Supplementary Information

Benzene-associated immunosuppression and chronic inflammation in humans: A systematic review

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Description

In the present systematic review, we utilized the ten key characteristics (KCs) of human carcinogens framework to identify and evaluate the mechanistic evidence for benzene, focusing on KC6: chronic inflammation and KC7: immunosuppression. The ten KCs are outlined in parallel with prior applications of the framework to benzene in **Supplementary Table 1**. We reviewed a total of *eighty-five* studies that reported on inflammatory or immunosuppressive effects in benzene-exposed populations. **Supplementary Table 2** outlines our inclusion and exclusion criteria for study selection. Data extracted from 85 reviewed studies include the author, year published, country, study population and size, exposure assessment methods, level of exposure, and relevant outcomes. Detailed information for each individual study related to chronic inflammation (KC6) and immunosuppression (KC7) can be found in **Supplementary Tables 3 and 4**, respectively. An additional six studies identified from an updated search in July, 2020 are summarized in **Supplementary Table 5**. Additionally, a comprehensive summary of the hematotoxicity outcomes observed is detailed in **Supplementary Table 6**. Following the table, **Benzene-Induced Hematotoxicity Outcomes** is also described. These outcomes are detailed in the supplement rather than the main paper, since the hematotoxicity of benzene exposure has already been well-characterized in many prior studies. Finally, a summary of the major outcomes relating to chronic inflammation, immunosuppression, and hematotoxicity (overlapped with KC6 and KC7) can be found in **Supplementary Figure 1**.

Note: A comprehensive reference list for the supplement can be found at the end. All original studies reviewed (**Tables S3** and **S4**) are documented here due to the limited number of references we can cite in the main paper.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
NK	Natural killer (cells)
RBC	Red blood cell
WBC	White blood cell

Table S1. The key characteristics of human carcinogens: evaluation of benzene. Modified from Smith *et al.*, 2016 (Table 1).[1]

Key Characteristics		Relevant Evidence	Benzene Evaluation		
			Smith *et al.* (2016)[1]	IARC (2018)[2]	Current Evaluation
1	Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts	Yes	Yes	N/A
2	Is genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronuclei)	Yes	Yes	N/A
3	Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)	Yes	Yes	N/A
4	Induces epigenetic alterations	DNA methylation, histone modification, microRNAs	Yes	No	N/A
5	Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)	Yes	Yes	N/A
6	**Induces chronic inflammation**	**Elevated WBCs, myeloperoxidase activity, altered cytokine and/or chemokine production**	**No**	**No**	**Suggestive**
7	**Is immunosuppressive**	**Decreased immunosurveillance, immune system dysfunction**	**Yes**	**Yes**	**Yes**
8	Modulates receptor-mediated effects	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)	Yes	Yes	N/A
9	Causes immortalization	Inhibition of senescence, cell transformation	No	No	N/A
10	Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell-cycle control, angiogenesis	Yes	Yes	N/A

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; IARC, International Agency for Research on Cancer; N/A, not applicable; PPAR, peroxisome proliferator-activated receptor; WBC, white blood cells.

Table S2. Inclusion and exclusion criteria for study selection.

	Types of Studies	Exposure	Outcomes
Inclusion Criteria	• Human studies that involve subjects of any age and any gender • Experimental animal studies (mammals only). • *In vitro* studies involving human cells	• Any level of benzene exposure • For *in vitro* studies: exposure to benzene or 6 major benzene metabolites: benzene oxide, HQ, CAT, BT, MA, SPMA.	• Only studies that report immunosuppressive or chronic inflammatory outcomes or biomarkers will be included.
Exclusion Criteria	• Any reviews • Letters, editorials, commentaries • Non-English language papers where reviewers don't have a means of translation • Any full-text articles that are not retrievable by reviewers	• Any studies that don't have any benzene exposure data or assessment	• Studies that do not record outcome data relevant to chronic inflammation or immunosuppression will be excluded.

Abbreviations: BT, 1,2,4-benzenetriol; CAT, catechol; HQ, hydroquinone; MA, E,E-muconic acid; SPMA, S-phenylmercapturic acid.

Table S3. Detailed summary of human benzene studies with inflammatory outcomes.

Ref #	Reference (Author, Year)	Study Type	Population	Subject # (N)	Location	Exposure Assessment	Exposure Level	Outcome	Results
[3]	Bogadi-Sare, 1997	Cross-sectional	Shoe factory workers	N=76; 49 exposed, 27 unexposed		General air sampling, BZ in blood (before work shift and in the middle of the working week), phenol in urine (before and end of the same working day)	**General air sampling:** 5.9 (1.9-14.8) ppm **BZ in blood:** Exp: 0.005 mg/L Ctrl: 0.000 mg/L **Phenol in pre-shift urine:** Exp: 3.840 mg/gCr creatinine Ctrl: 2.197 mg/gCr **Phenol in post-shift urine:** Exp: 5.240 mg/gCr Ctrl: 2.759 mg/gCr	**Hematological parameters:** CBC, Hb, HCT, MCV, MCH, MCHC, reticulocytes, serum iron, ALP in neutrophils, and GLT_{50}	↑ band neutrophils, ↑ MCV, ↓ Hb, ↓ MCHC[b], ↑ GLT_{50}[a], ↓ WBC[a], ↓ segmented neutrophils[a], ↓ lymphocytes[a]
[4]	Chen, 2019	Cross-sectional	Residents near a petrochemical complex	N=421; 240 exposed, 181 unexposed	China	Blood BZ levels	Mean Exp Level **Non-smokers**: Exp: 41 ng/L Ctrl: 15 ng/L **Smokers**: Exp: 49 ng/L Ctrl: 14 ng/L	**Hematological parameters**: WBCs, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBCs, Hb, HCT, MCV, MCHC, platelets	Correlated w/ t,t-MA: ↓ platelets, ↑ monocytes All exposed: ↓ neutrophil, ↓ RBC, ↓ Hb, ↓ platelet, ↑ monocytes, ↑ basophils
[5]	Doherty, 2017	Cross-sectional	Adult residents of U.S. Gulf Coast (oil spill workers)	N=406	U.S.A.	Blood BTEX concentration	Geometric Mean **Exp:** Tobacco Smoke Exp: 91 ng/L Tobacco Smoke-Unexp: 25 ng/L **Ctrl:** Tobacco Smoke-Exp**:** 188 ng/L Tobacco Smoke-Unexp: 22 ng/L	**Hematological parameters:** RBC, Hb, HCT, MCHC, RDW, platelets, neutrophils, lymphocytes, monocytes, eosinophils	**Tobacco Smoke Unexp**: ↓ Hb, ↓ MCHC; ↑ RDW **Tobacco Smoke Exp**: ↑ RBC, ↑ WBC[b], ↑ MCV, ↑ MCHC, ↑ neutrophils[b], ↑ lymphocytes[b], ↑ monocytes[a]
[6]	Dutta, 2013	Cross-sectional	Premenopausal rural women	N=345; 196 biomass users, 149 petroleum gas users	India	Urinary t,t-MA levels (PM_{10} air measurements were also taken)	**Exp**: 6.4 ± 4.3 mg/L ($p < 0.05$) **Ctrl**: 1.1 ± 0.7 mg/L	**Airway inflammation**: IL-6, IL-8, TNF-α **Sputum cytology** **Oxidative stress:** ROS, SOD	**Cellular count**: ↑ total cell count[b], ↑ neutrophils, ↑ eosinophils, ↑ lymphocytes, ↑ alveolar macrophages **Inflammation**: ↑ TNF-α[b], ↑ IL-6[b], ↑ IL-8[b]
[7]	Elango, 2013	Cross-sectional	Photocopier operators	N=124; 81 exposed, 43 unexposed	India	Air sampling of workplace (5 photocopy centers)	<1.0 ug/m^3	**Pulmonary function** **Hematological parameters** **Oxidative stress + inflammation:** CRP, IL-8**,** LTB4, TBARS, FRAC, 8-isoprostane, CC-16, ICAM-1 and ECP	**Hematological:** ↑ HCT, ↑ MCV, ↑ RDW **Oxidative-Inflammatory Status**: ↑ serum protein, ↑ globulin, ↓ FRAC[a], ↑ TBARS[b], ↑ LTB4[b], ↑ ECP, ↑ IL-8[a]

[8]	Fenga, 2016	Cross-sectional	Gas station workers	N=154; 91 exposed, 63 unexposed	Italy	Urinary t,t-MA levels	**Exp:** 0.89 ± 0.57 ug/ml **Ctrl:** 0.67 ±0.45 ug/ml	NF-kB, STAT3, p38-MAPK, SAPK./JNK signal transduction	↑ NF-kB, phospho-IkB-α proteins[b] ↓ pSTAT3[b]
[9]	Forrest, 2005	Cross-sectional	Shoe factory workers	N=12; 6 highly exposed workers, 6 ctrls	China (Tianjin)	Personal passive monitoring	47.3 ± 24.3 ppm	Global gene expression	↑ *CXCL16,* ↑ *ZNF33,* ↓ *JUN,* ↓ *PF4*
[10]	Haro-Garcia, 2012	Cross-sectional	Paint company workers	N=54; 24 high exposed, 30 low exposed	Mexico	Personal BTX sampling, urinary SPMA levels	**High**: 14.4 (3.2-16.3) mg/m^3 TWA **Low**: 3.2 (1.6-15.4) mg/m^3 TWA **High**: 3.4 ± 1.8 umol/molCr **Low**: 2.4 ± 1.0 umol/molCr	**Cytokine production**: IL-10, TNF-α, IL-12 production	↓TNF-α[a], ↓ aggregate production of all three cytokines[a]
[11]	Hotz, 1998	Cross-sectional	Mechanics	N=307; 199 exposed, 108 unexposed		Questionnaire; general workplace sampling (TWA during whole workshift)	<1.14 ppm	Hematological parameters; IL-1α production	No significant change in IL-1α production and in hematological parameters
[12]	Ibrahim, 2014	Cross-sectional	Ceramic factory workers	N=164; 81 exposed, 83 unexposed	Egypt	Urinary t,t-MA levels	**Exp**: 0.22 ± 0.48 mg/gCr **Ctrl**: 0.043 ± 0.008 mg/gCr	**Hematological parameters**: WBCs, RBCs, Hb, HCT, MCV, MCH, MCHC	↓ WBC, ↓ RBCs, ↓ Hb[b], ↑ MCV[a], ↓ platelets
[13]	Jorgensen, 2018	Cross-sectional	Tank workers	N=13; 8 exposed, 5 unexposed	Norway	Personal BTEX air monitoring (3 consecutive 12-h work shifts), BZ in blood, BZ in urine, urinary t,t-MA levels	Raw values **Air**: Exp: 0.21 ± 0.17 ppm **Blood**: Exp: 19.3 ± 12 nmol/L Ctrl: 0.9 ± 0.2 ± nmol/L **Urine BZ**: Exp: 71.3 ± 110 nmol/L Ctrl: 1.1 ± 0.8 nmol/L **Urine t,t-MA**: Exp: 4.2 ± 4.1 umol/L Ctrl: 2.6 ± 1.5 umol/L	**Gene expression**	↑ IL-6, ↓ IL-19; ↓ CLEC5, ↓ PRG2; ↑ ACSL1, ↑ IFNB1
[14]	Lehmann, 2001	Cohort	3 year old children	N=200	Germany	Indoor VOC exposure measured with bedroom air sampling	N/A	Prevalence of allergic sensitization; cytokine secretion profile of T cells	↑ percentage of IL-4 producing CD3+ T cells
[15]	Li, 2009a	Cross-sectional	Occupationally exposed workers	N=165; 138 exposed, 27 unexposed	China	Workplace air sampling or diagnosis of BZ poisoning	37.8 mg/m^3	TRECs levels	↓ TRECs, ↓ WBCs, ↓ Hb, ↓ platelets, ↓ RBCs

[16]	Liang, 2018	Cross-sectional	Petrochemical plant workers	N=1064; 532 exposed, 532 unexposed	China	General workplace air sampling (TWA)	**Low exposure:** 0.006 ppm **High exposure:** 0.035 ppm **Ctrl:** <0.006 ppm	Serum protein levels of PLG, PBP, ApoB100, hematological parameters	↑ in serum PLG levels (dose-response); no significant changes in serum PBP or ApoB100, ↑ RBC,
[17]	McHale, 2009	Cross-sectional	Shoe factory workers	N=16; 8 exposed, 8 unexposed	China (Tianjin)	Personal passive monitoring	47.3 ± 24.3 ppm	Global gene expression	↑ *CXCL16,* ↑ *ZNF331,* ↓ *JUN,* ↓ *PF4*
[18]	McHale, 2011	Cross-sectional	Clothes manufacturing workers	N=125; 83 exposed, 42 unexposed	China (Tianjin)	Individual air benzene measurements	>10 ppm, 5-10 ppm, <1 ppm, <<1 ppm	Global gene expression	↑ B-cell receptor signaling, Affected genes: SERPINB2, TNFAIP6, IL1A, KCNJ2, PTX3, F3, CD44, CCL20, ACSL1, PTGS2, CLEC5A, IL1RN, PRG2, SLC2A6, GPR132, PLAUR
[19]	Moro, 2015	Cross-sectional	Gas station attendants	N=88; 60 exposed, 28 unexposed	Brazil	Personal passive samplers, blood BTX levels, urinary t,t-MA levels	**Exp:** Air: 144.2 (58.1-2207.5) ug/m^3 Urinary: 334 (190-600) ug/gCr **Unexp:** Air: 42.0 (34.1-52.4) ug/m3 Urinary: 70.0 (50.0-120.0) ug/gCr	Hematological parameters, ALA-D activity, CD80 + CD86 expression, IL-8	↓ ALA-D activity[b], ↓ CD80 + CD86 expression[a], ↑ IL-8[b], ↑ neutrophils
[20]	Pelallo-Martinez, 2014	Cross-sectional	Children living near petrochemical area	N=105; 46 Allende, 38 Mundo Nuevo, 21 Lopez Mateos (all exposed)	Mexico	Urinary t,t-MA levels	Mean (range) **Allende**: 388 (44-1784) ug/gCr **Mundo Nuevo**: 363 (63-5521) ug/gCr **Lopez Mateos**: 369 (62-1414) ug/g Cr	**Genotoxicity**: DNA damage **Hematological effects**: WBC, Hb, HCT, RBC, platelets	**Lopez Mateos**: ↓ Hb[a], ↓ HCT[a], ↓ WBC, ↓ RBC
[21]	Qu, 2002	Cross-sectional	Factory workers (glue, shoe-making, sporting goods)	N=181; 130 exposed, 51 unexposed	China (Tianjin)	Individual passive monitoring	Median (range) = 3.2 (0.06-122) ppm daily	**Blood parameters**: RBC, platelets, WBC, neutrophils, lymphocytes, eosinophils, etc.	Exposure-dependent: ↓ RBC[b], ↓ WBC[b], ↓ neutrophils[b]
[22]	Ray, 2007	Cross-sectional	Petrol pump or automobile service workers	N=85; 25 petrol pump attendants, 25 automobile service station workers, 35 unexposed	India	Urinary t,t-MA levels	**Exp:** 2.72 ± 0.21 mg of t,t-MA/L **Unexp:**0.71 ± 0.11 mg/L	Hematological parameters and lymphocyte subsets	**Hematological parameters:** ↓ RBC, ↓ Hb, ↓ lymphocyte, ↓ platelets, ↑ MCV, ↑ eosinophils, ↑ monocytes, ↑ immature neutrophil, ↑ band cells, ↑ RBC aniso-poikilocytosis, ↑ target cells, ↑ giant platelets **Lymphocyte subsets:** ↓ CD4+, ↓ CD8+, ↓ CD19+ cells, ↑ CD16+56+ NK cells **P-selectin expression on platelet surface:** ↑ P-selectin expression

[23]	Rothman, 1996a	Cross-sectional	Occupational factory workers	N=88; 44 exposed, 44 unexposed	China	Organic vapor passive dosimetry badge (worn for a full workshift, 5 days during 1 or 2 weeks before phelobotomy), BZ urinary metabolites (t,t-MA, phenol, CAT, HQ)	Median 8-hr TWA = 31 ppm **Urinary:** Exp: <31ppm: ttMA: 8.15 ug/mg CAT: 7.0 ug/mg HQ: 12.8 ug/mg Phenol: 38.9 ug/mg >31ppm: ttMA: 46.8 ug/mg CAT: 65.7 ug/mg HQ: 64.3 ug/mg Phenol: 349.7 ug/mg Unexp: ttMA: 0.18 ug/mg CAT: 3.2 ug/mg HQ: 1.6 ug/mg Phenol: 17.3 ug/mg	**Hematological parameters:** WBC, lymphocyte, Hb, RBC, platelet, MCV, HCT	↓ WBC, ↓ lymphocyte count[a], ↓ platelets[a], ↓ RBCs; ↑ MCV
[24]	Rothman, 1996b	Cross-sectional	Occupational factory workers	N=88; 44 exposed, 44 unexposed	China	Organic vapor passive dosimetry badge (worn for a full workshift, 5 days during 1 or 2 weeks before phelobotomy), BZ urinary metabolites (t,t-MA, phenol, CAT, HQ)	Median 8-hr TWA = 31 ppm **Urinary:** Exposed: MA: 33.0 ug/mg Unexposed: MA: 0.3 ug/mg	**Hematological parameters:** WBC, lymphocyte, Hb, RBC, platelet, MCV, HCT **Cytokine Levels:** GM-CSF, IL-6, EPO, TNF-α, IL-3	↓ WBC, lymphocyte count, platelets, RBCs, HCT; ↑ MCV; no significant difference in cytokine values (IL-3, IL-6, EPO, GM-CSF, TNF-α)
[25]	Samadi, 2019	Cross-sectional	Adults exposed to an urban environment	N=219; 74 industrial, 74 high traffic, 71 low traffic	Iran	BTXS air sampling of industrial (28), high traffic (33), and low traffic areas (32) twice a day; Total: 18 stations, 93 air samples	**Industrial:** 15.92 ± 8.15 ug/m^3 **High traffic**: 7.33 ± 5.97 ug/m^3 **Low traffic:** 2.08 ± 1.15 ug/m^3	**Hematologic parameters**: WBC: neutrophils, eosinophils, monocytes, basophils, lymphocytes; RBC, Hb, HCT, MCV, MCHC, MCH **Pro-inflammatory biomarkers**: TNF-α, IFN-γ	**Btwn industrial and low traffic area groups**: ↓ RBCs[b], ↓ Hb, ↓ HCT[a], ↑ WBC, ↑ neutrophils[a], ↓ eosinophils, ↑ TNF-α[a], ↑ IFN-γ[a] **Btwn high and low traffic**: ↓ RBCs, ↑ TNF-α[a], ↑ IFN-γ[a] **Btwn industrial and high traffic:** ↑ MCHC[a], ↑ neutrophils, ↓ eosinophils
[26]	Schnatter, 2010	Cross-sectional	Factory workers (rubber, shoe, insulation materials)	N=928; 855 exposed, 73 unexposed	China	Individual monitoring of a random sample of workers	Median (range) = 7.4 (0.07-872) mg/m^3	**Hematological parameters**: WBCs, neutrophils, basophils, eosinophils, monocytes, lymphocytes, RBCs, Hb, MCV, RDW, platelets, MPV **SNPs**: NQO1, MPO, CYP2E1, GSTT1	↓ WBCs[a], ↓ lymphocytes, ↓ monocytes, ↓ neutrophils, ↓ RBCs[b], ↓ Hb[b], ↓ MCV[b], ↓ platelets[a], ↓ MPV[c]

[27]	Townsend, 1978	Cross-sectional	Employees	N=282; all exposed	N/A	TWA estimates of BZ based on environmental measurements	**Range**: <2 ppm TWA - 30 ppm TWA for periods of <1 yr - 20 yrs+	**Blood chemistries**: bilirubin, Cr, total protein, albumin, globulin, BUN, LDH, SGOT **Blood parameters**: HCT, Hb, WBC, RBC, MCV, MCH, MCHC	↓ RBC, ↓ bilirubin
[28]	Uzma, 2008	Cross-sectional	Petrol filling workers	N=78; 42 exposed, 36 unexposed	India	Proxy (occupation)		Respiratory, hematological, and thyroid functions	**Hematological** ↑ RBCs and ↑ Hb (10-15, >15 yrs of exposure), ↓ WBC (except eosinophils and platelets - ↑ observed in eosinophil count according to yrs of exposure) **Thyroid:** ↑ T4, ↑ T4F level, ↓ TSH, ↓ T3 **Respiratory:** ↓ VC, ↓ FVC, ↓ IC, ↓ FIVC (<10 years of exposure)
[29]	Ward, 1996	Retrospective cohort (nested case-control design)	Rubber hydrochloride manufacturing workers	N=657 (all exposed)		Proxy (occupation)	Max daily BZ exposure = 34 ppm	**Blood cell count**: WBC, RBC	↓ WBCs (strong exposure-response); ↓ RBCs (weak exposure-response)
[30]	Yang, 2014	Cross-sectional	Paint sprayers	N=8; 4 exposed, 4 unexposed	China	General air sampling	**BZ-exposed**: 6.68 ± 2.28 mg/m^3 **Ctrl**: 0.06 ± 0.01 mg/m^3	Genome-wide DNA methylation; mRNA expression	Hypermethylated genes with concurrent mRNA down-regulation: PRKG1, PARD3, EPHA8 Hypomethylated genes with concurrent mRNA down-regulation: STAT3, IFNGR1
[31]	Zhang, 2018	Cross-sectional	Chronic BZ poisoning patients	N=165; 90 normal, 53 mild, 8 moderate, 14 severe poisoning	China	Proxy (BZ poisoned patients)		Serum proteins that can serve as biomarkers of chronic BZ poisoning	10 total differentially expressed proteins: ↑ C3, ApoA-1 and AACT compared to normal; ↑ kininogen-1, ↑ transthyretin, ↑ vitronectin, ↑ clusterin, ↑ a1-AT; ↓ serum amyloid P-component, ↓ haptoglobin

Assume all mean differences are significant at $p < 0.05$ unless marked below:

[a]The mean difference is significant at 0.01 (equal or less)

[b]The mean difference is significant at 0.001 (equal or less)

Abbreviations: a1-AT, alpha-1-antitrypsin; AACT, alpha-1-antichymotrypsin; ALP, alkaline phosphatase; apo, apolipoprotein; BTEX, benzene, toluene, ethylbenzene, xylene; btwn, between; BTX, benzene, toluene, xylene; BUN, blood urea nitrogen; BZ, benzene; C3, complement 3; CAT, catechol; CBC, complete blood count; CC-16, clara cell protein; Cr, creatinine; CRP, C-reactive protein; Ctrl, control; ECP, eosinophil cationic protein; EPO, erythropoietin; Exp, exposed; FIVC, forced inspiratory vital capacity; FRAC, total ferric reducing antioxidant capacity; FVC, forced vital capacity; g, gram; gCr, gram creatinine; GLT_{50}, measure of red cell fragility; GM-CSF, granulocyte-macrophage colony-stimulating factor; GS, gas station workers; Hb, hemoglobin; HCT, hematocrit; HQ, hydroquinone; IC, inspiratory capacity; ICAM-1, intercellular adhesion molecule 1; L, liter; LDH, lactate dehydrogenase; LS, leather shoe factory workers; LTB4, leukotriene B4; max, maximum; mg, milligram; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin

concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; molCr, mole creatinine; ng, nanogram; OR, odds ratio; PAIg, platelet-associated antibody; PBP, platelet basic protein; PDW, platelet distribution width; P-LCR, large platelet cell ratio; PLG, plasminogen; PM, particulate matter; ppm, parts per million; RBC, red blood cell; RDW, red blood cell distribution width; Ref, reference; ROS, reactive oxygen species; SGOT, serum glutamic-oxaloacetic transaminase; SNP, single nucleotide polymorphism; SOD, superoxide dismutase; SPMA, S-phenyl-mercapturic acid; T3, triiodothyronine; T4, thyroxine; T4F, free thyroxine; TBARS, thiobarbituric acid reactive substances; t,t-MA, trans,trans-muconic acid; TREC, T-cell receptor excision DNA circles; TSH, thyroid stimulating hormone; TWA, time-weighted average; ug, microgram; umol, micromole; unexp, unexposed; U.S.A., United States of America; VC, vital capacity; VOC, volatile organic compound; WBC, white blood cell; yrs, years.

Table S4. Detailed summary of human benzene studies with immunosuppressive outcomes.

Ref #	Reference (Author, Year)	Study Type	Population	Subject # (N)	Location	Exposure Assessment	Exposure Level	Outcome	Results
[32]	Baiz, 2011	Prospective cohort	Pregnant persons exposed to air pollution	N=56	France	Personal exposure assessment of mothers w/ diffusive air sampler	3.3 ± 2.0 ug/m^3	**Development of newborn immune cells** (cord blood lymphocyte count): CD19+ B cells, CD16+56+ NK cells, CD3+ T cells, CD4+ T cells, CD8+ T cells, CD4+CD25+ T cells	↓ CD4+CD25+ T cells
[33]	Barman, 2016	Cross-sectional	Petrol pump workers	N= 100; 50 exposed, 50 unexposed	India	Proxy (occupation)	Cumulative exposure per worker: Median (Range) = 17.92 (1.71-74.2) mg/m^3	**Pulmonary function:** FVC, FEV1, FEV1/FVC, FEF 25-75%. PEFR, AEC **Eosinophil count**	↓ FVC, ↓ FEV1, ↓ FEF25-75%, ↓ PEFR, ↓ eosinophil count
[34]	Bassig, 2016	Cross-sectional	Shoe factory workers	N=390; 250 exposed workers, 140 unexposed workers	China (Tianjin)	Personal passive monitoring	Median (10th, 90th percentiles) = 1.2 ppm (0.3, 12.4)	Hematotoxicity, monosomy 7, B-cell activation	**Hematotoxicity**: All findings were exposure-dependent; ↓ WBCs[b], ↓ granulocytes[b], ↓ platelets[b], ↓ lymphocytes[a], ↓ CD4 T cells, ↓ CD4/CD8 ratio, ↓ B cells[b], ↓ NK cells[a] **B-cell activation**: ≥10 ppm: ↓sCD27 **Monosomy 7**: <10 ppm: ↓monosomy 7, ≥10 ppm: ↑monosomy 7[a]
[35]	Biro, 2002	Cross-sectional	Occupational workers	N=72; 10 styrene exposed, 10 PAH exposed, 9 BZ exposed, 14 mixed exposure, 29 unexposed	Hungary	Proxy (occupational)	N/A	**Lymphocyte populations:** CD3, CD4, CD8 CD14, CD19, CD25, CD38, CD45, CD45RO, CD54, CD56, CD62L, CD71, HLA-DR **Genotoxicological parameters**: CA, SCE, unscheduled DNA synthesis	**Lymphocytes:** **Mixed exposure**: ↓ leukocytes, ↓ neutrophils, ↓ CD3 T-cells, ↑ CD19+ B cells, ↓CD25+/CD3+, ↓ CD25+/CD4+, ↑ CD71+/CD3+, ↑ HLA-DR+/CD3+, ↑ CD45RO+/CD3+, ↑ CD45RO+/CD4+ **BZ-exp**: ↑ HLA-DR+/CD3+, ↑ CD71+/CD19+, ↓ CD62L+/CD3+

[3]	Bogadi-Sare, 1997	Cross-sectional	Shoe factory workers	N=76; 49 exposed, 27 unexposed		General air sampling, BZ in blood (before workshift and in the middle of the working week), phenol in urine (before and end of the same working day)	**General air sampling:** 5.9 (1.9-14.8) ppm **BZ in blood:** Exp: 0.005 mg/L Ctrl: 0.000 mg/L **Phenol in pre-shift urine:** Exp: 3.840 mg/gCr Ctrl: 2.197 mg/gCr **Phenol in post-shift urine:** Exp: 5.240 mg/gCr Ctrl: 2.759 mg/gCr	**Hematological parameters:** CBC, Hb, HCT, MCV, MCH, MCHC, reticulocytes, serum iron, ALP in neutrophils, and GLT_{50}	↑ band neutrophils, ↑ MCV, ↓ hemoglobin, ↓ MCHC[b], ↑RBC glycerol lysis time, ↑ GLT_{50}[a] ↓ WBC[a], ↓ segmented neutrophils[a], ↓ lymphocytes[a]
[36]	Bogadi-Sare, 2000	Cross-sectional	Shoe factory workers	N=75; 49 exposed, 26 unexposed	Croatia?	Workplace area monitoring (stationary sampling at 10 stations); blood BZ levels, urinary phonel levels	**Air**: Median (range) = 5.9 (1.9-14.8) ppm **Blood**: 0.005 (0.002-0.030) mg/l **Urine**: 5.240 (2.150-27.310) mg/gCr phenol post-shift	**Immunological parameters**: IgA, IgM, IgG, B- and T-lymphocytes	↑ IgG, ↓ B-lymphocytes[a]
[37]	Boscolo, 2000	Cross-sectional	Non-symptomatic atopic women exposed to an urban environment	N=60; 30 non-symptomatic atopic women, 30 non-atopic women	Italy	Urinary t,t-MA levels	Median (25th-75th percentiles) **Atopic**: 44.0 (18.5-111.8) ug/l **Control**: 60.0 (17.7-100.7) ug/l	**Lymphocyte subpopulations**: helper CD4-CD45RO T cells, CD3-CD8 lymphocytes, CD16-CD56 NK cells, CD19 B lymphocytes, CD3-HLA-DR (activated T, B, and NK lymphocytes), CD3-CD25 (T and B lymphocytes activated by IL-2) **Cytokines**: IL-4, IFN-γ **Trace elements**: blood Pb, serum Zn and Cu, urinary Cr and Ni	t,t-MA positively correlated with CD16+CD56+ NK cells

[38]	Casale, 2016	Cross-sectional	Outdoor police workers exposed to urban traffic areas	N=215; 112 traffic policemen, 69 drivers, 9 motorcyclists, 25 workers with other outdoor tasks (all exposed)	Italy	Blood BZ levels; individual air sampling (8 traffic policemen, 4 police drivers)	**Air**: Traffic police: 337.1 ± 287.09 ug/m^3 Drivers: 304 ± 365.2 ug/m^3 Motorcyclists: 206.33 ± 89.82 ug/m^3 Other: 185.04 ± 45.94 ug/m^3 **Blood**: Traffic: 17.28 ± 10.42 ng/l Drivers: 10.81 ± 7.85 ng/l	Blood cell counts	↓ WBCs, ↓ neutrophils, ↓ lymphocytes
[4]	Chen, 2019	Cross-sectional	Residents near a petrochemical complex	N=421; 240 exposed, 181 unexposed	China	Blood BZ levels	Mean **Non-smokers**: Exp: 41 ng/L Ctrl: 15 ng/L **Smokers**: Exp: 49 ng/L Ctrl: 14 ng/L	**Hematological parameters**: WBCs, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBCs, Hb, HCT, MCV, MCHC, platelets	Correlated w/ t,t-MA: ↓ MCHC, ↓ platelets, ↑ monocytes All exposed: ↓ neutrophil, ↓ RBC, ↓Hb, ↓ HCT, ↓ MCHC, ↓ platelet, ↑ monocytes, ↑ basophils
[39]	Cody, 1993	Retrospective cohort	Rubber hydrochloride workers	N=161; all exposed	U.S.A.	Proxy (occupation)		**Blood cell counts**: WBC, RBC	↓ WBC during first 4 months (p = 0.04), ↑ WBC during months 6-11 (p = 0.05)
[40]	D' Andrea, 2013a	Retrospective cohort	People exposed to flaring incident at the British Petroleum (BP) refinery	N=200; 100 exposed, 100 unexposed	U.S.A.	Subjects were chosen from residential areas in and surrounding Texas City, USA Urinary phenol levels	Mean = 22.7 mg/L	**Hematological function:** WBC count, platelet count, Hb, HCT, blood urea nitrogen (BUN), creatinine **Hepatic function:** ALP, AST, ALT **Renal function**: Creatinine	↑ WBC[b], ↑ platelet[a], ↑ ALP[b], ↑ AST[a]; ↓ BUN[b], ↓ creatinine
[41]	D' Andrea, 2013b	Retrospective cohort	Subjects exposed to oil spill and disperant	N=247; 117 exposed, 130 unexposed	U.S.A.	Participants in oil spill clean-up activities along the coast of Louisiana for a duration of over 3 months; urinary phenol levels	**20-29 years**: 8.7 ± 9.5 mg/L **30-39 years**: 7.6 ± 9.9 mg/L **40+ years**: 5.3 ± 5.9 mg/L	**Hematological function:** WBC, platelet, Hb, HCT, BUN, creatinine **Hepatic function:** ALP, AST, ALT **Renal function**: Creatinine **Somatic symptom complaints**	↓ platelet, ↓ BUN, ↑ Hb[b], ↑ HCT[b], ↑ALP[b], ↑ AST[a], ↑ HCT[b]

[42]	D' Andrea, 2014a	Retrospective cohort	Children (<17 years old) exposed to flaring incident at the British Petroleum (BP) refinery	N=312; 157 exposed,155 unexposed	U.S.A.	Subjects were chosen from residential areas in and surrounding Texas City, USA Urinary phenol levels	Exposed to BZ for a prolonged period up to 40 days from BP refinery flaring disaster that occurred on April 6, 2010 and lasted through May 16, 2010 Mean = 8.0 (1.0-64.2) mg/L	**Hematological function:** WBC count, platelet count, Hb, HCT, BUN, creatinine **Hepatic function:** ALP, AST, ALT **Renal function**: Serum creatinine **Somatic symptoms**	↓ WBC, ↑ platelet[a], ↑ ALP, ↑ AST, ↑ ALT[a], ↑ creatinine[b]
[43]	D' Andrea, 2014b	Retrospective cohort	Nonsmoking subjects exposed to flaring incident at British Petroleum (BP) refinery	N=1422; 1093 exposed and 329 unexposed	U.S.A.	Subjects were chosen from residential areas in and surrounding Texas City, USA	Exposed to BZ for a prolonged period up to 40 days from BP refinery flaring disaster that occurred on April 6, 2010 and lasted through May 16, 2010	**Hematological function:** WBC count, platelet count, Hb, HCT, blood urea nitrogen (BUN), creatinine **Hepatic function:** Alkaline phosphatase (ALP), aspartate amino transferase (AST), alanine aminotransferase (ALT) **Renal function**: Serum creatinine	↑ WBC[b], ↑ platelet[b], ↑ Hb[b], ↑ HCT[b], ↑ creatinine[b], ↑ BUN[b], ↑ ALP[b], ↑ AST[b], ↑ ALT[b]
[44]	D' Andrea, 2016	Retrospective cohort	Adults (18+) exposed to flaring incident at British Petroleum (BP) refinery	N=2123; 1826 exposed, 387 unexposed	U.S.A.	Self-reported exposure; subjects chosen from residential areas in and surrounding Texas City, USA	Exposed to BZ for a prolonged period up to 40 days from BP refinery flaring disaster that occurred on April 6, 2010 and lasted through May 16, 2010	**Hematological function:** WBC count, platelet count, Hb, HCT, BUN, creatinine **Hepatic function:** ALP, AST, ALT **Renal function**: Serum creatinine	↑ WBC[b], ↑ platelet[b], ↑ creatinine[b], ↑ ALP[b], ↑ AST[b], ↑ AST[b]
[45]	D' Andrea, 2017	Retrospective cohort	Smoking subjects exposed to flaring incident at British Petroleum (BP) refinery	N=791; 733 exposed, 58 unexposed	U.S.A.	Subjects were chosen from residential areas in and surrounding Texas City, USA	Exposed to BZ for a prolonged period up to 40 days from BP refinery flaring disaster that occurred on April 6, 2010 and lasted through May 16, 2010	**Hematological function:** WBC count, platelet count, Hb, HCT, BUN, creatinine **Hepatic function:** ALP, AST, ALT **Renal function**: Serum creatinine	↑ WBC[a], ↑ platelets[b], ↑ ALP[a], ↑ AST, ↑ ALT

[5]	Doherty, 2017	Cross-sectional	Adult residents of U.S. Gulf Coast (oil spill workers)	N=406	U.S.A.	Blood BTEX concentration	Geometric Mean **Exp:** Tobacco Smoke-exp: 91 ng/L Tobacco Smoke-unexp: 25 ng/L **Ctrls:** Tobacco Smoke-exp**:** 188 ng/L Tobacco Smoke-unexp: 22 ng/L	**Hematological parameters:** RBC, Hb, hematocrit, mean corpuscular hemoglobin concentration, RBC distribution width, Platelets, neutrophils, lymphocytes, monocytes, eosinophils	**Tobacco smoke unexposed**: ↓ Hb, ↓ MCHC; ↑ RDW **Tobacco smoke exposed**: ↑ RBC, ↑ WBC[b], ↑ Hb, ↑ HCT[b], ↑ MCV, ↑ MCHC, ↑ neutrophils[b], ↑ lymphocytes[b], ↑ monocytes[a]
[6]	Dutta, 2013	Cross-sectional	Premenopausal rural women	N=345; 196 biomass users, 149 petroleum gas users	India	Urinary t,t-MA levels (PM_{10} air measurements were also taken)	**Exp**: 6.4 ± 4.3 mg/l (p<0.05) **Ctrl**: 1.1 ± 0.7 mg/l	**Airway inflammation**: IL-6, IL-8, TNF-α **Sputum cytology** **Oxidative stress:** ROS, SOD	**Cellular count**: ↑ total cell count[b], ↑ neutrophils, ↑ eosinophils, ↑ lymphocytes, ↑ alveolar macrophages **Sputum cytology**: ↑ metaplasia[b] + ↑ dysplasia[b], ciliocytophthoria, Charcot-Leyden crystals, Curschmann's spiral **Inflammation**: ↑ TNF-α[b], ↑ IL-6[b], ↑ IL-8[b] **Oxidative stress**: ↑ ROS[b], ↓ SOD[b]
[46]	Erdei, 2003	Cross-sectional	Schoolchildren 9-11 years old	N=2788	Hungary	Passive monitoring of 33 children's homes (bedroom)		Immune biomarkers; hematological parameters	BZ displayed positive, but nonsignificant associations with # of lymphocytes and eosinophil granulocytes
[9]	Forrest, 2005	Cross-sectional	Shoe factory workers	N=12; 6 highly exposed workers, 6 ctrls	China (Tianjin)	Personal passive monitoring	47.3 ± 24.3 ppm	Global gene expression	↑ *CXCL16,* ↑ *ZNF33,* ↓ *JUN,* ↓ *PF4*
[47]	Froom, 1994	Case report	Pipe fitter	N=1	Israel	Unclear - personal detection Area monitoring (every 3 months for an year)	**Personal detection:** 0.9 ppm BZ TWA, 0.1 ppm phenol **Area monitoring:** 03-1.2 ppm	WBC counts, production of erythropoietin-independent BFU-E colonies	**During exposure:** Leukocytosis, ↑ WBCs, erythropoietin-independent BFU-E colonies **Exposure terminated:** ↓ BFU-E, WBC, and leukocyte alkaline phosphatase scores to normal over 12 months
[48]	Hancock, 1984	Cross-sectional	Coke oven workers	N= 91; 70 exposed, 21 unexposed		Available personal monitoring, general air sampling, estimates by plant environmental health engineers	Low-level BZ exposure: Acid plant : 0.1 ppm Litol Plant: 1.8 ppm Plant A: 1.9 ppm Plant B:1.9 ppm BZ Plant: 31.5 ppm	**Hematological parameters:** RBC, WBC, Hb	No significant difference in blood parameters

[49]	Harati, 2017	Cross-sectional	Painters	N=80; 40 exposed, 40 unexposed	Iran	Sampling of breathing zone	Range = 0.54-0.83 ppm daily TWA = 0.69 ± 0.14 ppm daily	**Hematological parameters**: RBC, WBC, HCT, Hb, platelet, white cell differential count	↓ eosinophils[b], ↑ MCHC[a]
[50]	Haufroid, 1997	Cross-sectional	Garage workers	N=309		Questionnaire, general workplace air sampling (during the whole workshift), urine HQ, CA, SPMA level (collected after shift)	**Air:** < 0.001 ppm **Urinary (mg/g):** Never smokers: MA:0.08 HQ:1.06 CA: 2.92 SPMA: 0.64 Phenol: 2.58 Ex-smokers: MA:0.08 HQ: 1.39 CA:4.6 SPMA:2.09 Phenol: 3.24 1-10 Cigarettes: MA: 0.13 HQ: 1.50 CA: 3.42 SPMA: 2.09 Phenol: 2.38 11-20 Cigarettes: MA: 0.17 HQ: 2.40 CA: 6.52 SPMA: 2.85 Phenol: 3.04 >20 Cigarettes: MA: 0.18 HQ: 2.49 CA: 6.31 SPMA: 2.55 Phenol: 3.19 Pipe, cigars, cigarillos: MA: 0.20 HQ: 2.22 CA: 5.92 SPMA: 2.62 Phenol: 4.95	**Hematological parameters**: leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, large unstained cells, erythrocytes, hematocrit, Hb, MCV, thrombocytes, IL-1a	↑ leukocytes[b], ↑ neutrophils[b], ↑ lymphocytes[b], ↑ monocytes[b], ↑ basophils[b], ↓ RBC[b], ↑ HCT[b], ↑ MCV

[11]	Hotz, 1998	Cross-sectional	Mechanics	N=307; 199 exposed, 108 unexposed		Questionnaire; general workplace sampling (TWA during whole workshift)	<1.14 ppm	Hematological parameters; IL-1α production	No significant change in IL-1α production and in hematological parameters
[51]	Hristeva-Mirtcheva, 1998	Cross-sectional	Petrol processing workers	N=208; 171 exposed, 37 unexposed	Bulgaria	Unclear	**Group 1**: exposed to 6-7 times above maximum allowable concentration (MAC) values **Group 2**: 2-3X above MAC **Group 3**: near MAC values	Hematological parameters	WBC count abnormalities (leukocytosis, slight leukopenia, neutropenia, lymphocytosis) - statistically significant
[52]	Huang, 2012	Cross-sectional	Chronically exposed patients	N=18; 9 patients, 9 unexposed (for validation, samples from 30 other cases and 30 controls were included)	China	Short-term exposure air concentrations at workplace, BZ concentrations in used solvent materials	**Mean BZ exposure concentration:** 357.996 mg/m^3; **Mean BZ concentration in solvent:** 55.43%	Proteomics, hematological parameters	↑ PLG, ↓ PBP, ↓ Apo B100 **Hematological parameters:** ↓ WBC, ↓ neutrophils, ↓ platelet, ↓ RBC, and ↓Hb
[53]	Huang, 2014	Cross-sectional	Petrochemical factory workers	N=231; 121 exposed, 110 unexposed	China	Workplace monitoring (7 sampling points in the workshop of the refinery between Jan 2008 - June 2012)	Cumulative exposure per worker: Median (Range) = 17.92 (1.71-74.2) mg/m^3	**Hematological**: WBC count, Hb, platelets, PDW, MPV, P-LCR **PAIgs**	↑ PDW, ↑ MPV, ↑ P-LCR[a], ↑ P AIgG, ↑PAIgA, ↑ PAIgM
[12]	Ibrahim, 2014	Cross-sectional	Ceramic factory workers	N=164; 81 exposed, 83 unexposed	Egypt	Urinary t,t-MA levels	**Exposed**: 0.22 ± 0.48 mg/gCr **Control**: 0.043 ± 0.008 mg/gCr	**Hematological parameters**: WBCs, RBCs, Hb, HCT, MCV, MCH, MCHC	↓WBC, ↓ RBCs, ↓ Hb[b], ↓ HCT[a], ↑ MCV[a], ↓ MCHC[a], ↓ platelets
[54]	Kamal, 2012	Cross-sectional	Automobile workers (mechanics and spray painters)	N=78; 24 mechanics, 25 painters, 29 unexposed	Pakistan	Workplace air sampling	Unreported	**Hematological parameters**: RBCs, WBCs, platelets, Hb, PCV, MCV	**Painters:** ↓ RBCs, ↓ WBCs, ↓ Hb, ↓ MCV[a], ↓ PCV **Mechanics**: ↓ RBCs, ↓ Hb **All exposed**: ↓ RBCs, ↓ Hb[a], ↓ MCV, ↓ PCV
[55]	Kasemy, 2019	Cross-sectional	Taxi drivers	N=400; 280 exposed, 120 unexposed	Egypt	Ambient air measurements inside 120 taxis	Mean = 0.89 ± 0.42 ppm	Complete blood count	↓ TLC[b], ↓ platelet[b], ↓ MCH[a], ↑ MCHC[b]

[56]	Kipen, 1988	Retrospective cohort	Rubber hydrochloride workers	N=459; all exposed	U.S.A	BZ concentrations estimated by period and area (see Table 1)		**Hematological parameters**: complete blood count, RBC, WBC, Hb, lymphocytes, monocytes, eosinophils, basophils	**Early effects (1940-1948)**: ↓ WBC, ↓ large lymphocytes[a] No persistent trend over the ensuing 25 years
[57]	Kirkeleit, 2006	Cross-sectional	Cargo tank workers	N=22; 13 exposed; 9 unexposed	Norway	Individual air sampling; urinary BZ levels; blood BZ levels	**Air**: 0.15 (0.01-0.62) ppm **Urine** (post-shift): mean = 27.0 nmol/l **Blood** (post-shift): mean = 12.3 nmol/l	**Lymphocytes**: total lymphocytes, CD3, CD4, CD8, CD19, CD56, CD4/CD8 ratio **Complement**: C3, C4 **Ig**: IgG, IgA, IgM, IgE	↓ IgM, ↓ IgA[a], ↓ CD4 T cells
[58]	Koh, 2015	Cross-sectional	Korean workers	N=10702	Korea	TWA personal air benzene measurements	0.192 ± 2.233 ppm	Blood cell counts	No statistically significant results (only significant when stratified by gender)
[59]	Lan, 2004	Cross-sectional	Clothes factory workers	N=390; 250 exposed, 140 unexposed	China (Tianjin)	Individual benzene exposure monitoring	Mean benzene exposure level: **Shoe factory A**: 21.86 ppm **Shoe factory B**: 3.46 ppm	**Hematological parameters:** Complete blood count, myeloid progenitor colony formation	↓ WBC[b], ↓ granulocytes[b], ↓ lymphocytes[a], ↓ CD4+ T cells, ↓ CD4+/CD8+ ratio, ↓ B cells[b], ↓ NK cells[b], ↓ platelets[b], ↓ progenitor cell colony formation
[60]	Lan, 2005	Cross-sectional	Shoe factory workers	N=90; 45 exposed, 45 unexposed	China (Tianjin)	Individual passive monitoring; urinary BZ levels	**Air**: 15.8 ± 17.9 ppm **Urine**: 452.6 ± 961.7 ug/l	T-cell receptor excision DNA circles (TRECs) levels	No significant difference in TREC levels per 10^6 peripheral blood leukocytes
[15]	Li, 2009a	Cross-sectional	Occupationally exposed workers	N=165; 138 exposed, 27 unexposed	China	Workplace air sampling or diagnosis of BZ poisoning by the Occupational Diseases Diagnosis Group in Guangzhou, China	37.8 mg/m^3	T-cell receptor excision DNA circles (TRECs) levels	↓ TRECs, ↓WBCs, ↓ Hb, ↓ platelets, ↓ RBCs
[61]	Li, 2009b	Cross-sectional	BZ exposed workers	N=25; 16 exposed, 9 unexposed	China	Air sampling of workplace	37.8 mg/m^3	CDR3 region of T cells	↓ Vβ subfamilies ($P<0.05$); most frequently used genes are Vβ3, Vβ21, Vβ6, Vβ16

[62]	Li, 2012	Cross-sectional	Paint factory workers	N=46; 20 exposed, 7 chronic mild BZ poisoning, 5 chronic severe BZ poisoning, 14 unexposed	China	Diagnosis of BZ poisoning according to the Diagnostic Criteria of Occupational Benzene Poisoning	Unclear	**Hematological**: CD3, CD4, CD8 lymphocyte levels **Gene expression**: CD3γ, CD3δ, CD3ε, CD3ζ	**Hematological:** ↓ CD4+ T lymphocytes, ↓ CD4+/CD8+ ratio (significant in each group except mild BZ-poisoned) **Gene expression:** BZ-exposed: ↑ CD3δ[a], ↑ CD3ε, ↑ CD3ζ Mild BZ-poisoned: no significant differences Severe BZ-poisoned: ↓ CD3γ[a], ↓ CD3ε[a], ↓ CD3ζ[a]
[63]	Li, 2018	Cross-sectional	Petrochemical factory workers	N=269; 147 exposed, 122 unexposed	China	Individual air sampling of 18 exposed workers, Urinary SPMA levels	**Air :** Exposed: 0.120 (0.007-0.345) mg/m^3 Unexposed: 0.120 (0.065-0.280) mg/m3 **Urinary SPMA:** Exposed: 100.12 ng/gCr Unexposed: 55.25 ng/g Cr	**Hematological parameters:** WBCs, neutrophils, lymphocytes, monocytes, RBC, platelets	↓ WBC[b], ↓ neutrophils, ↓ lymphocytes[b], ↓ monocytes[b]
[64]	Li, 2019	Cross-sectional	Residents around a petrochemical industrial zone	N=499 (all exposed)	China	Blood BZ levels	Median (25th, 75th percentiles) **Male**: 0.162 (0.053, 0.364) ug/L **Female**: 0.130 (0.062, 0.355) ug/L	**Hematological parameters**: WBC, neutrophil, lymphocyte, monocytes, eosinophil, basophil, RBC, Hb, MCV, MCH, MCHC, RDW, platelet, PDW, MPV, PCT	Abnormal rate of eosinophils (28.7%), basophils (16.2%), HCT (17.2%), MCHC (14.8%)
[17]	McHale, 2009	Cross-sectional	Shoe factory workers	N=16; 8 exposed, 8 unexposed	China (Tianjin)	Personal passive monitoring	47.3 ± 24.3 ppm	Global gene expression	↑ *CXCL16,* ↑ *ZNF331,*↓ *JUN,* ↓ *PF4*
[65]	Midzenski, 1992	Cohort	Shipyard workers (degassers)	N=15; all exposed	U.S.A	Industrial sampling of tanks	Range = 60 - 600 ppm	Clinical symptoms **Hematological parameters**: CBC, WBCs, lymphocytes, MCV, Hb, platelets, hematological abnormalities	**Hematological findings**: 9/15 workers had at least 1 hematological abnormalities; large granular lymphocytes observed in 6; 4 presented w/ persistent hematologic abnormalities one year after acute exposure; no consistent patterns of correlation observed for hematological parameters

[19]	Moro, 2015	Cross-sectional	Gas station attendants	N=88; 60 exposed, 28 unexposed	Brazil	Personal passive samplers, blood BTX levels, urinary t,t-MA levels	**Exposed:** Air: 144.2 (58.1-2207.5) ug/m^3 Urinary: 334 (190-600) ug/gCr **Unexposed:** Air: 42.0 (34.1-52.4) ug/m3 Urinary: 70.0 (50.0-120.0) ug/gCr	Hematological parameters, ALA-D activity, CD80 + CD86 expression, IL-8	↓ ALA-D activity[b], ↓ CD80 + CD86 expression[a], ↑ IL-8[b], ↑ neutrophils
[66]	Moszcynski, 1996	Cross-sectional	Workers exposed to organic solvents	N=139; 60 exposed, 79 unexposed	Poland	Air sampling; urinary phenol levels	**Air sampling**: TWA avg = 19 mg/m^3 (6 ppm) Mean annual avg = 48 mg/m^3 (15 ppm) **Phenol**: Smokers: 16.8 ± 6.2 mg/l Non-smokers: 18.4 ± 9.7 mg/l	**Blood counts:** T-cells (CD3+), T-helper (CD4+), T-suppressor (CD8+), NK cells (CD16+)	↓ T-cells, ↓ NK cells, ↑ T-suppressor cells, ↓ T-helper/T-suppressor (CD4/CD8) ratio
[67]	Moszczynski, 1985	Cross-sectional	Occupationally exposed workers	N=154; 108 exposed, 46 unexposed	Poland	Workplace air sampling; phenol in urine	**Air**: 0.370 mg/m^3 **Phenol**: 16.2 ± 9.6 mg/l	NAG-positive lymphocyte count	↓ T-lymphocytes (exposure-dependent), ↓ in lymphocytes w/ intact NAG-positive lysosomes
[20]	Pelallo-Martinez, 2014	Cross-sectional	Children living near petrochemical area	N=105; 46 Allende, 38 Mundo Nuevo, 21 Lopez Mateos (all exposed)	Mexico	Urinary t,t-MA levels	Mean (range) **Allende**: 388 (44-1784) ug/gCr **Mundo Nuevo**: 363 (63-5521) ug/gCr **Lopez Mateos**: 369 (62-1414) ug/g Cr	**Genotoxicity**: DNA damage **Hematological effects**: WBC, Hb, HCT, RBC, platelets	**Lopez Mateos**: ↓ Hb[a], ↓ HCT[a], ↓ WBC, ↓ RBC
[68]	Pitarque, 1996	Cross-sectional	Service station attendants	N=93; 50 exposed, 43 unexposed	Spain	Personal air sampling; phenol urinary levels	**Air**: 8-h TWA: 0.91 ± 0.14 mg/m^3 **Phenol**: Exposed: 5.06 ± 0.51 mg/gCr Control: 3.73 ± 0.53 mg/gCr	**Genetic damage**: MN **Hematological parameters**: differential WBC count	No significant differences in MN and differential WBC counts between exposed and control populations
[21]	Qu, 2002	Cross-sectional	Factory workers (glue, shoe-making, sporting goods)	N=181; 130 exposed, 51 unexposed	China (Tianjin)	Individual passive monitoring	Median (range) = 3.2 (0.06-122) ppm daily	**Blood parameters**: RBC, platelets, WBC, neutrophils, lymphocytes, eosinophils, etc.	Exposure-dependent: ↓ RBC[b], ↓ WBC[b], ↓ neutrophils[b]

[22]	Ray, 2007	Cross-sectional	Petrol pump or automobile service workers	N=85; 25 petrol pump attendants, 25 automobile service station workers, 35 unexposed	India	Urinary t,t-MA levels	**Exposed:** 2.72 ± 0.21 mg of t,t-MA/L **Unexposed:**0.71 ± 0.11 mg/L	Hematological parameters and lymphocyte subsets	**Hematological parameters:** ↓ RBC, ↓ Hb, ↓ lymphocyte, ↓ platelets, ↑ MCV, ↑ eosinophils, ↑ monocytes, ↑ immature neutrophil, ↑ band cells, ↑ RBC aniso-poikilocytosis and ↑ target cells, ↑ giant platelets **Lymphocyte subsets:** ↓ CD4+, CD8+, CD19+ cells, ↑ CD16+56+ NK cells **P-selectin expression on platelet surface:** ↑ P-selectin expression
[69]	Renzetti, 2009	Cross-sectional	Untreated allergic children w/ mild persistent asthma	N=37	Italy	Fixed air quality monitoring stations in the city (hourly)	Exposed: 3.9 ± 0.5 ug/m^3 Unexposed: 0.2 ± 0.1 ug/m^3	**Airway inflammation and airway function after relocation to rural area (days 0-7):** nasal eosinophils, FE_{NO} from lower airways, peak expiratory flow (PEF), urinary LTE_4	↓ nasal eosinophils[a], ↓ FE_{NO} concentration, ↑PEF[b]
[23]	Rothman, 1996a	Cross-sectional	Occupational factory workers	N=88; 44 exposed, 44 unexposed	China	Organic vapor passive dosimetry badge (worn for a full workshift, 5 days during 1 or 2 weeks before phelobotomy), BZ urinary metabolites (t,t-MA, phenol, catechol, HQ)	Median 8-hr TWA = 31 ppm **Urinary:** Exposed: <31ppm: MA: 8.15 ug/mg CA: 7.0 ug/mg HQ: 12.8 ug/mg Phenol: 38.9 ug/mg >31ppm: MA: 46.8 ug/mg CA: 65.7 ug/mg HQ: 64.3 ug/mg Phenol: 349.7 ug/mg Unexposed: MA: 0.18 ug/mg CA: 3.2 ug/mg HQ: 1.6 ug/mg Phenol: 17.3 ug/mg	**Hematological parameters:** WBC, lymphocyte, Hb, RBC, platelet, mean corpuscular volume, hematocrit	↓ WBC, ↓ lymphocyte count[a], platelets[a], RBCs; ↑ MCV

[24]	Rothman, 1996b	Cross-sectional	Occupational factory workers	N=88; 44 exposed, 44 unexposed	China	Organic vapor passive dosimetry badge (worn for a full workshift, 5 days during 1 or 2 weeks before phelobotomy), BZ urinary metabolites (t,t-MA, phenol, catechol, HQ)	Median 8-hr TWA = 31 ppm **Urinary:** Exposed: MA: 33.0 ug/mg Unexposed: MA: 0.3 ug/mg	**Hematological parameters:** WBC, lymphocyte, Hb, RBC, platelet, mean corpuscular volume, hematocrit **Cytokine Levels:** G-CSF, IL-6, erythropoietin, and TNF-a, IL-3	↓ WBC, lymphocyte count, platelets, RBCs, HCT; ↑ MCV; no significant difference in cytokine values (IL-3, IL-6, EPO, GMCSF, TNFa)
[25]	Samadi, 2019	Cross-sectional	Adults exposed to an urban environment	N=219; 74 industrial, 74 high traffic, 71 low traffic	Iran	BTXS air sampling of industrial (28), high traffic (33), and low traffic areas (32) twice a day; Total: 18 stations, 93 air samples	**Industrial:** 15.92 ± 8.15 ug/m^3 **High traffic**: 7.33 ± 5.97 ug/m^3 **Low traffic:** 2.08 ± 1.15 ug/m^3	**Hematologic parameters**: WBC: neutrophils, eosinophils, monocytes, basophils, lymphocytes; RBC: Hb, HCT, MCV, MCHC, MCH) **Pro-inflammatory biomarkers**: TNF-α, IFN-γ	**Between industrial and low traffic area groups**: ↓ RBCs[b], ↓ Hb, ↓ HCT[a], ↑ WBC, ↑ neutrophils[a], ↓eosinophils, ↑TNF-α[a], ↑IFN-γ[a] **Between high and low traffic**: ↓ RBCs, ↑ TNF-α[a], ↑ IFN-γ[a] **Between industrial and high traffic:** ↑ MCHC[a], ↑ neutrophils, ↓ eosinophils
[70]	Santiago, 2017	Case report	Gas station workers	N=2 (Case 1 8h/day, 6 days/week, 4years at a gas station; Case 2 48h/week, 9years at a gas station)	Brazil	Proxy (occupation)		Complex chromosomal rearrangements (CCR), NK cell count	**Case 1:** mild neutropenia, ↓ NK cells (all NK CD56+/CD16-), miscarriage in the first half of pregnancy, headache, dizziness, irritability, asthenia, changes in the thyroid gland, nodules in the right lobe, nonspecific pulmonary auscultation, found in 1/100 metaphases a CCR involving 8 chromosomal breakpoints, abnormal CD16 expression **Case 2:** one CCR found in 1/100 metaphases involving 3 breakpoint event, ↓ NK cells (all NK CD56+/CD16-) **Both:** CCRs. ↓ NK cells (all NK CD56+/CD16-), abnormal CD16 expression

[71]	Sauer, 2018	Cross-sectional	Gas station workers	N=145; 74 exposed, 71 unexposed	Brazil	Personal passive samplers, urinary t,t-MA	**Exposed:** Air: 0.216 (0.140-0.406) mg m^{-3} Urinary: 243.7 (106.1 - 617.8) ug/gCr **Unexposed:** Air: 0.040 (0.0-0.09) mg m-3 Urinary: 74.3 (40.9-114.9) ug/gCr	B7.1 + B7.2 protein and gene expression; C3+C4 serum levels, p53 gene expression	↓ B7.1 /CD80 + B7.2/CD86 protein and mRNA expression[b], ↓ C3 and C4 complement fraction levels[b]
[26]	Schnatter, 2010	Cross-sectional	Factory workers (rubber, shoe, insulation materials)	N=928; 855 exposed, 73 unexposed	China	Individual monitoring of a random sample of workers	Median (range) = 7.4 (0.07-872) mg/m^3	**Hematological parameters**: WBCs, neutrophils, basophils, eosinophils, monocytes, lymphocytes, RBCs, Hb, MCV, RDW, platelets, MPV **SNPs**: NQO1, MPO, CYP2E1, GSTT1	↓ WBCs[a], ↓ lymphocytes, ↓ monocytes, ↓ neutrophils, ↓ RBCs[b], ↓ Hb[b], ↓ MCV[b], ↓ platelets[a], ↓ MPV[c]
[72]	Shen, 2008	Cross-sectional	BZ-exposed workers	N=80; 40 exposed (20 in 1-10 ppm group, 20 in >10 ppm group), 40 unexposed	China (Tianjin)	Individual passive monitoring; urinary BZ levels	**Air**: 1-10 ppm: 5.06 ± 2.97 ppm >10 ppm: 26.30 ± 19.16 ppm **Urine**: 1-10 ppm: 99.76 ± 156.10 ug/L >10 ppm: 820.82 ± 1253.27 ug/L	**mtDNA copy numbe**r **Blood cell counts**: WBC, granulocytes, lymphocytes, CD4+, CD8+, B cells, NK cells, monocytes, platelets, Hb	**1-10 ppm**: ↓ WBC[a], ↓ granulocytes[a], ↓ CD4+, ↓ CD4+/CD8+ ratio[b], ↓ platelets[a], ↑ mtDNA **>10 ppm**: ↓ WBC[a], ↓ granulocytes[a], ↓ CD4+, ↓ CD4+/CD8+ ratio[b], ↓ B-cells[b], ↓ platelets[a], ↑ mtDNA
[73]	Singh, 2014	Cross-sectional	Petrol pump workers	N=94; 50 exposed, 40 unexposed	India	Proxy (occupation)		Eosinophil count	↓ in eosinophils according to years of exposure (1-5, 6-10, and >15, exception of those in the 11-15 years of exposure)
[74]	Smolik, 1973	Cross-sectional	Occupational workers	N=79; 34 exposed (group 1), 45 unexposed (group 2)	Poland	Area monitoring	Group 1: 0.011-0.022 mg/L of air; Group 2: 0.003-0.02 mg/L	Serum complement level	↓ Serum complement
[75]	Spatari, 2015	Cross-sectional	Oil refinery workers	N=67; 51 exposed, 16 unexposed	Italy	Personal air sampling (during work shift of 8h)		IL-10 serum levels	No significant difference between IL-10 in Groups A+B

[76]	Sukaisi, 2017	Cross-sectional	BZ-filling station workers	N=43; 35 exposed, 8 unexposed	Indonesia	Urinary t,t-MA levels	587 ± 1326.5 ug/gCr	**Hematological parameters**: Examination of CD4+ and CD8+ T cells	↑ CD8+ T cells
[77]	Sul, 2005	Cross-sectional	Factory workers (printing, shoe-making, chemical production)	N=61; all exposed	South Korea	Breath BZ levels (personal sampler); t,t-MA and phenol in urine	**Breath**: 0.268 ± 0.216 (0.005-2.03) ppm **t,t-MA:** 1.02 ± 0.45 (0.24-2.77) mg/gCr **Phenol**: 10.9 ± 8.66 (2.5-46.6) mg/gCr	DNA damage, hematological parameters (secondary outcome) - WBC, neutrophils, lymphocyte, monocyte	No statistically significant differences between worker groups (although no comparison to unexposed was investigated)
[78]	Swaen, 2010	Retrospective cohort	Dow employees with low BZ exposure	N=20705; 8532 exposed, 12173 unexposed	Netherlands	21,584 BZ air measurements (8h TWA) - job exposure matrix	Low concentrations of BZ	Hematological parameters	↓ eosinophils in stratified analysis and continuous analysis[b] but not in the categorical analysis ↑ monocytes in categorical[b], continuous and stratified analysis
[27]	Townsend, 1978	Cross-sectional	Employees	N=282; all exposed	N/A	TWA estimates of benzene based on environmental measurements	**Range**: <2 ppm TWA - 30 ppm TWA for periods of <1 yr - 20 yrs+	**Blood chemistries**: bilirubin, creatinine, total protein, albumin, globulin, BUN, LDH, SGOT **Hematological parameters**: HCT, Hb, WBC, RBC, MCV, MCH, MCHC	↓ RBC, ↓ bilirubin (not statistically significant)
[79]	Tsai, 2004	Retrospective cohort	Employees that participated in the Shell BMSP	N=4427; 1200 exposed, 3227 unexposed	U.S.A	Representative exposure monitoring data (personal sampling)	**1977-1988 mean**: 0.60 ppm **After 1988 mean**: 0.14 ppm	**Complete blood count**: WBC, RBC, lymphocyte, platelet, Hb, MCV	↓ MCV (no statistically significant changes)
[80]	Tunsaringkarn, 2013	Cross-sectional	Gasoline station workers	N=102; all exposed	Thailand	Urinary t,t-MA levels	1.45 ± 2.42 mg/gCr	**Hematological parameters:** Hb, HCT, MCV, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets	Inverse correlation between urinary t,t-MA and Hb[a]; inverse correlation between urinary t,t-MA and HCT[a]; higher urinary t,t-MA (>0.5 mg/gCr) correlated with lower eosinophil counts
[28]	Uzma, 2008	Cross-sectional	Petrol filling workers	N=78; 42 exposed, 36 unexposed	India	Proxy (occupation)		Respiratory, hematological, and thyroid functions	**Hematological** ↑ RBCs and Hb (10-15, >15 years of exposure), ↓ WBC (except eosinophils and platelets - ↑ observed in eosinophil count according to yrs of exposure) **Thyroid:** ↑ T4, ↑ T4F, ↓ TSH, ↓ T3 **Respiratory:** ↓ VC, ↓ FVC, ↓ IC, and ↓ FIVC (<10 years of exposure)

[81]	Uzma, 2010	Cross-sectional	Gasoline filling workers	N=506; 428 exposed; 78 unexposed	India	Individual air sampling; urinary BZ levels; blood BZ levels	**Air**: 0.345 (0.118-0.527) ppm **Blood** (post-shift): 12.1 ± 5 nmol/L **Urine** (post-shift): 42.6 ± 1.2 nmol/L	**Oxidative stress**: ROS, MDA, SOD, GSH **Immune parameters**: CD4, CD8, IgG **mRNA expression**: p53	**Oxidative stress**: ↑ ROS, ↑ MDA, ↓ SOD, ↓ GSH **Immune parameters**: ↓ CD4, ↓ CD4/CD8, ↓ IgG **mRNA expression**: ↑ p53
[82]	Vermeulen, 2005	Cross-sectional	Shoe factory workers	N=20; 10 exposed workers, 10 controls	China (Tianjin)	Personal passive monitoring	47.3 ± 24.3 ppm	Serum proteome	↓ 4.1 kDa protein, ↓ PF4, ↓ CTAP-III , ↓ PBP
[83]	Wang, 2012	Cross-sectional	Spray paint workers	N=101; 46 directly exposed (group A), 26 indirectly exposed (group B), 29 unexposed	China	Workplace air sampling (25 different locations of the spray-paint plant)	**Group A**: 0.21 ± 0.19 mg/m^3 **Group B**: 0.06 ± 0.12 mg/m^3	**Hematological parameters**: CD4+, CD8+, NK, WBCs, Hb, platelets, B-cells, T-cells **mRNA expression:** Cell cycle regulatory genes: *p53, p21, Bax, Mdm-2, Rad51* DNA repair genes: *Xpc, Xpa, Apel*	**Group A**: ↓ WBC, ↓ Hb, ↓ platelets[a], ↓ CD8+, ↓ CD4+[a], ↓ T-cells, ↓ B-cells **Group B**: ↓ platelets[a], ↓ CD8+[a], ↓ T-cells, ↓ B-cells
[29]	Ward, 1996	Retrospective cohort (nested case-control design)	Rubber hydrochloride manufacturing workers	N=657 (all exposed)		Proxy (occupation)	Max daily BZ exposure = 34 ppm	**Blood cell count**: WBC, RBC	↓ WBCs (strong exposure-response); ↓ RBCs (weak exposure-response)
[84]	Wiwanitkit, 2004	Cross-sectional	Occupational workers	N=30 (all exposed)	Thailand	t,t-MA levels in urine	0.71 (0-7.08) mg/gCr	Platelet count	No significant correlation between urine t,t-MA and platelet parameters ($p > 0.05$) although platelet count did decrease
[85]	Wu, 1998	Cross-sectional	Occupational workers	N=112; 29 low BZ, 29 high BZ, 25 BZ poisoning, 29 control	China	Environmental monitoring of workplace; diagnosis of CBP	**Low BZ**: <300 mg/m^3 **High BZ**: >300 mg/m^3	**Hematological parameters**: WBC count, Hb, SOD **Lymphocyte DNA damage** **Abs to Hsps**	**Hematological**: ↓ WBCs in BZ-poisoned compared to other three groups, ↑ SOD in BZ-poisoned compared to control **DNA damage**: ↑ DNA damage[a] **Abs**: ↑ Abs against Hsp71 in BZ-poisoned compared to other three groups
[86]	Yaneva, 1998	Prospective cohort	Sailors from chemical cargo tankers	N=257; 179 exposed, 78 unexposed	Bulgaria			**Hematological parameters**: RBCs, RBC morphology, HCT, Hb, WBCs, platelets	No statistically significant difference between exp and ctrl group

[87]	Zamanian, 2018	Cross-sectional	Gas station workers	N=160; 80 exposed, 80 unexposed	Iran	Interview-administered questionnaire to collect history of occupational exposure		**Blood parameters**: WBCs, neutrophils, lymphocytes, monocytes, leukocytes **Liver function**: AST, ALT	↓ TLC[b], ↑ lymphocyte[b], ↑ monocyte[b], ↑ neutrophils[b]

Assume all mean differences are significant at $p < 0.05$ unless marked below:

[a]The mean difference is significant at 0.01 (equal or less)

[b]The mean difference is significant at 0.001 (equal or less)

Abbreviations: a1-AT, alpha-1-antitrypsin; AACT, alpha-1-antichymotrypsin; Abs, antibodies; AEC, alveolar epithelial cells; ALP, alkaline phosphatase; ALT, alanine aminotransferase; apo, apolipoprotein; AST, aspartate transaminase; BMSP, Shell Benzene Medical Surveillance Program; BTEX, benzene, toluene, ethylbenzene, xylene; btwn, between; BTX, benzene, toluene, xylene; BUN, blood urea nitrogen; BZ, benzene; C3, complement 3; CA, chromosomal aberration; CAT, catechol; CBC, complete blood count; CC-16, clara cell protein; Cr, creatinine; CRP, C-reactive protein; Ctrl, control; ECP, eosinophil cationic protein; EPO, erythropoietin; Exp, exposed; FEF, forced expiratory flow; FEV, forced expiratory volume; FIVC, forced inspiratory vital capacity; FRAC, total ferric reducing antioxidant capacity; FVC, forced vital capacity; g, gram; gCr, gram creatinine; GLT_{50}, measure of red cell fragility; GM-CSF, granulocyte-macrophage colony-stimulating factor; GS, gas station workers; GSH, glutathione; h, hour; Hb, hemoglobin; HCT, hematocrit; HQ, hydroquinone; Hsp71, heat shock protein 71; IC, inspiratory capacity; ICAM-1, intercellular adhesion molecule 1; Ig, immunoglobulin; L, liter; LDH, lactate dehydrogenase; LS, leather shoe factory workers; LTB4, leukotriene B4; max, maximum; mg, milligram; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDA, malondialdehyde; molCr, mole creatinine; MN, micronuclei; MPV, mean platelet volume; mtDNA, mitochondrial DNA; ng, nanogram; NK, natural killer; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; PAIg, platelet-associated antibody; PBP, platelet basic protein; PDW, platelet distribution width; PEFR, peak expiratory flow rate; PF4, platelet factor 4; P-LCR, large platelet cell ratio; PLG, plasminogen; PM, particulate matter; ppm, parts per million; RBC, red blood cell; RDW, red blood cell distribution width; Ref, reference; ROS, reactive oxygen species; SCE, sister chromatid exchange; SGOT, serum glutamic-oxaloacetic transaminase; SNP, single nucleotide polymorphism; SOD, superoxide dismutase; SPMA, S-phenyl-mercapturic acid; T3, triiodothyronine; T4, thyroxine; T4F, free thyroxine; TBARS, thiobarbituric acid reactive substances; TLC, total leukocyte count; t,t-MA, trans,trans-muconic acid; TREC, T-cell receptor excision DNA circles; TSH, thyroid stimulating hormone; TWA, time-weighted average; ug, microgram; umol, micromole; unexp, unexposed; U.S.A., United States of America; VC, vital capacity; VOC, volatile organic compound; WBC, white blood cell; yrs, years.

Table S5. Summary of additional studies identified from an updated search in July, 2020.

Ref #	Reference (Author, Year)	Study Type	Population	Subject # (N)	Location	Exposure Assessment	Exposure Level	Outcome	Results
KC6: Chronic Inflammation									
[88]	Guo, 2019	Cross-sectional	Factory workers (spraying lacquer)	N=140; 69 exposed, 71 unexposed	China	General air sampling	1.82 ± 1.16 mg/m^3	**mRNA expression** **Hematological:** WBC, neutrophils, lymphocytes, RBC, Hb, platelets, ALT	**mRNA**: ↑ Caspase 1, ↑ IL-1β, ↑ TET2 **Cytokines**: ↑ IL-1β, ↑ IL-8, ↓ IL-10
KC7: Immunosuppression									
[89]	Aksoy, 1971	Cross-sectional	Shoe manufacturing workers	N=317; 217 exposed, 100 unexposed	Turkey	Area monitoring	30-210 ppm	**Hematological**: RBC, WBC, PCV, platelets, differential counts	↓ leukocytes
[90]	Li, 2019	Cross-sectional	Benzene-exposed workers and CBP patients	N=500; 61 short-term exposed, 237 long-term exposed, 53 CBP, 149 unexposed	China	Occupation Diagnosis for CBP	Not reported	Serological proteome analysis	↑ Apo-AI, ↓ transthyretin
[91]	Mukherjee, 2016	Cross-sectional	Petrol pump workers Traffic police	N=93; 73 exposed (40 petrol pump workers, 33 traffic police), 20 unexposed	India	General air sampling; individual passive monitoring; Urinary tt-MA + SPMA levels	**Exp:** *Petrol pump workers:* Static air: 86.5 ± 54.4 ug/m3 Personal exp: 195.3 ± 184.4 ug/m3 tt-MA: 1.10 ± 1.08 mg/gCr SPMA: 1.70 ± 1.69 mg/gCr *Traffic police:* Static air: 56.6 ± 35.6 ug/m3 Personal exp: 104.6 ± 99.0 ug/m3 tt-MA: 0.46 ± 0.31 mg/gCr SPMA: 0.91 ± 0.64 mg/gCr **Ctrl:** tt-MA: 0.36 tt-MA: 1.10 ± 1.08 mg/gCr SPMA: 1.70 ± 0.20 mg/gCr SPMA: 0.73 ±	**Hematological:** Hb, TLC, differential leucocytes count, RBC, platelet, HCT, reticulocyte count **Porphyrin Tests:** Serum ALA and PBG **Pulmonary function tests**	**Hematological:** ↓ platelets, ↑ lymphocytes, ↑ eosinophils, ↓ decreased neutrophils **Porphyrin Tests:** ↑ PBG[a]

							0.56 mg/gCr		
[92]	Ren, 2020	Cross-sectional	CBP patients (all factory workers)	N=44; 21 exposed, 23 unexposed	China	General air sampling (samples were collected within the breathing zone of the workers three times a day)	0.09 - 5 mg/m^3	**Genome-wide methylation** **Micronuclei frequency** **Hematological:** WBC, RBC, Hb, platelet, neutrophils, lymphocytes	**Methylation**: ↑ promoter methylation for CSF3Ra and F2R genes; ↓ neutrophil percentage in high CSF3R-methylation group compared to low CSF3R-methylation group ↑ **MN Frequency** **Hematological:** ↓ WBC, ↓ RBC, ↓ Hb, ↓ platelets, ↓ neutrophils
[93]	Vaughan Watson, 2020	Cohort	NHANES participants with VOC lab results	N-9203	U.S.A.	Blood VOC laboratory analysis	Mean (95% CI) **Smoke exp:** 0.148 (0.137, 0.16) ng/mL **Smoke unexp:** 0.021 (0.02, 0.022) ng/mL	**Hematological:** WBC, eosinophils, RBC, Hb, HCT, platelets	Smoke exp: ↓ HCT[a], ↓ Hb[b], ↓ platelets, ↓ WBC[b]

Note: These studies were identified from an updated PubMed search in July, 2020. We reviewed 182 studies and identified 6 new relevant studies.
Assume all mean differences are significant at $p < 0.05$ unless marked below:
[a]The mean difference is significant at 0.01 (equal or less)
[b]The mean difference is significant at 0.001 (equal or less)
Abbreviations: ALA, Delta-aminolevulinic acid; ALT, alanine aminotransferase; apo, apolipoprotein; CBP, chronic benzene poisoning; Ctrl, control; Exp, exposed; gCr, gram creatinine; Hb, hemoglobin; HCT, hematocrit; IL, interleukin; mL, milliliter; mg, milligram; MN, micronuclei; ng, nanogram; NHANES, National Health and Nutrition Examination Survey; PBG, porphobilinogen; PCV, packed cell volume; ppm, parts per million; RBC, red blood cell; Ref, reference; SPMA, S-phenyl-mercapturic acid; TET2, Tet methylcytosine dioxygenase 2; TLC, total leukocyte count; t,t-MA, trans,trans-muconic acid; ug, microgram; unexp, unexposed; U.S.A., United States of America; VOC, volatile organic compound; WBC, white blood cell.

Table S6. Major outcomes from benzene hematotoxicity studies in exposed people.

Hematotoxicity	Results		
	Increase	**No association**	**Decrease**
Mixed lineage			
WBC	D'Andrea (2014b)[43], D'Andrea (2016)[44], D'Andrea (2017)[45], D'Andrea (2013a)[40], Doherty (2017)[5], Froom (1994)[47], Haufroid (1997)[50], Hristeva-Mirtcheva (1998)[51], Samadi (2019)[25]	Hancock (1984)[48], Pitarque (1996)[68], Yaneva (1998)[86], Sul (2005)[77]	Uzma (2008)[28], Wang (2012)[83], Ward (1996)[29], Wu (1998)[85], Zamanian (2018)[87], Bassig (2016)[34], Biro (2002)[35], Bogadi-Sare (1997)[3], Schnatter (2010)[26], Rothman (1996a)[23], Rothman (1996b)[24], Shen (2008)[72], Casale (2016)[38], Cody (1993)[39], D'Andrea (2014a)[42], Huang (2012)[52], Li (2009a)[15], Ibrahim (2014)[12], Kipen (1988)[56], Kamal (2012)[54], Li (2018)[63], Pelallo-Martinez (2014)[20], Qu (2002)[21], Lan (2004)[59], Aksoy (1971)[89], Ren (2020)[92], Vaughan Watson (2020)[93]
CBC		Hancock (1984)[48], Spatari (2015)[75], Sul (2005)[77], Swaen (2010)[78], Koh (2015)[58], Hotz (1998)[11], Townsend (1978)[27], Erdei (2003)[46], Wiwanitkit (2004)[84], Tsai	

		(2004)[79], Yaneva (1998)[86]	
Hematological abnormalities	Midzenski (1992)[65]		
Myeloid lineage			
Granulocytes			Bassig (2016)[34], Shen (2008)[72], Lan (2004)[59]
Neutrophils	Samadi (2019)[25], Dutta (2013)[6], Zamanian (2018)[87], Haufroid (1997)[50], Doherty (2017)[5], Moro (2015)[19]		Casale (2016)[38], Hristeva-Mirtcheva (1998)[51], Huang (2012)[52], Chen (2019)[4], Qu (2002)[21], Schnatter (2010)[26], Li (2018)[63], Bogadi-Sare (1997)[3], Biro (2002)[35], Mukherjee (2016)[91], Ren (2020)[92]
Eosinophils	Dutta (2013)[6], Ray (2007)[22], Uzma (2008)[28], Li (2019)[64], Mukherjee (2016)[91]		Barman (2016)[33], Samadi (2019)[25], Swaen (2010)[78], Singh (2014)[73], Tunsaringkarn (2013)[80], Harati (2017)[49], Renzetti (2009)[69]
Basophils	Chen (2019)[4], Haufroid (1997)[50], Li (2019)[64]		
Monocytes	Chen (2019)[4], Doherty (2017)[5], Haufroid (1997)[50], Swaen (2010)[78], Zamanian (2018)[87], Ray (2007)[22]		Li (2018)[63], Schnatter (2010)[26]

Macrophages	Dutta (2013)[6]		
RBCs	Doherty (2017)[5], Liang (2018)[16], Uzma (2008)[28]	Hancock (1984)[48], Yaneva (1998)[86]	Samadi (2019)[25], Rothman (1996a)[23], Ray (2007)[22], Ibrahim (2014)[12], Pelallo-Martinez (2014)[20], Qu (2002)[21], Schnatter (2010)[26], Rothman (1996b)[24], Chen (2019)[4], Haufroid (1997)[50], Kamal (2012)[54], Li (2009a)[15], Townsend (1978)[27], Ward (1996)[29], Huang (2012)[52], Ren (2020)[92]
Platelets	D'Andrea (2013a)[40], D'Andrea (2014a)[42], D'Andrea (2014b)[43], D'Andrea (2016)[44], D'Andrea (2017)[45]	Wiwanitkit (2004)[84]	Kasemy (2019)[55], Schnatter (2010)[26], Wang (2012)[83], Shen (2008)[72], Chen (2019)[4], Rothman (1996a)[23], Rothman (1996b)[24], Ray (2007)[22], Bassig (2016)[34], Huang (2012)[52], Li (2009a)[15], D'Andrea (2013b)[41], Lan (2004)[59], Ibrahim (2014)[12], Mukherjee (2016)[91], Ren (2020)[92], Vaughan Watson (2020)[93]
Lymphoid lineage			
Lymphocytes	Doherty (2017)[5], Dutta (2013)[6], Haufroid (1997)[50], Zamanian (2018)[87], Mukherjee	Erdei (2003)[46]	Bogadi-Sare (1997)[3], Bassig (2016)[34], Rothman (1996a)[23], Rothman (1996b)[24], Casale (2016)[38], Ray (2007)[22], Schnatter (2010)[26], Li (2018)[63], Lan (2004)[59]

	(2016)[91]		
B-lymphocytes			Bogadi-Sare (2000)[36], Wang (2012)[83], Bassig (2016)[34], Shen (2008)[72], Lan (2004)[59]
T-lymphocytes			Wang (2012)[83], Moszczynski (1985)[67], Moszczynski (1996)[66]
CD4+ T-lymphocytes			Bassig (2016)[34], Kirkeleit (2006)[57], Li (2012)[62], Ray (2007)[22], Uzma (2010)[81], Wang (2012)[83], Lan (2004)[59], Shen (2008)[72]
CD8+ T-lymphocytes	Sukaisi (2017)[76]		Ray (2007)[22], Wang (2012)[83]
CD4+/CD8+T-cell ratio			Shen (2008)[72], Uzma (2010)[81], Bassig (2016)[34], Li (2012)[62], Moszczynski (1996)[66], Lan (2004)[59]
NK cells			Bassig (2016)[34], Moszczynski (1996)[66], Santiago (2017)[70], Lan (2004)[59]

Abbreviations: CBC, complete blood count; NK cells, natural killer cells; RBC, red blood cell; WBC, white blood cell

Benzene-Induced Hematotoxicity Outcomes

1. White blood cells

Many studies investigating the association between benzene exposure and altered blood cell counts demonstrate evidence of hematological suppression in exposed humans. A summary of the hematotoxicity outcomes observed can be found in **Table S6** above.

In particular, white blood cell (WBC) counts seem to be the most affected as a total of 27 studies have reported lower overall WBCs.[3, 12, 15, 20, 21, 23, 24, 26, 28, 29, 34, 35, 38, 39, 42, 52, 54, 56, 59, 63, 72, 83, 85, 87, 89, 92, 93] A much smaller number of studies reported an increase in overall WBC count,[5, 25, 40, 43-45, 47, 50, 51] and four studies reported no significant change.[48, 68, 77, 86]

WBC subsets were also observed in several studies. Three studies reported a decrease in granulocyte count.[34, 59, 72] Seven studies reported a significant decrease in eosinophil count in association with benzene exposure,[25, 33, 49, 69, 73, 78, 80] although five studies indicated an increase[6, 22, 28, 64, 91] and another study indicated no change.[4] For neutrophils, eleven studies reported a decrease,[3, 4, 21, 26, 35, 38, 51, 52, 63, 91, 92] but a separate six studies reported an increase.[5, 6, 19, 25, 50, 87]

The majority of studies have documented lower absolute lymphocyte levels in benzene-exposed humans,[3, 22-24, 26, 34, 38, 59, 63] although a few studies have reported an increase[5, 6, 50, 87, 91] and one study indicated no change.[46] Specifically, numbers of circulating B-lymphocytes[34, 36, 59, 72, 83] and T-lymphocytes[66, 67, 83] were decreased. In particular, $CD4^+$ T-lymphocytes were observed to decrease in all studies,[22, 34, 57, 59, 62, 72, 81, 83]. The results were slightly mixed in regards to $CD8^+$ T-lymphocytes with one study observing an increase in $CD8^+$ T-lymphocytes,[76] two studies observing a decrease,[22, 83]. Several studies also reported a decrease in the $CD4^+/CD8^+$ T cell ratio,[34, 59, 62, 66, 72, 81] which could indicate altered or suppressed immune function as the $CD4^+/CD8^+$ ratio test is most commonly used to detect AIDS (acquired immunodeficiency syndrome).[94] Four studies also reported an overall decrease in natural killer (NK) cells.[34, 59, 66, 70]

In the case of increased white blood cell counts, one study reported an increase in macrophages[6] and three studies reported an overall increase in basophils.[4, 50, 64] Six studies also reported an increase in monocytes,[4, 5, 22, 50, 78, 87] although another two studies reported a decrease.[26, 63]

There have also been a few studies that have revealed no statistically significant differences in complete blood cell counts examined.[11, 27, 46, 48, 58, 75, 77-79, 84, 86]

Finally, one study has reported unique hematological abnormalities in 15 shipyard workers from the U.S. By observing cells with peripheral blood smears, the study reported that 9 out of the 15 workers exhibited at least one hematologic abnormality and that 6 out of the 15 peripheral blood smears contained numerous large granular lymphocytes, indicating proliferation of cytotoxic T cells.[65]

2. Platelets

Platelets are traditionally known as having only one function: hemostasis and thrombosis (blood clotting). Recently, however, evidence has accumulated that suggests a potential role for platelets in elements of the immunological response. In particular, data suggests that platelets could play a role in

inflammation by releasing cytokines and chemokines to attract neutrophils, monocytes, and lymphocytes to sites of infection.[95] Additionally, studies have shown that platelets can function as immune cells by engulfing microbes, such as HIV and bacteria.[96, 97] Thus platelet count could be an indicator of immune system dysfunction or deficiency.

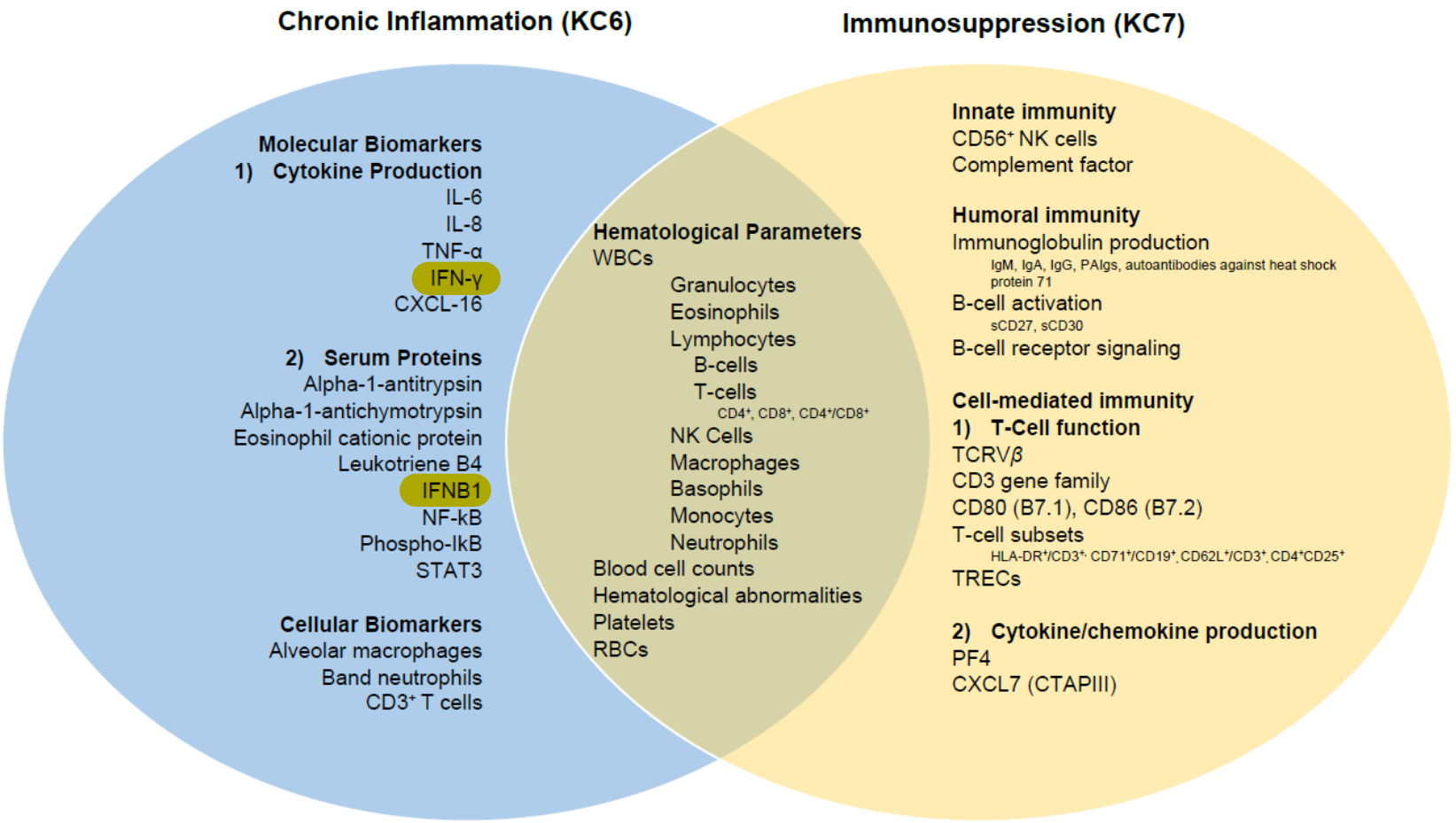
In relation to benzene exposure, 17 studies reported a decrease in platelet count,[4, 12, 15, 22-24, 26, 34, 41, 52, 55, 59, 72, 83, 91-93] five studies reported an increase,[40, 42-45] and one study reported no change.[84]

Many studies reporting on hematological parameters also observed changes in mean corpuscular volume and hemoglobin count, although these results are not included here since as of our current scientific understanding, the two measures do not correlate with inflammatory or immunosuppressive outcomes.

3. Red blood cells

A large number of studies reported a *decrease in red blood cells (RBC)*.[4, 12, 15, 20-27, 29, 50, 52, 54] RBCs typically play a role in oxygen transport to the various tissues of our body. Although RBCs do not play a direct role in the immune system, recent studies have revealed an emerging role for erythrocytes as modulators of innate immunity and cytokine signaling.[98, 99] This suggests that a lack of RBCs could play a role in the immune response to benzene exposure. A separate three studies reported an increase in RBCs.[5, 16, 28]

Figure S1. Summary of observed chronic inflammation, immunosuppression, and hematotoxicity outcomes in association with benzene exposure.



Abbreviations: CTAP III, connective tissue-activating peptide III; CXCL, CXC chemokine ligand; HLA-DR, human leukocyte antigen-DR isotype; IFN, interferon; Ig, immunoglobulin; IL, interleukin; NAG, N-acetyl-beta-glucosamine; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; PAIgs, platelet-associated immunoglobulins; PF4, platelet factor 4; RBC, red blood cell; sCD, soluble CD; STAT3, signal transducer and activators of transcription 3; TCRVβ, variable β-domain of T-cell receptors; TNF-α, tumor necrosis factor alpha; TRECs, T-cell receptor excision circles

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