

# Biomarkers and detection techniques for genotoxic damage in workers exposed to benzene, toluene, and xylene: a narrative review

## Biomarcadores y técnicas de detección de daño genotóxico en trabajadores expuestos al benceno, tolueno y xileno: una revisión narrativa

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### Abstract

Occupational exposure to BTX compounds (benzene, toluene, and xylene) continues to pose significant health risks, especially in industrial settings where these solvents are widely used in the manufacturing of rubber, paints, and plastics. Benzene, classified as a Group one carcinogen by the International Agency for Research on Cancer (IARC), has been linked to severe genotoxic effects, including DNA damage in bone marrow cells, increasing the risk of leukemia and aplastic anemia. Toluene and xylene, although less toxic, also present significant health concerns, particularly affecting vital organs and the central nervous system. This narrative review examines key biomarkers used to assess genotoxic damage in exposed workers, such as 8-oxoguanine, micronucleus assays, and gene expression analysis. Biomonitoring is emphasized as a critical strategy for early disease detection and the development of effective preventive measures. The review presents the strengths and limitations of these biomarkers and highlights their potential role in shaping future occupational health monitoring programs. By providing a comprehensive overview of current research, this work aims to support the implementation of policies that protect workers from hazardous chemical exposure and improve overall workplace safety.

*Keywords: biomarkers, cancer, cytogenetic analysis, DNA damage, genotoxicity, occupational exposure*

### Resumen

El riesgo de daño genotóxico asociado con la exposición ocupacional a compuestos (benceno, tolueno y xileno) BTX ha sido un problema ampliamente documentado y sigue siendo un desafío importante para la salud ocupacional. Estos compuestos, usados como disolventes industriales en la producción de caucho, pinturas y plásticos, son conocidos por su toxicidad. El benceno es clasificado como carcinógeno de tipo uno por la International Agency for Research on Cancer (IARC), mientras que el tolueno y el xileno son de tipo tres. La exposición prolongada al benceno puede provocar daño en el ácido desoxirribonucleico (ADN o DNA por sus siglas en inglés) de las células de la médula ósea, lo que incrementa el riesgo de leucemia y anemia aplásica. A su vez, el tolueno y el xileno causan efectos tóxicos en órganos vitales y el sistema nervioso central. Esta revisión

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narrativa describe los principales biomarcadores utilizados para evaluar el daño genotóxico en trabajadores expuestos a BTX, incluyendo la 8-oxoguanina, el análisis de micronúcleos y la expresión de genes específicos. Se destaca la importancia de la biomonitorización como herramienta para la evaluación de riesgo de daño en el ADN y la implementación de estrategias preventivas efectivas. Asimismo, se presentan las ventajas y limitaciones de los biomarcadores actuales y se propone su uso como base para futuros programas de vigilancia epidemiológica en entornos laborales. Este enfoque contribuye a la protección de la salud de los trabajadores y al desarrollo de políticas públicas informadas para minimizar el impacto de la exposición a sustancias químicas peligrosas.

**Palabras clave:** análisis citogenético, biomarcadores, cáncer, daño en el ADN, exposición ocupacional, genotoxicidad

## INTRODUCTION

The relationship between occupational exposure to chemicals and disease has been recognized since the 18th century, when Sir Percival Pott documented the connection between scrotal cancer and exposure to tar and soot (Calera Rubio et al., 2005). This discovery underscored the importance of investigating occupational diseases, due not only to the impact on workers' health and productivity, but also because of the high prevalence and mortality associated with harmful exposure in occupational settings, particularly to carcinogenic substances (Calera Rubio et al., 2005; World Health Organization, 2017).

The burden of disease resulting from chemical exposure is significant and exceeds occupational accidents in frequency. Although global quantification of this burden is complex, the World Health Organization (WHO) has estimated that millions of people lose their lives annually due to exposure to both environmental and occupational chemicals (Mitchell, 2014; Zubizarreta Solá et al., n. d.). Occupational hazards, such as exposure to carcinogens, contribute significantly to the incidence of chronic diseases, including several types of cancer and other debilitating conditions (International Agency for Research on Cancer (IARC), n. d.; Zubizarreta Solá et al., n. d.).

Benzene, toluene and xylene (BTX) are compounds widely used as solvents in various industries and are known to possess genotoxic and carcinogenic properties. According to the IARC classification, benzene is classified as a Group One carcinogen, while toluene and xylene are in Group Three. These substances, present in the manufacture of rubber, paints and plastics, have an affinity for the central nervous system and bone marrow,

posing a significant risk to workers exposed to high concentrations (IARC, n. d.).

Chronic exposure to benzene can cause aplastic anemia and leukemia, due to its ability to damage DNA in bone marrow cells. Similarly, toluene and xylene also have acute and chronic toxic effects, impacting vital organs such as the lungs, liver and brain. Exposure can produce symptoms ranging from euphoria to severe disorders such as leukoencephalopathy and psychosis (Agency for Toxic Substances and Disease Registry (ATSDR), 2016; Rodriguez Padilla, 2020; Universidad del Rosario, 2023).

Accurate assessment of BTX exposure is critical to mitigate its adverse effects. Biomonitoring through biomarkers, such as indicators of oxidative stress and inflammation, not only facilitates early diagnosis of occupational diseases, but also provides crucial tools for the development of effective preventive strategies (IARC, n. d.).

This review aims to describe and analyze the main biomarkers of genotoxic damage related to occupational exposure to BTX, with emphasis on their relevance for occupational health surveillance and the implementation of preventive measures.

## MATERIALS AND METHODS

The present study is a narrative review that responds to the objective of describing the main characteristics of research related to biomarkers of genotoxic damage associated with occupational exposure to BTX both worldwide and in Colombia. The purpose is to provide relevant information that can be used for the development of preventive measures and occupational health protection strategies.

## Keyword selection

A strategy was formulated based on a complete set of possible search terms, which consisted of listing indexing terms (from headings, subheadings of topics, types of research) and listing descriptor words for groups of concepts (single words or phrases).

Once these words were defined, they were validated as Health Sciences Descriptors to be used in the search and retrieval of scientific literature in the information sources selected for this study. This resulted in: "Biomarkers", "Genotoxicity/Genotoxicity", "DNA damage/DNA damage", "Cytogenetic Analysis", "Occupational exposure", "Benzene", "Toluene", "Xylene/Xilene" (Table 1). The following combinations were also established:

"Biomarkers and occupational exposure and benzene and toluene and xylene", "Biomarkers and genotoxicity or DNA damage and occupational exposure and benzene toluene and xylene", "cytogenetic analysis and occupational exposure and benzene and toluene and xylene".

## Eligibility Criteria

Inclusion criteria included articles published as open access, in Spanish and English, independent of year and country, as well as all types of publications that identified the relationship between biomarkers of exposure and genotoxic effect with occupational exposure to BTX, with the exception of correspondence, reviews, books, encyclopedias, conference abstracts and animal experiments (Table 2).

**Table 1.** Key words validated in health sciences descriptors

Key words		
Keyword in Spanish	Keyword in English	Registration number/code
Biomarkers	Biomarkers	D015415
Genotoxicity	Genotoxicity	D009152
Cytogenetic analysis	Cytogenetic Analysis	D020732
Occupational exposure	Occupational Exposure	D016273
Benzene	Benzene	D001554
Toluene	Toluen	D014050

Table design by the authors

## Research data

Data from previously published studies investigating the genotoxic effects of occupational exposure to BTX and the application of various biomarkers in the assessment of genetic damage were used to develop this narrative review. The data include biomonitoring results, such as 8-oxoguanine levels and the presence of micronuclei, as well as studies assessing the expression of genes related to oxidative stress and alterations in DNA repair.

These data cover information on the exposure of workers in different industries working with organic solvents such as petroleum, laboratories, paints, food, pharmaceuticals and other hydrocarbon derivatives, and the impact of BTX compounds on human health, with details on analytical techniques and assays used to assess DNA damage.

The studies reviewed provide a framework for understanding the magnitude of genotoxic damage and highlight the biomolecular tools available for monitoring it.

In this study, the data were used to synthesize and describe the main biomarkers and their applications in occupational health. Other authors could use these data to perform meta-analyses, develop new biomonitoring methodologies, or explore additional associations between BTX exposure and other biomarkers. In addition, the data could be useful in epidemiological studies to assess long-term risks or in research seeking to identify more effective preventive interventions.

This approach encourages scientific development and can contribute to a better understanding of chemical toxicity and worker protection.

**Table 2.** Selection of eligibility and exclusion criteria

Inclusion criteria	Exclusion criteria
Articles in English and Spanish.	Items that are not work-related.
Articles that are complete and freely accessible.	Experimental articles on animals.
Articles published in any country.	Articles focused on the health effects and management of occupational exposure to BTX.
Longitudinal, cross-sectional, case-control, review, epidemiological, experimental studies related to the topic of interest.	Articles of occupational exposure to BTX that are not related to biomarkers of genotoxic effect.
Articles related to biomarkers of genotoxic effect and occupational exposure to BTX.	Articles that do not provide information on cytogenetic analysis in occupational exposure to BTX.
Articles related to cytogenetic analysis and occupational exposure to BTX.	Correspondence articles, conference abstracts, book chapters and reviews, encyclopedia.

Table design by the authors

## Sources of information

A search was conducted in the databases of PubMed, Red de Revistas Científicas de América Latina y el Caribe, España y Portugal (Redalyc) and Science Direct of all existing information; from its inception until May 17, 2022, with the addition of other sources of literature, WEB sites, journal "Scientific Electronic Library Online" (SciELO) and organizations such as the World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute of Health of the United States (NIH).

## Search strategy

The outline of the search strategy was based on the PRISMA 2020 tool, which allows a step-by-step process to be followed in the selected databases, using the keyword combinations described above.

## Selection Processes

The studies were collected from the databases described above; no automated tool was used for this process. The selection process was based on the realization of an EXCEL format, duly raised for the eligibility of the articles by the authors of the current review, allowing each article to

have an individual selection process, with a drop-down list of options based on exclusion and inclusion criteria applied in duly structured steps. To increase the quality and credibility of the screening, the search was implemented and the comparison between them was performed by at least two observers independently, as well as a joint review in controversies.

## Data collection processes

For the reading of the articles selected through the aforementioned process, an EXCEL file was designed to record the most relevant information, including authors, year, type of study, sample, methodology, summary of the main results and biases (Annex 1).

## RESULTS

### Selection of studies

Based on the aforementioned combinations of search terms, an exhaustive search was carried out, which initially yielded 816 results in the selected databases. A total of 729 studies were eliminated before the screening process: 691 for not being complete and in open access, 10 for being in languages other than English and Spanish, and 28 duplicates. After this filter, 87 articles

remained, of which 33 were eliminated due to exclusion criteria after reviewing titles, abstracts and keywords. Finally, 54 full-text articles were evaluated, of which 45 were selected and grouped (Table 3). Three additional articles were included through alternative methods, resulting in a total of 48 articles (Figure 1).

## Characteristics of the results

Several biomarkers of both exposure and genotoxicity have been documented to identify DNA damage in BTX-exposed workers from different occupations such as petroleum, living near industrial complexes, gas stations, and in the paint industry (Campo et al., 2016; Kim et al., 2021; Londoño-Velasco et al., 2019; Moro et al., 2019; Palma et al., 2015; Salem et al., 2018; Varona-Uribe et al., 2020). For example, Moro et al. (2019) linked a decreased immune response to a reduction in the expression of the cytokines CD80, CD86 and interleukin six in individuals exposed to BTX. In addition, certain polymorphisms in CYP2E1 have been observed to increase cancer susceptibility in these populations (Kim et al., 2021; Varona-Uribe et al., 2020). Other exposure-

specific biomarkers, such as urinary benzene and urinary methyl benzene, have been shown to be sensitive and specific for the detection of BTX exposure (Campo et al., 2016; Kim et al., 2021; Lagorio et al., 1994; Sisto et al., 2020).

In Colombia, Palma et al. (2015) conducted a descriptive cross-sectional study in which they characterized the health and working conditions of vehicle painters in Bogotá exposed to organic solvents. Concentrations of BTX in air and its metabolites in urine (phenylmercapturic, hippuric and ortho-para methylhippuric acids) were measured. The results showed positive correlations between airborne toluene and urine hippuric acid, and between airborne xylene and o-methylhippuric acid. The study concluded that car painters are exposed to high levels of organic solvents and lack adequate industrial hygiene and safety conditions in their workplaces.

Biomarkers of genotoxicity have also been reported as chromosomal alterations, such as fragility, breaks and translocations, along with elevated levels of DNA fragmentation and a higher percentage of dead cells). Changes in the

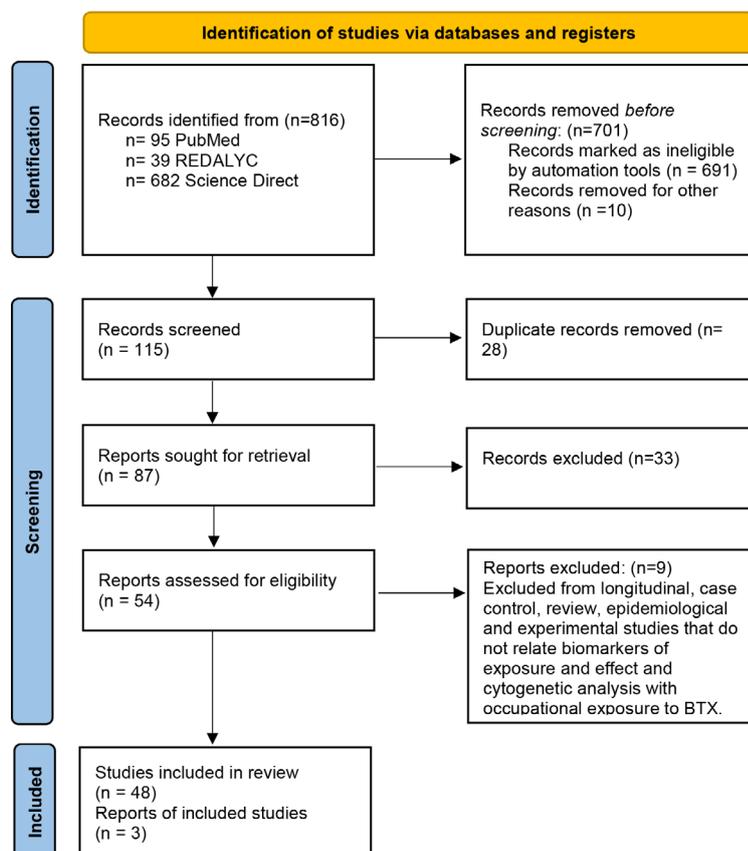


Figure 1. PRISMA flow diagram. Diagram adapted by the authors (Page et al., 2021).

**Table 3.** Number of study records analyzed for eligibility

Combination of search terms	Pubme	Redalyc	Science direct
<i>Biomarkers and occupational exposure and benzene and toluene and xylene</i>	<b>11</b> (Campo et al., 2016; Haro-García et al., 2008; Kim et al., 2021; Lagorio et al., 1994; Moro et al., 2019; Santos et al., 2013; Sisto et al., 2019, 2020a; Varona-Urbe et al., 2020; Villalba-Campos et al., 2016; Xiong et al., 2016)	<b>6</b> (Torres et al., 2008; Londoño-Velasco et al., 2019; Olivero et al., 2013; Pajaro-Castro et al., 2014; Palma et al., 2015; Vargas 2014)	<b>18</b> (Alses & Alzeer, 2021; Amoatey et al., 2018; Aragonés et al., 2008; Cakmak et al., 2020; Coronas et al., 2009; Croute et al., 2002; Decharat, 2014; Haines et al., 2017; Huang et al., 2021; Houry et al., 2018; Laffon et al., 2013; McNally et al., 2017; Mora-Barrantes et al., 2021; Rana et al., 2021; Rodríguez Padilla, 2020; Schnatter et al., 2020; Sisto et al., 2020b; Zubizarreta Solá et al., n. d. 2018)
<i>Biomarkers and genotoxicity or damage DNA and occupational exposure and benzene toluene and xylene</i>	<b>3</b> (Holz et al., 1995; Salem et al., 2018; Sha et al., 2014)	-	-
Cytogenetic analysis and occupational exposure and benzene and toluene and xylene	<b>2</b> (Santiago et al., 2014, 2017)	<b>5</b> (Aquino et al., 2016; Fuente et al., 2013; Gallego-Díez et al., 2016; Mendoza 2009; Santos et al., 2013)	-
<b>Total references:</b>	<b>16</b>	<b>11</b>	<b>18</b>

\*Search criteria: combination of keywords and database, open access, complete, English and Spanish language. Search dates: 30/01/2022, 31/01/2022, 05/05/2022, 17/05/2022. Table design by the authors.

expression of DNA methyltransferase and methyl-CpG-binding domain "protein two, MBD2" have been observed as indicators of DNA methylation status, showing that DNA methyltransferases are decreased in people exposed to BTX). The study by Londoño-Velasco et al. (2019) investigated oxidative and DNA methylation damage in lymphocytes from 62 car painters in Colombia exposed to organic solvents and paints, compared to 62 unexposed individuals. Using the high

efficiency comet assay coupled to Fpg and AlkA enzymes, three categories of DNA damage were evaluated: basal, oxidative and methylation. The results indicated that exposure to organic solvents and paints is associated with increased oxidative DNA damage in painter's lymphocytes, such as the production of 8-oxodG and other products such as formamidopyrimidine, which are considered highly mutagenic. Annex 1 summarizes the main findings of the studies reviewed.

## Utility of biomarkers for the assessment of genotoxic effects from occupational exposure to BTX

Benzene metabolism generates reactive oxygen species that damage DNA, increasing the risk of mutations and cancer. DNA damage is exacerbated by BTX metabolites, which also induce genotoxicity. The most common genotoxic changes include adduct formation, alterations in DNA repair, single strand breaks, sister chromatid exchange, and the appearance of micronuclei (Holz et al., 1995; Salem et al., 2018; Xiong et al., 2016).

The modified comet assay is a key technique that detects direct, oxidative DNA damage. The enzyme Formamidopyrimidine-DNA glycosylase recognizes and cleaves oxidized bases, primarily 8-oxoguanine, which can result in the generation of single strand breaks in DNA (Haines et al., 2017). This method has shown a significant increase in oxidative damage in painters exposed to BTX. The micronucleus technique is used as a biomarker that allows detection of structures that form outside the nucleus of cells (micronuclei-MN) and represent fragments or whole, lagging chromosomes present after cell division. The increase in the frequency of MN in the exposed population with respect to the non-exposed population makes it possible to identify the risk (International Agency for Research on Cancer (IARC), n. d.).

Another important biomarker is the detection of 8-hydroxydeoxyguanosine (8-OHdG), a sensitive indicator of DNA damage caused by benzene metabolites and hydroxyl radicals. Accumulation of 8-OHdG, which occurs upon chronic BTX exposure and exceeds DNA repair capacity, is associated with an increased risk of mutagenicity and cancer. This biomarker is measured in blood or urine, providing a useful tool to identify genotoxic damage in gas station workers (Lagorio et al., 1994; Xiong et al., 2016).

Other methods used include the <sup>32</sup>P post-labeling assay, an ultrasensitive method that allows for the identification of DNA adducts, strand breaks and sister chromatid exchanges. The findings can be corroborated by conventional cytogenetics and Fluorescence in situ hybridization (FISH) techniques to assess chromosomal damage (Holz et al., 1995; Santiago et al., 2014, 2017; Villalba-Campos et al., 2016). The "salting out" method is

also used to extract DNA and analyze fragments indicative of genotoxic damage (Salem et al., 2018).

Regulation of gene expression, influenced by complex processes such as DNA methylation, is altered in individuals exposed to high levels of BTX. The expression of genes related to DNA methylation patterns has been detected by real-time quantitative polymerase chain reaction (PCR), which is associated with an increased risk of cancer (Sha et al., 2014). On the other hand, studies have shown a significant increase in the frequency of micronuclei in individuals exposed to organic solvents such as benzene, toluene and xylenes (BTX), suggesting a relationship between such exposure and the observed genetic damage (Cardenas-Bustamante et al., 2007; Holz et al., 1995; Salem et al., 2018; Xiong et al., 2016).

## DISCUSSION

Since the toxicity of BTX was documented in the scientific literature, particularly in the case of benzene, for its carcinogenic potential and association with diseases such as aplastic anemia and leukemia, numerous studies have been conducted to investigate its adverse effects). One of the most significant investigations is that of Yin et al. (1996), who conducted a cohort study of 74,947 workers with chronic occupational exposure to benzene in 12 cities in China, comparing the results with 35,805 unexposed individuals. In this study, 42 cases of leukemia were reported in the exposed group and only nine in the unexposed group, demonstrating a clear association between benzene exposure and leukemia incidence. Similarly, Aksoy et al. (1974) documented 26 cases of leukemia among 28,500 workers in the shoe industry who used benzene as a solvent between 1967 and 1973, with a significantly higher incidence (13/100,000;  $p > 0.02$ ) compared to the general population (6/100,000).

The mechanism by which benzene generates genotoxic damage is not fully elucidated, but several pathways have been proposed. Benzene metabolism in the liver, mediated by the enzyme Cytochrome P4502E1, produces toxic metabolites, such as 1,4-benzoquinone, which inhibits topoisomerase II and prevents the proper repair of DNA breaks, leading to mutations. In addition, the production of free radicals during benzene metabolism generates oxidative damage, increasing



genotoxicity (Agency for Toxic Substances and Disease Registry (ATSDR), 2016; Rodríguez Padilla, 2020).

Although benzene is the most studied compound, toluene and xylene also have significant harmful effects, with lesser relative toxicity. Exposure to xylene, for example, can cause nasal irritation, shortness of breath, heart palpitations, gastrointestinal symptoms, nausea, anxiety and, in chronic cases, neurological damage such as diffuse brain atrophy and hearing loss (Rajan, 2014). The aforementioned adverse effects of combined exposure to BTX in occupational settings have been documented, as shown in studies indicating an increased risk of detrimental effects when the compounds are present simultaneously (Wang et al., 2021).

Biomonitoring has emerged as a critical tool in occupational health protection. Biomarkers of genotoxic damage, such as the modified comet assay, are essential for detecting direct and oxidative DNA damage. This technique allows the identification of single strand breaks and specific damage to DNA bases, such as 8-oxoguanine (Aquino et al., 2016; Haines et al., 2017). A significant increase in oxidative damage has been reported in individuals exposed to BTX, corroborated by the comet assay (Aquino et al., 2016; Sisto et al., 2020).

Detection of 8-hydroxydeoxyguanosine (8-OHdG) in blood or urine is another sensitive biomarker of oxidative DNA damage, useful for assessing genotoxic risk in populations chronically exposed to benzene. This DNA injury, if not properly repaired, can lead to mutations and cancer (Lagorio et al., 1994; Xiong et al., 2016). Furthermore, methods such as the "32P post-labeling assay" allow for an ultrasensitive assessment of DNA adducts, while conventional cytogenetics and techniques such as FISH provide additional evidence of chromosomal damage (Holz et al., 1995; Santiago et al., 2014, 2017; Villalba-Campos et al., 2016).

Epigenetic regulation also plays an important role in BTX-induced genotoxicity. Hypomethylation in gene expression patterns have been documented by PCR in exposed workers, which increases the risk of developing cancer (Salem et al., 2018; Sha et al., 2014). On the other hand, detection of micronuclei in lymphocytes or buccal epithelial

cells remains a reliable method to assess genetic damage. Studies have shown a significant increase of micronuclei in BTX-exposed workers compared to non-exposed individuals (Cardenas-Bustamante et al., 2007; Holz et al., 1995; Salem et al., 2018; Sha et al., 2014; Xiong et al., 2016).

These findings underscore the urgent need to implement continuous monitoring programs and robust preventive measures in occupational settings. Direct environmental monitoring allows for the real-time measurement of benzene concentrations in the work environment, facilitating the immediate identification of exposure peaks and the implementation of corrective measures. However, it may not reflect the internal dose absorbed by workers, as it does not consider individual factors such as inhalation rate or personal susceptibility. Hence the need for biological monitoring using biomarkers of exposure, which could provide an estimate of the internal dose of benzene by directly measuring the compound or its metabolites in body fluids, such as blood or urine. This allows a more accurate assessment of individual exposure. Thus, the integration of biomarkers of exposure, effect and susceptibility in longitudinal studies provides a comprehensive view of the risks associated with benzene exposure.

Exposure biomarkers allow for the quantification of the internal dose of benzene or its metabolites, providing a direct measure of the chemical load within the body. The detected biomarkers indicate biochemical or cellular changes that reflect a biological response to exposure, facilitating early identification of adverse health effects. For their part, susceptibility biomarkers reveal genetic or phenotypic variations that may influence individual response to benzene exposure, helping identify more vulnerable subpopulations (Cárdenas-Bustamante et al., 2007; Palma et al., 2015; Sha et al., 2014; Xiong et al., 2016). The joint application of these biomarkers in longitudinal studies then allows monitoring the temporal evolution of exposure and its health effects, identifying causal relationships between benzene exposure and specific health outcomes, and developing personalized intervention strategies based on individual susceptibility.

Public policies should promote safe working conditions and educational strategies that increase awareness of BTX risks. As progress is made in

understanding genotoxic mechanisms and risk assessment, a proactive approach is essential to minimize adverse effects and protect the health of workers and the community at large.

## CONCLUSION

In conclusion, this review highlights the relevance of the identified biomarkers and emphasizes the need for preventive actions and effective policies to mitigate the risks associated with BTX exposure, fulfilling the objective of protecting public health.

This narrative review aims to determine the different biomarkers to detect genotoxic damage due to occupational exposure to BTX, in order to generate future studies and implement a medical surveillance program in those entities interested in incorporating the different biomarkers and adjusting them to their purposes. It is essential to highlight that these tools facilitate the early detection of DNA damage caused by exposure to physical, chemical or biological agents; in this case, to chemical compounds such as BTX organic solvents (Londoño-Velasco et al., 2019; Palma et al., 2015). The integration of environmental and biological monitoring techniques, together with the complete analysis of biomarkers of exposure, effect and susceptibility, is key to assess the risk in a comprehensive manner and apply effective preventive measures in work environments where benzene is present.

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## AUTHOR CONTRIBUTION

Each of the authors of the text contributed significantly to its construction. Julieth Restrepo and Juan Camilo Areiza did most of the bibliographic

consultation and writing; David Velásquez contributed with writing, editing, bibliographic consultation, compilation and submission, Lina Barrera contributed with ideation, writing, editing and bibliographic consultation.

## CONFLICT OF INTEREST

This article, as well as the authors, do not present any conflict of interest.

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