ORIGINAL ARTICLE

Low-Level Benzene Exposure and Hematological Alterations among Petrochemical Workers

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Abstract

Background: Previous studies on the relationship between benzene exposure and hematotoxicity have reported inconclusive findings, particularly at low exposure levels. This study aimed to investigate the potential relationship between low-level benzene exposure and changes in hematological parameters among petrochemical workers.

Methods: In this cross-sectional study, 495 benzene-exposed workers and 217 sex-matched non-exposed controls were assessed. Demographic, occupational, and medical data were collected. Air monitoring was conducted to determine benzene exposure, and the time-weighted average (TWA) was calculated. Blood samples were analyzed for hematological parameters. Data were analyzed using SPSS version 22.0. All exposures were within the OSHA permissible exposure limit (PEL). The mean TWA benzene exposure among the exposed group was 0.07±0.37 ppm.

Results: After adjustment for confounders, statistically significant associations were observed for red blood cell (RBC) count and mean corpuscular volume (MCV). No significant associations were found for other hematological parameters.

Conclusion: RBC count and its indices, particularly MCV, appear to be more sensitive to low-level benzene exposure than other blood parameters. These findings suggest that benzene may exert hematotoxic effects even at concentrations below the current OSHA PEL-TWA.

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Introduction

Workers are frequently exposed to multiple occupational hazards, including chemical, physical, and biological agents. Excessive exposure to chemicals may lead to a wide spectrum of adverse health outcomes, ranging from reversible disorders to life-threatening or disabling illnesses.[1-4]

Benzene, a colorless liquid with a characteristic sweet odor, is one of the most widely used industrial solvents. It serves as a precursor in the production of chemicals such as styrene, cumene, and cyclohexane. It is also used in the manufacture of lubricants, dyes, detergents, pesticides, and certain types of rubber.[5] Due to its high volatility, inhalation is the primary route of occupational exposure; however, absorption through the gastrointestinal tract and, to a lesser extent, through the skin, has also been documented.[6, 7]

Benzene is classified as a Group I human carcinogen by both the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (EPA).[8] The hematopoietic system is considered the critical target of benzene toxicity. Hematological effects have been observed following both acute and chronic exposures[9, 10] with decreased lymphocyte counts recognized as an early biomarker

and a consistent finding among workers with evident benzene toxicity.

To limit occupational risks, the Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit–time weighted average (PEL-TWA) of 1 ppm for an 8-hour work shift, while the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value–time weighted average (TLV-TWA) of 0.5 ppm.[11] Previous studies have reported hematological effects at benzene concentrations well above these limits.[12, 13] The severity of such effects generally increases with both exposure concentration and duration.

However, increasing concern has been raised regarding the potential hematological effects of benzene even at concentrations below the current OSHA PEL-TWA.

There are three primary approaches to assessing occupational exposures: air monitoring, biological monitoring, and medical examinations.[14] Among these, medical examinations are essential for evaluating adverse health effects resulting from occupational hazards. The complete blood count (CBC) has long been used as a simple, inexpensive, and accessible method for assessing hematotoxicity.[15]

However, studies investigating the relationship between benzene exposure and hematological alterations have produced inconclusive results, particularly at low-level exposures. While reductions in white blood cell (WBC) counts and their subsets are well-documented in clinical cases of benzene-induced hematotoxicity,[16] emerging studies suggest that red blood cells (RBC) and their indices may be more sensitive indicators at low levels of benzene exposure.[17, 18] For example, reduced RBC counts have been reported as the only hematological alteration among workers exposed to concentrations below 1 ppm.[17] Similar findings have also been observed in animal studies.[19, 20]

In contrast, some studies have reported no significant associations between reduced blood parameters and benzene exposure.[21, 22] Given the above, the present study was conducted to investigate the potential association between exposure to low concentrations of benzene and the levels of blood parameters in a group of workers exposed to this hematotoxic solvent.

Methods

Subjects and Study Design

This cross-sectional study was conducted at a petrochemical plant in Iran. A total of 512 male workers occupationally exposed to benzene were enrolled, along with 217 age- and sex-matched non-exposed subjects from a nearby gas power plant.

Data were collected using a structured questionnaire that gathered information on demographic characteristics, smoking habits, alcohol and medication use, history of exposure to chemicals, and prior occupational exposures, particularly those known to pose a risk of hematotoxicity.

Eligibility criteria included: (i) at least one year of employment in the current job (exposure for the benzene group and duration of employment for the non-exposed group), (ii) no past or present exposure to other hematotoxic agents, and (iii) absence of underlying hematological or systemic diseases such as thalassemia, hepatitis, favism, or hemophilia.

Ethical Consideration

All participants provided written informed consent before enrollment. The study protocol was approved by the University Ethics Committee (IR.SUMS.SCHEANUT.REC.1402.028) and conducted in accordance with the principles outlined in the Declaration of Helsinki (1964, revised 2000).[23]

Hematology Studies

Venous blood samples were collected from the brachial veins of participants at their workplaces using standard venipuncture procedures. Samples were processed for complete blood count (CBC) analysis, including: 1) total WBC and differentials (monocytes, lymphocytes, and neutrophils), 2) total RBCs and hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), and 3) platelets, mean platelet volume (MPV), and platelet distribution width (PDW).

Exposure Assessment

The study population was divided into 34 similar exposure groups (SEGs), each consisting of 2 to 36 workers. From these groups, 175 workers were randomly selected for personal air sampling. Full-shift personal air samples were collected using constant-flow personal sampling pumps and charcoal tubes (SKC 226-01), following the NIOSH Method 1501 protocol to determine time-weighted average (TWA) exposures.

Air samples were transported to the laboratory on ice packs. Benzene was desorbed with 1 mL of carbon disulfide for 30 minutes of agitation, and one µL of the extract was injected into a gas chromatograph (Varian CP-3800). Analysis was performed using a flame ionization detector (GC–FID) equipped with a CP-Sil 5 CB capillary column (30 m × 0.25 mm). The chromatographic conditions were as follows: injector temperature, 240 °C; detector temperature, 300 °C;

oven temperature, initially held at 50 °C for 10 min, then increased at 20 °C/min to 250 °C and maintained for 1 min. Nitrogen was used as the carrier gas at a flow rate of 1 mL/min.

Statistical Analysis

Data analysis was performed using SPSS software (version 22.0). The student's t-test and multiple linear regression analyses were used. A P value<0.05 was considered statistically significant.

Results

Table 1 presents the demographic characteristics and benzene exposure levels of the study groups. Seventeen workers were excluded from the study because they did not meet the inclusion criteria. Significant differences were observed between exposed and non-exposed participants with respect to age, height, and job tenure. The mean TWA exposure to benzene among exposed workers was 0.07±0.37 ppm, which is well below the

Table 1: Demographic characteristics and benzene exposure levels among exposed and non-exposed groups.

Variables	Nonexposed group (n=217)	Exposed group (n=495)	P value**
	Mean±SD	Mean±SD	
Age (year)	34.87±6.84	42.96±5.06	<0.0001
Height (cm)	172.55±6.31	173.80±5.68	0.014
Weight (kg)	77.16±12.94	78.77±10.18	0.098
BMI (kg/m^2)	25.89±3.88	26.03±2.72	0.613
Job tenure (years)	5.51±1.64	14.46±5.50	<0.0001
Benzene exposure* (ppm)	NA	0.07±0.37	-

*Time-weighted average (TWA) exposure. ** Independent Samples t-test.

Table 2: Comparison of hematological parameters between benzene-exposed and non-exposed groups.

Blood parameters	Nonexposed group (n=217)	Exposed group (n=495)	P value**
	Mean±SD	Mean±SD	
WBC	6.60±1.56	6.63±1.59	0.79
Lymphocytes	2.54±0.69	2.45±0.68	0.12
Neutrophils	3.32±0.88	3.56±1.11	0.053
Platelets	241.13±69.88*	219.07±47.15	<0.0001
MPV	8.90±1.31*	9.85±1.15	<0.0001
PDW	11.13±2.49*	13.18±2.27	<0.0001
RBC	5.11±0.48*	5.42±0.55	<0.0001
HCT	44.75±3.43	45.06±3.35	0.26
HB	14.84±1.08*	15.24±1.54	0.0005
MCV	86.38±8.14*	83.66±7.02	<0.0001
MCH	29.19±2.38*	28.33±3.22	0.15
MCHC	33.40±1.50	33.76±1.67	0.73
RDW	12.59±1.21*	13.60±13.60	0.01

*Significantly different from the non-exposed group (** Independent Samples t-test). WBC: White blood cell; RBC: Red blood cell; HB: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width

Table 3: Adjusted associations between low-level benzene exposure and hematological parameters.

Blood parameters	B (95%CI)	P value
Hb	-0.0001 (-0.001, 0.001)	0.913
HCT	-0.0001 (-0.003, 0.003)	0.941
RBC	0.0004 (-0.00002, 0.001)	0.041
MCV	-0.01 (-0.01, 0.0001)	0.044
MCH	-002 (-0.005, 0.001)	0.145
MCHC	-0.0002 (-0.002, 0.001)	0.779
RDW	0.001 (-0.0004, 0.002)	0.223
WBC	0.001 (-0.001, 0.002)	0.339
Lymphocytes	0.001 (-0.00002, 0.001)	0.057
Neutrophils	0.0002 (-0.001, 0.001)	0.649
Platelets	-0.02 (-0.07, 0.02)	0.336
MPV	0.001 (-0.0003, 0.002)	0.177
PDW	0.001 (-0.0003, 0.002)	0.236

*Multiple linear regression analysis. Adjusted for age, BMI, and job tenure. WBC: White blood cell; RBC: Red blood cell; HB: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width

current permissible exposure limit (PEL-TWA) of 1 ppm.

Table 2 summarizes the comparison of hematological parameters between exposed and non-exposed workers. Statistically significant differences were observed in platelet count, MPV, PDW, RBC, hemoglobin, MCV, and RDW levels between the two groups. In contrast, no significant differences were found in total WBC count or its subsets.

Table 3 presents the adjusted associations between benzene exposure and blood parameters among the studied workers. After controlling for potential confounders, including age, BMI, and job tenure, statistically significant associations were observed only for RBC and MCV. Specifically, benzene exposure was associated with a 0.0004-unit increase in RBC and a 0.01-unit decrease in MCV. A borderline association was observed for lymphocytes (B=0.001, P=0.057). No significant associations were detected for other hematological parameters.

Discussion

In the present study, we investigated a group of workers exposed to low levels of benzene to assess the potential association between benzene exposure and hematological parameters. A relatively large sample of benzene-exposed workers (n=495) and a reference group were included. The exposed workers, employed in a petrochemical plant, experienced low-level benzene exposure (0.07±0.37 ppm). Accurate exposure assessment is critical when studying the toxic effects of chemicals on biological systems. A major limitation of some previous studies is the lack of detailed exposure data, which complicates drawing clear conclusions regarding exposure–outcome relationships. In contrast, our study employed a rigorous exposure assessment program, providing a reliable estimate of benzene levels among the workers.

Benzene is known to cause bone marrow suppression, potentially leading to progressive reductions in RBCs, platelets, and WBCs. Leukopenia, or a reduction in WBCs, is commonly reported in benzene-exposed workers.[12, 24] However, in the present study, no significant differences were observed in WBC counts or their subsets between the exposed and non-exposed groups (Table 2). This discrepancy may be explained by differences in benzene exposure levels across studies. The threshold dose of benzene required to induce leukopenia remains unclear. Previous research has reported leukopenia at a wide range of exposures, from 3.8 to 34 ppm.[12, 25, 26] For example, Kipen et al. observed decreased WBC counts in workers exposed to 75 ppm of benzene but not in those with 15–20 ppm exposure.[25] These findings suggest that leukopenia is primarily associated with high-dose benzene exposure, whereas low-level exposures, such as those in the present study, may not significantly affect WBC counts.

Recently, several studies have investigated the effects of low-level (<1 ppm) benzene exposure on hematological parameters. Growing evidence suggests that RBCs and their indices are particularly sensitive to benzene exposure, even at low doses.[17, 19] In the present study, all measured blood parameters remained within the normal range. However, compared with non-exposed subjects, significant differences were observed in platelets, MPV, PDW, RBC, hemoglobin (HB), MCV, and RDW (Table 2). To account for potential confounders, including age, BMI, and job tenure, multiple regression analyses were performed. After adjustment, statistically significant associations were identified between benzene exposure and RBC (B=0.0004, P=0.041) as well as MCV (B=-0.01, P=0.044) (Table 3).

These findings are consistent with previous research.[17, 19, 20, 27] For example, Koh et al. (2015) reported a reduction in RBC count as the sole hematological change among Korean male workers exposed to less than one ppm benzene. Similarly, Collins et al. observed no significant changes in other blood parameters in a study of 387 workers exposed to low levels of benzene.[28] Tsai et al. also reported minimal effects on hematological indices in a study of 1,200 workers with low exposure.[29]

The present study has several strengths. First, a large number of workers were included. Second, a robust exposure assessment program was conducted to determine the workers' exposure to benzene accurately. Third, none of the exposed workers had pre-existing conditions that could affect blood parameters, such as genetic disorders, infections, or inflammatory diseases.

However, the study also has important limitations. Non-occupational sources of exposure, such as smoking or environmental pollution, can be significant in cases of low-level benzene exposure. The potential effect of smoking was not considered. Additionally, workers with abnormal blood parameters may have been transferred to less contaminated areas or departments where no exposure was expected and, therefore, were not included in the study. Finally, the cross-sectional design limits the ability to establish a causal relationship.

Nevertheless, the following points support that the observed changes in blood parameters are likely attributable to benzene exposure:

1. The study included workers without pre-existing blood disorders,

2. The exposed subjects were not concurrently exposed to other hematotoxic chemicals, and

3. Regression analyses (adjusted for key confounders) demonstrated a significant relationship

between benzene exposure and certain blood parameters.

Conclusion

The findings indicate that RBC and its indices (e.g., MCV) are more sensitive to low-level benzene exposure than other blood parameters. Further studies with extended follow-up periods and detailed data on long-term occupational exposure are recommended to confirm and expand upon these preliminary findings.

Author's Contribution

Fereshteh Aliasghari: Methodology, data curation, writing original draft. Seyedeh Mahsa Taghavipour, Fatemeh Rahimian, Anahita Fakherpour: Data collection, writing original draft. Nadia Mohammadi and Mohammad Fararouei: Analyze and interpretation of the data; writing-reviewing and editing. Esmaeel Soleimani: Funding acquisition, supervision, methodology, writing-reviewing and editing.

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Conflict of Interest

The authors declare that they have no competing interests.

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