1530		+	-	De Meester et al. 1980
TA100		-	-	Victoria and Stahlberg 1988
TA1535		+	-	Arce et al. 1989

+ = positive result
- = negative result

TABLE 2-3. Genotoxicity of 1,3-Butadiene In Vivo

Species (test system)	End point	Results	Reference
Mammalian cells:			
B6C3F1 mice (inhalation)	Bone marrow:	+	Cunningham et al. 1986
Sprague-Dawley rats (inhalation)	Dose-dependent increase in SCEs	-	
B6C3F1 mice (inhalation)	Bone marrow: Increase in CA, SCEs, AGT and depression of MI	+	Tice et al. 1987
	Macrocytic-megaloblastic anemia	+	Irons et al. 1986a
	Bone marrow: 44% increase in proliferative index		
Swiss mice (inhalation)	Macrocytic-megaloblastic anemia	+	Irons et al. 1986b
	8-Fold increase in circulating micronuclei		
	Bone marrow damage		
B6C3F1 mice (inhalation)	Bone marrow: Alteration of hemopoietic stem cell development	+	Leiderman et al. 1986
	Peripheral blood erythrocytes: Induction of micronuclei	+	Jauhar et al. 1988
	Induction of MN	+	Tice et al. 1988
	Induction of SCEs		
	Chromosomal aberrations		
	Sperm abnormalities	+	Hackett et al. 1988a
	Dominant lethality	+	
C57Bl/6 mice (intraperitoneal injection)	Bone marrow increase in CA, SCE	+	Sharief et al. 1986

+ = positive result; - = negative result; AGT = average generation time; CA = chromosomal aberrations; MI = mitotic index; MN = micronucleated cells; SCEs = sister chromatid exchanges

The indication that 1,3-butadiene can cause malignancy in the respiratory system was demonstrated by finding an increased incidence of alveolar/ bronchiolar cell carcinomas in mice after chronic exposure (Melnick et al. 1989; NTP 1984). Inhalation is not only the main route of exposure to 1,3-butadiene, but as indicated by toxicokinetic studies, it is also an important route of 1,3-butadiene metabolite excretion (Bolt et al. 1983). The metabolic pathway of 1,3-butadiene was first proposed by Malvoisin and Roberfroid (1982), and the metabolites, including 1,2-epoxybutene-3, have been considered to be the ultimate genotoxic agents (De Meester et al. 1980). It was demonstrated that 1,2-epoxybutene-3 showed carcinogenic activity following skin applications in Swiss mice (Van Duuren et al. 1963). High formation of epoxides was observed in the lung tissue of mice and rats incubated with 1,3-butadiene, in contrast to undetectable levels found in lung tissues from monkeys and humans (Schmidt and Loeser 1985). These findings support the theory that metabolites are responsible for the carcinogenic effect of 1,3-butadiene on the respiratory tract in rodents.

An epidemiological study of mortality within a cohort of 6,678 male rubber workers examined the relationship between the deaths from malignant neoplasms and occupational exposure (McMichael et al. 1974). Significant increases of mortality due to malignancies of the stomach (SMR=187), prostate (SMR=142) and hemato-lymphopoietic system (SMR=226) were observed in the cohort. A subsequent study suggested an association between mortality from lymphatic leukemia with a history of working in multiple solvent-exposure jobs (McMichael 1975). However, in a follow-up case-control study an evaluation was made of the relationship of mortality excesses to specific jobs within the plant (McMichael et al. 1976). A clear association was found between the length of exposure to 1,3-butadiene and the occurrence of lymphatic and hematopoietic malignancy. The age-adjusted ratios of rates of exposure were 4.4 for those exposed for more than 2 years and 5.6 for those exposed for more than 5 years.

An increased incidence of neoplasms of the lymphatic system was also found in other rubber workers studies (Matanoski et al. 1982, 1988, 1989, 1990). This finding was confirmed by Downs et al. (1987) in an epidemiological study of mortality among workers in a 1,3-butadiene monomer manufacturing facility that supplied 1,3-butadiene to two styrene-butadiene rubber plants. No significant excesses were observed for any cause of death except lymphosarcoma and reticulum cell sarcoma. When the cohort was subdivided into routine, nonroutine, and low-exposure groups, the standard mortality ratios (SMRs) were consistently elevated for these causes of death in all three groups. In an update of this study, the observation period of the cohort was extended for another 6 years (Divine 1989; 1990). The increased SMR for lymphosarcoma and reticulosarcoma was confirmed; however, there was an absence of an association between length of exposure and cancer risk, because all deaths occurred in those employed fewer than 10 years. These data are particularly important because the workers were reported not to be significantly exposed to other chemicals as was the case in the styrene-

butadiene rubber plant studies. The lack of exposure duration and concentration data is a major deficiency of all epidemiological studies on 1,3-butadiene.

As for evidence of the carcinogenicity of 1,3-butadiene in laboratory animals, 1,3-butadiene was shown to cause an altered regulation of stem cell development in B6C3Fl mice after an intermediate inhalation exposure (Leiderman et al. 1986). The changes in proliferation and differentiation of hematopoietic cells were similar to those usually preceding the onset of the expression of lymphoma in B6C3Fl mice. These data were supported by the increased incidence of malignant lymphoma in mice after chronic exposure to 1,3-butadiene (NTP 1984). An increased incidence (57%) of thymic lymphoma in B6C3Fl mice was reported after exposure to 1,250 ppm 1,3-butadiene for 1 year (Irons 1989). This result agrees with the 60% incidence found previously in this strain after similar exposure (NTP 1984). In contrast, these tumors were found only in 14% of treated NIH Swiss mice (Irons 1989). There were no histopathological differences in the tumors induced in these two strains of mice, but increased amounts of murine leukemia retrovirus (MuLV) envelope antigens were observed only in lymphomas from B6C3Fl mice (Irons et al. 1987b). Furthermore, when these tumors were cloned, an increased expression of the c-myc proto-oncogene was found (Irons et al. 1986c). MuLV retroviruses, which are expressed only in B6C3Fl mice but not in NIH Swiss mice, may play an important role in the lymphoma-type tumorigenesis. The extrapolation of these results to humans is difficult because human leukemia retroviruses (HTLV) have been found only in a small part of the population, and it is not known if their presence in humans would affect susceptibility to lymphoma the same way MuLV appears to affect development of lymphoma in mice exposed to 1,3-butadiene (Turnbull et al. 1988). However, the presence of other forms of neoplasms in experimental animals provides limited evidence for the potential carcinogenic nature of 1,3-butadiene in humans. It would therefore be prudent to consider that 1,3-butadiene or its metabolites have the potential to induce a carcinogenic response in humans as well.

Multisite tumors were found among B6C3Fl mice after chronic exposure to 1,3-butadiene (NTP 1984), including hemangiosarcoma of the heart, malignant lymphoma, alveolar/bronchiolar adenoma and carcinoma, papilloma and carcinoma of the stomach, hepatocellular carcinoma, preputial gland carcinoma, Zymbal gland carcinoma, mammary gland carcinoma, and ovarian tumors. Multisite tumors, including Leydig cell adenomas, exocrine tumors of the pancreas, thyroid follicular cell adenoma, sarcoma of the uterus, mammary gland carcinoma, and Zymbal gland carcinoma were also found among Sprague-Dawley rats after chronic exposure to 1,3-butadiene (Owen et al. 1987). On the basis of the NTP data, IARC (1985) concluded that there is sufficient evidence for the carcinogenicity of 1,3-butadiene in experimental animals, but inadequate evidence for its carcinogenicity in humans. EPA (1985a) has classified 1,3-butadiene as a probable human carcinogen. However, the IARC and EPA conclusions were not based on the updated epidemiological data, as well as latest carcinogenicity and toxicokinetic studies in animals. Interspecies

differences in metabolism between mice and primates and resulting higher susceptibility of mice to 1,3-butadiene toxicity may limit the relevance of studies in mice for human risk assessment.

2.5 BIOMARRERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,3-butadiene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,3-butadiene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 1,3-Butadiene

No studies were located regarding tissue, fluid, or excreta levels of 1,3-butadiene in humans. For the distribution of 1,3-butadiene and its metabolites in animal tissues see Section 2.3.2. Excretion of 1,3-butadiene metabolites was reported to be high in the urine of exposed monkeys (Dahl et al. 1990). Detection of urinary metabolites may be possibly used for biomarkers of exposure in humans.

A linear accumulation of hemoglobin adducts was observed in B6C3F_1 mice and Sprague-Dawley rats after intraperitoneal administration of radiolabeled 1,3-butadiene (Sun et al. 1989b). The lifetimes of these adducts were in agreement with the expected lifetimes for red blood cells in these animals. The determination of 1,3-butadiene-derived adducts in hemoglobin was proposed as a method to measure prior exposure(s) to this chemical. The investigators used liquid scintillation counting of radioactivity to detect the adducts; therefore, the assay cannot be used in humans. Furthermore, the formation of 1,3-butadiene-hemoglobin adducts has not been demonstrated in humans. DNA adducts were detected in the livers of mice and rats exposed to radiolabeled 1,3-butadiene (Kreiling et al. 1986). Because humans are not likely to be exposed to radiolabeled 1,3-butadiene either under controlled conditions or in the environment, different methods for detecting and identifying the adducts would have to be developed in order to use hemoglobin or DNA adducts as a biomarker of exposure to 1,3-butadiene in humans.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,3-Butadiene

No biomarkers used to characterize effects caused by 1,3-butadiene were identified. Dermal, ocular, and/or upper respiratory irritation can occur following 1,3-butadiene exposure (MCA 1974) and may alert the exposed individual. However, the effects are not specific for 1,3-butadiene exposure and may be caused by several other chemicals.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding toxic effects of 1,3-butadiene in coexposure with other chemicals. In addition to 1,3-butadiene, workers in the rubber industry are exposed to other chemicals, including styrene and its metabolite, styrene oxide, which was also found to be mutagenic (Loprieno et al. 1978; Norppa et al. 1980; Pohlova et al. 1985; Watabe et al. 1978). Whether these other chemicals or their active metabolites have a synergistic harmful effect in humans is not known.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Black workers exposed to 1,3-butadiene in the production area of a styrene-butadiene (SBR) factory had a higher risk of mortality from lymphomas and leukemia than white workers (Matanoski et al. 1989). Furthermore, the

exposure of black workers to 1,3-butadiene was also associated with a higher risk of cardiovascular diseases (Matanoski and Schwartz 1987). These limited data suggest that members of the black population may be more susceptible to the effects of 1,3-butadiene, but the reason for the difference is not known.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,3-butadiene. This section is intended to inform the public of existing clinical practice and the status of research concerning such methods. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,3-butadiene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No specific antidotes for 1,3-butadiene are available; however, recommendations have been made for general treatment of intoxicated persons (Bronstein and Currance 1988; Stutz and Janusz 1988). First, the exposed individual should be removed from the contaminated area and contaminated clothing should be taken away. It has been suggested that exposed skin should be washed with soapy water and contaminated eyes flushed with water. Inhalation exposure to high 1,3-butadiene concentrations may result in narcosis leading to respiratory paralysis and death. Therefore, administration of oxygen has been used and ventilation has been assisted as needed in cases of 1,3-butadiene poisoning. Standard procedures have been used for the treatment of cardiac arrhythmias and pulmonary edema (Ellenhorn and Barceloux 1988).

Although no specific data were located regarding the mitigation of effects of 1,3-butadiene once it has entered the bloodstream, studies on the mechanism of action are available that may provide insight into possible means of mitigating effects. Great interspecies differences were observed in the susceptibility to 1,3-butadiene-induced toxicity. Toxicity studies found mice to be extremely sensitive (Melnick et al. 1989, 1990). Studies on the metabolism of 1,3-butadiene demonstrated that the chemical is converted to its epoxy derivatives in the presence of NADPH and oxygen in microsomes (Malvoison and Roberfroid 1982). It was found that monkeys had the lowest levels of epoxy-metabolites in the blood after exposure to low 1,3-butadiene concentrations, while mice had the highest levels (Dahl et al. 1990; Sun et al. 1989a). The epoxides may be responsible for most toxic and carcinogenic effects caused by 1,3-butadiene exposure. The harmful effect of epoxidemetabolites is due to the formation of alkylation products with DNA; specifically, by the reaction with guanine (Bolt et al. 1984; Jellito et al. 1989). The determination of DNA adducts found in mice and rats was proposed as a measure of 1,3-butadiene exposure (Kreiling et al. 1986a; Sun et al. 1989b). The epoxides are detoxified by conjugation with glutathione and by further enzymatic transformation (Kreiling et al. 1988). A higher rate of

epoxide formation and a greater depletion of hepatic nonprotein sulfhydryl content in mice is probably responsible for their higher susceptibility to 1,3-butadiene toxicity. Since only after a substantial decrease of glutathione levels the macromolecular covalent binding is enhanced (Kreiling et al. 1988), sufficient availability of glutathione should mitigate the effects of 1,3-butadiene exposure.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

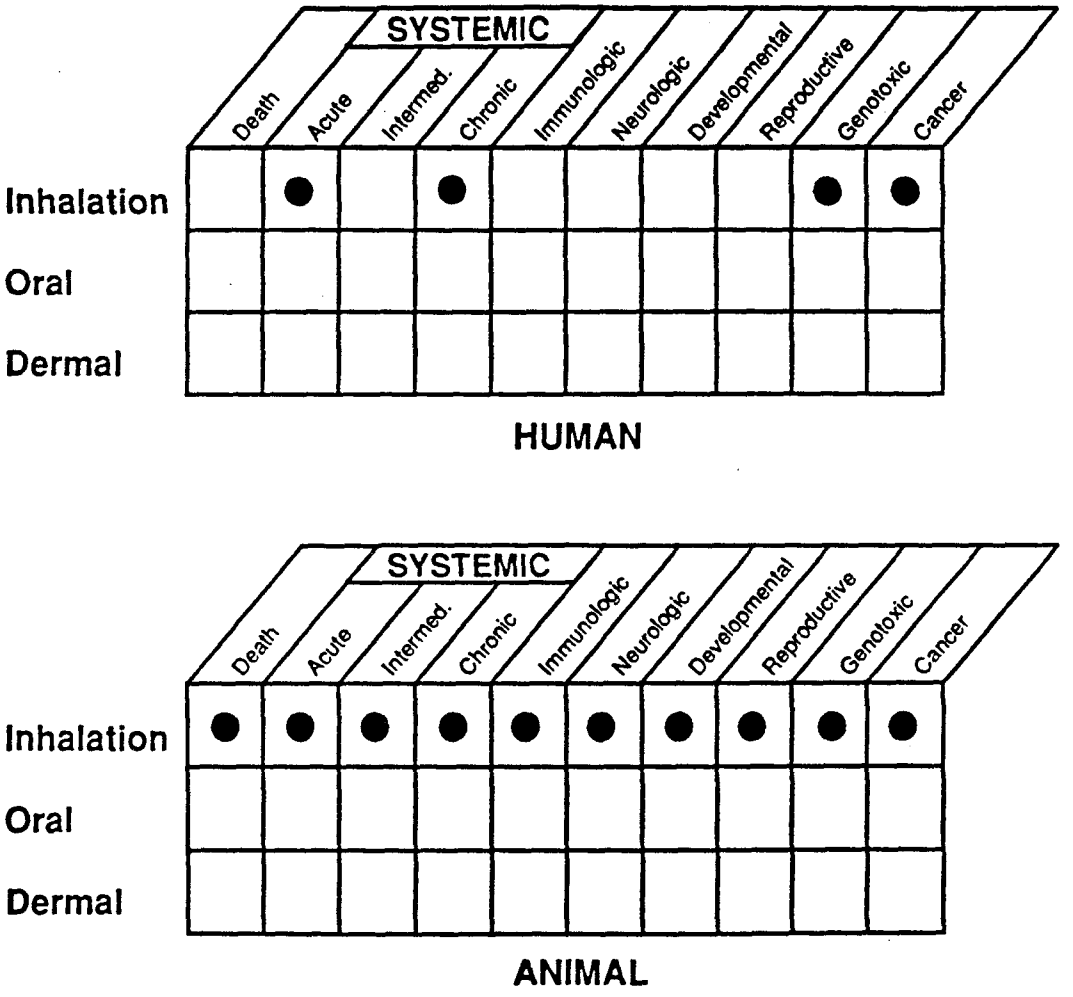
2.9.1 Existing Information on Health Effects of 1,3-Butadiene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,3-butadiene are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,3-butadiene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

As seen from Figure 2-3, information regarding acute systemic effects (respiratory tract irritation and narcotic effect), chronic systemic effects (cardiovascular and respiratory effects), genotoxicity and cancer exists for inhalation exposure in humans. No information was located regarding oral or dermal exposure of humans to 1,3-butadiene.

Inhalation studies in animals provide data on death, systemic effects, immunologic effects, neurologic effects, genotoxicity, and carcinogenicity. Information concerning developmental and reproductive effects was also located. No information was located regarding effects in animals after oral or dermal exposure to 1,3-butadiene.

FIGURE 2-3. Existing Information on Health Effects of 1,3-Butadiene



● Existing Studies

2.9.2 Data Needs

Acute-Duration Exposure. Acute inhalation exposure to very high concentrations of 1,3-butadiene may lead to narcosis and to death by respiratory paralysis in both humans and animals (Carpenter et al. 1944; Shugaev 1969). No studies were located that correlated the level of exposure with the first signs of toxicity in humans or animals. No NOAEL levels were identified in the available acute exposure studies. Developmental effects were seen in animals after exposure to the lowest concentration tested in acute studies (Hackett et al. 1987; Irvine 1981). A NOAEL value for developmental as well as systemic effects would be the most appropriate basis for the derivation of an acute inhalation MRL. No studies were located regarding effects following oral or dermal exposure, and no pharmacokinetic studies by the oral or dermal routes were located; therefore, it is not possible to predict if effects following oral or dermal exposure would be similar to those following inhalation exposure. Because 1,3-butadiene has been detected in soil off-gases at hazardous waste sites, inhalation exposure appears to be the greatest concern. However, it is not known if 1,3-butadiene is present in groundwater or soil at these hazardous waste sites because it is difficult to analyze these media for the compound. 1,3-Butadiene has been detected in industrial waste water and drinking water, and is quite soluble in water (735 ppm). Therefore, oral and dermal routes of exposure cannot be ruled out. Therefore, information concerning 1,3-butadiene toxicity by these routes of exposure would be useful. Because people living at or near these hazardous waste sites may be exposed for brief periods of time, more dose response data for acute exposures by all routes is considered to be important.

Intermediate-Duration Exposure. No information is available regarding effects of 1,3-butadiene during intermediate-duration exposure in humans. No studies were located regarding effects in humans or animals following oral or dermal exposure to 1,3-butadiene, and pharmacokinetic data for these routes of exposure are insufficient to predict whether the disposition or toxicity of 1,3-butadiene following oral or dermal exposure would be similar to that following inhalation exposure. Therefore, information regarding the toxicity of 1,3-butadiene by the oral and dermal routes of exposure would be useful. Several studies on intermediate duration inhalation exposure to 1,3-butadiene have been conducted in animals (Crouch et al. 1979; Irons et al. 1986a; NTP 1984). Although NOAEL values for several systemic effects were recorded from those studies, an MRL was not derived, because 1,3-butadiene-related anemia was found in mice exposed to a lower concentration of 1,3-butadiene (Irons et al. 1986a). The observed changes were similar to those found in human preleukemic syndrome (Biemer 1983). The experimental results suggested that 1,3-butadiene exposure might interfere with normal bone marrow cell development. Further investigation of this topic could be valuable since epidemiological studies in humans indicate that hematopoietic tissue may be a possible target for 1,3-butadiene toxicity. This information is important in identifying sensitive subpopulations surrounding hazardous waste sites.

Chronic-Duration Exposure and Cancer. Possible risk for hematological disorders was reported in humans after chronic inhalation exposure to 1,3-butadiene in occupational settings, but exposure levels are lacking, and exposure to other chemicals occurs in these settings (Checkoway and Williams 1982; McMichael et al. 1976). Well-conducted inhalation studies identified respiratory effects, liver necrosis, gonadal atrophy, and increased mortality in mice (Melnick et al. 1989, 1990; NTP 1984) and renal pathology and increased mortality in rats (Owen et al. 1987). Although NOAEL values were identified for systemic effects in mice exposed to low levels of 1,3-butadiene (Melnick et al. 1989, 1990), increased mortality was found at the same exposure levels. Therefore, no chronic MEL has been derived. Oral and dermal studies are lacking, and toxicokinetic data are insufficient to predict toxicity across routes of exposure. Therefore, information concerning the possible toxicity of 1,3-butadiene by these routes would be useful to identify the target organs and the thresholds for toxic effects. Further chronic inhalation studies in species other than mice using lower exposure levels might provide a NOAEL from which to derive a chronic inhalation MRL. This information is important because populations surrounding hazardous waste sites might be exposed chronically.

Epidemiological studies in humans indicate a possible increase in carcinogenic risk from occupational exposure to 1,3-butadiene (Downs et al. 1987; Matanoski et al. 1982, 1989, 1990; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982). This is supported by the information about mutagenic activity of 1,3-butadiene metabolites (De Meester et al. 1988) and by wellconducted chronic inhalation studies that provide information on carcinogenic effects of 1,3-butadiene in mice and rats (Melnick et al. 1989; NTP 1984; Owen et al. 1987). On the basis of the NTP data, IARC (1985) and EPA (1985a) concluded that there is sufficient evidence for the carcinogenicity of 1,3-butadiene in animals. IARC has classified 1,3-butadiene in group 2B, that is, as a possible human carcinogen. EPA has classified 1,3-butadiene as a probable human carcinogen. Further epidemiological investigation regarding the possible risk to humans would be useful.

No chronic oral or dermal carcinogenicity studies in animals were located, and pharmacokinetic data are insufficient to predict a carcinogenic potential of 1,3-butadiene by these routes.

Genotoxicity. Increased incidences of chromosomal aberrations and sister chromatid exchanges were found among petrochemical workers; however, the exposure was not solely to 1,3-butadiene (Zhou et al. 1986). 1,3-Butadiene has been tested in a number of *in vivo* studies using rats and mice following inhalation exposure (Cunningham et al. 1986; Tice et al. 1987). Inconclusive results from a dominant lethality study with rats (Hackett et al. 1988a) suggest that a repeat study should be performed. Information on the genotoxic effects of 1,3-butadiene is also obtained from *in vitro* studies in prokaryotic organisms (De Meester et al. 1980). These data sufficiently characterize the

genotoxic potential of 1,3-butadiene metabolites. However, reliable cytogenetic studies among exposed workers would be useful. These studies would provide the opportunity to determine if a correlation exists between the induction of chromosomal aberrations and sister chromatid exchanges in an individual and the concentration of 1,3-butadiene to which he is exposed.

Reproductive Toxicity. The atrophy of gonads in mice after chronic inhalation exposure to 1,3-butadiene was reported (Melnick et al. 1989; NTP 1984). The fertility of rats, guinea pigs, or rabbits was reported to be unaltered by intermediate-duration inhalation exposure to 1,3-butadiene (Carpenter et al. 1944), but the age of these studies should be taken into consideration. Sperm head abnormalities were found in male mice exposed to 1,3-butadiene by inhalation (Hackett et al. 1988a, 1988b).

No studies were located regarding reproductive toxicity of 1,3-butadiene by the oral or dermal routes in humans or animals, and pharmacokinetic data were insufficient to suggest the potential for 1,3-butadiene to cause reproductive effects by these routes of exposure. The potential for exposure of humans by the oral and dermal routes, however, is not known. Further information regarding the reproductive effects of 1,3-butadiene in animals such as multigeneration studies would be useful to estimate the possible risk for reproductive effects in humans. An epidemiological study among exposed populations concentrating on reproductive effects would be useful.

Developmental Toxicity. No information on developmental toxicity in humans was located. A developmental study by the inhalation route in rats indicated growth retardation in the rat fetuses and an increase in major skeletal abnormalities at a concentration of 1,000 ppm of 1,3-butadiene (Irvine 1981). Furthermore, fetotoxicity was observed in mice at concentrations as low as 40 ppm 1,3-butadiene (Hackett et a1.1987). More data on developmental toxicity in other species (at least one of them nonrodent) would be useful to identify possible developmental risk for humans. The developmental effects following other routes of exposure have not been studied, and pharmacokinetic data are insufficient to predict that responses would be similar to those by the inhalation route. Therefore, studies in animals to determine the possible developmental effects of 1,3-butadiene and the thresholds for these effects following oral and dermal exposure would strengthen confidence in the database obtained for these routes of exposure in other toxicity studies.

Immunotoxicity. No persistent immunological defects were detectable after the intermediate-duration exposure of mice to 1,3-butadiene (Thurmond et al. 1986). The indications of disturbances in hemato- and lymphatopoietic stem cell regulations were observed after inhalation exposure of mice to 1,3-butadiene (Liederman et al. 1986). The high incidence of lymphoma among mice after the chronic exposure (NTP 1984) also indicates that the immune system is a target. A battery of immune function tests has not been performed

in humans or in animals. More data regarding humans and animals would be useful for determining potential human immunotoxicity of, 1,3-butadiene. Studies regarding skin sensitization with 1,3-butadiene are lacking.

Neurotoxicity. Narcosis has been reported in humans (Sandmeyer 1981) and demonstrated in animals after acute inhalation exposure to very high levels of 1,3-butadiene (250,000 ppm) (Carpenter et al. 1944; Shugaev 1969). No reliable information was located regarding neurotoxicity due to chronic inhalation exposure or to oral or dermal exposure for any duration. Information regarding early, subtle signs of possible neurological effects with correlation to the exposure levels is lacking. A battery of neurological and neurobehavioral tests would be useful to better define the neurological endpoints.

Epidemiological and Human Dosimetry Studies. Several epidemiological studies on health effects of 1,3-butadiene have been conducted (Case and Hosker 1954; Fox et al. 1974; Matanoski and Schwartz 1987; Matanoski et al. 1989; McMichael et al. 1974, 1975, 1976; Meinhardt et al. 1982). The serious limitation of these studies is that the cohorts of exposed workers were found in the rubber industry, in which the people were exposed to a mixture of various chemicals. More studies similar to the Downs et a1.(1987) study, which was conducted among workers in a 1,3-butadiene manufacturing plant, would be useful. Reliable dosimetry data on the exposed populations would be useful for good epidemiological comparisons. Efforts to improve estimates of past exposures and to more accurately define current exposure levels to 1,3-butadiene would be valuable. Epidemiological studies should concentrate on the possible carcinogenic effect of 1,3-butadiene in humans and on changes in hemato- and lymphatopoietic systems as possible targets for 1,3-butadiene induced toxicity. The data obtained from workers exposed occupationally to low concentrations of 1,3-butadiene could possibly be extrapolated to populations living near hazardous waste sites.

Biomarkers of Exposure and Effect. The determination of 1,3-butadiene derived adducts in hemoglobin of rats and mice exposed to ^{14}C-1,3-butadiene has been proposed as a method to measure repeated exposures to this chemical (Sun et al. 1989). The investigators used liquid scintillation counting of radioactivity to detect the adducts. Because humans are not likely to be exposed to radiolabeled 1,3-butadiene in the environment, a different method for detecting adducts formation would have to be developed in order to use hemoglobin adducts to assess exposure in humans. Continued efforts to devise more specific early biomarkers of disease, especially hematological and oncological, would be valuable.

No biomarkers of effects of 1,3-butadiene have been identified.

Absorption, Distribution, Metabolism, and Excretion. In vitro studies have characterized some of the metabolism dynamics of 1,3-butadiene in animals

(Malvoisin and Roberfroid 1982; Malvoisin et al. 1979): Several toxicokinetic studies on 1,3-butadiene metabolism in vivo have been conducted in rats and mice following inhalation exposure (Bolt et al. 1983; Bond et al. 1987; Kreiling et al. 1986b; Shugaev 1969), but not following exposure by other routes. Thus, further studies in animals by the oral and dermal routes to determine possible target organs by these routes could be useful. Ethical considerations limit the testing of humans, but the development of methods to determine urinary and breath excretion of 1,3-butadiene and its metabolites by humans with known exposure to 1,3-butadiene may provide a means of monitoring humans for exposure.

Comparative Toxicokinetics. The study by Schmidt and Loeser (1985) indicated that there is a difference between the capability of mouse and rat liver postmitochondrial fractions to produce 1,2-epoxybutene-3 after incubation with 1,3-butadiene. Furthermore, monkey and human postmitochondrial liver preparations catalyzed the formation of only a small amount of the epoxide. Higher levels of the toxic epoxides were found in blood of mice following 1,3-butadiene exposure as compared to monkeys (Dahl et al. 1990; Sun et al. 1989a). Species differences in the toxicokinetics of a chemical may account for differences in toxic responses. Analysis of the blood, breath, and urine of humans exposed to 1,3-butadiene for parent compound and metabolites over time would provide a greater knowledge of the human metabolic pathways. Qualitative and quantitative comparison of human metabolites with those of animals could help identify the most appropriate species to serve as a model for predicting toxic effects and mechanisms of action in humans.

Mitigation of Effects. No specific information was located regarding mitigation of effects in 1,3-butadiene exposed individuals. The characteristic effects of 1,3-butadiene toxicity are known and nonspecific treatments for rescuing intoxicated persons have been recommended (Bronstein and Currance 1988; Stutz and Janusz 1988). The mechanism of toxicity involves a depletion of glutathione pool in the organs and binding of epoxide-metabolites to DNA (Bolt et al. 1983; Kreiling et al. 1988). The investigation of possible prevention of toxicity by obstruction of binding of active metabolites to DNA (possibly by increasing glutathione availability) would be useful.

2.9.3 On-going Studies

The Board Draft of toxicology and carcinogenesis studies of 1,3-butadiene in B6C3Fl mice (NTP 1991) has been peer reviewed. However, the final draft incorporating the peer reviewers' comments has not yet been published. The results showed clear evidence of 1,3-butadiene carcinogenicity in mice exposed at 6.25, 20, 62.5, or 200 ppm for 2 years (6 hours/day, 5 days/week). Carcinogenic findings included neoplasms in the hematopoietic system, heart, lung, forestomach, liver, and Harderian gland in both sexes. Furthermore,

neoplasms were found in the preputial gland, brain, and kidneys of males and in the ovary and mammalian glands of females. Preliminary results from the NTP study were already published (Melnick et al. 1990) and were discussed in Sections 2.2.1.1, 2.2.1.2, 2.2.1.6, and 2.2.1.8. In addition, genotoxicity studies were performed by NTP (1991). 1,3-Butadiene induced gene mutations in Salmonella typhimurium TA1535, but not in TA100, TA97, or TA98 strains. Negative results were also obtained in the mouse lymphoma assay. In contrast, chromosomal aberrations were induced at 625 ppm and sister chromatid exchanges at 62.5 ppm in bone marrow cells of mice exposed to 1,3-butadiene for 2 weeks (6 hours/day, 5 days/week).

Several other studies on 1,3-butadiene were reported to be in progress (CMA 1991). Species differences in the metabolism between rodents and primates and the fate of toxic and/or mutagenic metabolites will be investigated. Similar information will be obtained in in vitro human studies. The mechanism of 1,3-butadiene toxicity to the bone marrow and hematopoietic system will be investigated in mice and humans. Furthermore, studies of the interaction of 1,3-butadiene and its metabolites with DNA will be performed. An abstract from the meeting of the Society of Toxicology reported interspecies differences in 1,3-butadiene toxicokinetics (Sabourin et al. 1991). Two major urinary metabolites of 1,3-butadiene were N-acetyl-S-(l(or 2)-[3-butene-2(or 1)-ol)cysteine (I) and N-acetyl-S-(4-butane-1,2-diol)-cysteine (II) in all species tested. However, monkeys exposed to 1,3-butadiene produced predominantly metabolite II, while rodents produced l-4 times as much of metabolite I as II.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 1,3-butadiene are listed in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,3-butadiene are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 1,3-Butadiene

Characteristic	Information	Reference
Chemical name	1,3-Butadiene	CAS 1989
Synonyms	Butadiene; buta-1,3-diene; biethylene; bivinyl; vinylethylene; erythrene; α,α-butadiene; trans-butadiene; divinyl; pyrrolylene	SANSS 1989; Chemline 1989; HSDB 1989; CAS 1989
Trade name(s)	No data	
Chemical formula	C_4H_6	CAS 1989
Chemical structure		
Identification numbers:		
CAS registry	106-99-0	CAS 1989
NIOSH RTECS	EI9275000	SANSS 1989
EPA hazardous waste	RO377-0754	Miller 1978
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	181	Chemline 1989
NCI	C50602	Chemline 1989

CAS = Chemical Abstracts Service
NIOSH = National Institute for Occupational Safety and Health
RTECS = Registry of Toxic Effects of Chemical Substances
EPA = Environmental Protection Agency
OHM/TADS = Oil and Hazardous Materials Technical Assistance Data Base
DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/ International Maritime Consultive Organization
HSDB = Hazardous Substance Data Bank
NCI = National Cancer Institute
SANSS = Structure and Nomenclature Search System

TABLE 3-2. Physical and Chemical Properties of 1,3-Butadiene

Property	Information	Reference
Molecular weight	54.09	Weast et al. 1988
Color	Colorless	Sax and Lewis 1987
Physical state	Gas	Sax and Lewis 1987
Melting point	-108.9°C	Weast et al. 1988
Boiling point		
at 1 atm	-4.4°C	Weast et al. 1988
at 5 atm	47°C	Windholz et al. 1983
at 10 atm	76°C	Windholz et al. 1983
Density (liquid) at 20°C	0.6211 g/mL	Weast et al. 1988
Odor	Mildly aromatic	Sax and Lewis 1987
Odor threshold		
Water	0.0014 mg/L	Amoore and Hautula 1983
Air	1.0-1.6 ppm (recognition)	Amoore and Hautula 1983
	0.025 ppm (detection)	Verschueren 1983
Solubility		
Water at 25°C	735 ppm	McAuliffe 1966
Organic solvents	Alcohol, ether, acetone, benzene, polar and nonpolar organic solvents	Weast et al. 1988 Windholz et al. 1983
Partition coefficient		
Log octanol/water	1.99	Hansch and Leo 1985
Log K_{oc} (calculated from K_{ow})	2.46	Lyman et al. 1982
	2.59	Verschueren 1983
Vapor pressure at 25°C	2100 mmHg	Daubert and Danner 1985
Henry's law constant at 25°C (calculated)	7.05×10^{-2} atm-m^3/mol	Hine and Mookerjee 1975
Autoignition temperature	414°C	Sax and Lewis 1987
Flashpoint	-76°C	Sax and Lewis 1987
Flammability limits in air	Extremely flammable	Miller 1978
Conversion factors		
ppm (v/v) to mg/m^3 in air (20°C)	2.21	IARC 1986
mg/m^3 to ppm (v/v) in air (20°C)	0.445	IARC 1986
Bioconcentration factor (calculated from K_{ow})	19	Lyman et al. 1982
Explosive limits	2-11.5%	Kirshenbaum 1978

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

In 1985, 1,3-butadiene was the 36th highest-volume chemical produced in the United States (Sax and Lewis 1987). Domestic production of rubber-grade 1,3-butadiene in 1988 was approximately 3.2 billion pounds. Rubber grade monomer typically makes up 37% of the 1.8 billion pounds of the so-called 1,3-butadiene and butylene mixture produced in 1988 (Kirshenbaum 1978; USITC 1989). Similar data for 1987 were 2.9 and 1.2 billion pounds, respectively (USITC 1988). Total U.S. capacity for this compound stands at about 3.8 billion pounds (SRI 1991), although production capacity is highly dependent on the type of feedstock used (Chemical Marketing Reporter 1980). 1,3-Butadiene is currently produced by 11 manufacturers in Texas and Louisiana. These data are included in Table 4-1. 1,3-Butadiene is available as a liquified gas, with a stabilizer added for shipment (Kirshenbaum 1978).

According to the Toxic Chemical Release Inventory (TRI 1989), 146 facilities manufactured or processed 1,3-butadiene in 1987. Of these, 142 facilities reported the maximum amount of 1,3-butadiene that they would have on site. A summary of these data is presented in Table 4-2. The quality of the TRI data must be viewed with caution because the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

Examination of the key chemical profiles on 1,3-butadiene (Chemical and Engineering News 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1985, 1986) reveals that, during this time period, production volume, capacity, and prices have fluctuated in response to market pressures, which are outside of domestic use patterns. Descriptions such as "the odd world of 1,3-butadiene" (Chemical and Engineering News 1982), and "the maverick of the petrochemical business" (Chemical and Engineering News 1983) attest to the unpredictability of the 1,3-butadiene market. Recent estimates put the growth of domestic production at 0%-l% annually through 1992 (Chemical Marketing Reporter 1988).

Except for a small amount of 1,3-butadiene produced by the oxydehydrogenation of n-butene, all the 1,3-butadiene produced in the United States is a co-product of ethylene manufacture, due in part to an increased demand for ethylene (Chemical and Engineering News 1985; Chemical Marketing Reporter 1988; IARC 1986; SRI 1991). In this process, feed streams ranging from light hydrocarbons to heavy gas oils (hydrocarbon fractions boiling in the approximate range of 315-480°C) are cracked in the presence of steam at 700-900°C (Chemical and Engineering News 1986; Kirshenbaum 1978). The fraction of 1,3-butadiene produced by this process varies widely with the type of feedstock used and is lowest with low-boiling input streams (IARC 1986; Kirshenbaum 1978).

The oxidative dehydrogenation of n-butene, used in the production of 1,3-butadiene, is a highly selective, irreversible process that involves

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1. Current U.S. Producers of 1,3-Butadiene[a]

Company	Location
Amoco Corp.	Alvin, TX
Lyondell Petrochemicals	Channelview, TX
Exxon Corp.	Baton Rouge, LA
Exxon Corp.	Baytown, TX
Mobil Corp.	Beaumont, TX
Occidental Petroleum Corp.	Chocolate Bayou, TX
Occidental Petroleum Corp.	Corpus Christi, TX
Shell Oil Co.	Deer Park, TX
Shell Oil Co.	Norco, LA
Texaco, Inc.	Port Neches, TX
Texas Olefins Co.	Houston, TX

[a]Derived from SRI 1991; USITC 1989

TABLE 4-2. Facilities That Manufacture or Process 1,3-Butadiene[a]

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
AL	1	100-999	7
AR	1	1-9	1, 3
CA	12	0-9,999	1, 3, 4, 5, 6, 7, 8, 9
CO	2	1-99	3, 6, 7
CT	1	1,000-9,999	7
DE	2	100-999	1, 6, 7
GA	3	100-9,999	7
HI	1	10-99	1, 3, 6, 7
IA	2	100-9,999	1, 3, 7
IL	7	1-9,999	1, 3, 5, 6, 7
IN	3	0.1-99	1, 3, 4, 6, 7, 8
KS	3	0.1-99	1, 3, 5, 6, 7
KY	6	10-9,999	1, 4, 5, 6, 7
LA	16	1-49,999	1, 2, 3, 4, 5, 6, 7, 13
MI	1	100-999	7
MN	1	1,000-9,999	1, 6
MO	1	100-999	7
MS	2	1-999	3, 5, 7
MT	2	0.1-9	1, 3, 6, 7
NC	2	0-999	7, 8
NE	1	0-0.09	3, 9, 12
NJ	2	0-9	1, 3, 5, 6, 7
NY	3	1-99	2, 4, 6, 7
OH	15	0-9,999	1, 3, 5, 6, 7, 8, 9
OK	3 (1)[e]	100-999	1, 3, 6, 7, 13
PA	4 (1)[e]	0.1-99	1, 3, 6, 7, 9
SC	1	10-99	7
TN	3	0-9,999	5, 6, 7
TX	49 (1)[e]	0-99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13

TABLE 4-2 (Continued)

State[b]	Number of facilities	Range of maximum amounts on site in thousands of pounds[c]	Activities and uses[d]
VA	1	0.1-0.9	1, 4
WA	2	10-99	1, 5, 6
WV	2	100-9,999	7, 9

[a]TRI 1989
[b]Post office state abbreviations
[c]Data in TRI are maximum amounts on site at each facility.
[d]Activities/Uses:

1. synthesis
2. import
3. for on-site use/processing
4. for sale/distribution
5. as a byproduct
6. as an impurity
7. as a reactant
8. as a formulation component
9. as an article component
10. for repackaging only
11. as a chemical processing aid
12. as a manufacturing aid
13. ancillary or other use

[e]Number in parentheses indicates facilities reporting "no data" regarding maximum amount of the substance on site.

heating the starting material, air, and a suitable catalyst together at 400-450°C (IARC 1986; Kirshenbaum 1978). The hydrogen released in the dehydrogenation step combines with oxygen, producing large amounts of heat, which makes this process energy-efficient. Other products of this process include isobutylene, 1-butene, 2-butene, and n-butane.

Purification of the crude C^4 stream resulting from these processes cannot be achieved by a simple distillation due to the close boiling point of the various products (Kirshenbaum 1978). 1,3-Butadiene can be removed from the hydrocarbon stream by selective extraction with various solvents. These solvents include aqueous cupric ammonium acetate, acetonitrile, furfural, dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone and •-methoxypropionitrile (IARC 1986; Kirshenbaum 1978).

4.2 IMPORT/EXPORT

Large amounts of 1,3-butadiene are imported into the United States. The amount of 1,3-butadiene imported in 1987 represented 27% of the domestic production, a rise of 82% over the previous year (Chemical Marketing Reporter 1988). In 1986, approximately 500 million pounds were imported after a high of 900 million pounds in 1983 (Chemical and Engineering News 1983, 1986). As with production volumes, no clear import trends can be deduced. Export volumes of 1,3-butadiene from the United States are low, about 125 million pounds in 1986 (Chemical and Engineering News 1986), or about 4% of domestic production in 1987 (Chemical Marketing Reporter 1988). Exports may decrease with the expected increase in production of light hydrocarbons from petroleum sources in the North Sea, the Middle East and northern Africa.

4.3 USE

1,3-Butadiene is used as a monomer in the production of rubber and plastics, with approximately 75% going into the production of synthetic rubbers (Chemical and Engineering News 1986). 1,3-Butadiene uses can be broken down into the following categories: styrene butadiene rubber (SBR), 35%; polybutadiene, 22%; adiponitrile/hexamethylene diamine (HMDA), 12%; styrene-butadiene latex, 10%; neoprene rubber, 6%; ABS resins, 6%; exports, 4%; nitrile rubber, 3%; and other, 2% (Chemical Marketing Reporter 1988). It is also used extensively in copolymers including acrylics (Miller 1978).

4.4 DISPOSAL

1,3-Butadiene may be disposed of by incineration in a suitable combustion chamber or in a safe area. Gaseous 1,3-butadiene can be burned directly in most states; however, liquified 1,3-butadiene (in a compressed cylinder) must be converted to the gaseous state before burning (HSDB 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,3-Butadiene is a high-volume, volatile hydrocarbon used in the production of commercial plastics and rubbers. The chemical reactivity of this monomer is utilized in its transformation into polymeric materials. 1,3-Butadiene is also present in gasoline.

1,3-Butadiene may be released to the environment as an intentional or fugitive emission during its production, use, storage, transport, or disposal. Large amounts of this hydrocarbon are released to the atmosphere from commercial processes. According to the SARA Section 313 Toxic Release Inventory (TRI), an estimated total of 9.2 million pounds of 1,3-butadiene were released to the atmosphere from manufacturing and processing facilities in the United States in 1987 (TRI 1989). This total compares to a total release of approximately 9.6 million pounds to air, soil, water, public treatment works, and off-site areas during the same year. TRI data can be found in Table 5-1. The quality of the TRI data must be viewed with caution because the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. 1,3-Butadiene is also released to the atmosphere in motor vehicle exhaust, cigarette smoke, the smoke of brush fires, the thermal breakdown or burning of plastics, and by volatilization from gasoline.

Large amounts of 1,3-butadiene are released to the atmosphere. Data on the detection of 1,3-butadiene in soil and water are scarce due to the lack of a reliable analytical method to detect this compound in these media. It has been qualitatively detected in drinking water. 1,3-Butadiene has been detected at three hazardous waste sites (View 1989). The states in which these hazardous waste sites are located can be found in Figure 5-1.

1,3-Butadiene is a highly volatile gas; therefore, it is expected to partition predominantly to the atmosphere. In the atmosphere, 1,3-butadiene is expected to undergo rapid destruction, primarily by photo-initiated reactions. The reaction with photochemically produced hydroxyl radicals has a calculated half-life of approximately 6 hours and is expected to be the dominant pathway for atmospheric removal. Destruction of atmospheric 1,3-butadiene by the gas-phase reaction with ozone and by the night-time reaction with nitrate radicals in urban areas is also expected to be significant.

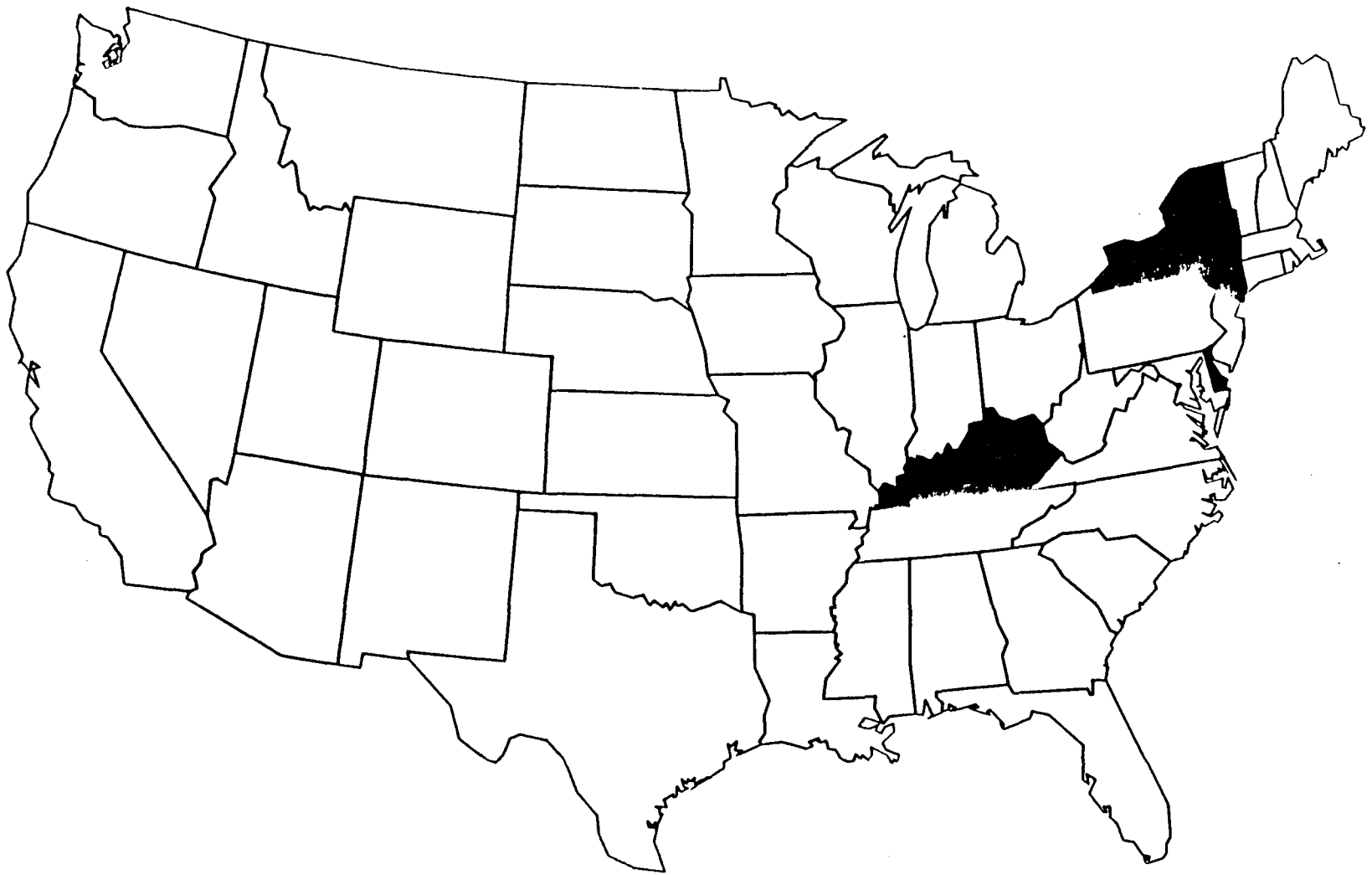
Limited data have been located on the fate of 1,3-butadiene in soil or water. Based on its physical properties, rapid volatilization of 1,3-butadiene from either soil or water to the atmosphere is expected to dominate over all other potential environmental processes. Studies performed with pure cultures indicate that 1,3-butadiene may be susceptible to microbial attack. Based on estimated values, 1,3-butadiene is not expected to adsorb significantly to soil or sediment, nor is it expected to bioconcentrate in

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process 1,3-Butadiene[a]

State[d]	No. of facilities	Range of reported amounts released in thousands of pounds[b]						
		Air	Underground injection	Water	Land	Total environment[e]	POTW[c] transfer	Off-site waste transfer
AL	1	3.4-3.4	0-0	0.3-0.3	0-0	3.7-3.7	0-0	0.3-0.3
AR	1	0.3-0.3	0-0	0-0	0-0	0.3-0.3	0-0	0-0
CA	12	0-2.1	0-0	0-0.3	0-0	0-2.4	0-0	0-0.3
CO	2	0.3-0.8	0-0	0-0	0-0	0.3-0.8	0-0	0-0
CT	1	41.3-41.3	0-0	0.1-0.1	0-0	41.3-41.3	0-0	17-17
DE	2	24-78.3	0-0	0-0	0-0	24-78.3	0-0	0-0
GA	3	105-403.5	0-0	0-0	0-0	105-403.5	0-0	0-93
HI	1	0.5-0.5	No Data	0-0	0-0	0.5-0.5	0-0	0-0
IA	2	175-278	0-0	0-0.1	0-0	175-278	0-0	0-0
IL	7	0.1-113.8	0-0	0-0.3	0-0	0.1-113.8	0-0	0-0
IN	3	0.4-40.2	0-0	0-0	0-0	0.4-40.2	0-0	0-0
KS	3	0.2-0.4	0-0.1	0-0	0-0	0.2-0.4	0-0	0-0.1
KY	6	1.7-161	0-0	0-0.1	0-0.1	1.8-161	0-0.3	0-1.3
LA	16	0.1-150	0-0	0-0.2	0-0.1	0.1-150	0-0	0-181.7
MI	1	63.5-63.5	0-0	0-0	0-0	63.5-63.5	0-0	0-0
MN	1	0-0	0-0	0.1-0.1	0-0	0.1-0.1	0-0	0-0
MO	1	0.2-0.2	0-0	0-0	0-0	0.2-0.2	0.1-0.1	0.2-0.2
MS	2	0.5-2.2	0-0	0-0	0-0	0.5-2.2	0-0	0-0
MT	2	0.3-0.9	0-0	0-0	0-0	0.3-0.9	0-0	0-0
NC	2	0-9.6	0-0	0-0	0-0	0-9.6	0-0.1	0-0
NE	1	0-0	0-0	0-0	0-0	0-0	0-0	0-0
NJ	2	0.1-0.1	0-0	0-0	0-0	0.1-0.1	0-0	0-0
NY	3	0.1-65.8	0-0	0-0.1	0-0	0.1-65.8	0.1-0.1	0-0.3
OH	15	0-146.8	0-0	0-0.3	0-0.1	0.1-146.8	0-36	0-65.5
OK	3	0.1-1.9	0-0	0-0	0-0	0.1-1.9	0-0	0-0
PA	4	0-115.6	0-0	0-0.3	0-0	0.2-115.6	0-0	0-0
SC	1	14-14	0-0	0-0	0-0	14-14	0-0	0-0
TN	3	9.9-640.2	0-0	0-0	0-0	9.9-640.2	0-0.1	0-0
TX	49	0-960	0-0	0-430	0-2.9	0-1,392	0-0	0-1,802
VA	1	0.1-0.1	0-0	0-0	0-0	0.1-0.1	0-0	0-0
WA	2	4.2-5.7	0-0	0-0.1	0-0	4.2-5.7	0-0	0-0
WV	2	6.1-700	0-0	0-0.1	0-0	6.1-700	0-0	0-0

[a]TRI 1989
[b]Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities >1 million pounds, which have been rounded to the nearest thousand pounds.
[c]Publicly owned treatment works
[d]Post office state abbreviation
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 1,3-BUTADIENE CONTAMINATION *



* Derived from View 1989

fish or aquatic organisms; however, experimental data is necessary to verify these conclusions.

Although 1,3-butadiene undergoes rapid destruction in the atmosphere, it is almost always present at very low concentrations in urban and suburban areas. Automobile exhaust is a constant source of 1,3-butadiene release to the atmosphere. Because of the compound's presence in the atmosphere, the general population is exposed ***to*** ppb levels of 1,3-butadiene through inhalation. Exposure to 1,3-butadiene may also occur from the inhalation of gasoline fumes, cigarette smoke, or possibly the smoke from wood fires. Possible ingestion of contaminated drinking water may also lead to low levels of exposure, although we do not know the concentration of this compound in water samples, nor do we have a good understanding of its frequency of detection. The levels of 1,3-butadiene in soil are not known. Dermal exposure to low levels of 1,3-butadiene may occur for members of the general population if they spill gasoline on themselves. Elevated levels of exposure for the general population may occur for those near its site of manufacture or facilities where it is made into polymeric materials.

Occupational exposure to 1,3-butadiene is expected to be limited to those working at facilities that manufacture 1,3-butadiene or convert it into commercial polymers. Exposure by inhalation is expected to be the dominant pathway for exposure. Theoretically, dermal exposure to liquified 1,3-butadiene could occur during an explosion of a pressurized storage tank or some other catastrophic event; however, no such accidents have been reported in the available literature.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

The dominant sources for the release of 1,3-butadiene to the atmosphere are fugitive or accidental emissions during its manufacture, use, transport, and storage. Low levels of 1,3-butadiene are constantly emitted to the atmosphere from many sources including exhaust from motor vehicle engines using petroleum-based fuels.

A correlation of data from the EPA Air Toxic Emission Inventory with industrial source codes (SIC) indicates that volatile emissions of 1,3-butadiene are associated with 14 different industrial classifications, which are dominated by rubber and chemical products (Pacific Environmental Services 1987). Fugitive emissions of 1,3-butadiene from seals, valves, vents, flanges, and the like in petrochemical plants manufacturing this compound were estimated to be 1,112 metric tons/year (Hughes et al. 1979). The authors believed that this level of release was lower than that released by refineries. Emissions of 1,3-butadiene from equipment leaks and process vents in 1984 were estimated at 3.8 million pounds/year during its production, 5 million pounds/year during the synthesis of styrene-butadiene copolymers,

900,000 pounds from polybutadiene production, and 86,000 pounds from neoprene/chloroprene production (Mulling 1990).

According to the TRI (1989), 155 facilities that manufacture or process 1,3-butadiene released an estimated 9,205,532 pounds of this compound to the atmosphere in 1987. The largest air emission from a single facility was 960,000 pounds. The quality of the TRI data must be viewed with caution because the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. TRI data can be found in Table 5-1.

1,3-Butadiene is a component of motor vehicle exhaust; this is a constant source of release to the atmosphere (Stump and Dropkin 1985). In high-traffic areas, the release of 1,3-butadiene to the atmosphere occurs continually. In a recent study, it was measured in the exhaust of typical automobiles and light trucks using both winter and summer gasoline formulations and accounted for up to 0.12% of total hydrocarbon emissions (Stump et al. 1989). An earlier study determined that the concentration of 1,3-butadiene in automobile exhaust was 20-60 ppb (Neligan 1962). 1,3-Butadiene has also been detected in the exhaust of diesel engines (Hayano et al. 1985) and high-altitude jet aircraft engines operating under simulated conditions (Katzman and Libby 1975). 1,3-Butadiene has also been identified in modern formulations of unleaded gasolines (Sigsby et al. 1987) and may be released to the atmosphere by direct volatilization from the fuel.

There are several minor sources for the release of 1,3-butadiene to the atmosphere; all involve the thermal breakdown of other materials. 1,3-Butadiene has been detected as a component of the sidestream smoke from cigarettes (Bartle et al. 1969; Blomberg and Widmark, 1975). The average amount of 1,3-butadiene in sidestream cigarette smoke is 205-361 μg/cigarette (Brunnemann et al., 1990), with an average airborne yield of 400 μg/cigarette (Lofroth et al. 1989). The burning of plastics or rubber has been shown to release small amounts of 1,3-butadiene (Miller 1978). In a test designed to simulate a real-life electrical overload condition, 1,3-butadiene was detected when polyurethane coated wire was heated to 250°C for 40 minutes,(Rigby 1981). 1,3-Butadiene has also been measured as a component of the smoke from a brush fire (Stephens and Burleson 1969), and as a stack emission from waste incinerators (Junk and Ford 1980). The concentrations of 1,3-butadiene were not presented in these studies.

5.2.2 Water

Very limited data on release of 1,3-butadiene to environmental waters were located in the available literature. According to the TRI (1989), 155 facilities that manufacture or process 1,3-butadiene discharged an estimated total of 432,857 pounds of 1,3-butadiene to surface water in 1987. A single facility was responsible for 430,000 pounds of this discharge.

Transfer of 1,3-butadiene to publicly owned treatment works (POTWs) amounted to 56,490 pounds in 1987 (TRI 1989). The quality of the TRI data must be viewed with caution because the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

5.2.3 Soil

Limited data on releases of 1,3-butadiene to soil were located in the available literature. According to the TRI (1989), 155 facilities that manufacture or process 1,3-butadiene released an estimated total of 3,672 pounds of 1,3-butadiene to land in 1987. However, the quality of the TRI data must be viewed with caution because the 1987 data represent firsttime reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Experimental data on the partitioning of 1,3-butadiene in the environment were not located in the available literature. The following discussion on the partitioning of 1,3-butadiene in the environment is based on the physical and chemical properties of this compound. The estimation techniques used in this discussion are well-established in the literature; however, without adequate experimental data, we do not know exactly how this compound will behave in the environment.

The high volatility of this compound suggests that it will partition predominantly to the atmospheric compartment, where it is not expected to be adsorbed to particulate matter to any significant extent (Eisenreich et al., 1981).

An estimated Henry's law constant of 7.05×10^{-2} atm/m^3-mol at 25°C can be obtained using the method of Hine and Mookerjee (1975). Based on this value, the half-life for volatilization of 1,3-butadiene from a model river 1 m deep, flowing at 1 m/set, with a wind velocity of 3 m/set is 2.2 hours (Lyman et al. 1982). Based on an experimental log octanol/water partition coefficient of 1.99 (Hansch and Leo 1985), a calculated soil adsorption coefficient of 288 (Lyman et al. 1982) suggests that adsorption to sediment and suspended organic matter will not be a significant fate process. From the log octanol/water partition coefficient, a calculated bioconcentration factor of 19 (Lyman et al. 1982) indicates that 1,3-butadiene will not bioconcentrate in fish and aquatic organisms to any significant extent. However, no experimental data have been located to verify these theoretical values.

If released to soil, 1,3-butadiene is expected to volatilize rapidly from either moist or dry soil to the atmosphere. This follows from the estimated

lack of any appreciable adsorption to soil, and consideration of 1,3-butadiene's calculated Henry's law constant for moist soil or its vapor pressure, 2,100 mmHg at 25°C (Daubert and Danner 1985), for dry soil. Both values suggest a rapid rate of volatilization from their respective media.

The calculated soil adsorption coefficient of 288 (Hansch and Leo 1985; Lyman et al. 1982) suggests that 1,3-butadiene may display moderate mobility in soil (Swann et al. 1983). However, the expected rapid rate of volatilization and the possibility of rapid degradation in soil suggest that there is little potential for 1,3-butadiene *to* leach into groundwater. But until adequate groundwater monitoring for 1,3-butadiene has been performed, the partitioning of 1,3-butadiene in soil cannot be adequately addressed.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Butadiene is a reactive, electron-rich chemical that is expected to undergo rapid reactions with the electrophilic oxidants typically present in the atmosphere: ozone, photochemically produced hydroxyl radicals, nitrate radicals, and molecular oxygen. Among these, the most rapid reaction in the atmosphere is with photochemically produced hydroxyl radicals.

The atmospheric destruction of 1,3-butadiene by photo-initiated processes has been established empirically by early studies. These studies typically involved irradiating urban air samples in atmospheric chambers of varying complexity and monitoring the disappearance of each constituent. Using this technique, 1,3-butadiene, at an average concentration of 12.4 ppb, disappeared in 6 hours when irradiated with natural sunlight during October (Kopczynski et al. 1972). In another study, a half-life of 2 hours was determined for the atmospheric removal of 1,3-butadiene using natural sunlight in October or November (Altshuller et al. 1970). In smog chamber studies, the sunlight oxidation of 1,3-butadiene led to the formation of fairly potent eye irritants, suggesting destruction of this compound with concomitant formation of oxygenated species (Dimitriades et al. 1975; Heuss and Glasson 1968). It is believed that the destruction of 1,3-butadiene occurs by photo-initiated bimolecular processes rather than direct photochemical degradation (Kopczynski et al. 1972). It is important to note that the rate of destruction of 1,3-butadiene when it was irradiated with natural light depended on the time of day in which the irradiation occurred. Furthermore, these studies were performed in October and November, when the amount and the intensity of available sunlight is diminished over that of summer months; thus, these values probably represent the high end of the compound's atmospheric lifetime. The individual processes responsible for the destruction of 1,3-butadiene in the atmosphere are discussed below.

Numerous studies have determined the rate constant for the gas-phase reaction of 1,3-butadiene with photochemically produced hydroxyl radicals

(Atkinson 1985; Atkinson and Aschmann 1984; Atkinson et al. 1977, 1979; Maldotti et al. 1980). The experimental rate constant 6.85×10^{-11} cm^3/molecule-sec at 26°C (Atkinson et al. 1977) is representative. Given an average hydroxyl radical concentration of 5×10^5 molecule/cm^3 (Atkinson 1985), the half-life for this second-order process is 5.6 hours. In an attempt to classify the potential for atmospheric destruction of organic compounds by hydroxyl radicals, a rating system based on nonreactive methane (class I) to highly reactive compounds (class V) was established (Darnall et al. 1976). In this classification system, 1,3-butadiene was assigned between classes IV and V, signifying its high reactivity towards photochemically produced hydroxyl radicals.

Gas-phase 1,3-butadiene also reacts with ozone in the atmosphere. Rate constants ranging from 6.7×10^{-18} to 8.4×10^{-18} cm^3/molecule-sec at 25°C have appe,ared in the literature (Atkinson and Carter 1984; Jaspar et al. 1974). Using an average atmospheric ozone concentration of 7×10^{11} molecules/cm^3 (Atkinson and Carter 1984), half-lives ranging from 1.4 to 1.7 days can be calculated for this second-order process. Therefore, the reaction of 1,3-butadiene with ozone is expected to contribute to the overall destruction of atmospheric 1,3-butadiene. The initial products from the reaction of 1,3-butadiene with ozone are acrolein, formaldehyde, acetylene, ethylene, and formic anhydride (Niki et al. 1983). All of these products are susceptible to secondary reactions with ozone and other atmospheric oxidants.

1,3-Butadiene can also be destroyed in the atmosphere by the reaction with ground-state, triplet oxygen. Rate constants for this addition reaction range from 1.9×10^{-11} to 2.07×10^{-11} cm^3/molecule-sec (Atkinson and Pitts 1977; Gaffney and Levine 1979; Nip et al. 1979), in a reaction that appears to be essentially independent of temperature (Nip et al. 1979). Given the average atmospheric concentration of oxygen of 2.54×10^4 molecules/cm^3 (Graedel et al. 1986), the half-life for the destruction of 1,3-butadiene by this process can be calculated as 15-16 days. Although this reaction will not be significant under conditions where the facile pathways described above are operating, it may occur under conditions where they are not.

The night-time degradation of 1,3-butadiene is also expected to occur via the gas-phase reaction with nitrate radicals; this tends to be significant in urban areas, where the concentration of this oxidant is typically higher than in rural areas (Altshuller and Cohen 1964; Gay and Bulfalini 1971; Maldotti et al. 1980). A rate constant of 5.4×10^{-14} cm^3/molecule-sec at 22°C has been determined for this reaction. This corresponds to a half-life of 14.9 hours using an average atmospheric nitrate radical concentration of 2.4×10^8 molecule/cm^3 (Atkinson et al. 1984), typical of mildly polluted urban centers. Acrolein has been identified as a primary product of this reaction.

In summary, there are four gas-phase pathways that can destroy 1,3-butadiene in the atmosphere. Depending on local conditions, any one or all of these reactions may occur. Destruction of atmospheric 1,3-butadiene by

the gas-phase reaction with photochemically produced hydroxyl radicals is expected to be the dominant photo-initiated pathway. Destruction by nitrate radicals is expected to be a significant night-time process in urban areas.

5.3.2.2 Water

Data on the degradation of 1,3-butadiene in aquatic systems are limited. Experimental data are restricted to microbial degradation studies performed under aerobic conditions. The bulk of these data were obtained from isolated Bacterial strains, not with mixed microbial populations typically found in natural systems. 1,3-Butadiene biodegraded when inoculated with methane-utilizing,or methanotrophic, organisms under aerobic conditions. Cell suspensions of these bacteria oxidized 1,3-butadiene to 3,4-expoxybutene (Hou et al. 1979, 1980; Pate1 et al. 1982a). None of the authors reported further degradation of the epoxide to the corresponding diol.

Bacteria isolated from lake water and raised on propane also oxidized 1,3-butadiene to 3,4-expoxybutene (Hou et al. 1983). 1,3-Butadiene was listed as a synthetic organic chemical that should degrade in a biological sewage treatment system, provided that suitable acclimation could be achieved, although no experimental details *were* provided (Thorn and Agg 1975).

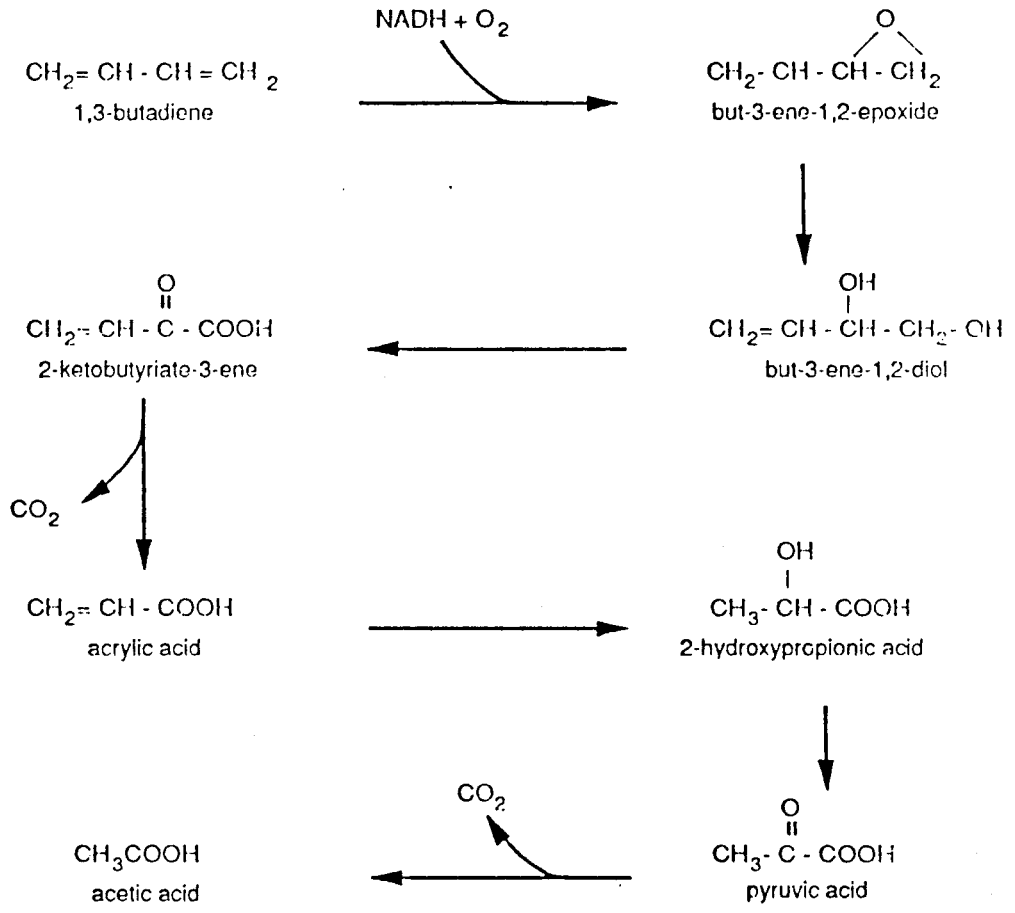
A Nocardia species isolated from water and soil completely degraded 1,3-butadiene to acetic acid under aerobic conditions (Watkinson and Somerville 1976). The proposed route for this degradation involves initial stereospecific epoxidation to but-3-ene-1,2-epoxide followed by ring opening to but-3-ene-1,2-diol, oxidation to the corresponding •-keto acid (2-ketobutyrate-3-ene), loss of CO_2 to acrylic acid, hydroxylation to 2-hydroxypropionic acid, oxidation to pyruvic acid, and loss of CO_2 to acetic acid. This pathway is described in Figure 5-2 (Verschueren 1983; Watkinson and Somerville 1978). Although this pathway is reasonable, experimental evidence establishing the formation of all the key intermediates was not provided. Most importantly, cleavage of the initially formed epoxide was not rigorously established. No data were located on the biodegradation of 1,3-butadiene under anaerobic conditions.

5.3.2.3 Soil

As is the case for the degradation of 1,3-butadiene in water, very limited data on the destruction of this compound in soil could be located in the available literature. The experimental data obtained from pure culture studies on the microbial degradation of 1,3-butadiene suggest that this compound can biodegrade in soil.

Methane-utilizing bacteria isolated from the soil of an oil refinery epoxidized 1,3-butadiene under aerobic conditions (Hou et al. 1979; Pate1 et al. 1979, 1982a, 1982b). Cell suspensions of Mycobacterium obtained from soil and raised on ethylene oxidized 1,3-butadiene under aerobic conditions;

FIGURE 5-2. Catabolic Pathway for the Biodegradation of 1,3-B, by Norcardia Cultures in Aqueous Media*



*Source: Verschueren 1983; Watkinson and Somerville 1976

however, cultures raised on ethane or succinate did not (DeBont et al. 1979). Microorganisms isolated from soil (Nocardia, Mycobacterium, Xanthobacter, and Pseudomonas) and raised on gaseous alkenes oxidized 1,3-butadiene to the corresponding epoxide under aerobic conditions (VanGinkel et al. 1987). These bacteria may convert the initially formed epoxide to the diol, although no evidence was presented to support this point.

A Nocardia species isolated from soil and water degraded 1,3-butadiene under aerobic conditions to acetic acid (Watkinson and Somerville 1976). The proposed sequence for this transformation is described in Section 5.3.2.2 and presented in Figure 5-2. No data on the degradation of 1,3-butadiene under anaerobic soil conditions were located in the available literature.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

In an analysis of the ambient air monitoring data for the United States contained in published and unpublished experimental reports from 1970 to 1987, Shah and Heyerdahl (1988) compiled median daily concentrations for volatile organic compounds. For 1,3-butadiene, the median concentrations are 0.29 ppb in urban areas, 0.32 ppb in suburban areas, and 0.10 ppb in rural areas. The value for rural areas must be interpreted carefully, as it is based on only two data points. The suburban and urban values are based on 196 and 385 data points, respectively. Representative data on the concentration of 1,3-butadiene in urban and remote areas can be found in Table 5-2. Reports on the detection of 1,3-butadiene in urban areas have also been published from areas monitored in the Netherlands (Guicherit and Schulting 1985), Australia (Mulcahy et al. 1976), and South Africa (Louw et al. 1977).

On a monitoring trip in 1986, the Texas Air Control Board (1990) measured ambient air concentrations within a mile of a petrochemical complex in Allendale, Texas, suspected of exceeding air quality limits. The average concentration of 1,3-butadiene was 100 ppb, with the highest daily and hourly average measured at 143 and 905 ppb, respectively. A 1989 monitoring trip to Port Neches, Texas, found that air samples within 1 mile of another petrochemical complex had a highest 1 hour average 1,3-butadiene concentration of 642 ppb and a highest 12-hour average concentration of 240 ppb. This manufacturing plant was also suspected of exceeding air quality limits. The highest single value for 1,3-butadiene measured in this study was 1,740 ppb. Residential areas were located near the monitoring stations used in these two studies.

1,3-Butadiene has been detected in indoor air samples. The concentrations of 1,3-butadiene in a tavern were 11 and 19 $\mu g/m^3$ (4.98 and 8.60 ppb) in two separate studies, while the outside air concentration was less than or equal to 1 $\mu g/m^3$ (0.45 ppb) at the same time (Lofroth et al. 1989). The difference in the indoor versus outdoor concentration may be

TABLE 5-2. Detection of 1,3-Butadiene in Air

Media type/location	Sampling dates	No. of samples	Concentration (ppb) Range	Mean	Reference
Urban					
Houston, TX	1973	9	ND-150[a]	33.4[a]	Lonneman et al. 1979
	1974	7	8.0-57	27.2	
	1974	4	ND-8.4	3.0	
Los Angeles, CA	1968	NS	NS	12.4[a]	Kopczynski et al. 1972
Riverside, CA	1965-66	8	ND-2.0	NS	Stephens and Burleson 1967
Los Angeles, CA	1960	16	ND-9	3.1	Neligan 1962
Boone, NC	1981-82	3	ND-0.34[a]	0.11	Seila et al. 1984
Boone, NC (downtown)		3	0.34-5.0	4.2	
Boone, NC (outskirts)		3	0.11-0.22	0.15	
Remote					
Roan Mt., NC	1981-82	3	ND-0.22[a]	0.74	Seila et al. 1984
Grandfather Mt., NC		3	ND-0.15	0.37	
Linville Gorge, NC		3	ND-0.45	0.19	

[a]Data reported in ppbC (parts per billion carbon). Converted to ppb using the conversion factor 1 ppb = 1.12 ppbC (54.1 ppb/48.4 ppbC)

ND = below detection limit
NS = not stated

ascribed to the presence of 1,3-butadiene in cigarette smoke. The concentration of 1,3-butadiene in a smoke-filled bar was 2.7-4.5 μg/m^3 (1.2-2.0 ppb) (Brunnemann et al. 1990). 1,3-Butadiene was also detected in a public building in Riverside, California, in 1965 at a concentration of 9.0 ppb, although its source was not specified (Stephens and Burleson 1967).

5.4.2 Water

Limited data on the occurrence of 1,3-butadiene in water were located in the available literature. 1,3-Butadiene was found in 1 of 204 water samples taken in 1975-76 from surface waters near known industrialized areas across the United States. The single positive sample was obtained in the Carquinez Strait, Posta Corta, California, at an approximate concentration of 2 ppb (Ewing et al. 1977).

No specific data on its presence in drinking water, such as monitoring dates or concentration, were located; however, 1,3-butadiene has been;. qualitatively detected in U.S. drinking water (EPA 1978; Kraybill 1980).

5.4.3 Soil

No data on the occurrence of 1,3-butadiene in soil were located in the available literature.

5.4.4 Other Environmental Media

1,3-Butadiene is used to, manufacture synthetic rubber and plastics that are frequently used for food packaging. Because residual 1,3-butadiene may be present in the polymers used to make the containers, both the packaging and the food contained therein have been analyzed. In one study, 1,3-butadiene at a concentration of 8-9 ng/g (ppb) was detected in 3 of 3 brands of olive oil packaged in 1,3-butadiene rubber-modified acrylonitrile-acrylic bottles (McNeal and Breder 1987). Analysis of the bottles themselves found 1,3-butadiene residues as high as 6600 ng/g (ppb). Soft-plastic packaging tubs used as containers for potato salad, cottage cheese, and yogurt had residual 1,3-butadiene levels in the range 21-1700 ng/g (ppb). However, no 1,3-butadiene was detected in any of the food packed in these containers (detection limit 1 ppb). Chewing gum made with a 1,3-butadiene rubber base did not show residual traces of this diene (McNeal and Breder 1987). Soft plastic margarine tubs from five major name brands in the United Kingdom contained 1,3-butadiene residues ranging from 5 to 310 μg/kg (ppb), but none of the monomer was detected in the margarine samples themselves (detection limit 0.2 μg/kg) (Startin and Gilbert 1984). The authors concluded that migration of the 1,3-butadiene monomer from plastic packaging to food is unlikely to present a problem. Residual levels of 1,3-butadiene in food containers are closely regulated by the Food and Drug Administration.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

1,3-Butadiene is almost always present in the air at low levels due to its emission from motor vehicles. Therefore, the general population is probably routinely exposed to ppb levels of this compound, although adverse health effects have not been noted at this level of exposure. Exposure to 1,3-butadiene by the general population is expected to be dominated by inhalation. Low level exposure by ingestion of contaminated drinking water may also occur as 1,3-butadiene has been qualitatively detected in U.S. drinking water supplies (EPA 1978; Kraybill 1980).

Inhalation of 1,3-butadiene by the general population may also occur due to other sources. 1,3-Butadiene has been identified in cigarette smoke; therefore, smokers and those nearby are exposed to this compound (Lofroth et al. 1989; Bartle et al. 1969; Blomberg and Widmark 1975; Brunnemann et al. 1990). Limited data suggest that 1,3-butadiene is present in the smoke from brush fires (Stephens and Burleson 1969), suggesting that inhalation of the smoke from wood fires will lead to low level exposure to 1,3-butadiene. Its presence in waste incinerator emissions (Junk and Ford 1980) suggests that exposure to the general population may occur for those living nearby. Due to its presence in gasoline formulations (Sigsby et al. 1987; Stump et al. 1989), members of the population who pump their own gasoline may inhale small amounts of 1,3-butadiene. The concentration of 1,3-butadiene in gasoline vapor is 4.4 ppb (IARC 1986). Small amounts of 1,3-butadiene are produced by the thermal degradation of polyurethane-coated wire, an event that may occur during an electrical overload (Rigby 1981). The thermal degradation of other 1,3-butadiene-based plastics or rubbers may produce 1,3-butadiene (Miller 1978), also leading to low-level exposure of the general population by inhalation.

If the mean daily urban air concentration of 1,3-butadiene is 0.29 ppb, as determined in an analysis and compilation of experimental reports of ambient monitoring data obtained from 1970 to 1987 (Shah and Heyerdahl 1988), a nonoccupational daily intake of 12.8 μg per person can be obtained based on an average human intake of 20 m^3 air/day.

No data are available that quantify general population exposure to 1,3-butadiene by other routes of intake, such as ingestion of contaminated drinking water. Given that residues of 1,3-butadiene have been found in plastic and rubber food containers and in a few samples of the food contained in these containers (McNeal and Breder 1987), very low-level exposure to the general population may occur by ingestion of contaminated foods packaged in these containers. 1,3-Butadiene has been identified as a constituent of modern gasoline formulations, and the general population may receive dermal exposure to 1,3-butadiene upon contact with gasoline (Sigsby et al. 1987), although the rate of absorption of 1,3-butadiene through the skin has not been investigated.

5. POTENTIAL FOR HUMAN EXPOSURE

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1980 and 1983, 9,456 workers, of which 286 are women, were estimated to be exposed to 1,3-butadiene (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any chemicals listed therein. These surveys provide only an estimate of the number of workers potentially exposed to chemicals in the workplace. Occupational exposure to 1,3-butadiene is expected to be limited to inhalation of this compound, although dermal contact with liquified 1,3-butadiene may occur during a large spill, tank explosion, pipeline rupture, or similar catastrophic event, although no reports of this type have been reported in the available literature. Specific industrial classifications or job descriptions involving exposure to 1,3-butadiene are provided below.

A field study conducted in the process control room of a styrenebutadiene rubber plant using 12 different sampling locations concluded that the 1,3-butadiene concentration ranged from 0.044 to 6.5 ppm over a 3-day testing period (Jones and Harris 1983). Health hazard evaluation surveys conducted by NIOSH at six facilities utilizing 1,3-butadiene found that the air concentration ranged from 0.06 ppm to 39 ppm. These facilities manufactured helmets, visors, synthetic rubber, rubber tires and tubes, automotive weather stripping, braided hoses, or plastic components for aircraft. According to this NIOSH report, workers involved in the industrial classifications listed in Table 5-3 have been potentially exposed to 1,3-butadiene (NIOSH 1984). A walk-through survey of 11 monomers, 17 polymers, and 2 end-user plants found that personal exposures ranged from less than 0.006 ppm to 374 ppm (Fasen et al. 1990).

Environmental sampling at two Texas styrene butadiene rubber plants had time-weighted average concentrations of 1,3-butadiene ranging from 0.11 to 4.17 ppm (mean, 1.24 ppm) and 0.34 to 174 ppm (mean, 13.5 ppm) for samples taken in 1977 (Meinhardt et al. 1982). The range of 1,3-butadiene concentrations for individuals at the plant is given in Table 5-4.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

High levels of exposure to 1,3-butadiene are likely to be limited to those resulting from an occupationally related use of this compound. Inhalation is the most likely route of high exposure to 1,3-butadiene. 1,3-Butadiene is stored and transported in pressurized tanks, and it is possible that high levels of exposure by inhalation or dermal contact with the liquified gas may occur during the loading and unloading of these tanks, or by the accidental rupture of these tanks. However, no such accidents have been reported in the available literature.

TABLE 5-3. Industrial Workers Potentially Exposed to 1,3-Butadiene[a]

Industry	Number of workers exposed
Paper and allied products	1,221
Chemicals and allied products	44,980
Petroleum and coal products	84
Rubber and plastic products	9,086
Primary metal industries	55
Fabricated metal products	96
Machinery, except electrical	1210
Electrical equipment and supplies	121
Transportation equipment	175
Instruments and related products	145
Miscellaneous manufacturing industries	2244
Miscellaneous business services	5339
Medical and other health services	493

[a]Derived from NIOSH 1984

TABLE 5-4. Air Concentrations of 1,3-Butadiene in a Styrene Butadiene Rubber Plant[a]

Affected individuals	Concentration (ppm)
Technical services personnel	0.21-114.6
Production foreman	1.16 (1 sample)
Head production operator	0.25-69.61
Production operator	0.23-33.21
Operator helper	0.26-1.81
Pipefitter	0.18-1.78
Electrician	0.18-0.34
Maintenance mechanic	0.19-44.38
Carpenter	0.20-30.60
Common laborer	0.17-8.22
Instrument man	0.17-174.14

[a]Derived from Meinhardt et al. 1982

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,3-butadiene are well documented (Sax and Lewis 1987; Windholz et al. 1983), and its environmental fate can be estimated from these properties (Lyman et al. 1982). Experimental verification of these calculated values used to determine the partitioning of 1,3-butadiene in the environment are necessary to establish accurate levels of human exposure.

Production, Import/Export, Use, and Disposal. The trends in the production and use of 1,3-butadiene are well documented (Kirshenbaum 1978; Chemical Marketing Reporter 1980; USITC 1988), and there do not appear to be any critical information gaps. 1,3-Butadiene monomer does not occur in most products used in the home, although residues of this compound in commercial packages, especially food containers (McNeal and Breder 1987), are not well described. Although it is clear that the majority of 1,3-butadiene is released to the atmosphere (TRI 1989), data on the release of 1,3-butadiene are not well correlated with specific sources. The disposal of 1,3-butadiene appears to be a straightforward process (HSDB 1989); however, the amount of 1,3-butadiene released or destroyed annually is not well documented. As the TRI program is improved, this type of information will become more readily available.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

5. POTENTIAL FOR HUMAN EXPOSURE

Environmental Fate. The fate of 1,3-butadiene in the atmosphere is well understood (Atkinson 1985; Atkinson and Carter 1984; Atkinson et al. 1984; Kopczynski et al. 1972). The fate of 1,3-butadiene in soil and water is not well understood, and partitioning from these media has to be determined from the physical and chemical properties of this compound (Lyman et al. 1982). A reliable method capable of detecting 1,3-butadiene in soil and water was not located in the available literature, and it is not clear whether 1,3-butadiene is absent from these media or simply not yet detected. The persistence of 1,3-butadiene in soil and water is not known, and the degree of partitioning from one environmental compartment to another can only be estimated. Exposure via ingestion or dermal contact to populations surrounding hazardous waste sites cannot, therefore, be accurately determined. Experimental data that addresses the partitioning of 1,3-butadiene in the environment, its potential to enter drinking water supplies, and its lifetime in soil and water are necessary to completely characterize the environmental fate of this compound.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 1,3-butadiene from air. No data on the bioavailability of 1,3-butadiene from other sources (water or soil, for example) were located in the available literature. In conjunction with the data needs for determining 1,3-butadiene in environmental media, bioavailability studies from environmental media would be useful.

Food Chain Bioaccumulation. In theory, 1,3-butadiene is not believed to bioconcentrate significantly in fish and aquatic organisms; thus, it is not expected to biomagnify in the food chain (Hansch and Leo 1985; Lyman et al. 1982). No data addressing this point, however, were located in the available literature. Validation of these theories by valid experimental studies will aid in establishing a quantitative determination of 1,3-butadiene exposure to the general public.

Exposure Levels in Environmental Media. Data on the levels of 1,3-butadiene in environmental media are limited. Extensive data on the occurrence of 1,3-butadiene in ambient air samples are available (Shah and Heyerdahl 1988), but recent data appear to be lacking. Further, current correlations between the levels of 1,3-butadiene in the atmosphere and its sources of release are not available. Levels of 1,3-butadiene at hazardous waste sites are not available. Data on the occurrence of 1,3-butadiene in water samples are limited (Ewing et al. 1979). The presence of 1,3-butadiene in drinking water has been noted in the literature, but no concentrations or frequency of detection are available (EPA 1978; Kraybill 1980). The concentration of 1,3-butadiene in soil, water, and air at hazardous waste sites is not known (CLPSD 1989); therefore, the potential for exposure to populations residing nearby cannot be established. The development of reliable analytical techniques for the analysis of 1,3-butadiene in soil and

water will establish unambiguously the levels at which this compound is found in environmental media.

Exposure Levels in Humans. Limited data on levels of occupational exposure to 1,3-butadiene were available in the literature; however, occupational exposure to this compound appears to be limited to a readily definable group of industrial classifications (NIOSH 1984, 1989). Exposure levels for the general population are not well defined. No data on its presence in human tissue were located. Studies that correlate personal exposure with daily activities are necessary to establish adequately exposure levels for 1,3-butadiene. Biological monitoring studies cannot be performed until acceptable experimental techniques are developed. Exposure levels for those living near hazardous waste sites are not available and should be established.

Exposure Registries. No exposure registries for 1,3-butadiene were located. This compound is not currently one for which a subregistry has been established in the National Exposure Registry, but it will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to the compound.

5.7.2 On-going Studies

On-going atmospheric monitoring studies for 1,3-butadiene performed by S. Sigsby have been identified (EPA 1989b), although no other specific information was provided.

Remedial investigations and feasibility studies conducted at the NPL sites known to be contaminated with 1,3-butadiene could add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries, and may increase knowledge regarding the fate of 1,3-butadiene in the environment. No other long-term research studies pertaining to the environmental fate of 1,3-butadiene or to occupational or general population exposures to 1,3-butadiene were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,3-butadiene in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 1,3-butadiene. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 1,3-butadiene in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

No standardized method to test for the presence of 1,3-butadiene in biological materials presently exists. Only a limited number of techniques have been employed to determine this compound in biological materials.

An early method for the determination of 1,3-butadiene in blood was developed in 1944 (Miller 1978). It involves heating a blood sample containing iodine pentoxide to 200 °C, followed by determining the amount of 1,3-butadiene present by titrating any free iodine (produced during the reduction of iodine pentoxide) with sodium thiosulfate. This method is not specific to 1,3-butadiene; thus, its usefulness in obtaining an accurate indication of human exposure to 1,3-butadiene is unlikely.

Techniques for the determination of ^{14}C-labeled 1,3-butadiene in rat or mice blood and tissue after experimental exposure to enriched material have appeared in the literature (Bond et al. 1986, 1987). 1,3-Butadiene is removed from the sample matrix by vacuum distillation or by sparging with an inert gas. The desired material is recovered by collection in a cryogenic trap. The amount of 1,3-butadiene can then be ascertained by measuring the activity in the traps by scintillation counters. This technique cannot be applied to measure 1,3-butadiene exposure for the general population. However, the sample preparation step may be amenable to standardized gas chromatography (GC) techniques presently used in the determination of other organic compounds.

A technique for the determination of 1,3-butadiene in margarine samples was reported by Starting and Gilbert (1984). The margarine sample is placed in a vial, sealed, and heated to 70°C where it is allowed to equilibrate for 1 hour. The amount of 1,3-butadiene in the sample is determined by withdrawing a headspace sample, and injecting it directly into a GC equipped with a mass spectrometer (MS) detection system. Quantitation is obtained by

comparison of the peak height to that of a standard of known concentration. The sensitivity of this method allows quantitation down to 0.001 mg/kg (1 ppb). A similar headspace technique was used to test for the presence of butadiene in olive oil, vegetable oil, and yogurt samples (McNeal and Breder 1987).

6.2 ENVIRONMENTAL SAMPLES

Standardized methods for determining 1,3-butadiene in environmental samples are limited to air samples, as no methodology has been described for analyzing this compound in water or soil samples (EPA 1982, 1986, 1988a). A representative list of the methods available for the determination of 1,3-butadiene in air samples can be found in Table 6-l. The determination of 1,3-butadiene in personal air can be obtained using the procedure outlined in NIOSH Method 1024 (NIOSH 1987), which is described below.

The air sample is obtained by passing a known volume of air (3-25 L) through a set of tandem coconut charcoal tubes, which adsorb 1,3-butadiene and remove it from the air stream. The collected 1,3-butadiene is then removed from the adsorption tube by extraction with methylene chloride. Injection of the methylene chloride solution into a GC equipped with a flame ionization detector (FID) separates 1,3-butadiene from any interfering compounds that may be present. The choice of chromatography column for this determination is not crucial, as long as it cleanly separates 1,3-butadiene from other compounds.

The estimated quantitation limit of this method is 0.02 ppm, with an applicable range of l-480 μg per sample (approximately 0.02-8.7 ppm) for a 25 L sample. The precision of this method appears to change as a function of the concentration being measured, due to desorption efficiencies changing as a function of sample concentration. With increasing concentration, the preparation of a standard becomes *more* difficult.

In NIOSH Method 1024, quantitation of 1,3-butadiene is accomplished by comparing the area under the sample's response signal to that of a known amount of 1,3-butadiene. The preparation and injection of a gaseous. 1,3-butadiene standard is a difficult procedure; it must be performed carefully or erroneous results will occur. Sample storage appears to dramatically affect the results of the measurement. Samples stored at -4°C displayed an average recovery of between 93% and 98% over a 21-day period, while samples stored at room temperature ranged from 61% to 95%. Literature methods for the determination of 1,3-butadiene in personal air samples overcome some of these problems (Hendricks and Schultz 1986; Lunsford 1987; Lunsford and Gagnon 1987).

1,3-Butadiene, along with other volatile hydrocarbons, has been found in ambient air samples by a technique that uses cryogenic concentration before GC analysis. This technique is performed by collecting a large volume of air in

TABLE 6-1. Analytical Methods for Determining 1,3-Butadiene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Personal air	Pass air through charcoal tube CH_2Cl_2 desorption	GC/FID	0.02 ppm	No data	NIOSH 1987
Air	Collect air in Tedlar bag, concentrate on Tenax cartridge, thermal desorption	GC/FID	No data	No data	Stump and Dropkin 1985
Air	Pass air through charcoal tube, solvent desorption	GC/MS	No data	No data	Texas Air Control Board 1990
Air (real time)	Draw air into 12 foot sampling loop, direct injection	GC/MS	No data	No data	Texas Air Control Board 1990

FID = flame ionization detector
GC = gas chromatography
MS = mass spectrometry

a specially designed bag or other sampling container and concentrating the volatile components by condensation at low temperatures. The sample is separated into its components by GC and quantified with an internal standard. Numerous variations of this method were found in the literature (Lonneman et al. 1979; Neligan 1962; Stephens and Burleson 1967, 1969; Stump and Dropkin 1985).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,3-butadiene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,3-butadiene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No standardized method for the determination of biomarkers of exposure and effect for 1,3-butadiene was located. A recent paper has demonstrated that 1,3-butadiene forms a hemoglobin adduct in mice and rats (Sun et al. 1989b). However, the 1,3-butadiene used in this study was tagged with a radioactive tracer, a technique which is only rarely utilized in the determination of environmental exposure in humans. In conjunction with the data needs discussed in Chapter 2, a method to monitor the formation of a 1,3-butadiene adduct with human hemoglobin needs to be established. The development of an analytical technique to measure this biomarker of exposure can then be achieved. Once a unique biomarker has been identified and an experimental technique to detect it has been established, a quantitative assessment of routes and levels of human exposure to 1,3-butadiene can be undertaken.

No known biomarkers of effect specifically for 1,3-butadiene have been reported, but recent advances have been made (Gallagher 1989; Weston et al. 1989) in ^{32}P-post labelling and other DNA adduct assays.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Data on the determination of 1,3-butadiene in environmental media were limited. 1,3-Butadiene in air samples has been detected by techniques routinely used for detecting volatile hydrocarbons (Stump and Dropkin 1985; Texas Air Control Board 1990). Procedures accepted for the determination of volatile hydrocarbons in other environmental media (soil, water, sediment, plants, etc.) may also be suitable for 1,3-butadiene. This question can be answered only by the data obtained from properly designed experiments. The information will assist in determining the prevalence of this compound in the environment and aid in a quantitative determination of human exposure to 1,3-butadiene.

6.3.2 On-going Studies

On-going studies performed by J. Pau at EPA's Atmospheric Research and Exposure Assessment Laboratory in Research Triangle Park, NC, on new analytical methods for the determination of 1,3-butadiene have been identified (EPA 1989b), although no other specific information was provided.

7. REGULATIONS AND ADVISORIES

The International Agency for Research on Cancer (IARC) and national and state regulations and guidelines pertinent to human exposure to 1,3-butadiene are summarized in Table 7-l.

1,3-Butadiene has been deleted from the list of extremely hazardous substances (EPA 1988b).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 1,3-Butadiene

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1985,1987
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Intent to list under Section 112 of Clean Air Act	Yes	EPA 1985b (40 CFR 61.01)
OSHA	PEL	1000 ppm (transitional limit; in process of 6(b) rulemaking)	OSHA 1989 (29 CFR 1910.2926)
	PEL	2 ppm (proposed)	OSHA 1990 (29 CFR 1910.32736)
	STEL	10 ppm (proposed	
b. Nonspecific media:			
EPA OERR	Reportable quantity (statutory)	1 lb	EPA 1987 (40 CFR 300 and 355)
	Threshold planning quantity	10,000 lb	
Guidelines:			
a. Air:			
ACGIH	TLV	10 ppm (suspected human carcinogen)	ACGIH 1989
NIOSH	REL	Carcinogen; lowest feasible concentration	NIOSH 1988
b: Other:			
EPA	Carcinogenic classification	Group B2[b]	EPA 1985a
	Inhalation slope factor	1.8 $(mg/kg/day)^{-1}$	IRIS 1991
	Inhalation unit risk[c]	6.2×10^{-4} $(ppb)^{-1}$	
		2.8×10^{-4} $(\mu g/m^3)^{-1}$	
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
Connecticut		22,000 $\mu g/m^3$ (8-hr avg)	NATICH 1988
Kentucky		11 mg/m^3 (8-hr avg)	State of Kentucky 1986
Massachusetts		0.0350 $\mu g/m^3$ (24-hr avg)	NATICH 1988
Michigan		0.0030 $\mu g/m^3$ (annual)	NATICH 1988
North Carolina		0.0350 $\mu g/m^3$ (annual)	NATICH 1988
Nevada		52.40 mg/m^3 (8-hr avg)	NATICH 1988
Virginia		220.0000 $\mu g/m^3$ (24-hr avg)	NATICH 1988

[a]Group 2B: Possible human carcinogen
[b]Group B2: Probable human carcinogen
[c]The unit risk should not be used if the air concentration exceeds 7.2 ppb, since above this concentration, the slope factor may differ from that stated (IRIS 1991).

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; OAQPS = Office of Air Quality Planning and Standards; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; STEL = Short-Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A workplace concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentrationo$_{(Lo)}$(LC_{Lo}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$(LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(Lo)}$(LD_{50}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$(LD_{Lo}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$(LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIDX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELS), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Freauency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote “c”).

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 16 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10). Reference The complete reference citation is given in Chapter 8 of the profile.

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. GELS are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-l

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15.) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16.) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17.) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5	6	7	8	9		10
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)		Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)		NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)		NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

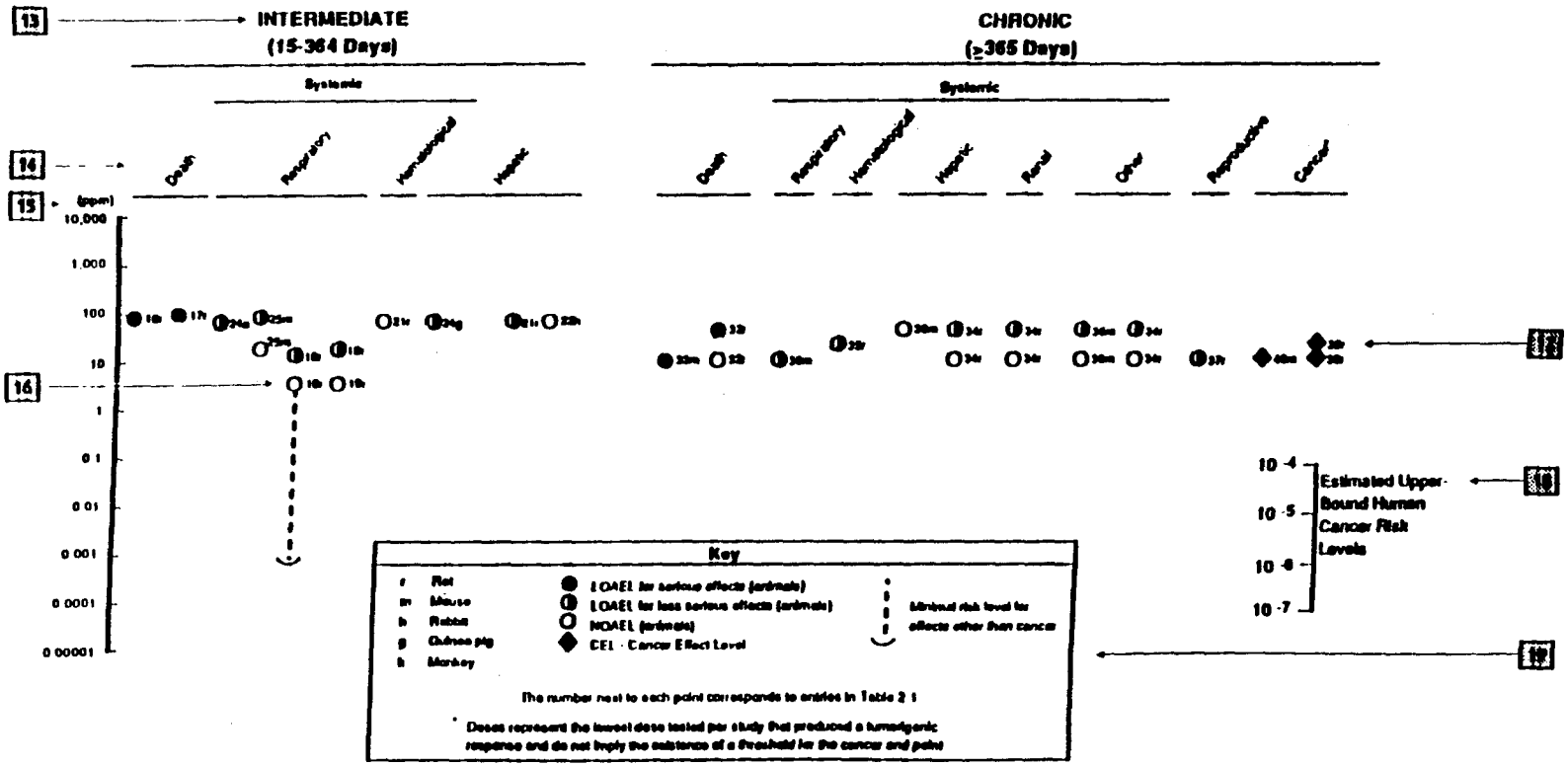

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanheaith effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is *not* available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
K_{oc}	octanol-soil partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill

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LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppbC	parts per billion carbon
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average

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U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
µm	micron
µg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 1,3-butadiene. The panel consisted of the following members: Dr. Arthur Gregory, Private Consultant, Techto Enterprises, Sterling, Virginia; Dr. V.M. Ramanujam, Associate Professor, Department of Preventive Medicine, University of Texas, Galveston, Texas; and Dr. Rogene Henderson, Biochemist, Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico. These experts collectively have knowledge of 1,3-butadiene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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