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Chapter 5

ADVERSE HEALTH EFFECTS OF BENZENE EXPOSURE IN CHILDREN: CURRENT UNDERSTANDINGS AND PERSPECTIVES

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ABSTRACT

Despite significant advances, the adverse health effects of benzene exposure in children have rarely been studied. Children at various developmental stages have unique physical risk factors when exposed to toxic chemicals such as benzene due to their levels of mobility, oxygen consumption, hormonal production, and overall growth. They are more susceptible to leukemogenesis because their hematopoietic cell populations are differentiating and undergoing maturation. The susceptibility to benzene may vary due to its effect that arises, in part, from genetic variations in its metabolism, DNA repair, genomic stability, and immune function. The pharmacokinetics of benzene differ widely between children and adults due to childrens' incomplete metabolic systems, rapid tissue regeneration, immature host defenses, activity

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patterns, and high rates of infection by respiratory pathogens. Thus, exposure to benzene can cause deleterious health effects among children. Given the importance of the toxicity of benzene, this chapter provides summaries of the current scientific knowledge and understanding of the clinical findings and health consequences of benzene exposure among children.

ABBREVIATIONS

ACQ = Asthma Control Questionnaire;
ALP = Alkaline phosphatase*;*
ALT = Alanine amino transferase;
AST = Aspartate amino transferase;
BP = British petroleum;
BUN = Blood urea nitrogen;
RBC = Red blood cells;
WBC = White blood cells.

INTRODUCTION

Benzene is a volatile aromatic hydrocarbon ubiquitously found in the environment [1]. It arises mostly from anthropogenic sources, notably combustion. Benzene is a natural component of both crude and refined petroleum and formed because of the incomplete combustion of fossil fuels such as petroleum products and coal [2]. It is also a component of tobacco smoke, gasoline, vehicle exhaust, and industrial emissions, and was used historically as an industrial solvent in industry and in consumer products [3]. The uses of benzene as a solvent are now restricted in many countries, but it is still produced in high volumes for use primarily as a chemical intermediate. Benzene ranks in the top 20 most abundantly produced chemicals in the United States and is a commercially important intermediate of many chemicals manufactured in the industry [4].

Over 98% of the benzene produced is derived from the petrochemical and petroleum refining industries [5]. Owing to its volatile properties, benzene is known as one of the main contributors to air pollutants in the environment [6]. As a contaminant, ambient benzene is found in the environment from both human activities and natural processes [7, 8]. As the primary pollutant of concern, the International Agency for Research on Cancer (IARC) has long been classified benzene as a carcinogen because it in fact causes leukemia and other malignancies in humans after their exposure to benzene [9].

HEALTH CONCERNS OF BENZENE EXPOSURE

Environmental benzene exposure is an important health concern. The human population at large can be exposed to benzene in polluted air and water and through the use of benzene-containing products. It has been clearly established that human exposure to benzene leads not only to malignant cancers [10, 11], but also to a wide range of adverse non-cancerous adverse health effects including functional aberration of respiratory, nervous, immune, hematological, hepatic, renal, cardio-vascular, and reproductive systems [12-17]. After its exposure, benzene is easily absorbed, widely distributed, and extensively metabolized, resulting in a complexity of reactive electrophiles through multiple metabolic pathways in various tissues, including the bone marrow. Following its absorption, benzene is metabolized by cytochrome P450 in the liver and forms active metabolites such as phenol, catechol, hydroquinone, and benzene oxide [18]. A schematic illustration of benzene's metabolism, its mechanisms of toxicity, and its toxic effects in humans is shown in Figure 1. These benzene metabolites suppress the immune system and leads to hematological toxicity, which is important not only as a health effect in its own right, but also as a biomarker and risk factor for leukemia [19, 20]. Additionally, benzene exposure induces oxidative DNA damage, DNA strand breaks, gene mutations, and micronuclei [20, 21]. Moreover,

benzene can affect both B-cell and T-cell proliferation, reduce the host resistance to infection and produce chromosomal aberrations [22].

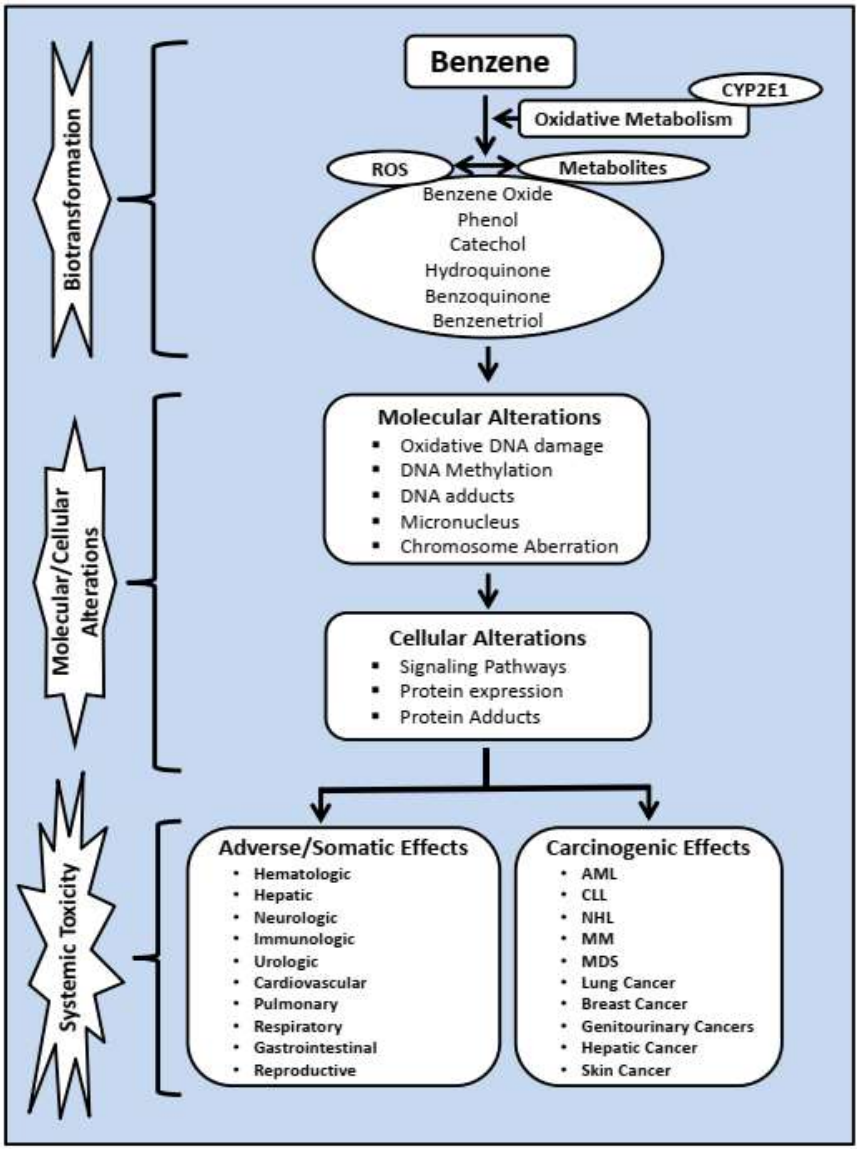

Figure 1. A schematic illustration of benzene metabolism, its mechanisms of toxicity, and its toxic effects in humans.

CHILDREN'S VULNERABILITY

The health effects of benzene exposure have been studied extensively in adults. Whereas, studies evaluating the health consequences of benzene exposure have rarely been reported in children. Emerging studies are demonstrating that benzene exposure can cause harmful health effects in children. Epidemiological studies suggest that benzene exposure is a major cause of childhood leukemia and other hematologic cancers [23-26]. The fact that children are growing and developing makes them more susceptible than adults to the adverse effects of environmental toxic pollutants. The higher susceptibility of children may be due to rapid growth and accompanying anatomical changes in various organs and organ systems, which critically differentiate children from adults. In addition, children are more sensitive than adults to the toxic effects of the chemicals due to their differences in physiology, immaturity of enzyme systems and clearance mechanisms [27-30]. Furthermore, children are more susceptible to leukemogenesis because their hematopoietic cell populations are differentiating and metabolic systems, immature host defenses, high rates of infection by respiratory pathogens [27, 28]. The activity patterns also make children more vulnerable to the toxic effects of benzene exposure. Moreover, the pharmacokinetics of benzene and its metabolites differs widely between children and adults. Given the importance of the toxic effects of the benzene, this chapter provides the current scientific knowledge and understanding of the clinical findings and health consequences of benzene exposure among children (Table 1).

Table 1. Summary of Studies on the effect of benzene exposure among children

Location of Study	Study Design	Childrens' Age	Sample Size	Observed Clinical Health Effects	Reference
Ulsan, Korea	Cohort	8-11 Years	192 (97 Benzene Exposed and 95 Control)	Reduced WBC, RBC, platelets, and lymphocytes counts, decreased hemoglobin in benzene exposed children compared with unexposed childrem	Lee et al. 2002 [31]

Table 1. (Continued)

Location of Study	Study Design	Childrens' Age	Sample Size	Observed Clinical Health Effects	Reference
Texas City, Texas, USA	Cohort	8-11 Years	312 (157 Benzene Exposed and 155 95 Control) children	Reduced WBC counts, increased platelet counts, elevated creatinine levels, and increased liver enzymes such as ALP, AST and ALT in benzene exposed children compared with unexposed children.	D'Andrea and Reddy 2014 [32]
Texas City, Texas, USA	Cohort	8-11 Years	899 (641 Benzene Exposed and 258 Control) children	Reduced WBC counts, increased platelet counts, decreased hemoglobin, hematocrit, and BUN levels, and increased liver enzymes such as ALP, AST and ALT in benzene exposed children compared with unexposed children.	D'Andrea and Reddy 2016 [33]
Four townships with 83 small villages on the west coast in the Republic of Korea	Cohort	5-16 Years	655 children	Exposure was associated with aggravation and persistence of asthma symptoms	Noh et al. 2019 [34]
Taean, The Republic of Korea	Cohort	Range: <9 Years to >12 Years	1361 children	Exposure was associated with significantly higher symptom risk of depression	Ha et al. 2013 [35]
Taean, The Republic of Korea	Cohort	6-12 Years	436 children	Significantly impaired lung function, increased prevalence of 'asthma, elevated bronchial hyper reactivity, and higher on-set of wheezing	Jung et al. 2013 [36]
Kanawha County, West Virginia, USA	Cohort	7-8 Years	7,796 children	Increased incidence of chronic respiratory symptoms in children attending schools located in a close proximity to chemical industries. Significant trends were observed for asthma-related responses such as a physician's diagnosis of asthma, persistent wheezing, and attacks of shortness of breath with wheezing in school children	Ware et al. 1993 [37]

Location of Study	Study Design	Childrens' Age	Sample Size	Observed Clinical Health Effects	Reference
				enrolled within a close proximity to chemical plants regions than those in the non-industrial region.	
La Plata, Argentina	Cohort	6-12 Years	1,191 (282 living close to the petro-chemical plants, 270 exposed to heavy traffic, and 639 living in non-polluted areas)	Significantly elevated asthma and respiratory symptoms including wheezing, cough, dyspnea, and rhinitis, and reduced lung function in children living near the petrochemical plant compared with those living in non-polluted areas.	Wichmann et al. 2009 [38]
Rio Grande do Norte, Brazil	Cross-sectional	0-14 Years	209 children	Higher incidence of respiratory symptoms in children exposed to petrochemicals	Moraes et al. 2010 [39]
El Paso, Texas, USA	Panel study	6-12 Years	36 children	Increased Asthma Control Questionnaire Score in children exposed to traffic pollution with benzene, toluene, and other toxins.	Zora et al. 2013 [40]
Asturias, Gipuzkoa, Sabadell, and Valencia, Spain	Cohort	12-18 Months	2,199 infants	Increased respiratory tract infections	Aguilera et al. 2013 [41]
Los Angeles, USA	Panel study	10-16 Years	21 children	Increased asthma and lung function among the children exposed to benzene	Delfino et al.2003 [42]
Viseu, Portugal	Panel study	6-8 Years	51 children	Deteriorated lung function in children exposed to benzene	Martins et al. 2012 [43]
Texas City, Texas, USA	Cohort	8-11 Years	312 (157 Benzene Exposed and 155 95 Control) children	Upper Respiratory (67%), neurological symptoms (57%), diarrhea (25%), cough (24%), dermatological (24%), nausea/vomiting (21%), gastrointestinal (12%), wheezing (9%), chest pain (6%), vision (6%), painful joints (6%), and urinary irritation (3%)	D'Andrea and Reddy 2016 [49]

WBC = White blood cells; RBC = Red blood cells; ALP = Alkaline phosphatase; AST = Aspartate amino transferase; ALT = Alanine amino transferase. BUN = Blood urea nitrogen.

BENZENE EXPOSURE AND ALTERATIONS OF HEMATOLOGICAL FUNCTIONS AMONG CHILDREN

Alterations in hematological functions are not only relevant for diagnosing disorders of the hematological system but also helpful in the diagnosis of many organ and systemic diseases. A cohort study by Lee and coauthors [31] assessed the hematological changes in children living near vicinity of a petrochemical estate region in Ulsan, Korea, and who were environmentally exposed to volatile organic compounds containing low levels of benzene. This study included a total of 192 children between the ages of 8 years and 11 years who were living in close proximity to the petrochemical estate region or a suburban region of Ulsan, Korea. The exposed group was comprised of 48 boys and 49 girls who lived near the estate region and went to an elementary school located near the petrochemical site. The unexposed group was comprised of 46 boys and 49 girls who had lived in the suburban region 10 miles from the petrochemical estate region. Both the unexposed and benzene exposed groups had similar age and sex distributions. Hematological assessment revealed that, the total WBC counts and absolute lymphocytes counts of 11-year-old children living near the estate region were significantly lower than those of children living in the suburban region further away from the petrochemical site ($P = 0.009$, $P = 0.032$, respectively). Although the 8-year-old children living near the petrochemical estate region had decreased WBC counts and absolute lymphocytes counts compared with those living in the suburban region, they did not reach statistical significance. The RBC counts and hemoglobin levels of the 8-year-old exposed children were significantly lower than those of the unexposed children ($P < 0.001$, $P < 0.001$, respectively). A similar, but not statistically significant, trend was seen in the parameters of the 11-year-old exposed and unexposed groups. Whereas the platelet counts were significantly decreased in both the 8- and 11-year-old exposed children compared with those of the unexposed children (P-0.001, P-0.001, respectively). A follow up assessment at 3 and 6 months after their initial evaluation yielded similar differences but there

were not consistent findings in the exposed and unexposed groups of the 8- and 11-year-old children.

The generalized linear model analysis of variance for the CBC values showed that the region where the exposure took place was a significant independent variable for the total WBC counts, RBC counts, and platelet counts ($P = 0.007$, $P = 0.004$, $P = 0.036$, respectively), and the childrens' sex was a significant independent variable for the RBC counts ($P = 0.001$). Similarly, age was a significant independent variable for the total WBC counts, absolute lymphocyte counts and platelet counts $P < 0.001$, $P = 0.004$, and $P = 0.005$, respectively). Overall, the study findings showed that environmental exposure to the volatile organic compounds containing low levels of benzene was associated clinically with a higher prevalence of hematological abnormalities in children living near the petrochemical estate region.

In a pilot study [32] we evaluated the hematological functions in children who were less than 17 years-old and exposed to benzene following BP's flaring incident in Texas City, Texas. A total of 312 children were included in the study. Of the 312 children, 157 were exposed to benzene and 155 were not exposed to benzene. Both unexposed and benzene exposed groups had similar age and sex distributions. Clinically, hematologic analysis showed that WBC counts were significantly decreased in the benzene exposed children compared with the unexposed children ($P = 0.022$). Conversely, the platelet counts were increased significantly in the benzene exposed group compared with the unexposed group ($P = 0.005$). Similarly, the serum creatinine levels were significantly increased in the benzene exposed children compared with the unexposed children ($P = 0.000$). However, no significant alterations were observed in the mean hemoglobin or hematocrit or BUN levels between the benzene exposed and unexposed children. The results of this pilot study indicated that environmental exposure to benzene was associated clinically with altered hematological profiles in those children who were exposed to benzene from the flaring incident at the BP refinery facility in Texas City, Texas.

In a larger cohort study, we further assessed the hematological changes that occured in children exposed to benzene following the flaring incident [33]. A total of 899 children aged < 17 years were included in the study. Of the 899 children, 258 were unexposed and 641 were exposed to benzene. The mean age of the unexposed and exposed children was 10.5 and 9.5 years, respectively. Among the unexposed children, there were 57% male and 43% female children. In the benzene exposed group, there were 52%males and 48% females.

Hematological analysis indicated that those children exposed to benzene had significantly decreased mean WBC counts compared with those of the unexposed children (P = 0.001). Conversely, the mean platelet counts in the benzene exposed group were significantly higher when compared with those of the unexposed children group (P = 0.001). Whereas the mean hemoglobin levels decreased significantly in the benzene exposed group compared with those of the unexposed group P = 0.001). Similarly, the percentage of hematocrit decreased significantly among the benzene exposed children compared with those of the unexposed children (P = 0.001). BUN was also found to be reduced significantly in the benzene exposed group compared with those of the unexposed group (P = 0.001). However, no significant differences were noted in the serum creatinine levels between the benzene exposed and unexposed groups. Furthermore, sub-analysis indicated that, regardless of age or gender, significant alterations in the hematological profiles were seen in those children exposed to benzene. Overall, the findings of the hematological profiles confirmed the pilot study findings indicating that children who have been exposed to benzene have significantly increased health risks compared to unexposed children.

BENZENE EXPOSURE AND ALTERATIONS OF HEPATIC FUNCTION AMONG CHILDREN

The liver is the principal organ of xenobiotic metabolism and hence it is very important to monitor its function in people exposed to benzene or

other toxins. It is well known that phosphatases, amino transferases, and dehydrogenases are important enzymes in biological processes. They are involved in the detoxification, metabolism and biosynthesis of energetic macromolecules for different essential functions. Any interference in these enzymes leads to biochemical impairment and lesions in the tissue and cellular function. Thus, the measurement of these liver enzyme such as ALP, AST and ALT are routinely assessed as indicators for hepatic dysfunction and damage.

Currently, there are no published studies in literature that have evaluated the harmful effects of benzene exposure on the liver functions in children except the research work published by the authors [32, 33]. The initial pilot study included 157 benzene exposed and 155 unexposed children and assessed their liver function enzymes such as alkaline phosphatase (ALP), aspartate amino transferase (AST), and alanine amino transferase (ALT). The study findings revealed that benzene exposed children had clinically significantly higher levels of ALP ($P = 0.04$), AST ($P = 0.015$), and ALT ($P = 0.005$) compared with the unexposed children.

Subsequently, the larger cohort study [33] assessed the liver function enzymes in 641 benzene exposed children and compared with the 258 unexposed children. Serum ALP, AST and ALT levels were reported to be increased significantly in children exposed to benzene compared with the unexposed children ($P = 0.001$). Furthermore, sub-group analysis indicated that, regardless of age or gender, significant alterations in hepatic enzymes were seen in those children exposed to benzene. Overall, the findings of the hepatic profiles confirmed the pilot study findings indicating that children who have been exposed to benzene have significantly increased health risks compared to unexposed children.

BENZENE EXPOSURE AND ILLNESS SYMPTOMS AMONG CHILDREN

Among all, respiratory illness symptoms are the most often studied health complaints in children exposed to either benzene or oil spill or

petrochemicals or urban traffic pollutants. Upper respiratory symptoms were the most frequently reported followed by other illness symptoms. Other illness symptoms included neurological symptoms, cough, and shortness of breath, chest tightness and vision difficulty.

It is well known that crude oil is mixture of multiple volatile organic compounds including benzene, toluene ethylbenzene, xylene and other toxic chemicals. Following oil spill, these toxic chemicals pollute surroundings and persist in various environmental media and bioaccumulate over the long-term. Noh and colleagues [34] recently assessed the long-term effect of the Hebei Spirit's oil spill in 655 middle school children. Specifically, the investigators assessed children's asthma symptoms using survey questionnaire at one year (n = 655), three years (n = 664), and five years (n = 611) after their exposure to oil spill following the accident. A significant longitudinal relationship was seen between oil spill exposure and asthma symptoms in children. Specifically the study found oil spill exposure was associated with aggravation and persistence of asthma symptoms from cross-sectional and longitudinal observations up to five years after the accident. In addition, an increase in the prevalence of asthma symptoms was observed at one year, three years, and five years after the oil spill suggesting long-lasting and perhaps irreversible airway damage in children following their exposure to toxic chemical of the oil spill.

The mental health effects of the *Hebei Spirit* oil spill were assessed by Ha et al. [35] in schoolchildren living in the affected area, where most of their families were victims of the disaster. The investigators divided the child population according to distance of school they attended from the contaminated coastline. A cross-sectional questionnaire survey was conducted using the Children's Depression Inventory and State Anxiety Inventory in children attending elementary schools in the affected area. The information on distances between the nearest contaminated coastline to the child's residential house or attending school were obtained using a web-based map by inputting two address points. Of the 1,467 children who responded to the questionnaire at baseline, 1,361 were included in the analysis. The study showed that children whose schools were located

closest to the contaminated coastline had a significantly higher symptom risk of depression compared to those who lived farthest from the affected areas (odds ratio [OR], 2.73; 95% confidence interval, 1.40 - 5.33). However, no significant association was seen between anxiety symptoms and distance.

Jung and colleagues [36] evaluated the respiratory effects in schoolchildren who lived along the affected area of the *Hebei Spirit* oil spill. Of 662 children living in the area exposed to the oil spill, 436 were participated as subjects. The Modified International Study of Asthma and Allergies in Childhood questionnaire was used to evaluate characteristics related to asthma. The findings of the study revealed that children who lived close to the oil spill area showed a significantly impaired lung function, increased prevalence of 'asthma, elevated prevalence of bronchial hyper reactivity, and higher on-set of wheezing compared to those who resided far from the oil spill area. Collectively, the study findings suggest that oil spill exposure is a risk factor for asthma in children.

A study by Ware and co-investigators [37] evaluated the respiratory and irritant health effects of ambient volatile organic compounds in 7,796 children attending 74 elementary schools located in chemical industry regions. The findings indicated that exposure to volatile organic compounds from chemical manufacturing plants was associated with an increased incidence of chronic respiratory symptoms in children attending schools located in a close proximity to the chemical industries. Significant trends were observed for asthma-related responses such as a physician's diagnosis of asthma, persistent wheezing, and attacks of shortness of breath with wheezing in school children enrolled within a close proximity to regions containing chemical plants than those in the non-industrial regions.

Similar findings were reported in a study by Wichmann et al. [38] that assessed the effects of exposure to petrochemical pollution on the respiratory health of children aged 6 to 12 years living close to petrochemical plants (n = 282) and compared them with those living in a region with exposure to heavy traffic (n = 270) or in relatively non-polluted areas (n = 639) in La Plata, Argentina. The findings showed that children living near the petrochemical plant had significantly elevated

asthma and respiratory symptoms (wheezing, cough, dyspnea, and rhinitis) and significantly reduced lung functions than those living in non-polluted regions ($P < 0.001$). Moraes and coworkers [39] investigated the health impacts of living near petrochemical plants by assessing respiratory illnesses in 209 Brazilian children. The results from this study revealed that respiratory symptoms were found to be increased in children among communities in the vicinity of a petrochemical complex particularly those living downwind from the plant.

A panel study conducted by Zora et al. [40] assessed the associations between urban air pollution of benzene and pediatric asthma control using an Asthma Control Questionnaire (ACQ) score in two elementary schools located in high and low traffic areas of El Paso, Texas. Eligibility criteria included age of the children between 6 and 12 years, a physician diagnosis of asthma, no other lung disease or major illness, a non-smoking household, and residence proximal to their school. Data was reported for 36 of the 38 children who completed the protocol. The study found that benzene levels in the air of a school located in high traffic area ranged from 0.2 to 2.4 $\mu g/m^3$. Although no significant associations between benzene and other pollutants with an increase in ACQ score were found, an increase in ACQ score was related with an increase in benzene levels among children inhaling corticosteroids daily. Aguilera et al. [41] investigated the association of air pollution exposure during pregnancy and respiratory illnesses, ear infections, and eczema during the first 12–18 months of life in a Spanish birth cohort of 2,199 infants. These authors observed that during the second trimester of pregnancy, an increase in 1.0 $\mu g/m^3$ of benzene exposure was associated with an increased risk of lower respiratory tract infections in those infants.

In a panel study, Delfino et al. [42] examined the longitudinal relationship of the daily asthma severity among asthmatic children exposed to volatile organic compounds such as benzene. The study included 21 asthmatic children between 10-16 years of age. The study revealed that increased mean concentrations of benzene ($5.7\mu g/m^3$) levels were associated with increased asthma and poor lung function among the children. Martins and co-authors [43] evaluated the relationship between

air polluted by benzene exposure and airway changes in a group of wheezing children. The investigators included a total of 51 wheezing children with a mean age 7.3 years from Viseu, Portugal. Benzene levels were monitored for 4 weeks and using a dispersion model, personal exposure was determined based on time-activity patterns according to the estimations. These authors reported that an increase in 10.0 $\mu g/m^3$ of benzene exposure was associated with deteriorated lung function-related outcomes in wheezing children.

In a pilot study, we investigated the clinical presentation of the illness symptoms experienced by children who were exposed to benzene following a flaring incident at the BP refinery in Texas City, Texas [32]. The study included a total of 157 children who were exposed to benzene. Among the illness symptoms, neurological symptoms such as unsteady gait, memory loss, and headaches were the most (80%) frequently reported symptoms in children exposed to benzene. Upper respiratory symptoms were reported by 48% of the benzene exposed children followed by cough (48%), nausea/vomiting (43%), dermatological (36%), shortness of breath (32%), wheezing (27%), dizziness (22%), chest pain (15%), painful joints (15%), and weight loss (13%). To complement these findings, recently we conducted a full-fledged study in 641 children (n = 641) who were exposed to benzene following a flaring incident at the BP refinery in Texas City, Texas [44]. A total of 1,790 illness symptoms were observed in 641 children exposed to benzene.

Among all clinically presented illness symptoms, upper respiratory symptoms occurred as the most frequently (67%) followed by neurological symptoms (57%), diarrhea (25%), and cough (24%). Logistic regression analysis indicated that neurological symptoms (R^2 = 0.75), chest pain (R^2 = 0.64), joint pain (R^2 = 0.57), vision difficulty (R^2 = 0.54) were positively associated with increasing age of the children. Overall, the findings revealed that children exposed to benzene experienced a range of illness symptoms indicating their vulnerability to increased risks and health complications to benzene exposure.

CLINICAL IMPLICATIONS

Clinical evidence suggests that hemotoxicity is the major effect and is unique to benzene. Exposure to benzene causes bone marrow injury resulting in hemotoxicity leading to changes in white blood cells, platelets, hemoglobin, hematocrit, and other blood cells formation. Multiple mechanisms including alterations in the expression of numerous genes and proteins, DNA methylation patterns, and RNA profiles appear to play an important role in benzene induced hemotoxicity in exposed children [45].

Although several studies have investigated the effect of benzene exposure on the hematological changes in adults, only a handful of studies published so far have evaluated the clinical changes in the hematological functions among children following their exposure to benzene [31-33]. The findings of these studies demonstrate that children exposed to benzene experienced significantly reduced hematological indices compared with those of unexposed children. However, conflicting findings in platelet counts were observed in the benzene exposed children. Our recently published studies demonstrated significantly elevated platelet counts in children who were exposed to benzene compared with unexposed children [32, 33]. However, in the study reported by Lee and associates [31] significantly decreased platelet counts were observed in children exposed to benzene compared with those of unexposed children. Although the discrepancies in the platelet counts in benzene exposed children currently cannot fully explained, Ceresa and coworkers [46] have found that thrombocytopenia was not a constant finding in most of the adult subjects who were exposed to benzene. Nevertheless, additional studies are warranted to clarify the effect of benzene exposure on the platelet counts in children.

The liver is the principal organ of xenobiotic metabolism and hence it is very important to monitor its function in people exposed to benzene or other toxins. It is well known that phosphatases, amino transferases, and dehydrogenases are important enzymes in biological processes. They are involved in the detoxification, metabolism and biosynthesis of energetic macromolecules for different essential functions. Any interference in these

enzymes leads to biochemical impairment and lesions in the tissue and altered cellular function. Thus, the measurement of these liver enzyme such as ALP, AST and ALT are routinely used as indicators for hepatic dysfunction and damage [47, 48]. In normal conditions, these enzymes are confined to the cells and are released into circulating blood when there is a necrosis or hepatic injury. Despite its importance, until recently, there were no published studies available in the literature evaluating the effect of benzene exposure on the hepatic functions in children. The two recent studies reported by the authors [32, 33] revealed that the serum levels of ALP, AST and ALT were found to be elevated among those children who were exposed to benzene indicating hepatic abnormalities in these children. The increase in the levels of these liver enzymes in their serum suggests the impairment or damage of the hepatic functions in children exposed to benzene.

Studies assessing the somatic or clinically presenting illness symptoms such as the respiratory, neurological, gastrointestinal, and other symptoms in children exposed to benzene are also limited in published literature. However, evidence from available studies suggests that benzene exposure is associated clinically with increased illness symptoms in children. The most common clinical presentation of these illness symptoms include those involving neurological and respiratory symptoms with shortness of breath, wheezing, dizziness, chest pain, and painful joints.

CONCLUSION

Together, studies evaluating the clinical changes in the hematologic, cardiac, hepatic, renal, and other vital organ functions in children who were exposed to benzene are sparse. We have yet to learn and to understand the full extent of all the adverse effects that benzene exposure has on pediatric populations. Findings from the currently available literature reveal that benzene exposure is associated with clinical abnormalities in the hematologic, hepatic, respiratory, and pulmonary functions in children. The hematological abnormalities were characterized

by changes in RBC, WBC, absolute lymphocytes, platelets, hemoglobin, hematocrit and creatinine in benzene exposed children. Similarly, the hepatic abnormalities were characterized by elevated levels of ALP, AST and ALT enzymes in the serum of the children exposed to benzene. Few studies have evaluated the somatic or illness symptoms such as respiratory, neurological, gastrointestinal, and other symptoms in children exposed to benzene. Together these findings indicate that exposure to benzene may lead to clinically detectable detrimental health effects in children. However, to fully understand the importance and nature of these effects, further longitudinal and mechanistic studies on the health effects of benzene exposure in children are warranted.

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The authors have no financial relationships relevant to this article to disclose.

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