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REVIEW

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The effects of genetic polymorphisms on benzene-exposed workers: A systematic review

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Abstract

Background and Aims: Benzene is a group I carcinogen, which has been associated with leukemia and myelodysplastic syndrome. Moreover, it has been proposed that polymorphisms in benzene metabolizing genes influence the outcomes of benzene exposure in the human body. This systematic review aims to elucidate the existent relationship between genetic polymorphisms and the risk of developing adverse health effects in benzene-exposed workers.

Methods: Three databases were systematically searched until April 2020. The preferred reporting items for systematic reviews and meta-analyses method was used to select articles published between 2005 and 2020. Quality assessment and risk of bias were evaluated by the Newcastle-Ottawa scale.

Results: After full-text evaluation, 36 articles remained out of 645 initially screened. The most studied health effects within the reviewed papers were chronic benzene poisoning, hematotoxicity, altered urinary biomarkers of exposure, micronucleus/ chromosomal aberrations, and gene methylation. Furthermore, some polymorphisms on *NQO1*, *GSTT1*, *GSTM1*, *MPO*, and *CYP2E1*, among other genes, showed a statistically significant relationship with an increased risk of developing at least one of these effects on benzene-exposed workers. However, there was no consensus among the reviewed papers on which specific polymorphisms were the ones associated with the adverse health-related outcomes, except for the *NQO1* rs1800566 and the *GSTT1* null genotypes. Additionally, the smoking habit was identified as a confounder, demonstrating worse health outcomes in exposed workers that smoked.

Conclusion: Though there is a positive relationship between genetic polymorphisms and detrimental health outcomes for benzene-exposed workers, broader benzene-exposed cohorts that take into account the genetic diversity of the population are needed in order to determine which specific polymorphisms incur in health risks.

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KEYWORDS
benzene, chronic benzene poisoning, genetic polymorphisms, hematotoxicity, occupational health

1 | INTRODUCTION

Benzene is an important chemical and ubiquitous environmental pollutant usually used as a solvent in industrial environments (eg, petrochemical industry, steel plants, shoe manufacturing, etc.). Moreover, it is an important toxicant, given that it is the main component of cigarette smoke, gasoline, crude oil, and automotive emissions.[1-4] Benzene is classified by the International Agency for Research on Cancer (IARC) as a group I human carcinogen[5]; furthermore, it is the cause of several hematological disorders, such as anemia, leukopenia, thrombocytopenia, acute myeloid and lymphocytic leukemia, myelodysplastic syndrome, and non-Hodgkin lymphoma.[6]

The toxicity of benzene has been related to its metabolism, which is illustrated in Figure 1. After benzene inhalation, a number of reactions occur, which involve different enzymes such as NADPH quinone oxidoreductase-1 (NQO1), myeloperoxidase (MPO), glutathione S-transferases (GST), hydrolases and CYP enzymes (mainly CYP2E1).[2,6-8] These metabolic pathways produce metabolites that are excreted in the urine, for instance *trans*,*trans*-muconic acid (t,t-MA) and S-phenylmercapturic acid (S-PMA). Additionally, enzymes like NQO1 or GSTs catalyze detoxification reactions.[2,7]

Even though the mechanisms by which benzene exerts its genotoxic and hematotoxic effects have not yet been fully elucidated,[8] it is widely accepted that benzene reactive intermediates can bind covalently to macromolecules including DNA, tubulin, histones, and topoisomerase II in the tissue. Furthermore, the resultant metabolites are produced in conjunction with reactive oxygen species, and therefore, cause oxidative stress and subsequent genotoxicity. This results in cell damage and DNA double-strand breaks; thus, altering the normal cell cycle, generating carcinogenic effects on the bone marrow and the lympho-hematopoietic system. It has also been proposed that this aromatic hydrocarbon can produce direct damage to hematopoietic progenitor cells, which could lead to apoptosis or altered responsiveness to cytokines and cellular adhesion molecules.[7,9-11] Moreover, benzene toxicity to mature blood cells or stromal cells could disrupt the regulation of hematopoiesis, including maturation, hematopoietic commitment, or mobilization, through the network of chemokines, adhesion molecules, and cytokines.[8]

As mentioned above, industrial environments are an important source of benzene exposure, with workers in major industry sectors (such as petrochemical plants, petroleum refineries, coke and coal chemicals or tire manufacturers) exposed to ranges that vary from 0 to 0.325 mg/m^3 to more than 32.5 mg/m^3 of benzene, contrasting the environmental exposure of the general population that varies from 0.0028 to 0.04 mg/m^3.[12,13] Consequently, international agencies have set occupational exposure limits in order to reduce the risk for adverse health outcomes in subjects exposed to this hydrocarbon at their workplace.[14,15] Nonetheless, uniformity between these guidelines when establishing occupational exposure limits is lacking,[14-17] especially considering that some individual factors such as genetic diversity predispose the population to benzene-related adverse health effects, even at low levels of exposure.[18]

For example, several studies have reported a relationship between polymorphisms of benzene-metabolizing enzymes and higher susceptibility to benzene toxicity.[18-22] Dougherty et al, De Palma et al, and Carbonari et al reviewed, in 2008, 2014, and 2016, respectively, the effect of genetic polymorphisms on biomarkers of exposure and biomonitoring, among benzene-exposed workers.[8,10,23] However, since then, new studies have surfaced, and a review that includes benzene health-related effects other than biomarker excretion is in order. Consequently, in this systematic review, we aim to elucidate the existent relationship between genetic polymorphisms and the risk of developing adverse health outcomes in benzene-exposed workers.

2 | METHODS

2.1 | Search strategy

A systematic search, based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[24] was conducted on Scielo, Pubmed, and Medline databases using Boolean operators, Medical Subjects Heading (MeSH), and non-MeSH terms: *Benzene*, *occupational*, *mutations*, *and polymorphism*. The full search strategy was adapted for each database and is listed on the Supporting Information.

2.2 | Study eligibility criteria

We only included studies that evaluated the effect of at least one polymorphism in different variables, with human subjects older than 18, whose main source of benzene exposure was occupational. We also exclusively added papers written in English or Spanish. Additionally, we filtered the results by only using articles published from 2005 to April 2020. Papers that only focused on environmental exposure were rejected, as were in-vitro studies. The accepted types of research were solely observational studies such as cross-sectional and case-control studies.

2.3 | Study selection

Article selection was conducted independently by two reviewers (VR-L and DU-C), and this process is illustrated in Figure 2.[24] The first search retrieved 645 results, and after the application of two filters (year-of-publication and not-in-vitro-studies), followed by narrowing of the search strategy with the use of Boolean operators (see

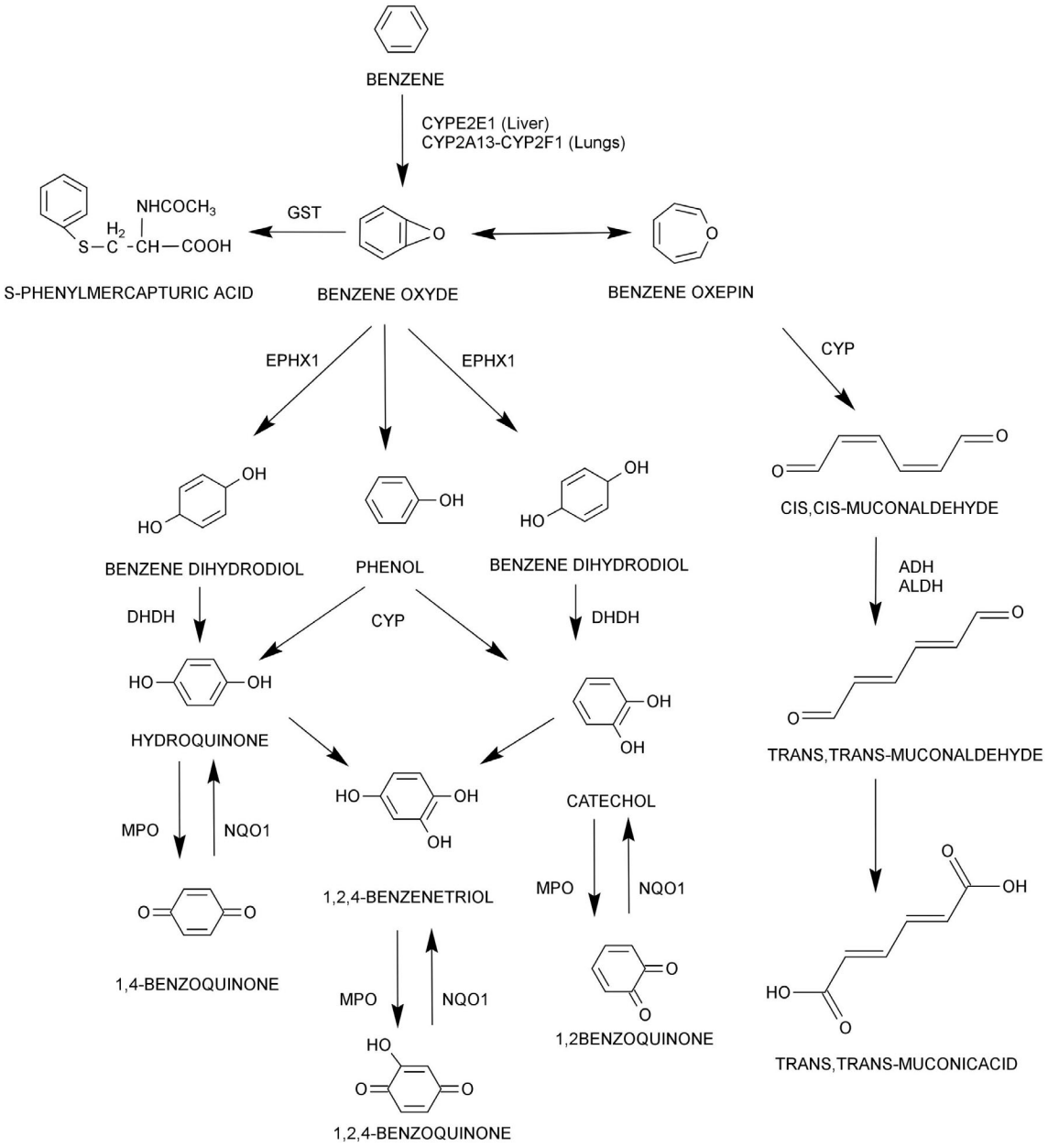

FIGURE 1 Metabolic pathways of benzene. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P-450; DHDH, dihydrodiol dehydrogenase; EPHX1, microsomal epoxide hydrolase 1; GST, glutathione S-transferase; MPO, myeloperoxidase; NQO1, NAD(P)H quinone dehydrogenase 1

Supporting Information), 549 papers were excluded. We added 21 cross-references to the remaining 96 articles, found either on the searched databases or on the remaining-papers references. Those articles were then screened by their titles, and 35 duplicates as well as nine titles that fulfilled the exclusion criteria were excluded. The results of the search were imported to the Zotero software, which was used as a reference manager. Afterward, two reviewers analyzed whether or not the abstracts met the inclusion criteria previously established, and then the same procedure was conducted with the full-text articles. If there was a disagreement, a third reviewer (TLP-C) resolved it. After that, 36 papers were included. To avoid the omission of articles relevant to the research, the references included in the reviewed articles were compared and checked.

2.4 | Data extraction

A table was created for summarizing the following characteristics from each paper: authors and year of publication, country of publication, sample size, age, gender, evaluated variable, evaluated genes and polymorphisms, quality assessment, and relevant results. The mean summary measures used in this review were odds ratios (OR), adjusted odds ratios (ORadj), *P* values (*P*), risk ratios (RR), and frequency ratios (FR).

2.5 | Protocol and study quality assessment

This systematic review was indexed in the prospective register of systematic reviews (PROSPERO). To assess the quality of these studies, the Newcastle-

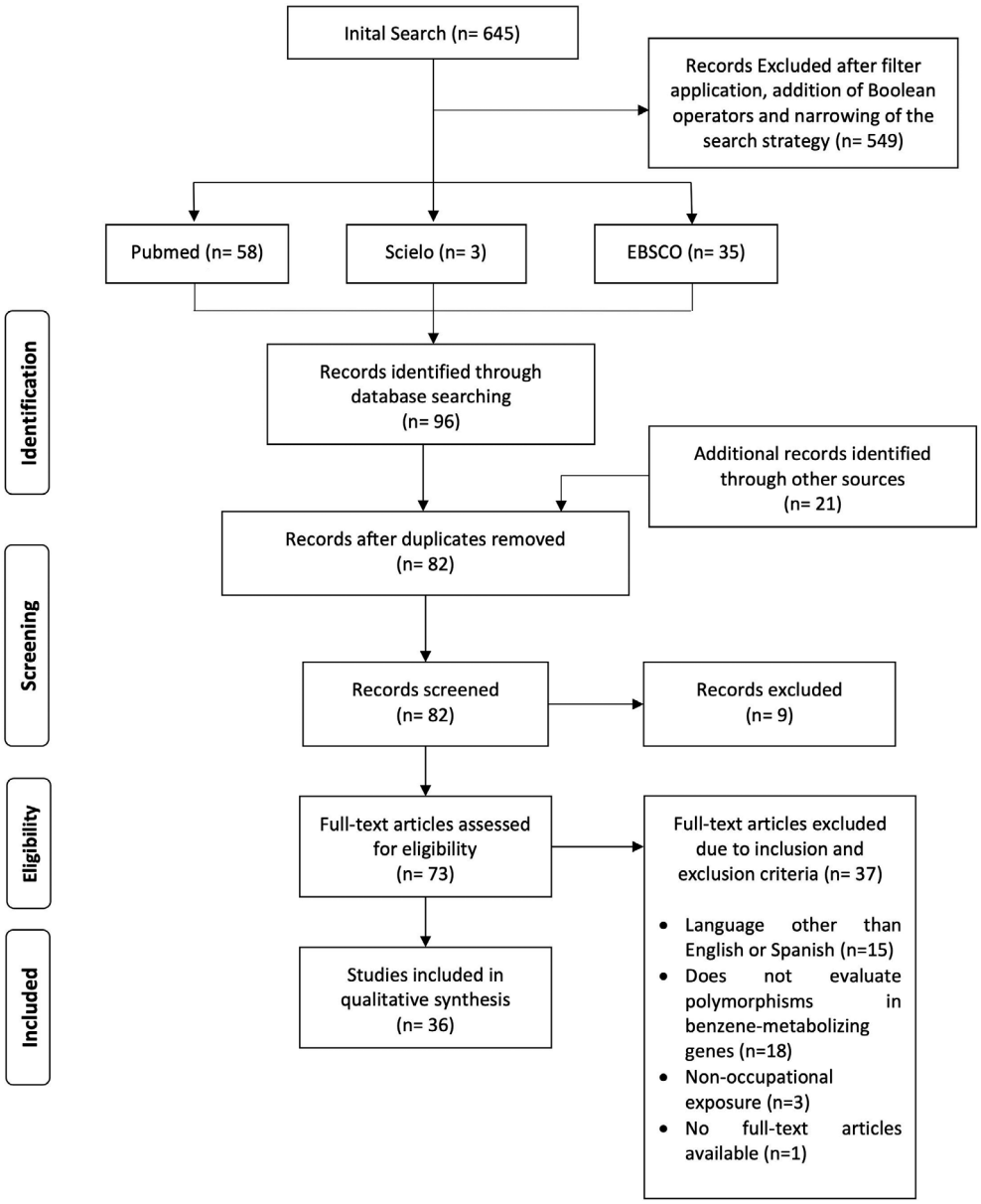

FIGURE 2 PRISMA search strategy flowchart

Ottawa Scale (NOS) was modified to fit each study type, as stated on the Supporting Information.[25] For case-control studies, three categories were evaluated: selection, comparability, and exposure; for cross-sectional studies, the exposure category was replaced with "outcome." Points were assigned according to the study's quality and bias risk, the maximum number of points each study could get was 9. The higher the number of points, the lower the bias risk was (see Supporting Information, Appxs. B-E).

3 | RESULTS

3.1 | Characteristics of eligible studies

A total of 36 articles were retrieved from the conducted systematic search, six were cross-sectional studies and 30 were case-control studies. All of them assessed occupationally benzene-exposed population and evaluated one or more of the following benzene effects: chronic benzene poisoning (CBP), hematotoxicity, altered urinary biomarkers, micronucleus/chromosomal aberrations (CA), and gene methylation. Regarding the NOS, both case-control and cross-sectional studies reached an average of 6 points out of 9, the former ranging from 5 to 8, and the latter from 5 to 7. These results are summarized in Table 1.

3.2 | Effects of polymorphisms on susceptibility to CBP

There were 10 studies that researched the relationship between polymorphisms and CBP (see Table 2).

TABLE 1 Characteristics of the included studies

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Hosgood et al[26]	China	250 workers exposed to benzene 140 unexposed controls	21.5-39.03 y.o. 138 male 252 female	Exposed workers: 5.4 ppm (SD 12.1 ppm) Unexposed controls: <0.04 ppm	Total WBC count	***VEGF*** rs3025030 rs833058 rs699946 ***ERCC3*** rs4150441 rs6731176 Other genes: *BLM*, *GPX3*, *IL8RB/IL8RA*, *RIPK2*, *IL6*, *IL6R*, *IL10/IL19*, *IL12RB1*, *WRN*, *IFNAR2*	Increased WBC count was evidenced in exposed workers with: • *VEGF* rs3025030 (variant allele C; $P < 0.001$) • *VEGF* rs833058 (variant allele C; $P = 0.0011$) • Homozygous variant alleles of rs3025030 - rs833058 • *ERCC3* rs4150441 (variant allele T; $P = 0.0086$) • *ERCC3* rs6731176 (variant allele C; $P = 0.0087$)	8/9
Xiao et al[27]	China	102 patients with CBP 204 patients without CBP	18-63 y.o. 63 male 243 female	—	Risk of developing CBP	***ERCC1*** rs11615 rs3212986 ***ERCC2/XPD*** rs13181 rs1799793 rs238406	Increased risk of CBP in non-smokers with: *ERCC1* rs11615 (TT genotype) [OR = 3.21 (95% CI 1.36-7.60), $P = 0.006$]	6/9
Sun et al[11]	China	303 benzene-poisoned patients 295 workers occupationally exposed to benzene (controls)	18-68 y.o. 379 male 219 female	—	Risk of developing CBP	***GADD45A*** rs581000 rs11544978 rs532446 ***MDM2*** Del1518 rs2279744 ***p14ARF*** rs3731217 rs3731245 rs3088440	Increased risk of CBP in individuals with: • *p14ARF* TGA/TAG diplotype ($P = 0.0006$) • Decreased risk of CBP in individuals with: • *p14ARF* rs3731245 (GA + AA genotypes) [ORadj = 0.57 (95% CI 0.36-0.89)] • *p14ARF* TGG/TAA diplotype ($P < 0.001$) • *MDM2* Del1518 (WW genotype) **plus** *p14ARF* rs3731245 (GA + AA genotypes) [ORadj = 0.25 (95% CI 0.10-0.62), $P = 0.003$]	6/9
Sun et al[28]	China	345 benzene-poisoned patients 336 (controls) 37 non-exposed workers	18–68 y.o. 440 male 280 female	—	Risk of developing CBP	***TP53*** rs17878362 rs1042522 rs1625895 ***p21*** rs1801270 rs1059234	Decreased risk of CBP in individuals with: • p21 rs1801270 (CA + AA genotype) [OR = 0.51 (95% CI 0.32-0.83)] rs1059234 (CT + TT genotype) [OR = 0.53 (95% CI 0.29-0.95)]	5/9

(Continues)

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Pesatori et al[29]	Bulgaria	158 petrochemical workers exposed to benzene 50 unexposed subjects	30.5-52.1 y. o. 171 male 32 female	1.71 ppm	Total blood cell count	***NQO1*** rs1800566 ***CYP2E1*** rs2031920 (RsaI) rs6413432 (DraI)	None of the investigated polymorphisms was related with blood cell count	7/9
Torres et al[30]	Colombia	30 directly exposed and 60 without occupational exposure	19-56 y.o. 65 male 25 female	—	DNA damage and urinary biomarker PH	***CYP2E1*** rs3813867/ rs203192 (PstI/RsaI) rs6413432 (DraI) ***GSTT1*** Null and no null ***GSTM1*** Null and no null	No significant differences were found between DNA damage, urinary phenol level and the polymorphisms evaluated	6/9
Chanvaivit et al[31]	Thailand	62 cases 34 controls	16-60 y.o. 87 male 9 female	Laboratory workers: 24.4 ppb Gasoline service attendants: 112.41 ppb Controls: 1.39 ppb	DNA repair-capacity, blood biomarkers (blood benzene levels) and urine biomarkers (t,t-MA)	***CYP2E1*** *CYP2E1*1/*5* *CYP2E1*5/*5* *CYP2E1*1/*1* ***NQO1*** rs1800566 ***GSTT1*** Null and no null ***XRCC1*** rs25487	*XRCC1* rs25487 (399Gln allele) had a lower DNA repair-capacity than those with 399Arg/Arg genotype ($P < 0.01$, in laboratory workers only) *CYP2E1*1/*5* and *CYP2E1*5/*5* genotypes had lower benzene levels in blood than those with the *CYP2E1*1/*1* genotype (in laboratory workers only) *NQO1* and *GSTT1* genotypes: no effects on *t,t-MA* levels	5/9
Gu et al[32]	China	152 benzene poisoning patients 152 control workers (occupationally exposed to benzene)	19-61 y.o. 118 male 186 female	40 mg/m^3: Cases: 18.4% Controls: 21.7% 41-100 mg/m^3: Cases: 61.2% Controls: 61.8% >100 mg/m^3 Cases: 20.4% Controls: 16.5%	Risk of developing CBP	***CYP1A1*** rs4646903 ***CYP2D6*** rs1065852 rs1135840 c. 212 G > A ***UGT1A6*** c.181 T > A ***UGT1A7*** 208Trp > Arg ***SULT1A1*** c.638G > A	More susceptibility to CBP in subjects with: • *CYP1A1* rs4646903 (TT genotype) [ORadj = 1.21 (95% CI 1.03–1.42), $P < 0.05$] • *CYP2D6* rs1065852 (CC or CT genotypes) [ORadj = 2.11 (95% CI 1.22-3.65), $P < 0.05$] • *CYP2D6* rs1135840 (CC genotype) [ORadj = 1.69 (95% CI 1.04-2.74), $P < 0.05$]	6/9
Wu et al[33]	China	152 benzene poisoning patients 152 control workers (occupationally exposed to benzene)	19–61 y.o. 118 male 186 female	40 mg/m^3: Cases: 18.4% Controls: 21.7% 41-100 mg/m^3: Cases: 61.2% Controls: 61.8% >100 mg/m^3 Cases:20.4% Controls: 16.5%	Risk of developing CBP	***hMTH1*** rs4866 (Val83Met) ***hOGG1*** rs1052133 (Ser326Cys) ***hMYH*** rs3219489 (His324Gln)	Higher risk of CBP with: • *hMTH1* 83Val/Met + Met/Met [ORadj = 2.47 (95% CI 1.03-5.92)] compared to Val/Val (only in non-smokers) • *hOGG1* 326Cys/Cys [ORadj = 3.06 (95% CI (1.74-5.35)] compared to Ser/Ser + Ser/Cys (only in non-smokers)	6/9

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied		Results	Quality assessment score
								• *hMTH1* 83Val/Val and *hOGG1* 326Cys/Cys at the same time [ORadj = 2.57 (95% CI 1.49-4.42), $P < 0.01$] • Lower risk of CBP with: • *hMYH* 324His/Gln + Gln/Gln [ORadj = 0.15 (95% CI 0.03-0.68)] (only in smokers)	
Zhang et al[34]	China	152 benzene poisoning patients 152 control workers (occupationally exposed to benzene)	19–61 y.o. 118 male 186 female	40 mg/m^3: Cases:18.4% Controls: 21.7% 41-100 mg/m^3: Cases: 61.2% Controls: 61.8% >100 mg/m^3 Cases: 20.4% Controls: 16.5%	Risk of developing CBP	***XRCC1*** rs1799782 (Arg194Trp) rs25489 (Arg280His) rs25487 (Arg399Gln) ***APE1*** rs1130409 (Asp148Glu)	***ADPRT*** rs1136410 (Val762Ala) ***XRCC2*** rs3218536 (Arg188His) ***XRCC3*** rs861539 (Thr241Met)	Higher risk of CBP with: • -*XRCC1* rs25489 • *Arg/His [ORadj = 1.67 (95% CI 1.02-2.74), $P = 0.04$] compared to Arg/Arg • *Arg/His+His/His in non-smokers [ORadj = 1.96 (95% CI 1.14-3.38)] and non-alcohol users [ORadj = 1.78 (95% CI 1.05-3.03)] only • Haplotypes of *XRCC1* • *194Arg, 280His and 399Arg [ORadj = 2.96 (95% CI 1.60-5.49), $P = 0.001$] • Lower risk of CBP with: • *XRCC1* rs1799782 • *Arg/Trp + Trp/Trp [ORadj = 0.60 (95% CI 0.37-0.98), $P = 0.041$] compared to Arg/Arg • *APE1* rs1130409 • *Asp/Glu + Glu/Glu in alcohol users [ORadj = 0.11 (95% CI 0.02-0.69)]	6/9
Xue et al[35]	China	102 CBP patients 204 controls	18–63 y.o. 63 male 243 female	—	Risk of developing CBP	***XRCC1*** rs25487 rs25489 rs1799782 ***CD3EAP*** rs96759 ***PPP1R13L*** rs1005165	***XPB/ERCC3*** rs4150441 ***XPC*** rs2228001 rs227901 ***XPF*** rs4781560	Higher risk of CBP with: • *XRCC1* rs25487 (AA genotype) [ORadj = 14.89 (95% CI 6.54-30.21), $P < 0.001$] • *XRCC1* rs1799782 (TT genotype): only in alcohol drinkers [OR = 8.0 (95% CI 1.32-48.64), $P = 0.022$], males [OR = 9.33 (95% CI 1.59–54.67), $P = 0.019$] and < 12 year exposure [OR = 2.61 (95% CI 1.05-6.51), $P = 0.035$]	6/9

(Continues)

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
							• *XPB/ERCC3* rs4150441: GA [OR = 1.73 (95% CI 1.00-2.99), $P = 0.049$] and GA + AA genotypes [OR = 1.72 (95% CI 1.01-2.9), $P = 0.043$] compared to GG genotype • Lower risk of CBP in **males** with: • *PPP1R13L* rs1005165 (CT, TT and CT + TT genotypes) ($P < 0.05$) • *CD3EAP* rs967591 (GA and GA + AA genotypes) ($P < 0.05$)	
Mansi et al[4]	Italy	181 occupationally exposed petrochemical workers (cases) 134 administrative employees (controls)	23-65 y.o. 309 male 6 female	0.0368 mg/m^3 (0.01 ppm)	Urinary biomarkers: S-PMA, t,t-MA and t,t-MA/S-PMA ratio	***GSTP1*** rs1695 ***GSTM1*** Null and no null ***GSTT1*** Null and no null	Lower S-PMA and higher t,t-MA/S-PMA ratio in subjects with *GSTT1* null genotype (compared to no null genotype) ($P < 0.001$) Lower S-PMA and higher t,t-MA/S-PMA ratio in subjects with *GSTM1* null genotype compared to no null genotype ($P < 0.001$, only in smokers)	7/9
Mitri et al[36]	Brazil	114 gas-station attendants: 72 with clinical findings (CF) 52 with no clinical findings (NCF)	19-82 y.o. 87 male 27 female	—	Risk of developing CBP	***CYP2E1*** rs2031920 rs6413432 ***NQO1*** rs1800566 ***MPO*** rs2333227 ***GSTM1*** Null and no null ***GSTT1*** Null and no null	*GSTM1* null genotype was associated with changes related to CBP (ie, symptoms, altered MCV and neutrophil %) [OR = 5.13 (95% CI 1.13-23.15)]	7/9
Xing et al[37]	China	77 benzene-exposed workers 25 unexposed controls	43-67 y.o. 38 male 64 female	For 34 exposed workers: 324 ppm-years For 43 exposed workers: >100 ppm-years	Altered DNA methylation and total WBC count	***CYP1A1*** rs4646903 ***EPHX1*** rs1051740 rs2234922 ***NQO1*** rs1800566 Methylation levels of: *BLM*, *CYP1A1*, *EPHX1*, *ERCC3*, *NQO1*, *NUDT1*, *p15*, *p16*, *RAD51*, *TP53*, and *WRAP53*	*ERCC3* showed an increased methylation level in exposed workers ($P = 0.048$) Increased number of C allele for *EPHX1* rs1051740 was associated with decreased methylation level of the *ERCC3* gene in exposed workers ($P = 0.001$) Reduced WBC count was associated with increasing number of G allele for *EPHX1* rs2234922 in exposed workers ($P = 0.044$) Increased WBC count was related to increasing number of C allele for *CPY1A1* rs4646903 in exposed workers ($P = 0.001$)	6/9

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Fustinoni et al[2]	Italy	308 cases (urban policemen, gas station attendants and bus drivers) 107 controls	28.9-48.1 y. o. 352 male 63 female	Gas station attendants: 61 μg/m^3 Urban policemen: 22 μg/m^3 Bus drivers: 21 μg/m^3 Controls: 7.5 μg/m^3	Urinary biomarkers: S-PMA, t,t-M, U-benzene and U-cotinine	***CYP2E1*** rs2031920 (RsaI) rs6413432 (DraI) ***NQO1*** ****Polymorphism not specified***	Higher t,t-MA in exposed subjects with at least one variant allele in *CYP2E1* rs6413432 ($P = 0.03$) Reduced U-benzene excretion in subjects with at least one mutant allele of *CYP2E1* rs2031920 ($P < 0.01$) All the biomarkers were influenced by smoking	7/9
Manini et al[5]	Italy	239 workers (taxi drivers, traffic policemen and gasoline pump attendants)	27.7-54.5 y. o. 170 male 69 female	38.3 μg/m^3	Urinary biomarkers: S-PMA, t,t-MA and biomarkers of nucleic acid oxidation: 8-oxodGuo, 8-oxoGuo and 8-oxoGua	***NQO1*** rs1800566 *NQO1*1*1* *NQO1*1*2* ***GSTM1*** Null and no null ***GSTT1*** Null and no null ***GSTA1*** *GSTA1*A*A* *GSTA1*A*B* *GSTA1*B*B*	Subjects bearing the *NQO1*1*1* (wild-type genotype) showed lower levels of oxidative damage to RNA compared to subjects with at least one variant allele ($P < 0.05$) Lower S-PMA excretion with *GSTM1* null ($P = 0.01$), *GSTT1* null ($P = 0.023$) and *GSTA1*B*B* ($P = 0.048$) genotypes compared to positive genotypes In subjects defective for one GST enzyme, the other one could effectively play a vicarious activity	7/9
Sun et al[38]	China	268 benzene-poisoned patients 268 workers occupationally exposed to benzene	17-68 y.o. 342 male 194 female	40 mg/m^3: Cases: 53.7% Controls: 55.6% 41-100 mg/m^3: Cases: 34.7% Controls: 35.1% >100 mg/m^3 Cases: 11.6% Controls: 9.3%	Risk of developing CBP	***CYP1A1*** rs4646421 rs4646422 rs1048943 rs4646903 ***CYP1A2*** rs2445618 rs762551 rs2472304 rs2470890 ***CYP1B1*** rs1056836 ***ADH1B*** rs1229984 ***EPHX1*** rs2854451 rs3738047 rs2234922 rs1051741 ***EPHX2*** rs781141 ***NQO1*** rs1800566 ***MPO*** rs7208693 ***GSTP1*** rs1695 ***UGT1A6*** rs6786892 rs1105879 rs4124874 rs3755319 rs887829 rs4148323 Haplotypes and diplotypes of *CYP1A1* *CYP1A2* *EPHX1* *UGT1A6*	Higher risk of CBP in: -*EPHX1* GGAC/GAGT ($P = 0.00057$) or AGAC/GAGT ($P = 0.00086$) diplotypes Decreased risk of CBP in *GSTP1* rs1695 (AG + GG genotype) [OR = 0.44 (95% CI 0.24-0.81), $P = 0.007$] only in non-alcohol drinkers Higher risk of CBP in **alcohol drinkers** with: *EPHX1* rs3738047 GA + AA genotype [OR = 5.0 (95% CI 0.89-30.52), $P = 0.073$] compared to GG genotype Decreased risk of CBP in **alcohol drinkers** with: *EPHX1* rs2234922 AG + GG compared to GG ($P = 0.008$) or rs1051741 CT + TT compared to CC ($P = 0.043$)	7/9

(Continues)

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Chen et al[39]	China	100 workers with CBP 90 controls	37 male 63 female	—	Risk of developing CBP	***NQO1*** rs1800566 ***MPO*** rs2333227 ***CYP2E1*** rs2031920 rs6413432 ***GSTM1*** Null and no null ***GSTT1*** Null and no null	Higher risk of CBP in: • *NQO1* rs1800566 TT genotype [OR = 2.82 (95% CI 1.42-5.58)] compared to CT + CC genotypes • *GSTT1* null genotype [ORadj = 1.91 (95% CI 1.05-3.45)] • *NQO1* rs1800566 TT genotype **plus** *GSTT1* null genotype [OR = 4.59 (95% CI 1.73-12.20)] compared to CT + CC plus no null genotypes • *NQO1* rs1800566 TT genotype **plus** *GSTT1* null genotype **plus** *GSTM1* null [OR = 16.13 (95% CI 3.15-83.33) • *NQO1* rs1800566 CT + CC genotype **plus** *GSTT1* null genotype [OR = 2.21 (95% CI 1.09-4.46)] compared to CT + CC genotype **plus** no null genotype	6/9
Lan et al[9]	China	250 workers exposed to benzene 140 unexposed controls	21.5-39.03 yo 138 male 252 female	Exposed workers: 5.4 ppm (SD 12.1 ppm) Unexposed controls: <0.04 ppm	Total WBC count	***ICAM1*** rs5491 ***VCAM1*** rs1041163 rs3176879 ***CSF2*** rs1469149 ***CSF3*** rs1042658 ***IL-1A*** rs1800587 ***IL-1B*** rs16944 ***IL-2*** rs2069762 ***IL-4*** rs2243248 ***IL-4R*** rs1805010 ***IL-5*** rs2069812 ***IL-10*** rs1800871 ***IL-12A*** rs568408 ***IL-12B*** rs3212227 ***IL-13*** rs20541 ***IL-16*** rs859 ***LTA*** rs909253 ***TNF*** rs1800629 ***CCR2*** rs1799864 ***CCR5*** rs2734648 ***IL-8*** rs4073	Decreased WBC count in exposed workers with: • *IL-1A* rs1800587 CT + TT genotype ($P < 0.001$) compared to CC • *IL-4* rs2243248 TG genotype ($P = 0.0046$) compared to TT • *IL-10* rs1800871 CC genotype ($P = 0.0034$) compared to TT • *IL-12A* rs568408 AA genotype ($P < 0.001$) compared to GG • *VCAM1* rs1041163 CC genotype ($P = 0.0022$) compared to TT • Increased WBC count in exposed workers with: *CSF3* rs1042658	8/9

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied		Results	Quality assessment score
Shen et al[40]	China	250 workers exposed to benzene 140 unexposed controls	21.5–39.03 y.o. 138 male 252 female	Exposed workers: 5.4 ppm (SD 12.1 ppm) Unexposed controls: <0.04 ppm	Total WBC count	***WRN*** rs4987236 rs2725349 rs1800392 rs2725362 rs4987036 rs1346044 ***TP53*** rs1042522 ***NBS1*** rs1805794 ***BRCA1*** rs16940 rs799917 rs16941	***BRCA2*** rs1799943 rs1801406 rs543304 rs766173 rs144848 rs1799944 rs1799955 ***XRCC3*** rs861539 ***XRCC4*** rs3734091 rs1805377 rs1056503	Decreased WBC count in exposed workers with: • WRN • Homozygous variants in: • rs4987236 (P = 0.0003), rs2725349 (P = 0.022), rs1800392 (P = 0.001), rs2725362 (P = 0.0003) • TP53 rs1042522 (P = 0.001) • BRCA2 • Homozygous for uncommon allele of: rs1801406 (P = 0.045)	8/9
Shen et al[1]	China	250 workers exposed to benzene 140 unexposed controls	21.5–39.03 y.o. 138 male 252 female	0.36 ± 0.31 ppm	Total WBC count	***MBP*** rs470261 ***VCAM1*** rs1041163 rs3176867 ***ALOX5*** rs4948671 rs7099684 ***MPO*** rs2071409 ***RAC2*** rs2239773 ***CRP*** rs180094		Decreased granulocyte, lymphocyte, and monocyte population counts in: • *VCAM1* rs3176867 (*P* < 0.0001) • *ALOX5* rs709968 (*P* = 0.0001) • *MPO* rs2071409 (*P* = 0.0001)	8/9
Lan et al[41]	China	250 workers exposed to benzene 140 unexposed controls	21.5–39.03 y.o. 138 male 252 female	Exposed workers: 5.4 ppm (SD 12.1 ppm) Unexposed controls: <0.04 ppm	Total WBC count	***APOB*** rs3791981 ***IGF2R*** rs1570070 ***IL1A*** rs17561 ***GSK3B*** rs1719888 ***WRN*** rs2230009 rs2725362 ***TP53*** rs12951053 ***GPX3*** rs8177426	***RXRA*** rs1805352 ***BLM*** rs2270132 ***CSF3*** rs3917979 ***RAD51*** rs4924496 ***EFNB3*** rs3744262 ***IL10b*** rs1800871 ***MPO*** rs2071409 ***WDR79*** rs17885803 rs2287499	Decreased WBC count in exposed subjects with: • *BLM* rs2270132 (*P* = 0.00021), rs1694489 (*P* = 0.0038) and rs414634 (*P* = 0.0077) • *RAD51* rs4924496 (*P* = 0.00053) • *TP53* rs12951053 (*P* = 0.0011) • *WRN* rs2725362 (*P* = 0.00029) and rs2230009 (*P* = 0.0002) • *WDR79* rs2287499 (*P* = 0.005)	8/9

(Continues)

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Ye et al[7]	China	Cases: 385 exposed workers Controls: 220 healthy subjects	19-57 y.o. 317male 288 female	6.4 mg/m^3	Total WBC count	***GSTT1*** Null and no null ***GSTM1*** Null and no null ***GSTP1*** rs1695 ***CYP2E1*** rs3813867 rs2031920 rs6413432 ***mEH*** rs1051740 rs2234922	Decreased WBC counts in exposed subjects with: • *GSTT* null genotype ($P = 0.045$) compared to no null genotype • *GSTM1* null genotype ($P = 0.03$) compared to no null genotype • *CYP2E1* rs2031920 CT genotype compared to CC ($P = 0.020$) and rs3813867 GC genotype compared to GG ($P = 0.014$)	7/9
Kim et al[42]	Korea	108 workers directly exposed to benzene 33 office workers	30–52 y.o.	0.51 ppm	MN and CA	***NQO1*** rs1800566 ***MPO*** rs2333227 ***XRCC1*** rs25487	Exposed workers with *NQO1* TT genotype had increased MN [RR = 1.9 (95% CI 1.5–2.3)] and CA [RR = 2.6 (95% CI 1.7-3.9)] compared to those with CT or CC genotypes A rise in CA on subjects with *MPO* GG genotype [RR = 2.3 (95% CI 1.3-4.0)] and *XRCC1* AA genotype [RR = 2.2 (95% CI (1.5-3.1)] compared to those with *MPO* GA or AA and *XRCC1* GG or AG respectively	6/9
Fang et al[43]	China	461 exposed workers 88 controls	25.1-27.7 y.o. 484 male 65 female	Less than 0.6 mg/m^3	MN	***NQO1*** rs1800566 ***CYP2E1*** rs3813867	Lower MN frequencies in exposed subjects with *NQO1* TT genotype [FR = 0.79 (95% CI 0.66-0.95), $P < 0.05$] compared to the CC genotype	6/9
Zhang et al[44]	China	294 benzene-exposed participants 102 controls indoor workers	17-71 y.o. 174 male 222 female	6.4 mg/m^3	MN and methylation	***XRCC1*** rs25489 rs25487 ***APE1*** rs1130409 ***XPA*** rs1800975 ***XPC*** rs2228000 rs2228002 ***ERCC2*** rs13181 rs1799793 ***XPG*** rs17655 ***ERCC1*** rs3212986	Higher MN frequency on workers with: -*XRCC1* rs25487 AA genotype [FR = 1.50 (95% CI 1.16–1.9), $P = 0.002$] compared to GG; and GA genotype [FR = 1.20 (95% CI 1.06-1.37), $P = 0.006$] -*APE1*: rs1130409 GG genotype [FR = 1.28 (95% CI 1.05-1.55), $P = 0.01$] compared to TT; and GT genotype [FR = 1.20 (95% CI 1.04-1.37), $P = 0.012$] -*XPG* rs17655 GC genotype [FR = 1.18 (95% CI 1.02-1.38), $P = 0.038$] compared to GG	6/9

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied		Results	Quality assessment score
								-*ERCC1*: rs3212986 TT genotype [FR = 1.55 (95% CI 1.31-1.83), $P < 0.001$] compared to GG Low global DNA methylation in subjects with *APE1* rs1130409 GG + GT genotype ($P = 0.045$)	
Nourozi et al[6]	Iran	Cases: 124 petrochemical plant benzene-exposed workers Controls: 184 subjects with a similar exposure scenario	27.62-40.9 y. o. All male	Cases: 0.10 ± 0.195 ppm Controls: 0.12 ± 0.284 ppm	Total WBC count	***GSTP1*** rs1695 ***CYP2E1*** rs3813867 ***GSTM1*** null and no null ***GSTT1*** null and no null		*GSTT1* null was associated with lower platelet count ($P = 0.015$) and higher risk for hematological disorders [OR = 2.1 (95% CI 1.23-3.56)] compared to *GSTT1* positive Higher leukocyte counts with *GSTM1* null compared to *GSTM1* positive ($P = 0.026$)	8/9
Kim et al[3]	China	250 benzene-exposed workers 136 control workers	21-43 y.o. 248 males 138 females	0.512 ppm	Urinary biomarkers: t,t-MA, S-PMA, PH, CAT, and HQ	***CYP2E1*** rs203192 ***NQO1*** rs1800566 rs4986998 ***EPHX1*** rs1051740 rs2234922 ***GSTT1*** Null and no null ***GSTM1*** Null and no null ***GSTP1*** rs947894 ***MPO*** rs2333227		*NQO1* rs1800566 lowered t,t-MA, S-PMA ($P = 0.001$), PH ($P = 0.022$), CAT ($P = 0.036$) and HQ ($P = 0.036$) *CYP2E1* rs2031920 affected t,t-MA ($P < 0.001$), PH ($P < 0.001$), HQ ($P < 0.001$) and S-PMA *EPHX1* rs1051740 or rs2234922 affected CAT and S-PMA *GSTT1* null and *GSTM1* null lowered S-PMA ($P = 0.018$) *MPO* rs2333227 showed no effect on urinary biomarker excretion	8/9
Carbonari et al[45]	Italy	301 oil refinery workers in Italy	30.6-53.4 y. o.	0.021 mg/m^3	Urinary biomarkers: S-PMA, t,t-MA	***GSTA1*** rs3957356 ***GSTT1*** Null and no null ***GSTM1*** Null and no null ***EPHX1*** rs67892231	***NQO1*** rs1800566 ***CYP2E1*** rs2031920 ***CYP1A1*** rs1048943 ***MPO*** rs2333227	Lower median S-PMA urinary concentration and a consequently higher t,t-MA/S-PMA (*R* value) in smokers with *GSTT1* null and *GSTM1* null compared to no null genotypes ($P < 0.05$ for both genes) Higher *R* value in non-smokers with *GSTT1* null compared to no null ($P < 0.05$)	7/9

(Continues)

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
							Lower median *R* value (higher S-PMA) in non-smokers with: • *NQO1* rs1800566 wild-type compared to heterozygous and mutant genotypes ($P < 0.05$) • *GSTA1* rs3957356 wild-type compared to heterozygous and mutant genotypes ($P < 0.05$)	
Zhang et al[46]	China	410 benzene-exposed shoe factory workers 102 control participants	236 male 276 female	6.4 mg/m^3	MN and methylation	***DNMT3A*** rs36012910 rs1550117 R882 ***DNMT3B*** rs1569686 rs2424909 rs2424913	Increased MN frequency in subjects with *DNMT3A* rs1550117 variant allele (AG + AA) [FR = 1.19 (95% CI 1.05-1.36), $P = 0.003$] Lower global DNA methylation ($P = 0.094$) and higher MN frequency [FR = 1.18 (95% CI 0.99-1.40), $P = 0.054$] in subjects with *DNMT3A* (R882) variant allele (R882C + R882H) compared to wild-type genotype Decreased global DNA methylation in subjects with *DNMT3B* rs2424909 GG genotype ($P = 0.031$)	7/9
Lin et al[47]	Taiwan	105 exposed workers from Taiwan	33-57 y.o. all males	Groups: High benzene exposure (1 ppm; n = 33) 15 ± 19 ppm Low benzene exposure (<1 ppm; n = 37) 0.20 ± 0.22 ppm	Urinary biomarkers: S-PMA, PH and t,t-MA	***GSTT1*** Null and no null ***GSTM1*** Null and no null ***GSTP1*** rs1695	*GSTT1* null is related to a reduced S-PMA excretion ($P = 0.041$), compared to *GSTT1* no null	5/9
Qu et al[48]	China	130 exposed workers 51 unexposed workers	-	Groups: GSTT1 null: 7.5 ± 9.1 ppm no null: 11.7 ± 20.6 ppm *NQO1* rs1800566 Wild-type variant: 12.1 ± 23.6 ppm Homozygous variant:8.4 ± 11.8 ppm Heterozygous variant:10.3 ± 11.8 ppm	Urinary biomarkers: S-PMA, PH and t,t-MA	***CYP2E1*** rs2031920 rs6413432 ***NQO1*** rs1800566 ***GSTT1*** null and no null ***MPO*** rs 2 333 227 (not analyzed)	*GSTT1* null is related to a reduced S-PMA excretion ($P < 0.0001$), compared *to GSTT1* no null	8/9
Carrieri et al[49]	Italy	28 petrochemical workers from Italy	33.3-50.3 yo All males	34.5 μg/m^3	Urinary biomarkers: S-PMA and t,t-MA	***GSTT1*** null and no null ***GSTM1*** null and no null	*GSTT1* null is related to a reduced S-PMA excretion ($P = 0.0098$) compared to *GSTT1* no null *GSTM1* null did not influence biomarker excretion	6/9

TABLE 1 (Continued)

Authors and year of publication	Country	Sample size	Participants (age range or mean [in years], gender)	Mean benzene exposure	Evaluated variable*	Genes and polymorphisms studied	Results	Quality assessment score
Zhang et al 2014	China	Cases: 385 benzene-exposed workers Controls: 197 non-exposed workers	289 male 293 female	6.4 mg/m^3	MN	***GSTM1*** null and no null ***GSTT1*** null and no null ***GSTP1*** rs1695 ***CYP2E1*** rs3813867 rs2031920 rs6413432 ***mEH exon 3*** rs1051740 ***mEH exon 4*** rs2234922	Higher MN frequency in subjects with: *CYP2E1* rs3813867 mutant allele (CC + GC) [FR = 1.15 (95% CI 1.02-1.29), $P = 0.02$] and rs2031920 variant allele (CT + TT) [FR = 1.23 (95% CI 1.09-1.37), $P < 0.01$] both SNPs compared with the wild type Higher MN frequency (adjusted for age, gender and cumulative exposure dose) in subjects with rs2031920 variant allele (CT + TT) [FR = 1.17 (95% CI 1.04-1.31), $P < 0.01$], compared to the wild type	7/9
Wan et al[50]	China	120 workers	46 male 74 female	—	Risk of developing CBP	***GSTM1*** Null and no null ***GSTT1*** Null and no null ***NQO1*** rs1800566 ***CYP2E1*** rs3813867	Increased risk of CBP in exposed workers with • *GSTT1* null [OR = 4.45 (95% CI 1.13-17.54)] • *NQO1* rs1800566 **plus** *GSTT1* null at the same time [OR = 1.14 (95% CI 0.42-3.05)]	5/9
Carrieri et al[51]	Italy	146 workers employed at an oil refinery 25 non-exposed participants as a control group	All males 20-72 y.o.	32.6 ± 50.6 (μg/m^3) for exposed workers 11.5 ± 3.2 (μg/m^3) for controls	Urinary biomarkers: S-PMA, urinary benzene and t,t-MA	***GSTT1*** Null and no null ***GSTM1*** Null and no null	*GSTT1* no null significantly increases the urinary levels of S-PMA ($P < 0.0094$), compared to *GSTT1* null *GSTM1* null and no null showed no effect on biomarker excretion	8/9

Abbreviations: CA, chromosomal aberrations; CAT, catechol; CBP, chronic benzene poisoning; FR, frequency ratio; HQ, hydroquinone; MN, micronucleus; OR, odds ratio; ORadj, adjusted odds ratio; PH, phenol; RR, risk ratio; S-PMA, S-phenylmercapturic acid; t,t-MA, *trans*,*trans*-muconic acid; WBC, white blood cell; y.o., years old.

*The evaluated variables were changed in risk of developing chronic benzene poisoning, excretion of urinary biomarkers, blood cell count or hematotoxicity; the presence of micronucleus, chromosomal aberrations, and methylation.

TABLE 2 Effect of different polymorphisms on the development of CBP

Group/gene	Genes and polymorphisms	Effect on CBP	Risk	References
NQO	*NQO1*	Possible[a]		38
	rs1800566		No change	39
	rs1800566 (T/T genotype)		Increased	50
	rs1800566 (combined with null GSTT1)		Increased	
MPO	*MPO*	No[b]	No change	38
	rs7208693		No change	39
	rs2333227			
CYP	*CYP1A1*	Conflicting[c]	No change	38
	rs4646421		No change	38
	rs4646422		No change	38
	rs1048943		No change	38
	rs4646903		Increased	32
	rs4646903 (T/T genotype)			
	CYP1A2	No[b]	No change	38
	rs2445618		No change	38
	rs762551		No change	38
	rs2472304		No change	38
	rs2470890			
	CYP2D6	Yes[d]	Increased	32
	rs1065852 (C/C + C/T genotype)		Increased	32
	rs1135840 (C/C genotype)			
	CYP1B1	No[b]	No change	38
	rs1056836			
	CYP2E1	No[b]	No change	39
	rs2031920			
GST	*GSTT1*	Yes[d]	No change	39,50
	non-null		Increased	39,50
	null			
	GSTM1	Conflicting[c]	Increased	39
	null (in combination with *NQO1* rs1800566 variation [T/T], *GSTT1* null)		No change	50
	null and non-null			
	GSTP1	Yes[d]	Increased	38
	rs1695 (AA genotype, non-alcohol drinkers)			
XRCC	*XRCC1*	Yes[d]	Increased	35
	rs25487 (AA genotype)		Increased	35
	rs1799782 (TT genotype)		Increased	34
	rs25489 (Arg/His+His/His genotype combination)		Decreased	34
	rs1799782(Arg/Trp + Trp/Trp genotype combination)			
	XRCC2[**]	-	-	34
	rs3218536			
	XRCC3	No[b]	No change	34
	rs861539			
ERCC	*ERCC1*	Yes[d]	Increased	27
	rs11615		No change	27
	rs3212986			27
	ERCC2	No[b]	No change	27
	rs13181		No change	35
	rs1799793			
	ERCC3	Yes[d]	Increased	
	rs4150441 (GA and GA + AA genotypes)			

TABLE 2 (Continued)

Group/gene	Genes and polymorphisms	Effect on CBP	Risk	References
CDKN2A	*CDKN2A* rs3731245 (GA + AA genotypes in combination with *MDM2* rs3730485 WW)	Yes[d]	Decreased	11
CDKN1A	*CDKN1A* rs1801270 (CA + AA genotype) rs1059234 (CT + TT genotypes)	Yes[d]	Decreased Decreased	28 28
POLR1G[*]	*POLR1G* rs967591 (GA and GA + AA genotypes)	Yes[d]	Decreased	35
PPP1R13L[*]	*PPP1R13L* rs1005165 (T genotype)	Yes[d]	Decreased	35
hMTH	*hMTH* rs4866	Yes[d]	Increased	33
OGG1	*OGG1* rs1052133	Yes[d]	Increased	33
MUTYH	*MUTYH* rs3219489	No[b]	No change	33
TP53	*TP53* rs17878362 rs1042522 rs1625895	No[b] No[b] No[b]	No change No change No change	28 28 28
UGT	*UGT1A6* rs2070959	No[b]	No change	32
	UGT1A7 rs11692021	No[b]	No change	32
SULT1A1	*SULT1A1* rs9282861	No[b]	No change	32
ADH1B	*ADH1B* rs1229984	No[b]	No change	38
EPH	*EPHX1* rs3738047 (GA + AA genotypes) rs2854451 rs2234922 rs1051741	Yes[d]	Increased No change No change No change	38 38 38 38
	EPHX2 rs781141	No[b]	No change	38
UGT1A6	*UGT1A6* rs6786892 rs1105879 rs4124874 rs3755319 rs887829 rs4148323	No[b]	No change No change No change No change No change No change	38 38 38 38 38
GADD45A	*GADD45A* rs581000 rs532446 rs11544978	Yes[d]	Decreased Decreased No change	11 11 11
MDM2	*MDM2* rs3730485 (in combination with CDKN2A rs3731245) rs2279744	Yes[d]	Decreased No change	11 11
APE1	*APE1* rs1130409	No[b]	No change	34
ADPRT	*ADPRT* rs1136410	No[b]	No change	34
XPB	*XPB* rs4150441 (GA and GA + AA genotypes)	Yes[d]	Increase	35

(Continues)

TABLE 2 (Continued)

Group/gene	Genes and polymorphisms	Effect on CBP	Risk	References
XPC	*XPC* rs2279017 rs2228001	No[b]	No change No change	35 35
XPF	*XPF* rs4781560	No[b]	No change	35

[a]Possible: More than half of all the studies that researched that polymorphism has encountered a relationship between it and the development of CBP.
[b]No: None of the studies that researched the polymorphism encountered a relationship between it and CBP.
[c]Conflicting: Half of the studies that researched said polymorphism found a relationship between it and CBP, yet the other half did not.
[d]Yes: All of the studies that researched the polymorphism found a relationship between it and a higher risk of developing CBP.
*This effect was exclusively observed in males.
**The study did not detect any subjects with the desired allele.

3.2.1 | *NQO1* and *MPO*

Three publications evaluated the difference in susceptibility of developing CBP among patients with polymorphisms in the *NQO1* and *MPO* genes; however, none of these studies found any relationship between the latter gene and the outcome.[38,39,50] Conversely, only one article found no association between *NQO1* polymorphisms and the risk of developing CBP,[38] while the other two found to some degree a greater risk of benzene poisoning on individuals with a *NQO1* polymorphism. Chen et al found that the *NQO1* rs1800566 TT homozygous genotype was associated with an increased risk of CBP [OR = 2.82 (95% CI 1.42-5.58)].[39] Wan et al found that the increase in the risk of CBP was only significant when the *NQO1* rs1800566 genotype was present simultaneously as the null *GSTT1* gene [OR = 1.14 (95% CI 0.42-3.05)].[50]

3.2.2 | Cytochrome P450 encoding polymorphisms

There were three articles that studied the different *CYP* gene polymorphisms. Two of them researched *CYP1A1*, one of which found no relation between the polymorphisms and the risk of CBP,[38] while the other found that the exposed workers with polymorphisms in *CYP1A1* rs4646903 are at a greater risk of CBP [ORadj = 1.21 (95% CI 1.03-1.42)].[32] Gu et al also discovered that people with *CYP2D6* polymorphisms are more susceptible to CBP: [ORadj = 2.11 (95% CI 1.22-3.65)] for rs1065852 (CC + CT genotype) and [ORadj = 1.69 (95% CI 1.04-2.74)] for rs1135840 (CC genotype).[32] Nevertheless, none of the articles found any correlation between the possibility of developing CBP and the *CYP1A2*, *CYP1B1*, and *CYP2E1* polymorphisms.[32,38,39]

3.2.3 | *GSTT1* and *GSTM1*

Three studies examined this correlation. Mitri et al found a relationship between the *GSTM1* null genotype and a higher risk of developing CBP [OR = 5.13 (95% CI 1.13-23.15)][36] while Chen et al only found it when said polymorphism was combined with the *NQO1* rs1800566 TT homozygous genotype and the *GSTT1* null [OR = 16.13 (95% CI 3.15-83.33)].[39] Two of the papers found that the *GSTT1* null genotype was related to a higher CBP risk with an [ORadj = 1.91 (95% CI 1.05-3.45)] for Chen et al and an [OR = 4.45 (95% CI 1.13-17.54)] for Wan et al.[39,50]

3.2.4 | XRCC1, XRCC2, and XRCC3

Two papers studied this relationship; however, *XRCC2* could not be evaluated because the selected variant genotype was not detected. Additionally, they did not find any correlation between the *XRCC3* rs861539 variant and variation in CBP risk.[34,35] Regarding *XRCC1*, Zhang et al detected that individuals carrying *XRCC1* rs1799782 and rs25489 alleles had a decreased [ORadj = 0.60 (95% CI 0.37-0.98)] and an increased [ORadj = 1.67 (95% CI 1.02-2.74)] risk of CBP, respectively.[34] According to Xue et al, the workers who had the *XRCC1* rs25487 AA [ORadj = 14.898 (95% CI 6.55-30.21)] and the rs1799782 TT genotypes also had an increased risk of developing CBP; it is important to mention that the increased risk with rs1799782 was exclusive to male [OR = 9.33 (95% CI 1.59-54.67)], alcohol drinkers [OR = 8.0 (95% CI 1.32-48.65), with an exposure lesser than 12 years [OR = 2.61 (95% CI 1.05-6.51)].[35]

3.2.5 | *ERCC1* and *ERCC2*

One of the studies evaluated the effect of *ERCC1* and *ERCC2* and did not find any association between the latter gene and the risk of CBP; nonetheless, it found that individuals carrying the *ERCC1* rs11615 TT genotype had an increased risk of benzene poisoning, compared to those carrying the CC genotype [OR = 3.21 (95% CI 1.36-7.60), $P = 0.006$].[27]

3.2.6 | Other genes

More information about other genes can be found in Table 2.[11,28,32-35,38]

3.3 | Susceptibility to hematotoxicity and changes in blood cell count

Polymorphisms on certain genes could increase susceptibility to hematotoxicity, which could be reflected with an altered blood cell count.[8] We found eight studies that researched this correlation (Table 3).

TABLE 3 Effect of different polymorphisms on the development of hematological changes

Gene/Group	Polymorphisms and/or genotypes	Hematological effect	Effects on blood cell count	References
NQO1	rs1800566	No[a]	—	29
MPO	rs2071409	Yes[b]	Decreased WBC count	1
CYP2E1	rs2031920 CT genotype	Yes[b]	Decreased WBC count	7
	rs3813867	Conflicting[c]	Decreased WBC count	6,7
	rs2031920 and rs6413432	No[a]	-	29
GST	*GSTP1* rs1695	No[a]	-	7
	GSTM1 Null genotype	Conflicting[c]	Decreased WBC count	6,7
	GSTT1 Null genotype	Conflicting[c]	Decreased WBC count	6,7
IL-1A	rs1800587	Yes[b]	Decreased WBC count	9
IL-4	rs22432484	Yes[b]	Decreased WBC count	9
IL-10	rs1800871	Yes[b]	Decreased WBC count	9,41
IL-12A	rs568408	Yes[b]	Decreased WBC count	9
VCAM1	rs1041163	Yes[b]	Decreased WBC count and CFU-GEMM	9
	rs3176867	Yes[b]	Decreased WBC count	1
CSF3	rs1042658	Yes[b]	Augmented CFU-GEMM and WBC count	9
ALOX5	rs7099684	Yes[b]	Decreased WBC count	1
WRN	rs4987236	Yes[b]	Decreased WBC count	40
	rs2725349	Yes[b]		
	rs1800392	Yes[b]		
	rs2725362	Yes[b]		40,41
	rs2230009	Yes[b]		41
TP53	rs1042522	Yes[b]	Decreased WBC count	40,41
	rs12951053	Yes[b]		41
BRCA2	rs1801406	Yes[b]	Decreased WBC count	40
BLM	rs2270132	Yes[b]	Decreased WBC count	41
	rs414634	Yes[b]		
	rs16944894	Yes[b]		
RAD51	rs4924496	Yes[b]	Decreased WBC count	41
WRAP53	rs2287499	Yes[b]	Decreased WBC count	41
ERCC3	rs4150441	Yes[b]	Increased WBC count	26
	rs6731176	Yes[b]		
VEGF	rs3025030	Yes[b]	Increased WBC count	26
	rs833058			

[a]No: None of the studies investigated that the polymorphism encountered a relationship between it and hematological changes.
[b]Yes: All of the studies investigated that the polymorphism encountered a relationship between it and hematological changes.
[c]Conflicting: Half of the studies researched said that polymorphism found a relationship between it and CBP, yet the other half did not.

3.3.1 | *NQO1* and *MPO*

Two papers researched these two genes. One of them demonstrated that the *MPO* rs2071409 polymorphism decreases the white blood cell (WBC) count in exposed subjects, and possibly affects WBC subtypes ($P < 0.001$).[1] *NQO1* rs1800566 polymorphism was studied by Pesatori et al, and they found no association between this SNP and blood cell count.[29]

3.3.2 | CYP2E1

There were three studies that reported about *CYP2E1*. A research carried out by Ye et al found that WBC count was lower for individuals who possessed the CT genotype of the *CYP2E1* rs2031920 polymorphism compared to the CC genotype ($P = 0.02$). The GC genotype of the *CYP2E1* rs3813867 polymorphism was associated with a significantly lower WBC count when compared to the GG genotype

($P = 0.02$).[7] rs3813867 polymorphism was also researched by Nourozi et al; however, they did not find a statistically significant relationship between this *CYP2E1* SNP and altered blood analysis values.[6] Both *CYP2E1* rs2031920 and rs6413432 polymorphisms were evaluated by Pesatori et al, again no significant relationship was found between those SNPs and blood cell count.[29]

3.3.3 | GST enzymes (*GSTT1*, *GSTM1*, and *GSTP1*)

Two of the papers analyzed all three enzymes,[6,7] evaluating the *GSTM1* null genotype, *GSTP1* rs1695 polymorphism, and *GSTT1* null genotype. None of them found a correlation between the *GSTP1* polymorphism and anomalous hematological indices. However, regarding *GSTM1* and *GSTT1*, the results disagreed: one of the studies found that WBC count in *GSTT1* null ($P = 0.045$) and *GSTM1* null ($P = 0.03$) genotypes decreased compared to the *GSTT1/GSTM1* present group,[7] while the other study found that individuals with *GSTM1* null genotype had a significantly higher mean value of leukocytes ($P = 0.026$), and subjects with *GSTT1* null genotype presented a lower platelet count ($P = 0.015$). Nonetheless, this same study observed that subjects with *GSTT1* null genotype had a higher risk for hematological disorders compared to those with positive genotype [OR = 2.1 (95% CI 1.23-3.56)].[6]

3.3.4 | Other genes

More information about other genes can be found in Table 3.[1,9,26,40,41]

3.4 | Effect on urinary biomarker

Eleven studies researched the influence that several polymorphisms have on the production of different urinary excreted metabolites produced in the metabolism of benzene, commonly used as biomarkers of exposure.

3.4.1 | GST enzymes (*GSTT1*, *GSTM1*, and *GSTP1*)

Ten studies analyzed the relationship between the polymorphisms of GST enzymes and the urinary excretion of benzene metabolites. Four of them studied both the enzyme's *GSTM1* null and no null genotypes, and they found no correlation between the genotypes and the biomarkers of benzene exposure.[30,47,49,51] Conversely, four other studies found a significant correlation: both Mansi et al and Manini et al found that an expression of the *GSTM1* null polymorphism was involved in a lower urinary excretion of S-PMA ($P < 0.001$ and $P = 0.010$ respectively); furthermore, Carbonari et al ($P < 0.05$) and Kim et al ($P = 0.018$) discovered similar results.[3-5,45] Eight studies established an inverse relationship between the *GSTT1* null polymorphism and the quantity of the S-PMA marker excreted, both in smokers and non-smokers (*P* values on Table 1).[3-5,45,47-49,51] Also, according to Chanvaivit et al and these eight studies, there was no association between *GSTT1* null and the t,t-MA metabolite.[3-5,31,45,47-49,51] Three studies screened the influence of the *GSTP1* polymorphism on urinary biomarkers; however, none found any interaction between these two factors.[3,4,47]

3.4.2 | CYP2E1

Six papers studied the effect of this polymorphism; four of them did not find any correlation.[30,31,45,48] The other two found conflicting results: Kim et al concluded that the workers with an homozygous variant genotype for the *CYP2E*1 rs2031920 SNP, produced significantly lower levels of t,t-MA ($P < 0.001$), phenol (PH) ($P < 0.001$), and hydroquinone (HQ) ($P < 0.001$) than workers who had the wild-type variant allele.[3] Fustinoni et al found a higher t,t-MA and a lower U-benzene on subjects with at least one variant allele in *CYP2E1* rs6413432 ($P = 0.03$) and rs2031920 ($P < 0.01$), respectively.[2]

3.4.3 | NQO1

Two out of four studies researched the influence of the *NQO1* rs1800566 polymorphism and the biomarkers excretion that did not find any significant relationship between these two variants.[31,48] Instead, one found that patients with at least one variant allele of *NQO1* rs1800566 affected five metabolites: t,t-MA, S-PMA ($P = 0.001$), PH ($P = 0.022$), catechol (CAT) ($P = 0.036$) and HQ ($P = 0.036$), as they found lower levels of them in these participants.[3] The other study found that the *NQO1* rs1800566 wild-type polymorphism decreased the t,t-MA/S-PMA fraction in non-smokers ($P = 0.04$).[45]

3.5 | Micronucleus and CAs

Four studies reported the existing relationship between polymorphisms on certain genes and the expression of cytokinesis-block micronucleus (MN) and/or the frequency of CA in benzene-exposed workers and non-exposed controls.

3.5.1 | *NQO1* and *MPO*

Two papers studied either or both of these enzymes.[42,43] One of them showed that exposed workers with *NQO1* rs1800566 polymorphism (TT genotype) had significant increases in MN [RR = 1.9 (95% CI 1.5-2.3)] and CA [RR = 2.6 (95% CI 1.7-3.9)] frequencies when compared to controls with CC and CT genotypes; moreover, it suggested that the benzene-exposed population with the *MPO* rs2333227 polymorphism (GG wild-type genotype) had a significant rise in CA frequency [RR = 2.3 (95% CI 1.3-4.0)] compared to non-

exposed population with GA or AA genotypes.[42] In contrast, the other paper evidenced that mutated homozygous genotype of *NQO1* rs1800566 polymorphism (TT genotype) was related with lower MN frequencies [FR = 0.79 (95% CI 0.66-0.95)] when compared to the homozygous wild-type genotype (CC genotype).[43]

3.5.2 | DNA repair genes

One study analyzed the relationship between polymorphisms on genes involved in the DNA repairing process and the frequency of MN.[44] Both the base excision (*XRCC1* and *APE1*) and nucleotide excision repair pathway genes (*XPA*, *XPC*, *XPG*, *ERCC1*, and *ERCC2*) were studied. They found that MN frequencies were higher in *XRCC1* rs25487 GA [FR = 1.20 (95% CI 1.06-1.37), $P = 0.006$] and AA [FR = 1.50 (95% CI 1.16-1.90), $P = 0.002$] alleles, *APE1* rs1130409 GT [FR = 1.20 (95% CI 1.04-1.37), $P = 0.012$] and GG [FR = 1.28 (95% CI 1.05-1.55), $P = 0.01$], *XPG* rs17655 GC [FR = 1.18 (95% CI 1.02-1.38), $P = 0.038$] and *ERCC1* rs3212986 TT [FR = 1.55 (95% CI 1.31-1.83), $P < 0.001$] with a directly proportional relationship between the number of present mutant alleles of these polymorphisms and MN frequency.[44] Kim et al also studied *XRCC1* rs25487 polymorphism, finding that, among exposed workers, subjects with AA variant type displayed a significantly higher CA frequency compared to its wild-type controls [RR = 2.2 (95% CI 1.5-3.1)].[42]

3.5.3 | CYP2E1

One case-control study carried out by Zhang et al, showed significantly increased MN frequency for carriers of *CYP2E1* rs3813867 (CC + GC genotypes) [FR = 1.15 (95% CI 1.02-1.29), $P = 0.02$] and rs2031920 (CT + TT genotypes) [FR = 1.23 (95% CI 1.09-1.37), $P < 0.01$]; while the opposite was found with the *CYP2E1* rs6413432 polymorphism.[52] Another paper also studied the relationship between rs3813867 polymorphism and MN expression in benzene-exposed workers without a statistically significant increase in MN frequencies for individuals carrying this SNP.[43]

3.6 | Methylation

Two of the reviewed studies explored the association between genetic polymorphisms and DNA methylation, and whether this methylation was related to benzene exposure. One of them genotyped four commonly studied SNPs on three metabolic enzymes: *CYP1A1* (rs4646903), *EPHX1* (rs1051740 and rs2234922), and *NQO1* (rs1800566); they also analyzed DNA methylation on 11 genes associated with benzene-induced hematotoxicity (*BLM*, *CY1A1*, *EPHX1*, *ERCC3*, *NQO1*, *NUDT1*, *p15*, *p16*, *RAD51*, *TP53*, and *WRAP53*). The authors found that *ERCC3* methylation was higher on exposed individuals. Furthermore, they established that a larger number of C alleles on *EPHX1* rs1051740 polymorphism was related to a reduction of *ERCC3* methylation ($P = 0.001$), concluding that this SNP may be protective against benzene-induced hypermethylation.[37] On the contrary, Zhang et al demonstrated that benzene-exposed workers experienced significant global DNA hypomethylation compared to non-exposed subjects. As factors that influenced this process, *DNMT3A* (R882) variant allele (R882C + R882H) ($P = 0.094$) and *DNMT3B* rs2424909 polymorphism (GG genotype) ($P = 0.031$) showed an association with decreased global DNA methylation.[46]

3.7 | Results adjustment to smoking status

thirty-one out of 36 included studies incorporated in their analysis a multivariate adjustment for the population that smoked, some demonstrating worse outcomes for smokers compared to non-smokers.[1-7,9,11,26-29,33-35,37-46,48-52] For instance, seven papers found that smoking was an important confounder for benzene biomarkers, as smokers excreted higher concentrations of benzene metabolites than non-smokers.[2-5,45,49,51] In five studies, the health outcomes of benzene exposure were only statistically significant when they stratified the population in smokers and non-smokers.[11,27,29,33,34] Moreover, two articles found evidence that smoking affects the prognosis of benzene poisoning and lowers the WBC count in exposed workers.[7,50] On the other hand, six papers did not find a statistically significant association between the smoking habit and the researched health outcome.[28,35,38,43,44,52] Furthermore, in two out of five studies that did not adjust for smoking habits, all of the participants were non-smokers.[31,47]

4 | DISCUSSION

In this review, we aimed to evaluate the existent relationship between genetic polymorphisms and the risk of developing adverse health effects in benzene-exposed workers. Among the assessed studies, we encountered that the most researched outcomes of benzene exposure were the development of CBP, the increase or decrease on the excretion of urinary biomarkers and hematotoxic effects. The genes that showed some consistent associations in the effects of their polymorphisms in the human body were *NQO1*, *GSTT1*, *GSTM1*, *XRCC1*, *MPO*, and *CYP2E1*.

NQO1 is a key enzyme involved in benzene metabolism because it reduces benzoquinones to HQ and CAT, resulting in the detoxification of those metabolites. It has been theorized that polymorphisms that cause a decrease in this enzyme's activity probably increase the risk of bone marrow toxicity and other adverse effects.[53] In this review, regarding the polymorphisms on the *NQO1* encoding gene, we found that they have a significant effect on the risk of developing CBP,[39,50] on MN frequencies[42] and urinary biomarker excretion,[3,45] further validating this hypothesis. Two of the evaluated studies found an increased frequency of CBP in individuals with *NQO1* rs1800566.[39,50] Those results are consistent with a modification in

NQO1's detoxifying properties; thus, making the individual's organism more permissive to long-term toxic effects.

On the other hand, only one study found no relationship between CBP and *NQO1* polymorphisms, but it also stated that the sample of exposed workers with the studied polymorphism was probably not big enough to establish a statistically significant relationship in this variable.[38] According to Pesatori et al, changes in the expression of *NQO1* in combination with a *MPO* polymorphism did not show a correlation with altered WBC count[29]; however, this study did not have enough study subjects to be statistically significant; making it clear that more papers are necessary to reinforce these results.

Regarding biomarkers of exposure, theoretically, if you pare *NQO1* activity, fewer benzoquinones will be reduced, subsequently producing less urinary biomarkers. Two studies found that the patients who had the variant *NQO1* rs1800566 (C → T) polymorphism (which decreases NQO1's activity) showed a lower excretion of biomarkers, which produced a lower t,t-MA/S-PMA fraction.[3,45] Conversely, Chanvaivit et al and Qu et al did not find any significant change.[31,48] This discrepancy is likely caused by the median level of benzene exposure, which was lower in the subjects of the studies that did not find any correlation between *NQO1* polymorphisms and the excretion of urinary biomarkers, compared to the ones that did.

Both Kim et al and Fang et al studied *NQO1* rs1800566 involvement in MN frequency and CA; however, their results were contradictory.[42,43] This disagreement can be explained by the difference in the population size, as it was bigger in Fang et al's study, which established that the *NQO1* CC genotype had a higher MN frequency than the TT genotype.[43] Nonetheless, there are few studies that explore this subject and research with a bigger population sample is needed to understand this phenomenon better.

Considering that GSTs help in the benzene oxide (BO) detoxification process and, by extension, reduce the carcinogenic potential of benzene,[54] the two most studied enzymes of this family within the papers that we reviewed were *GSTT1* and *GSTM1*. All of them considered the null and no null genotypes of these genes as modifying factors of biomarker excretion, CBP, and hematological changes. Regarding urinary biomarker excretion, almost all of the analyzed papers concluded that *GSTT1* null genotype was related to lower excretion of S-PMA,[3-5,45,47-49,51] while the results were very conflicting for *GSTM1* null genotype, with four of the articles finding no correlation between this genotype and S-PMA excretion.[30,47,49,51] However, this is consistent with in vitro studies, which have identified that *GSTT1* is more important in the BO detoxification process than *GSTM1* because the latter is affected by competing non-enzymatic product formation and lower enzymatic activity.[54]

Regarding CBP, the importance of *GSTT1* was once again demonstrated as a toxicity-protector enzyme. Two studies associated the *GSTT1* null genotype to an increased risk of benzene poisoning[39,50]; moreover, it was found that *GSTM1* null genotype has a strong relationship with CBP.[36] The effects of GST enzymes on hematological abnormalities are related to their protective function against benzene, with the reviewed papers showing that *GSTT1* null genotype is correlated with lower WBC and platelet count.[6,7] It has been recently reported that GST appears to defend against benzene-induced DNA damage; therefore, with the loss of *GSTT1* its DNA-defensive characteristic is also gone.[7]

CYP2E1 is a phase I enzyme, which plays a key role on the metabolic pathway of benzene, given that it is responsible for the first step of benzene breakdown, producing BO and then intermediate metabolites, which accumulate in the bone marrow and undergo autoxidation or activation by peroxidases to yield the corresponding quinones, which are believed to be among the ultimate toxic metabolites of benzene.[7] Consequently, some of the articles we reviewed determined a relationship between *CYP2E1* polymorphisms and effects on hematological abnormalities and biomarker excretion. Concerning hematological abnormalities, the rs2031920 and rs3813867 were two *CYP2E1* of the polymorphisms that showed a statistically significant association with an altered WBC count.[7]

As for biomarker excretion, two studies reported a relationship between some of the *CYP2E1* polymorphisms and different biomarkers levels.[2,3] In accordance with the *CYP2E1* function on benzene metabolism, one study showed that the rs2031920 polymorphism was related to lower levels of t,t-MA, PH, and HQ.[3] Another study demonstrated a relationship between rs2031920 and rs6413432 variant allele polymorphisms with lower U-benzene and higher t,t-MA, respectively.[2] Nonetheless, four of the reviewed works did not find a correspondence between *CYP2E1* polymorphisms and biomarker excretion changes.[30,31,45,48] This lack of consistency with the results among papers may be a consequence of the diversity of populations in the studies, as the family of cytochrome P450 (CYP450) enzymes might present several SNPs on different ethnical groups, which determines the toxicity of and response to a number of substrates, benzene included.[55]

Another relevant enzyme is MPO, which converts CAT, HQ and 1,2,4-benzenetriol to highly reactive intermediates: 1,2-benzoquinone, 1,4-benzoquinone, and 1,2,4-benzoquinone.[56] Few studies correlated the MPO encoding gene polymorphisms and human physiological changes, and only one of them found statistically relevant results regarding the rs2071409 polymorphism and hematological changes.[1] Another one suggested that the rs2333227 polymorphism had a significant rise in CA frequency, compared to the non-exposed population with the GA or AA genotype.[42] All of this can be explained by CAT's increased toxic effect in progenitor cells, which is caused by a decreased MPO metabolic activity.[57,58]

Though not directly involved in the benzene metabolic pathway, the polymorphisms in *XRCC1* have shown consistent relationship with worsening adverse effects secondary to benzene exposition. Specifically, the rs25487 polymorphism was found to be associated with higher MN and CA frequencies,[42,44] which are indicators of the extent of chromosomal damage in human populations exposed to genotoxic agents, such as benzene, and some studies have found a link between chromosomal damage and an increased cancer risk.[42] Furthermore, rs25487, rs1799782, and rs25489 polymorphisms were found to have an increased risk of developing CBP.[34,35] *XRCC1* plays an important role in single-strand break repair and base-excision repair, acting as a scaffolding protein for other repair factors, including DNA ligase IIIα,

DNA polymerase β or APE1.[59] If this repairing function was impaired (which happens with the aforementioned polymorphisms), DNA lesions would accumulate; thus, configuring a threat to genetic stability and cell survival, accelerating mutation rates and increasing CA levels.

Concerning the relationship of the smoking habit and benzene health effects, several authors have found that it is an important source of environmental benzene contamination, and it is directly related to some adverse health outcomes.[60,61] In this review, most studies predicted that smoking was a confounding factor and therefore adjusted their analysis to have more reliable results. For instance, some of the reviewed papers found that the smoking habit correlates with worse health outcomes and suggested that future research should take into account this factor while studying occupational exposure.[2-5,7,27-29,33,34,45,49-51] Conversely, a minority of the included articles did not find a statistically significant interaction between those two variables; however, these results may be caused by the scarce quantity of smokers compared to non-smokers both in the group with exposed workers and the controls in most of these studies.[28,35,38,43,44,52]

These statistically relevant outcomes have established the link between genetic polymorphisms and the risk of developing adverse health effects in benzene-exposed workers with a different genetic background. These findings should enable occupational medicine specialists, local governments and policy makers to create and improve new evidence-based guidelines for benzene exposure limits that take into account the genetic diversity of the workforce. Those improved regulations will help workers to avoid health risks, thus lowering public health costs and overall making the population healthier while providing insight for future research.

4.1 | Strengths and limitations

By using the PRISMA guidelines and the Newcastle-Ottawa quality assessment score, this review captures a significant number of studies, anticipating and working around bias; nevertheless, weak selection bias could be induced by limiting the language of the included studies to English and Spanish. In addition, publishing bias should not be ignored, because papers that found a correlation between polymorphisms and different benzene-exposure outcomes are more likely to be published than those with no significant findings. Additionally, some papers used the same study population, which can lead to more bias. Moreover, some polymorphisms did not have the same quantity of evidence as others, which may affect the results.

5 | CONCLUSION

Overall, this review highlights the detrimental effects of occupational exposure to benzene. It also establishes a clear relationship between some polymorphisms and the extent of the consequences that come with the occupational exposure to this toxicant. While there are several studies investigating this topic, there are not enough papers to establish a consensus with statistically relevant results regarding some of the polymorphisms. Future research should focus on gathering broader cohorts with the desired polymorphism, given that the expression of genetic variants was not present in all of the participants, even when the cohort had a higher population. In conclusion, benzene is an important threat to occupational health worldwide; therefore, regulations should be adjusted to protect all the exposed workers, especially those with high-risk genetic variants.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Verónica Ramírez-Lopera had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The corresponding author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Shen M, Zhang L, Lee KM, et al. Polymorphisms in genes involved in innate immunity and susceptibility to benzene-induced hematotoxicity. *Exp Mol Med*. 2011;43(6):374-378.
2. Fustinoni S, Consonni D, Campo L, et al. Monitoring low benzene exposure: comparative evaluation of urinary biomarkers, influence of cigarette smoking, and genetic polymorphisms. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol*. 2005;14(9):2237-2244.
3. Kim S, Lan Q, Waidyanatha S, et al. Genetic polymorphisms and benzene metabolism in humans exposed to a wide range of air concentrations. *Pharmacogenet Genom*. 2007;17(10):789-801.
4. Mansi A, Bruni R, Capone P, et al. Low occupational exposure to benzene in a petrochemical plant: modulating effect of genetic polymorphisms and smoking habit on the urinary t,t-MA/SPMA ratio. *Toxicol Lett*. 2012;213(1):57-62.
5. Manini P, De Palma G, Andreoli R, et al. Occupational exposure to low levels of benzene: biomarkers of exposure and nucleic acid oxidation and their modulation by polymorphic xenobiotic metabolizing enzymes. *Toxicol Lett*. 2010;193(3):229-235.
6. Nourozi MA, Neghab M, Bazzaz JT, Nejat S, Mansoori Y, Shahtaheri SJ. Association between polymorphism of GSTP1, GSTT1, GSTM1 and CYP2E1 genes and susceptibility to benzene-induced hematotoxicity. *Arch Toxicol*. 2018;92(6):1983-1990.
7. Ye LL, Zhang GH, Huang JW, et al. Are polymorphisms in metabolism protective or a risk for reduced white blood cell counts in a Chinese population with low occupational benzene exposures? *Int J Occup Environ Health*. 2015;21(3):232-240.
8. De Palma G, Manno M. Metabolic polymorphisms and biomarkers of effect in the biomonitoring of occupational exposure to low-levels of benzene: state of the art. *Toxicol Lett*. 2014;231(2):194-204.
9. Lan Q, Zhang L, Shen M, et al. Polymorphisms in cytokine and cellular adhesion molecule gene and susceptibility to hematotoxicity among workers exposed to benzene. *Cancer Res*. 2005;65(20):9574-9581.
10. Carbonari D, Chiarella P, Mansi A, Pigini D, Iavicoli S, Tranfo G. Biomarkers of susceptibility following benzene exposure: influence of genetic polymorphisms on benzene metabolism and health effects. *Biomark Med*. 2016;10(2):145-163.
11. Sun P, Zhang Z, Wan J, Zhao N, Jin X, Xia Z. Association of genetic polymorphisms in GADD45A, MDM2, and p14ARF with the risk of chronic benzene poisoning in a Chinese occupational population. *Toxicol Appl Pharmacol*. 2009;240(1):66-72.
12. World Health Organization. Regional office for Europe. *Air Quality Guidelines for Europe*. 2nd ed.; Copenhagen: World Health Organization. Regional Office for Europe; 2000;1-273. https://apps.who.int/iris/handle/10665/107335
13. Wilbur S, Keith S, Faroon O, et al. Toxicological profile for benzene. *Agency Toxic Subst Dis Regist*. 2007;438:266-280.
14. Safety and health legislation – safety and health at work – EU-OSHA [Internet]. [cited April 2021]. https://osha.europa.eu/en/safety-and-health-legislation.
15. Great Britain: Health and Safety Executive. Workplace exposure limits: containing the list of workplace exposure limits for use with the … control of substances hazardous to health regulations. Place of publication not identified: HSE Books; 2020.
16. EUR-Lex – 31998L0024 – EN – EUR-Lex [Internet]. https://eur-lex.europa.eu/legal-content/EN/NIM/?uri=CELEX:31998L0024%20.
17. 1910.1450 – Occupational exposure to hazardous chemicals in laboratories. Occupational Safety and Health Administration [Internet]. [cited April 2021]: https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1450.
18. Lan Q, Zhang L, Li G, et al. Hematotoxicity in workers exposed to low levels of benzene. *Science*. 2004;306(5702):1774-1776.
19. Garte S, Taioli E, Popov T, Bolognesi C, Farmer P, Merlo F. Genetic susceptibility to benzene toxicity in humans. *J Toxicol Environ Health A*. 2008;71(22):1482-1489. http://doi.org/10.1080/15287390802349974.
20. Smith MT. Advances in understanding benzene health effects and susceptibility. *Annu Rev Publ Health*. 2010;31(1):133-148. http://doi.org/10.1146/annurev.publhealth.012809.103646.
21. Ross D. Functions and distribution of NQO1 in human bone marrow: potential clues to benzene toxicity. *Chem Biol Interact*. 2005;153–154:137-146.
22. Buthbumrung N, Mahidol C, Navasumrit P, et al. Oxidative DNA damage and influence of genetic polymorphisms among urban and rural schoolchildren exposed to benzene. *Chem Biol Interact*. 2008;172(3):185-194.
23. Dougherty D, Garte S, Barchowsky A, Zmuda J, Taioli E. NQO1, MPO, CYP2E1, GSTT1 and GSTM1 polymorphisms and biological effects of benzene exposure—a literature review. *Toxicol Lett*. 2008;182(1):7-17.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(1):b2535-b2535. http://doi.org/10.1136/bmj.b2535.
25. Wells G, Shea B, Tetzlaff J. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses [Internet]. *Ottawa Hospital Research Institute*. 2014;1-4. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
26. Hosgood HD, Zhang L, Shen M, et al. Association between genetic variants in VEGF, ERCC3 and occupational benzene haematotoxicity. *Occup Environ Med*. 2009;66(12):848-853.
27. Xiao S, Gao L, Liu Y, et al. Association of genetic polymorphisms in ERCC1 and ERCC2/XPD with risk of chronic benzene poisoning in a Chinese occupational population. *Mutat Res Genet Toxicol Environ Mutagen*. 2013;751(1):52-58.
28. Sun P, Qiu Y, Zhang Z, et al. Association of genetic polymorphisms, mRNA expression of p53 and p21 with chronic benzene poisoning in

a Chinese occupational population. *Cancer Epidemiol Biomarkers Prev*. 2009;18(6):1821-1828.
29. Pesatori AC, Garte S, Popov T, et al. Early effects of low benzene exposure on blood cell counts in Bulgarian petrochemical workers/Effetti ematologici dell'esposizione a basse dosi di benzene in lavoratori petrolchimici bulgari. *Med Lav Work Environ Health*. 2009;100(2):83-90.
30. Torres CH, Varona ME, Lancheros A, Patiño RI, Groot H. DNA damage assessment and biological monitoring of occupational exposure to organic solvents, 2006. *Biomedica*. 2008;28(1): 126-138.
31. Chanvaivit S, Navasumrit P, Hunsonti P, Autrup H, Ruchirawat M. Exposure assessment of benzene in Thai workers, DNA-repair capacity and influence of genetic polymorphisms. *Mutat Res Genet Toxicol Environ Mutagen*. 2007;626(1–2):79-87.
32. Gu SY, Zhang ZB, Wan JX, Jin XP, Xia ZL. Genetic polymorphisms in CYP1A1, CYP2D6, UGT1A6, UGT1A7, and SULT1A1 genes and correlation with benzene exposure in a Chinese occupational population. *J Toxicol Environ Health Part Curr Issues*. 2007;70(11): 916-924.
33. Wu F, Zhang Z, Wan J, et al. Genetic polymorphisms in hMTH1, hOGG1 and hMYH and risk of chronic benzene poisoning in a Chinese occupational population. *Toxicol Appl Pharmacol*. 2008;233(3): 447-453.
34. Zhang Z, Wan J, Jin X, et al. Genetic polymorphisms in XRCC1, APE1, ADPRT, XRCC2, and XRCC3 and risk of chronic benzene poisoning in a Chinese occupational population. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol*. 2005;14 (11 Pt 1):2614-2619.
35. Xue P, Gao L, Xiao S, et al. Genetic polymorphisms in XRCC1, CD3EAP, PPP1R13L, XPB, XPC, and XPF and the risk of chronic Benzene poisoning in a Chinese occupational population. Wei Q-Y, editor. *PLOS One*. 2015;10(12):e0144458.
36. Mitri S, Fonseca ASA, Otero UB, Tabalipa MM, Moreira JC, Sarcinelli P d N. Metabolic polymorphisms and clinical findings related to Benzene poisoning detected in exposed Brazilian Gas-Station workers. *Int J Environ Res Public Health*. 2015;12(7):8434-8447.
37. Xing C, Chen Q, Li G, et al. Microsomal epoxide hydrolase (EPHX1) polymorphisms are associated with aberrant promoter methylation of ERCC3 and hematotoxicity in benzene-exposed workers. *Environ Mol Mutagen*. 2013;54(6):397-405.
38. Sun P, Qian J, Zhang Z-B. Polymorphisms in phase I and phase II metabolism genes and risk of chronic benzene poisoning in a Chinese occupational population. *Carcinogenesis*. 2008;29(12):2325-2329.
39. Chen Y, Li G, Yin S, et al. Genetic polymorphisms involved in toxicant-metabolizing enzymes and the risk of chronic benzene poisoning in Chinese occupationally exposed populations. *Xenobiotica*. 2007;37(1):103-112.
40. Shen M, Lan Q, Zang L, Chanok S, Lin G. Polymorphisms in genes involved in DNA double-strand break repair pathway and susceptibility to benzene-induced hematotoxicity. *Carcinogenesis*. 2006;27(10): 2083-2089.
41. Lan Q, Zhang L, Min S, Jo W, Roel V, Li G. Large-scale evaluation of candidate genes identifies associations between DNA repair and genomic maintenance and development of benzene hematotoxicity — Johns Hopkins University. *Carcinogenesis*. 2009;30(1):50-58.
42. Kim YJ, Choi JY, Paek D, Chung HW. Association of the NQO1, MPO, and XRCC1 polymorphisms and chromosome damage among workers at a petroleum refinery. *J Toxicol Environ Health Part Curr Issues*. 2008;71(5):333-341.
43. Fang Y, Wu H-T, Ye Y-J, et al. Association between polymorphisms of metabolic enzyme genes and chromosomal damage in benzene-exposed workers in China. *J Occup Environ Med*. 2017;59(11):e215-e220.
44. Zhang GH, Ren JC, Luo M, et al. Association of BER and NER pathway polymorphism haplotypes and micronucleus frequencies with global DNA methylation in benzene-exposed workers of China: effects of DNA repair genes polymorphisms on genetic damage. *Mutat Res Genet Toxicol Environ Mutagen*. 2019;839:13-20.
45. Carbonari D, Proietto A, Fioretti M, et al. Influence of genetic polymorphism on t,t-MA/S-PMA ratio in 301 benzene exposed subjects. *Toxicol Lett*. 2014;231(2):205-212.
46. Zhang GH, Lu Y, Ji BQ, et al. Do mutations in DNMT3A/3B affect global DNA hypomethylation among benzene-exposed workers in Southeast China?: effects of mutations in DNMT3A/3B on global DNA hypomethylation. *Environ Mol Mutagen*. 2017;58(9):678-687.
47. Lin LC, Chen WJ, Chiung YM, Shih TS, Liao PC. Association between GST genetic polymorphism and dose-related production of urinary benzene metabolite markers, trans, trans-muconic acid and S-phenylmercapturic acid. *Cancer Epidemiol Biomarkers Prev*. 2008;17 (6):1460-1469.
48. Qu Q, Shore R, Li G, et al. Biomarkers of benzene: urinary metabolites in relation to individual genotype and personal exposure. *Chem Biol Interact*. 2005;153–154:85-95.
49. Carrieri M, Bartolucci GB, Scapellato ML, et al. Influence of glutathione S-transferases polymorphisms on biological monitoring of exposure to low doses of benzene. *Toxicol Lett*. 2012;213(1): 63-68.
50. Wan JX, Zhang ZB, Guan JR, et al. Genetic polymorphism of toxicant-metabolizing enzymes and prognosis of Chinese workers with chronic benzene poisoning. *Ann N Y Acad Sci*. 2006;1076:129-136.
51. Carrieri M, Spatari G, Tranfo G, et al. Biological monitoring of low level exposure to benzene in an oil refinery: effect of modulating factors. *Toxicol Lett*. 2018;298:70-75.
52. Zhang GH, Ye LL, Wang JW, et al. Effect of polymorphic metabolizing genes on micronucleus frequencies among benzene-exposed shoe workers in China. *Int J Hyg Environ Health*. 2013;217(7): 726-732.
53. Nebert DW, Roe AL, Vandale SE, Bingham E, Oakley GG. NAD(P)H: quinone oxidoreductase (NQO1) polymorphism, exposure to benzene, and predisposition to disease: a HuGE review. *Genet Med*. 2002;4(2):62-70.
54. Zarth AT, Murphy SE, Hecht SS. Benzene oxide is a substrate for glutathione S-transferases. *Chem Biol Interact*. 2015;242: 390-395.
55. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther*. 2017;102(4): 688-700.
56. Zhang J, Zhu FY, Pu YP, et al. Analysis of multiple single nucleotide polymorphisms (SNPs) of myeloperoxidase (MPO) to screen for genetic markers associated with acute leukemia in Chinese Han population. *J Toxicol Environ Health Part Curr Issues*. 2007;70(11): 901-907.
57. Wierda D, Irons RD. Hydroquinone and catechol reduce the frequency of progenitor B lymphocytes in mouse spleen and bone marrow. *Immunopharmacology*. 1982;4(1):41-54.
58. Barreto G, Madureira D, Capani F, Aon-Bertolino L, Saraceno E, Alvarez-Giraldez LD. The role of catechols and free radicals in benzene toxicity: an oxidative DNA damage pathway. *Environ Mol Mutagen*. 2009;50(9):771-780.
59. Brem R, Hall J. XRCC1 is required for DNA single-strand break repair in human cells|nucleic acids research | Oxford academic. *Nucleic Acids Res*. 2005;33(8):2512-2520.
60. Fiebelkorn S, Meredith C. Estimation of the leukemia risk in human populations exposed to benzene from tobacco smoke using epidemiological data. *Risk Anal Off Publ Soc Risk Anal*. 2018;38(7):1490-1501.

61. Korte JE, Hertz-Picciotto I, Schulz MR, Ball LM, Duell EJ. The contribution of benzene to smoking-induced leukemia. *Environ Health Perspect*. 2000;108(4):333-339.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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