CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

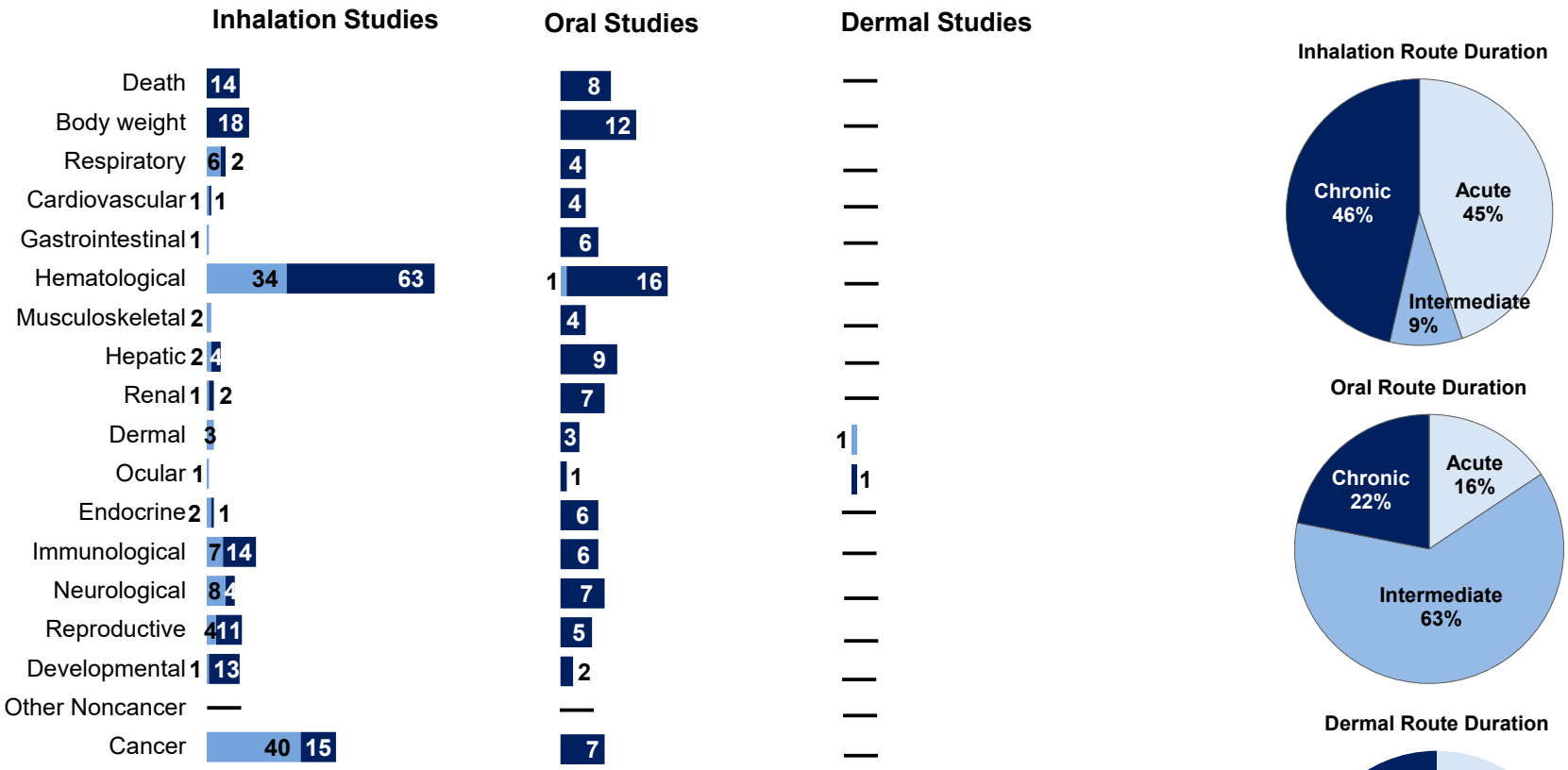
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to benzene that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of benzene. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Benzene by Route and Endpoint*

Potential hematological, cancer, and body weight effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. If no studies were included in the profile for a specific organ system and route of exposure, this is shown by a dash (–). Note that most studies examined multiple endpoints.

Acute-Duration MRLs. Studies in laboratory animals have identified hematopoietic effects (specifically, decreased peripheral WBCs) as the most sensitive effect of acute-duration inhalation exposure to benzene. A provisional acute-duration inhalation MRL was derived based on a LOAEL of 10.2 ppm for decreased peripheral lymphocytes in mice (Rozen et al. 1984). Dempster and Snyder (1991) also reported similar hematological effects at 10.3 ppm in mice. Additional studies examining hematological effects at lower exposure levels in laboratory animals would provide additional information to define the NOAEL-LOAEL boundary. Acute-duration oral studies did not provide sufficient data to derive an MRL. However, the intermediate-duration oral MRL was adopted for the acute-duration oral MRL. Additional acute-duration inhalation studies examining comprehensive toxicological endpoints, including hematological effects, for extended dose ranges may provide information to derive an acute-duration oral MRL.

Intermediate-Duration MRLs. Provisional intermediate-durations inhalation and oral MRLs have been developed. The intermediate-duration inhalation is based on a LOAEL of 10.2 ppm for immunological effects (delayed splenic lymphocyte reaction to foreign antigens evaluated in *in vitro* mixed lymphocyte reaction) in mice (Rosenthal and Snyder 1987). The LOAEL of 10 ppm is the lowest value for adverse effects in the intermediate-duration inhalation database. However, a NOAEL was not identified in this study. Additional intermediate-duration inhalation studies evaluating effects at lower exposure levels may provide information to define the NOAEL-LOAEL boundary, decreasing uncertainty in the MRL. The intermediate-duration oral MRL is based on the LOAEL of 1 mg/kg/day for hematological effects (decreased number of WBCs, lymphocytes, neutrophils, and monocytes) in mice (Li et al. 2018). This study also identified a NOAEL of 0.1 mg/kg/day. The NOAEL and LOAEL values of 0.1 and 1 mg/kg/day, respectively, are the lowest doses evaluated for intermediate-duration oral studies on benzene. Additional studies at these low doses could provide additional supportive data for the intermediate-duration oral MRL and perhaps identify a lower LOAEL value for adverse health effects. Most intermediate-duration oral studies were conducted at doses much greater than 1 mg/kg/day.

Chronic-Duration MRLs. The primary target for adverse systemic effects of benzene following chronic-duration inhalation exposure is the hematological system. A provisional chronic-duration inhalation MRL was derived based on data from a study in humans that observed hematological effects (decreased B-cell count) (Lan et al. 2004a). Lan et al. (2004a) reported the lowest LOAEL of 0.57 ppm for hematotoxicity in the chronic-duration inhalation database for humans. The MRL is supported by numerous occupational exposure studies and studies in laboratory animals showing that chronic-duration

exposure to benzene is hematotoxic. Additional occupational studies at low exposure levels may identify lower LOAEL values for hematological effects.

No human data are available to evaluate hematological effects following oral exposure. Although chronic-duration oral animal studies are available for hematological effects (Maltoni et al. 1983, 1985; NTP 1986), the most extensive study (NTP 1986) did not conclusively define a NOAEL or a less serious LOAEL for endpoints that could be used to derive an MRL. A provisional chronic-duration oral MRL of 0.0003 mg/kg/day was derived based on a route-to-route extrapolation of the provisional chronic-duration inhalation MRL. The critical effect was decreased number of peripheral lymphocytes (B-cell lymphocytes) in shoe manufacturing workers exposed to benzene (Lan et al. 2004a). A total uncertainty factor of 3 was applied for route-to-route extrapolation. Note that the provisional chronic-duration inhalation included an uncertainty factor of 10 for intraspecies variability. Additional chronic-duration oral animal data at low doses could provide a chronic-duration oral MRL and assist in defining threshold levels for populations living near hazardous waste sites.

Health Effects.

Hematological. The hematological system is a well-established target for benzene toxicity, with numerous studies providing support for adverse effects. Additional occupational and animal studies evaluating low benzene air concentrations may provide additional information to further define the NOAEL-LOAEL boundary. The database of oral exposure studies is much smaller for inhalation. Additional studies evaluating hematological effects at lower oral doses benzene for acute, intermediate, and chronic durations would provide information to more fully define oral dose-response relationships.

Immunological. Immunological effects can be categorized as: (1) indirect effects resulting from decreased WBCs due to hematotoxicity, or (2) direct effects on the function of immune cells. Discussions above consider the indirect effects benzene on the immunological system. However, relatively little information is available on the direct effects on immune function. Additional studies in humans and animals across a wide range of exposures and exposure levels would provide important information. Additional mechanism studies may identify critical effects on the immune system that would broadly inform the immunological effects of benzene.

Neurological. In humans, exposure to high levels of benzene can be neurotoxic and fatal. However, at lower occupational exposures, neurological effects have not been reported. Studies

evaluating neurological function in workers would define the potential for occupational exposure to benzene to produce adverse effects. Few studies in animals have evaluated neurological effects of benzene. Inhalation and oral studies in animals evaluating a full observational battery of effects over a large dose range and all exposure durations would provide information to better determine the neurotoxicity of benzene.

Reproductive. Reproductive effects of benzene exposure were studied in one inhalation study of workers and one study of exposure to contaminated drinking water; no reproductive effects were observed in either study. Additional epidemiological studies evaluating the potential effects of benzene by inhalation and oral exposures would provide important information to determine if reproductive effects are a concern in humans. Studies in animals have identified adverse reproductive effects; however, additional studies specifically designed to evaluate reproductive effects could further define these adverse effects. In addition, no 2-generation reproductive studies were identified; such studies would provide important information in understanding the potential for benzene to produce adverse reproductive effects.

Developmental. No reliable studies evaluating developmental effects in humans were identified. Studies in animals have evaluated developmental effects of benzene. However, additional studies in animals would provide data to further define effects. For example, an inhalation study identified effects on the hematological system in neonates and 6-week-old offspring (Keller and Snyder 1988); however, no other studies have evaluated hematological effects as a developmental endpoint. Studies identifying the potential of benzene to produce hematological or other systemic effects in offspring can provide important information regarding nontraditional developmental endpoints.

Cancer. EPA (IRIS 2003), IARC (2018), and NTP (2021) have concluded that benzene is a human carcinogen based on sufficient data in humans supported by animal evidence. Epidemiological studies and case reports provide clear evidence of associations between occupational exposure to benzene and the occurrence of AML (IARC 2018; IRIS 2003; Yin et al. 1996a, 1996b), as well as suggestive evidence of associations between benzene and NHL and multiple myeloma (Hayes et al. 1997; Rinsky et al. 1987). Strong support for the carcinogenicity of benzene is also provided in numerous animal studies. Additional occupational studies could better characterize exposure level and exposure duration relationships for benzene and leukemia,

particularly at low levels of exposure, and clarify the potential of benzene to induce NHL and multiple myeloma.

Epidemiological and Human Dosimetry Studies. For inhalation exposure, several occupational exposure studies provide data that evaluate associations between measured exposure to benzene and hematological effects. Additional studies at low occupational exposure levels would provide more insight into effects of lower measured exposures. In addition, little data are available for associations between urinary benzene and benzene metabolites and hematological effects. Urinary metabolites can confirm that exposure to benzene has occurred; however, due to human variability in benzene metabolism to toxic metabolites, quantitative associations between various benzene metabolites and adverse effects need further investigation. Very little data are available to examine associations between oral exposure to water or food contaminated with benzene and health effects. Additional studies could provide important information to establish these relationships and possibly provide dose-response data.

Biomarkers of Exposure and Effect. Several biomarkers of exposure have been identified to demonstrate exposure to benzene. These include unmetabolized benzene in the expired air and urine and urinary metabolites of benzene, including phenol, *trans,trans*-muconic acid, and PhMA. Urinary metabolites are commonly used as biomarkers of exposure (IARC 2018; Section 3.3.1). Urinary benzene and PhMA are specific biomarkers for benzene exposure; however, urinary *trans,trans*-muconic acid and phenol are not specific for benzene exposure as they also are metabolites of other metabolites (Section 3.3.1). Studies examining the relationships between various urinary metabolites and external benzene exposure would provide additional information for quantifying exposures.

There are no clinical effects that are unique to benzene. However, blood counts of benzene workers are routinely monitored for decreased cell counts. Thus, a combination of blood counts and known exposure to benzene provide information on measures of effect. Additional studies could further define threshold levels of adverse hematological effects based on blood count monitoring. DNA adducts with benzene metabolites, chromosomal aberrations in bone marrow and peripheral blood lymphocytes, and sister chromatid exchanges could be used to monitor for benzene effects; however, other than the formation of DNA adducts with benzene metabolites, these biomarkers are not specific to benzene (IARC 2018; McHale et al. 2012).

Absorption, Distribution, Metabolism, and Excretion. Data from both humans and animals consistently indicate that inhaled benzene is rapidly absorbed through the lungs (Eutermoser et al. 1986;

Nomiyama and Nomiyama 1974a; Sabourin et al. 1987; Schrenk et al. 1941; Srbova et al. 1950; Yu and Weisel 1996). Although experimentally-acquired data are not available on oral absorption of benzene in humans, case reports of accidental or intentional poisoning suggest that benzene is rapidly absorbed from the gastrointestinal tract (Thienes and Haley 1972). The efficient absorption of oral doses in animals is well documented (Cornish and Ryan 1965; Parke and Williams 1953; Sabourin et al. 1987). Benzene can be absorbed through the skin, but the rate of absorption is much lower than that for inhalation (Maibach and Anjo 1981; Susten et al. 1985; Tsuruta 1989). Following absorption into the body, benzene is widely distributed to tissues, with the relative uptake dependent on the perfusion of the tissue by blood and the total potential uptake dependent on fat content and metabolism (Sato et al. 1975; Tauber 1970).

There is no evidence to suggest that the route of administration has any substantial effect on the subsequent metabolism of benzene, either in humans or animals. Benzene is metabolized primarily in the liver; however, production of reactive metabolites in the bone marrow also contributes to toxicity (Section 3.1.3). Benzene is a preferential substrate of CYP2E1, which also metabolizes alcohol. The induction of CYP2E1 by benzene (and some of its metabolites) with subsequent generation of reactive metabolites, oxygen radicals, circulating lipid peroxides, and hydroxyl radicals could be associated with hematopoietic toxicity and carcinogenicity of benzene (Irons 2000; Parke 1989; Ross 1996, 2000; Smith 1996a, 1996b; Snyder 2000a, 2000b, 2002; Snyder and Hedli 1996; Snyder and Kalf 1994). CYP2E1 is not confined to the liver: it has also been detected in bone marrow. Andrews et al. (1979) demonstrated that rabbit bone marrow is capable of metabolizing benzene. Schnier et al. (1989) subsequently found that rabbit bone marrow contains CYP2E1. Irons et al. (1980) demonstrated that benzene metabolism by rat bone marrow (*in situ*) was complete and independent of metabolism by the liver, with concentrations of phenol greater than catechol and hydroquinone. Although the total metabolism by bone marrow was limited (total metabolites present were 25% of those in blood), the concentration of metabolites in the bone marrow exceeded that in the blood. Similar studies have been conducted in mice (Ganousis et al. 1992). Benzene metabolism in bone marrow is not well understood; additional data regarding the initial oxidation step and the comparatively low levels of CYP2E1 activity in bone marrow would be useful in identifying the mechanisms of benzene's hematotoxicity. This aspect of metabolism may have implications for long-term exposures, which could be explored in chronic-duration exposure studies. The intermediary metabolites of benzene are responsible for many of the toxic effects observed (Eastmond et al. 1987; Gad-El-Karim et al. 1985). Biotransformation is believed to be essential for benzene-induced bone marrow damage.

Reactive metabolites of benzene formed in liver and bone marrow contribute to hematologic toxicity to benzene (Section 3.1.5). Studies that quantify the relative contributions of metabolism in liver and bone marrow to hematopoietic toxicity would improve modeling of tissue dosimetry and toxicodynamics. Additionally, more information is needed on the pathways of metabolism in humans, the chemical nature of the toxic metabolites, and the mechanism of toxicity. Data comparing urinary metabolite profiles of orally administered benzene and phenol in mice suggest that zonal differences in metabolism in the liver may be responsible for relative differences in the production of hydroquinone, thus explaining the higher toxicity observed after benzene administration compared with phenol administration (Kenyon et al. 1995). Additional work in this area would aid in further understanding the kinetic determinants of benzene toxicity. Ethanol and dietary factors such as food deprivation and carbohydrate restriction enhance the hematotoxic effects of benzene. Therefore, more information regarding differences in metabolic pattern according to sex, age, nutritional status, and species, and correlation to differences in health effects would be useful.

Humans and animals both excrete inhaled benzene via expiration. Additionally, benzene metabolites are excreted primarily in the urine in both humans and animals. No studies in humans exist for excretion of oral doses of benzene. Studies in several animal species indicate that the route of excretion of benzene and/or its metabolites is a function of exposure level and the saturation of metabolic systems (Henderson et al. 1989). Data regarding excretion following dermal exposure in humans are limited. However, the major route of excretion in both humans and animals following dermal exposure is the urine.

Comparative Toxicokinetics. Qualitatively, absorption, distribution, metabolism, and excretion appear to be similar in humans and laboratory animals. However, quantitative variations in the absorption, distribution, metabolism, and excretion of benzene have been observed with respect to exposure routes, sex, nutritional status, and species. Further studies that focus on these differences and their implications for human health would be useful. Additionally, *in vitro* studies using human tissue and further research into PBPK modeling would contribute significantly to the understanding of the kinetics of benzene and would aid in the development of pharmacokinetic models.

Children's Susceptibility. No evidence of age-related differences in susceptibility to benzene toxicity was located. Fetal exposure occurs as benzene crosses the placenta. In addition, nursing infants can be exposed to benzene in the breast milk. Children could potentially be at increased risk for benzene toxicity via the inhalation exposure route based on higher activity levels and ventilation rates than adults. Age-related differences in benzene metabolism could potentially affect susceptibility. However, the

susceptibility of children relative to adults is unknown. Well-designed animal studies should be performed to adequately assess the potential for age-related increased susceptibility to benzene, including gestational exposure and exposure in neonates followed through maturation. Specifically, the most sensitive endpoints (hematological and immunological) should be examined.

Production, Import/Export, Use, Release, and Disposal. Benzene is one of the top 20 highest volume chemicals produced in the United States. In 1994, the U.S. production volume of benzene was 14.7 billion pounds (C&EN 1995). The production volume during the 1984–1994 period increased by 4% annually (C&EN 1995). The United States currently reports nationally aggregated production between $10x10^{10}$ and $20x10^{10}$ pounds (EPA 2022a). Imports of benzene into the United States have generally ranged from 3,643 to 4,715 billion pounds from 2020 to 2022 (USITC 2023). Exports were 352–678 billion pounds during the same time period (USITC 2023). The major use of benzene is in the production of other chemicals (primarily ethylbenzene, cumene, and cyclohexane), accounting for approximately 99% of benzene production volume. Benzene is also used as an anti-knock agent in unleaded gasoline (EPA 2023a; NESCAUM 1989; NTP 1994). The widespread use of benzene as a solvent has decreased in recent years due to benzene's listing as a human carcinogen (IRIS 2003). Many products that used benzene as a solvent in the past have replaced it with other organic solvents; however, benzene may still occur as a trace impurity in these products. Less than 2% of the amount of benzene produced is used as a solvent in such products as trade and industrial paints, rubber cements, adhesives, paint removers, artificial leather, and rubber goods. Benzene has also been used in the shoe manufacturing and rotogravure printing industries (EPA 1978; OSHA 1977). In the past, certain consumer products (such as some paint strippers, carburetor cleaners, denatured alcohol, and rubber cement used in tire patch kits and arts and crafts supplies) contained small amounts of benzene (Young et al. 1978). Other consumer products that contained benzene were certain types of carpet glue, textured carpet liquid detergent, and furniture wax (Wallace et al. 1987). Benzene-containing wastes, such as commercial chemical products, manufacturing chemical intermediates, and spent solvents, are subject to federal and/or state hazardous waste regulations. Currently, the recommended method of disposal is to incinerate solvent mixtures and sludges at a temperature that ensures complete combustion. No additional information on the production, import/export, use, release, or disposal of benzene is needed at this time.

Environmental Fate. Benzene released to the environment partitions mainly to the atmosphere (Mackay and Leinonen 1975; NLM 2023). However, the compound can also be found in surface water and groundwater. Benzene is mobile in soil (Karickhoff 1981; Kenaga 1980); however, there is a need for more information on the leachability potential of benzene to groundwater in different soil types.

Benzene is transformed in the atmosphere by photooxidation. Biodegradation, principally aerobic, is the most important fate process of benzene in water (Delfino and Miles 1985; McAllister and Chiang 1994; Salanitro 1993) and soil (Gibson 1980; Hopper 1978; Salanitro 1993). Benzene can persist in groundwater. Other than leachability potential, no additional information on the environmental fate of benzene is needed at this time.

Bioavailability from Environmental Media. Benzene can be absorbed following oral, dermal, and inhalation exposure (see Section 3.1.1). These routes of exposure may be of concern to humans because of the potential for benzene to contaminate the air, drinking water, and soil (see Section 5.2). Information on inhalation exposure and on the absorption of benzene following ingestion of plants grown in contaminated environments near hazardous waste sites would be helpful in determining bioavailability of the compound in these media.

Food Chain Bioaccumulation. Benzene has an estimated low-to-moderate bioconcentration potential in aquatic organisms (Miller et al. 1985; Ogata et al. 1984) and some plants (Geyer et al. 1984). Most of the benzene accumulation on vegetation results from air-to-leaf transfer (Collins et al. 2000). Root uptake is not believed to be important (Hattemer-Frey et al. 1990). Biomagnification in aquatic food chains does not appear to be important (Ogata et al. 1984). No further information appears to be needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of benzene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of benzene in the environment can be used in combination with the known body burden of benzene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Benzene is widely distributed in the environment and has been detected in air (EPA 2023b; Mohamed et al. 2002; Morello-Frosch et al. 2000), water (Rowe et al. 2007; USGS 2014, 2020; WQP 2023), and some foods (Fleming-Jones and Smith 2003; Medeiros Vinci et al. 2012). Limited soil and sediment monitoring data are available; benzene is typically not detected in ambient samples (WQP 2023) but has been detected at hazardous waste sites (ATSDR 2019a, 2023d). The levels of benzene in air and water are well documented, but there is a need for more current information at hazardous waste sites. Benzene is not expected to be a significant contaminant in aquatic foods (Geyer et al. 1984; Gossett et al. 1983; Miller et al. 1985; Ogata et al. 1984); however, some contamination of food crops consumed by humans may occur, primarily from air-to-leaf transfer (Hattemer-Frey et al. 1990). The total concentration of benzene on exposed food crops consumed by humans was estimated to be 587 ng/kg (Hattemer-Frey et al.

1990). An estimated daily dietary intake of 0.020 µg/kg body weight/day was derived based on detections in food available in Belgian markets (Medeiros Vinci et al. 2012). Humans are at risk of exposure to benzene because of its widespread distribution in the environment, and are typically exposed to higher concentrations in indoor air (George et al. 2011; Kinney et al. 2002; Weisel et al. 2008). Releases to the air from gasoline, smoking, and automobile exhaust constitute the major risk of potential exposure for the general population (Wallace 1995). Indoor air may also be a major risk of potential exposure based on measured benzene pollution from cars in attached garages, pollution in residences that used fuel oil for heating or burned wood in fireplaces, and emission rates during cooking (Kashtan et al. 2023; Maine DEP 2014; NYSDOH 2005; Schauer et al. 2001; Thomas et al. 1993; Weisel et al. 2008). Additional data characterizing the concentration of benzene in drinking water, outdoor and indoor air, and soil surrounding hazardous waste sites would be helpful in assessing human exposure for populations living near these waste sites.

Exposure Levels in Humans. Benzene has been detected in human body fluids and tissues such as blood, urine, and breast milk (CDC 2022a, 2022b; Kim et al. 2007b). Most of the monitoring data have come from occupational studies of specific worker populations exposed to benzene (Inoue et al. 1989; Karacic et al. 1987; OSHA 1987; van Wijngaarden and Stewart 2003). Biological monitoring studies exist for the general population (CDC 2022a). There is information for background levels in breath of smokers and nonsmokers (Wallace 1989b), baseline blood levels (CDC 2022a), and levels of urinary metabolites in unexposed people (CDC 2022b). Information on exposure levels for populations living in the vicinity of hazardous waste sites would be helpful in estimating exposure in these groups. More recent information on worker exposure levels would be helpful in estimating current occupational exposure.

Exposures of Children. Benzene levels have been monitored in children and the environments in which they live. This information gives levels found for infants and children in rural and urban areas as well as the levels found for children in homes of parents who smoke (Duarte-Davidson et al. 2001). There have been many studies relating oil and petroleum exposure to childhood leukemia and other diseases; however, the majority of these studies have not recorded benzene levels. More information about the exposures of children, particularly those subject to high exposures such as smoking, busy roads, and gasoline stations, are needed.

6.3 ONGOING STUDIES

Ongoing studies identified in the National Institute of Health (NIH) RePORTER (2024) database, which tracks projects funded by NIH, are provided in Table 6-1.

Table 6-1. Ongoing Studies on Benzene

Investigator	Affiliation	Research description	Sponsor
Cassidy-Bushrow, Andrea	Wayne State University	Nested case-control study on the effects of volatile organic compounds and preterm birth	NIEHS
Mor, Gil G	Wayne State University	Effect of benzene on fetal T-cell development	NICHD
Sadagurski, Marianna	Wayne State University	Investigation on benzene exposure of neuroinflammation and metabolic dysregulation	NIEHS
Zelko, Igor	University of Louisville	Studies on the effects of benzene and the exacerbation of cardiac function	NIEHS

NICHD = National Institute of Child Health and Human Development; NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER (2024)