ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR BENZENE

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ADDENDUM for BENZENE
Supplement to the 2007 Toxicological Profile for Benzene

Background Statement

This addendum to the Toxicological Profile for Benzene supplements the profile that was released in 2007.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances. CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 2007.

Chapter numbers in this addendum coincide with the Toxicological Profile for Benzene (2007). This document should be used in conjunction with the profile. It does not replace it.

3. HEALTH EFFECTS

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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Hepatic Effects. Uzma et al. (2008) evaluated peripheral blood from 154 healthy benzene-exposed male filling station attendants (94 with <10 years of exposure and 60 with >10 years of exposure); a control group of 33 healthy subjects matched for demographics was included. Analysis included evaluation of serum total protein, albumin, total bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST) as indicators of liver function. There were no significant differences between controls and filling station attendants regarding serum total protein, albumin, total bilirubin, and AST. Statistically significantly lower mean serum ALP and ALT (18 and 35% lower, respectively, than controls) were noted in the filling station attendants. The study is limited by small numbers of subjects, lack of measured benzene levels, and lack of accounting for exposure to other potential toxicants.

Hematological Effects. Uzma et al. (2008) evaluated peripheral blood from 154 healthy benzene-exposed male filling station attendants (94 with <10 years of exposure and 60 with >10 years of exposure); a control group of 33 healthy subjects matched for demographics was included. Analysis included total white blood cell and differential leukocyte counts. Among the controls, lymphocytes accounted for 37.92% ±1.89 (standard deviation [SD]) of total white blood cells; decreased percentages of lymphocytes were noted for filling station attendants (32.3% ±1.65 for attendants with <10 years of exposure, p=0.056; 29.3±1.76 for attendants with >10 years of exposure, p=0.03). Exposure duration-related significantly decreased absolute numbers of lymphocytes were noted as well. The study is limited by small numbers of subjects, lack of measured benzene levels, and lack of accounting for exposure to other potential toxicants.

Li et al. (2009) evaluated selected hematological parameters in peripheral blood from 68 healthy benzene-exposed workers whose workplace air benzene levels measured 37.8 mg/m^3 (11.7 ppm) and 27 healthy subjects without documented occupational exposure to benzene (control subjects). There were no statistically significant differences between the groups regarding red blood cell or white blood cell counts or hemoglobin or platelet levels. The study report included findings of significantly decreased white blood cell and red blood cell counts, hemoglobin, and platelets within groups of workers from a variety of workplaces who had been diagnosed with mild (n=23), medium (n=12), or severe (n=35) chronic benzene

poisoning (diagnosis based on white blood cell counts). However, benzene exposure levels were not presented for the groups with diagnosed chronic benzene poisoning.

Schnatter et al. (2010) evaluated 12 peripheral blood indices within a group of 928 workers in five factories in the area of Shanghai, China, who were exposed to estimated weekly benzene levels ranging from 0.07 to 872 mg/m^3 (0.02–270 ppm); the median benzene air concentration was 7.4 mg/m^3 (2.3 ppm). Estimates of benzene levels were based on individual monitoring. At exposure levels >10 ppm, effects on peripheral blood were noted for red cell indices such as anemia and macrocytosis. Decreases in neutrophils and mean platelet volume were noted at benzene air concentrations in the range of 7.8–8.2 ppm.

Swaen et al. (2010) evaluated hematological parameters in 8,532 blood samples from Dow employees with low benzene exposure (8-hour time-weighted average [TWA] mean benzene concentrations in the range of 0.06–1.24 ppm and 12,173 blood samples from employees with no exposure to benzene. There was no indication of benzene-induced effects on any hematological parameter. Upon stratification of the benzene-exposed population into subgroups according to benzene level (<0.5, 0.5–1, and >1 ppm), there were no significant differences in hematological parameters among the three groups or between benzene-exposed groups and unexposed controls.

3.2.1.3 Immunological and Lymphoreticular Effects

Kirkeleit et al. (2006) investigated the effects of benzene exposure on selected immunological end points among 10 workers exposed to benzene while maintaining cargo tanks containing crude oil residues on a crude oil vessel; a group of 9 catering workers on the same vessel served as referents. Individual benzene exposure was measured daily during a study period that spanned three consecutive 12-hour work shifts. Blood and urine samples were collected at baseline (prior to the first work shift), at the end of the third work shift, and prior to the work shift on the day following the three consecutive work shifts for evaluation of blood and urine benzene levels; blood levels of lymphocytes (total lymphocytes, lymphocytes in subpopulations CD3, CD4, CD8, CD19, CD56, and CD4/CD8 ratio) and complement factors C3 and C4 were determined as well as serum levels of immunoglobulins IgA, IgE, IgG, and IgM. The mean measured benzene air concentration was 0.15 ppm (range 0.01–0.62 ppm) for the tank workers. Mean measured post-shift blood benzene levels were 12.3 nmol/L (range 2–38 nmol/L) for the tank workers and 0.7 nmol/L (0.5–1.0 nmol/L) for the referents. Mean measured post-shift urinary benzene levels were 27.0 nmol/L (range 3.0–333 nmol/L) for the tank workers and 0.7 nmol/L (range 0.5–2.0 nmol/L) for the referents. At baseline, mean serum IgM was significantly lower in the tank workers

than in the referents. Baseline to post-shift IgM declined by 4.9% among the tank workers, but increased by 5.1% among the referents. Baseline to post-shift IgA declined by 5.1% among the tank workers, but increased by 0.6% among the referent. The declines in IgM and IgA among the tank workers were statistically significant. The tank workers also exhibited significantly decreased blood CD4 T cell levels from baseline to post-shift. Mean serum IgE among the tank workers was 30% that of controls (36.7 kU/L; 95% confidence interval [CI] 0, 76.2 compared to 123 kU/L; 95% CI 2.75, 243); however, based on wide individual variation in serum IgE, the mean serum IgE values were not statistically significantly different (p=0.15). There were no statistically significant benzene exposure-related effects on IgG; blood levels of total lymphocytes or lymphocyte subpopulations CD3, CD8, CD19, CD56, or CD4/CD8 ratio; or complement factors C3 or C4. The study authors stated that serum levels of IgG and IgE were not significantly correlated with any measure of exposure.

Lan et al. (2005) measured selected hematological parameters in peripheral blood from 49 benzene-exposed workers in shoe-manufacturing factories (measured workplace air level of 15.8±17.9 ppm [mean±SD]) and 45 unexposed controls from clothing-manufacturing factories in the same vicinity. The benzene-exposed workers exhibited significant decreases in white blood cell count and numbers of granulocytes (18–23% lower than control values) and borderline significantly (p=0.054) decreased lymphocyte count (10% lower than controls). Lymphocyte subset analysis revealed significant decreases in numbers of B cells and CD4+-T cells and CD4+/CD8+ ratio. These findings are in concordance with the results of Lan et al. (2004a, 2004b) summarized in the current Toxicological Profile for Benzene.

Brandão et al. (2005) compared lymphocyte subpopulation between 24 subjects with diagnosed chronic benzene poisoning and 24 subjects with other diagnosed occupational diseases in Brazil. The group of chronic benzene poisoning subjects exhibited significantly greater proportion of T-cytotoxic cells (TCD8) controls and significantly lower proportion of T-helper memory cells (CD4CD45RO) than controls. A meaningful association between exposure to benzene and altered lymphocyte subpopulations is precluded by small numbers of subjects, absence of benzene exposure data, and lack of comparative data for healthy controls.

Li et al. (2009) measured levels of T-cell receptor excision DNA circles in peripheral blood mononuclear cells (an indicator of recent thymic output function) from 68 benzene-exposed workers (measured benzene concentration in the workplace air averaged 37.8 mg/m^3 [11.7 ppm]). A control group consisted of 27 healthy subjects without documented benzene exposure. Levels of T-cell receptor excision DNA

circles in the benzene-exposed group were significantly lower than those of controls, indicating that benzene may have impaired thymic output function and T-cell immune function.

3.2.1.4 Neurological Effects

Lee et al. (2007) reported a significant trend ($p<0.05$) for increased prevalence of acquired dyschromatopsia (partial color blindness) in the left eye (but not the right eye) with increasing benzene exposure (mean exposure levels ranging from 0.27 to 2.43 ppm-years) among 736 workers employed in a petrochemical distillation factory compared with 172 non-exposed office workers. Prevalence of dyschromatopsia was significantly correlated with age and duration of work. The results indicate that chronic low-level exposure to benzene may lead to acquired dyschromatopsia, which may be a relatively sensitive indicator of neurological damage.

3.2.1.5 Reproductive Effects

Katukam et al. (2012) collected semen samples from 160 workers with occupational exposure to benzene and 200 unexposed age- and sex-matched control subjects and evaluated semen volume and sperm quality. The benzene-exposed workers were grouped according to duration of exposure (group 1, 0–5 years of exposure, n=52; group 2, 5–10 years of exposure, n=73; group 3, 10–15 years of exposure, n=35). There were no statistically significant differences between controls and benzene-exposed groups regarding macroscopic semen characteristics (e.g., volume, appearance, pH, viscosity, liquefaction). However, the benzene-exposed workers exhibited exposure duration-related statistically significant effects that included decreases in total sperm count and sperm motility, increased percentages of morphologically abnormal sperm, and increased sperm comet tail length (a measure of DNA integrity). The study report did not include evaluation of reproductive success.

3.2.1.6 Developmental Effects

In a population-based case-control study in Texas, Lupo et al. (2011) evaluated possible associations between maternal exposure to ambient air levels of selected pollutants (including benzene) and risk of neural tube defects (spina bifida, anencephaly). Ambient air levels for each pollutant were obtained from the U.S. Environmental Protection Agency (EPA) 1999 National-Scale Air Toxics Assessment (EPA 2011) that employed the Assessment System for Population Exposure Nationwide (ASPEN) model (EPA 2015). For benzene, estimated air levels ranged from 0.12 to 7.44 $\mu g/m^3$ (0.037–2.28 ppb) and were grouped into ranges described as low (0.12–0.45 $\mu g/m^3$; referent), medium-low (>0.45–0.98 $\mu g/m^3$), medium (>0.98–1.52 $\mu g/m^3$), medium-high (>1.52–2.86 $\mu g/m^3$), and high (>2.86–7.44 $\mu g/m^3$). Compared to the referent group, significantly increased risk of spina bifida was associated with the

medium-low (odds ratio [OR] 1.77; 95% CI 1.04, 3.00), medium (OR 1.90; 95% CI 1.11, 3.24), and high (OR 2.30; 95% CI 1.22, 4.33) exposure groups. The medium-high exposure group exhibited an OR of 1.40 (95% CI 0.82, 2.38), indicating the lack of a monotonic exposure-response relationship. There was no significant association between estimated benzene exposure level and risk of anencephaly. Zahran et al. (2012) reported significantly increased risk of low birth weight with increasing benzene level in ambient air in a study of resident births in the United States. Ramakrishnan et al. (2013) found no significant association between estimated ambient air benzene levels and risk of oral cleft among offspring of mothers who delivered in Texas between 1999 and 2008. However, these population-based studies are of limited usefulness for hazard identification because they did not include measurements of individual benzene exposure; ambient air benzene levels were census-tract estimates of annual air levels using models developed for the U.S. EPA National Air Toxic Assessment (EPA 2013a, 2015).

3.2.1.7 Cancer

As summarized in the 2007 ATSDR Toxicological Profile for Benzene (Agency for Toxic Substances and Disease Registry 2007), the International Agency for Research on Cancer (IARC 1982) determined that benzene is carcinogenic to humans based on sufficient evidence including a demonstrated relationship between benzene exposure and development of acute myelogenous leukemia (AML; also known as acute myeloid leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia). At that time, IARC (1982) determined that there was limited evidence that benzene was carcinogenic to laboratory animals. The evidence for benzene-induced carcinogenicity in humans was strengthened by results from subsequent epidemiological studies in which exposure to benzene was associated with leukemia (IARC 1987).

More recently, IARC convened a Working Group to reassess the carcinogenicity of benzene by evaluating numerous cohort and case-control studies of leukemia or its subtypes, non-Hodgkin's lymphoma (NHL), multiple myeloma, and other tumor types in adults and children, as well as several meta-analyses for selected tumor sites; results were published in the IARC Monograph Volume 100F (IARC 2012). Based on extensive evaluation of available occupational cohort studies and case-control studies, the Working Group reaffirmed its earlier designation that benzene is carcinogenic to humans (Group 1) based on sufficient evidence that benzene causes AML in humans. The Working Group considered the evidence for associations between exposure to benzene and acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), multiple myeloma, and NHL sufficient to consider the associations positive, although in most cases, observed associations did not reach the level of statistical

significance. Review of available animal studies resulted in the determination that there is sufficient evidence for the carcinogenicity of benzene in experimental animals.

Individual epidemiological studies published subsequent to the time period encompassed by the IARC (2012) publication include a study in which NHL incidence was significantly higher in census tracts that were closer, on average, to benzene release sites (Bulka et al. 2013), a population-based prospective occupational cohort study in which risk of NHL was significantly associated with women ever exposed to benzene (Bassig et al. 2014), a hospital-based case-control study in which no significant association was found between exposure to benzene (as determined from self-reported occupational history) and risk of NHL or lymphoproliferative syndrome (Orsi et al. 2010), a hospital-based case-control study in which no significant association was found between exposure to benzene (as determined from self-reported occupational or nonoccupational exposure) and risk of chronic myelomonocytic leukemia (Gross et al. 2012), and a nested case-control study of petroleum workers in which no convincing association was found between risk of chronic myeloid leukemia or myeloproliferative disease and relatively low level benzene exposure (average 0.17 ppm for myeloproliferative disease cases, 0.3 ppm for chronic myeloid leukemia cases) (Glass et al. 2014).

Reports from several recent meta-analyses were not available to the Working Group. Vlaanderen et al. (2011) evaluated possible associations between occupational exposure to benzene and risk of lymphoma subtypes (Hodgkin's lymphoma, NHL, multiple myeloma, ALL, and CLL). Results from all peer-reviewed occupational cohort studies (identified from PubMed searching) that reported results for any of the lymphoma subtypes were included in the meta-analysis. The impact of individual study quality variation on risk was evaluated using stratification by strength of the reported association between benzene exposure and acute myelogenic leukemia (commonly been associated with benzene exposure), by year of start of follow-up (prior to 1970 versus during or after 1970), and by quality of benzene exposure assessment. The meta-relative risks (mRRs) for multiple myeloma, ALL, and CLL increased with increasing quality of reported ALL association, more recent start of follow-up, and increasing quality of benzene exposure assessment. The mRRs for NHL increased in a similar, but less pronounced, manner. There was no evidence of an association between occupational exposure to benzene and risk of Hodgkin's lymphoma. Vlaanderen et al. (2012) similarly designed a meta-analysis of possible associations between occupational exposure to benzene and risk of chronic myeloid leukemia. The overall mRR was nonsignificantly elevated; mRRs increased with increasing study quality for all dimensions with a significant elevation for studies with start of follow-up after 1970. The results of Vlaanderen et al. (2011, 2012) provide support for possible associations between occupational exposure

to benzene and risk of selected lymphoma subtypes (multiple myeloma, ALL, and CLL, and NHL) and risk of chronic myeloid leukemia.

Schnatter et al. (2012) updated three nested case-control studies on cohorts of petroleum distribution workers in Canada (Schnatter et al. 1996), the United Kingdom (Rushton and Romaniuk 1997), and Australia (Glass et al. 2003), and pooled the cases and controls in a meta-analysis. The Canadian study included 31 case subjects (gender ratio not specified) with lymphohematopoietic cancers (including 16 cases of leukemia) who died within the time period of 1964–1983, each paired with 4 male age-matched controls; an update was performed for the years 1984–1994 and included 29 additional cases. The United Kingdom study included 90 case subjects (men) with leukemia who died prior to 1993, each paired with 4 male age-matched controls; an update was performed through 2005 and included 103 additional cases. The Australian study included 79 case subjects (men) with lymphohematopoietic cancers identified between 1981 and 1999, each matched to 5 controls; an update was performed through 2006 and included 38 additional cases. The pooled study thus included 370 case subjects and 1,587 controls. There were 168 cases of leukemia (60 cases of acute myeloid leukemia, 28 cases of chronic myeloid leukemia, and 80 cases of CLL), 59 cases of other myeloid disorders (29 cases of myelodysplastic syndrome and 30 cases of myeloproliferative disease), and 143 cases of "other diagnoses" (NHL, multiple myeloma, and diagnoses with too few cases for statistical analysis). After controlling for age, sex, and time period, a significant dose-response association was observed between cumulative benzene exposure and myelodysplastic syndrome (OR 4.33; 95% CI 1.31, 14.3; highest versus lowest tertile, >2.93 versus ≤0.348 ppm-years). In the pooled analysis, no significant association was observed between measures of benzene exposure and risk of acute or chronic myeloid leukemia, CLL, or myeloproliferative disease.

Two other meta-analyses evaluated possible associations between exposure to benzene and risk of NHL (Alexander and Wagner 2010; Kane and Newton 2010). The meta-analysis of Alexander and Wagner (2010) included 8 cohort studies with quantitative benzene exposure estimates, industrial hygiene records, job-exposure matrices, or benzene-specific work history information; and 14 case-control studies for which benzene exposure had been analyzed as an independent variable. No significant associations were observed between benzene exposure and risk of NHL for measures of any measure of benzene exposure (i.e., any benzene exposure, highest level of benzene exposure, and meta-analysis of 5 studies that reported results for ≥60 ppm-years). The meta-analysis of Kane and Newton (2010) included 6 cohort studies, 16 case-control studies, and 2 studies of other designs (all studies were published in peer-reviewed journals and reported relative risks and CIs of NHL associated with benzene exposure or

provided sufficient information from which to compute relative risk with CI). Twenty-two of the studies found no association between NHL and ever exposed to benzene compared to never exposed. Random-effects meta-analysis resulted in a pooled risk estimate of 1.11 (95% CI 0.94, 1.30). Among six studies for which benzene exposure was estimated from historical measurements, there were no statistically significant associations between benzene exposure and risk of NHL relative to increasing cumulative, average, peak, or duration of benzene exposure.

3.2.2 Oral Exposure

3.2.2.1 Death

In a study of male Sprague-Dawley rats (6/group) administered benzene (in distilled water vehicle) by gavage once per day for up to 14 days at 0 (controls), 0.5 mL/kg body weight (440 mg/kg), or 1.0 mL/kg (880 mg/kg), all high-dose rats died prior to treatment day 10 (Singh and Bansode 2011).

3.2.2.2 Systemic Effects

Hematological Effects. The National Toxicology Program (NTP 2007) administered benzene to groups of male and female haploinsufficient p16Ink4a/p19Arf mice (15/sex/group) by gavage (in corn oil) once/day, 5 days/week for 27 weeks at 0, 25, 50, 100, or 200 mg benzene/kg/day. All benzene-treated groups of male mice and the 100 and 200 mg/kg/day groups of female mice exhibited significantly decreased numbers of erythrocytes, leukocytes, and lymphocytes, and significantly decreased mean cell volume at weeks 13 and 27 of treatment; the 50 mg/kg/day group of female mice also exhibited significantly decreased numbers of leukocytes and lymphocytes at weeks 13 and 27. Significantly decreased hematocrit and hemoglobin were observed at weeks 13 and 27 at doses ≥50 mg/kg/day in males and in the high-dose females. At week 27 (but not week 13), significantly decreased numbers of segmented neutrophils were observed in male mice dosed at ≥50 mg/kg/day. Male mice exhibited significantly increased incidence of hemosiderin pigmentation in bone marrow at all benzene dose levels, significantly increased incidence of bone marrow atrophy and lymphoid follicle atrophy in the spleen at the two highest dose levels, and significantly increased incidence of hematopoietic cell proliferation in the spleen at the highest dose. There were no indications of treatment-related effects on spleen or bone marrow of female mice.

Body Weight Effects. Treatment-related effects on body weight were reported in a study of male Sprague-Dawley rats (6/group) administered benzene (in distilled water vehicle) by gavage once per day for up to 14 days at 0 (controls), 0.5 mL/kg body weight (440 mg/kg), or 1.0 mL/kg (880 mg/kg) (Singh and Bansode 2011). Mean final body weight of the low-dose group was not significantly different from

that of controls; however, the high-dose group lost 5% of its initial mean body weight (final mean body weight 22% less than that of controls) and all high-dose rats had died prior to treatment day 10. Significantly decreased food and water intakes were noted in the high-dose group during treatment days 4–9 and in the mid-dose group at most time points from treatment day 8 onward.

NTP (2007) administered benzene to groups of male and female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (15/sex/group) by gavage (in corn oil) once/day, 5 days/week for 27 weeks at 0, 25, 50, 100, or 200 mg benzene/kg/day. Male mice exhibited dose-related lower mean body weight than controls, which was most notable for treatment weeks 14–27, at which time body weights of the 25, 50, 100, and 200 mg/kg dose groups were 9, 12, 22, and 24%, respectively, less than that of controls. Mean body weight of benzene-treated female mice were generally within 2% that of controls throughout the treatment period, with the exception of the high-dose females that exhibited 7% lower mean body weight for the period of 14–27 weeks.

3.2.2.3 Immunological and Lymphoreticular Effects

NTP (2007) administered benzene to groups of male and female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (15/sex/group) by gavage (in corn oil) once/day, 5 days/week for 27 weeks at 0, 25, 50, 100, or 200 mg benzene/kg/day. Male mice exhibited dose-related increased incidences of atrophy of thymus and lymph nodes (mandibular, mediastinal, and mesenteric) that reached the level of statistical significance in the two highest dose groups. Female mice exhibited dose-related increased incidences of mesenteric lymph node atrophy that reached the level of statistical significance in the two highest dose groups.

3.2.2.5 Reproductive Effects

Treatment-related effects on selected reproductive end points were reported in a study of male Sprague-Dawley rats (6/group) administered benzene (in distilled water vehicle) by gavage once per day for up to 14 days at 0 (controls), 0.5 mL/kg body weight (440 mg/kg), or 1.0 mL/kg (880 mg/kg) (Singh and Bansode 2011). The high-dose group was necropsied at day 10 due to 100% mortality after 9 treatment days. The low-dose group was necropsied on day 14. Both groups of benzene-treated rats exhibited significantly decreased mean seminal vesicle weight (approximately 40% less than that of controls). Histopathological examination of testes revealed degenerative changes in benzene-treated groups characterized by giant cell formation, cytoplasmic vacuolization, pycnosis, chromatolysis, and desquamation and dissolution of germ cells in tubular lumen. The low-dose group exhibited significantly decreased numbers of non-pachytene and pachytene spermatocytes (48 and 88%, respectively, less than that of controls) and round and elongated spermatids (93 and 98%, respectively, less than that of

controls), and significantly decreased diameters of seminiferous tubules and Leydig cell nuclei (23% less than those of controls). Gross and histopathological evaluations of high-dose rats revealed effects on reproductive end points similar to those observed in low-dose rats, but of greater magnitude; the high-dose group also exhibited significantly decreased mean number of type a spermatogonia. There were no statistically significant treatment-related effects on weights of testis, epididymis, or ventral prostate among low- or high-dose groups.

3.2.2.7 Cancer

NTP (2007) administered benzene to groups of male and female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (15/sex/group) by gavage (in corn oil) once/day, 5 days/week for 27 weeks at 0, 25, 50, 100, or 200 mg benzene/kg/day. High-dose male mice exhibited significantly increased incidence of malignant lymphoma (5/15 high-dose males compared to 0/15 for each of the other groups, including controls). Multiple organs including the spleen, thymus, lymph node, kidney, lung, and/or brain were infiltrated with neoplastic cells. There were no signs of treatment-related increased incidences of any cancer in the female mice.

3.2.3 Dermal Exposure

3.2.3.2 Systemic Effects

Dermal Effects. Application-site dermal irritation was observed in male hairless rats receiving a single occlusive dermal application of benzene at 230 µL for 1 hour or repeated unocclusive applications at 15µL every 2 hours for 8 hours/day during 4 days (Chatterjee et al. 2005). Evidence of dermal irritation included visual signs of erythema, decreased skin moisture content, increased transepidermal water loss, increased expression of tumor necrosis factor-α at the application site, and increased interleukin-1α in the blood. The repeated unoccluded application scenario was more irritative than the single occluded application.

3.3 GENOTOXICITY

Several groups of investigators have reported significant associations between occupational exposure to benzene and increased rates of chromosomal aberrations (e.g., breaks, deletions, translocations, aneuploidy) for a number of chromosomes in peripheral blood lymphocytes (Ji et al. 2012; Zhang et al. 2005, 2007, 2011a, 2012) or sperm (Ji et al. 2012; Kim et al. 2010; Marchetti et al. 2012; Schmid et al. 2006; Xing et al. 2010). For example, using the FISH (fluorescence in situ hybridization) assay, Zhang et al. (2007) observed increased aneuploidy (significant increases in monosomy in chromosomes 2, 4, 6, 11, 12, and 13; trisomy in chromosomes 2, 4, 6, 11, and 18; tetrasomy in chromosomes 2, 4, 6, 11, 12, 13,

and 18) and significantly increased frequency of long-arm deletions in chromosome 6 among a group of 22 workers exposed to benzene at levels >31 ppm compared to a group of 44 unexposed controls. Zhang et al. (2007) also observed translocations between chromosomes 14 and 18 among 4/22 of the workers exposed at concentrations >31 ppm and no such translocations among 21 workers exposed at concentrations ≤31 ppm or among 44 unexposed controls. However, DNA from the workers was not of suitable quality to quantify the results. In a subsequent study that included 31 unexposed controls and 37 highly-exposed workers (mean benzene concentration of 22.6 ppm, median 13.8 ppm) and employed real-time quantitative polymerase chain reaction (PCR) to quantify translocations, the benzene-exposed group exhibited a lower frequency of translocations between chromosomes 14 and 18 than that of the unexposed group (McHale et al. 2008). The study authors stated that the apparent discrepancy between the finding of decreased frequency of translocations between chromosomes 14 and 18 in the benzene-exposed workers and the report of increased frequency of this translocation in benzene-exposed workers of a previous study (Zhang et al. 2007) might be explained by different target cell populations and differential sensitivities of the two assays.

Tunsaringkarn et al. (2011) evaluated the frequency of sister chromatid exchange (SCE) in peripheral blood lymphocytes from 33 gasoline station workers and 30 office workers and students (controls). The frequency of SCE was significantly higher among the gasoline station workers (13.47±0.26 SCEs/cell [mean±standard error]) than controls (8.52±0.40 SCEs/cell). Benzene exposure estimates were not included in the study report, although urinary trans,trans-muconic acid (a minor metabolite of benzene) levels were significantly higher in the gasoline station workers than the controls.

Zhang et al. (2014) evaluated the frequency of micronuclei in peripheral blood lymphocytes from 385 benzene-exposed shoe factory workers and 197 unexposed controls. The benzene-exposed workers were evaluated as a total group and also grouped according to duration of exposure (≤5.02, >19.90, >31.81, and >59.00 mg/m^3-year) and according to exposure level (>3.25, <6.00, and ≥6.00 mg/m^3). The benzene-exposed workers exhibited both concentration- and duration-related significantly increased frequency of micronuclei compared to controls.

Kim et al. (2010) evaluated the frequency of micronuclei in peripheral blood lymphocytes from 30 workers exposed to benzene in the petroleum refining process (mean exposure level 0.51 ppm; cumulative exposure level <5 ppm-years) and 10 office workers not associated with the petroleum refinery process. The mean frequencies of micronuclei and centromere-negative micronuclei were significantly greater within the group of benzene-exposed workers compared to frequencies within the

group of office workers. There was no significant difference between groups regarding frequency of centromere-positive micronuclei.

Katukam et al. (2012) collected semen samples from 160 workers with occupational exposure to benzene and 200 unexposed age- and sex matched control subjects and evaluated sperm quality. The benzene-exposed workers were grouped according to duration of exposure (group 1, 0–5 years of exposure, n=52; group 2, 5–10 years of exposure, n=73; group 3, 10–15 years of exposure, n=35). Exposure duration-related significantly increased sperm comet tail length (a measure of DNA damage) was observed in the benzene-exposed workers compared to controls. Mean sperm tail length (±SD) were 1.89±0.28, 4.98±2.44, 5.86±0.2.46, and 6.13±0.2.11 µm, for controls, group 1, group 2, and group 3, respectively).

Bassig et al. (2014) evaluated telomere length in leukocytes from peripheral blood samples collected from 43 benzene-exposed workers and 43 matched unexposed controls. Mean telomere length was 9% longer (p=0.03) among 22 workers with benzene exposure levels >31 ppm (n=22) than the unexposed controls. Significantly increased frequency of micronuclei was observed in polychromatic erythrocytes from bone marrow of male CD-1 mice exposed to benzene vapor for 6 hours/day for 8 of 15 days at 50 ppm, a 2.4-fold increase over the frequency of micronuclei in air-only control mice (Wetmore et al. 2008). Similar exposure during 8 consecutive days resulted in a nearly 5-fold increased frequency of micronuclei (Bird et al. 2010). Lau et al. (2009) reported significantly increased percentages of micronuclei in bone marrow cells of adult mice following single intraperitoneal injection of benzene at 400 mg/kg. Following intraperitoneal injections of benzene to timed-pregnant female mice at 400 mg/kg/day during gestation days 7–15 significantly increased percentages of micronuclei were noted in fetal liver and postnatal day 9 bone marrow cells.

Billet et al. (2010) evaluated the mutational pattern induced by benzene on the TP53 gene in human type II-like alveolar epithelial A549 cells *in vitro*. A total of 17 mutations were linked to benzene exposure: 3 one- or two-base deletions and 14 single nucleotide substitutions. Benzene induced micronuclei, chromosomal aberrations, and DNA damage in Chinese hamster ovary cells (Pandey et al. 2009a, 2009b).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The observation that levels of the benzene urinary metabolite trans,trans-muconic acid in a group of ceramic factory workers exposed to benzene were higher than those of nonexposed control workers (Ibrahim et al. 2014) indicates that benzene was absorbed via inhalation and/or dermal routes.

3.4.1.3 Dermal Exposure

Modjtahedi and Maibach (2008) reported absorption of benzene through forearm skin and palm of volunteers. Absorption through the forearm skin and palm averaged 0.7 and 0.13%, respectively, of the applied dose, based on recovery in the urine. Fent et al. (2014) reported increased benzene levels in the breath of firefighters exposed to benzene and other substances during controlled structure burns, indication that some degree of dermal absorption of benzene had occurred because the subjects wore their protective breathing systems during the burns.

3.4.1.4 Other Routes of Exposure

Adami et al. (2006) applied benzene to human skin *in vitro* and recovered 0.43% of the applied dose in the receptor fluid; a permeability coefficient of 0.000438 cm/hour was determined. Hui et al. (2009a, 2009b) observed dose-related increased absorption of benzene through human skin *in vitro* and reported that occlusion increased the extent of absorption.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

3.4.5.1 Summary of PBPK Models

Three studies have expanded or enhanced the Cole et al. (2001) mouse PBPK model (Knutsen et al. 2013a, 2013b; Manning et al. 2010; Yokely et al. 2006). Yokely et al. (2006) estimated parameter values for humans, including human population distributions for several metabolism parameters. Knutsen et al. (2013a, 2013b) expanded the Yokely et al. (2006) human model to include two additional compartments representing bone marrow and urinary bladder. This enabled dosimetry predictions for benzene and metabolites in bone marrow and provided a compartment for simulating background levels (e.g., pre-exposure) of benzene metabolite conjugates in urine. Manning et al. (2010) extended the Cole et al. (2001) mouse model to include a kidney compartment and subdivided the liver compartment into three

zones to represent heterogeneous distribution of enzymes that participate in the production of benzene metabolites.

Yokely et al. (2006). Yokely et al. (2006) estimated human population distributions of metabolism parameters for the Cole et al. (2001) model (described in Agency for Toxic Substances and Disease Registry 2007). Parameters evaluated included the specific activity of CYP2E1 in liver (V2E1), maximum rates of conjugation of phenol (VPH1, VPH2) and hydroquinone (VHQ), and first-order clearances for formation of phenylmercapturic acid (k3) and muconic acid (k4) from benzene oxide. Data from *in vitro* studies of human liver tissue were used to establish prior log-normal distributions for V2E1, VPH1, VPH2, and VHQ. Parameters k3 and k4 were assigned log-normal prior distributions with means equal to the mouse model values and SDs of 0.1 and 2, respectively. Posterior distributions were computed from Markov Chain Monte Carlo (MCMC) simulations with calibration data from human subjects. These data included a clinical study in which 3 subjects were exposed to 1.7 or 10 ppm benzene for 4 hours and benzene in blood and exhaled air were measured (Pekari et al. 1992), and an occupational study in which benzene metabolites in urine were monitored in 35 workers who were exposed to 25 ppm benzene during their work shifts (Rothman et al. 1998; Waidyanatha et al. 2004). The population model predicted the observed variability in blood benzene and exhaled benzene and urinary levels of muconic acid, phenylmercapturic acid, phenol, and hydroquinone; however, it under-predicted urinary catechol and benzenetriol levels.

Manning et al. (2010). Manning et al. (2010) developed a PBPK model of benzene and its major metabolites benzene oxide, phenol, and hydroquinone. The model is an extension of the Cole et al. (2001) model (described in Agency for Toxic Substances and Disease Registry 2007), with the addition of a kidney compartment, and expansion of the liver compartment to include three subcompartments. The three liver compartments were included in the model to simulate the heterogeneous distribution of CYP2E1 and sulfotransferases. CYP2E1 is more strongly expressed in the pericentral region of the liver and sulfotransferases are more strongly expressed in the periportal region of the liver (Ingelman-Sundberg et al.1988; Tsutsumi et al. 1989). This heterogeneous, or zonal, distribution of enzymes is thought to give rise to different metabolic patterns following an external dose of benzene or phenol (Hoffman et al. 1999; Koop e al. 1989). Following an external dose of phenol, sulfotransferases in the periportal region of the liver convert a large fraction of the absorbed dose to sulfate esters before it can be delivered to the pericentral region of the liver where it can be metabolized to benzene oxide through the CYP2E1 pathway and to downstream metabolites, including hydroquinone. Following an external dose of benzene, phenol

is formed in the pericentral region of the liver and, as a result, a larger fraction of the benzene dose is converted hydroquinone.

The three-compartment liver model has flow-limited transfer of chemical from blood to liver compartment 1, representing the periportal region, through an intermediate compartment 2, to compartment 3, representing the pericentral region. Each compartment is assumed to comprise one-third of the total volume of the liver. Hepatic sulfotransferase and glucuronlytransferase activity are assigned to compartment 1, whereas CYP2E1, epoxide hydrolase, and GST activities are assigned to compartment 3. Non-enzymatic conversion of benzene oxide to phenol is assumed to occur in all three compartments. Sulfate and glucuronic acid conjugates of phenol and hydroquinone are formed in liver compartment 1. Metabolites formed in compartment 3 include the CYP2E1 metabolites benzene oxide (from phenol), hydroquinone and catechol (from phenol), and benzenetriol (from hydroquinone), the epoxide hydrolase metabolite of benzene oxide (muconic acid), and the GST metabolite of benzene oxide (phenyl-mercapturic acid). The kidney compartment is assigned 10% of the CYP2E1 activity relative to the liver. Formation of phenylmercapturic acid is assumed to occur in blood, kidney, fat, slowly perfused tissue, and rapidly perfused tissues.

Tissue/blood partition coefficients for benzene metabolites, phenol and hydroquinone, were estimated from physical-chemical properties (Poulin and Krishnan, 1995). Phenol and hydroquinone were assumed to bind in all tissues. Binding was represented in the model with first order clearance terms which were optimized. Information regarding tissue/blood partition coefficients for benzene was taken from the literature (Medinsky et al. 1989). The partition coefficients for benzene were used for benzene oxide. Parameters governing CYP2E1 and conjugation rates (Km, Vmax) were scaled to the whole liver from estimates made in in vitro studies (Lovern et al. 1999; Seaton et al. 1995). First-order clearances for GST-mediated formation of phenylmercapturic acid and epoxide hydrolase-mediated formation of muconic acid were optimized.

Data used in optimizing the model were derived from benzene oral dosing studies (Henderson et al. 1989; Kenyon et al. 1995; Mathews et al. 1998; Sabourin et al. 1987) and inhalation studies (Sabourin et al. 1988) conducted in mice. The introduction of three liver compartments to account for zonal distribution of metabolism improved some aspects of performance of the model at predicting dose-dependent metabolism of benzene. For example, it improved agreement between observed and predicted benzene concentrations in liver and phenol concentrations in blood following inhalation of benzene, and predictions of formation of phenol and hydroquinone conjugates following oral dosing with benzene.

Knutsen et al. (2013a, 2013b). Knutsen et al. (2013a, 2013b) expanded the Yokely et al. (2006) human model to include two additional compartments representing bone marrow and urinary bladder. Saturable metabolism was assumed for the formation of benzene oxide from benzene, hydroquinone and catechol from phenol, benzenetriol from catechol and hydroquinone, and conjugates. Bone marrow is assumed to oxidize to benzene oxide at approximately 4% of the hepatic maximal rate. Maximal rates for all other saturable conversions in liver and bone marrow (per mg tissue protein) were assumed to be proportional to tissue masses. First-order metabolic clearance was assumed for formation of muconic acid and phenylmercapturic acid from benzene oxide and phenol from benzene oxide, with first-order clearance rates identical in liver and bone marrow. The bladder compartment receives conjugated metabolites resulting from exposure to benzene and was assigned values for background levels of metabolites expected in the absence of exposure to benzene. Background levels of urinary metabolites were assigned values based on measurements made in humans who were not exposed to benzene (Waidyanatha et al. 2004).

Metabolism parameters for CYP2E1 were assigned initial values from quantitative studies of human liver CYP2E1 (Lipscomb et al. 2003a, 2003b) and all metabolism parameters were calibrated to achieve agreement with measurements of urinary benzene metabolites in workers exposed to benzene during the work shift (Waidyanatha et al. 2004). The calibrated model was validated by comparing observed levels of benzene in blood and exhaled air in three subjects who inhaled benzene (1.9 and 9.4 ppm) for 4 hours (Pekari et al. 1992) and observed and predicted urinary metabolite levels measured in workers exposed to benzene (Kim et al. 2006).

In comparison to the Yokely et al. (2006) human model, calibration of the Knutsen et al. (2013a, 2013b) model resulted in lower values for the maximal rate of metabolism of phenol and first-order clearance of benzene to benzene oxide and higher values for first-order clearance of phenol to catechol and hydroquinone to benzenetriol. Good agreement was achieved between observed and predicted levels of benzene in blood and exhaled air, and benzene metabolites in urine (Kim et al. 2006; Pekari et al. 1992). The model was used to compare predicted blood and bone marrow metabolite exposures resulting from an 8-hour exposure to air concentrations of benzene ranging from 5 to 100 ppm. The total metabolites formed (24-hour area under the curve [AUC]) were higher in blood compared to bone marrow. Both compartments exhibited saturation kinetics, with saturation in bone marrow predicted at lower exposures.

3.5 MECHANISMS OF ACTION

3.5.2 Mechanisms of Toxicity

As discussed in the ATSDR Toxicological Profile for Benzene (Agency for Toxic Substances and Disease Registry 2007), benzene hematotoxic and carcinogenic effects are dependent upon benzene metabolism; reactive metabolites produced in liver and bone marrow can lead to production of reactive oxygen species and damage to tubulin, histone proteins, topoisomerase II, other DNA associated proteins, and DNA itself (clastogenic effects such as strand breakage, mitotic recombination, chromosome translocations, and aneuploidy). A number of recent findings add to the present understanding of mechanisms of benzene hematotoxicity and carcinogenicity.

Hirabayashi and coworkers (Hirabayashi and Inoue 2010; Hirabayashi et al. 2008; Yoon et al. 2002; 2003) demonstrated a role for a hematopoietic stem cell-specific, aryl hydrocarbon receptor (AhR) in benzene-induced bone marrow toxicity using wild-type and AhR-knockout mice exposed to benzene at levels resulting in marked decreases in numbers of peripheral white blood cells and red blood cells in the wild-type mice. No such effects were seen in benzene-exposed AhR-knockout mice or in wild-type mice that had been whole-body irradiated and repopulated using bone marrow from AhR-knockout mice prior to benzene exposure. AhR expression may be involved in the regulation of hematopoietic stem cells (Singh et al. 2009). It has been suggested that the absence of AhR makes hematopoietic stem cells susceptible to benzene-induced DNA damage and subsequent apoptosis (IARC 2012). Based on evaluation of available mechanistic data, IARC (2012) determined that there is strong evidence that benzene metabolites produce multiple genotoxic effects on pluripotent hematopoietic stem cells resulting in chromosomal changes consistent with those observed in hematopoietic cancer.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Benzene

Several recent reports (Fracasso et al. 2010; Garte et al. 2005; Hoet et al. 2009; Lovreglio et al. 2010, 2011; Lv et al. 2014; Zhang et al. 2011b) provide support to the usefulness of selected benzene metabolites (particularly urinary trans,trans-muconic acid and S-phenylmercapturic acid and urinary benzene itself) as biomarkers of exposure to benzene, as discussed in the 2007 Toxicological Profile for Benzene (Agency for Toxic Substances and Disease Registry 2007).. In addition, results of Lovreglio et al. (2011) indicate that urinary benzene may serve as a more reliable biomarker of exposure than urinary trans,trans-muconic acid or S-phenylmercapturic acid at environmentally-relevant benzene exposure levels. Lin et al. (2007) evaluated possible usefulness of albumin adducts of electrophilic benzene

metabolism in workers with relatively low-level exposure to benzene (0.026–54.5 ppm). The results indicate that albumin adducts of benzene oxide and benzoquinones reflect exposures to benzene at levels ≥1 ppm, but would not be useful biomarkers of exposure at levels <1 ppm.

3.8.2 Biomarkers Used to Characterize Effects Caused by Benzene

Benzene-induced effects such as alterations in selected gene expression (Bai et al. 2014a, 2014b; Park et al. 2008; Yang et al. 2014), DNA damage and altered DNA repair capacity (Chanvaivit et al. 2007; Fracasso et al. 2010), and increases in chromosomal aberrations (Kim et al. 2010; Tunsaringkarn et al. 2011) have been suggested as potential biomarkers of effects, particularly at relatively low levels of benzene exposure. However, these biomarkers are not specific to benzene exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Coexposure of mice to benzene and toluene resulted in higher frequency of micronuclei in polychromatic erythrocytes compared to exposure to benzene or toluene alone (Bird et al. 2010; Wetmore et al. 2008). Li et al. (2009) subjected groups of mice to intratracheal instillation of either benzene or carbon nanotubes or combined instillation of benzene and carbon nanotubes. Combined instillation resulted in considerably more severe histopathological pulmonary toxicity than that observed in mice exposed to benzene or carbon nanotubes alone.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Reports from several studies indicate that susceptibility to benzene-induced hematotoxicity among workers may be associated with polymorphisms in multiple genes involved in benzene metabolism (Garte et al. 2008; Gu et al. 2007; Kim et al. 2007; Shen et al. 2011; Sun et al. 2007, 2008, 2009a, 2009b; Wu et al. 2008; Zhang et al. 2011a). In addition, results from Hosgood et al. (2009) indicate that genetic variation in vascular endothelial growth factor (VEGF), which plays a role in blood vessel growth, and excision repair cross-complementing 3 (ERCC3), which is part of the DNA repair pathway, may contribute to individual susceptibility to low-level benzene-induced hematotoxicity.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Several groups of investigators have evaluated possible roles of selected antioxidants in decreasing the hematotoxicity of benzene. Melatonin inhibited benzene-induced lipid peroxidation in the rat liver (Sharma and Rana 2010). Progesterone inhibited formation of reactive oxygen species in benzene-treated rats (Verma and Rana 2008). Green tea was observed to attenuate benzene-induced oxidative stress in

filling station workers (Emara and El-Bahrawy 2008). Saha et al. (2012) reported that methanolic leaf extract of *Ocimum basilicum* L. reduced benzene-induced hematotoxicity in mice. Polyphenolic acetates demonstrated time-dependent inhibition of CYP450-linked mixed function oxidases in rat bone marrow and lung cells *in vitro* (Kumar et al. 2011). Acetylsalycilic acid decreased selected hematotoxic effects of inhaled benzene in rats (Kowalówka-Zawieja et al. (2013).

Yu et al. (2007) found that amifostine (a well-known cytoprotective agent used to protect normal tissues from toxic effects of chemotherapy and radiotherapy) reduced benzene-induced hematotoxic effects in bone marrow of treated mice. Polyphenolic acetates inhibited the formation of micronuclei in rat bone marrow and lung cells *in vitro* (Kumar et al. 2011).

3.12 ADEQUACY OF THE DATABASE

3.12.3 Ongoing Studies

The following ongoing studies pertaining to benzene were identified in National Institutes of Health (NIH) Research Portfolio Online Reporting Tools (RePORTER 2014):

Dr. Anneclaire De Roos, Public Health and Preventive Medicine, Schools of Public Health, Drexel University, Philadelphia, Pennsylvania, College of Public Health, University of Iowa, is conducting a meta-analysis of 13 case-control studies of multiple myeloma to evaluate risks associated with occupational solvent exposures, including benzene.

Dr. Edward Paul Hasty, University of Texas Health Science Center, San Antonio, Texas is investigating the dynamics of repairing benzene-induced DNA lesions and the development of myelodysplastic syndrome and acute myeloid leukemia.

4. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Table 5-1 lists the facilities in each state that manufacture or process benzene, the intended use, and the range of maximum amounts of benzene that are stored on-site. There are 981 facilities that produce,

process, or use benzene in the United States (TRI13 2014). The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 2005). This is not an exhaustive list.

5.2 IMPORT/EXPORT

Imports of benzene (from mineral fuels and pure benzene) into the United States were approximately 4,757 million L (9,131 million pounds) in 2013 and 4,751 million L (9,143 million pounds) in 2012. The largest exporters of benzene to the United States during 2013–2014 were Saudi Arabia, Iraq, Korea, and Venezuela (USITC 2014).

Table 5-1. Facilities that Produce, Process, or Use Benzene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	9	1,000	49,999,999	1, 3, 4, 5, 6, 7, 9, 13
AL	12	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AR	8	100	49,999,999	1, 2, 3, 5, 6, 7, 9, 12
AZ	16	100	9,999,999	1, 5, 9, 11, 12, 13
CA	67	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
CO	10	0	499,999,999	1, 3, 5, 7, 8, 9, 12, 13
CT	7	100	9,999,999	9
DE	1	100,000	999,999	1, 2, 3, 4, 5, 6, 7, 9
FL	26	100	9,999,999	1, 2, 4, 5, 7, 9
GA	15	1,000	9,999,999	1, 5, 7, 9, 10
GU	2	100	999,999	7, 9
HI	8	100	9,999,999	1, 2, 3, 4, 5, 6, 9, 12, 13, 14
IA	36	100	9,999,999	1, 4, 5, 7, 8, 9, 12
ID	3	1,000	999,999	2, 4, 7, 9
IL	42	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
IN	39	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
KS	18	0	499,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12
KY	20	0	49,999,999	1, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14
LA	61	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	12	10,000	49,999,999	1, 2, 4, 5, 7, 8, 9, 12
MD	10	1,000	9,999,999	2, 4, 9, 12
ME	5	0	9,999,999	2, 3, 4, 7, 9, 12
MI	38	0	9,999,999	1, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MN	18	10,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
MO	16	0	9,999,999	1, 5, 7, 8, 9, 12, 14
MP	2	100	99,999	7, 9
MS	15	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Benzene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MT	5	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
NC	19	0	9,999,999	1, 2, 4, 5, 7, 9, 12
ND	14	0	49,999,999	1, 2, 3, 4, 5, 6, 9, 12, 13, 14
NE	20	1,000	99,999	1, 5, 7, 12
NH	1	10,000	99,999	1, 5, 12
NJ	13	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 9
NM	6	100,000	9,999,999	1, 3, 4, 6, 7, 9
NV	3	1,000,000	9,999,999	9
NY	38	0	99,999,999	1, 2, 4, 5, 7, 8, 9, 12
OH	42	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
OK	13	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
OR	8	10,000	9,999,999	1, 5, 7, 9, 12
PA	23	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
PR	7	0	499,999,999	2, 4, 5, 7, 8, 9, 13
RI	2	1,000,000	9,999,999	7, 9
SC	6	100	9,999,999	1, 2, 4, 5, 8, 9, 12, 14
SD	11	10,000	99,999	7, 9
TN	12	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13, 14
TX	146	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	9	10,000	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
VA	11	0	999,999	1, 2, 4, 5, 7, 9, 12
VI	2	10,000	999,999	1, 2, 4, 5, 7, 9, 12
WA	17	0	49,999,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14
WI	22	0	9,999,999	1, 2, 5, 7, 9, 11, 12, 13, 14
WV	7	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13
WY	8	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6.. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI13 2014 (Data are from 2013)

Exports of benzene (both pure benzene and benzene derived from mineral fuels) to other countries were approximately 372 million L (716 million pounds) in 2013 and 178 million L (341 million pounds) in

2012. The largest importers of benzene from the United States are Canada, the Netherlands, and Belgium (USITC 2014).

6. POTENTIAL FOR HUMAN EXPOSURE

6.2 RELEASES TO THE ENVIRONMENT

Data from EPA's Toxics Release Inventory (TRI) on facilities that release benzene in 2012 are shown in Tables 6-1 (TRI13 2014).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Benzene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	9	11,201	9	0	19	1	11,229	1	11,230
AL	11	57,712	2	0	305	29	57,731	317	58,048
AR	8	25,447	8	10	0	429	25,465	429	25,894
AZ	15	18,444	0	0	0	0	18,444	0	18,444
CA	58	48,810	2,936	42	167,324	365	218,489	988	219,477
CO	11	15,165	2	0	3	2	15,167	4	15,171
CT	8	2,121	1	0	0	0	2,122	0	2,122
DE	1	11,893	5	0	0	0	11,898	0	11,898
FL	27	103,351	11	0	12	215	103,362	227	103,590
GA	14	14,363	36	0	17	0	14,399	17	14,416
GU	2	1,345	0	0	1	0	1,345	1	1,347
HI	9	13,745	16	0	6	1	13,763	5	13,768
IA	36	62,355	5	0	1	0	62,360	1	62,361
ID	3	1,080	0	0	0	0	1,080	0	1,080
IL	42	120,415	304	4	1,076	63	120,847	1,016	121,862
IN	39	178,044	156	10,620	1,382	1,660	188,825	3,037	191,862
KS	17	58,579	34	184	585	3	58,818	568	59,385
KY	19	58,539	5	0	31	0	58,554	21	58,575
LA	58	468,108	489	3,409	1,511	1,973	472,040	3,450	475,490
MA	13	3,733	4	0	14	278	3,736	292	4,029
MD	8	2,053	7	0	3	0	2,060	3	2,063
ME	6	2,414	37	0	0	14	2,451	14	2,465
MI	35	156,500	33	0	109	428	156,537	533	157,070
MN	19	14,836	30	0	8	0	14,866	8	14,874
MO	15	32,532	0	0	0	0	32,532	0	32,532
MP	2	188	0	0	0	0	188	0	188
MS	15	44,354	6	0	16	0	44,361	15	44,376

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Benzene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
MT	6	28,396	17	0	49	0	28,431	30	28,462
NC	16	11,137	0	0	0	0	11,137	0	11,137
ND	9	23,778	0	0	8	0	23,782	4	23,786
NE	21	1,428	0	0	58	0	1,428	58	1,486
NH	1	43	0	0	0	1	43	1	44
NJ	15	22,796	389	0	164	10	23,188	171	23,359
NM	6	28,937	0	230	6,026	0	29,516	5,677	35,193
NV	3	976	0	0	0	0	976	0	976
NY	39	43,314	3	0	7	234	43,321	237	43,558
OH	41	138,303	9	185	180	45	138,511	211	138,722
OK	12	107,565	261	0	275	5	107,826	280	108,106
OR	8	2,443	1	0	17,103	0	19,491	57	19,548
PA	24	174,915	116	0	121	13	175,032	134	175,166
PR	6	7,637	0	0	1	2	7,638	2	7,641
RI	2	801	9	0	0	413	810	413	1,223
SC	7	42,796	0	0	0	5	42,796	5	42,801
SD	12	274	0	0	1	0	275	0	275
TN	12	29,981	3	0	254	410	29,984	664	30,648
TX	149	1,130,400	991	225,855	7,336	9,857	1,353,861	20,578	1,374,439
UT	9	25,743	5	0	131	9,019	25,750	9,148	34,898
VA	14	12,783	102	0	2	14	12,885	16	12,901
VI	2	12,386	0	0	30	1	12,386	31	12,418
WA	17	31,476	421	0	146	2	31,965	80	32,045
WI	22	144,132	1	0	751	8	144,133	759	144,893
WV	6	56,554	5	0	142	21	56,559	163	56,722

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Benzene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	8	19,951	5	0	578	0	19,956	578	20,534
Total	967	3,626,277	6,474	240,539	205,787	25,521	4,054,354	50,245	4,104,598

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI13 2014 (Data are from 2013)

6.2.1 Air

Estimated releases of 3,626,277 pounds (~1,645 metric tons) of benzene to the atmosphere from 967 domestic manufacturing and processing facilities in 2012 accounted for about 88% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). These releases are summarized in Table 6-1.

U.S. EPA's National Emission Inventory (NEI) database contains a detailed estimate of air emissions of criteria air pollutants and their precursors from all air emission sources, including point, nonpoint, onroad, offroad, and events (wildfires, prescribed burns, etc.), provided by state, local, and tribal air agencies, and supplemented by data developed by the U.S. EPA. According to data obtained from the NEI, 542 million pounds (~246,000 metric tons) of benzene were released to air from 54 different emission source categories in 2011, with the highest percentage coming from wildfires (EPA 2013b).

6.2.2 Water

Estimated releases of 6,474 pounds (~2.94 metric tons) of benzene to surface water from 967 domestic manufacturing and processing facilities in 2012 accounted for about 0.2% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs) (TRI13 2014). These releases are summarized in Table 6-1.

6.2.3 Soil

Estimated releases of 205,787 pounds (~93 metric tons) of benzene to soils from 967 domestic manufacturing and processing facilities in 2012 accounted for about 5% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2014). An additional 240,539 pounds (~109 metric tons), constituting about 6% of the total environmental emissions, were released via underground injection (TRI13 2014). These releases are summarized in Table 6-1.

6.3 ENVIRONMENTAL FATE

6.3.2 Transformation and Degradation

Bacterium strain, *Mycobacterium cosmeticum* byf-4, has been reported to aerobically biodegrade benzene, toluene, ethylbenzene, and o-xylene, simultaneously or individually, via mineralization and incorporation into cell materials (Zhang et al. 2013). Benzene alone or in a mixture of benzene, toluene, ethylbenzene, and o-xylene, at an initial concentration of 100 mg/L, was completely degraded within 36–42 hours.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

The U.S. EPA's Air Quality System (AQS) takes direct measurements of pollutant concentrations in ambient air at monitoring stations around the country (EPA 2014a). The data for benzene concentrations measured by the AQS in 2013 are presented in Table 6-2.

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Alaska	Anchorage	2.91
Arizona	Phoenix	2
Arizona	Phoenix	1.97
Arizona	Phoenix	2.03

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Arizona	Phoenix	0.995
Arizona	Queen Valley	0
Arizona	Queen Valley	0
California	Livermore	1.61
California	Livermore	0.954
California	Oakland	2.14
California	Oakland	1.77
California	Livermore	0.401
California	Chico	1.64
California	Concord	1.06
California	Richmond	1.43
California	Crockett	0.88
California	Bethel Island	1.27
California	San Pablo	1.29
California	Martinez	1.09
California	San Ramon	0.664
California	Fresno	1.84
California	Parlier	0.59
California	Clovis	0.64
California	Calexico	2.61
California	Bakersfield	1.54
California	Bakersfield	1.45
California	Bakersfield	0.842
California	Shafter	1.11
California	Azusa	1.68
California	Burbank	2.63
California	Los Angeles	2.29
California	Pico Rivera	1.69
California	Long Beach	1.79
California	Madera	0.554
California	San Rafael	1.23
California	Mill Valley	0.496
California	Napa	1.84
California	Roseville	1.25
California	Rubidoux	1.85
California	Arden-Arcade	0.622
California	Elk Grove	0.38
California	Folsom	0.564
California	Chula Vista	1.16
California	El Cajon	1.29
California	El Cajon	2.22

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
California	El Cajon	1.58
California	Alpine	0.657
California	Alpine	0.874
California	Camp Pendleton South	0.541
California	Camp Pendleton South	1.08
California	San Francisco	1.34
California	San Francisco	0.88
California	San Francisco	1.26
California	Stockton	1.67
California	Redwood City	1.73
California	San Jose	2.17
California	San Jose	2.03
California	Cupertino	0.92
California	Vallejo	1.77
California	Santa Rosa	1.23
California	Simi Valley	0.719
California	Simi Valley	1.15
California	Oxnard	0.274
Colorado	Denver	3.03
Colorado	Parachute	3.6
Colorado	Rifle	2.85
Colorado	Silt	2.15
Colorado	Carbondale	1.07
Colorado	Grand Junction	1.86
Colorado	Platteville	6.81
Connecticut	Westport	0.326
Connecticut	East Hartford	0.463
Connecticut	New Haven	1.22
Delaware	Delaware City	0.989
Delaware	Wilmington	1.81
District Of Columbia	Washington	0.691
District Of Columbia	Washington	1.03
District Of Columbia	Washington	0.888
District Of Columbia	Washington	1.42
Florida	Fort Lauderdale	1.53
Florida	Davie	1.54
Florida	Dania	2.84
Florida	Valrico	0.723
Florida	Winter Park	0.663
Florida	Saint Petersburg	0.714
Florida	Pinellas Park	0.876

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Georgia	Macon	6.93
Georgia	Savannah	0.74
Georgia	Nicholls	0.638
Georgia	Dawsonville	1.54
Georgia	Decatur	1.03
Georgia	Decatur	0.926
Georgia	Decatur	1.68
Georgia	Rockmart	0.059
Georgia	Rockmart	0.605
Georgia	Rockmart	0.567
Georgia	Conyers	0.508
Georgia	Conyers	0.765
Illinois	Schiller Park	1.39
Illinois	Northbrook	0.884
Illinois	Northbrook	1.05
Illinois	Roxana	1.82
Indiana	Clarksville	1
Indiana	Gary	2.43
Indiana	Gary	2.2
Indiana	Gary	2.68
Indiana	Indianapolis (Remainder)	0.869
Iowa	Cedar Rapids	1.17
Iowa	Cedar Rapids	0.68
Iowa	Des Moines	1.12
Iowa	Des Moines	0.647
Iowa	Davenport	1.1
Iowa	Davenport	0.63
Kentucky	Ashland	2.85
Kentucky	Grayson	0.912
Kentucky	Lexington-Fayette (corporate name for Lexington)	1.25
Kentucky	Smithland	1.26
Kentucky	Calvert City (RR name Calvert)	1.94
Kentucky	Calvert City (RR name Calvert)	2.01
Kentucky	Calvert City (RR name Calvert)	1
Kentucky	Calvert City (RR name Calvert)	0.928
Kentucky	Calvert City	1.17
Louisiana	Geismar	1.45
Louisiana	Geismar	1.37
Louisiana	Baton Rouge	1.57
Louisiana	Baton Rouge	1.73
Louisiana	Zachary	0.861

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Louisiana	Zachary	0.842
Louisiana	Plaquemine	1.26
Louisiana	Plaquemine	1.24
Maine	Lewiston	1.25
Maine	Presque Isle	1.16
Maine	Portland	1.18
Maine	Portland	1.16
Maine	Cape Elizabeth	0.523
Maine	Acadia National Park	0.287
Maine	Rumford (census name for Rumford Compact)	1.3
Maine	Bangor	1.08
Maryland	Essex	0.869
Maryland	Essex	1.6
Maryland	Essex	1.36
Maryland	Beltsville	0.605
Maryland	Beltsville	0.79
Maryland	Beltsville	0.898
Maryland	Baltimore	1.46
Massachusetts	Lynn	0.394
Massachusetts	Lynn	0.74
Massachusetts	Lynn	0.733
Massachusetts	Chicopee	0.368
Massachusetts	Boston	1.08
Massachusetts	Boston	1.15
Michigan	Midland	0.602
Michigan	Midland	0.872
Michigan	Midland	0.498
Michigan	Midland	0.516
Michigan	Detroit	1.18
Michigan	Dearborn	1.2
Michigan	Detroit	2.48
Michigan	Detroit	2.31
Michigan	Detroit	2.39
Michigan	Detroit	3.74
Michigan	Detroit	2.54
Minnesota	Blaine	0.861
Minnesota	Rosemount	0.953
Minnesota	Inver Grove Heights (RR name Inver Grove)	0.635
Minnesota	Rosemount	0.677
Minnesota	Rosemount	0.629
Minnesota	Apple Valley	0.768

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Minnesota	Richfield	0.888
Minnesota	Minneapolis	1.45
Minnesota	Minneapolis	1.14
Minnesota	Minneapolis	1.05
Minnesota	Minneapolis	1.05
Minnesota	Minneapolis	1.07
Minnesota	Minneapolis	1.25
Minnesota	St. Louis Park	0.96
Minnesota	St. Paul	1.2
Minnesota	St. Paul	0.984
Minnesota	Duluth	1.03
Minnesota	St. Paul Park	1.21
Minnesota	St. Paul Park	1.2
Minnesota	Newport	1.32
Minnesota	Bayport	0.696
Mississippi	Columbus	1
Mississippi	Columbus	1.14
Missouri	St. Louis	1.14
New Hampshire	Nashua	0.237
New Hampshire	Nashua	1.37
New Hampshire	Peterborough (Peterboro)	0.385
New Hampshire	Peterborough (Peterboro)	0.553
New Jersey	Camden	1.6
New Jersey	North Brunswick Township	1.22
New Jersey	East Brunswick	0.345
New Jersey	Chester	0.921
New Jersey	Elizabeth	1.51
New York	New York	1.37
New York	New York	1.27
New York	New York	1.3
New York	New York	1.71
New York	New York	1.18
New York	New York	1.29
New York	Buffalo	0.911
New York	Tonawanda	1.62
New York	Tonawanda	1.53
New York	Tonawanda	1.67
New York	Tonawanda	1.01
New York	Wilmington	0.493
New York	New York	1.32
New York	Rochester	0.807

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
New York	New York	1.04
New York	New York	1.14
New York	New York	1.4
New York	Addison	0.613
North Carolina	Asheville	0.889
North Carolina	Asheville	0.68
North Carolina	Winston-Salem	1.19
North Carolina	Winston-Salem	1.08
North Carolina	Sanford	0.63
North Carolina	Charlotte	1.23
North Carolina	Candor	0.69
North Carolina	Candor	0.433
North Carolina	Wilmington	0.633
North Carolina	Wilmington	1.31
North Carolina	Raleigh	1.03
North Carolina	Raleigh	1.04
Ohio	Middletown	1.27
Ohio	Middletown	1.21
Ohio	Middletown	1.14
Ohio	Cleveland	1.92
Ohio	Brook Park	1.58
Ohio	Columbus	1.28
Ohio	Cincinnati	1.21
Ohio	Cincinnati	1.21
Ohio	Steubenville	8.27
Ohio	Portsmouth	0.804
Ohio	Franklin Furnace	0.895
Ohio	Franklin Furnace	0.947
Oklahoma	Yukon	0.931
Oklahoma	Oklahoma City	0.989
Oklahoma	Oklahoma City	1.45
Oklahoma	Tulsa	1.89
Oklahoma	Tulsa	2.26
Oklahoma	Tulsa	1.81
Oregon	Medford	4.36
Oregon	Portland	1.19
Oregon	Portland	1.2
Oregon	La Grande	0.966
Oregon	Hillsboro	1.15
Pennsylvania	Pittsburgh	1.61
Pennsylvania	Liberty	1.36

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Pennsylvania	Philadelphia	0.84
Pennsylvania	Philadelphia	1.21
Pennsylvania	Philadelphia	1.22
Pennsylvania	Philadelphia	1.64
Pennsylvania	Philadelphia	1.74
Pennsylvania	Philadelphia	0.78
Pennsylvania	Philadelphia	1.96
Pennsylvania	Philadelphia	1.89
Pennsylvania	Philadelphia	1.02
Rhode Island	West Greenwich	0.605
Rhode Island	Providence	1.08
Rhode Island	Pawtucket	1.5
Rhode Island	East Providence	0.511
Rhode Island	East Providence	0.87
Rhode Island	East Providence	0.827
Texas	San Antonio	1.33
Texas	Clute (corporate name for Clute City)	0.952
Texas	Brownsville	1.21
Texas	Dallas	0.871
Texas	Dallas	1.21
Texas	Denton	1.42
Texas	Odessa	1.95
Texas	Midlothian	0.844
Texas	Italy	0.905
Texas	El Paso	1.47
Texas	El Paso	1.79
Texas	El Paso	1.99
Texas	Socorro	1.6
Texas	El Paso	1.01
Texas	Texas City	2.08
Texas	Galveston	1.01
Texas	Longview	2.63
Texas	Houston	2.02
Texas	Channelview	2.6
Texas	Cypress	1.8
Texas	Channelview	5.49
Texas	Houston	1.58
Texas	Galena Park	5.89
Texas	Baytown	2.21
Texas	La Porte	4.72
Texas	Houston	1.73

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Texas	Houston	2.98
Texas	Houston	2.83
Texas	Houston	6.5
Texas	Houston	2.05
Texas	Deer Park	1.9
Texas	Deer Park	2.46
Texas	Deer Park	2.76
Texas	Pasadena	4.49
Texas	Houston	2.16
Texas	Marshall	1.61
Texas	Mission	1.3
Texas	Greenville	0.958
Texas	Beaumont	2.28
Texas	Beaumont	1.77
Texas	Port Arthur	2.11
Texas	Port Arthur	4.34
Texas	Port Neches	1.54
Texas	Port Arthur	1.58
Texas	Port Arthur	2.74
Texas	Nederland	1.43
Texas	Beaumont	2.01
Texas	Alvarado	0.926
Texas	Kaufman	1.31
Texas	Conroe	1.41
Texas	Corpus Christi	2.41
Texas	Corpus Christi	5.38
Texas	Corpus Christi	1.96
Texas	Corpus Christi	1.65
Texas	Fort Worth	0.988
Texas	Fort Worth	1.25
Texas	Grapevine	1.01
Texas	Austin	1.49
Texas	Laredo	3.67
Utah	Bountiful	1.78
Utah	Bountiful	2.15
Vermont	Underhill (Town of)	0.588
Vermont	Burlington	1.24
Vermont	Burlington	1.2
Vermont	Rutland	1.56
Virginia	Corbin	0.775
Virginia	Groveton	0.89

Table 6-2. Benzene Ambient Air Concentrations by City in 2013

State	City	Mean concentration (ppbC)[a]
Virginia	East Highland Park	0.788
Virginia	East Highland Park	1.02
Virginia	East Highland Park	1.07
Virginia	Hopewell	1.02
Virginia	Hopewell	1.13
Virginia	Virginia Beach	1.18
Washington	Seattle	1.05
West Virginia	Wheeling	1.68
Wisconsin	Horicon	1.11
Wisconsin	Horicon	0.7
Wisconsin	Milwaukee	2.34

[a]Units are parts per billion carbon, which is equivalent to ppb times the number of carbon atoms.

Source: EPA 2014a

During the Detroit Exposure and Aerosol Research Study, which measured daily average ambient air concentrations of benzene from 2004 to 2007 in Detroit, Michigan, the mean average daily ambient air concentration ranged from 1.3 to 4.1 µg/m^3 (0.4–1.3 ppb) for 1,483 samples and the mean average daily indoor air concentration ranged from 2.3 to 6.0 µg/m^3 (0.7–1.8 ppb) for 934 samples (George et al. 2011).

6.4.2 Water

The U.S. Geological Survey (USGS) conducted a national assessment of 55 volatile organic compounds in well water samples collected from 2,401 domestic wells around the country during 1985–2002. Benzene was detected in 37 of 1,208 well samples, or 3.1% of the samples, at concentrations mostly <1 µg/L (Rowe et al. 2007). The USGS also evaluated benzene concentrations from 1,973 wells in California State Water Board's Groundwater Ambient Monitoring and Assessment Program and 12,417 wells from California Department of Public Health. The median concentration of benzene detected was 0.024 µg/L and the frequency of detection was 1.7%.

6.4.4 Other Environmental Media

In a study analyzing the benzene concentration in 455 food samples from the Belgian market, benzene was detected in 58% of samples collected (Medeiros Vinci et al. 2012). The highest concentrations of benzene were found in processed foodstuffs, including fish (smoked or canned) with a reported maximum concentration of 76.21 µg/kg. Raw meat, fish, eggs, and other unprocessed foods had no or lower concentrations of benzene, with values ranging from 0 to 9.44 µg/kg. Using this study, an estimated

mean benzene intake for all foods in the Belgian market was reported as 0.020 µg/kg body weight/day (0.00002 mg/kg/day).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

During the Detroit Exposure and Aerosol Research Study, which measured daily average ambient breathing zone concentrations of benzene for the general population from 2004 to 2007 in Detroit, Michigan, the mean average daily personal air concentrations ranged from 2.7 to 7.7 µg/m^3 (858 samples) (George et al. 2011).

Bogen and Sheehan (2014) estimated that workers' dermal exposure to benzene in mineral spirits solvents (MSS), used in parts washing and degreasing operations, averaged 33% of their total (dermal and inhalation) benzene uptake. The estimated average benzene doses from parts washing by dermal exposure and total exposure were reported as 0.0093 and 0.054 mg/day, respectively, using current 'low-aromatic' MSS formulations from 1995 to 1999. In a study assessing the dermal exposure and absorption of combustion contaminants in firefighters during six different controlled structure burns, the median increase in breath concentrations of benzene post versus pre-burn were 48.1, 2.81, 39.2, -0.33, 7.39, and 18.8 µg/m^3 (Fent et al. 2014). The benzene metabolite, S-phenylmercapturic acid, could not be detected in urine samples collected from the firefighters (minimum detectable concentration 8.5 µg/g).

In a study comparing the urinary benzene metabolite trans,trans-muconic acid between 81 ceramic factory workers exposed to low levels of benzene and 83 nonexposed controls, the workers and the control group had mean trans,trans-muconic acid concentrations of 0.22 and 0.043 mg/g creatinine, respectively (Ibrahim et al. 2014).

One study assessed the exposure of 133 male petrochemical industry operators to benzene by both environmental (personal air) and biological monitoring (metabolites trans,trans-muconic acid and S-phenylmercapturic acid in end-shift urine). The mean reported values of benzene exposure were 0.014 ppm, 101 µg/g creatinine, and 2.8 µg/g creatinine for benzene, trans,trans-muconic acid, and S-phenylmercapturic acid, respectively (Carrieri et al. 2010). Another study assessed the occupational exposure of urban and rural female workers to benzene, toluene, and xylenes by monitoring urban air for traffic policewomen (street) versus police drivers (vehicle); monitoring urban air versus rural air; and biological monitoring of workers in urban areas versus rural areas (Ciarrocca et al. 2012). Mean personal air exposures to benzene over an 8-hour sampling period were similar for urban street (16.7 µg/m^3) and vehicle workers (18.7 µg/m^3), but were reported to be higher when compared to rural workers (less than

the limit of detection [LOD] of 1.6 µg/m^3). Mean blood and urine levels of benzene, and trans,trans-muconic acid and S-phenylmercapturic acid, respectively, were similar among the street (244.4 ng/L, 62.0 µg/g creatinine, 3.5 µg/g creatinine) and vehicle workers (241.1 ng/L, 61.8 µg/g creatinine, 3.4 µg/g creatinine), but blood levels of benzene were higher in urban workers compared to rural workers (113.1 ng/L, 40.8 µg/g creatinine, 2.8 µg/g creatinine) (Ciarrocca et al. 2012). In a study measuring the mean benzene exposure in 33 petrochemical plant workers, 30 small town residents 2 km from the plant, 26 small town residents 2–4 km from the plant, and 54 urban residents 25 km from the plant, measured median personal air benzene concentrations were 25, 9, 7, and 6 µg/m^3, respectively, while median urinary metabolite concentrations were 236, 48, 63, and 120 ng/L and 692, 470, 421, and 1,090 ng/L, for nonsmokers and smokers, respectively (Fustinoni et al. 2012).

A study determined benzene exposure in 33 petrochemical industry operators (PIOs), 28 service station attendants (SSAs), 21 gasoline pump maintenance workers (GPMWs), and 51 nonexposed controls by measuring personal air concentrations and benzene metabolites, trans,trans-muconic acid and S-phenylmercapturic acid, in end-of-shift urine samples (Fracasso et al. 2010). The levels of benzene (in µg/m^3) in personal air for PIOs, SSAs, GPMWs, and controls were 1.7–593.50 (median 27.8), 8.00–260.00 (median 40.00), 4.60–514.90 (median 24.20), and 1.97–16.3 (median 5.40), respectively. Urinary levels of metabolites (in µg/g creatinine), trans,trans-muconic acid and S-phenylmercapturic acid, in PIOs, SSAs, GPMWs, and controls were 49.00–422.00 (median 128.00) and 0.40–35.60 (median 8.60), 30.00–418.00 (median 117.00) and 1.55–15.00 (median 5.55), 13.40–242.50 (median 92.00) and 0.21–10.53 (median 1.77), and 3.00–460.50 (median 84.00) and 0.30–10.08 (median 1.90), respectively. The results show that in all groups of workers, the level of personal air exposure to benzene was higher than the control groups, while the level of urinary metabolites was higher in the SSA and PIO groups compared to the control. No increase in urinary metabolites was measured in GPMWs, but it was noted that for these workers, benzene exposure was not continuous and only occurred on specific days.

6.6 EXPOSURES OF CHILDREN

Lagorio et al. (2013) conducted a study in Italy assessing the exposure of benzene to children by repeated weekly measurements in breathing zone and ambient outdoor air samples along with determination of cotinine, trans,trans-muconic acid, and S-phenylmercapturic acid in urine. In 108 children, all between the ages of 2 and 12 years, the average benzene concentrations in personal and outdoor air samples were reported as 3 and 2.7 µg/m^3 (0.92 and 0.81 ppb), respectively. The average urinary cotinine, trans,trans-muconic acid, and S-phenylmercapturic acid concentrations were 3.73, 116.65, and 1.28 µg/g creatinine, respectively.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In a study measuring the mean benzene exposure by monitoring urinary benzene excretion in 33 petrochemical plant workers, 30 small town residents 2 km from the plant, 26 small town residents 2–4 km from the plant, and 54 urban residents 25 km from the plant, nonsmokers had median urinary benzene concentrations of 236, 48, 63, and 120 ng/L, respectively, while smokers had median concentrations of 692, 470, 421, and 1,090 ng/L, respectively (Fustinoni et al. 2012).

A study compared the urinary benzene metabolite, trans,trans-muconic acid, between smokers and nonsmokers among 81 ceramic factory workers exposed to low levels of benzene and 83 general population controls (Ibrahim et al. 2014). Among the factory workers, 26 smokers had an average urinary trans,trans-muconic acid concentration of 0.252 mg/g creatinine, while 55 nonsmokers had an average of 0.183 mg/g creatinine. In the nonexposed control group, 25 smokers had an average urinary trans,trans-muconic acid concentration of 0.043 mg/g creatinine, while 58 nonsmokers had an average of 0.035 mg/g creatinine.

7. ANALYTICAL METHODS

7.1 BIOLOGICAL SAMPLES

A method for detecting benzene, toluene, ethylbenzene, and xylenes in environmental waste water and human hair samples using hollow fiber solid-phase microextraction (SPME) containing carbon nanotube reinforced sol-gel followed by gas chromatography (GC)/flame ionization analysis was described (Es'haghi et al. 2011). The LOD for benzene using this method was reported as 0.7 ng/L (5.2% relative standard deviation [RSD] and 87% recovery for five samples) for human hair.

Gagne (2013) described a method for detecting benzene metabolite, trans,trans-muconic acid, in the urine of workers exposed to benzene using ultra-performance liquid chromatography (UPLC) coupled with tandem mass spectrometry (MS/MS). In this method, urine samples can be diluted and injected directly into the system instead of using a solid-phase extraction (SPE) procedure to prepare the sample. The LOD was reported as 69.6 µg/L (precision of 98%).

7.2 ENVIRONMENTAL SAMPLES

Bianchin et al. (2012) described a method using SPME followed by GC-MS separation and detection for determining polycyclic aromatic hydrocarbons and benzene, toluene, ethylbenzene, and xylene isomers in

water simultaneously. This SPME technique uses an optimized fiber coating (PDMS/DVB 65 µm) and careful combination of extraction time, temperature, and extraction mode in order to maximize the extraction of both semivolatile and volatile compounds. The final method proceeds using direct immersion extraction for 48 minutes at 80°C, followed by headspace extraction for 32 minutes at 10°C. The LOD for benzene is 0.15 µg/L (1.7% RSD for five samples of 1 µg/L).

A method for detecting benzene, toluene, ethylbenzene, and xylenes in environmental waste water and human hair samples using hollow fiber solid phase microextraction containing carbon nanotube reinforced sol-gel followed by GC/flame ionization analysis was described (Es'haghi et al. 2011). The LOD for benzene using this method was reported as 0.61 ng/L (4.1% RSD for five samples) for waste water.

A method for extracting benzene from various foodstuffs using distillation and isotope dilution headspace-GC with MS has been described (Vinci et al. 2010). The sample preparation involves distillation with the addition of a borate buffer solution (pH 11). The LOD for this method was ≤0.5 µg/L.

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Benzene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 1[a]	IARC 2015
WHO	Air quality guidelines	$6x10^{-6}$ unit risk	WHO 2010
	Drinking water quality guidelines	0.01 mg/L[b]	WHO 2011
NATIONAL			
Regulations and guidelines:			
a. Air			
ACGIH	TLV (TWA)	0.5 ppm[c]	ACGIH 2014
	STEL	2.5 ppm[c]	
AIHA	ERPGs		AIHA 2014
	ERPG-1	50 ppm	
	ERPG-2	150 ppm	
	ERPG-3	1000 ppm	
DOE	PACs		DOE 2012
	PAC-1	52 ppm	
	PAC-2	800 ppm	
	PAC-3	4,000 ppm	
EPA	Hazardous air pollutant	Yes	EPA 2013c
	AEGL-1[d]		EPA 2014b
	10 minutes	130 ppm	
	30 minutes	73 ppm	
	60 minutes	52 ppm	
	4 hours	18 ppm	
	8 hours	9.0 ppm	
	AEGL-2[d]		
	10 minutes	2,000 ppm[e]	
	30 minutes	1,100 ppm	
	60 minutes	800 ppm	
	4 hours	400 ppm	
	8 hours	200 ppm	
	AEGL-3[d]		
	3 – 10 minutes	9,700 ppm[f]	
	30 minutes	5,600 ppm[e]	
	60 minutes	4,000 ppm[e]	
	4 hours	2,000 ppm[e]	
	8 hours	990 ppm	

Table 8-1. Regulations and Guidelines Applicable to Benzene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	REL (10-hour TWA)	0.1 ppm[g]	NIOSH 2015
	STEL (15-minute TWA)	1.0 ppm[g]	
	IDLH	500 ppm[g]	
OSHA	PEL (8-hour TWA) for general industry	1 ppm	OSHA 2013a, 2013b
	STEL (15-minute TWA) for general industry	5 ppm	29 CFR 1910.1000 29 CFR 1910.1028
	PEL (8-hour TWA)	10 ppm[h]	
	Acceptable ceiling concentration	25 ppm[h]	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift (maximum duration is 10 minutes)	50 ppm[h]	
	PEL (8-hour TWA) for construction industry	1 ppm	OSHA 2014a, 2014b 29 CFR 1926.55, Appendix A 29 CFR 1926.1128
	STEL(15- minute TWA) for construction industry	5 ppm	
	PEL (8-hour TWA) for shipyard industry	1 ppm	OSHA 2014c,2014d 29 CFR 1915.1000 29 CFR 1915.1028
	STEL(15- minute TWA) for shipyard industry	5 ppm	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2013d 40 CFR 116.4
	Drinking water health advisories		EPA 2012
	1-day health advisory for a 10-kg child	0.2 mg/L	
	10-day health advisory for a 10-kg child	0.2 mg/L	
	RfD	0.004 mg/kg/day	
	DWEL	0.1 mg/L	
	Life-time health advisory	0.003 mg/L	
	10^{-4} Cancer risk	1 – 10 mg/L	
	Cancer descriptor	H[i]	
	National primary drinking water standards		EPA 2009
	MCLG	Zero	
	MCL	0.005 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Benzene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2013e 40 CFR 117.3
	Water quality criteria for human health consumption of:		EPA 2013f
	Water + organism	2.2 µg/L[j]	
	Organism only	51 µg/L[J]	
	Water + organism	0.45–1.6 µg/L[k]	EPA 2014c
	Organism only	6.2–23 µg/L[k]	
c. Food			
FDA	Bottled drinking water	0.005 mg/L	FDA 2004 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	A1[l]	ACGIH 2014
	Biological exposure indices (end of shift)		
	S-phenylmercapturic acid in urine	25 µg/g creatinine	
	Trans,trans-muconic acid in urine	500 µg/g creatinine	
EPA	Carcinogenicity classification	Group A[m]	IRIS 2015
	Oral slope factor	$1.5x10^{-2} – 5.5x10^{-2}$ per (mg/kg)/day	
	Inhalation unit risk	$2.2x10^{-6} – 7.8x10^{-6}$ per µg/m^3	
	RfC	$3x10^{-2}$ mg/m^3	
	RfD	$4x10^{-3}$ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2014d 40 CFR 302.4
	Reportable quantity	10 pounds[n]	
	RCRA hazardous waste number	U019	
	Effective date of toxic chemical release reporting	01/01/87	EPA 2014e 40 CFR 372.65
	Standards for the management of specific hazardous wastes		EPA 2014f 40 CFR 266 Appendix V
	Risk specific doses (10^{-5})		
	Unit risk	$8.3x10^{-6}$ m^3/µg	
	RsD	1.2 µg/m^3	
	Health-based limits for exclusion of waste-derived residues	$5x10^{-3}$ mg/kg	EPA 2014g 40 CFR 266 Appendix VII

Table 8-1. Regulations and Guidelines Applicable to Benzene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
DHHS	Carcinogenicity classification	Known to be a human carcinogen	NTP 2014

[a]Group 1: carcinogenic to humans.
[b]For substances that are considered to be carcinogenic, the guideline value is the concentration in drinking water associated with an upper-bound excess lifetime cancer risk of 10^{-5} (1 additional cancer per 100,000 of the population ingesting drinking water containing the substance at the guideline value for 70 years). Concentrations associated with upper-bound estimated excess lifetime cancer risks of 10^{-4} and 10^{-6} can be calculated by multiplying and dividing, respectively, the guideline value by 10.
[c]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[d]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.
[e]Values denoted as having safety considerations against the hazard of explosion, whereas the Lower Explosive Limit (LEL) =14,000 ppm and each value should be ≥10% LEL.
[f]Value denoted as having extreme safety considerations against the hazard of explosion must be taken into account, whereas the LEL =14,000 ppm and each value should be ≥50% LEL.
[g]NIOSH potential occupational carcinogen.
[h]This standard applies to the industry segments exempt from the 1 ppm 8-hour TWA and 5 ppm STEL of the benzene standard at 1910.1028.
[i]H: carcinogenic to humans.
[j]This criterion is based on carcinogenicity of 10^{-6} risk.
[k]EPA has updated its national recommended water quality criteria for human health for 94 chemical pollutants to reflect the latest scientific information and EPA policies. This is the draft update to the value for benzene on the human health criteria table.
[l]A1: confirmed human carcinogen.
[m]Group A: known human carcinogen.
[n]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) and 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Emergency Exposure Guideline Levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; RsD = risk specific dose; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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