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Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects

1,3-Butadiene

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1,3-Butadiene

INTRODUCTION

1,3-Butadiene (CAS Registry Number 106-99-00, C_4H_6, molecular weight = 54.1) (Figure 11) is a colorless gas used as a monomer in the production of plastics, synthetic rubber, and other polymers. It was used in large volumes during World War II to make synthetic rubber when supplies of natural rubber were cut off. At the time, butadiene was assumed to have low toxicity.

At one atmosphere pressure and 25°C, 1 ppm butadiene is equivalent to 2.21 mg/m^3.

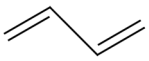

Figure 11. Structure of 1,3-butadiene.

BENCHMARK LITERATURE

The following evaluation of research literature on 1,3-butadiene is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from the International Agency for Research on Cancer (IARC 2004a), the EPA (2002b,c), the Agency for Toxic Substances and Disease Registry (ATSDR 1993), and Himmelstein and colleagues (1997). Most of the exposure information was summarized from recent studies and databases listed in the exposure tables in Appendices B and D. Most of the health-effects data were obtained from studies listed in the health tables in Appendix C, the California EPA (1992), the EPA (2002b,c), Albertini and colleagues (2003b), Delzell and colleagues (2001), and Sathiakumar and colleagues (2005).

EXPOSURE

SOURCES AND EMISSIONS

1,3-Butadiene is a component of motor-vehicle emissions, formed by the incomplete combustion of olefins in gasoline and diesel fuel. It is not a component of evaporative emissions. Except in areas near petrochemical plants, motor-vehicle emissions are the dominant source of 1,3-butadiene in ambient air. Other sources of non-occupational exposure include emissions from synthetic-rubber and plastics factories, cigarette smoke, and forest fires. 1,3-Butadiene reacts in the atmosphere, where it is oxidized by hydroxyl radicals, nitrate radicals, and ozone to produce acrolein and formaldehyde (Skov et al. 1992; Atkinson 1994). Because of its short half-life in air (1 to 9 hours), 1,3-butadiene at low concentrations is measurable only close to its emission sources (Atkinson and Carter 1984; Atkinson et al. 1989).

According to the 1999 National Air Toxics Assessment (NATA), on-road motor vehicles account for 51% of emissions in urban counties and 25% in rural counties in the U.S. Non-road motor vehicles account for 20% of emissions in urban counties and 12% in rural counties (EPA 2006b).

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 5 and Figure 12 show the range of mean and maximum concentrations of 1,3-butadiene in µg/m^3 measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring.

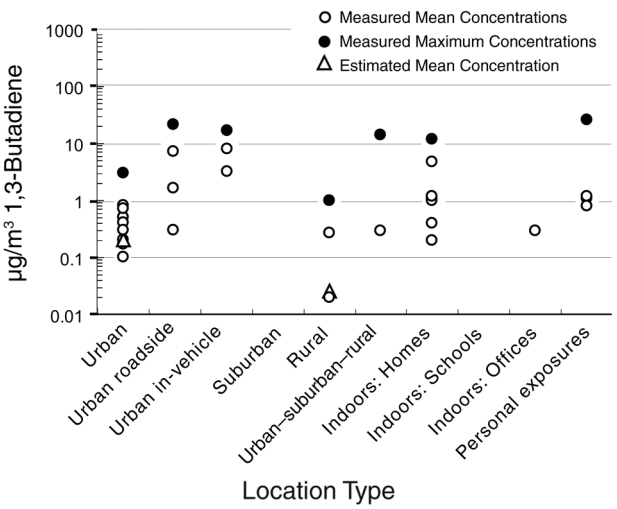

Figure 12. Concentrations of 1,3-butadiene (µg/m^3) at various locations. Data for figure are from Table 5.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

Table 5. 1,3-Butadiene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments[b]
Outdoor Areas						
Urban						
	> 1000	24 hr	0.16	0.78	Dann (Unpublished)	Canister measurement
	35	48 hr	0.14	—	Kinney et al. 2002	Summer
	36	48 hr	0.13	—	Kinney et al. 2002	Winter
	~ 600	24 hr	0.80	—	South Coast Air Quality Management District 2000	Canister measurement; MATES II Study
	4–17	24 hr	0.46	0.60	Zielinska et al. 1998	Canister measurement
	4–17	24 hr	0.44	0.84	Zielinska et al. 1998	Canister measurement
	4–17	24 hr	0.18	0.22	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.71	2.8	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.29	1.1	Zielinska et al. 1998	Canister measurement
	~ 480	24 hr	0.29	1.4	Dann (Unpublished)	Canister measurement; high-traffic sites
	60–83	24 hr	0.11–2.2	0.55–4.0	California Air Resources Board 2003	6 cities monitored
Urban in-vehicle						
	35	6 hr	7.9	—	Kim et al. 2001	
	50	~ 9 hr	3.3	17.2	Chan et al. 1991a,b	
	16	2 hr	0.24–2.7	5.7	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	13	2 hr	0.20–2.8	4.4	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	31	1–15 hr	2.0	2.9	Fitz et al. 2003	
Urban roadside						
	12	2 hr	—	4.9	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	9	2 hr	—	1.1	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	21	3 hr	7.2	20.5	Sapkota et al. 2005	Summer
	4–17	24 hr	1.6	4.8	Zielinska et al. 1998	Canister measurement
Suburban						
	~ 60	24 hr	0.20	1.1	Zielinska et al. 1998	Small community

Table continues on next page

[a] Data extracted from published studies.

[b] Given the gas-phase reactivity of 1,3-butadiene with NO_2, some investigators have suggested that sampling with canisters may result in post-sample degradation if canisters are stored for more than 1 week (Atkinson et al. 1984). Accordingly, studies using canister sampling for 1,3-butadiene may report measured concentrations that are lower than actual. Studies using canister measurements are noted.

Table 5 (*Continued*). 1,3-Butadiene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (µg/m^3) Mean	Concentration (µg/m^3) Maximum	Citations	Comments[b]
Outdoor Areas (*Continued*)						
Rural						
	> 1000	4 hr	0.01	0.63	Dann (Unpublished)	Canister measurement
	~ 60	24 hr	0.26	0.99	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.02	0.60	Zielinska et al. 1998	Canister measurement
Urban–suburban–rural combined						
	1550	24 hr	0.29	1.4	EPA 2004d	Includes canister measurements
Indoor Spaces						
Residences						
	12	12 hr	1.1	—	Kim et al. 2001	
	35	48 hr	1.0	12	Kinney et al. 2002	Summer
	36	48 hr	1.2	5.8	Kinney et al. 2002	Winter
	32	48 hr	0.2	1.5	Sax et al. 2004	Fall
	62	24 hr	4.7	10	California Air Resources Board 1992; Sheldon et al. 1992	
	39	24 hr	0.42	2.5	Van Winkle and Scheff 2001	10 homes
Offices						
	12	12 hr	0.3	—	Kim et al. 2001	
Personal Exposures						
	473	2 hr	1.1	26.3	Kim et al. 2001	Day
	99	2 hr	0.8	7.9	Kim et al. 2001	Night
	35	48 hr	1.2	—	Kinney et al. 2002	Summer
	36	48 hr	0.87	—	Kinney et al. 2002	Winter

[a] Data extracted from published studies.

[b] Given the gas-phase reactivity of 1,3-butadiene with NO_2, some investigators have suggested that sampling with canisters might result in post-sample degradation if canisters are stored for more than 1 week (Atkinson et al. 1984). Accordingly, studies using canister sampling for 1,3-butadiene might report measured concentrations that are lower than actual. Studies using canister measurements are noted.

Ambient Air

In North America, annual mean concentrations of 1,3-butadiene range from 0.015 to 1.0 µg/m^3 (EPA 2004a; Environment Canada 2004) as shown in Figures 12–14. The overall U.S. mean concentration is 0.27 µg/m^3 (EPA 2006b). The Canadian National Air Pollution Surveillance system reported mean concentrations of 0.015 µg/m^3 for 14 rural sites and 0.16 µg/m^3 for 39 urban sites between 2002 and 2004 (Dann T, unpublished). In the U.S., the mean concentrations measured at two high-traffic sites ranged from 1.6 to 7.2 µg/m^3; the highest reported mean concentration was 20.5 µg/m^3 (Sapkota et al. 2005; Zielinska et al. 1998). Distributions and trend data for urban sites in the Canadian monitoring network are presented in Figures 13 and 14. The trend data indicate some decreases in ambient concentrations in the 1990s, with relatively small changes evident in more recent years. In the U.S., the NATA reported higher modeled mean concentrations in urban counties (0.17 µg/m^3) than in rural counties (0.03 µg/m^3) (EPA 2006b). This difference was also reported by Zielinska and colleagues (1998). The data from their monitoring program in Arizona showed that 1,3-butadiene concentrations ranged from 0.29 to 0.71 µg/m^3 in urban sites and was 0.02 to 0.26 µg/m^3 in rural sites. The mean background site (rural as opposed to urban) concentration was 0.02 µg/m^3. Concentrations of 1,3-butadiene at urban sites correlated with those of toluene, xylene, and benzene (Zielinska et al. 1998).

The California Children's Environmental Health Protection Program monitored six urban locations in California for approximately 1 year and reported site averages of

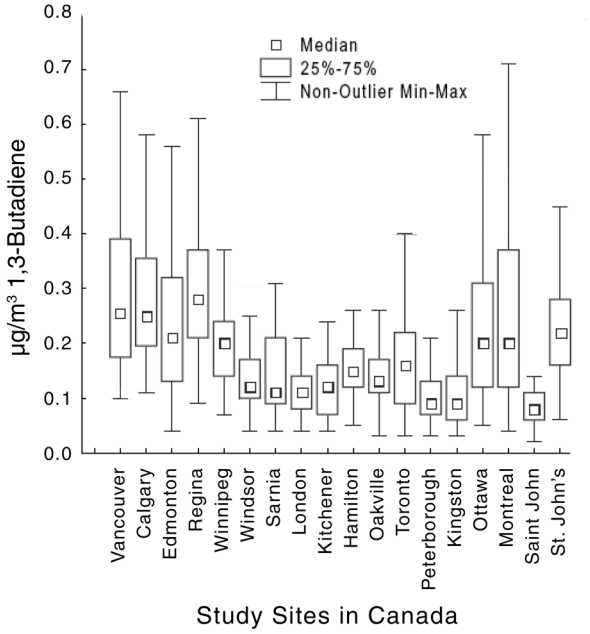

Figure 13. Annual mean concentrations of 1,3-butadiene in Canadian cities in 2001. (Reprinted from Environment Canada 2004, with permission.)

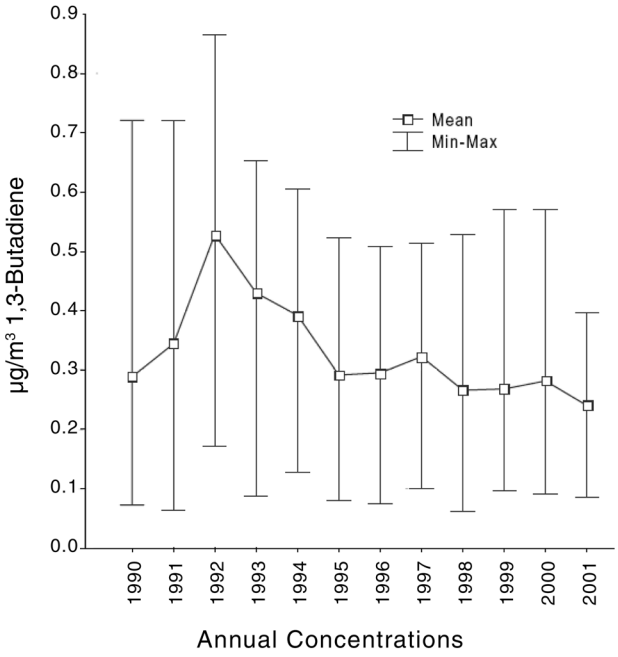

Figure 14. Concentrations of 1,3-butadiene measured in urban sites in Canada from 1990 to 2001 as part of the National Air Pollution Surveillance program. (Reprinted from Environment Canada 2004, with permission.)

0.1 to 2.2 µg/m^3 1,3-butadiene (the highest site average was measured in San Diego), with an overall mean of 0.76 µg/m^3 (California Air Resources Board 2003). The Multiple Air Toxics Exposure Study (MATES-II study) reported an overall mean concentration of 0.8 µg/m^3 at 10 monitoring sites over a 1-year period (South Coast Air Quality Management District 2000). Zielinska's monitoring program in Arizona reported a mean concentration (24-hour samples) of 1.6 µg/m^3 at a high-traffic urban roadside monitoring site (Zielinska et al. 1998). Sapkota and colleagues (2005) reported a mean concentration (3-hour samples) of 7.2 µg/m^3 near tollbooths in Baltimore, Md. At the tollbooths, the changes in 1,3-butadiene concentrations over time corresponded to the changes in traffic counts. Regression analyses suggested that vehicles with more than two axles were much larger contributors to concentrations than vehicles with two axles (based on significance of vehicle-class traffic counts in regression-model classes correlated at $r = 0.5$).

Zielinska and colleagues (1998) reported higher mean concentrations in winter than in summer and attributed the difference to lower levels of photochemical reactivity in winter. This contrasted with most of the other MSATs measured in the study. Kinney and associates (2002) measured 1,3-butadiene as part of a study of personal exposures of New York City high school students and found similar mean concentrations in summer (0.14 µg/m^3) and winter (0.13 µg/m^3). But when it came to mean personal exposures, they reported somewhat lower exposures in winter (0.87 µg/m^3) than in summer (1.2 µg/m^3).

Outside of North America, studies of ambient concentrations of 1,3-butadiene have been limited, but reported measures have been in the same range as those found in North American urban areas (Figure 12). A study in the U.K. (Kim et al. 2001) described in more detail below, also reported monitoring-site concentrations similar to those reported in the U.S. studies.

In-Vehicle Exposures

A study conducted in Raleigh, N.C., found that 1,3-butadiene concentrations measured in vehicles during commutes were about three times higher than those measured outdoors. A mean concentration of 3.3 µg/m^3 and a maximum of 17.2 µg/m^3 were measured (Chan et al. 1991a,b). Kim and colleagues (2001) also reported high mean concentrations in vehicles in the U.K. (7.9 µg/m^3 for 35 6-hour samples). Rodes and colleagues (1998) reported high mean concentrations (0.24 to 2.7 µg/m^3 for 16 2-hour samples with a maximum value of 5.7 µg/m^3) in single-occupant vehicles in Sacramento and Los Angeles. These concentrations were higher than urban roadside concentrations measured in both locations. In contrast, Fitz and colleagues

(2003) measured 1,3-butadiene concentrations in school buses on standard routes in Southern California and reported that 1,3-butadiene was detectable only on 8 of 31 windows-closed morning runs and on both of the 2 windows-open afternoon runs. Overall, 70% of their samples were below the 1.1 μg/m^3 limit of detection. In the remaining 30%, a mean 1,3-butadiene concentration of 2.0 μg/m^3 (maximum 2.9 μg/m^3) was measured.

Indoor Exposures

Only limited measurements of 1,3-butadiene have been made in indoor microenvironments. Additionally, in several such studies, the 1,3-butadiene in the majority of samples taken proved to be below the limits of detection (0.38 to 1.2 μg/m^3), which limited the conclusions that could be drawn from the studies (Chan et al. 1991a; California Air Resources Board 1992; Gordon et al. 1999; Sax et al. 2004). In New York City, Kinney and colleagues (2002) measured elevated concentrations of 1,3-butadiene in the homes of nonsmoking high school students. Personal exposures were similar to indoor concentrations and higher than ambient concentrations.

In the U.K., Kim and colleagues (2001) also reported elevated indoor concentrations, with a mean concentration (12-hour samples) of 1.1 μg/m^3 in 12 homes (6 with smokers) and an overall indoor/outdoor ratio of 6.6. Indoor concentrations in the homes with smokers were 3.4 times those in nonsmoking homes, and smoking was estimated to account for 60 to 70% of the 1,3-butadiene measured in these homes. In the nonsmoking homes, the changes in indoor concentrations over time generally followed the changes measured outdoors. A mean concentration (12-hour samples) of 0.3 μg/m^3 was measured in 12 office buildings. Concentrations in stores, cinemas, and libraries were between those in offices and homes; measurements in pubs (2-hour samples) were substantially higher (mean = 3 μg/m^3; N = 6) (Kim et al. 2001).

Similar instances of indoor concentrations exceeding those measured outdoors were reported by Mukerjee and colleagues (1997) for nine homes (six rural and three urban) in the Rio Grande Valley of Texas (median concentrations were 0.8 μg/m^3 indoors and 0.20 μg/m^3 outdoors) and by Van Winkle and Scheff (2001) for 10 nonsmoking homes in Chicago (median concentrations were 0.26 μg/m^3 indoors and 0.04 μg/m^3 outdoors). No specific activities or circumstances were found to be associated with these indoor 1,3-butadiene concentrations. It is possible that the concentrations result from reduced photochemical degradation of 1,3-butadiene indoors compared with outdoors, but this hypothesis has not been specifically addressed.

Personal Exposures

Kim and colleagues measured mean personal exposures to 1,3-butadiene in 12 nonsmoking adults in Birmingham, U.K., of approximately 1.1 μg/m^3 (Kim et al. 2001). Maximum daytime exposures were more than three times higher than night-time exposures. Exposure in the home was estimated to account for 50 to 90% of total 1,3-butadiene exposure. Kinney and colleagues (2002) observed average personal exposure measurements similar to those of Kim and colleagues (2001).

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

No studies were found of ambient 1,3-butadiene concentrations in Africa, and only one study was found for Asia, citing 1.8 μg/m^3 in Pakistan (Barletta et al. 2002). In Europe, 1,3-butadiene measurements have been taken in the U.K. and ranged from 0.06 to 0.88 μg/m^3 (Dollard et al. 2001; U.K. National Air Quality Archive 2006b). In Latin America, 1,3-butadiene concentrations of 2.7 μg/m^3 were measured in Brazil (Grosjean et al. 1998, 1999), and concentrations of 0.9 μg/m^3 were measured in Mexico (Serrano-Trespalacios et al. 2004). These are similar to ambient concentrations measured in the U.S. Ambient concentrations measured in Canada are shown in Figures 13 and 14 and are similar to those in the U.S.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The metabolism of 1,3-butadiene is shown in Figure 15 (as adapted from Himmelstein et al. 1997). Minor updates to the proposed pathways in Figure 15 can be found in Albertini and associates (2003a).

1,3-Butadiene can be oxidized by cytochrome P450 enzymes to three electrophilic epoxide forms: 1,2-epoxy-3-butene (a monoepoxide), 1,2:3,4-diepoxybutane (a diepoxide), and 3,4-epoxy-1,2-butanediol (an epoxy diol). The epoxides are detoxified by hydrolytic enzymes called epoxide hydrolases or by conjugation with glutathione. The initial metabolite in all species studied is 1,2-epoxy-3-butene, which can then be further metabolized by any or all of three pathways; it can be oxidized to 1,2:3,4-diepoxybutane, it can be conjugated with glutathione and then excreted in urine as M2 (a mercapturic acid); or it can be hydrolyzed to 3,4-epoxy-1,2-butanediol and, by a series of enzyme reactions, excreted in the urine as M1 (another mercapturic acid).

Concentrations of diepoxybutane in blood and of M1 and M2 in urine can be used to determine how much of the metabolism followed the oxidative pathway and how much

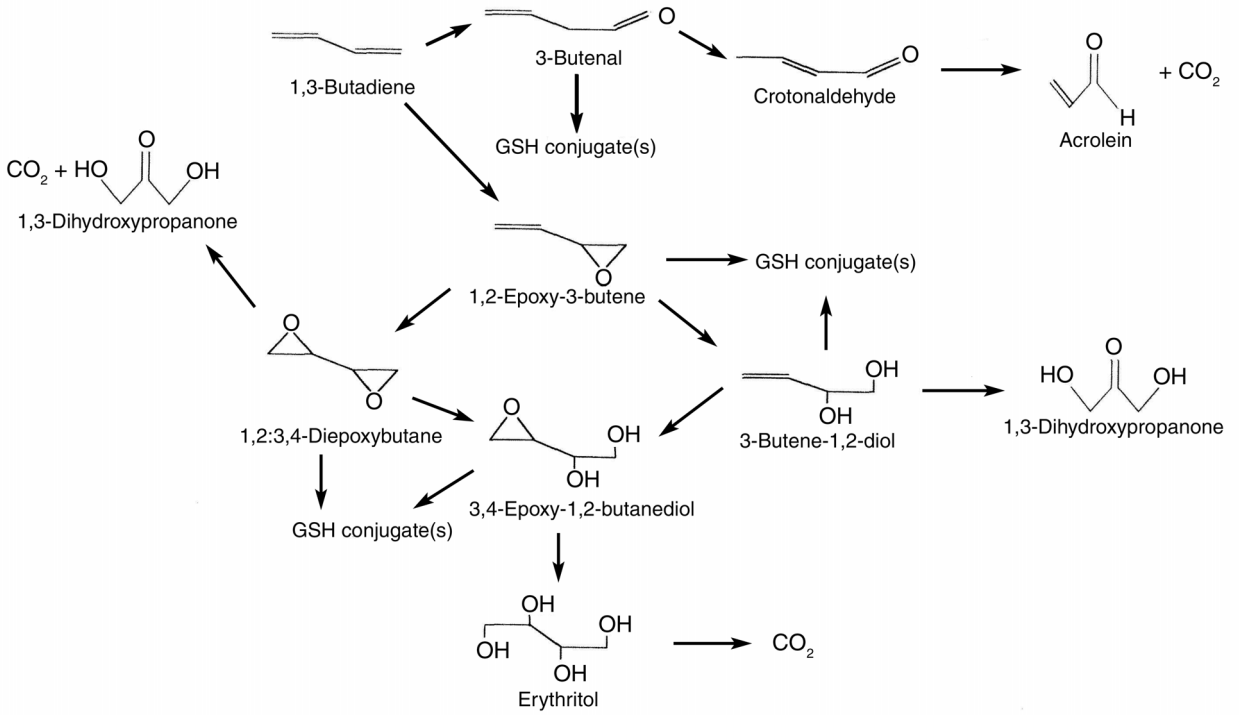

Figure 15. Proposed pathways of 1,3-butadiene metabolism. GSH = Glutathione. (Adapted from Himmelstein et al. 1997, with the permission of Informa Healthcare Journals and the author.)

followed the hydrolytic pathway. Mice have a much higher ratio of oxidizing enzymes to hydrolyzing enzymes than do rats or primates. The highly mutagenic 1,2:3,4-diepoxybutane can be readily detected in the blood of exposed mice but is difficult to detect in exposed rats. The ratio of M2 (the marker of the oxidative pathway) to M1 (a marker of a hydrolytic pathway) is higher in mice than in rats. The amount of 1,2:3,4-diepoxybutane formed in humans is not known, but the ratio of M2 to M1 in Czech rubber workers exposed to 1,3-butadiene was quite low, suggesting that humans metabolize 1,3-butadiene more by the hydrolytic (detoxifying) pathway than the oxidative pathway.

BIOMARKERS

The principal protein adduct formed in rodents and humans exposed to 1,3-butadiene is a trihydroxybutyl adduct, which appears to be formed from 3,4-epoxy-1,2-butane diol, but not from 1,2:3,4-diepoxybutane (Swenberg et al. 2000). In a study of Czech 1,3-butadiene workers, Albertini and colleagues (2003b) found this adduct to be the best biomarker of exposure. Various potential biomarkers of exposure were compared with careful measures of occupational exposure. The M1 urinary metabolite also proved to be useful as a biomarker of exposure (Albertini et al. 2003b). Later work by Swenberg's group (Boysen et al. 2004) developed a 1,2:3,4-diepoxybutane–specific adduct, which could be useful in determining the extent of the formation of 1,2:3,4-diepoxybutane (a potent mutagen) in various exposed species, including humans.

NONCANCER HEALTH EFFECTS

The noncancer effects of 1,3-butadiene exposure are well summarized in a review by Himmelstein and colleagues (1997). Some of the following information came from this review.

In Vivo

Single 6-hour exposures of rats and mice to high concentrations (1100 to 2200 mg/m^3) of 1,3-butadiene deplete the lung and liver of reduced glutathione. This depletion was more dramatic in mice (the highest depletion was 75% in lungs) than in rats (up to about 40% in liver) (Himmelstein et al. 1995). Many studies indicate that 1,3-butadiene exposure can induce metabolic enzymes, although the results depend on exposure conditions and the species of rodent used.

The toxicity of 1,3-butadiene in reproduction and development has been studied by the National Toxicology Program (NTP) (Morrissey et al. 1990). Rats and mice were exposed to up to 2200 mg/m^3 1,3-butadiene, 6 hours/day,

on days 6 to 15 of gestation. No developmental toxicity was observed in fetal rats, but the mice showed fetal anomalies after exposure to concentrations as low as 440 mg/m^3. Dominant-lethal and sperm-head-morphology studies suggested that 1,3-butadiene might also be a germ-cell mutagen in mice.

Gonadal atrophy is a major health effect observed in mice exposed to 1,3-butadiene. In the NTP studies, testicular atrophy was observed in male B6C3F1 mice exposed to 1380 mg/m^3 1,3-butadiene, and ovarian atrophy was observed in female mice exposed to concentrations as low as 13.8 mg/m^3 (Melnick et al. 1990). This effect was not observed in rats.

There are also large differences between rats and mice in the effect of 1,3-butadiene on the hematopoietic and immune systems. Sprague-Dawley rats exposed to up to 18,000 mg/m^3 1,3-butadiene for 6 hours/day, 5 days/week for 13 weeks showed no sign of hematologic toxicity nor any sign of general toxicity (Crouch et al. 1979). Similar exposures in B6C3F1 mice resulted in suppression of the immune system (spleen cell toxicity) and bone marrow toxicity (Thurmond et al. 1986). Later studies showed that 1,3-butadiene adversely affects hematopoiesis in mice (Irons et al. 1986; Leiderman et al. 1986; Colagiovanni et al. 1993).

In Vitro

In cell-culture studies, Irons and colleagues (1986) found that the 1,3-butadiene metabolite 1,2-epoxy-3-butene adversely affects cytokine-mediated cell differentiation in the bone marrow of mice but not of rats or humans. The authors concluded that mice have a unique hematopoietic progenitor-cell population that is sensitive to this metabolite and that does not exist in rats or humans.

Many in vitro studies have been conducted to determine the rate at which microsomal enzymes from mice, rats, and humans metabolize 1,3-butadiene (Himmelstein et al. 1997). The results of these studies are the same as those observed in vivo. Compared with rats and humans, mice have a much higher rate of oxidation of 1,3-butadiene and its metabolites than of hydrolysis of the metabolites. These metabolic differences lead to much higher concentrations of the potent mutagen 1,2:3,4-diepoxybutane in mice than in rats, which is consistent with the much higher observed toxicity of 1,3-butadiene in mice. No one has measured 1,2:3,4-diepoxybutane (the key metabolite in the oxidative pathway) in exposed humans. But the metabolite M1 (a key biomarker of the hydrolytic pathway) has been measured in the urine of workers exposed to 1,3-butadiene.

GENOTOXICITY

In Vivo

Mutations induced by 1,3-butadiene exposure of mice include chromosomal aberrations and *Hprt* mutations (Walker and Meng 2000; Walker et al. 2003). Extensive work has been conducted on the ability of 1,3-butadiene and its metabolites to induce *Hprt* mutations in the T lymphocytes of exposed rodents. The mutagenic potency of 1,3-butadiene and its metabolites was studied in female mice and rats (Walker and Meng 2000; Walker et al. 2003). Mice and rats were exposed by inhalation to 1,3-butadiene, 1,2-epoxy-3-butene, 1,2:3,4-diepoxybutane, or 3-butene-1,2-diol to determine: (1) if *Hprt* mutant frequencies in T cells from 1,3-butadiene–exposed mice and rats would correlate with the species differences in terms of cancer susceptibility and (2) if mutagenic potency data from mice and rats exposed to 1,3-butadiene and its individual epoxy metabolites would reveal the intermediates responsible for mutations in each species. These studies demonstrated important trends in mutagenic responses that begin to distinguish the relative contribution of specific intermediates to the induction of mutations in exposed mice and rats. The studies suggested that 1,2:3,4-diepoxybutane is the major contributor to the mutagenicity of the parent compound in mice and that 1,2-epoxy-3-butene is the principal mutagen in rats. Two weeks of exposure to 6.6 mg/m^3 1,3-butadiene yielded significant increases above background in *Hprt* mutant frequency in exposed mice, but repeated exposures to 1380 mg/m^3 1,3-butadiene were required to produce such mutations in rats. The mutagenic potency of 1,3-butadiene in mice at exposure concentrations of less than 138 mg/m^3 can be explained largely by its ultimate conversion to 1,2:3,4-diepoxybutane. In mice, when the exposure concentration of 1,3-butadiene exceeded 440 mg/m^3, the mutagenic effects of the metabolites derived from 3-butene-1,2-diol reached a plateau. They contributed less than 15% of the total mutagenic effects found in mice exposed to 1380 mg/m^3 1,3-butadiene. Most of the remainder of the mutagenic effects at high-concentration exposures in mice were probably attributable to 1,2:3,4-diepoxybutane, and minor amounts were attributable to 1,2-epoxy-3-butene–induced DNA adducts. In rats, minimal amounts of diepoxybutane have been measured in blood after exposures to 1,3-butadiene concentrations of 138 mg/m^3 and higher. Yet nearly all of the mutagenic effects observed after repeated exposures to 1380 mg/m^3 can be attributed to 1,2:3,4-diepoxybutane–derived metabolites.

Analyses of 1,3-butadiene–induced mutant fractions demonstrated that 1,3-butadiene exposure increased the frequencies of most types of spontaneous mutations occurring in *Hprt* (i.e., base substitutions, frameshifts, and deletions) in both mice and rats. The major difference between the two was the significant induction of base substitutions at GC and AT base pairs in exposed mice but only at AT base pairs in exposed rats (Walker and Meng 2000; Meng et al. 2004).

The stereochemistry of 1,3-butadiene metabolites is not a major factor in the mutagenicity of 1,3-butadiene (Walker and Meng 2000).

In Vitro

All three of the epoxide metabolites of 1,3-butadiene are mutagenic. But in a test system using human lymphocytes, 1,2:3,4-diepoxybutane was found to be approximately 100 times more mutagenic than the other two (Cochrane and Skopek 1994). The resulting mutational spectrum indicated that 1,2:3,4-diepoxybutane induced a substantial fraction of mutations with deletions and rearrangements of *HPRT.*

CANCER

In Vivo

Carcinogenicity studies indicated that 1,3-butadiene is a weak carcinogen in rats and a potent carcinogen in mice. Sprague-Dawley rats were exposed for 2 years to either 2200 or 18,000 mg/m^3 1,3-butadiene. There was an increase in the incidence of thyroid follicular adenomas, uterine tumors, and exocrine pancreatic tumors only at the high concentration (Owen et al. 1987). In females, the incidence of mammary tumors increased at both concentrations. By contrast, carcinogenicity studies conducted by the NTP (Huff et al. 1985; Melnick et al. 1990) indicated that 1,3-butadiene was a potent multisite carcinogen in B6C3F1 mice. Chronic low exposures (as low as 13.8 mg/m^3 for 2 years) resulted in an increased incidence of lung tumors in female mice. Chronic exposures to concentrations ranging from 44 to 138 mg/m^3 induced increases in lung carcinomas, hemangiosarcomas of the heart, and neoplasms of the forestomach, Harderian gland, preputial gland, liver, mammary gland, and ovary. Again, these dramatic differences in the responses of rats and mice appear to be based on the different patterns of 1,3-butadiene metabolism in the two species (Henderson et al. 1996).

Exposure of B6C3F1 mice to concentrations of 440 mg/m^3 1,3-butadiene or higher induced lymphomas that led to early deaths. This response was determined to have been caused by the activation of an endogenous retrovirus and was not considered applicable to humans.

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

One of the difficulties encountered in occupational studies has been exposure estimation. If valid and reliable measures of butadiene exposure could be identified, these could be investigated in relation to effects that are thought to be involved in genotoxicity, the main concern with 1,3-butadiene. A number of studies have investigated urinary metabolites or adducts of hemoglobin as possible biomarkers of 1,3-butadiene exposure in humans (reviewed in Albertini et al. 2003a). Most of these have reported associations between such biomarkers and occupational exposure. A recent comprehensive study by Albertini and colleagues (2003b), conducted among Czech workers, compared groups engaged in butadiene-monomer production, styrene-butadiene synthetic-rubber (SBR) production, or nonexposed administrative work. Smoking was less frequent in the nonexposed group. Detailed and comprehensive exposure assessment took place prospectively for 60 days before collection of biologic samples. Concentrations of both urinary metabolites (M1 and M2) and especially hemoglobin adducts correlated well with exposure. These biomarkers were not associated with genetic polymorphisms for glutathione *S*-transferase (GST) or P450 isoenzymes. Neither the urinary-metabolite nor the hemoglobin-adduct concentrations were affected by smoking.

Biomarkers of Effect

1,3-Butadiene is metabolized by a number of enzymes, including GST and P450, to various substances, including the potent mutagen 1,2:3,4-diepoxybutane. The biomarkers of effect investigated in the Czech study were T-cell variations in *HPRT* and cytogenetic changes in DNA, indicated by sister-chromatid exchanges and chromosomal aberrations. There was no association between 1,3-butadiene exposure and *HPRT* mutations or cytogenetic changes. Neither of these was associated with metabolic genotypes for GST and P450 isoenzymes. Results for the *HPRT* test were not consistent with positive evidence reported in a study of U.S. workers (Ward et al. 2001). Further, the study did not establish a connection between biomarkers of effect and actual exposure or biomarkers of exposure. Otherwise, it did provide evidence that biomarkers of the process of carcinogenesis are absent in workers exposed at concentrations up to 1.79 mg/m^3.

CANCER

Occupational Studies

In the current regulatory literature, the available human evidence is confined to studies of one large cohort of SBR workers in eight plants in the U.S. and Canada (Delzell et al. 1995, 1996) and three small cohorts of 1,3-butadiene–production workers at plants operated by Texaco (Divine and Hartman 1996), Union Carbide (Ward et al. 1995), and Shell (Cowles et al. 1994), respectively. By far the most influential is the study of SBR workers, among whom there was an increase in mortality from leukemia (compared with national rates) but not from lymphomas or other causes of death. The risk was greater in those with indications of higher and longer exposures. The leukemia mortality was not explained by exposure to benzene; however, the individual contributions of styrene and 1,3-butadiene could not be distinguished. Mortality at six of the plants was investigated using quantitative methods to assess exposure, focusing on leukemia as the outcome (Macaluso et al. 1996). An exposure–response relationship between 1,3-butadiene and leukemia was observed, even when styrene was in the model. There was a somewhat similar, but less convincing, association with styrene and leukemia. It was also found that the combined effects of 1,3-butadiene and styrene were less than additive. In a more detailed account of the SBR cohort, exposure was quantified retrospectively and analyzed with respect to a wide range of causes of death (Delzell et al. 1995). There were more leukemia deaths than expected for seven of the eight plants, with 11 excess deaths overall. Risk was related to length and intensity of exposure to 1,3-butadiene and styrene. As in the earlier analysis (Macaluso et al. 1996), the association with styrene was less convincing than that for 1,3-butadiene, but the high correlation between the two (0.5) made their effects difficult to disentangle statistically. There was little evidence for associations between either 1,3-butadiene or styrene and non-Hodgkin's lymphomas, and the incidence of other tumors was in line with that expected for the general population. Benzene exposure was uncommon and low and did not confound these associations.

Despite the small number of studies, there is reasonable evidence that exposure to 1,3-butadiene while working in SBR or 1,3-butadiene production is likely to be associated with an increased risk of lymphohematopoietic cancer. The large SBR-cohort study found an excess of leukemia; the 1,3-butadiene–production studies found an excess of non-Hodgkin's lymphoma and a lesser increase in leukemia. Although this has been presented as an inconsistency, it should be noted that the 1,3-butadiene–production studies did not have enough statistical power to show a significant increase in non-Hodgkin's lymphoma, a relatively uncommon cause of death, nor to exclude an association between 1,3-butadiene and this cancer. If the main evidence for the carcinogenicity of 1,3-butadiene comes from on the SBR-cohort study, then the question becomes whether the 1,3-butadiene associations are explained by correlations with the presence other chemicals, such as styrene and dimethyldithiocarbamate (DMDTC). The carcinogenicity of styrene is classified as Group 2A ("probably carcinogenic to humans") by the IARC, based on limited evidence in human populations and sufficient evidence in laboratory animals (IARC 2004a). The epidemiologic arguments in favor of 1,3-butadiene being a cause of cancer include exposure response, relative robustness to inclusion of styrene in 1,3-butadiene models, and the fact that styrene has not been associated with leukemia in workers exposed to high styrene concentrations in other industries (Delzell et al. 1996).

New Analyses of Occupational Studies

More recent human evidence is confined to updates and reanalyses of existing occupational studies. Mortality data on the 17,924 workers in the SBR cohort previously studied by Delzell and colleagues (1996) and Macaluso and colleagues (1996) have recently been updated by seven more years of follow-up and now include data on an additional 34% deaths (Sathiakumar et al. 2005, Delzell et al. 2006). The increased statistical power of this update has consolidated the evidence that working in the SBR industry is associated with an increased risk of leukemia, but it has not yet resolved uncertainties about the responsible agent. For all causes of death, the standardized mortality ratio (SMR), based on rates expected in the relevant state or province, was lower than expected (SMR = 92). For all leukemias combined, the SMR was 116 (71 observed leukemia deaths compared with 61 expected). There was no convincing evidence that this increase was confined to one type of leukemia. Among the lymphohematopoietic cancers, the association appeared to be specific for leukemia. There was no apparent increase in non-Hodgkin's lymphoma or multiple myeloma. The main increase in leukemia was seen among subjects who were ever-hourly workers with 20 to 29 years since hire and 10 or more years of employment. It was also largely confined to certain groups of workers, most of whom were exposed to multiple agents, including 1,3-butadiene, styrene, and DMDTC.

In an update of the Texaco cohort of 2800 1,3-butadiene–production workers, mortality from all causes and from cancers was lower than expected. But mortality from all lymphohematopoietic cancers was significantly higher, because of increases in these cancers in workers first employed before 1950 and in short-term workers (Divine

and Hartman 2001). However, using an estimate of cumulative 1,3-butadiene exposure, no exposure–response relationship with lymphohematopoietic cancers was found. Mortality was increased for most of the main subgroups, non-Hodgkin's lymphoma and leukemia, though these increases were not statistically significant. Mortality data on the small cohort of 614 workers with potential exposure to 1,3-butadiene in the Shell petrochemical plant was updated (Tsai et al. 2001). Total mortality and all-cancer mortality were low compared with rates in the reference population. Mortality from lymphohematopoietic cancers was similar to that of the reference population. The small size of this cohort, with only three deaths from lymphohematopoietic cancer, does not allow conclusions to be drawn about the effects of 1,3-butadiene.

Workers in the SBR industry are also exposed to DMDTC. It has been postulated that the apparent differences in types of lymphohematopoietic cancer observed in 1,3-butadiene–production workers as compared with SBR workers might be explained by coexposure of the latter to DMDTC (Irons et al. 2001). DMDTC has not been evaluated for carcinogenicity by the IARC (2005a,b), and it has no toxicologic profile in the ATSDR (2005f). It is not generally thought to be carcinogenic, although it has immunosuppressant qualities and is known to inhibit the activity of CYP2E1, a major enzyme responsible for the oxidation of 1,3-butadiene to its epoxide intermediates (Bird et al. 2001). Thus, one might expect DMDTC to inhibit, rather than enhance, the carcinogenicity of 1,3-butadiene.

NONCANCER HEALTH EFFECTS

Biomarkers of Reproductive Effects

Studies in mice suggest that 1,3-butadiene can cause testicular and ovarian atrophy. Testicular injury in men is associated with suppression of inhibin B, a Sertoli-cell secretory protein, and with an increase in follicle-stimulating hormone through a feedback mechanism. In an exploratory study, the utility of these molecules as biomarkers was investigated in stored serum from a group of workers exposed to a variety of potential reproductive toxins, including styrene, acrylonitrile, and 1,3-butadiene, at a polymer-production plant in the mid-1970s (Lewis et al. 2002). Using an index that combined the measured levels of inhibin B and follicle-stimulating hormone, there was an increase in abnormal values in exposed workers compared with controls. There was a correlation between abnormal values and subsequent changes in fertility, but it was not statistically significant. These results require confirmation.

REGULATORY SUMMARY

Current regulatory risk assessments are based mainly on occupational evidence for cancer risk and on animal studies for noncancer risk. 1,3-Butadiene is classified by the IARC (2004a) as a Group 2A carcinogen ("probably carcinogenic to humans") based on limited evidence in humans and sufficient evidence in animals. It is classified by the EPA (2002b,c) as "carcinogenic to humans by inhalation." The difference in classification between the IARC and EPA reflects uncertainty about the interpretation of available epidemiologic evidence.

The EPA has estimated a lifetime risk ("unit risk") of 3×10^{-5} for a 1 μg/m^3 exposure. This estimate is based entirely on the evidence from the cohort of SBR workers (Delzell et al. 1995, 1996; Macaluso et al. 1996) and uses linear extrapolation below the lowest observed concentrations in these occupational data. A similar estimate was made by Health Canada (Hughes et al. 2001). Based on the occupational evidence, a cancer-potency factor of 1.7×10^{-4} was determined by the California EPA (1992). In the U.K., the Expert Panel on Air Quality Standards considered that the occupational evidence indicated no increased risk in workers exposed to less than 2250 μg/m^3 1,3-butadiene and arrived at a recommendation of 2.25 μg/m^3 as a running annual average, taking into account ambient lifetime exposure and the likelihood of individual variability (U.K. Department for Environment, Food and Rural Affairs 2002). All of these risk assessments have recognized that 1,3-butadiene is a known carcinogen in animals. The risk assessments are founded on numerous assumptions, including the specificity of 1,3-butadiene's association with occupational health effects and the accuracy of exposure estimates for worker cohorts.

Noncancer risk assessments by both the EPA and California EPA have relied on evidence of reproductive and developmental effects in mice, including testicular and ovarian atrophy. This information led to an inhalation reference concentration (RfC) of 2 μg/m^3, based on a benchmark concentration of 1.94×10^3 μg/m^3 for ovarian atrophy and an uncertainty factor of 1000 (EPA 2002b,c). The California EPA (2000) set a chronic reference exposure level (REL) of 20 μg/m^3, based on a lowest observed adverse effect level (LOAEL) of 600 μg/m^3 and an uncertainty factor of 30. The occupational evidence on the reproductive effects of 1,3-butadiene is limited to the study discussed above.

The U.K. has set an ambient air quality objective of 2.25 μg/m^3 of 1,3-butadiene as a running mean average concentration (U.K. National Air Quality Archive 2006a).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Long-term average ambient concentrations of 1,3-butadiene are typically less than 1 to 2 $\mu g/m^3$. These concentrations are generally much lower than occupational exposures. Concentrations measured at high-traffic sites have been found to be higher than those typically found at general urban and rural locations. Mobile sources contribute 51% of the exposure in urban locations and 25% in rural locations. Based on only a small number of studies, it is believed that indoor concentrations are typically higher than ambient concentrations; personal exposures are similar to indoor concentrations. Total exposure is therefore dominated by exposure to indoor sources. Ambient sources are different from occupational sources and are accompanied by different coexposures. 1,3-Butadiene is subject to atmospheric reactivity and can produce atmospheric acrolein and formaldehyde.

TOXICITY

Species differences in susceptibility to cancer are related to differences in metabolism. Mice, which metabolize 1,3-butadiene mainly by oxidative reactions to form a toxic diepoxide, are more susceptible than rats, which have a higher capacity to hydrolyze the epoxide metabolites of 1,3-butadiene to nontoxic forms. Humans are more similar to rats than mice in this respect. Adverse reproductive outcomes are also observed in mice but not rats.

HUMAN HEALTH

Working in the SBR industry is associated with increased hematopoietic cancer. On epidemiologic evidence alone, it is not possible to completely distinguish with confidence the effects of 1,3-butadiene from those of other coexposures. The extrapolation of occupational risk to risk at ambient concentrations is highly sensitive to a variety of assumptions. Biomarkers of exposure have been identified. Biomarkers of effect are identified inconsistently in exposed workers and are not correlated with biomarkers of exposure.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of 1,3-butadiene?

Emissions estimates and comparisons of measurement data between urban and rural areas—as well as comparisons of roadside and in-vehicle with urban background measurements—indicate that mobile sources are important contributors to ambient concentrations of 1,3-butadiene. Limited indoor and personal-exposure measurements also indicate, however, that indoor concentrations are higher than outdoor concentrations. Environmental tobacco smoke is a source of indoor 1,3-butadiene. But even in nonsmoking environments, indoor concentrations of 1,3-butadiene are higher than outdoor concentrations, suggesting the presence of other indoor sources or the absence of indoor photochemical degradation as possible explanations for the observed differences in concentrations.

2. Does 1,3-butadiene affect human health?

The human evidence, though limited, is consistent with the possibility that 1,3-butadiene causes lymphohematopoietic cancers in high-exposure occupational settings. This is plausible, moreover, because there is good evidence that certain metabolites of 1,3-butadiene cause cancer and adverse reproductive effects in mice. In humans, however, the metabolism of 1,3-butadiene appears to be more like that of rats, a less susceptible species. At high exposure concentrations, such as those once found in the U.S. in certain industries, 1,3-butadiene is likely to be a human health hazard because of its carcinogenicity. The confounding of 1,3-butadiene's health effects by coexposure to styrene and DMDTC cannot be ruled out. But on epidemiologic and toxicologic grounds, 1,3-butadiene seems likely to be the active agent.

3. Does 1,3-butadiene affect human health at environmental concentrations?

If a monotonic exposure–response relationship with no threshold is assumed (as for a genotoxic substance), then 1,3-butadiene can be assumed to be a hazard at ambient concentrations. It is not realistic to expect that this hazard can be demonstrated using epidemiologic methods, because the relevant outcome is uncommon and because community exposure to 1,3-butadiene is almost always associated with coexposure to other agents from the same sources, principally emissions from traffic and tobacco smoke. Estimates of community effect can be made by extrapolation from the exposure–response relationships in the SBR cohort evidence. But they are sensitive to a variety of assumptions about the magnitude and slope of the exposure–response relationship. Possibly there are subgroups that are especially sensitive to 1,3-butadiene because of age or genetic polymorphisms in the genes involved in 1,3-butadiene metabolism or because of combined exposures from a number of sources.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

The current NATA estimates of 1,3-butadiene exposure appear to be low, compared with measured ambient concentrations. Research recommendations for 1,3-butadiene–exposure studies include the following:

- Develop improved emissions estimates, including a better understanding of the relative effect of different vehicle types (e.g., light versus heavy duty) for future risk assessments.
- Identify the determinants of indoor 1,3-butadiene concentrations and personal exposures given that several studies have found indoor concentrations to be higher than outdoor concentrations.
- Systematically analyze the trends in ambient concentrations of 1,3-butadiene at U.S. monitoring locations, especially high-traffic sites.
- Assess the effect of alternative fuels on ambient 1,3-butadiene concentrations.

TOXICOLOGY

Given the large differences in the metabolism of 1,3-butadiene in mice and rats, there is a need to conduct well-controlled metabolism and toxicity studies in species more similar to humans, such as nonhuman primates. Humans are more like rats than mice in how they metabolize 1,3-butadiene. Exposed rats do not show the hematologic toxicity observed in exposed mice and develop tumors (mainly mammary) only after chronic high exposures to 1,3-butadiene. Research recommendations for 1,3-butadiene–toxicology studies include the following:

- Conduct parallel metabolism and toxicity studies in primates to improve the assessment of risk to humans, particularly in hematopoietic tissues, by linking the concentration of specific metabolites to specific toxic effects.

HUMAN HEALTH

There is a need for more research on cancer incidence in high-exposure populations. These are only found in occupational settings. However, it is unlikely that suitable opportunities now exist for such research. These studies would require very large and well-characterized cohorts followed over many years. Research recommendations for human-health studies of 1,3-butadiene include the following:

- Carry out additional investigations of biomarkers of exposure and effect in occupational settings. This can be done in smaller and better-characterized occupational cohorts than those typically needed in cohort studies examining cancer occurrence as an endpoint. Hemoglobin adducts are promising as biomarkers of exposure. Additional research on these should be carried out to help in the development of valid biomarkers for community studies.
- Further research on biomarkers in general, with refinements to make them sufficiently sensitive for use in community studies. Biomarkers for use in more highly exposed community samples should be considered, too, but these should be part of an integrated assessment that includes other air toxics, such as benzene. In addition, biomarkers, such as hemoglobin adducts, and *HPRT*-mutant assays should be validated in primates in order to better understand human responses to low exposures to 1,3-butadiene.

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