Environmental exposure to benzene: evaluation of urinary S-PMA and polymorphism (CYP2E1-1293G>C and NQO1 609C>T) in Campos Elíseos residents, Duque de Caxias, Rio de Janeiro State, Brazil

Abstract

Benzene is one of the most important substances for assessment, due to its significant use, the environmental contamination resulting from its emission and the effects on human health. It is classified by the International Agency for Research on Cancer (IARC) as a known carcinogen to humans (group 1) and associated with the development of leukemia. In general, the population is exposed to this substance by inhaling contaminated air, which varies according to the location and intensity of its potential sources. The petrochemical industry is one of the most important sources of this compound. The municipality of Duque de Caxias, specifically the Campos Elíseos district, in Rio de Janeiro State, Brazil, houses the Industrial Complex of Campos Elíseos (PICE), a grouping of over 25 industries, which includes the second largest oil refinery in Brazil. Environmental contamination from the PICE has been recognized, but there is a lack of studies concerning its impact on the health of the surrounding population. S-phenylmercapturic acid (S-PMA) concentrations ranging from 0.80 to 8.01 μg.g⁻¹ creatinine were observed in the local population, apparently related to hematological changes also observed in exposed population. The quantifiable presence of urinary S-PMA from the benzene metabolism is associated with the fact that 60% of the participants present specific hematological changes, which may be due to the environmental benzene exposure. The allele and genotype frequencies of the CYP2E1 and NQO1 enzymes observed in the study population were similar to those reported in other studies. The presence of the variant allele in the NQO1 genotype may be a risk factor for the observed hematological changes.

Benzene; Environmental Pollution; Biomarkers; Genetic Polymorphism

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Introduction

Benzene requires significant attention due to its toxicity and ubiquitous presence in several areas at low concentrations. It is an organic compound present and/or used as a raw material in several products, such as gasoline and plastic, and is classified by the International Agency for Research on Cancer (IARC) as a group 1 compound, a proven carcinogen to humans. It is currently one of the ten priority chemicals for study and regulation according to the World Health Organization (WHO).

In terms of public health, the most significant benzene contamination route is through respiration. Most inhaled benzene is eliminated by expiration, while the retained portion accumulates, mainly, in fatty tissues. After absorption, the biotransformation of benzene occurs, primarily, in the liver, with its secondary metabolism occurring in the bone marrow. Several enzymes are involved in this metabolism, including Cytochrome P450E1 (CYP2E1), NADPH:quinone oxidoreductase 1 (NQO1) and Glutathione S-transferase (GST). The kidneys are the main responsible organs for the excretion process of the generated metabolites.

Effects resulting from acute exposure include headaches, fatigue, dizziness, mucosal irritation, convulsions, excitement, depression and, eventually, death due to respiratory failure, while the bone marrow is the main target organ for benzene toxicity.

Chronic exposure to low benzene concentrations is associated with certain diseases, such as aplastic anemia and leukemia. Some studies also suggest that exposure at different concentrations may increase the risk of developing non-Hodgkin's lymphoma, multiple myeloma and various other hematopoietic disorders.

Benzene exposure in humans is monitored through biomarkers that significantly correlate to exposure intensity and/or biological effect caused by the substance, such as S-phenylmercapturic acid (S-PMA) and metabolic polymorphisms (CYP2E1; NQO1).

S-PMA is an aliphatic metabolite excreted in urine, with only 0.11% of absorbed benzene being biotransformed into this product. Its elimination half-life is of approximately 10 hours, which makes this metabolite a strong candidate for biomarker exposure, due to its high residence time. However, smoking acts as a confounding factor in S-PMA analyses, while urinary S-PMA levels are not subject to dietary interference. Urinary S-PMA has a biological exposure limit value of 25μg.g\(^{-1}\) creatinine.

Because these are individual characteristics inherent to the exposed organism, these variations should be considered when assessing the potential health impacts of population groups.

Recent studies have led to great interest in the CYP enzymatic system, since this system plays a significant role, mainly in phase I of the metabolism of most endogenous substances and xenobiotics, including organic chemicals such as ethanol, acetone and benzene. In humans, this family of enzymes is present in several organs, mainly in the liver, and is encoded by more than 50 genes, distributed throughout 10 large families, with subfamilies subdivided into isozymes.

The CYP2E1 isoform is the most active in benzene metabolism. CYP2E1 catalyzes the conversion of benzene to benzene oxide (BO), as well as the conversion of hydroquinone (HQ) and catechol to 1,2,4-trihydroxybenzene. The location of the CYP2E1 gene in the human genome is on chromosome 10, in 10q24.3.

Studies investigating this isoform have reported the presence of polymorphisms in the promoter region at -1293 (restriction endonuclease site Rsal) and at position 7632 of the gene (restriction endonuclease site Dral), whose variants are associated with increased enzyme activity and increased risk for leukemia development, probably due to the high production of toxic intermediates.

The enzyme NQO1 acts preferentially in the bone marrow, considered a phase II enzyme in the chemical metabolism. It acts by reducing benzoquinones to dihydroxy-quinones, less toxic, in the...
benzene metabolism pathway. Thus, the higher the NQO1 activity, the lower the action of intermediary reactive metabolites in the organism.

In humans, the gene encoding this enzyme is located on chromosome 16 (16q22.1) and exhibits a functional polymorphism originating from a substitution of C→T bases at position 609 of the gene, which determines the exchange of proline by serine at position 187 of the protein.

Studies have shown that the presence of the variant allele is related to decreased enzymatic efficiency and, consequently, protective NQO1 action. Individuals presenting the homozygous genotype may display absence of enzymatic activity.

Currently, there is a need for studies aiming at promoting the joint evaluation of biomarkers, susceptibility and effect in residents living around petrochemical poles exposed to benzene, in order to find possible justifications for the high leukemia hospitalization rates in these areas. In this context, the aim of this study was to evaluate the association of environmental exposure to benzene to several biomarkers in the surrounding Industrial Complex of Campos Elíseos (PICE) population, Municipality of Duque de Caxias, Rio de Janeiro State, Brazil.

Methodology

This study was carried out at the Center of Studies on Worker’s Health and Human Ecology (CESTEH), approved by the Sergio Arouca National School of Public Health (ENSP) Ethics Committee (Opinion 971.927, CAAE: 40514415.0.0000.5240) at the Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil.

The design was of observational descriptive sectional type, applying the description of the resident population surrounding the petrochemical industries, with sampling by convenience, due to the difficult access to this locality.

The geographical study area was the Campos Elíseos district, located in the municipality of Duque de Caxias, near the PICE. The main activity in the area concerns the petrochemical industry. This region is home to several industries, including the Caxias Refinery (Reduc), the largest industrial unit in the Greater Rio de Janeiro area, Braskem, which produces as by-product a pyrolysis gasoline containing about 40% benzene, and the Synthetic Rubberd Factory (Fabor), both displaying significant importance in the development of the study area.

Inclusion criteria

The study group consisted of individuals residing up to 1,000 meters from the petrochemical Campos Elíseos complex, comprising male and female adults (age ≥ 18 years), of different ages and races, living in the area for at least 3 months.

Individuals who agreed to participate in the study signed an informed consent form, as required by the Brazilian Ministry of Health, Resolution n. 466/2012 concerning research involving humans. A total of 194 residents volunteered. Four subjects were excluded from the study, due to insufficient biological material for the laboratory analyses, with 190 remaining.

Information collection

First, participants answered a semi-structured questionnaire for characterizing population exposure and obtaining sociodemographic data and information regarding dietary habits, daily routine, housing conditions and health and illness records, among others. Information was also collected to identify confounding factors in the study. The data were then analyzed in order to investigate possible exposure-outcome associations, and finally, to characterize the risk to which these residents are subjected to in their environment.
Biological material sampling

Urine samples were collected in 20mL polyethylene bottles and sent to the CESTEH Toxicology Laboratory/ENSP/Fiocruz, where they were stored in an ultrafreezer (-80°C) until the laboratory analyses. Blood samples for molecular analyses and blood cell counts were collected in vacuum tubes containing EDTA K2 as anticoagulant and stored in an ultrafreezer (-80°C) in the same laboratory.

Organization and characterization of the study groups

To characterize the study groups, a semi-structured questionnaire was applied to obtain data regarding sex, race, age, schooling and professions, and to verify frequency regarding chemical product handling, alcohol consumption and smoking habits in their social circles. The obtained data were used to minimize the influence of the confounding variables, promote the definition of resident profiles and delineate common habits, accurately and qualitatively identify relevant symptoms for assessments concerning possible exposure-outcome associations, and characterize the risk to which these residents are subjected to in their environment.

Analytical procedures

• Urinary S-PMA analyses

S-PMA was determined by liquid chromatography coupled to sequential mass spectrometry (HPLC-MS/MS) applying the methodology described by Gomes. Liquid-liquid extraction by low temperature partition (LLE-LTP) was applied, consisting in the addition of a reduced amount of an organic solvent in the sample and subsequent refrigeration of the obtained mixture to -20°C for at least 3 hours. Under these conditions, the aqueous phase solidifies and the organic solvent is separated, forming a supernatant phase containing the solubilized analyte, which is then removed and analyzed.

After extraction, S-PMA concentrations were determined by high performance liquid chromatography (Scientific Surveyor, Thermo Fisher Scientific, Waltham, United States) coupled to a triple quadrupole tandem-MS sequential mass spectrometer with electrospray ionization (ESI) (TSQ Quantum model, Thermo Fisher Scientific, Waltham, United States), using the Xcalibur software (https://www.thermofisher.com/order/catalog/product/OPTON-30487).

• Creatinine determination

Creatinine concentrations in urine samples were determined using the Doles Colorimetric Kit (Pamá, Goiás State, Brazil) applying a picric acid reaction in an alkaline medium, after deproteinization, through spectrophotometry.

• CYP2E1 – 1293G>C and NQO1 609C>T polymorphism determinations

Polymorphisms were determined by genotyping using the real-time polymerase chain reaction (PCR) technique. Template DNA samples of each individual were obtained by extraction of genomic DNA by the Salting-Out technique, from 500μL aliquots of whole blood. Quantitation of extracted DNA was performed by fluorescence using the Qubit 2.0 fluorometer (Invitrogen, Life Technologies, Carlsbad, United States). A 50μg.mL⁻¹ ratio of DNA per optical density was adopted for calculation purposes. Real-time PCR was carried out in a final volume of 8μL, containing 1x4μL of TaqMan Genotyping Master Mix (Thermo Fisher Scientific), 1x0.5μL of the TaqMan SNP Genotyping Assay probes (Thermo Fisher Scientific) specific for each polymorphism, CYP2E1 – 1293G>C (rs3813867) and NQO1 609C>T (rs1800566). Amplification conditions followed the recommendations suggested by the probe manufacturer.
Statistical analyses

All statistical analyses were carried out using Excel (https://products.office.com/) and SPSS Statistics v.20 (https://www.ibm.com/) software programs. The frequency of each variable, urinary S-PMA concentrations and metabolic polymorphisms, was first investigated. Subsequently, data distribution was verified by the Kolmogorov-Smirnov test. As a normal distribution for urinary S-PMA was observed, parametric tests were applied. The Mann-Whitney test was used to verify possible differences in the mean concentrations of urinary S-PMA, residence time, smoking and metabolic polymorphisms. Associations between polymorphisms and urinary S-PMA levels were investigated through odds ratio (OR). The representation of the reference values was expressed as means, standard deviations and 95% confidence intervals (95%CI).

Results and discussions

Urinary S-PMA analyses

After optimization of the spectrometric conditions, S-PMA m/z ratios in the negative ionization mode were determined, as well as the multiple reaction monitoring (MRM) transitions, which were used for metabolite quantification, alongside retention time for compound confirmation. The analytical curves were prepared ranging from 10 to 500ng.mL⁻¹ and were repeated for each sample batch. The recovery percentage of the analyte in the extraction procedure was evaluated using concentrations referring to three points of the analytical curve. For each point, urine was fortified with the predetermined amount of the S-PMA standard prior to extraction, while another extraction was carried out in another aliquot of the same urine, and the same amount of S-PMA was added to the extract, considered as corresponding to 100% recovery. For the extraction method to be considered efficient, the point means should be between 70 and 120%.

All samples were extracted and analyzed over two weeks and the processing order was held after the collection sequence. For each day of analysis, an analytical curve was prepared, comprising three concentration points, and recovery evaluation was carried for one point using a single fresh pool of urine, used as a urine blank, composed of a mixture of five urine samples donated by non-smoking CESTEH workers.

To verify the daily sample processing and quality controls, the angular and linear areas of the curve were observed in the matrix and visually evaluated in the software for equipment analysis and qualitative evaluation module, concerning the fortification areas at the three concentration levels, as described in Rosa.

The final sample evaluation was performed by assessing the relationships between quantifier and qualifier ions. If this value was within the ion ratio range established as acceptable for qualification on that day of analysis, the area of the 109m/z ion obtained in each sample was then applied to the straight-line equation, to calculate urinary S-PMA concentration values, in μg.g⁻¹.

From the total of 190 participants, 21 samples displayed quantifiable urinary S-PMA levels by the adopted method, expressed as means, median, maximum and minimum values and 25, 50, 75 and 95 percentiles, displayed in Table 1.

The urinary S-PMA results were tested concerning normality by the Kolmogorov-Smirnov test, and the general data did not present a normal distribution (p < 0.05).

Of the 21 samples presenting quantifiable S-PMA levels, only two were from smokers, determined at 0.88 and 1.56μg.g⁻¹ creatinine, thus indicating that exposure through smoking did not significantly influence group findings.

The S-PMA levels found herein are similar to findings from other studies investigating this biomarker in non-occupationally exposed populations, and below the biological exposure limit of 25μg.g⁻¹ creatinine, as defined by the American Conference of Governmental Industrial Hygienists (ACGIH) regarding occupational exposure.

Gomes applied the same extraction method and separation and detection technique to volunteers who were environmentally exposed to benzene and obtained a S-PMA median of 2.56μg.g⁻¹.
creatinine, similar to that reported in a method and application development study carried out by Fan et al. 42, with a median of 3.35μg.g⁻¹ creatinine found in non-occupationally exposed groups, while the study carried out by Protano et al. 43 reported a median of 0.62μg.g⁻¹ creatinine when evaluating 395 children and adolescents not exposed to direct benzene emission sources. Johnson et al. 44, in a data review study on exposure of non-occupational populations to benzene (including children) reported mean/median urinary S-PMA values ranging from 1.2 to 16.0μg.g⁻¹ creatinine among the different groups.

In this study, urinary S-PMA data were grouped into two large groups: samples presenting quantifiable S-PMA levels (n = 21), termed Positive for S-PMA, and the remaining samples, whose results were below the limit of quantification of the method (n = 169), classified as Negative for S-PMA.

Subsequently, both groups were compared to the results for hematological parameters, through the association measure of the OR. Hematological components widely described as altered during benzene exposure were selected, namely leukocyte values (< 4,500/mm³), mean corpuscular volume (MCV) (above 89 fl) and neutrophils (sum of segmented rods < 3,000/mm³). The chi-square test was applied and the odds ratios were then calculated. The results are described in Table 2.

The results indicate that samples with quantifiable urinary S-PMA levels, which derive from the benzene metabolism, are associated to changes in neutrophil and MCV parameters. Although a non-statistically significant association was observed, a trend was noted regarding the association between MCV and S-PMA.

Associations between the pathologies detected in this study and urinary S-PMA concentrations were investigated by calculating the OR of these variables. Participants presenting detectable S-PMA levels displayed an increased risk of also presenting one of the hematological alterations identified herein (dehydration, eosinophilia, thrombocytopenia associated to anemia, anemia, thrombocytopenia, eosinophilia, leukocytosis, leukocytosis associated to neutrophilia, leukopenia, and leukopenia associated to neutropenia) (Table 3).

The values observed herein are consistent with those reported in the literature and corroborate that the hematological alterations observed in this study may be associated with benzene exposure, even at low levels, as described by other authors 9,25,44,45,46.

The OR for other variables related to levels of urinary S-PMA were also calculated, allowing the qualitative identification of possible benzene exposure sources, such as handling of gasoline and other solvents, which increases the risk of presenting quantifiable urinary S-PMA levels in 12% and 41%, respectively. These results were expected, as gasoline contains benzene and the types of solvents used by the population were not classified as to their nature.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary S-phenylmercapturic acid (S-PMA) concentrations in samples collected in 2016 and 2017 from Campos Elíseos residents included in the study. Duque de Caxias, Rio de Janeiro State, Brazil.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S-PMA (µg.g⁻¹ creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td>P25</td>
</tr>
<tr>
<td>P50</td>
</tr>
<tr>
<td>P75</td>
</tr>
<tr>
<td>P95</td>
</tr>
</tbody>
</table>
Table 2
Risk ratios of the S-phenylmercapturic acid (S-PMA) groups concerning changes in leukocyte, mean corpuscular volume (MCV) and neutrophil values.

<table>
<thead>
<tr>
<th>S-PMA</th>
<th>Leukocytes OR (95%CI)</th>
<th>MCV OR (95%CI)</th>
<th>Neutrophils OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Positive</td>
<td>0.78 (0.17-3.62)</td>
<td>1.29 (0.52-3.21)</td>
<td>2.30 (0.90-5.84)</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval; OR: odds ratio.

Table 3
Odds ratio (OR) of S-phenylmercapturic acid (S-PMA) groups for hematological alterations identified in the study.

<table>
<thead>
<tr>
<th>S-PMA</th>
<th>Hematological alterations OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Positive</td>
<td>1.60 (0.64-4.02)</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.

Molecular analyses

- **Genotype and allele frequencies of CYP2E1 - 1293G>C and NQO1 609C>T polymorphisms in the study population**

The genotype and allele frequencies of the study population are presented in Table 4.

The allele and genotype distribution obtained in this study is similar to that reported in other studies evaluating the same polymorphisms in populations subjected to varying occupational and environmental exposure benzene concentrations. The genotype distribution displayed a Hardy-Weinberg shift for the NQO1 and CYP2E1 genes. Several studies concerning genes encoding metabolic enzymes that are candidates for susceptibility to toxic substances and related diseases have been carried out. The greater or lesser susceptibility to the development of certain pathologies due to differences in metabolism determined by genetic variability has been increasingly studied.

To evaluate the relationship between the data and the hematological parameters obtained in this study, an association measure (OR) was carried out. Hematological alterations related to benzenism were selected, namely leukocytes (< 4,500/mm³), MCV (above 89 fl) and, mainly, neutrophils (< 3,000/mm³). The chi-square test was applied and the OR calculated. Results are displayed in Table 5.

The results indicate that being a carrier of the variant allele may be a risk factor for changes in leukocyte and MCV values, although this was not statistically significant, probably due to the small sample size. This association between indicators can be explained by the presence of the variant allele that, in the case of CYP2E1, is associated with increased enzyme activity and increased risk, probably due to the high production of toxic intermediates, while in NQO1 a decreased enzymatic activity and accumulation of toxic intermediates increased the risk for leukemia development. The values obtained in this study are similar to those reported in other studies, which also indicate increased risk for the same hematological alterations in the presence of the variant allele.

When evaluating the association between the genotypes of both investigated polymorphisms and the different hematological changes as a group – (1) eosinophilia; (2) plateletopenia + anemia; (3)
anemia; (4) plateletopenia; (5) plateletopenia + eosinophilia; (6) leukocytosis; (7) leukocytosis and neutrophilia; (8) leukopenia; and (9) leukopenia and neutropenia –, the presence of the NQO1 609C>T variant allele was suggested as a risk factor, despite the lack of statistical significance, probably due to the small sample size. This was not observed for the CYP2E1 – 1293G>C polymorphism. Although these results show no association in the literature, it is possible to observe that benzene exposure is present, due to the indicators assessed in this study.

Ye et al. 45 also observed that the presence of the variant allele confers a greater susceptibility to hematological changes related to benzene. Thus, participants who presented the CC genotype displayed a reduction in white cell counts. This corroborates the study carried out by Wan et al. 47, who described that the CC genotype confers greater susceptibility to benzene-benzene intoxication for CYP2E1 – 1293. In addition, the same study noted increased risk for the development of acute lymphoblastic leukemia in heterozygous individuals.

The association of the variant allele of the two analyzed polymorphisms with the risk for benzene hematotoxicity development after exposure has also been reported in other studies 58,59. Zhang et al. 57 evaluated the influence of genetic polymorphisms on the frequency of micronucleus formation in workers in the benzene-exposed footwear industry and found a small increase in the risk of micronucleus formation in individuals with the variant allele.

Studies described in the literature that aimed to study the CYP2E1 as promoter of region polymorphism at -1293 (Rsal restriction site) justify that the variant form is associated with increased enzyme activity and increased risk for the development of leukemia, probably due to the higher production of toxic intermediates 6,26,35,36. However, the presence of the NQO1 variant allele decreases the protective action of the enzyme, due to lower enzymatic activity and consequent toxic metabolite accumulation 38,55.

### Table 4
Genotype and allele frequencies of CYP2E1 – 1293G>C and NQO1 609C>T polymorphisms in the study population.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CYP2E1 Genotype</th>
<th>NQO1 Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG 93% (n = 176)</td>
<td>CC 57% (n = 108)</td>
</tr>
<tr>
<td></td>
<td>GC 7% (n = 14)</td>
<td>CT 38% (n = 73)</td>
</tr>
<tr>
<td></td>
<td>CC 0% (n = 0)</td>
<td>TT 5% (n = 9)</td>
</tr>
<tr>
<td>Allele</td>
<td>G 96%</td>
<td>C 76%</td>
</tr>
<tr>
<td></td>
<td>C 4%</td>
<td>T 24%</td>
</tr>
</tbody>
</table>

95%CI: 95% confidence interval.

### Table 5
Odds ratio (OR) of the homozygous and heterozygous genotypes of the CYP2E1 – 1293G>C variant alleles and NQO1 609C>T on changes in leukocyte, mean corpuscular volume (MCV) and neutrophil values.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Leukocytes OR (95%CI)</th>
<th>MCV OR (95%CI)</th>
<th>Neutrophils OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2E1 1293G&gt;C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>GC</td>
<td>1.30 (0.27-6.23)</td>
<td>1.76 (0.57-5.46)</td>
<td>0.70 (0.23-2.17)</td>
</tr>
<tr>
<td>NQO1 609C&gt;T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>CT, TT</td>
<td>1.11 (0.45-2.71)</td>
<td>1.06 (0.60-1.89)</td>
<td>0.71 (0.40-1.28)</td>
</tr>
</tbody>
</table>
Conclusions

This study carried out a biological characterization associating the evaluation of the internal dose biomarker (S-PMA) with susceptibility biomarkers (metabolic polymorphisms) and hematological alterations suggestive of benzene exposure in Campos Elíseos residents, evidencing the current precarious situation of resident individuals.

Urinary S-PMA concentrations presented results similar to those reported in other studies evaluating non-exposed populations. Thus, according to the results, there is no evidence to suggest that Campos Elíseos exposure is high when compared to other regions. However, when associations between S-PMA levels and other variables were investigated, increased risk with increased urinary S-PMA levels was observed, i.e. the greater the presence of benzene, the higher the occurrence of hematological alterations and associated pathologies. However, further studies are required in the Campos Elíseos region, including the determination of environmental indicators.

The allele and genotype frequencies of metabolic polymorphisms CYP2E1 – 1293 and NQO1 609C>T were determined in the studied population, and the presence of the variant alleles was associated to certain blood cell count alterations, possibly related to benzene exposure.

The need to carry out new studies in this region and in other regions, particularly near petrochemical industries, was demonstrated herein, and further investigations concerning relationships between the concentrations or the presence of biomarkers assessed herein, as well as others, with environmental benzene levels and potential pathologies are required.

Contributors

C. B. Silva, C. L. Mota, Y. R. Almeida, V. Emídio, A. S. A. Fonseca, S. Mitri, and J. C. Moreira contributed to the elaboration and initial structuring of work; collection of biological material and information; laboratory analysis and results; and elaboration and revision of the manuscript.

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References

5. Rasera IM. Toxicidade do benzeno, fontes de contaminação e analyses laboratoriais [Monogra-phy]. Novo Hamburgo: Instituto de Ciências da Saúde, Centro Universitário Feevale; 2009.


11. Infante PF. The IARC October 2009 evaluation of benzene carcinogenicity was incomplete and needs to be reconsidered. Am J Ind Med 2011; 54:157–64.


21. American Conference of Governmental Industrial Hygienists. Threshold limit values (TLVs) for chemical substances and physical agents biological exposure indices for 2013. Cincinnati: American Conference of Governmental Industrial Hygienists; 2013.


53. Oliveira VS, Canalle R, Scrideli CA, Queiroz RGP, Toni LG. Role of the CYP2D6, EPHX1, MPO, and NQO1 genes in the susceptibility to acute lymphoblastic leukemia in Brazilian children. Environ Mol Mutagen 2010; 51:48-56.
Resumo

O benzeno é uma das substâncias mais importantes para a biomonitorização, em função do uso disseminado, da contaminação ambiental que resulta da emissão e dos efeitos sobre a saúde humana. O benzeno é classificado pela Agência Internacional de Pesquisa em Câncer (IARC) como carcinógeno conhecido em seres humanos (grupo 1) e está associado ao desenvolvimento de leucemias. Em geral, a população fica exposta a essa substância através da inalação do ar contaminado, que varia de acordo com a localização e a intensidade das fontes potenciais. A indústria petroquímica é uma das fontes mais importantes desse composto. O Município de Duque de Caxias, especificamente o Distrito de Campos Elíseos, no Estado do Rio de Janeiro, Brasil, é sede do Polo Industrial de Campos Elíseos (PICE), um conjunto de mais de 25 indústrias que inclui a segunda maior refinaria de petróleo no Brasil. A contaminação ambiental produzida pelo PICE já é conhecida, mas faltam estudos sobre o impacto na saúde da população local. Foram observadas concentrações de ácido S-fenilmercaptúrico (S-PMA) entre 0,80 e 8,01μg.g\(^{-1}\) creatinina na população local, aparentemente relacionadas com alterações hematológicas também observadas na população exposta. A presença quantificável do S-PMA urinário do metabolismo do benzeno está associada ao fato de 60% dos participantes apresentarem alterações hematológicas específicas, o que pode ser devido à exposição ambiental ao benzeno. As frequências alélicas e genotípicas das enzimas CYP2E1 e NQO1, observadas na população do estudo, foram semelhantes àquelas relatadas em outros estudos. A presença da variante alélica do genótipo NQO1 pode ser um fator de risco para as alterações hematológicas observadas.

Benzeno; Poluição Ambiental; Biomarcadores; Polimorfismo Genético

Resumen

El benceno es una de las sustancias más importantes susceptibles de estudio, debido a su uso significativo, la contaminación ambiental resultante de sus emisiones y sus efectos sobre la salud humana. Está clasificado por el Centro Internacional de Investigaciones sobre el Cáncer (IARC) como un conocido carcinógeno para los humanos (grupo 1) y está asociado con el desarrollo de leucemias. En general, la población está expuesta a esta sustancia por inhalación de aire contaminado, que varía según el lugar y la intensidad de las emisiones. La industria petroquímica es un de las fuentes emisoras más importantes de este compuesto. La municipalidad de Duque de Caxias, específicamente el distrito de Campos Elíseos, en Río de Janeiro, Brasil, alberga el Complejo Industrial de Campos Elíseos (PICE), un conglomerado de más de 25 industrias, que incluye la segunda mayor refinaria de petróleo en Brasil. La contaminación ambiental procedente del PICE ya ha sido reconocida, pero es notable la falta de estudios respecto a su impacto en la salud de la población circundante. Se observaron en la población local concentraciones de ácido s-fenilmercaptúrico (SPMA por sus siglas en inglés) que oscilan entre los 0,80 a 8,01μg.g\(^{-1}\) creatinina, aparentemente relacionadas con cambios hematológicos también hallados en la población expuesta. La presencia cuantificable de SPMA en la orina, procedente del metabolismo del benceno, está asociada con el hecho de que un 60% de los participantes presenta cambios específicos hematológicos, los cuales tal vez se deben a la exposición ambiental al benceno. Las frecuencias alélicas y genotípicas del CYP2E1 y enzimas NQO1 observadas en el estudio fueron similares a las reportadas en otros estudios. La presencia de la variante alélica en el genotipo NQO1 podría ser un factor de riesgo para los cambios hematológicos observados.

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