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.

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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

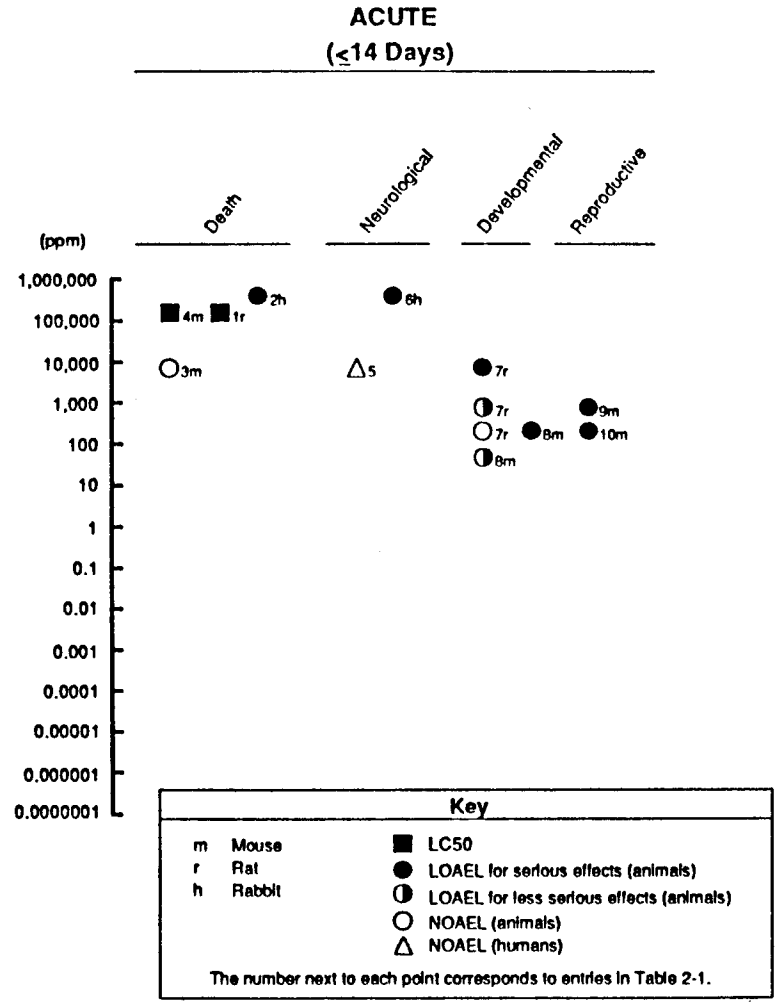


FIGURE 2-1 (Continued)

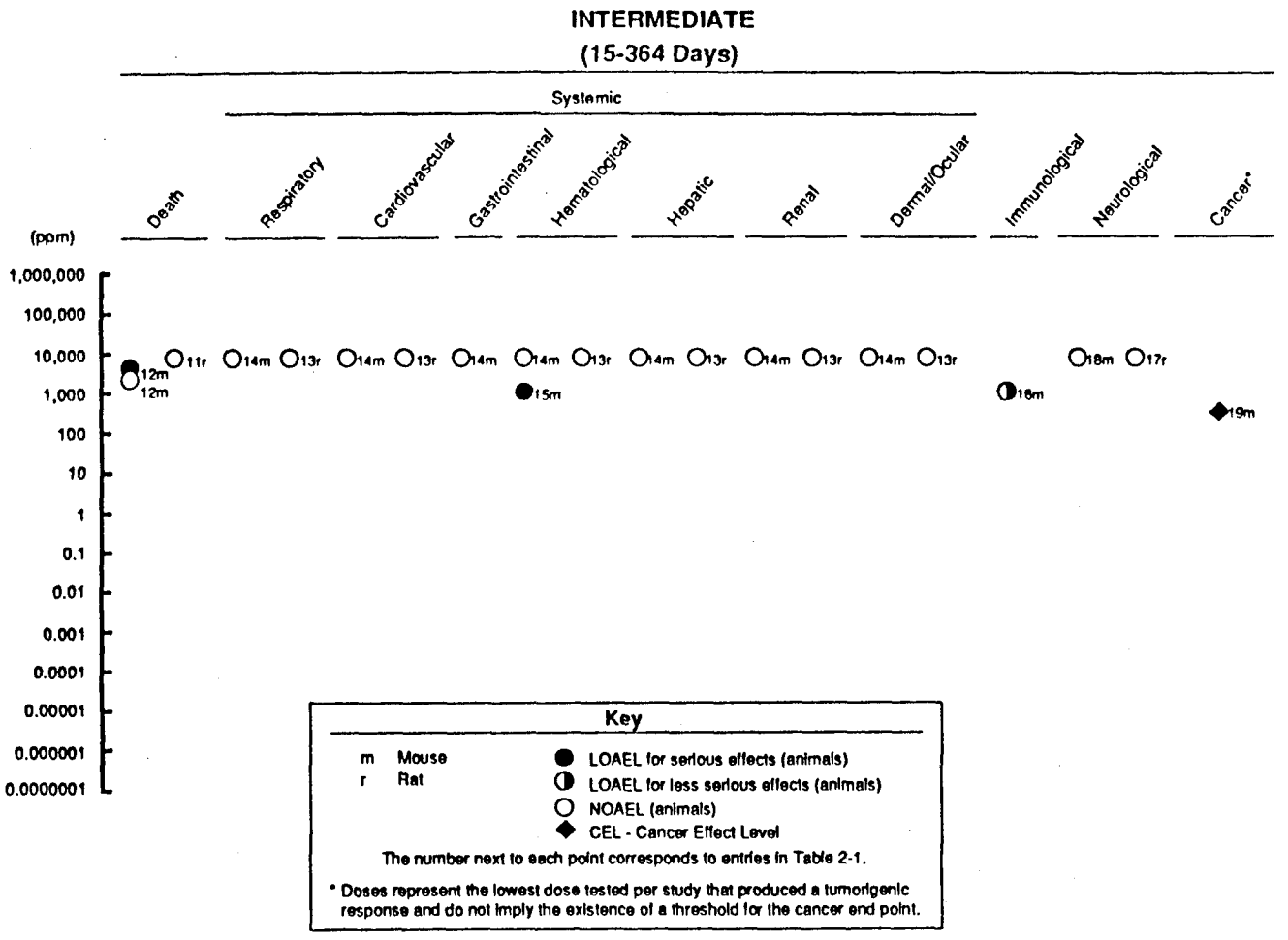
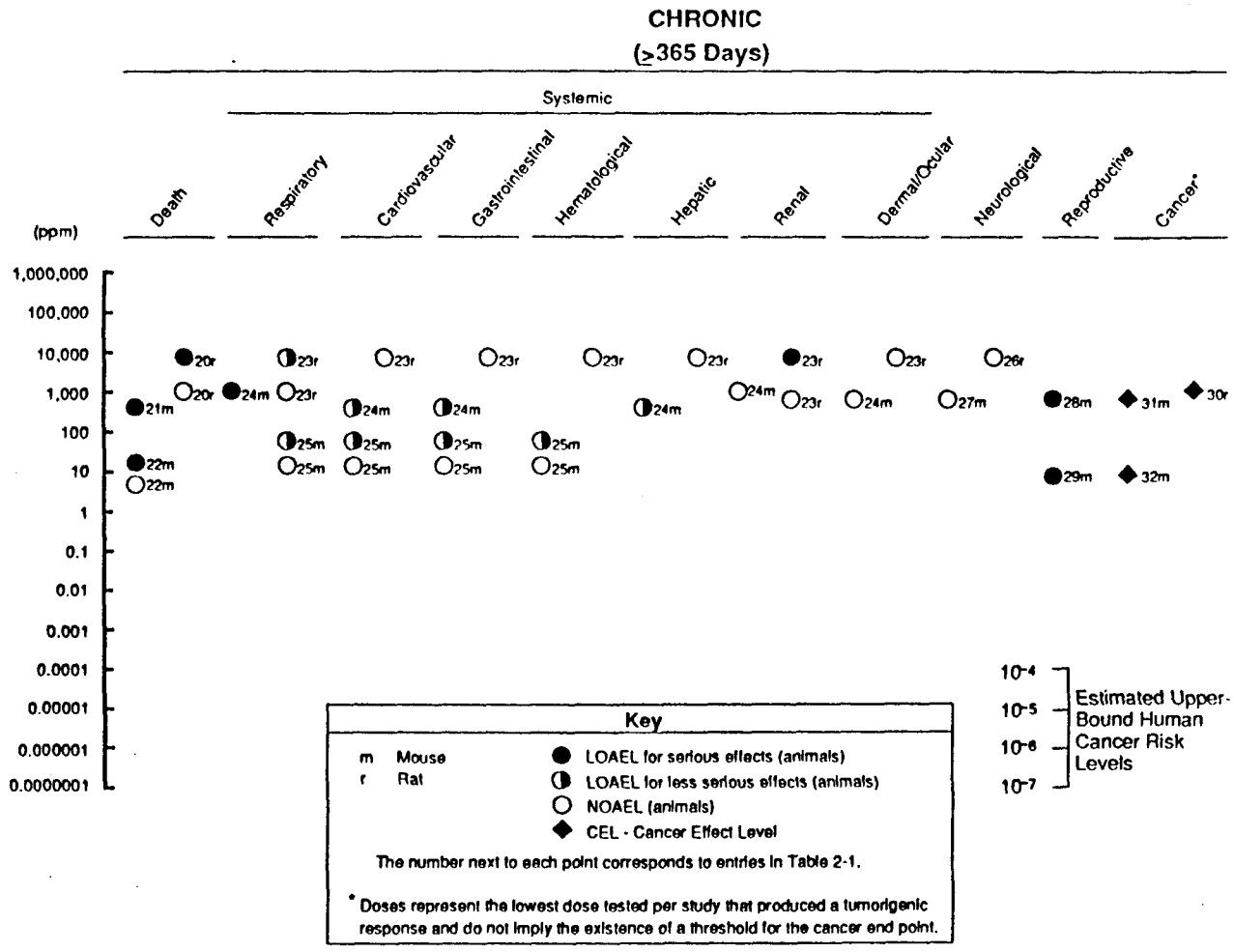


FIGURE 2-1 (Continued)



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

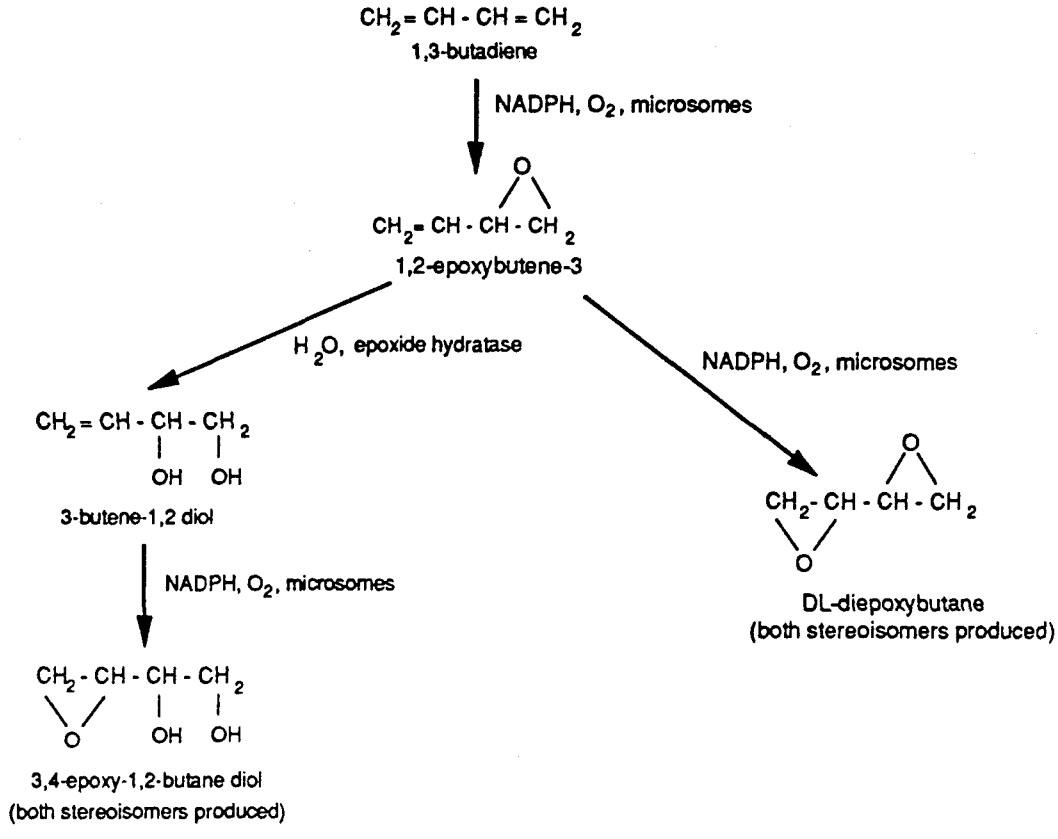
No studies were located regarding distribution in humans or animals after dermal exposure to 1,3-butadiene.

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.

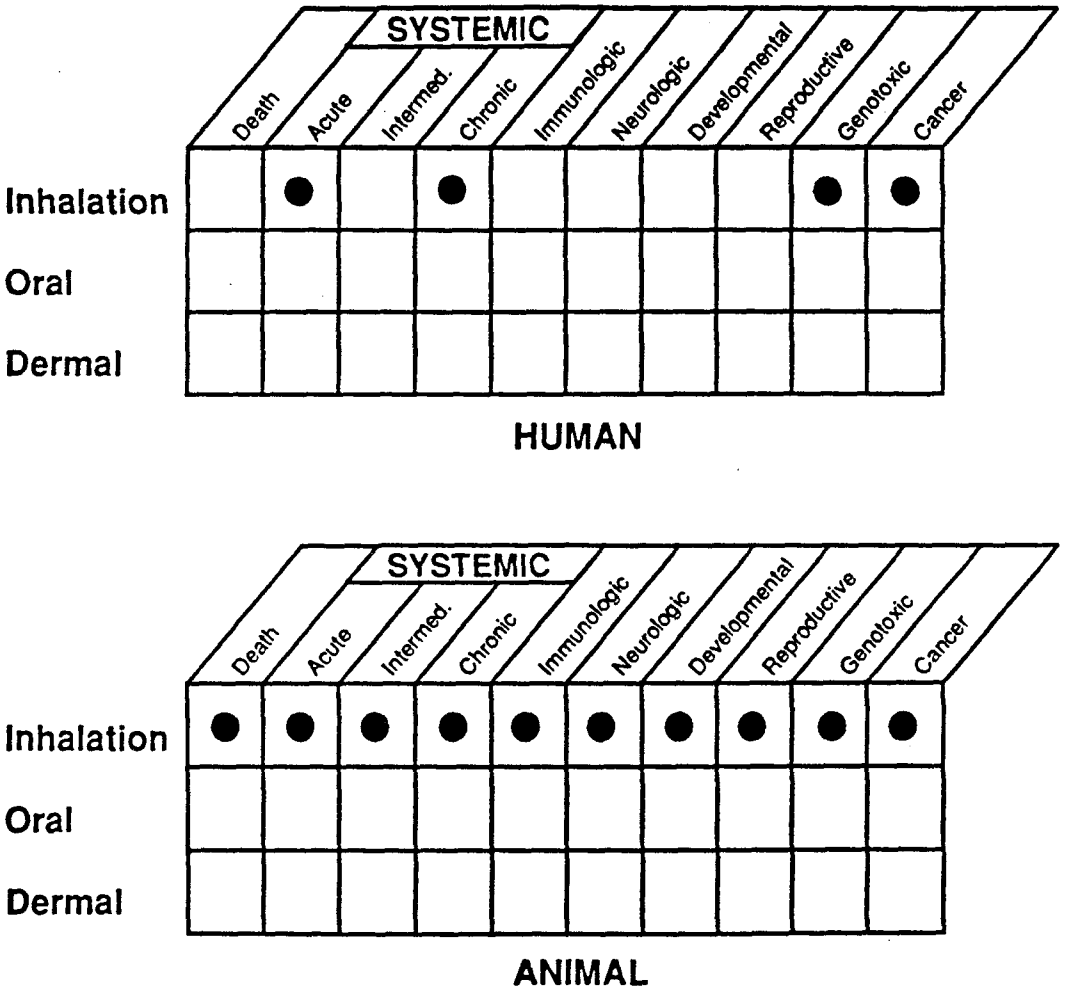
2.9.1 Existing Information on Health Effects of 1,3-Butadiene

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.