Benzene

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For further information please contact the Health Effects Institute:
+1-617-886-9330
pubs@healtheffects.org
www.healtheffects.org

INTRODUCTION

Benzene (CAS Registry Number 71-43-2; C_6H_6; molecular weight = 78.1) (Figure 7) is a clear, colorless, volatile, highly flammable liquid with a characteristic odor. It is the smallest of the aromatic compounds, with a single six-member unsaturated carbon ring. Benzene is soluble in lipids and has an octanol–water partition coefficient of 2.14. At 1 atmosphere and 20°C, benzene has a density of 0.879, a boiling point of 80.1°C, and a melting point of 5.5°C. It is derived from petroleum and is used extensively as a solvent or raw material in many manufacturing processes. Benzene is one of the leading chemicals produced and used around the world.

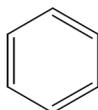At one atmosphere pressure and 25°C, 1 ppm benzene is equivalent to 3.26 mg/m^3.

Figure 7. Structure of benzene.

BENCHMARK LITERATURE

The following evaluation of research literature on benzene 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 Agency for Toxic Substances and Disease Registry (ATSDR 2005b,d), EPA (1998a, 2000d, 2002e), and the International Agency for Research on Cancer (IARC 1987).

EXPOSURE

SOURCES AND EMISSIONS

Although natural sources of benzene include volcanoes and forest fires, the sources of most ambient benzene are emissions from coal and oil combustion, motor-vehicle exhaust, evaporation from gasoline service stations, evaporation of

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

industrial solvents, and hazardous waste sites. According to National Air Toxics Assessment (NATA) data, the major source of benzene emissions into ambient air in the U.S. is on-road mobile-source emissions, which account for 49% of all emissions nationwide and 57% of all emissions in urban areas (EPA 2006b). In the outdoors, the highest exposures to benzene are likely to occur in heavy traffic, during the filling of vehicle gas tanks, and at or near gasoline filling stations. Sources of indoor benzene exposure include tobacco smoke, several household products, and ambient air entering the home through ventilation or infiltration (EPA 2000d; ATSDR 2005d). Tobacco combustion is a major source of indoor benzene exposure. Estimates of the amount of benzene released by cigarette smoking range from 5.9 to 75 µg per cigarette in mainstream smoke and from 345 to 653 µg per cigarette in sidestream smoke (ATSDR 2005d; National Toxicology Program 2005).

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

The literature search yielded 34 ambient, outdoor, indoor, and personal-exposure studies of benzene. More air-monitoring data are available for benzene than for any other MSAT considered in this report. Table 4 and Figure 8 show the range of mean and maximum concentrations of benzene
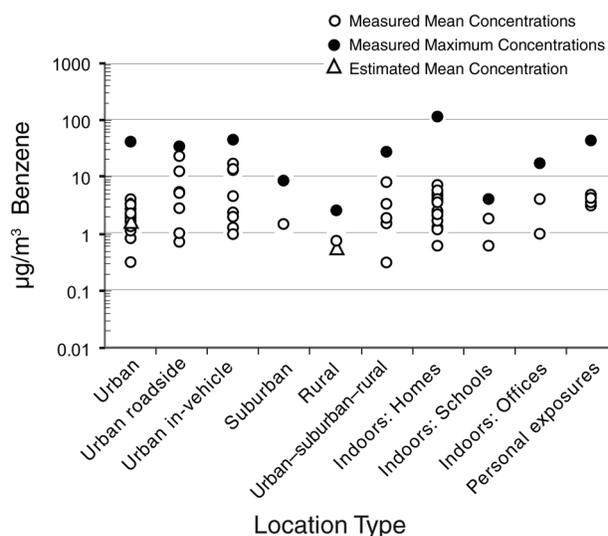
Figure 8. Concentrations of benzene (µg/m^3) at various locations. Data for figure are from Table 4.

Table 4. Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (n)	Averaging Sampling Time	Concentration ($\mu g/m^3$) Mean	Maximum	Citations	Comments
Outdoor Areas						
Urban						
	152 averages*	Yearly	1.6	6.1**	EPA 2004a	
	69	17 months	3.2	10.0	California Air Resources Board 2003	
	74	16 months	3.9	22.0	California Air Resources Board 2003	
	81	1.5 yr	0.1	1.9	California Air Resources Board 2003	
	65	1 yr	1.8	8.2	California Air Resources Board 2003	
	83	1.5 yr	2.0	7.5	California Air Resources Board 2003	
	60	1 yr	2.2	9.5	California Air Resources Board 2003	
	33	18 months	1.8	3.1+	Payne-Sturges et al. 2004	
	50	9 hr	0.3	2.0	Riediker et al. 2003	
	10	5 wk	1.1***	1.6+	Adgate et al. 2004b	
	8	4 wk	1.3***	2.2+	Adgate et al. 2004b	
	35	8 wk	1.3	—	Kinney et al. 2002	
	36	8 wk	2.6	—	Kinney et al. 2002	
	132	7 months	1.6	3.3+	Sexton et al. 2004	
	≈ 60	1 yr	3.5	—	South Coast Air Quality Management District 2000	
	≈ 60	1 yr	3.1	—	South Coast Air Quality Management District 2000	
	≈ 30	1 yr	—	4.1**	Mohamed et al. 2002	
	16	—	—	6.6**	Rodes et al. 1998	Samples taken during commuting times
	12	—	—	2.9**	Rodes et al. 1998	Samples taken during commuting times
	—	Yearly	1.56	—	EPA 2006b	Model
	250	1 yr	—	39.0	Zielinska et al. 1998	
	555	Yearly	2.2	11.1	Weisel et al. 2005	2 seasons
Urban in-vehicle						
	20	Bus commutes	—	9.5**	Fitz et al. 2003	Bus commutes
	42	Police patrols	1.3	44.0	Riediker et al. 2003	Police patrols
	74	4 days	4.5	11.0	Batterman et al. 2002	
	1	90 min	2.4	—	Fedoruk and Kerger 2003	1 car test

Table continues on next page

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a);
** = maximum average; *** = median value; + = 90th percentile; ++ = 95th percentile; +++ = 99th percentile.

Table 4 (*Continued*). Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration ($\mu g/m^3$)		Citations	Comments
			Mean	Maximum		
Outdoor Areas (*Continued*)						
Urban in-vehicle (*Continued*)						
	3	90 min	1.0	14.0	Fedoruk and Kerger 2003	3 car tests
	3	90 min	—	14.0	Fedoruk and Kerger 2003	3 car tests
	32	Commute time	13.0–17.0	22.0	Rodes et al. 1998	Cars
	26	Commute time	2.0–14.0	16.0	Rodes et al. 1998	Cars
Urban roadside						
	50	9.1 hr	0.7	2.6	Riediker et al. 2003	Samples taken 3PM–12AM
	56	7 days	2.7–22.0	33.0	Sapkota and Buckley 2003	Tunnel roadside
	24	Commutes	5.2–12.0	20.0	Rodes et al. 1998	
	18	Commutes	1.0–5.0	5.9	Rodes et al. 1998	
Suburban						
	155 averages*	Yearly	1.5	8.6**	EPA 2004a	
Rural						
	—	Yearly	0.6	—	EPA 2006b	Model
	64 averages*	Yearly	0.7	2.5**	EPA 2004a	
Urban–suburban–rural combined						
	1550	Yearly	1.5	8.8	EPA 2004d	
	3650	Yearly	1.8	26.0	Pratt et al. 2000	
	100	5 months	3.3	4.6++	Adgate et al. 2004b	
	300	Yearly	0.3–7.9	24.0	Zielinska et al. 1998	
	—	1 hr	—	16.0**	Seigneur et al. 2003	
Indoor Spaces						
Tollbooths						
	280	3 hr	4.1	14.9	Sapkota et al. 2005	
Residences						
	282	6 days	4.6	13.0++	Adgate et al. 2004b	
	101	6 days	3.9	7.5++	Adgate et al. 2004b	
	88	4 wk	2.1***	7.2+	Adgate et al. 2004a	
	93	2 days	2.2***	6.2+	Adgate et al. 2004a	
	402	6 days	7.2	13.0+	Clayton et al. 1999	
	185	6–7 days	1.3***	9.0	Gordon et al. 1999	
	9	3 wk	2.4***		Mukerjee et al. 1997	

Table continues on next page

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median value; + = 90th percentile; ++ = 95th percentile; +++ = 99th percentile.

Table 4 (*Continued*). Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (µg/m³)		Citations	Comments
			Mean	Maximum		
Indoor Spaces (*Continued*)						
Residences (*Continued*)						
	6	10 days	2.4***		Mukerjee et al. 1997	
	33	3 days	3.7	8.3[+]	Payne-Sturges et al. 2004	
	40	12 hr	0.6	14.0	Phillips et al. 2005	
	40	12 hr	1.2	110.0	Phillips et al. 2005	
	40	2 days	4.9	17.0	Sax et al. 2004	
	32	2 days	2.5	6.3	Sax et al. 2004	
	30	2 days	1.7	6.3	Sax et al. 2004; Kinney et al. 2002	
	36	2 days	5.3	39.0	Sax et al. 2004; Kinney et al. 2002	
	292	2 days	5.8	15.0[+]	Sexton et al. 2004	
	104	2 days	2.2***	8.3[+]	California Air Resources Board 1992	
	48	10 months	4.1	34.0	Van Winkle and Scheff 2001	
	554	Yearly	3.5	36.4	Weisel et al. 2005	2 seasons
Schools						
	47	5 wk	0.6***	1.0[+]	Adgate et al. 2004a	
	39	4 wk	0.6***	1.6[+]	Adgate et al. 2004a	
	—	—	—	3.4	Shendell et al. 2004	20 classrooms
	73	6–8 hr	1.8	4.1[++]	Whitmore et al. 2003b	210 classrooms from 67 schools
Offices						
	—	8 hr	1.0	2.7	Daisey et al. 1994	
	> 200	8 hr	—	17.0	Girman et al. 1999	
Personal Exposures						
	36	2 days	4.7	—	Kinney et al. 2002	High school students, winter
	41	2 days	3.1	—	Kinney et al. 2002	High school students, summer
	545	2 days	3.6	27.4[+++]	Weisel et al. 2005	Adults
	209	2 days	4.2	43.6[+++]	Weisel et al. 2005	Children

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median value; [+] = 90th percentile; [++] = 95th percentile; [+++] = 99th percentile.

in units of µg/m³, as reported in the published literature. Ambient data are sorted into six categories: urban, urban roadside, urban in-vehicle, suburban, rural, and combined urban–suburban–rural. Indoor data are sorted into four categories: residences, schools, offices, and toll booths. Two recent studies reported personal-monitoring data for adults, high school students, and children.

This report focuses on benzene concentrations in the U.S. as found in publications dating from 2000 to the present. In the 1980s, the Total Exposure Assessment Methodology (TEAM) studies, a series of large-scale studies of nonoccupational exposures to volatile organic compounds (VOCs), funded by the EPA, compiled a large database on outdoor, indoor, and personal-exposure concentrations of benzene. A summary of the TEAM study design and findings as well as

a review and comparison of these findings with other large studies conducted in the early 1990s was published in 1996 (Wallace 1996). The earlier studies provided a global average and range of averages for ambient, indoor, and personal-exposure benzene concentrations during the 1980s. Although direct comparisons between the TEAM studies' results and those from the more recent studies used in this report are not appropriate, the TEAM results do provide a rough frame of reference. Benzene concentrations measured in the studies conducted in the early 1990s were in general similar to those reported both by Wallace (1996) and the TEAM studies.

Sampling times for the studies shown in Figure 8 and listed in Table 4 ranged from 1 hour (Seigneur et al. 2003) to 6 days (Adgate et al. 2004b). Sample-averaging times ranged from hours (e.g., Fitz et al. 2003) to 1.5 years (California Air Resources Board 1992). The number of observations per study, from which the mean and maximum concentrations were determined, ranged from a low of 1 for an in-vehicle study (Fedoruk and Kerger 2003) to a high of 113,343 for the combined urban–suburban–rural category (EPA 2004a). Three large studies (Pratt et al. 2000; EPA 2004a,d), all with more than 1000 observations, reported results as combined urban–suburban–rural. It should be noted that the mean rural concentration of 0.56 µg/m^3 and one of the mean urban values (1.6 µg/m^3) shown in Table 4 and Figure 8 were estimated by modeling (EPA 2006b).

There was great variability in the number of measurements, season of measurement, and geographic areas in which measurements were taken. The mean concentrations recorded in the Air Quality System database, the report with the largest number of observations in urban, suburban, and rural areas (EPA 2004a), indicated that concentrations in rural areas (0.7 µg/m^3) are approximately half those found in suburban and urban areas (1.6 µg/m^3 and 1.5 µg/m^3, respectively). This is consistent with the expectation that on-road mobile-source emissions would be lowest in rural areas and highest in urban areas. All studies taken together, however, and independent of the number of observations or constituent studies, suggest that the concentrations in urban, suburban, and rural areas are in the range of approximately 1 to 10 µg/m^3. Peak concentrations for urban, suburban, and rural air appear to be in the 15 to 50 µg/m^3 range, with the rural maximum being at the low end of the range.

Through the National Air Pollution Surveillance network of Canada, data on concentrations of a variety of air toxics are collected at urban, suburban, rural, and industrial sites. This effort is carried out in cooperation with provincial and municipal environmental agencies. It includes measurements of a large number of VOCs, including benzene. In 2004, there were 51 active sites where benzene measurements were taken. Thirty-eight sites were located in 18 cities across Canada, and the other 13 sites were in rural locations. For the urban sites, the annual mean concentrations ranged from 0.4 to 7.6 µg/m³; 35 of the 38 sites recorded annual mean concentrations of less than 2.0 µg/m³ (Dann T, unpublished).

The TEAM studies found an ambient global average for benzene of 6 µg/m^3 in the 1980s (Wallace 1996), with a range of mean concentrations between 2 and 19 µg/m^3 and a maximum concentration of approximately 100 µg/m^3. Current mean ambient concentrations appear to be somewhat lower than those measured in the 1980s in the TEAM studies.

Two studies (Rodes et al. 1998; Sapkota and Buckley 2003) found that urban roadside and urban in-vehicle concentrations were higher (10 to 22 µg/m^3) than the typical highest ambient concentrations measured in other studies (<10 µg/m^3). This is not surprising, given that higher benzene concentrations might be expected at such sites, where motor-vehicle emissions are highest. However, when all mean concentrations from all studies are considered together, urban roadside and urban in-vehicle concentrations appear similar to those in other outdoor settings. Peak concentrations for the urban roadside and urban in-vehicle categories are in the same range as those for the rural, suburban, urban categories.

Mean benzene concentrations in residences appear to be in the same range as those in ambient air—0.5 to 10 µg/m^3. The highest peak concentration found in all 34 benzene studies (110 µg/m^3) was measured in a residence. While some studies were careful to select homes without cigarette smokers (e.g., Kinney et al. 2002 and Weisel et al. 2005), smoking might have occurred in homes included in some of the studies. Although there were few studies with data on schools, schools tended to have mean and peak benzene concentrations at the low end of those found outdoors and in residences. The maximum peak value (3.4 µg/m^3) of all 34 studies was measured in a classroom. The one study reporting a mean benzene concentration in offices (1 µg/m^3) (Daisey et al. 1994) was at the low-to-middle end of the range of ambient concentrations, while another study reported a peak of 17 µg/m^3 (Girman et al. 1999). One study reported a peak concentration (99th percentile observation) in schools of 4.1 µg/m^3 (Whitmore et al. 2003b). Mean and peak concentrations reported for toll booths were similar to those in the urban roadside and urban in-vehicle categories. Residential concentrations of benzene measured in the TEAM studies (Wallace 1996) averaged approximately 10 µg/m^3, with a range of 2 to 19 µg/m^3 and a peak concentration near 100 µg/m^3. Current residential concentrations

of benzene appear to be lower than those recorded in the 1980s in the TEAM studies.

Mean personal benzene exposures reported for adults, high school students, and children showed a very narrow range of concentrations (3.1 to 4.7 µg/m^3). The maximum personal exposure (43.6 µg/m^3) was similar to that recorded for ambient air and lower than the maximum concentration recorded for residences. The TEAM studies reported a global average personal exposure to benzene for nonsmokers of 15 µg/m^3, with a range of 7 to 29 µg/m^3 and several maximum readings of well over 100 µg/m^3 (Wallace 1996). A rough comparison of the TEAM studies and the more current data shown in Table 4 and Figure 8 suggests that personal exposures to benzene have decreased since the 1980s.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of benzene measured in several other countries are generally higher than those measured in the U.S. In urban areas of China, for example, concentrations of 7.9 to 120.9 µg/m^3 were measured (Zhao et al. 2004). In residential areas of India, concentrations of 26 to 195 µg/m^3 were measured (Srivastava et al. 2004). Concentrations measured at urban roadside locations tended to be higher than those measured in the U.S., ranging from 5.2 to 73 µg/m^3 in China (reported in Chang et al. 2005) and 15.8 to 18,816 µg/m^3 in India (Samana et al. 1998; Srivastava et al. 2004) and concentrations measured at urban roadside locations tended to be higher than those measured in ambient air. The higher concentrations of benzene at ambient locations were also seen in Korea (9.4 µg/m^3, Baek et al. 1997), Pakistan (17 µg/m^3, Barletta et al. 2002), the Philippines (12.6 µg/m^3, Gee and Sollars 1998), and Turkey (38 to 57 µg/m^3, Muezzinoglu et al. 2001). Concentrations in Japan, however, were measured at 1.8 to 2.9 µg/m^3, closer to those in the U.S. (reported in Chang et al. 2005; Japan Ministry of the Environment 2005b). Ambient concentrations of benzene ranged from nondetectable to 47 µg/m^3 in the Philippines (Gee and Sollars 1998), 3.6 to 228 µg/m^3 in Taiwan (Chang et al. 2005; Lin et al. 2005), and 3.5 to 50.2 µg/m^3 in Thailand (Gee and Sollars 1998; Muttamara and Leong 2000; Gioda et al. 2004).

In Europe, ambient concentrations of benzene varied considerably, ranging from 3 to 534 µg/m^3 in Denmark (reported in Gioda et al. 2004), 1.1 to 2.1 µg/m^3 in Finland (Hellén et al. 2005), 3.3 to 16 µg/m^3 in France (Ferrari et al. 1998), 1 to 30 µg/m^3 in Germany (Slemr J et al. 1996; reported in Gioda et al. 2004; Umweltbundesamt 1998), 13 to 26 µg/m^3 in Greece (Chatzis et al. 2005), 1.3 to 12.6 µg/m^3 in Italy (Crebelli et al. 2001; Bono et al. 2003), and 0.7 to 1.94 µg/m^3 in the U.K. (U.K. National Air Quality Archive 2006a). Only

minor differences were seen between ambient and urban roadside measurements in most of these countries.

In Latin American countries, benzene concentrations were more consistent, ranging from around 4 to 40 µg/m^3 (Baez et al. 1995; Gee and Sollars 1998; Bravo et al. 2002; Serrano-Trespalacios et al. 2004), although concentrations were higher in Brazil, ranging from 11.3 to 11,800 µg/m^3 (Grosjean and Miguel 1988; Gee and Sollars 1998; Fernandes et al. 2002; Gioda et al. 2004).

TEMPORAL TRENDS

The National Air Pollution Surveillance benzene-monitoring program began in 1989. For the years 1991 to 2004, there were complete annual data records (with valid annual means in at least 10 of the 14 years) for 20 urban sites in 12 cities. The composite annual mean for this group of sites is shown in Figure 9. Also shown in the figure are composite annual means for a group of rural sites with complete (8 of 11 years) data for the years 1994 to 2004 (Dann T, unpublished).

These Canadian data indicate a trend toward decreasing concentrations of benzene in the air in both urban and rural areas. Data from the U.S. for 95 sites monitoring urban ambient air indicate a 47% decrease in benzene concentrations between 1994 and 2000 (EPA 2006b). During this period, the mean urban concentration in Canada dropped from approximately 3.3 to 1.8 µg/m^3. In 1994, 90% of the sites reported concentrations below 6.2 µg/m^3, and by 2004 the concentrations were below 3.0 µg/m^3. Over the same time period, there was a corresponding decrease in the benzene content of Canadian gasoline,
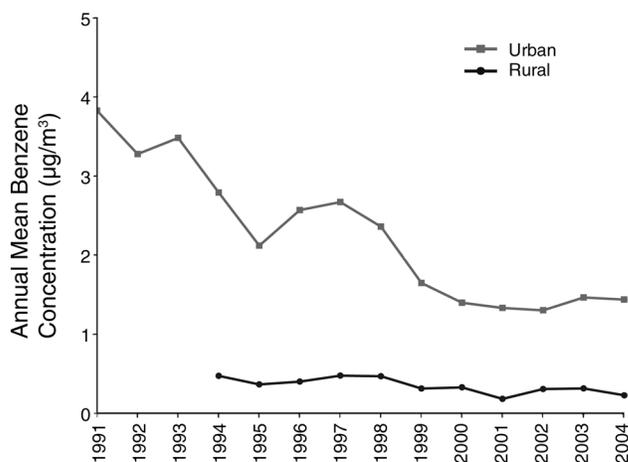

Figure 9. Annual mean concentrations of benzene measured in Canadian urban and rural locations from 1991 to 2004. (Courtesy of T. Dann, Head, Air Toxics Analysis and Air Quality, Environment Canada, 2007. Data are available from the National Air Pollution Surveillance (NAPS) Network at *www.etc-cte.ec.gc.ca/naps/index_e.html*.)

with the largest decrease in concentration occurring during the second half of 1999, as a result of regulatory action (Environment Canada 2003b).

Measurements of ambient benzene concentrations at sites in California's South Coast Air Basin from 1990 through March 1997, reported as part of the Multiple Air Toxics Exposure Study (MATES) (South Coast Air Quality Management District 2000), demonstrated a trend similar to that observed for Canada and urban areas in the U.S., with concentrations dropping from approximately 2.8 to 0.8 μg/m^3 (a 70% drop).

The MATES-II study, conducted from April 1998 through March 1999, again measured benzene at sites in California's South Coast Air Basin (South Coast Air Quality Management District 2000). Benzene concentrations demonstrated a pronounced seasonal trend, with peak concentrations occurring during the colder months of October through January (2 to 2.25 μg/m^3) and the lowest concentrations occurring during the warmer months of April through October, when concentrations were typically less than 1 μg/m^3. In this study, seasonal trends for 1,3-butadiene closely followed the seasonal benzene trends. Sax and colleagues (2004) also reported maximum benzene concentrations in the colder months, in both Los Angeles and New York.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

Some of the metabolites of benzene are responsible for its toxicity and carcinogenicity (Longacre et al. 1981; Snyder and Hedli 1996). This is supported by the observation that benzene toxicity is inhibited by toluene, a competitive inhibitor of benzene metabolism; by the reduced toxicity of benzene in animals that have had a partial hepatectomy, reducing their ability to metabolize benzene; and by the reduced toxicity of benzene in mice lacking the enzyme CYP2E1, known to be the major determinant of in vivo benzene metabolism (Sabourin et al. 1988). The metabolism of benzene is illustrated in Figure 10.

Benzene is first oxidized to benzene oxide, which can spontaneously rearrange to phenol, be further oxidized to the ring-breakage compound muconaldehyde, or form a conjugate with glutathione and be excreted in the urine as *S*-phenylmercapturic acid (SPMA). Phenol is excreted in the urine or oxidized to catechol or hydroquinone. Catechol can be further oxidized to trihydroxybenzene, and hydroquinone can be oxidized to the highly reactive bipolar benzoquinone. All of the phenolic metabolites can
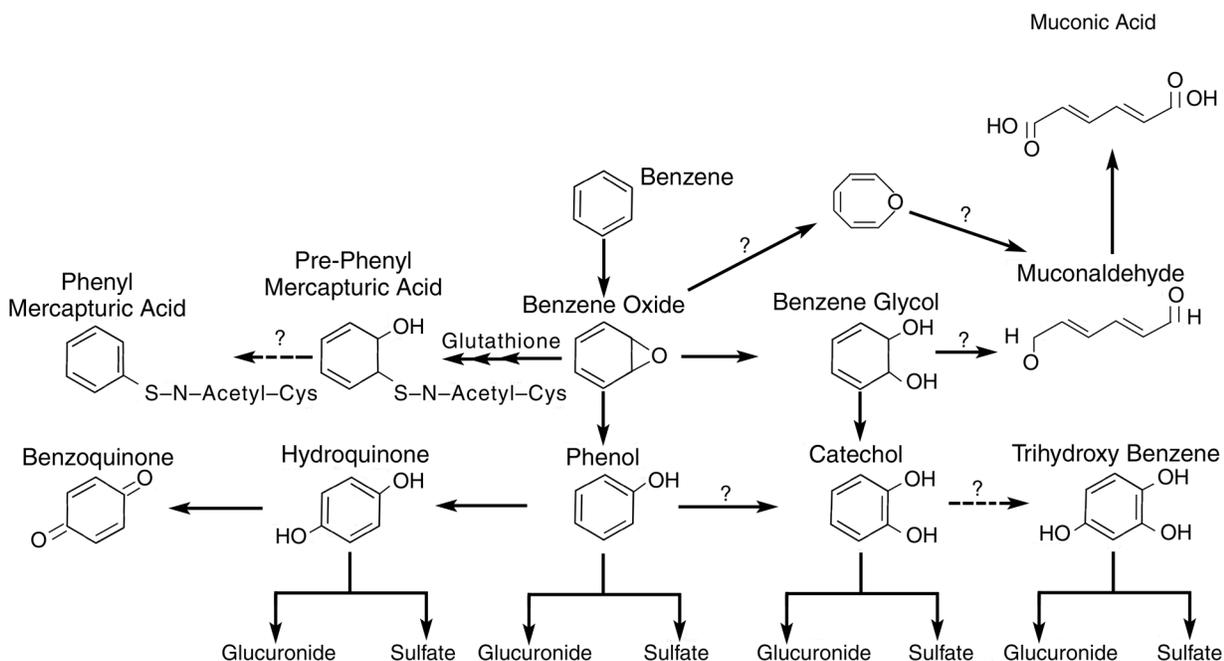

Figure 10. **Metabolic pathway of benzene.** (Reprinted from Sabourin et al. 1988, with the permission of Elsevier.)

form conjugates (glucuronides or sulfates) prior to excretion in the urine. Muconaldehyde is further oxidized to muconic acid, which is excreted in the urine (Sabourin et al. 1988).

The key toxic metabolites for cytotoxicity and the induction of leukemia are thought to be benzoquinone, benzene oxide, and muconaldehye. The formation of muconic acid and the quinones is favored at low exposure concentrations (Sabourin et al. 1988). The genotoxicity is thought to be clastogenic (i.e., consisting of chromosomal damage) in nature rather than being caused by point mutations.

There are species differences in the metabolism of benzene (Sabourin et al. 1988). In metabolizing benzene, rats convert a large portion of the benzene to phenol, a marker of a detoxication pathway. By contrast, mice form much greater amounts of hydroquinone, hydroquinone glucuronide, and muconic acid, all markers of pathways leading to putative toxic metabolites. Metabolism in humans appears to resemble that in mice (Sabourin et al. 1989).

There are two key enzymes involved in the detoxication of benzene metabolites (Recio et al. 2005). One is NAD(P)H:quinone oxidoreductase-1 (NQO1), which reduces the benzene quinone metabolites, and the other is the microsomal epoxide hydrolase, which hydrolyzes the epoxide group on benzene oxide. NQO1-knockout mice have increased sensitivity to benzene-induced hematotoxicity and demonstrate myeloid hyperplasia after benzene exposure (Ross 2005).

BIOMARKERS

Biomarkers of benzene exposure have been studied in animals for potential use in assessing exposure in humans. Exposure biomarkers in humans are discussed below, in the section on human health. Biomarkers of benzene health effects are based on hematotoxicity and on indicators of genotoxicity. Hematotoxicity is detected by alterations in complete blood counts, including hemoglobin concentration, hematocrit, erythrocyte count, leukocyte count, and differential and platelet counts. For genotoxicity, chromosomal aberrations in bone marrow and peripheral-blood lymphocytes and sister-chromatid exchange can be used (ATSDR 2005d). However, none of the biomarkers of effect are specific for benzene.

NONCANCER HEALTH EFFECTS

In Vivo

Exposure to high concentrations of benzene is acutely toxic because of narcotic effects on the central nervous system and cardiac sensitization (Bingham et al. 2001). Inhalation exposures of animals (in rats, mice, and rabbits) to

benzene concentrations greater than 32,600 mg/m^3 benzene for several minutes up to several hours usually result in death from central nervous system depression or ventricular fibrillation (in rabbits).

Hematopoietic effects have been studied mainly in mice, showing reduced bone-marrow cell counts and anemia after 2 weeks of exposure, 4 or 5 days/week, 6 hours/day, to 980 mg/m^3. Exposure of mice to as little as 32.6 mg/m^3 benzene for 6 hours/day for 5 days resulted in a decrease in bone-marrow cells.

Animal studies indicate that benzene exposure affects humoral and cellular immunity. Mice exposed to 81 mg/m^3 benzene for 6 hours/day for 5 days had a decrease in spleen weight as well as in the number of circulating leukocytes (Wells and Nerland 1991). Mitogen-induced blastogenesis of B and T lymphocytes was depressed in mice exposed to 33 mg/m^3 benzene (Rozen et al. 1984). Mice exposed to 33 mg/m^3 also showed delayed splenic reaction to foreign antigens when evaluated in vitro (Rosenthal and Snyder 1987). Prior exposure of mice to 98 mg/m^3 benzene decreased resistance to subsequent infections (Rosenthal and Snyder 1985).

Benzene-induced effects on the reproductive system have been observed in animals, but most studies were conducted at exposure concentrations well above those currently found in occupational settings or ambient air (ATSDR 2005d). In one 13-week study (Ward et al. 1985), mice were exposed to 980 mg/m^3 benzene, and gonadal alterations were observed, with greater severity in males.

In Vitro

Bioactivation of benzene has also been shown to produce reactive oxygen species, which are cytotoxic and can lead to oncogene activation (Wan et al. 2005). Muconic acid and muconaldehdye are both hematotoxic (Witz et al. 1996) and cytotoxic (Zhang et al. 1997).

The studies cited above on the effects of benzene exposure on the immune system often used in vitro tests to assess effects on lymphocyte function.

GENOTOXICITY

Benzene acts mainly as a clastogenic agent, as opposed to causing point mutations. Benzene-induced chromosomal aberrations in bone marrow and lymphocytes have been observed in mice, rats, Chinese hamsters, and humans. An increase in micronuclei has been observed in the bone marrow and peripheral blood of mice, rats, and Chinese hamsters. An increase in sister-chromatid exchanges has been observed in bone marrow or lymphocytes of mice, rats, and humans (ATSDR 2005d).

CANCER

In Vivo

After chronic exposures of rats and mice, benzene was found to be carcinogenic in both, but mice are the more sensitive of the two species (Cronkite et al. 1984; Huff et al. 1989; Maltoni et al. 1989). Tumors induced by exposures to 326 or 980 mg/m^3 benzene for 104 weeks or longer include hepatomas, Zymbal-gland tumors, and tumors of the lung and ovary as well as thymic and nonthymic lymphomas. Intermittent lifetime exposure to 980 mg/m^3 benzene was found to be more tumorigenic than short-term exposure (10 weeks) to 3900 mg/m^3 followed by lifetime observation (Snyder et al. 1988).

The toxicity of benzene in animals has been studied widely, but no animal model of the induction of the acute myeloid leukemia (AML, also referred to as acute myelogenous leukemia) observed in exposed humans (see *Human Health* section below) has been found. However, genetically modified mice, in which key detoxication enzymes are missing, have been shown to develop myeloid-cell hyperplasia after benzene exposure (Ross 2005).

In Vitro

The mechanisms of benzene's carcinogenicity and its ultimate toxic metabolite(s) are not known, although recent studies are adding to our knowledge. Cytogenetic studies have indicated that benzene acts as a clastogenic agent (rather than causing point mutations) (Whysner et al. 2004). It has been postulated that 1,4-benzoquinone (Irons 1985; Pellack-Walker et al. 1985; Jowa et al. 1986) and *t,t*-muconaldehyde (Goldstein et al. 1981; Witz et al. 1985) are toxic metabolites of benzene. Both of these compounds are bipolar, which is consistent with the clastogenic properties of benzene.

In vitro studies of the inhibition of enzymes involved in DNA replication and maintenance, such as topoisomerases, have indicated that these enzymes play a role in benzene-induced chromosomal aberrations (Eastmond et al. 2005; Lindsey et al. 2005). Other epigenetic studies indicated that benzene modifies the chromatin structure, giving rise to heritable changes not affecting DNA (Morgan and Alvares 2005).

HUMAN HEALTH

BIOMARKERS

The use of biomarkers in benzene studies has been reviewed by Albertini and colleagues (2003a). Biomarkers fall into three general categories—biomarkers of exposure, susceptibility, and effect. While not in themselves health effects, these biomarkers indicate that an individual or group has been exposed to benzene or that benzene is causing metabolic or cellular effects that might be part of the mechanistic chain leading to effects on human health such as cancer (Albertini et al. 2003a). All three categories of biomarkers might be useful in assessing the risk of exposure to benzene from mobile-source emissions by extending investigative opportunities at the low end of exposure concentrations in occupational settings and in ambient air.

Biomarkers of Exposure

Biomarkers of exposure include metabolic products such as S-phenylmercapturic acid, *t,t*-muconic acid (*t,t*-MA), and adducts of benzene oxide, albumin, and hemoglobin. The relative sensitivity and usefulness of exposure biomarkers have been explored in a number of studies.

A study of Chinese workers concluded that S-PMA was a sensitive marker for exposure at around 32.6 mg/m^3 but was affected by a polymorphism (genetic variants in enzymes) in glutathione-S-transferase T1 (GSTT1) (Qu et al. 2005). Two genetic variants in the enzymes that metabolize benzene, myeloperoxidase and NAD(P)H:quinone oxidoreductase, were related to changes in cell counts.

In another study of Chinese workers, a variety of urinary metabolites were found to be elevated after benzene exposure, including *t,t*-MA and S-PMA at 0.65 mg/m^3 benzene, phenol and hydroquinone at 1.63 mg/m^3 benzene, and catechol at 6.5 mg/m^3 benzene (Kim et al. 2006). The study also indicated that metabolism of benzene to hydroquinone and *t,t*-MA was favored at low exposures, confirming earlier studies in mice (Sabourin et al. 1988).

The technologies used in the new "omics" fields of study (genomics, proteomics, etc.) have been used to study alterations in DNA and proteins in humans exposed to benzene (Forrest et al. 2005; Smith et al. 2005; Vermeulen et al. 2005; Zhang et al. 2005a). More than 100 genes were shown to be differentially expressed, and serum protein profiles indicated that several proteins were differentially expressed in benzene-exposed subjects compared with controls. Such changes, if confirmed, might be useful as exposure biomarkers in the future.

In contrast, in a study of occupational exposure, S-PMA and *t,t*-MA were found to be useful as biomarkers only in the most highly exposed workers and the most sensitive biomarker was the presence of benzene in the urine at exposure concentrations of less than 32.6 mg/m^3 (Farmer et al. 2005). In a study of school children in Thailand, measures of *t,t*-MA and benzene in the blood were significantly different in two groups exposed to ambient concentrations of 27.71 μg/m^3 and 8.8 μg/m^3 benzene, respectively (Navasumrit et al. 2005).

This evidence suggests that exposure biomarkers are sensitive indicators of benzene exposure at the lower end of occupational concentrations and the higher end of concentrations in the community. It appears, however, that the

most sensitive and specific method of measuring exposure is by direct measurement of benzene in urine, exhaled air, or blood. This method avoids unwanted variations associated with other substances that might share the same metabolic pathways and with age and genetic differences in benzene metabolism.

Biomarkers of Effect

The distinction between biomarkers of effect and health effects is not clear-cut. Indicators of hematotoxicity, for example, such as a reduction in circulating blood cells, can be regarded variously as markers of exposure, as health effects in their own right, or as evidence of a link in the causal chain leading to cancer. These biomarkers of effect might be connected mechanistically to the eventual development of cancer through damage to DNA. The main markers investigated have been direct DNA damage, mutations, and structural and numerical chromosomal aberrations (Albertini et al. 2003a).

In a study of a Chinese cohort exposed in an occupational setting, there was evidence of chromosomal aberrations (chromosomal loss and an increase in breakage of chromosomes) at benzene concentrations as low as 1.6 mg/m^3. Exposure was associated with increased concentrations of urinary metabolites of benzene and reductions in blood counts. The various biomarkers tended to correlate with one another (Qu et al. 2003). There was no evidence of aneuploidy (an abnormal number of chromosomes) in peripheral-blood cells in this study. But in another study of a Chinese occupational cohort, aneuploidy was associated with exposures greater than 16 mg/m^3 (Zhang et al. 2005b). A third study, of 250 Chinese workers, found that white blood cell counts and platelet counts were significantly lower than for 140 controls even with exposures of less than 3.25 mg/m^3 (Lan et al. 2004).

In a recent study from Thailand, ambient benzene concentrations, individual benzene exposure, blood benzene, urinary t,t-MA, and cytogenetic markers (DNA-strand breaks and DNA-repair capacity) were investigated in gasoline service station attendants, roadside street vendors, and students in schools within 500 meters of a main road and compared with control populations exposed to low concentrations of benzene (Navasumrit et al. 2005). Differences in ambient concentrations were demonstrated and corresponded to differences in measurements of personal exposure and blood benzene. Exposure was correlated with urinary t,t-MA and cytogenetic abnormalities. Median ambient concentrations were 28 μg/m^3 for schools near main roads in Bangkok and 8.2 μg/m^3 for schools in provincial areas. These results suggested that biomarkers of exposure and effect might be sensitive to benzene concentrations experienced in community settings.

Biomarkers of Susceptibility

Biomarkers of susceptibility would be very useful in helping to determine acceptable exposure concentrations for susceptible individuals. Two genetic markers, CYP2E1 and NQO1, are associated with the variations in the ways benzene is metabolized. Little is known about the distribution of these genotypes in the general population. It has also been found that polymorphisms in the genes that regulate hematopoiesis through cytokines, chemokines, and cellular-adhesion molecules modify the hematotoxic effects of benzene (Lan et al. 2005). Knowledge of such genetically based variations in the response to benzene will be important in helping to define susceptible subpopulations.

CANCER

Most of the epidemiologic evidence on benzene and cancer is based on a relatively small number of studies of occupational cohorts. These cohorts tended to be studied repeatedly as additional workers died over the course of the years. Perhaps the most influential was the cohort of rubber-hydrochloride workers in three U.S. factories (the Pliofilm cohort) in a study conducted through the mid-1970s. The strengths of this cohort included good characterization of exposure to benzene and little coexposure to other potentially toxic substances (Rinsky et al. 1981, 1987). There was an increased risk of leukemia, predominantly of myeloid origin, with increasing exposure to benzene.* The risk of multiple myeloma was also increased, but this did not seem to be related to exposure. Another important study was of workers in 12 Chinese cities (Hayes et al. 1996, 2000). A variety of industrial processes were included, all of which involved exposure to benzene, among other substances. There was an increased risk for the larger grouping of "all hematologic neoplasms," with mixed evidence of dose-related responses for subcategories. Specifically, increased risks were observed for acute nonlymphocytic leukemias with or without myelodysplastic syndrome (preleukemia) and nonsignificant increases for non-Hodgkin's lymphoma. The benefit of the large sample size of this study was offset to some extent by the less well-characterized and more heterogeneous exposure, less standardization and validation of outcome measurements, and

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* The classification of cancers of the lymphohematopoietic system has undergone considerable change over the time spanned by these cohort studies. Leukemia mainly arises from stem or progenitor cells in the bone marrow. Leukemias are classified as myeloid or lymphoid according to whether they resemble normal cells of myeloid phenotype (granulocytic, monocytic, megakaryocytic, or erythroid) or lymphoid type (lymphocytes or plasma cells). If the malignant cells are well differentiated, the leukemia is classified as chronic; if undifferentiated, as acute. The main types of leukemia are chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, and acute myeloid leukemia (AML, also referred to as acute myelogenous leukemia). Myelodysplastic syndromes can develop into AML. Nonlymphocytic leukemia, a classification used by some studies, is leukemia of myelogenous origin.

less convincing reference populations. It has been argued that the exposure of these Chinese workers might have been underestimated (Wong 2002). Overall, however, the epidemiologic evidence points fairly convincingly toward a causal association between benzene exposure and leukemia.

It is reasonably clear that an association with leukemia exists under the exposure conditions in these occupational cohorts. However, it is less clear which model of exposure–response should be adopted for risk assessment at the lower end of occupational exposures and, by extrapolation, to the general population, which is exposed to benzene at even lower levels and as part of a different mixture of compounds arising from different sources. These uncertainties arise because nearly all the key inputs into models of exposure–response can be (and, in the literature, have been) questioned. For example, for the Pliofilm cohort, different approaches to estimating exposure and to statistical modeling resulted in large differences in risk estimates (Crump 1994). In the Chinese studies, questions have been raised about possible underestimation of exposures, confounding by other exposures, bias in the ascertainment of cases, the validation of causes of death, and the suitability of comparison populations (Wong 2002). The shape of the exposure–response curve is critical for extrapolation to ambient concentrations. While there have been arguments for various nonlinear models with or without a threshold, most investigators conclude that based on available evidence a linear model cannot be excluded.

New Evidence from Existing Occupational Cohort Studies

An extended follow-up of the Pliofilm cohort through 1996 was reported by Rinsky and colleagues (2002). At the time of the follow-up, it had been 20 years since any cohort member had been exposed. The follow-up provided further confirmation of the association between benzene exposure and the risk of leukemia. This association tended to decrease with time since exposure. Another comprehensive examination of the benzene exposure of the Pliofilm cohort suggested that other studies had over- or underestimated exposures to varying degrees (Williams and Paustenbach 2003).

One of the uncertainties remaining from earlier analyses of the Pliofilm cohort had been an increased risk of multiple myeloma (Rinsky et al. 1987) reported by some other occupational studies. It was noted that the risk of multiple myeloma in the cohort was not related to gradients of exposure. In the follow-up through 1996, analysis showed an increased but nonsignificant risk of multiple myeloma, though again no evidence of an exposure–response relationship (Rinsky et al. 2002).

Results from a follow-up of Dow chemical workers provided modest evidence for an increase in leukemia with increased cumulative benzene exposure. This was compared with a reduced mortality from major causes. The average exposure concentration of 31 mg/m^3 and average cumulative exposure of 129 mg/m^3-year were higher than those in most studies of refineries and distribution workers but similar to those of the lowest exposure grouping in the Pliofilm cohort (Bloemen et al. 2004). The study did not have the statistical power to provide a basis for extrapolation to the concentrations found in ambient air nor to clarify the specificity of benzene exposures for leukemia subgroups.

New Occupational Cohort Studies

Exposure to benzene might affect human health even at low concentrations. A nested case–control study of lymphohematopoietic cancers in the Health Watch cohort of Australian petroleum workers exposed to benzene concluded that excess leukemia risk (both acute nonlymphocytic and chronic lymphocytic leukemias) existed at cumulative benzene exposures lower than those observed in previous studies (higher than 6 mg/m^3-year) and that no threshold of cumulative exposure could be identified (Glass et al. 2003, 2005). No relationship with non-Hodgkin's lymphoma or multiple myeloma was found.

There is considerable interest in specifying the relationship between types of benzene (or benzene-related) exposures and types of lymphohematopoietic cancers. There is clear and widely accepted evidence from a variety of occupational studies that the risks of AML are increased, but the evidence for other lymphohematopoietic cancers is less clear. A review of available studies concluded that evidence for the risk of chronic lymphocytic leukemia was inconsistent and that evidence for the risk of chronic myeloid leukemia and acute lymphocytic leukemia was insufficient (Schnatter et al. 2005). In a meta-analysis of 26 occupational cohorts, no association with non-Hodgkin's lymphoma was observed overall or in any individual study (Wong and Raabe 2000). This conclusion was supported by a second review of existing evidence by the same investigators (Wong and Fu 2005).

Seventy-seven cases of leukemia in gas and electric utility workers were compared with 285 controls in a large nested case–control study in which benzene exposure was estimated using a job–exposure matrix (Guenel et al. 2002). The risk of leukemia was found to increase at cumulative exposures greater than or equal to 54.8 mg/m^3-year, with evidence of an exposure–response relationship. The risks of acute lymphocytic leukemia and AML were both increased, but there was apparently little affect on the risk of chronic leukemia. The exposures at which changes in risk were observed were lower than those reported for the Pliofilm cohort (130 mg/m^3-year). The median time-weighted

average (TWA) exposure to benzene was 0.52 mg/m^3 (90% of exposures were below 6.5 mg/m^3). The median cumulative exposure was 3.6 mg/m^3-year (90% of exposures were below 282 mg/m^3-year).

The association between peak and cumulative benzene exposure and lymphohematopoietic cancers was examined in a study of a cohort of chemical-production workers (Collins et al. 2003). The study suggested that peak exposures of more than 326 mg/m^3 are a better predictor of risk than cumulative exposure and that the risk of multiple myeloma might be more affected than that of other cancers. However, the study was too small to draw firm conclusions.

In a study from the U.K., a cohort of workers occupationally exposed to benzene in 233 companies since 1966 or 1967 was followed up for cancer registrations to 2001 and mortality to 2002 (Sorahan et al. 2005). Study subjects worked in a wide range of industries, some of which were associated with other potential hazards. Compared with population predictions, registrations and mortality for acute nonlymphocytic leukemia were increased, but there was no evidence of effects on other lymphohematopoietic cancers. While largely in line with other evidence that acute nonlymphocytic leukemia is associated with benzene exposure, the study did not yield information on exposure–response relationships at lower concentrations. The use of registrations was a strength of the study, given recent improvements in the survival rates for various leukemias. But in this study, the registration results were somewhat less conclusive than those for mortality.

Community Exposure Studies

A number of community studies have examined the association between the incidence of leukemia and proximity to sources of benzene (and other hydrocarbons), such as petrochemical works and gas stations (Knox and Gilman 1997; Harrison et al. 1999; Wilkinson et al. 1999; Reynolds et al. 2003; Steffen et al. 2004). All but one of these (Wilkinson et al. 1999) observed an association with childhood leukemia. An English study and a French study examined proximity to gas stations and reported positive associations (Harrison et al. 1999; Steffen et al. 2004). In the larger of these two studies, the risks of both acute non-lymphocytic leukemia and acute lymphocytic leukemia were increased (Steffen et al. 2004). A study in California found evidence of an association between childhood leukemia and modeled exposure to hazardous air pollutants originating from all sources (Reynolds et al. 2003). These studies pointed to the possibility that community exposure to organic compounds, including benzene, might cause childhood leukemia. Although it is not possible to single out benzene at this time, it is notable that both the English and French studies found an association with living near a gas station (benzene is a major constituent of gasoline vapor).

A number of studies have investigated the relationship between traffic exposure and childhood leukemia. Four of these found evidence of positive associations (Savitz and Feingold 1989; Nordlinder and Jarvholm 1997; Feychting et al. 1998; Harrison et al. 1999). Three found little or no evidence of an association (Raaschou-Nielsen et al. 2001; Langholz et al. 2002; Steffen et al. 2004).

The lack of consistency in the results of these community studies might be explained by variations in design, power, definition of exposure, window of exposure, and definition of outcome. Overall, however, the body of evidence points to an association between childhood leukemia and exposure to mixtures that contain benzene. Indeed, in view of what is already known from occupational and animal studies, a causal link between childhood leukemia and benzene exposure seems plausible.

Occupational Exposure during Pregnancy and Risk of Leukemia in Offspring

There is evidence associating childhood leukemia with the occupational exposure of parents to hydrocarbons (Buckley et al. 1989; McKinney et al. 1991; Shu et al. 1999), though some studies have found no association (van Duijn et al. 1994). The association, if causal, has important implications for the risks of community exposure, because it points to the possibility that the critical window of exposure is during the time of conception or in early pregnancy. None of these studies have been able to demonstrate that benzene is the hydrocarbon responsible for the association observed.

NONCANCER HEALTH EFFECTS

Acute exposure to very high concentrations of benzene (several thousand mg/m^3) is associated with anesthetic effects and severe damage to the blood-forming elements of the bone marrow. But this is not relevant to ambient exposures from mobile sources, which are lower by many orders of magnitude. The acute exposure guideline level one (AEGL-1), for minor effects on health, is based on a no observed adverse effect level (NOAEL) of 3.40×10^5 μg/m^3 observed in studies of humans (EPA 2006a). No new evidence is available since the guidelines were set. The AEGL-2, for more serious effects on health, is based on a NOAEL of 1.24×10^7 in inhalation studies in animals. These concentrations were far higher than those associated with mobile sources.

Effects on Reproductive Health

Animal studies have found that various reproductive outcomes, such as birth weight, are affected by benzene exposure; the evidence for effects on human fertility is inconclusive. There is little recent human evidence. The risk of congenital malformations was investigated in a study of women working in biomedical-research laboratories (Wennborg et al. 2005). Although it was a small study (1951 pregnancies), exposure to solvents before the third trimester was significantly associated with an increased risk of major malformations. The risk associated with the use of benzene around the time of conception or organogenesis was even higher.

Hematologic Effects

Benzene exposure can lead to hematotoxicity, which is important not only as a health effect in its own right, but also as a biomarker and risk factor for leukemia (Rothman et al. 1997). Criteria for studying the effects of benzene exposure (both orally and by inhalation) have been developed. The reference concentration (RfC) and California EPA reference exposure level (REL) for benzene (30 μg/m^3 and 60 μg/m^3, respectively; EPA 2003b; California EPA 2005a) are based on evidence that inhalation of benzene has effects on circulating blood cells in humans (EPA 2003b).The most influential study of hematologic effects was a study of 44 exposed workers and nonexposed control subjects in Chinese factories (Rothman et al. 1996). Reductions in circulating lymphocytes were observed at 8-hour TWA median exposures as low as 24 mg/m^3. The ATSDR inhalation minimal-risk level (MRL) is 0.2 mg/m^3 and is based on immunologic effects observed in mice.

More recent studies in occupational settings have revealed effects on hematologic indices at even lower benzene concentrations. Qu and colleagues (2002) studied peripheral-blood counts and white blood cell differential counts in 130 benzene-exposed workers and 51 age- and sex-matched controls. Personal benzene exposures in the exposed workers ranged from 0.2 to 398 mg/m^3 on the day of biologic sampling, and their 4-week averages ranged from 3.3 to 178 mg/m^3. The researchers observed an exposure–response relationship between increasing exposure and reductions in red and white blood cells, as well as in neutrophils. Compared with control subjects, effects were observed even in the group with the lowest exposures (0.82 mg/m^3 and lower). The reductions in red and white blood cells and in neutrophils were correlated with various biomarkers of exposure, including urinary metabolites and albumin adducts. A prospective study of 250 workers in three Chinese shoe factories and 140 controls found that white blood cell and platelet counts decreased, even in the group with the lowest exposures (Lan et al. 2004). Mean exposure concentrations ranged from less than 3 mg/m^3 to more than 33 mg/m^3. Hemoglobin concentrations were reduced only in the highest exposure group. Progenitor-cell-colony formation declined with increasing exposure and was the most sensitive of all the cell markers. Two genetic variants in the enzymes that metabolize benzene, myeloperoxidase and NAD(P)H:quinone oxidoreductase, were related to the declines in cell counts. A letter to the editor challenged the clinical significance of the findings at the lower exposures (Lamm and Grunwald 2006). The authors responded that the declines in blood cell counts were not of immediate concern but that the effects on progenitor cells were more pronounced and should be a matter of concern because they reflected alterations in bone marrow that might be associated with health effects in the future.

In contrast to the studies reported above, a recent study of U.S. petrochemical workers using routine monitoring data found no association between mean benzene exposures (8-hour TWA) of 0.46 to 1.9 mg/m^3 and any hematologic indicator (Tsai et al. 2004). This disparity might be explained by differences in the concentration and distribution of exposure between the U.S. and Chinese workers. Alternatively, the differences might lie in the fact that the Chinese studies were purposely designed to test the hypothesis and were thus superior in their exposure assessment and timing of biologic sampling in relation to exposure. While there is increasing evidence that effects on hematologic indices might occur at exposure concentrations lower than 3.26 mg/m^3, considerable uncertainty remains as to what is the lowest concentration associated with these effects.

REGULATORY SUMMARY

Benzene is classified by the IARC (1987) as Group 1 ("carcinogenic to humans") and by the EPA (1998a, 2003b) as Group A ("a known human carcinogen"). These classifications are based on evidence from both humans and animals. Various risk assessments have been carried out for the purpose of defining acceptable occupational and ambient exposure concentrations. These have generally relied on evidence from occupational studies (California EPA 2005a; U.K. Department for Environment, Food and Rural Affairs 2006; EPA 2000d; ATSDR 2005d).

The EPA (2003b) has estimated a lifetime cancer risk of 2.2×10^{-6} to 7.8×10^{-6} from 1 μg/m^3 benzene exposure over a lifetime—a concentration similar to that measured in ambient air. The risk estimate is based largely on evidence from a cohort of rubber workers (the Pliofilm cohort)

in which exposure to benzene was not associated with exposure to other chemicals (Rinsky et al. 1981, 1987; Paustenbach et al. 1993; Crump 1994). The California EPA calculated a cancer unit risk factor (URF) of 2.9×10^{-5} from 1 µg/m^3 benzene exposure over a lifetime (California EPA 2002), based on leukemia risk after occupational exposures (Rinsky et al. 1981).

For the purposes of reference values, however, much reliance has been placed on a small quantity of evidence from occupational studies that found an association between very low exposure concentrations and detectable abnormalities in blood cells, measured as absolute lymphocyte counts (Rothman et al. 1996). On this basis, together with some evidence from animal studies, the EPA determined a chronic inhalation RfC of 30 µg/m^3 benzene based on a benchmark concentration of 8.2 mg/m^3 benzene that was found to be associated with decreased lymphocyte counts in an occupational study (Rothman et al. 1996) and based on applying an uncertainty factor of 300. Using much the same evidence, the California EPA (2005a) determined an inhalation REL of 60 µg/m^3 for benzene based on a lowest observed adverse effect level (LOAEL) of 1.73 mg/m^3, an average occupational exposure of 60 µg/m^3, and an uncertainty factor of 10 (Tsai et al. 1983). In contrast, in the U.K., the occupational risk of cancer together with several safety factors was used to set an ambient standard of 16 µg/m^3 (with a target of 3 µg/m^3) (U.K. Department for Environment, Food and Rural Affairs 2006). Other regulatory standards include a maximum concentration of 1 mg/m^3 benzene in Cambodia (Kingdom of Cambodia 2000) and annual average concentrations of 3 µg/m^3 in Japan (Japan Ministry of the Environment 2005a), 20 µg/m^3 in Nepal, 10 µg/m^3 (with a target of 3.6 µg/m^3 to be achieved by 2010) in New Zealand, 10 µg/m^3 in Germany and Italy, 5 µg/m^3 in the Netherlands, and 16.25 µg/m^3 (as an annual running mean) in the U.K. (U.K. National Air Quality Archive 2006b). Austria has proposed an annual average concentration of 10 µg/m^3 as a standard and 2.5 µg/m^3 as a long-term target. Portugal has proposed an annual concentration of 10 µg/m^3 as a standard, and Sweden has set guidelines of 1.3 µg/m^3 for annual average concentrations (and a 5 µg/m^3 annual mean concentration to be achieved by 2010) (European Commission 1982; Swedish Environmental Protection Agency 1999; Bangladesh Department of Environment 2005; Netherlands Environmental Assessment Agency 2005; Clean Air Initiative–Asia 2006). The European Commission has recommended an annual average concentration of 5 µg/m^3 (with a 100% tolerance level of 10 µg/m^3) as a target to be met by 2010 (European Union 1998).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

On-road mobile sources account for half of the benzene found in ambient air; tobacco combustion is a major source in indoor air. A relatively large and growing database of measures of environmental concentrations exists for benzene, in contrast to other mobile-source air toxics. Mean ambient, outdoor, and indoor concentrations of benzene typically range from 1 to 10 µg/m^3. Peak concentrations range from 14.9 µg/m^3 in rural settings to 110 µg/m^3 in residences. The highest mean concentrations are found in urban roadside (22 µg/m^3) and urban in-vehicle (17 µg/m^3) locations, where close proximity to direct motor-vehicle emissions is likely. Over the past several years, urban ambient concentrations of benzene have decreased. Seasonal data indicate that ambient benzene concentrations tend to peak during the cooler months. Personal exposures to benzene appear to be in the same range as ambient concentrations. Based on 1999 data, the NATA found mean benzene concentrations of 1.4 µg/m^3 overall, 1.56 µg/m^3 for urban areas, and 0.56 µg/m^3 for rural areas (EPA 2006b). A comparison with historical data suggests that current ambient and indoor concentrations and personal exposures to benzene are lower than those observed in the 1980s.

Differences in sampling and sample analysis might have influenced the absolute concentrations reported in the various studies, but it was beyond the scope of this report to assess such differences. Smoking, for example, in the environment sampled would probably have affected the observed concentrations. Additional limitations sometimes included the number and type of environments sampled, the number of samples collected, methods of accounting for the presence or absence of sources, the extent of geographic and seasonal variability, the representativeness of residences and populations sampled, and the extent of sampling for sensitive or at-risk populations.

TOXICITY

The carcinogenicity of benzene depends on how it is metabolized, but it is not certain which metabolites (or combinations of metabolites) are carcinogenic. Probable candidates are the metabolites benzoquinone and *t,t*-muconaldehyde, which are known to cause the type of clastogenic damage induced by exposure to benzene. Benzene metabolism also produces reactive oxygen species, which can lead to oxidative damage to DNA and interference with DNA repair. No good animal models are known for the benzene-induced AML associated with human exposures to

benzene. However, benzene is hematotoxic in mice. It is carcinogenic in both rats and mice; mice are the more sensitive of the two species. Humans metabolize benzene more like mice than like rats, suggesting that humans are sensitive to benzene in ways similar to mice.

HUMAN HEALTH

From epidemiologic studies, it is clear that there is an association between occupational exposure to benzene and the development of AML. There is less clarity about which model of exposure response should be adopted in assessing risk at the lower end of occupational exposures or, by extrapolation, to the general population, which is exposed to benzene at even lower concentrations and in mixtures of various compounds arising from various sources. The EPA's current risk assessment proposes a lifetime cancer risk of 2.2×10^{-6} to 7.8×10^{-6} for an exposure of 1 μg/m^3 over a lifetime (EPA 2003b)—an exposure that is similar to that measured in ambient air today. More recent studies have shown effects on hematologic indices even at low chronic occupational exposures—i.e., at or below 0.82 mg/m^3. Hematotoxicity is important not only as a human health effect in its own right, but also as a biomarker and risk factor for leukemia. Recent research on biomarkers of benzene exposure and its effects indicates that such markers might be sensitive to concentrations encountered in ambient air.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of benzene?

Mobile sources contribute almost half the benzene found in ambient air. There are other important sources of exposure, including smoking and environmental tobacco smoke.

2. Does benzene affect human health?

It is clear that there is an association between occupational exposure to benzene and the development of AML.

3. Does benzene affect human health at environmental concentrations?

Recent studies have shown effects on hematologic indices even at benzene concentrations that are lower than those of most occupational exposures (i.e., at or below 0.82 mg/m^3) but still higher than those of most ambient exposures. Community studies in which benzene is only one of many potential carcinogens in the air have shown inconsistent associations with cancer incidence.

RESEARCH GAPS AND RECOMMENDATIONS

It is known that benzene is a carcinogenic health hazard, specifically for acute nonlymphocytic leukemias with or without myeloidysplastic syndrome; the association with non-Hodgkin's lymphoma needs to be clarified. The exposure–response relationship, especially at the observed or extrapolated low concentrations found in occupational and ambient air, needs to be clarified as well. It is likely that there will be no feasible new epidemiologic approaches capable of directly assessing the risk of benzene exposure at current ambient concentrations. This is because exposures are characteristically low, the incidence of known relevant health effects is small, and benzene is encountered as part of a complex mixture of potential carcinogens. All of these make it very difficult to associate specific health effects with exposure to benzene in ambient air. There would appear to be little more to be gained by new analyses of existing cohorts or by meta-analysis. These have already been done. The only feasible epidemiologic approach would probably use biomarkers of benzene exposure and toxicity. Research recommendations for benzene include the following:

- New epidemiologic studies at low benzene exposure concentrations should include extensive use of biomarkers of exposure, effects, and susceptibility to permit better classification of exposure groups and determination of toxicity.
- Continue the development of sensitive analytical biomarkers of exposure, effect, and susceptibility.
- Validate biomarkers used as predictors of adverse health effects in worker cohorts exposed to benzene.
- Use the biomarkers to better characterize the shape of the benzene exposure–response curve at low ambient concentrations.
- Elucidate the possible association between exposure to benzene and non-Hodgkin's lymphoma.

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