REVIEW

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Recent Advances in Biomonitoring of Gas Station Workers: A Systematic Review

Simone Lima[1], Fabio Santiago[1,2]*, Rafaele Tavares Silvestre[1,3], Stêphanie Rocha Vieira Elexias[1], Maria Helena Ornellas[1,4], Marilza de Moura Ribeiro Carvalho[1,4]

Abstract

Background: In Brazil, gas stations are not self-service; attendants fill fuel tanks, leading to chronic exposure to BTEX (benzene, toluene, ethylbenzene, and xylenes), which can cause bone marrow degeneration and immunosuppression. This systematic review highlights recent advances in biomonitoring gas station workers (GSW). **Methods:** We searched PubMed, Medline, and Cochrane databases for articles in English, French, Portuguese, and Spanish from 2014 to April 30, 2024, using multiple search terms. **Results:** A total of 1,086 articles were identified, 322 were analyzed, and 13 were included in the final review. We highlighted recent technologies in GSW biomonitoring, such as immunophenotyping, molecular cytogenetics (FISH), and measuring miRNAs and inflammatory markers via ELISA. We also explored the link between benzene exposure and immunosuppression and suggested a potential association with chronic inflammation. **Conclusion:** GSWs face significant health risks and require continuous clinical monitoring, even in the absence of overt disease. Effect biomarkers may indicate early biological responses to benzene toxicity and highlight potential health risks. However, there is no universally accepted gold standard for assessing these biomarkers.

Keywords: Benzene- gas station employees- gas station attendants- hematological changes- immunological changes

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Introduction

Unlike in many developed countries, there are no self-service fuel stations in Brazil. Gas station attendants are chronically exposed to BTEX (benzene, toluene, ethylbenzene, and xylenes), which has been linked to various hematological disorders, including aplastic anemia, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and non-Hodgkin lymphoma (NHL) [1, 2].

The term benzeneism refers to the range of harmful effects caused by benzene on multiple systems in the human body, including the endocrine, immune, nervous, and hematological systems. These effects can impair blood cell formation, leading to hematological disorders, infertility, and fetal malformations [2]. Gas station workers are particularly at risk due to frequent exposure from fuel spills, vapor emissions, and contact with fuel-soaked clothing, especially in regions with high absorption areas like the groin and neck [1, 2].

Hydrocarbons are readily absorbed through the respiratory tract and can cause a variety of adverse health effects. Benzene metabolites, formed in the liver and bone marrow, cause damage to hematopoietic cells through several mechanisms, including chromosomal aberrations, oxidative stress, altered gene expression, apoptosis, DNA repair errors, epigenetic modifications, and tumor surveillance disruption [3-10]. However, susceptibility to benzene's effects varies among individuals, influenced by genetic factors related to benzene metabolism, DNA repair, genomic stability, and immune function [7].

Recent research has focused on biomonitoring BTEX toxicity, particularly early immune system alterations and genetic damage [5-7]. Even at exposure levels below 3.25 mg/m^3, benzene has demonstrated genotoxic effects [11]. These findings provide a critical scientific foundation for revising occupational health prevention strategies. Greater emphasis should be placed on monitoring the health of workers exposed to BTEX and improving health management for this occupational population [9, 12].

This study aimed to systematically and comprehensively review recent advances in biomonitoring workers, with a particular focus on gas station workers (GSWs) who experience chronic BTEX exposure.

*[1]Graduation Program of Medical Sciences (PGCM), Medical Sciences Faculty (FCM), State University of Rio de Janeiro (UERJ), Brazil. [2]Department of Pathology Faculty of Medical Sciences, Rio de Janeiro State University (UERJ), Rio de Janeiro, Brazil. [3]Laboratory of Circulating Biomarkers, Department of Pathology, Faculty of Medical Sciences, Rio de Janeiro State University (UERJ), Rio de Janeiro, Brazil. [4]Laboratory of Circulating Biomarkers, Department of Pathology, Faculty of Medical Sciences (FCM), State, Brazil. *For Correspondence: fabiosantiago.uerj@gmail.com*

Materials and Methods

This systematic review was conducted following the guidelines of the Cochrane Library and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13-16]. The PRISMA checklist is presented in Appendix A. On April 30, 2024, we performed a database search in Medline, the Cochrane Library, and PubMed Central. Two search strategies were employed for PubMed. The first used the following sets of Medical Subject Heading (MeSH) terms: (1) benzene, toluene, xylenes, ethyl benzene, and hematological/immune system; (2) benzene, toluene, xylenes, gas station attendants/workers; (3) benzene, toluene, xylene, genotoxicity/immune system; (4) benzene, toluene, xylene, lymphoma/leukemia; (5) benzene, toluene, xylene, hematological changes/benzeneism. The second search used the phrase "gas station worker."

Inclusion criteria were: (1) indexed from 2014 to April 30, 2024; (2) included letters to the editor, case presentations, case series, original research reports, or reviews; (3) focused on clinical research in adults; and (4) written in English, French, Portuguese, or Spanish. Search results were merged with EndNote X7 (Thomson Reuters, Carrolton, TX), and duplicate records were removed. Article abstracts were independently reviewed by all authors (F.S., R.S., S.E., M.C., and S.L.). Full texts were obtained and reviewed for eligibility when needed. Disagreements were resolved through discussion with a senior researcher (M.O.).

Results

A total of 1,086 articles were identified, 322 were analyzed, and 13 met the inclusion criteria for this systematic review, as summarized in Table 1. All studies used a retrospective design (see Tables 2 and 3). Figure 1 presents a flow diagram of the study selection process. For comparative analysis, the selected papers were grouped into three main themes: hematological alterations, immunosuppression, and genotoxicity.

The majority of studies focused on hematological alterations (44.1%), followed by genotoxicity (28.6%), and immunosuppression (27.3%) (Table 3). However,

Table 1. Combination of the Following Descriptive "exposure to benzene AND hematological changes", "exposure to benzene AND immune system" and "exposure to benzene AND genotoxicity"

Combinations	Total articles (2014-2024)
Hematological changes	44.1% (142)
Immunosuppression	27.3% (8)
Genotoxicity	28.6% (92)

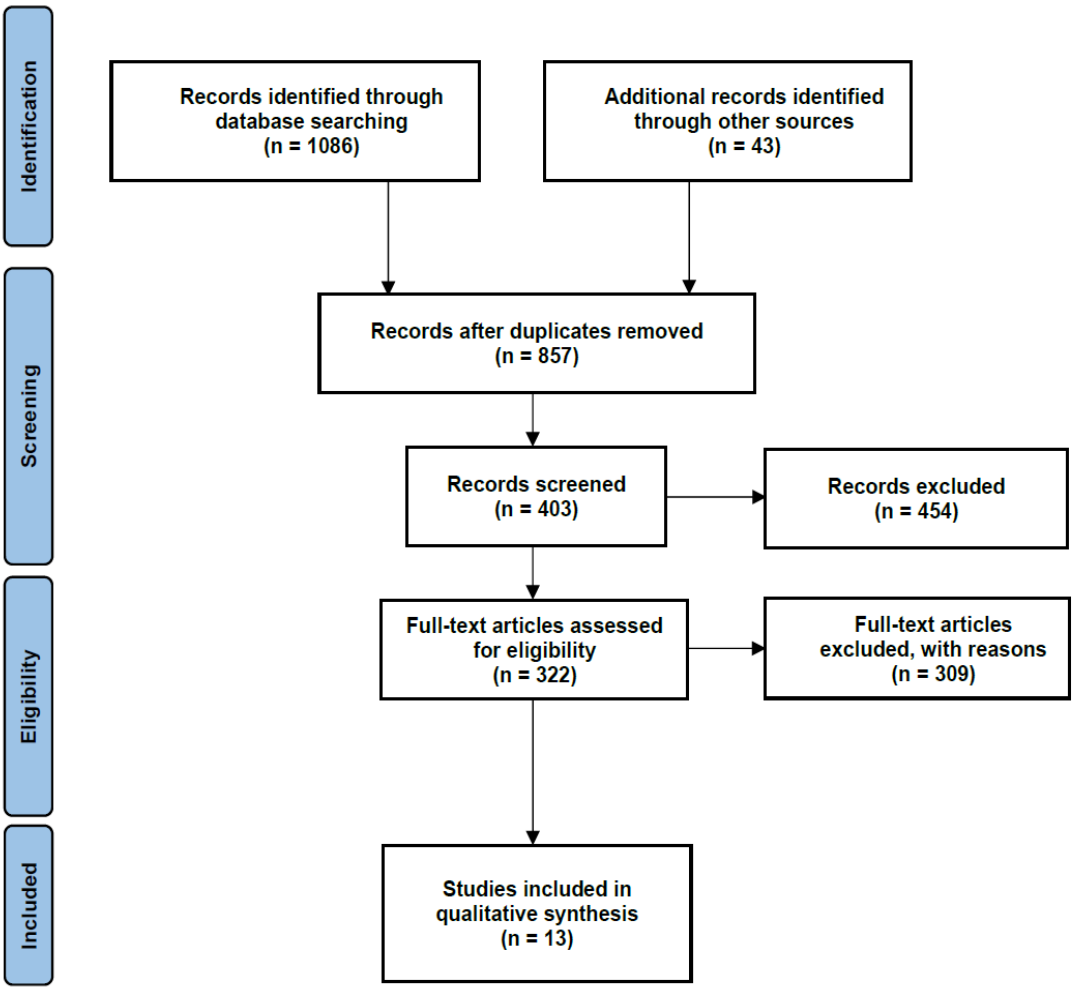

Figure 1. Flow Diagram Depicting Article Selection Steps. Databases were searched for articles published from 2013 to July 1, 2023. Of the 1086 articles identified, 12 were considered eligible by 2 authors (F.S. and S.M.).

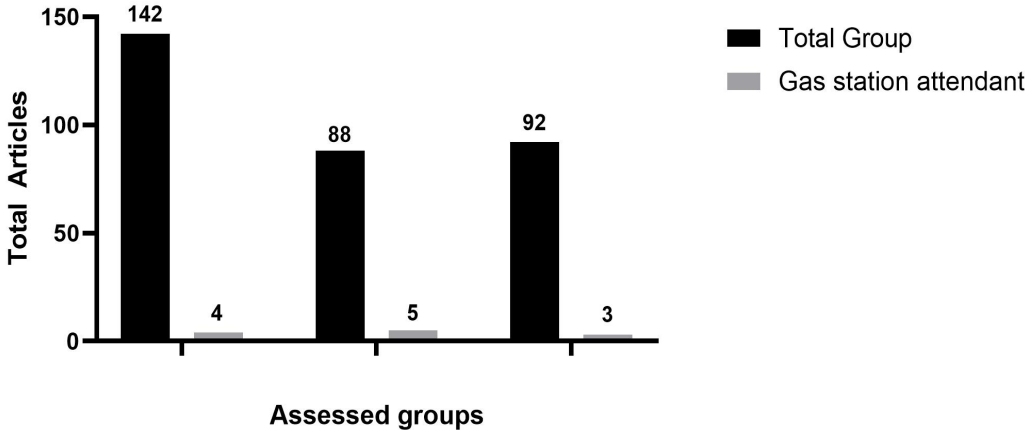

Figure 2. Decrease in the Number of Articles Published when We Included this Gas Station Attendant Group. In view of the previous data, we sought to direct our bibliographical review.

Table 2. Combination "exposure to benzene" AND "hematological changes" AND "gas station attendant"

Title	Author	Magazine and year
Early hematological and immunological alterations in gasoline station attendants exposed to benzene	Moro AM et al. [17]	Environ Res. 2015
Biomonitoring of gasoline station attendants exposed to benzene: Effect of gender	Moro AM et al. [18]	Mutat Res Genet Toxicol Environ Mutagen. 2017
Association of environmental exposure with hematological and oxidative stress alteration in gasoline station attendants	Ahmadi Z et al. [3]	Environ Sci Pollut Res Int. 2019
Hematological Changes in Gas Station Workers	Giardini I, et al. [1]	Int J Environ Res Public Health 2023

only 13 studies specifically addressed GSW, as shown in Figure 2.

Hematological alterations

Table 2 summarizes four studies investigating hematological abnormalities in GSWs. Moro et al. [17] reported reduced ALA-D (aminolevulinic acid dehydratase) activity, decreased CD80 and CD86 expression in monocytes, and elevated IL-8 levels in GSWs compared to controls, suggesting these markers could serve as early indicators of benzene-induced changes.

Moro et al. [18] highlighted an increased susceptibility to blood changes in female GSWs, emphasizing the need for gender-specific protective measures. Ahmadi et al. [3] associated environmental benzene exposure with

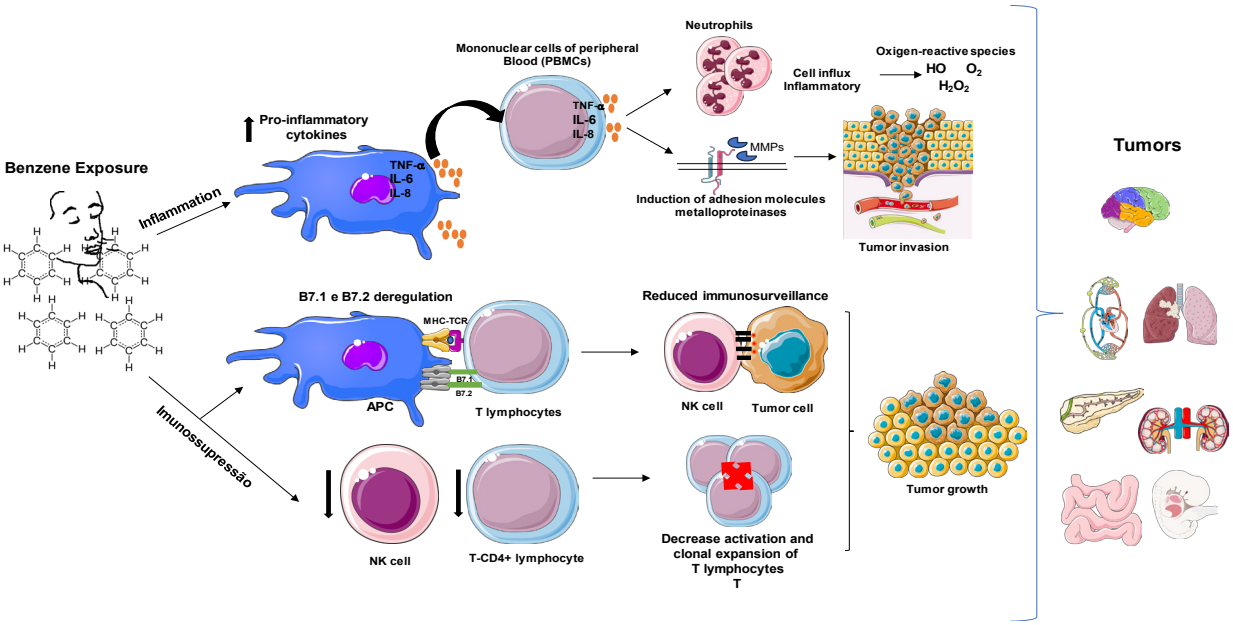

Figure 3. Proposed Mechanism of Benzene-Facilitated Carcinogenesis via Chronic Inflammation and Immunosuppression.

Table 3. Combination "exposure to benzene" AND "immune system" AND "gas station attendant"

Title	Author	Magazine and year	Immune system	Genotoxicity
Gasoline-station workers in Brazil: Benzene exposure; Genotoxic and immunotoxic effects.	Poça KSD et al. [11]	Mutat Res Genet Toxicol Environ Mutagen. 2021	x	
Low-dose occupational exposure to benzene and signal transduction pathways involved in the regulation of cellular response to oxidative stress.	Fenga C et al. [20]	Life Sci. 2016	x	
Occupational exposure to gasoline in gasoline station male attendants promoter M1 polarization in macrophages.	Toson EA et al. [21]	Environ Sci Pollut Res Int. 2022	x	
Overexpression of miR-221 in peripheral blood lymphocytes in petrol station attendants: A population based cross-sectional study in southern China.	Hu D et al. [22]	Chemosphere, 2016. 149:8-13	x	
Imunophenotypic evaluation as a tool for monitoring risks for blood malignancies in gas station workers.	Santiago F et al. [23]	Asian Pac J Cancer Prev. 2019.	x	
Monitoring of gas station attendants exposure to benzene, toluene, xylene (BTX) using three-color chromosome painting	Santiago F et al. [9]	Mol Cytogenet. 2014		x
Benzene poisoning clinical, and blood abnormalities in two Brazilian female gas station attendants: two case reports	Santiago F et al. [10]	BMC Res Notes. 2017		x
Health survey and assessment of the polymorphisms *BRCA1*/P871L, *BRCA1*/Q356R, and BRCA2/N372H in female gas station workers in Rio de Janeiro	Silvestre RT et al. [33]	Environ Mol Mutagen. 2017		x
The association of three DNA repair genes polymorphisms on the frequency of chromosomal alterations detected by fluorescence in situ hybridization	Santiago F et al. [34]	Int Arch Occup Environ Health. 2021		x

hematological alterations and oxidative stress in GSWs, recommending antioxidants to mitigate oxidative stress. Giardini et al. [1] found that occupational exposure via inhalation and/or dermal contact with benzene led to clinical signs of benzene poisoning (e.g., drowsiness, headache, dizziness) and altered hematological parameters, including elevated total leukocyte counts and borderline lymphocyte counts.

Benzene exposure has been linked to altered blood cell counts and cytokine profiles, with several studies reporting its toxicological effects. Chronic exposure is associated with signs of benzene poisoning and increased risk of hematological malignancies [5, 9-11]. Changes in myeloid and lymphoid cells, particularly B cells and CD4+ T cells, along with markers of B cell activation, may play a role in the development of hematological cancers [19].

Immunosuppression

Immunosuppression refers to a weakened immune response, which can result in frequent infections and increased cancer susceptibility [6]. Table 3 (Immune System) shows five studies investigating immunosuppression in GSWs. Poça et al. [11] identified significant biological effects, including elevated DNA damage, increased micronuclei, lower CD4/CD8 T cell ratios, and elevated NK (Natural Killer) cell levels, suggesting benzene exposure has both genotoxic and immunosuppressive effects. Fenga et al. [20] examined benzene exposure's impact on signal transduction pathways, showing significant differences in NF-κB, phospho-IκBα, and phospho-STAT3 protein levels in GSWs. Chronic low-dose exposure to benzene may modulate oxidative stress pathways and contribute to carcinogenicity. Toson et al. [21] demonstrated that gasoline exposure led to a significant increase in tumor necrosis factor-α (TNF-α) levels. Additionally, total leukocyte and lymphocyte counts increased significantly. However, the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios showed a significant decrease. The study also reported a marked reduction in hemoglobin concentration, the reduced form of plasma glutathione, and the activities of key antioxidant enzymes, including catalase and superoxide dismutase, in red blood cells. These findings suggest that prolonged gasoline exposure may activate the immune system, particularly through the polarization of M1 macrophages, potentially driven by an oxidative stress-mediated mechanism.

Acquired chromosomal aberrations are well-known to correlate with increased cancer and reproductive risks [9, 10, 22]. A decrease in NK cell cytotoxicity also elevates cancer risk [23]. Santiago et al. [10] studied two female gas station attendants working in an environment with proven harmful concentrations of BTX. The study identified complex chromosomal rearrangements (RCCs), reduced NK cell levels with abnormal CD16 expression, and early pregnancy loss. These findings led the authors to conclude that detecting chromosomal abnormalities and NK cell downregulation could serve as new biomarkers for monitoring workers exposed to BTX, particularly benefiting women by preventing severe diseases affecting them and their children. MicroRNAs (miRNAs) are important regulators of gene expression and contribute

significantly to the epigenetic landscape. Their role in human health is well established, and research interest in miRNAs continues to grow [24-31]. Benzene, a known environmental leukemogen, has unclear mechanisms of carcinogenesis. Recently, miR-221 has been suggested as an oncogene implicated in various malignancies [25]. For instance, in chronic myeloid leukemia (CML), dysregulation of miR-221, miR-150, miR-20a, and miR-17 leads to dysfunctions in their target genes, which encode proteins responsible for regulating the cell cycle, growth, and several signaling pathways relevant to CML development [26].

MiRNAs can act as oncogenes and are associated with the initiation, progression, and prognosis of various cancers [31]. A single miRNA can regulate the expression of multiple genes involved in diverse cellular pathways [27]. Consequently, miRNAs have been proposed as biomarkers for diagnosing and predicting cancer outcomes and are being explored as potential targets for biological therapies [28].

In a population-based cross-sectional study, Hu et al. [22] investigated the relationship between benzene exposure and miR-221 expression in a group of 97 gas station attendants and 103 control group participants from southern China. The findings suggested that benzene exposure may be linked to elevated miR-221 expression in human lymphocytes. Genetic damage caused by exogenous chemicals is not only a sensitive indicator of early health effects but also a critical mechanism driving the impact of carcinogens. Thus, genetic damage can serve as an early biomarker for health risks associated with exposure to carcinogenic substances.

MiRNAs hold great promise as biomarkers in occupational medicine, as they can provide insights into the mechanisms of benzene carcinogenicity. Present in all human biological fluids, miRNAs are easily measurable with commercial kits [29], making them practical tools for identifying the effects of specific exposures. Their use could lead to advancements in disease prevention and health promotion. Mozzoni et al. [30] highlighted the role of miRNAs in the biological response induced by environmental and occupational carcinogens. The identification and validation of specific miRNA signatures related to benzene exposure could significantly enhance workplace safety.

Genotoxicity

The primary mechanism by which benzene induces leukemia is believed to involve its phenolic metabolites, which work synergistically to cause DNA damage [32]. This damage can lead to mitotic recombination, chromosomal translocations, and aneuploidy. These genotoxic events contribute to the activation of proto-oncogenes, loss of heterozygosity, and the inactivation of tumor suppressor genes [8]. In the third stage of our bibliographic survey (Table 3 - Genotoxicity), we identified four articles addressing genotoxicity in gas station workers (GSW). A key finding across studies is that benzene, toluene, ethylbenzene, and xylene (BTEX) exposure induces chromosomal alterations, which have been observed in multiple human studies. Most structural chromosomal changes manifested as gaps and breaks, with both stable and unstable alterations detected in leukemia cases and exposed individuals [12]. Chromosomal loss and gain in the C-group were particularly common among patients with benzene-associated leukemia and pre-leukemia. Results from leukemia cases potentially linked to prior BTEX exposure were largely consistent with other benzene-associated leukemia case reports. Similar to aneuploidy, nonspecific structural changes are characteristic of both benzene poisoning and pre-leukemia cases [33]. An increased frequency of chromosomal aberrations persists even years after recovery, making them a potentially reliable indicator of elevated cancer risk [9, 10]. Most studies in Table 3 (Genotoxicity) show a positive association between benzene exposure and an increase in both numerical and structural chromosomal aberrations. Recent advancements in molecular cytogenetics, specifically fluorescence in situ hybridization (FISH), have enabled the analysis of specific chromosomal aberrations in populations exposed to benzene [9, 10]. In conclusion, current evidence suggests that benzene may act both as an alkylating agent, causing alterations in chromosomes 1, 5, and 7, and as a topoisomerase II inhibitor, inducing the t(21q22) translocation [12, 34].

Discussion

The association between benzene exposure and altered blood cell counts is well-established, with numerous studies demonstrating hematological suppression in exposed individuals. Leukocyte counts appear to be the most affected, with the majority of studies reporting lower leukocyte levels in those exposed to benzene. Additionally, many studies have documented lower absolute lymphocyte counts, with reductions in circulating B lymphocytes and T lymphocytes. CD4+ T lymphocytes were consistently found to be decreased across all the studies reviewed. A reduction in the CD4+/CD8+ T cell ratio was also commonly reported. Although the outcomes of the studies reviewed were heterogeneous—spanning gene expression, cytokine/chemokine production, serum protein levels, blood cell counts, and both humoral and cellular immunity several trends emerged. First, it is clear that benzene exposure is associated with an immunosuppressive effect on white blood cell production, particularly lymphocytes such as CD4+ T cells, B cells, and NK cells. CD4+ T cell deficiency is particularly concerning, as these helper T cells are critical to nearly all adaptive immune responses. They activate B cells to produce antibodies and CD8+ T cells and macrophages to destroy infected target cells. The depletion of CD4+ T cells and subsequent impairment of cellular immunity is reminiscent of immunodeficiency diseases like AIDS, where immune suppression can lead to fatal infections and secondary illnesses. Second, a substantial number of studies reported increased levels of inflammatory cytokines or other pro-inflammatory molecules. While these markers are indicative of general inflammation, we cannot rule out the possibility that acute or widespread inflammation caused by benzene exposure may evolve into chronic inflammation. Third, the dysregulation

of soluble factors such as TNFα and IL-6, along with the promotion of local inflammation by benzene, may disrupt key functions involved in tissue homeostasis. This disruption could contribute to cancer initiation, immune evasion, and tumor progression (Figure 3). The data synthesized in this review thus suggest a link between benzene exposure, immunosuppression, and the potential for chronic inflammation. Benzene appears to activate the innate immune system to provoke inflammation, while concurrently suppressing the adaptive immune system. These findings indicate that gas station workers are a high-risk population, highlighting the need for changes in their work processes and environments. Additionally, it is essential to monitor the clinical health of these workers, even in the absence of overt disease symptoms.

Biological monitoring offers a valuable tool for assessing integrated exposures to BTEX (benzene, toluene, ethylbenzene, and xylene) and could contribute to the diagnosis and treatment of diseases among gas station workers. Effect biomarkers, a diverse group of indicators reflecting early biological changes due to BTEX toxicity, are particularly useful in identifying health risks. This evidence provides a scientific foundation for developing new prevention strategies for occupational diseases among gas station workers. Greater attention must be given to the ongoing health surveillance of gas station workers, with enhanced health management efforts aimed at preventing diseases related to BTEX exposure. The focus should be on tracking biomarkers or indicators of genotoxicity linked to BTEX exposure. This review enhances our understanding of the risks faced by these workers, enabling us to implement more effective disease prevention measures to protect both their health and potentially the health of future generations. However, a universal consensus on a gold-standard biomarker for benzene exposure has not yet been established. In general, it is recommended that more than one biomarker be used for improved accuracy. Without a consensus, the choice of biomarkers whether genetic, immunological, or metabolic depends on the tools available in each laboratory.

Author Contribution Statement

All authors contributed equally in this study.

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General

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Approval

The study protocol was approved by the Ethics Committees of Universidade do Estado do Rio de Janeiro (UERJ), registry and the registration number of the study/trial: UERJ – 34310014.9.0000.5259/14; INCA – 121/09.

Conflict of Interest

The authors declare no conflict of interest.

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