Advances in biomarkers of benzene exposure and toxicity: From mechanistic insights to occupational health applications (Review)

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Received July 6, 2026; Accepted August 12, 2026

DOI: 10.3892/mmr.2026.14028

Abstract. Benzene is a toxic aromatic hydrocarbon widely used in industrial production, posing a notable occupational health threat. Classified as a Group 1 carcinogen, chronic benzene exposure primarily targets the hematopoietic system, causing leukopenia, thrombocytopenia, aplastic anemia and acute myeloid leukemia. Furthermore, emerging evidence highlights its multi-systemic toxicity, inducing oxidative stress, DNA damage and cellular dysfunction, across the nervous, respiratory, dermatological, reproductive, immune and cardiovascular systems. The present review systematically summarizes recent advances in these occupational hazards and the evolving landscape of benzene biomonitoring. Traditional exposure biomarkers, such as urinary phenol and hydroquinone, are increasingly being supplemented by highly specific metabolites, notably S-phenylmercapturic acid, for low-dose exposure assessments. Effect biomarkers capture early biological damage through hematological indices and molecular alterations, while susceptibility biomarkers, such as cytochrome P450 2E1, glutathione S-transferase mu 1 and DNA repair gene polymorphisms, identify genetically vulnerable populations. Additionally, emerging non-invasive tools, particularly exhaled breath metabolomics, show promise in correlating specific metabolites with hematopoietic function. By integrating mechanistic insights into multi-organ toxicity with advanced multi-omics profiling, the present review highlights a critical paradigm shift from reactive traditional monitoring to artificial intelligence-driven, multi-biomarker integration frameworks. Ultimately, it provides a forward-looking roadmap for individualized risk stratification and precision occupational health surveillance in the low-dose exposure era.

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Key words: benzene, occupational exposure, biomarkers, exposure biomarkers, effect biomarkers, susceptibility biomarkers, hematopoietic toxicity, exhaled breath metabolomics

Contents

1. Introduction

Benzene, a ubiquitous aromatic hydrocarbon, remains a cornerstone of the global petrochemical industry, widely employed in the synthesis of plastics, resins and synthetic fibers, as well as in solvents for paints, coatings and adhesives (1). However, its volatility and lipophilicity render it a pervasive occupational hazard. Despite stringent engineering controls, chronic exposure to benzene vapor persists in industries such as shoe manufacturing, chemical processing and fuel refining, posing a notable threat to global occupational health (2).

The hematotoxicity and leukemogenicity of benzene are well-established. Classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC), benzene is causally linked to aplastic anemia, myelodysplastic syndromes and acute myeloid leukemia (AML) (3-5). Beyond the hematopoietic system, emerging evidence indicates that benzene exerts systemic toxicity, inducing oxidative stress and functional impairment in the nervous, immune, reproductive and respiratory systems (6). The mechanism of toxicity is complex, primarily involving the hepatic metabolic activation of benzene by cytochrome P450 2E1 (CYP2E1) into reactive metabolites (such as benzoquinones and hydroquinones), which drive DNA damage, chromosomal aberrations and epigenetic dysregulation (7).

A notable challenge in current occupational health is the 'low-dose' paradox. While regulatory standards, such as China's occupational exposure limit (PC-TWA of 6 mg/m^3)

and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (0.5 ppm), aim to protect workers, recent epidemiological studies reveal that hematotoxicity and genotoxicity occur at concentrations well below these permissible limits (8,9). This underscores a notable gap in the understanding of low-level exposure risks. Furthermore, conventional monitoring relies heavily on biomarkers such as trans,trans-muconic acid (tt-MA) or S-phenylmercapturic acid (SPMA). While superior to the historical marker urinary phenol, these indicators still face limitations in sensitivity and specificity when distinguishing low-dose occupational exposure from environmental background sources (for example smoking or traffic exhaust) (9).

Therefore, there is a need to elucidate the molecular mechanisms of benzene toxicity at low doses and to validate novel, non-invasive biomarkers for early effect monitoring (10). The present review synthesizes advances in domestic and international research, focusing on three key areas: i) The mechanistic basis of benzene-induced multi-organ toxicity, with a focus on oxidative stress and immune dysregulation; ii) the evolution of biomarkers, transitioning from traditional metabolites to emerging 'omics-based' markers (metabolomics, microRNA panels and DNA methylation); and iii) the clinical implications for precise risk assessment and health surveillance (11). By integrating these perspectives, the present review aimed to provide a theoretical foundation for updating occupational health standards and improving early intervention strategies (12). Consequently, integrating these multifaceted biomarkers into a cohesive framework utilizing artificial intelligence represents the next frontier in occupational medicine. The systematic literature search and study selection process for this review is detailed in Fig. 1.

2. Occupational hazards and systemic toxicity of benzene

Neurotoxicity and nervous system dysfunction. Benzene exerts cumulative neurotoxic effects involving both the central nervous system and peripheral nervous system (13). Chronic exposure induces a spectrum of neurobehavioral deficits-often termed 'chronic benzene encephalopathy', characterized by persistent cephalalgia, dizziness, insomnia and cognitive decline (14). These manifestations are underpinned by the disruption of neurotransmitter homeostasis. Mechanistic studies reveal that benzene metabolites inhibit tyrosine hydroxylase and other rate-limiting enzymes in dopamine and serotonin synthesis, thereby impairing synaptic transmission and neuronal signaling efficiency (15,16).

Neurobehavioral batteries corroborate these findings; for example, exposed workers demonstrate notably prolonged reaction times and a ~20% reduction in bilateral coordination scores compared with controls (17). Due to its high lipophilicity, benzene readily traverses the blood-brain barrier. Its accumulation, along with bioactive metabolites such as phenol, induces histopathological alterations in hippocampal neurons, including vacuolar degeneration and nuclear pyknosis (18). Furthermore, benzene compromises glial cell integrity, leading to myelin sheath instability and irregular Node of Ranvier spacing, which consequently reduces nerve conduction velocity (19). Peripheral neuropathy is equally prevalent (20). In a cohort of shoemaking workers, ~30% reported sensory anomalies, including paresthesia and hypoesthesia (21). Electrophysiological assessments confirmed axonal damage, evidencing motor conduction velocities in median and ulnar nerves that were 3-5 m/sec slower than population norms (22). Notably, owing to the limited regenerative capacity of neural tissue, neurological deficits often persist irreversibly even after exposure cessation (23).

Hematotoxicity and malignancy risks. The hematopoietic system represents the primary target of benzene toxicity, displaying a dose-dependent vulnerability (24). Chronic exposure precipitates hematological dyscrasias ranging from leukopenia ($<3.5x10^9$/l) and thrombocytopenia ($<100x10^9$/l) to severe pancytopenia (25). In advanced stages, this progresses to aplastic anemia or hematologic malignancies (26). The mechanism is driven by hepatic metabolic activation via CYP2E1, generating reactive electrophiles (1,4-benzoquinone, hydroquinone) (27) (Fig. 2).

Due to their lipophilic nature and stability in circulation, these toxic intermediates are readily transported via the systemic bloodstream to the bone marrow microenvironment. Upon entering the hematopoietic niche, they induce severe oxidative stress, rapidly deplete intracellular glutathione reserves and form covalent adducts with topoisomerase II and DNA, ultimately causing double-strand breaks (28). Consequently, the genomic integrity of hematopoietic stem cells (HSCs) is markedly compromised, forcing the cells to arrest at the G_2/M phase and triggering widespread apoptosis (29) (Fig. 3).

In vitro assays indicate a >50% reduction in colony-forming units (CFU-GM/BFU-E) following metabolite exposure. Clinical data mirror this suppression, with exposed workers exhibiting reductions in leukocytes (18%), platelets (22%) and hemoglobin (15%) relative to controls (30). Aplastic anemia remains a critical complication, characterized histologically by hypocellular marrow and adipocyte replacement (31,32). Epidemiologically, exposure >50 mg/m^3 associates with a 6-8-fold increased incidence of aplastic anemia (33,34). Furthermore, benzene is a confirmed leukemogen. IARC data associate benzene with a 3- to 5-fold elevated risk of AML, mediated via chromosomal aneuploidy (such as -5, -7), oncogene activation (*c-Myc*) and tumor suppressor inactivation (*p53*) (35,36).

Respiratory system inflammation and fibrosis. Benzene vapor acts as a potent respiratory irritant and pro-inflammatory agent (37). Acute high-level exposure (>1,000 mg/m^3) triggers chemical bronchitis and pneumonitis, characterized by mucosal edema, goblet cell hyperplasia and airway obstruction (38,39). In severe acute poisoning, pulmonary edema occurs in ~15% of cases, with CT imaging revealing diffuse ground-glass opacities indicative of alveolar-capillary barrier disruption and a cytokine storm (TNF-α, IL-6) (40,41). Conversely, chronic low-dose exposure (<50 mg/m^3) is implicated in chronic obstructive pulmonary pathologies (42). Workers in coating industries show a 28% prevalence of chronic bronchitis vs. 11% in controls (43). Spirometry indicates obstructive deficits, with reductions of 8-12% in vital capacity, forced vital capacity and forced expiratory volume in 1 sec (44). Long-term inhalation models in rats (50 mg/m^3)

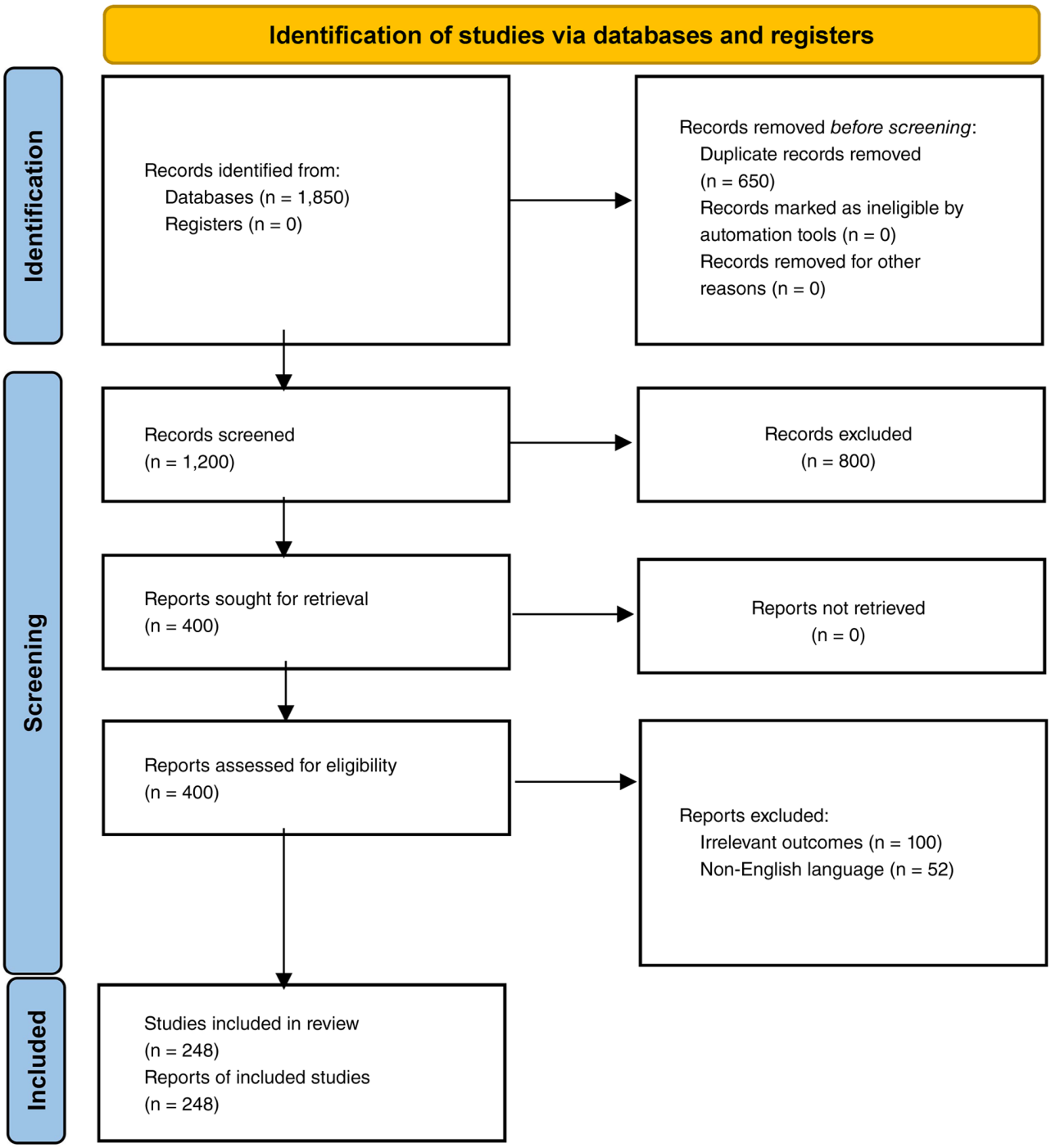

Figure 1. PRISMA flow diagram detailing the literature search and study selection process. The flow diagram illustrates the systematic approach used to identify, screen, and select studies for this review. A total of 1,850 records were initially identified from databases. After removing 650 duplicate records, 1,200 records underwent title and abstract screening. A total of 800 records were excluded at this stage, leaving 400 reports sought for retrieval and full-text eligibility assessment. Among these, 100 reports were excluded due to irrelevant outcomes, and 52 were excluded for being in a non-English language. Ultimately, 248 eligible studies were included in the final review.

demonstrate alveolar septal thickening and collagen deposition, suggesting that chronic benzene-induced oxidative stress may drive pulmonary fibrotic remodeling and impair gas exchange (45,46).

Dermal barrier dysfunction and sensitization. Cutaneous toxicity arises from the solvent properties and sensitizing potential of benzene (47). As a lipophilic solvent, benzene extracts epidermal lipids (ceramides, fatty acids), disrupting the stratum corneum barrier and increasing transepidermal water loss (48,49). This manifests clinically as xerosis, scaling and reduced resistance to pathogens. Additionally, benzene metabolites (such as hydroquinone) act as haptens, triggering allergic contact dermatitis (50). Symptoms range from erythema to vesiculation, with chronic exposure leading to lichenification (51). In rubber manufacturing cohorts, 42% of exposed workers exhibited dermatoses, with 15% suffering from recurrent allergic dermatitis (52). Pigmentary disorders,

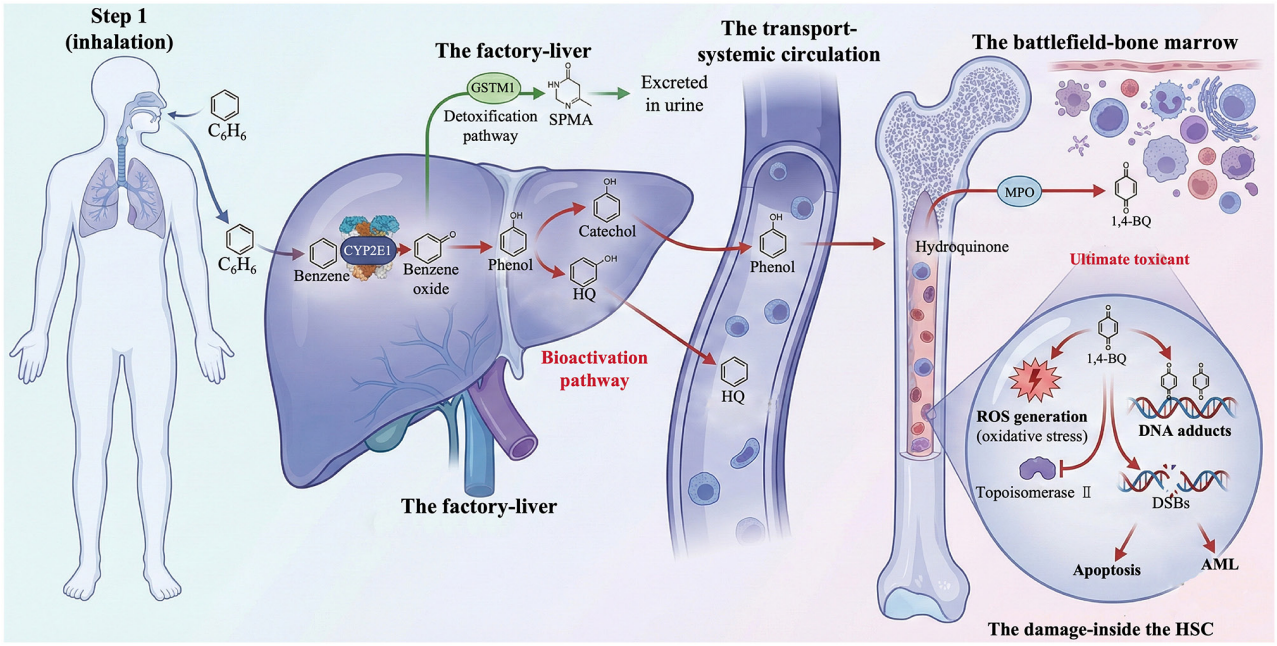

Figure 2. Metabolic activation pathways of benzene and molecular mechanisms of hematopoietic toxicity. Benzene inhaled into the body is primarily metabolized in the liver by CYP2E1 into benzene oxide, which is further converted into phenolic intermediates, including phenol, catechol, and HQ. Alternatively, benzene oxide can be detoxified by glutathione S-transferase M1 to form SPMA and excreted in urine. The phenolic metabolites are transported via the systemic circulation to the bone marrow, where MPO catalyzes the oxidation of HQ into the markedly reactive ultimate toxicant, 1,4-BQ. Within HSCs, 1,4-BQ induces severe toxicity through multiple mechanisms: generating ROS that cause oxidative stress, forming covalent DNA adducts, and inhibiting topoisomerase II. These molecular events collectively lead to DNA double-strand breaks, ultimately triggering cellular apoptosis or driving leukemic transformation, such as AML. SPMA, S-phenylmercapturic acid; CYP2E1, cytochrome P450 2E1; MPO, myeloperoxidase; HQ, hydroquinone; ROS, reactive oxygen species; 1,4-BQ, 1,4-benzoquinone; HSCs, hematopoietic stem cells; AML, acute myeloid leukemia.

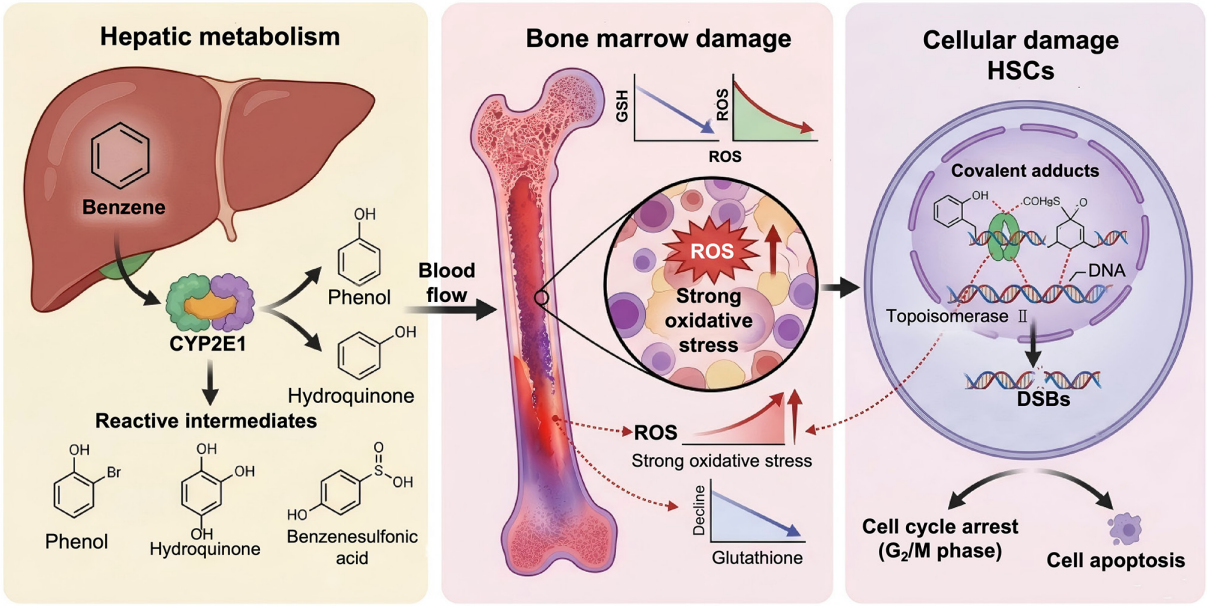

Figure 3. Metabolic bioactivation of benzene and the molecular mechanisms of hematopoietic toxicity. Hepatic metabolism: Inhaled benzene is primarily metabolized in the liver by CYP2E1 into reactive phenolic intermediates, including phenol and hydroquinone. Bone marrow damage: These metabolites are transported via the systemic circulation to the bone marrow microenvironment, where they induce severe oxidative stress, characterized by the accumulation of ROS and the rapid depletion of the antioxidant glutathione. Cellular damage in HSCs: Within HSCs, the synergistic effect of ROS and reactive intermediates leads to the inhibition of topoisomerase II and the formation of covalent DNA adducts. These molecular insults culminate in DSBs, forcing the HSCs into cell cycle arrest at the G_2/M phase and ultimately triggering apoptosis. CYP2E1, cytochrome P450 2E1; ROS, reactive oxygen species; HSCs, hematopoietic stem cells; DSBs, DNA double-strand breaks.

including hyperpigmentation or vitiligo-like leukoderma, affect ~8% of long-term workers, likely due to melanocyte toxicity (53). Compromised skin integrity further predisposes workers to secondary bacterial infections (54).

Reproductive and developmental toxicity. Benzene acts as a reproductive toxicant and endocrine disruptor (55). In males, it crosses the blood-testis barrier, inducing oxidative stress in germ cells. Murine models show arrested spermatogenesis and apoptosis of spermatogonia (56). Clinically, exposed workers exhibit markedly reduced sperm concentration (35 vs. $60x10^6$/ml), decreased motility (Grade A+B reduced by ~25%) and elevated morphological abnormalities (18%) (57,58). Mechanistically, this is associated with increased sperm DNA fragmentation index driven by reactive oxygen species (59). In females, benzene disrupts the hypothalamic-pituitary-ovarian axis, causing menstrual dysfunction (oligomenorrhea) in 38% of exposed workers-a rate 2.3 times that of controls (60,61). Furthermore, benzene is teratogenic; it crosses the placental barrier, interfering with fetal organogenesis (62). Pregnancies in exposed workers are associated with a 60% increased risk of spontaneous abortion, a 15% preterm birth rate and a 3.2% incidence of congenital malformations (such as neural tube defects), highlighting its marked developmental toxicity (63).

Multi-organ carcinogenicity. Beyond leukemia, benzene (IARC Group 1 carcinogen) is associated with solid tumors (64,65). Cohort studies indicate a 2.1-fold increased risk of non-Hodgkin lymphoma and a 1.8-fold increase in multiple myeloma (66). Evidence also links exposure to lung and gastric cancers; for instance, coking plant workers exhibit a lung cancer mortality rate of 35 per 100,000 person-years (relative risk=2.7) (67,68). The carcinogenic mechanism is multifactorial, involving genotoxicity (DNA adduct formation), inhibition of DNA repair enzymes (such as XRCC1) and epigenetic dysregulation (69,70). Benzene simultaneously activates survival signaling (PI3K/Akt) and suppresses apoptosis (Bax downregulation), facilitating the clonal expansion of initiated cells (71). Long-term surveillance confirms a notably elevated all-cancer mortality rate in exposed populations (180 vs. 110 per 100,000 person-years) (72).

Immunotoxicity and immune surveillance suppression. Benzene is a potent immunotoxicant, compromising both innate and adaptive immunity (73). Inhalation studies demonstrate thymic atrophy and splenic T-cell depletion (30-40% reduction) (74). Human data reveal a global immunosuppressive profile: 15-20% lymphopenia, inverted $CD4^+/CD8^+$ ratios and hypogammaglobulinemia (IgG, IgA reduced by 10-15%) (75). Functionally, this manifests as increased susceptibility to infection. In influenza challenge models, benzene-exposed mice exhibited 45% mortality compared with 12% in controls (76). At the cellular level, oxidative stress impairs lymphocyte proliferation and cytokine production (IL-2, IFN-γ), thereby weakening immune surveillance against pathogens and neoplastic cells (77).

Cardiovascular impairment. Emerging evidence implicates benzene in cardiovascular pathology (78). Exposed workers show a higher prevalence of hypertension [28%; odds ratio (OR)=1.6] and coronary heart disease (1.5-fold increase) (79). Pathophysiologically, benzene promotes endothelial dysfunction by reducing nitric oxide availability and upregulating endothelin-1 (80,81). Furthermore, it disrupts lipid metabolism, elevating total cholesterol (+20%) and triglycerides (+30%) while lowering high-density lipoprotein cholesterol, thus accelerating atherogenesis. Autonomic dysfunction is also observed: 32% of workers exhibit abnormal heart rate variability and sinus turbulence, indicating arrhythmogenic potential (82,83). Electrocardiogram abnormalities, such as ST-T changes, occur in ~18% of cases (84).

Ocular surface toxicity. Benzene vapor is an ocular irritant affecting the conjunctiva and cornea (85). Acute exposure (>500 mg/m^3) causes immediate lacrimation and conjunctival hyperemia (86). Chronic low-level exposure induces ocular surface disease, including keratoconjunctivitis sicca (dry eye) (87). Diagnostic metrics reveal reduced Schirmer scores (tear secretion -30%) and shortened tear film break-up time (<10 sec) (88). In catastrophic leakage events (>2,000 mg/m^3), chemical burns can cause corneal epithelial necrosis and permanent opacity, necessitating keratoplasty for visual rehabilitation (89).

Summary. As summarized comprehensively in Table I, the multi-systemic effects of benzene are characterized not only by severe hematological suppression but also by significant quantitative declines in nerve conduction, respiratory function and immune surveillance, underscoring the necessity for whole-body risk assessment.

3. Biomarkers of benzene

As detailed, benzene exerts profound multi-organ toxicity, affecting the nervous, cardiovascular and reproductive systems. However, it must be noted that the current landscape of validated benzene biomarkers notably skews toward hematotoxicity and genotoxicity (90). Specific effect biomarkers designed to reflect early benzene-induced neurotoxicity or cardiovascular dysfunction are currently lacking or remain strictly in the exploratory experimental phase (91). Therefore, the biomarkers discussed in the following sections primarily represent internal dose monitoring and hematopoietic/genomic impairments, highlighting a gap that future non-hematopoietic biomarker research must address (92). As summarized in Fig. 4, the landscape of benzene biomonitoring can be systematically categorized into exposure, effect and susceptibility biomarkers.

Exposure biomarkers. Exposure biomarkers reflect the internal dose of benzene absorbed by the human body (90). They mainly include the parent compound and its metabolites, which can be measured in biological samples such as blood, urine and exhaled air (89). These indicators provide objective and direct evidence for assessing exposure levels in both occupational and environmental contexts (93).

Benzene in blood. The concentration of benzene in blood is a direct marker of recent exposure (94). After inhalation or dermal absorption, a portion of benzene rapidly enters systemic circulation before being redistributed to tissues and organs (95). Due to its short half-life in blood (~4 h), blood benzene measurement is particularly suitable for evaluating acute exposure scenarios, such as accidental leakage events (96). For instance, blood benzene testing can be rapidly

Table I. Summary of benzene-induced multisystem toxicity: Clinical manifestations, mechanisms and key epidemiological findings.

Target system	Clinical manifestations	Key pathological mechanisms	Quantitative observations (from occupational cohorts)	(Refs.)
Hematopoietic	Leukopenia, thrombocytopenia, aplastic anemia, AML	Oxidative stress, DNA double-strand breaks, cell cycle arrest (G_2/M phase), stem cell apoptosis	Leukocytes ↓18%; Platelets ↓22%; AML risk elevated 3-5 fold	(24-36)
Nervous	Neurasthenia, cognitive decline, peripheral neuropathy	Neurotransmitter disruption (dopamine/ serotonin), demyelination, hippocampal damage	Bilateral coordination ↓20%; Nerve conduction velocity ↓ 3-5 m/sec	(13-23)
Respiratory	Cough, dyspnea, pulmonary fibrosis, chronic bronchitis	Alveolar epithelial injury, cytokine storm (TNF-α, IL-6), collagen deposition	Chronic bronchitis prevalence: 28% (vs. 11% control); FEV_1 ↓8-12%	(37-46)
Reproductive (Male)	Oligospermia, asthenospermia, teratospermia	Oxidative stress in germ cells, DNA fragmentation, apoptosis of spermatogonia	Sperm concentration: $35x10^6$/ml (vs. $60x10^6$/ml control); Abnormal morphology: 18%	(55-59)
Reproductive (Female)	Menstrual disorders, spontaneous abortion, fetal defects	Endocrine disruption (HPO axis), placental barrier crossing, interference with organogenesis	Menstrual abnormalities: 38%; Miscarriage risk ↑ 60%; Preterm birth rate: 15%	(60-63)
Immune	Increased susceptibility to infection, lymphopenia	Thymic atrophy, suppression of T-cell proliferation, cytokine dysregulation (IL-2, IFN-γ)	Lymphocytes ↓15-20%; $CD4^+/CD8^+$ ratio inversion; IgG/IgA ↓10-15%	(73-77)
Cardiovascular	Hypertension, arrhythmias, atherosclerosis	Endothelial dysfunction (NO↓, ET-1↑), lipid metabolism disorder, autonomic dysregulation	Hypertension prevalence: 28%; HRV abnormalities: 32%; ST-T changes: ~18%	(78-84)
Dermal/ocular	Dermatitis, xerosis, conjunctivitis, corneal injury	Lipid extraction (stratum corneum disruption), sensitization (hapten formation)	Skin disorder incidence: 42%; Tear secretion ↓30%; BUT <10 sec	(47-54,85-89)

AML, acute myeloid leukemia; FEV_1, forced expiratory volume in 1 sec; HPO, hypothalamic-pituitary-ovarian; NO, nitric oxide; ET-1, endothelin-1; HRV, heart rate variability; BUT, break-up time.

applied to rescue personnel or nearby residents exposed to high concentrations over a short period (97).

The primary analytical method is gas chromatography (GC) (98). Blood samples are pretreated (for example by solid-phase extraction or headspace sampling), then introduced into the chromatograph, where benzene is separated and quantified using detectors such as flame ionization detection or mass spectrometry (MS) (99). However, a critical limitation lies in the strict timing of sample collection; blood must be obtained within a narrow time window (ideally within 24 h post-exposure), as concentrations markedly decline due to metabolism and excretion (100). Delayed sampling may thus underestimate true exposure levels (101).

Benzene in exhaled air. Exhaled air analysis offers a non-invasive approach to monitoring benzene exposure and is associated with blood concentrations (102). Since a fraction of absorbed benzene is excreted via respiration at a relatively stable rate, this biomarker is well-suited for real-time exposure assessment in occupational settings (103). For example, exhaled air collection during paint-spraying operations allows immediate estimation of exposure levels during work shifts (104).

The commonly used detection technique is solid-phase microextraction coupled with GC-MS) (105). Here, benzene is adsorbed onto a solid-phase microextraction fiber, desorbed into the chromatograph, and identified by MS (106). This approach provides high sensitivity, operational simplicity and

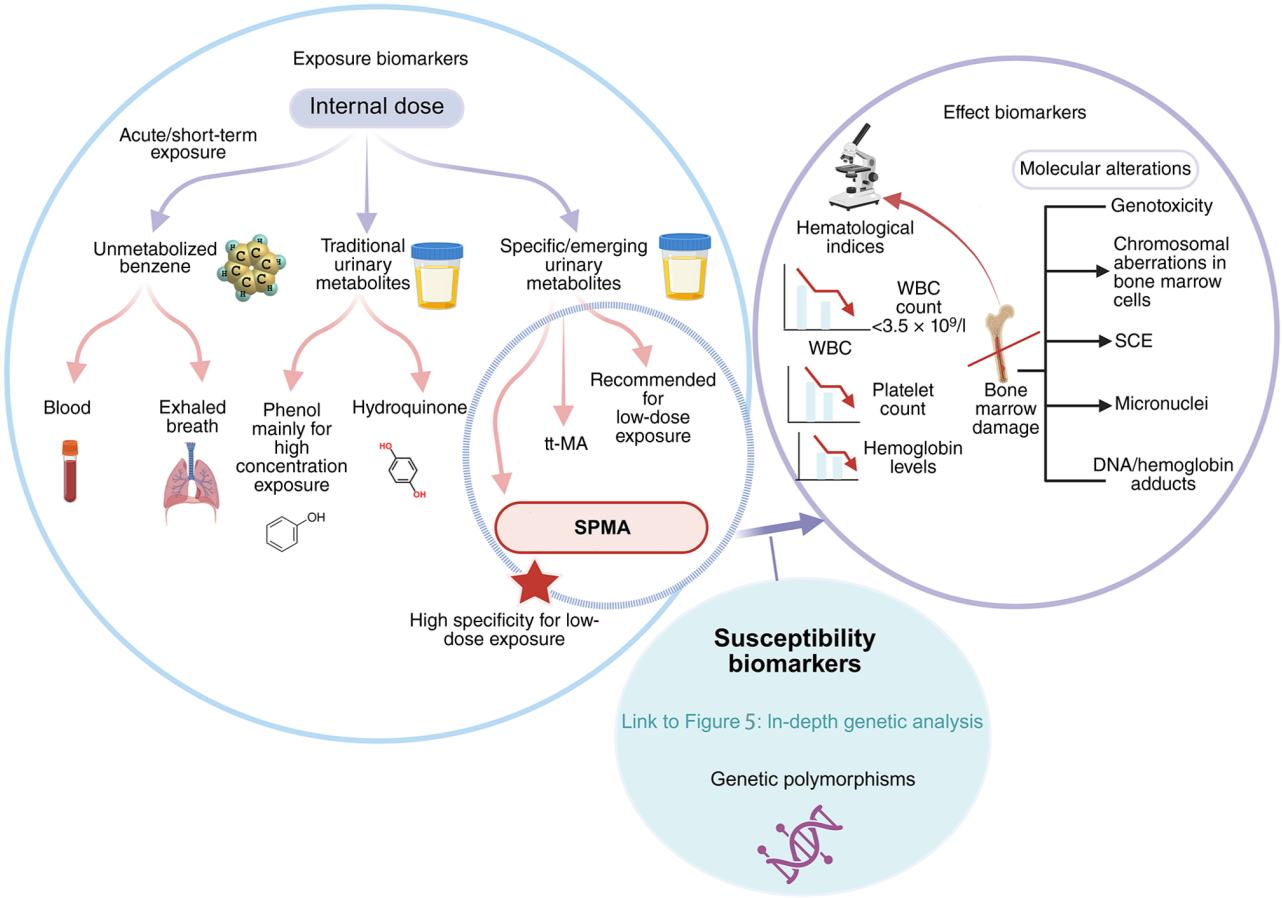

Figure 4. Landscape of traditional and emerging biomarkers for benzene exposure and toxicity. A comprehensive classification of benzene biomarkers categorized into exposure, effect and susceptibility markers. Exposure biomarkers reflect the internal dose, encompassing unmetabolized benzene and tracing the paradigm shift from traditional urinary metabolites (phenol, hydroquinone) typically used for high-concentration scenarios, to specific/emerging metabolites such as tt-MA and SPMA. Notably, SPMA is recommended for biological monitoring of low-dose exposure due to its superior specificity. Effect biomarkers capture early biological damage, predominantly featuring hematological indices (reduced white blood cell and platelet counts) and structural molecular alterations indicative of genotoxicity (chromosomal aberrations, micronuclei, and adduct formation). Susceptibility biomarkers, primarily representing genetic polymorphisms, act as modulators that influence the individual vulnerability and the mechanistic link between benzene exposure and subsequent toxicological effects. Tt-MA, trans, trans-muconic acid; SPMA, S-phenylmercapturic acid; WBC, white blood cell; SCE, sister chromatid exchange.

notably, the advantage of being repeatable and non-invasive, making it suitable for large-scale workplace screening (107).

Nevertheless, exhaled benzene concentrations are easily influenced by respiratory parameters (such as breathing rate and depth) and ambient environmental contamination (108). Thus, standardized sampling protocols and strict quality control are essential to ensure reliability (109).

Phenol in urine. Phenol is one of the principal urinary metabolites of benzene and has long been used as a biomarker for occupational exposure (110). After benzene is metabolized by the hepatic cytochrome P450 enzyme system, phenol is produced and subsequently conjugated with sulfuric acid or glucuronic acid (111). A total of ~30% of benzene is excreted as conjugated phenol, whereas free phenol accounts for only ~5% (112). Urinary phenol levels generally associate with the extent of benzene exposure and typically normalize within 24-48 h after exposure cessation (113).

Detection methods include the aminopyrine colorimetric method and GC (114). The aminopyrine method relies on a color reaction between phenolic compounds and specific reagents, whereas GC provides higher sensitivity (down to 0.01 mg/l) and reproducibility (115). For example, a study on paint-stripping workers demonstrated a notable dose-response relationship, where workplace benzene concentrations ranging from 0.6 to 65.9 mg/m^3 corresponded with urinary phenol levels of 4.3-52.8 mg/l (116).

However, urinary phenol has limitations. Baseline levels in the general population range from 0.15-0.25 mg/l (and can be higher in smokers), which reduces specificity for low-level exposures (117). Moreover, notable inter-individual variability exists-phenol excretion under similar exposure conditions may differ by as much as 12-fold, partly due to differences in liver function and the influence of medications (such as phenobarbital), which alter cytochrome P450 activity (118). Therefore, urinary phenol is more reliable for monitoring high-concentration exposure, whereas its sensitivity for low-level exposure remains inadequate (119).

Hydroquinone in urine. Hydroquinone is a more specific urinary metabolite of benzene compared with phenol and provides enhanced accuracy for exposure assessment (120). Following benzene oxidation to benzene oxide, further metabolism yields hydroquinone, which is excreted in urine (121). Quantification is typically performed using high-performance

liquid chromatography (HPLC) with ultraviolet detection after appropriate sample pretreatment (122).

Epidemiological investigations show that urinary hydroquinone levels exhibit a notable dose-response relationship with benzene exposure concentration (123). Compared with phenol, hydroquinone is less affected by confounding factors and therefore more reliable in detecting low-concentration exposures (124). Nonetheless, hydroquinone measurement is not completely specific, as certain dietary components or medications may also elevate urinary hydroquinone, necessitating combined measurement with phenol or other metabolites to improve diagnostic accuracy (125).

Catechol in urine. Catechol is a minor urinary metabolite of benzene and may serve as a supplementary biomarker of exposure (126). Its metabolic pathway is similar to that of hydroquinone, both being products of benzene oxidative metabolism (127). Although catechol is less commonly employed than phenol and hydroquinone in routine biomonitoring, several studies suggest that combined analysis of catechol with other metabolites can provide a more comprehensive picture of benzene biotransformation and exposure burden (128-131). Detection is typically performed using HPLC (129). However, its relatively low urinary concentration and susceptibility to various endogenous and exogenous interferences limit its specificity and sensitivity (130). At present, catechol is primarily used as an auxiliary indicator within a biomarker panel rather than as a standalone marker of benzene exposure (131).

tt-MA in urine. tt-MA is a benzene metabolite generated via the epoxidation pathway, with a half-life of ~16 h (132). This relatively long persistence makes tt-MA suitable for detecting low-dose or subacute benzene exposure (133). Benzene oxide, an intermediate metabolite, is further metabolized into muconic acid, among which tt-MA is the predominant isomer (134).

Detection methods such as GC-MS and HPLC-MS/MS enable accurate qualitative and quantitative analysis of tt-MA in urine (135). Epidemiological studies have demonstrated that urinary tt-MA levels are positively associated with both the concentration and duration of occupational benzene exposure (135,136). Furthermore, tt-MA decreases relatively slowly after cessation of exposure, thus serving as a retrospective indicator of recent exposure (137). Accordingly, tt-MA is widely recognized as a valuable biomarker for monitoring low-level occupational benzene exposure and plays an notable role in environmental health risk assessment (138).

SPMA in urine. SPMA is produced via the conjugation of benzene oxide with glutathione under the catalysis of glutathione S-transferases (GSTs), followed by subsequent metabolic reactions leading to urinary excretion (139). SPMA is considered a markedly specific and sensitive biomarker of benzene exposure, even at low concentrations (140). Studies indicate that urinary SPMA levels notably increase in workers exposed to low ambient benzene levels, and these levels associate with biomarkers of oxidative stress, such as 8-hydroxy-2'-deoxyguanosine, suggesting potential genotoxic risk even at low-dose exposure (140,141).

Advanced analytical techniques such as HPLC-MS/MS allow sensitive detection of trace SPMA in urine with minimal interference from other sources (142). Given its high specificity, SPMA is increasingly regarded as a robust biomarker for early biological monitoring of benzene exposure and has promising potential for occupational health surveillance and risk prevention (143). As comprehensively compared in Table II, while traditional metabolites such as phenol suffer from low specificity and high background interference, emerging biomarkers such as SPMA and tt-MA offer superior sensitivity for low-dose exposure assessments, underscoring the critical transition in modern biomonitoring strategies.

Effect biomarkers. Effect biomarkers reflect biological damage or functional alterations induced by benzene exposure (144). Since the hematopoietic system is the primary toxicological target of benzene, most effect biomarkers are associated with hematopoietic suppression and genotoxicity (145).

Peripheral white blood cell (WBC) count. A decrease in peripheral WBC count, particularly neutropenia, is a common early hematological effect of benzene exposure (146). Benzene and its metabolites impair the proliferation and differentiation of hematopoietic stem and progenitor cells, resulting in reduced leukocyte production (147). Occupational studies have shown that chronic low-level benzene exposure leads to a gradual decline in WBC count, which positively associates with exposure intensity and duration (148,149). For instance, health examinations in benzene-exposed shoe factory workers revealed notably lower WBC counts and neutrophil proportions compared with reference values, indicating compromised immune function and increased susceptibility to infection (149).

Although WBC monitoring is useful for early detection of hematotoxicity, it lacks specificity since infections, medications and other conditions can also reduce leukocyte levels (150). Thus, WBC count should be interpreted in conjunction with other biomarkers (151).

Platelet count. Thrombocytopenia is another hematological effect of benzene exposure, reflecting bone marrow suppression of megakaryocyte development and platelet production, as well as enhanced platelet destruction (152). Clinically, benzene-related thrombocytopenia often manifests as coagulation dysfunction, including epistaxis, gingival bleeding and cutaneous ecchymoses (153). Platelet reduction is dose-dependent, with more pronounced decreases in populations exposed to higher benzene concentrations (154). Given its simplicity and clinical availability, platelet count is a valuable indicator of benzene-induced hematotoxicity, although differential diagnoses such as autoimmune diseases or hypersplenism must be excluded (155).

Red blood cell count and hemoglobin. Chronic benzene exposure may result in anemia, characterized by reduced red blood cell count or hemoglobin concentration (156). Mechanistically, benzene inhibits hematopoietic stem cell activity and disrupts key enzymes involved in erythropoiesis (157). Additionally, oxidative stress induced by benzene metabolites can damage erythrocyte membranes and shorten red cell lifespan. Clinically, patients with chronic benzene poisoning often present with pallor, fatigue and dizziness, alongside hematological findings of anemia (158). Routine monitoring of red blood cell indices in exposed populations is useful for early detection of hematopoietic impairment,

Table II. Comparative evaluation of traditional and emerging biomarkers for benzene exposure assessment.

Biomarker category	Specific biomarker	Matrix	Metabolic pathway	Half-life	Sensitivity (low-dose)	Specificity	Key limitations	(Refs.)
Parent compound	Benzene	Blood	Unmetabolized	~4 h	High	High	Invasive; rapid decline requires immediate sampling (<24 h).	(96)
	Benzene	Breath	Excretion via lungs	Minutes	High	High	Highly variable; influenced by breathing rate and background air.	(102,103)
Traditional metabolites	Phenol	Urine	CYP2E1 oxidation	24-48 h	Low	Low	High background in general population; lacks correlation at <10 ppm exposure.	(113)
	Hydroquinone	Urine	CYP2E1 oxidation	24-48 h	Moderate	Low	Influenced by dietary intake and medications; not specific to benzene.	(123,124)
Specific metabolites	*trans*, *trans*-muconic acid	Urine	Ring opening	~16 h	High	Moderate	False positives due to dietary sorbic acid (preservative); influenced by smoking.	(132)
	S-phenylmercapturic acid	Urine	GSH conjugation (GSH S-transferases)	12-48 h	Very high	High	Requires sensitive detection (LC-) MS/MS); considered the gold standard for low-level exposure.	(139,140
Macromolecular adducts	Albumin/Hemoglobin Adducts	Blood	Covalent binding	Weeks to Months	High	High	Reflects cumulative exposure; technically demanding; primarily for research.	(181)

CYP2E1, cytochrome P450 2E1; PPM, parts per million; GSG, glutathione; LC-MS/MS, liquid chromatography tandem mass spectrometry.

although the multifactorial etiology of anemia necessitates comprehensive evaluation (159).

Chromosome aberrations in bone marrow cells. Benzene metabolites are genotoxic and can induce structural chromosome aberrations such as breaks, translocations and deletions (160). Cytogenetic analysis of bone marrow cells, often via chromosome banding, enables visualization of these aberrations and quantification of their frequency (161).

Occupational studies consistently report elevated rates of chromosomal abnormalities in benzene-exposed populations, with a dose-response relationship observed (162-164). Since chromosomal aberrations are generally irreversible, they may predispose to genetic instability and tumorigenesis (163). Despite its diagnostic value, chromosomal aberration testing requires specialized expertise and high-quality samples, limiting its application in large-scale screening (164).

Sister chromatid exchange (SCE). SCE serves as a marker of DNA damage and repair activity (165). Under normal conditions, SCE frequency is low, but exposure to mutagens such as benzene markedly increases its occurrence (166). SCE analysis involves BrdU incorporation into cultured lymphocytes, followed by differential staining and microscopic evaluation (167). Numerous studies show markedly higher SCE frequencies in benzene-exposed workers compared with unexposed controls, associating with both exposure level and duration (168,169). Although SCE is sensitive to DNA damage, it lacks specificity since other environmental and pathological factors can also elevate SCE frequency; thus, it should be interpreted alongside other genotoxicity indicators (169).

Micronuclei. Micronuclei are extranuclear chromatin bodies formed during mitosis when chromosome fragments or whole chromosomes fail to be incorporated into daughter nuclei (170). Elevated micronucleus frequency in peripheral lymphocytes or bone marrow cells indicates chromosomal damage and is widely used as a biomarker of genotoxicity (171). Detection methods include conventional Giemsa staining and flow cytometry, both of which facilitate quantification of micronucleated cells (172). Multiple studies have documented notably higher micronucleus rates in benzene-exposed populations, with a positive dose-response relationship (173,174). Micronucleus assays are simple and suitable for large-scale biomonitoring, although their low specificity necessitates complementary testing (174).

DNA adducts. DNA adducts are covalent complexes formed between reactive benzene metabolites (such as benzoquinone) and DNA, directly reflecting molecular damage (175). Adduct formation interferes with DNA replication and transcription, thereby increasing mutagenic and carcinogenic risk (176). Detection methods include ELISA, which utilizes specific antibodies for semiquantitative analysis, and HPLC-MS/MS, which provides precise structural and quantitative information (177). In benzene-exposed populations, multiple types of DNA adducts have been identified, with levels linked to exposure intensity (178). DNA adduct analysis is therefore crucial for elucidating benzene genotoxic mechanisms and evaluating long-term health risks, and it remains a research focus in toxicogenomics (179).

Hemoglobin adducts. Hemoglobin adducts are stable complexes formed between benzene metabolites and hemoglobin residues (180). Given the long half-life of hemoglobin, these adducts provide an integrated measure of cumulative benzene exposure over weeks to months (181). MS-based techniques enable their detection and quantification (182). Occupational studies, such as those involving long-term gasoline station attendants, have reported elevated hemoglobin adduct levels, associating with exposure duration and intensity (183). This biomarker offers unique advantages in tracing chronic low-level exposure, although specialized instrumentation and further research on dose-response relationships are required to strengthen its utility in health risk assessment (184).

Susceptibility biomarkers. Susceptibility biomarkers reflect inter-individual genetic variations that influence vulnerability to benzene toxicity (185). They are mainly associated with polymorphisms in genes encoding metabolic enzymes and DNA repair proteins (186). Such biomarkers can help identify high-risk populations and support the development of personalized protection strategies in occupational and environmental settings (187).

Cytochrome P450 enzyme system (CYP). The CYP plays a central role in benzene metabolism, with *CYP2E1* being the most critical enzyme (188). The *CYP2E1* gene exhibits polymorphisms such as the *5B* mutation, which alters enzyme activity and affects benzene metabolic rates (189). Individuals carrying the *CYP2E15B* variant tend to show enhanced enzymatic activity, leading to accelerated formation of toxic metabolites and increased susceptibility to benzene-induced hematotoxicity (190). Occupational studies have demonstrated that workers with the *CYP2E15B* allele exhibit elevated levels of benzene metabolites in blood, higher chromosomal aberration frequencies, and increased micronucleus formation in bone marrow cells compared with wild-type carriers under equivalent exposure levels (191). Genotyping of *CYP2E1* polymorphisms can be performed using polymerase chain reaction-restriction fragment length polymorphism, enabling identification of at-risk individuals for targeted preventive interventions (192).

Beyond *CYP2E1*, *CYP1A1* and *CYP1B1* also contribute to benzene metabolism. Polymorphic variants such as *CYP1A12A* and *2B* enhance benzene bioactivation (193). For instance, carriers of *CYP1A12A* have been shown to display notably higher urinary hydroquinone-to-phenol ratios, suggesting more efficient conversion to toxic intermediates (194). A 2023 cohort study of 523 benzene-exposed workers in southern China revealed that individuals harboring both *CYP2E15B* and *CYP1A12A* mutations had a 2.3-fold higher frequency of micronucleated blood cells compared with wild-type individuals (95% CI: 1.8-2.9), particularly at exposure levels >10 mg/m^3 (195). These findings highlight the importance of polygenic interactions in determining susceptibility to benzene toxicity (196). Furthermore, marked ethnicity disparities exist in the distribution of *CYP2E1* polymorphisms. For example, the frequency of the vulnerable CYP2E1*5B variant is notably higher in East Asian populations (20-30%) compared with Caucasian populations (2-5%) (189).

GST. The GST family mediates detoxification of benzene metabolites (197). Among them, the null genotypes of *GSTM1* and *GSTT1* are the most studied (198-200). *GSTM1* catalyzes conjugation of glutathione with reactive metabolites such as benzoquinone; individuals with the *GSTM1* null genotype lack enzymatic activity and have impaired detoxification capacity (201,202). A meta-analysis of 12 case-control studies (1,892 cases and 3,247 controls) reported that *GSTM1* deletion increased the risk of benzene-induced leukemia by 1.62-fold (OR=1.62, 95% CI: 1.35-1.94) (203,204).

Table III. Genetic polymorphisms in metabolic and DNA repair enzymes associated with susceptibility to benzene toxicity.

Gene category	Gene symbol	Function	Key polymorphism	Functional consequence	Associated risk (odds ratio/findings)	(Refs.)
Bioactivation (Phase I)	*CYP2E1*	Oxidative metabolism	*CYP2E1*5B*	Increased enzyme activity (rapid metabolizer)	Elevated micronucleus frequency and chromosomal aberrations.	(188-191)
	CYP1A1	Oxidative metabolism	*CYP1A1*2A*	Enhanced bioactivation	Higher urinary hydroquinone/phenol ratio.	(192-194)
Detoxification (Phase II)	*GSTM1*	GSH conjugation	Null genotype (Deletion)	Loss of function (impaired detoxification)	1.62-fold increased leukemia risk; 18.7% higher SPMA levels.	(201-204)
	GSTT1	GSH conjugation	Null genotype (Deletion)	Loss of function	Combined *GSTM1*/*GSTT1* null: 2.17-fold increased leukemia risk.	(197-205)
	NQO1	Quinone reduction	*NQO1*2* (C609T)	Null activity	2.03-fold increased leukemia risk; 37.2% increase in DNA adducts.	(206-208)
DNA repair	*XRCC1*	BER (base excision)	Arg399Gln	Reduced repair capacity	1.45-fold risk of hematotoxicity; increased micronuclei.	(211-213)
	XPD (*ERCC2*)	NER (nucleotide excision)	Lys751Gln	Reduced helicase activity	Notable association with chromosomal aberrations.	(214-216)
	p53	Cell cycle control	Arg72Pro	Altered apoptosis	23.6% reduction in apoptotic clearance of damaged cells.	(217- 220)

BER, base excision repair; NER, nucleotide excision repair; GSH, glutathione; CYP2E1, cytochrome P450 2E1; CYP1A1, cytochrome P450 family 1 subfamily a member 1; NQO1, NAD(P)H quinone oxidoreductase 1; GSTM1, glutathione S-transferase Mu 1; GSTT1, glutathione S-transferase theta 1; XRCC1, X-ray repair cross-complementing protein 1.

The combined effect of GSTT1 and GSTM1 double deletions further elevated risk to 2.17-fold (OR=2.17, 95% CI: 1.76-2.67) (205).

Quinone Reductase 1 (NQO1). NQO1 catalyzes the detoxification of benzoquinone by reducing it to hydroquinone (206). The *NQO1*2 (C609T) polymorphism abolishes enzyme activity, and homozygous carriers accumulate 2.5-fold higher benzoquinone levels compared with wild-type individuals (207). A prospective cohort study (5-year follow-up, n=836) demonstrated that workers with the *NQO1*2/2* genotype had markedly elevated DNA adduct levels (+37.2%) and a higher incidence of leukemia (hazard ratio=2.03, 95% CI: 1.12-3.68) (208). The combined presence of *NQO1*2 and *GSTM1* deletion further increased the risk of DNA damage by 3.1-fold, indicating that multi-gene testing may improve accuracy in identifying susceptible populations (209). Similar to other metabolic enzymes, the prevalence of the NQO1*2 variant exhibits notable ethnicity variation, with the mutant allele frequency reaching 30-40% in Asian cohorts compared with ~15% in Caucasian cohorts (208).

XRCC1 gene. The *XRCC1* gene encodes a DNA repair protein involved in single-strand break repair (210). Its Arg399Gln polymorphism (rs25487) reduces repair efficiency (211). Carriers of the Gln allele have been reported to exhibit a 29.4% higher micronucleus frequency following benzene exposure compared with Arg homozygotes (212). A 2021 meta-analysis of six studies confirmed that *XRCC1* Arg399Gln is associated with an elevated risk of benzene-induced hematotoxicity (OR=1.45, 95% CI: 1.18-1.78), particularly in populations with cumulative benzene exposure >100 mg·year/m^3 (213).

XPD (ERCC2) gene. *XPD* encodes a helicase essential for nucleotide excision repair (214). The Lys751Gln polymorphism (rs13181) reduces enzymatic activity, leading to compromised DNA repair capacity. Benzene-exposed individuals carrying the Gln allele show markedly higher chromosomal aberration rates, with a positive association to exposure levels (215). A study of 112 patients with benzene-induced leukemia found a notably higher prevalence of the Gln/Gln genotype (38.4%) compared with healthy controls (21.5%), suggesting that XPD Lys751Gln is a potential risk marker for benzene-related leukemia (216).

ATM and p53 genes. The *ATM* gene plays a crucial role in DNA double-strand break repair (217). Its rs189037 polymorphism has been linked to increased chromosomal instability in benzene-exposed populations (218). Similarly, the codon 72 polymorphism (Arg72Pro) of the p53 gene affects cell cycle regulation (219). In benzene-exposed individuals carrying the

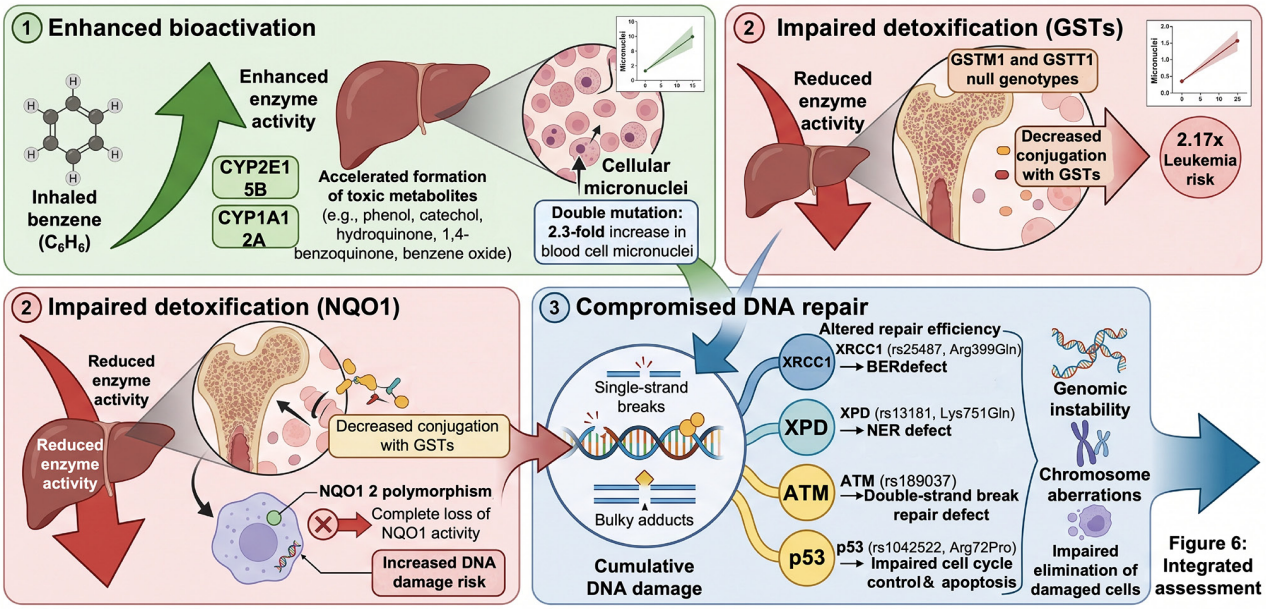

Figure 5. Genetic susceptibility network and multi-gene interactions in benzene-induced toxicity. The individual vulnerability to benzene toxicity is co-amplified by genetic polymorphisms across three critical metabolic and repair pathways: (1) Enhanced bioactivation: Polymorphisms in cytochrome P450 enzymes (CYP2E1*5B, CYP1A1*2A) increase enzymatic activity, accelerating the hepatic formation of reactive metabolites and significantly increasing micronuclei frequencies in blood cells. (2) Impaired detoxification: Null genotypes in glutathione S-transferases (*GSTM1*, *GSTT1*) and polymorphisms in quinone reductase 1 (NQO1*2) compromise the clearance of toxic intermediates, with combined *GSTM1*/*GSTT*1 deletions synergistically elevating the risk of benzene-related leukemia by 2.17-fold. (3) Compromised DNA repair: Variants in DNA repair and cell cycle control genes (*XRCC1* Arg399Gln, *XPD* Lys751Gln, ATM rs189037 and *p53* Arg72Pro) impair single/double-strand break repair and disrupt the apoptosis of damaged cells. Together, these genetic variations drive cumulative DNA damage, genomic instability, and chromosomal aberrations, emphasizing the necessity of integrating multi-gene profiling into comprehensive risk assessments. GSTs, glutathione S-transferases; CYP2E1, cytochrome P450 2E1; CYP1A1, cytochrome P450 family 1 subfamily A member 1; NQO1, NAD(P)H quinone oxidoreductase 1; GSTM1, glutathione S-transferase mu 1; GSTT1, glutathione S-transferase theta 1; XRCC1, X-ray repair cross-complementing protein 1.

Pro allele, lymphocyte apoptosis rates are reduced by 23.6%, indicating impaired clearance of damaged cells (220).

Combinatorial assessment of these genetic polymorphisms allows the construction of susceptibility scoring models for benzene toxicity, offering a more comprehensive tool for individualized risk evaluation and occupational health management (221). To systematically illustrate this, Table III details the specific functional consequences and quantitative risks-such as elevated odds ratios for leukemia and hematotoxicity-associated with key polymorphisms across bioactivation, detoxification, and DNA repair pathways, which directly correspond to the integrated susceptibility network mapped in Fig. 5.

Ethnicity disparities and regulatory implications. As detailed in the preceding subsections, ethnic differences in gene frequency play a pivotal role in population-specific susceptibility, with Asian populations often exhibiting higher frequencies of vulnerable genotypes (GSTM1 null, CYP2E1*5B and NQO1*2) (201-203). These distinct genetic landscapes raise a critical regulatory question regarding Occupational Exposure Limits (OELs) (203). Currently, OELs vary markedly across regions, such as China's PC-TWA of 6 mg/m^3 vs. the US ACGIH TLV of 0.5 ppm. Given these genetic disparities, relying on a universal or less stringent OEL may leave substantial proportions of the workforce inadequately protected (204). Consequently, future standard-setting bodies must factor in ethnic genetic susceptibility, potentially moving toward region-specific or genetically tailored occupational exposure thresholds (205).

Emerging and comprehensive biomarkers. With advances in analytical technologies, exhaled breath metabolomics and multi-biomarker integration strategies have emerged as novel approaches for benzene exposure assessment (222). These methods overcome the limitations of single biomarkers and improve both monitoring accuracy and early warning efficiency (223).

Exhaled breath metabolomics: A promising non-invasive tool. Exhaled breath metabolomics is a newly developed non-invasive technique characterized by convenient sample collection, real-time monitoring and suitability for longitudinal surveillance. It employs high-resolution analytical platforms-such GC-MS, LC-MS and proton transfer reaction (PTR)-MS, to profile small-molecule metabolites (typically <1,000 Da) in exhaled air, and links them to physiological or pathological states (224).

Animal studies have identified two metabolite classes negatively associated with peripheral WBC decline: ω-carboxylic fatty acids (such as valeric acid-ω-carboxylic acid, $C_5H_{10}O_3$; hexanoic acid-ω-carboxylic acid, $C_6H_{12}O_3$) and glutamic acid. Elevated ω-carboxylic fatty acids, intermediates of β-oxidation, may indicate disrupted energy metabolism in the bone marrow hematopoietic microenvironment (225). Conversely, reduced glutamic acid levels may reflect impaired immune cell production or function, showing causal links with WBC reduction (226).

These findings suggest exhaled breath metabolites as promising non-invasive markers of hematopoietic impairment. Portable devices enable real-time, bedside analysis, making this approach particularly valuable for long-term surveillance of

exposed workers or patients undergoing chemotherapy (227). Preliminary cohort data from benzene-exposed workers show correlation coefficients (r=-0.62 to -0.71) between exhaled $C_5H_{10}O_3$/$C_6H_{12}O_3$ and WBC counts, consistent with animal results (r=-0.58 to -0.67), thereby confirming translational potential (228-230).

Multi-biomarker integration: Overcoming the limitations of single indicators. Single biomarkers often fail to capture low-dose pollutant exposure-effect relationships due to limited specificity, interference and narrow coverage (231). By contrast, the multi-marker integration strategy achieves a comprehensive evaluation of exposure intensity and accumulated damage by combining multiple biomarkers across temporal and mechanistic dimensions (230-232). This approach has been validated in low-dose exposure scenarios involving benzene, formaldehyde, and polycyclic aromatic hydrocarbons (PAHs) (231).

The strategy of 'interference correction + effect complementation' improves exposure assessment accuracy, therefore, improving low-dose exposure assessment (232). For instance, tt-MA, a specific benzene metabolite, can be confounded by smoking and dietary factors, as urinary tt-MA levels in smokers are ~4-fold higher than in non-smokers (233). A study on benzene-exposed workers proposed a composite detection protocol integrating tt-MA, PAH-DNA adducts (PLG) and peripheral blood micronucleus frequency: i) tt-MA, reflects short-term exposure (1-3 days); interference corrected via smoking questionnaires (234); ii) PLG, indicates medium-term cumulative exposure (half-life 1-3 months), unaffected by smoking (235); and iii) micronucleus frequency, reflects chromosomal damage, establishing a causal link between exposure and genotoxicity (236). This combined approach achieved 89% accuracy in identifying low-dose benzene exposure (8 h TWA <0.5 mg/m^3), compared with 62% using tt-MA alone (237).

Multi-marker integration can be structured along exposure timelines, forming a chain of 'acute response-cumulative damage', therefore, allowing dynamic monitoring. Acute phase (hours to days): Short half-life metabolic biomarkers (such as tt-MA and SPMA) allow rapid detection (238). For example, in the 2024 styrene storage tank leakage incident, urinary SPMA screening within 6 h identified three overexposed workers, preventing acute poisoning (239). Cumulative phase (months to years): Long half-life biomarkers (hemoglobin adducts, DNA adducts) and epigenetic markers (*STAT3* methylation) are employed (240). Workers with >5 years of benzene exposure showed a *STAT3* methylation positivity rate of 68 vs. 21% in those exposed <1 year, with methylation levels negatively associated with WBC count (241).

Clinical applications are increasingly adopting a combined panel of acute, cumulative, and epigenetic biomarkers in annual occupational health surveillance. Tracking biomarker trajectories over 3 years enables prediction of hematopoietic impairment 1-2 years in advance, extending the early warning window beyond traditional hematological testing (242).

4. Integration of biomarkers into precision occupational health surveillance

Taken together, exhaled breath metabolomics and multi-biomarker integration strategies represent two complementary directions at the frontier of benzene exposure monitoring (243). Exhaled breath metabolomics, with its advantages of non-invasiveness, convenience and real-time assessment, provides novel insights into dynamic changes in hematopoietic function and holds translational promise for large-scale occupational surveillance (244). Multi-marker integration, by combining exposure biomarkers, effect biomarkers and epigenetic signatures, overcomes the inherent limitations of single indicators and enables a more comprehensive evaluation of both short-term exposure and long-term cumulative effects (245).

To actualize this paradigm shift, AI and machine learning (ML) algorithms are increasingly being employed to decode complex multi-omics datasets. Advanced ML models, such as Random Forest and Support Vector Machines, excel at identifying non-linear patterns within high-dimensional metabolomic and genomic data (246). By feeding simultaneous variables-such as exhaled ω-carboxylic fatty acids, genetic polymorphisms (*GSTM1* null) and traditional metabolites (SPMA)-into these AI algorithms, researchers can construct robust predictive models (247). These AI-driven frameworks not only enhance the accuracy of detecting low-dose exposures but also automatically stratify workers into personalized risk tiers, alerting occupational physicians to sub-clinical hematotoxicity before irreversible bone marrow failure occurs (248).

Looking ahead, these approaches are expected to converge into integrated monitoring frameworks that leverage high-throughput omics platforms and AI-driven data analytics (246). Such frameworks may facilitate the construction of individualized biomarker panels that are predictive of early hematotoxicity and long-term carcinogenic risks (247). To operationalize the dynamic monitoring paradigm illustrated in Fig. 6, we propose a hierarchical strategy for integrated benzene health surveillance (Table IV). This approach stratifies occupational monitoring into four actionable clinical tiers, ranging from acute exposure screening (Tier 1) to lifetime susceptibility profiling (Tier 4). However, despite the promise of exhaled breath metabolomics (Tier 2) and epigenetic profiling (Tier 3), their routine implementation in large-scale occupational surveillance faces notable clinical and logistical hurdles (246,247). Cost-effectiveness remains a primary barrier, as high-resolution LC-MS/MS or epigenetic sequencing is substantially more expensive than traditional complete blood counts. Furthermore, deploying portable analytical devices, such as PTR-MS, in resource-limited factory settings presents standardization challenges. The stability of breath metabolites can be severely compromised by field conditions, including high ambient humidity and fluctuating factory temperatures. Therefore, optimizing sample collection protocols and developing robust point-of-care devices are prerequisite steps before these advanced tiers can be broadly integrated into occupational health guidelines (248).

5. Conclusion and future perspectives

Benzene remains a pervasive occupational hazard, inducing profound multi-systemic toxicity that extends far beyond classic hematopoiesis to encompass neurotoxic, cardiovascular and reproductive impairments. Despite decades of research,

Table IV. Proposed hierarchical strategy for integrated benzene health surveillance: From exposure to early effect.

Monitoring tier	Objective	Recommended biomarker panel	Time window	Clinical utility
Tier 1: Exposure screening	Rapid identification of recent exposure & 'body burden'	Urinary SPMA + breath benzene	Hours to days (acute)	Gold standard for low-dose compliance; differentiates occupational vs. background exposure.
Tier 2: Early effect (sub-clinical)	Detect early biological perturbations before disease onset	Exhaled breath metabolomics (fatty acids) + micronuclei (CBMN)	Weeks to months	Non-invasive warning of hematopoietic microenvironment stress and genotoxicity.
Tier 3: Cumulative risk	Assess long-term damage and cancer risk	Hemoglobin/DNA adducts + epigenetic markers (*STAT3* methylation)	Months to years (chronic)	Reflects historical burden; predicts long-term hematological malignancy risk.
Tier 4: Susceptibility profiling	Identify high-risk individuals for personalized protection	Genotyping panel (*CYP2E1*, *GSTM1*, *NQO1*, *XRCC1*)	Lifetime (static)	Personalized risk stratification; guides job placement and protective equipment standards.

CYP2E1, cytochrome P450 2E1; CYP1A1, cytochrome P450 family 1 subfamily A member 1; NQO1, NAD(P)H quinone oxidoreductase 1; GSTM1, glutathione S-transferase Mu 1; GSTT1, glutathione S-transferase theta 1; XRCC1, x-ray repair cross-complementing protein 1.

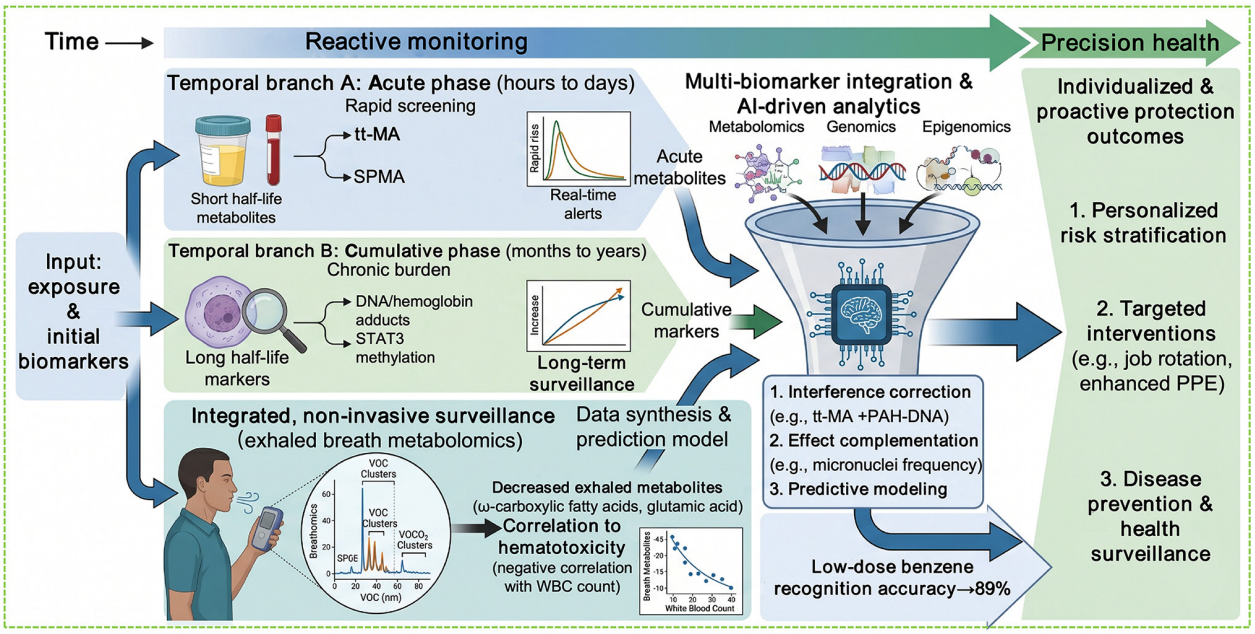

Figure 6. Integrated and dynamic monitoring framework for precision occupational health in benzene exposure. The framework illustrates the paradigm shift from traditional reactive monitoring to proactive precision health. The system synthesizes multi-dimensional data across two temporal branches: Temporal Branch A focuses on acute phase screening (hours to days) using short half-life metabolites such as tt-MA and SPMA for real-time alerts; Temporal Branch B targets cumulative burden (months to years) utilizing long half-life markers such as DNA/hemoglobin adducts and epigenetic alterations (STAT3 methylation). Concurrently, exhaled breath metabolomics (ω-carboxylic fatty acids) provides an integrated, non-invasive surveillance tool directly associated with hematotoxicity. Through an AI-driven analytics funnel, these diverse multi-omics data (metabolomics, genomics, epigenomics) are integrated to perform interference correction and effect complementation. This data synthesis significantly improves the recognition accuracy of low-dose benzene exposure (up to 89%) and enables predictive modeling, ultimately facilitating individualized risk stratification, targeted interventions, and enhanced disease prevention. Tt-MA, trans, trans-muconic acid; SPMA, S-phenylmercapturic acid.

traditional reactive monitoring strategies, heavily reliant on late-stage hematological indices and low-specificity markers such as urinary phenol, are inadequate for chronic low-dose exposure scenarios (245-248).

The present review underscores a necessary paradigm shift. The integration of high-specificity exposure markers (SPMA), advanced effect markers (exhaled breath metabolomics) and susceptibility profiling (*GSTM1*/*CYP2E1* polymorphisms)

provides a robust foundation for early warning systems. Notably, the pronounced ethnicity disparities in genetic susceptibility dictate that a 'one-size-fits-all' regulatory approach is no longer tenable; future OELs must be re-evaluated through the lens of population-specific genetic vulnerability. Moving forward, bridging the gap between molecular insights and occupational health applications requires overcoming logistical barriers-such as the cost and field-stability of multi-omics tools-and harnessing AI-driven analytics to manage complex biomarker datasets. By transitioning to proactive, individualized and multi-dimensional biomarker frameworks, occupational health authorities can achieve precision risk stratification, ultimately mitigating the global burden of benzene-induced malignancies and systemic diseases.

Acknowledgements

The authors would like to acknowledge Professor Dr Li Sheng and Mr. Li Wang from Chongqing Medical and Pharmaceutical College (Chongqing, China) for their invaluable contributions to the data collection process; their meticulous efforts ensured the accuracy and reliability of the research findings.

Funding

The authors declare that financial support was received for the research, authorship and publication of this article. The present work was funded by the Scientific Research Project of AnShun University, Guizhou Province [grant nos. asxybsjj (202307) and asxykypt (202402)], the Natural Science Research Project of Guizhou Provincial Department of Education (grant no. Qian Jiao He KY [2020] No. 063), the Guizhou Provincial Department of Education (grant no. Qian Ke He KY [2013] No. 130), the Guizhou Provincial Department of Science and Technology (grant no. Qian Ke He LH [2015] No. 7687), the 2023 Chongqing Medical Scientific Research Project (Joint Project of Chongqing Health Commission and Science and Technology Bureau) (grant no. 2023GGXM006), the Joint Project of Chongqing Health Commission and Science and Technology Bureau (Joint Key Laboratory Open Project) (grant no. 2026KFXM051), the Chongqing Municipal Education Commission Youth Project (grant nos. KJQN202402821 and KJQN202502819), the Natural Science Foundation of Chongqing (grant no. CSTB2025NSCO-GPX1116), the 2026 Key Project of Special Scientific Research of First Affiliated Hospital of Chongqing Medical and Pharmaceutical College (grant no. YGZZKFS2026104) and The Key Laboratory Project of Chongqing Medical and Pharmaceutical College (grant no. YGZPT2025101).

Availability of data and materials

Not applicable.

Authors' contributions

YH, ZX, JM and XL contributed to the writing of the original draft and the preparation of figures. YH contributed to the systematic literature search, data extraction, and synthesis of the reviewed studies. JM and XL reviewed and edited the manuscript, and provided supervision. All authors read and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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