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Environmental and Occupational Exposures, Organ Toxicity and Biomarkers

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Abstract

Environmental and occupational pollutants represent a persistent threat to global public health, contributing substantially to the global burden of non-communicable diseases. These diverse agents—including heavy metals, particulate matter, and emerging contaminants—frequently converge on a core set of toxic mechanisms, most notably oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, and dysregulated autophagy. The resulting multi-organ toxicity, affecting the pulmonary, nervous, hepatic, and renal systems, underscores the need for early and reliable detection of biological effects. This review synthesizes current knowledge on typical environmental and occupational toxicants, their mechanisms of action across different organ systems, and the evolving landscape of early effect biomarkers. We critically evaluate exposure assessment methodologies and key epidemiological evidence, including dose-response relationships. Finally, we discuss prevention strategies, current research challenges, and future directions, emphasizing the potential of high-throughput detection and multi-omics approaches to transform exposure surveillance and targeted intervention.

Keywords

Environmental Pollutants, Occupational Dust, Organ Toxicity, Biomarkers, Oxidative Stress, Inflammation

1. Introduction

Environmental and occupational pollutants remain a major global health threat, accounting for an estimated nine million premature deaths annually—one in six of all deaths worldwide [1] [2]. These exposures, which include ambient and indoor air pollution, toxic chemicals, heavy metals, and occupational dusts, contribute substantially to the global burden of non-communicable diseases (NCDs) [3]

[4]. Importantly, pollution is no longer a local issue but a planetary threat that requires urgent, coordinated action [2].

Despite the structural diversity of these toxicants, they often converge on a limited set of shared pathogenic mechanisms. Oxidative stress, triggered by an overproduction of reactive oxygen species, is a central event [3] [5]. This is followed by activation of pro-inflammatory cascades, mitochondrial dysfunction, and the induction of programmed cell death pathways such as apoptosis and autophagy [4] [6]. Epigenetic alterations further mediate the long-term consequences of early-life exposures, linking developmental insults to adult disease [7]. Understanding these common pathways is essential for identifying early biological effects before overt organ damage occurs.

Biomarkers of early toxic effects have gained significant attention. They offer a window of opportunity for intervention, allowing detection of subclinical injury in the lung, liver, kidney, or nervous system [8] [9]. The exposome paradigm—encompassing the totality of lifelong environmental exposures—provides a powerful framework for integrating biomarker data with internal biological responses [8] [9]. However, challenges remain in assessing complex chemical mixtures and translating mechanistic findings from in vitro models to human populations [5] [10].

The review is to summarise current research on typical environmental and occupational pollutants, their multi-organ toxicity and underlying mechanisms, and the emerging landscape of early effect biomarkers. We also critically evaluate exposure assessment approaches and epidemiological evidence, and discuss prevention strategies and future research directions, with an emphasis on high-throughput and multi-omics technologies.

2. Typical Environmental and Occupational Pollutants

Environmental and occupational pollutants encompass a diverse array of chemical and physical agents that share the ability to induce adverse health effects in exposed populations. Based on their sources, physicochemical properties, and exposure pathways, these toxicants can be conveniently categorized into four major groups: heavy metals and persistent organic pollutants (POPs), particulate matter and occupational dust, emerging environmental contaminants, and food-related contaminants. **Table 1** provides a comparative overview of these categories.

2.1. Heavy Metals and Persistent Organic Pollutants

Heavy metals such as lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As) are naturally occurring elements with high atomic weights and densities at least five times that of water [11]. Their widespread industrial, agricultural, and domestic applications have led to significant environmental dissemination, raising serious public health concerns [11] [12]. These metals are considered systemic toxicants that induce multi-organ damage even at low exposure levels and are classified as known or probable human carcinogens by the US EPA and IARC [11].

Table 1. Typical environmental and occupational pollutants.

Category	Key Agents	Major Sources	Primary Health Concerns
Heavy Metals & POPs	Pb, Cd, Hg, As; PCBs, PBDEs, OCPs	Industrial emissions, mining, e-waste, agricultural use	Neurotoxicity, nephrotoxicity, carcinogenicity, endocrine disruption
Particulate Matter & Occupational Dust	$PM_{2.5}$, PM_{10}; coal dust, silica, asbestos	Combustion processes, traffic, construction, mining	Pulmonary fibrosis, copd, lung cancer, cardiovascular effects
Emerging Contaminants	Microplastics, PFAS, pharmaceuticals, nanomaterials	Consumer products, wastewater, industrial effluents	Immunotoxicity, hepatotoxicity, reproductive effects (emerging evidence)
Food-Related Contaminants	Aflatoxins, acrylamide, pesticide residues, heavy metals	Contaminated crops, processed foods, food packaging	Hepatocellular carcinoma, neurotoxicity, endocrine disruption

Lead remains particularly hazardous to children due to high gastrointestinal uptake and a permeable blood-brain barrier, with neurotoxic effects observed at lower levels than previously recognized [12]. Cadmium, primarily from nickel-cadmium batteries and cigarette smoke, causes kidney damage and bone effects, while mercury exposure via fish consumption poses risks to fetal neurological development [12]-[14]. The primary mechanisms involve oxidative stress, enzyme inactivation, and interference with DNA repair [13] [15].

Persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and organochlorine pesticides (OCPs), share the characteristics of environmental persistence, bioaccumulation, and long-range transport [16]. Many POPs act as endocrine-disrupting chemicals (EDCs), interfering with hormone synthesis, metabolism, and signaling [17]. Epidemiological evidence has linked POP exposure to endometriosis, reproductive disorders, neurodevelopmental deficits, and metabolic diseases [18] [19].

2.2. Particulate Matter and Occupational Dust

Particulate matter (PM), particularly fine ($PM_{2.5}$) and inhalable (PM_{10}) fractions, is a complex mixture of sulfates, nitrates, organic carbon, metals, and biological materials [20]. The Global Exposure Mortality Model (GEMM) estimates that ambient air pollution causes 8.8 million excess deaths annually, with a loss of life expectancy of 2.9 years—exceeding that of tobacco smoking [21]. The WHO Global Air Quality Guidelines (2021) have substantially lowered recommended exposure limits based on growing evidence of adverse effects at very low concentrations [22]. $PM_{2.5}$ penetrates deep into lung alveoli, enters the bloodstream, and triggers oxidative stress and pulmonary inflammation, contributing to cardiorespiratory diseases, lung

cancer, and adverse birth outcomes [20] [23]. A joint ERS/ATS policy statement provides an analytical framework for interpreting the adversity of air pollution effects across multiple organ systems, including the cardiovascular and central nervous systems [20].

Occupational dusts—coal mine dust, crystalline silica, asbestos, and wood dust—remain major causes of preventable lung diseases in industrial settings. These particles induce chronic inflammation, fibrosis (pneumoconiosis), and malignant transformation, with clear exposure-response relationships documented in mining, construction, and textile workers [24].

2.3. Emerging Environmental Contaminants

Emerging contaminants are chemicals or materials that have recently been detected in the environment and are not yet routinely monitored, but have known or suspected adverse health effects. Microplastics (plastic particles < 5 mm, including nanoplastics < 1 μm) are ubiquitous in water, air, food, and even human biological samples such as breast milk, urine, and semen [25] [26]. Human exposure occurs via ingestion, inhalation, and dermal contact. Hazard assessment suggests that microplastics can induce oxidative stress, inflammatory lesions, and particle toxicity, with potential chronic inflammation and neoplastic risk [25]. Advanced analytical methods, including pyrolysis-GC-MS, have confirmed microplastic presence in drinking water supplies [27].

Per- and polyfluoroalkyl substances (PFAS, "forever chemicals") comprise over 4000 synthetic compounds widely used for their water- and grease-repellent properties [28]. PFAS accumulate in the ocean, groundwater, and human serum. Epidemiological studies have demonstrated significant associations with dyslipidemia, adverse immune outcomes in children, liver disease, kidney disease, and certain cancers [28] [29]. Exposure occurs via seafood, drinking water, food packaging, and indoor environments, with contaminated sites often located near airports and military bases where aqueous film-forming foams were used [28]. Other emerging contaminants include pharmaceutical residues, engineered nanomaterials, and disinfection by-products, which are increasingly detected through non-targeted screening methods based on high-resolution mass spectrometry [30] [31].

2.4. Food-Related Contaminants

Dietary intake represents a major route of human exposure to many environmental toxicants. Food-related contaminants include naturally occurring toxins (e.g., aflatoxins produced by Aspergillus species), process-induced chemicals (e.g., acrylamide from high-temperature cooking), and environmental pollutants that enter the food chain through contaminated water, soil, or feed (e.g., heavy metals, pesticide residues, POPs) [16]. The FAO/WHO has developed stepwise approaches for dietary exposure assessment, using screening methods followed by more refined estimates when safety concerns cannot be ruled out. Long-term aflatoxin exposure is causally linked to hepatocellular carcinoma, particularly in individuals

with chronic hepatitis B infection [16]. Acrylamide, formed during frying and baking, is classified as a probable human carcinogen. Pesticide residues, even at low levels, raise concerns about endocrine disruption and neurodevelopmental toxicity, especially in children [17] [18]. The Global Environment Monitoring System (GEMS/Food) Consumption Cluster Diets have been recommended as tools for international chronic dietary exposure assessments.

3. Multi-Organ Toxicity and Underlying Mechanisms

The diverse array of environmental and occupational pollutants ultimately converges on a limited set of organ systems, with the lung, brain, liver, and kidney being the most frequently affected targets. The pathological outcomes are determined by both the physicochemical properties of the toxicant and the vulnerability of the target organ. This section synthesizes current knowledge on multi-organ toxicity, highlighting the shared and distinct mechanisms that underpin pollutant-induced injury, with a particular focus on oxidative stress, inflammation, mitochondrial dysfunction, and disrupted cellular quality control pathways. **Table 2** summarizes major environmental/occupational pollutants, target organs, and key toxic mechanisms.

Table 2. Environmental/occupational pollutants, target organs, and key toxic mechanisms.

Pollutant Class	Examples	Primary Target Organ (s)	Key Mechanisms
Particulate Matter ($PM_{2.5}$, PM_{10})	Diesel exhaust, ambient PM	Lung, brain	Mitophagy-ferroptosis, microglial activation, neuroinflammation
Occupational Dusts	Coal dust, crystalline silica	Lung	NLRP3 inflammasome, fibrosis, macrophage activation
Heavy Metals	Cadmium, lead, arsenic, manganese	Kidney, liver, brain	Oxidative stress, mitochondrial dysfunction, ER stress, ATF4-CHOP axis
POPs & EDCs	PCBs, dioxins, PFAS, bisphenol A	Liver, kidney	Nuclear receptor interference, epigenetic changes, transporter inhibition
Emerging Contaminants	Microplastics, pharmaceuticals	Liver, gut	Gut-liver axis disruption, dysbiosis, LPS translocation
Mixed Exposures	Pesticides, solvents	Liver (TAFLD)	Steatosis, steatohepatitis, lipid metabolism dysregulation

3.1. Pulmonary Toxicity

As the primary portal of entry for inhaled pollutants, the lung is a principal target organ for environmental and occupational toxicants. Airborne particulate matter ($PM_{2.5}$ and PM_{10}), diesel exhaust, coal dust, and crystalline silica are well-established inducers of respiratory morbidity and mortality. A workshop report from the American Thoracic Society concluded that long-term exposure to air

pollution, particularly traffic-related metrics such as nitrogen dioxide and black carbon, is causally associated with the onset of childhood asthma [32]. However, the evidence for adult-onset asthma or chronic obstructive pulmonary disease (COPD) remains insufficient, although plausible mechanistic pathways exist [32].

Fine particulate matter ($PM_{2.5}$) induces lung injury through complex molecular cascades. Recent work has uncovered that $PM_{2.5}$ exposure upregulates the m6A methyltransferase METTL3, which stabilises PINK1 mRNA, thereby activating PINK1-dependent mitophagy. Excessive mitophagy, in turn, promotes ferroptosis—an iron-dependent lipid peroxidation-driven cell death—in bronchial epithelial cells, leading to inflammatory infiltration and mucus hypersecretion [33]. This study provides a compelling mechanistic link between epigenetic modification and pollutant-induced ferroptosis.

Occupational dusts remain a major global health burden. Coal workers' pneumoconiosis and silicosis are progressive fibrotic lung diseases resulting from prolonged inhalation of coal and silica particles [34]. The pathogenesis of silicosis involves the uptake of crystalline silica by alveolar macrophages, triggering NLRP3 inflammasome activation, release of pro-inflammatory cytokines (IL-1β, IL-18), and subsequent fibroblast proliferation and extracellular matrix deposition [35]. Despite advances in understanding these molecular events, no curative treatment currently exists, although nanoparticle-based drug delivery systems offer a promising therapeutic avenue [36].

3.2. Neurotoxicity

The central nervous system (CNS) is increasingly recognised as a critical target of air pollution, contributing to both neurodevelopmental and neurodegenerative disorders [37] [38]. Epidemiological studies have linked ambient pollutant exposure to increased incidence of autism spectrum disorders, Alzheimer's disease, and Parkinson's disease [38] [39]. A systematic review by Grandjean and Landrigan identified manganese, fluoride, chlorpyrifos, and other industrial chemicals as developmental neurotoxicants, underscoring the vulnerability of the developing brain [39].

The mechanisms by which pollutants reach the CNS and incite pathology involve systemic inflammation, translocation via the olfactory nerve, and disruption of the blood-brain barrier. Once within the brain parenchyma, pollutants activate microglia—the resident innate immune cells—leading to chronic neuroinflammation and sustained production of reactive oxygen species (ROS) [37]. In animal models, acute exposure to diesel exhaust (250 - 300 μg/m^3 for 6 hours) induces microglial activation, increased lipid peroxidation, and impaired adult neurogenesis in the hippocampus and olfactory bulb, with more pronounced effects in male mice, possibly due to lower expression of the antioxidant enzyme paraoxonase 2 [38].

Manganese-induced Parkinsonism exemplifies metal-specific neurotoxicity. High

manganese exposure triggers oxidative stress, transporter dysfunction, dysregulation of signaling pathways, and impaired autophagy, culminating in dopaminergic neuronal loss and extrapyramidal symptoms resembling idiopathic Parkinson's disease [39]. Chelation therapy with $CaNa_2EDTA$ and natural compounds such as vinpocetine and curcumin has shown promise in preclinical models, though clinical translation remains limited [39].

3.3. Hepatotoxicity and Nephrotoxicity

The liver, as the primary site of xenobiotic metabolism, is highly susceptible to pollutant-induced injury. Toxicant-associated fatty liver disease (TAFLD) has emerged as a distinct entity within the spectrum of non-alcoholic fatty liver disease (NAFLD). A systematic screen of rodent toxicology databases (ToxRefDB and CEBS) identified 123 chemicals associated with fatty liver, including pesticides, solvents, polychlorinated biphenyls (PCBs), and dioxins [38]. Pesticides were the most frequently identified, while PCBs/dioxins exhibited the highest potency [38].

Endocrine-disrupting chemicals (EDCs), such as bisphenol A and phthalates, interfere with nuclear receptor signaling and mitochondrial function, promoting hepatic steatosis through epigenetic mechanisms, including altered DNA methylation and microRNA expression [40]. Microplastics represent an emerging threat. Co-exposure of zebrafish to polystyrene microplastics and the antibiotic oxytetracycline at environmentally realistic concentrations induced significant lipid accumulation, hepatic oxidative stress, and inflammation, accompanied by gut dysbiosis and elevated serum lipopolysaccharide (LPS), suggesting a gut-liver axis-mediated mechanism [41]. Per- and polyfluoroalkyl substances (PFAS, "forever chemicals") accumulate in the liver and kidney, where they interfere with hepatic transporters (e.g., OATP, BSEP), resulting in altered lipid metabolism and elevated serum cholesterol—a finding consistently reported in human epidemiological studies [42].

The kidney—particularly the proximal tubule—is exquisitely vulnerable to metal toxicity due to its high mitochondrial density and role in concentrating filtrate. A meta-analysis of 31 studies (195,015 participants) demonstrated a significant inverse association between cadmium exposure and estimated glomerular filtration rate (eGFR), especially for blood cadmium levels ($\beta = -0.12$) [43]. Cadmium disrupts renal homeostasis by activating the ATF4-CHOP transcriptional axis, inducing ER stress, mitochondrial ROS production, and impaired autophagy/mitophagy, ultimately leading to apoptosis of proximal tubular cells [44]. Mechanistic reviews of arsenic, cadmium, and lead confirm that these metals inhibit electron transport chain complexes, deplete mitochondrial membrane potential, and promote oxidative imbalance in a dose- and metal-dependent manner [45] [46]. The gut-liver axis further modulates hepatic pathology: microbial metabolites and LPS translocate to the liver via the portal vein, aggravating inflammation, fibrosis, and even hepatocarcinogenesis [44] [47].

3.4. Oxidative Stress and Inflammatory Pathways

Oxidative stress is the central unifying mechanism underlying pollutant-induced organ toxicity. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated by tightly regulated enzymes, including NAD(P)H oxidase and nitric oxide synthase; however, excessive ROS production—either from mitochondrial electron transport chain leakage or exogenous pollutant stimulation—overwhelms endogenous antioxidant defences (glutathione, superoxide dismutase, catalase), leading to oxidative damage to lipids, proteins, and DNA [48] [49]. This "two-faced" character of ROS is well established: at low/moderate levels, ROS act as secondary messengers in cell signaling, whereas at high levels they drive pathogenesis across numerous diseases, including cancer, neurodegeneration, and ageing [6].

The transcription factor NF-κB plays a pivotal role in mediating pollutant-induced inflammation. ROS activate NF-κB, which translocates to the nucleus and upregulates pro-inflammatory genes encoding cytokines (TNF-α, IL-1β, IL-6), chemokines, and adhesion molecules [8]. In parallel, the NLRP3 inflammasome is activated by diverse triggers, including mitochondrial dysfunction, lysosomal damage, and ionic flux; its activation leads to caspase-1-mediated cleavage of pro-IL-1β and pro-IL-18, amplifying the inflammatory cascade [50]. Aberrant NLRP3 activation is linked to cryopyrin-associated periodic syndromes, atherosclerosis, diabetes, and Alzheimer's disease [50], all of which have been associated with environmental pollutant exposure.

3.5. Mitochondrial Damage, Apoptosis, and Autophagy

Mitochondria are both sources and primary targets of pollutant-induced oxidative injury. Environmental toxicants—including metals, pesticides, and air pollutants—impair mitochondrial function through multiple mechanisms: inhibition of electron transport chain complexes, depletion of mitochondrial DNA (mtDNA), opening of the permeability transition pore (mPTP), and loss of membrane potential [51] [52]. The concept of "ROS-induced ROS release" (RIRR) describes a regenerative cycle in which initial ROS production triggers mPTP opening, causing further ROS release that can propagate from mitochondrion to mitochondrion, ultimately culminating in cell death [52]. Brief, reversible mPTP openings may serve a physiological housekeeping role by releasing accumulated ROS and Ca^{2+}, whereas sustained openings lead to mitochondrial destruction [52].

When damage is sublethal, autophagy—particularly mitophagy—serves as a quality control mechanism to remove dysfunctional mitochondria. Autophagy is mediated by a complex molecular machinery (Atg proteins and lysosomal hydrolases) that sequesters damaged organelles into autophagosomes for lysosomal degradation [53] [54]. However, chronic pollutant exposure can dysregulate autophagy. For example, $PM_{2.5}$-induced METTL3-mediated mitophagy becomes excessive, driving ferroptosis rather than cytoprotection [33]. Similarly, cadmium inhibits

autophagic flux, leading to accumulation of damaged organelles and exacerbation of apoptosis [55]. The interplay between mitochondrial dysfunction, autophagy, and oxidative stress is particularly relevant to degenerative diseases, where failure of these pathways contributes to progressive tissue injury [53].

4. Early Biomarkers of Toxic Effects

The early detection of biological effects induced by environmental and occupational exposures is critical for preventing progression to overt disease. Biomarkers of effect—measurable indicators of cellular or systemic alterations following exposure—provide a window of opportunity for intervention before irreversible organ damage occurs [56] [57]. These biomarkers span multiple hierarchical levels, from relatively non-specific oxidative stress and inflammatory indices to tissue-specific damage markers and high-resolution molecular signatures (genes, proteins, metabolites). The integration of such biomarkers into human biomonitoring (HBM) frameworks, as exemplified by the European HBM4EU initiative, has demonstrated their utility in detecting early biological changes and identifying vulnerable subpopulations [56].

4.1. Oxidative Stress Biomarkers

Oxidative stress represents the final common pathway for a wide array of environmental toxicants, including heavy metals, particulate matter (PM), and organic pollutants [58] [59]. The overproduction of reactive oxygen species (ROS) and the consequent damage to lipids, proteins, and DNA form the basis for a panel of well-established biomarkers [60] [61].

Commonly measured oxidative stress biomarkers include (**Table 3**):

1) Lipid peroxidation products: Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are the most frequently quantified end-products, detectable in plasma, urine, and exhaled breath condensate [60] [62].

2) Protein oxidation markers: Protein carbonyls and advanced oxidation protein products (AOPP) reflect oxidative modification of amino acid residues [60].

3) DNA oxidation marker: 8-hydroxy-2'-deoxyguanosine (8-OHdG) is a widely used urinary biomarker of oxidative DNA damage, with elevated levels observed following exposure to PM and metals [60] [62].

A systematic review of occupational exposure to nanomaterials found that although no single specific biomarker exists, a panel comprising multiple oxidative stress markers (e.g., MDA, 8-OHdG, and reduced glutathione) appears more feasible for exposure assessment than any single indicator [58]. Recent advances in analytical chemistry, including chemical isotope labeling and mass spectrometry imaging, have significantly improved the sensitivity and specificity of these measurements, enabling detection of subtle exposure-induced changes in human biofluids [60]. The HBM4EU project has successfully implemented urinary MDA and 8-OHdG as effect biomarkers in occupational studies of hexavalent chromium exposure, confirming their ability to detect early biological responses [56].

Table 3. Representative early effect biomarkers of environmental and occupational exposures.

Category	Biomarker	Biological Sample	Main Utility
Oxidative Stress	MDA, 8-OHdG, protein carbonyls	Urine, plasma, exhaled breath condensate	Lipid peroxidation, DNA damage
Inflammatory Cytokines	CRP, IL-6, TNF-α, fibrinogen	Serum/plasma	Systemic inflammation
Lung Injury	CC16, SP-D	Serum	Bronchiolar/alveolar damage
Kidney Injury	KIM-1, NGAL, microalbuminuria	Urine, plasma	Early tubular injury
Apoptosis/ Autophagy	HMGB1 (acetylation, redox isoforms)	Serum	Inflammatory cell death
Epigenetic	BDNF and KISS1 methylation	Whole blood	Neuroendocrine disruption
Metabolomic	Eicosanoids, ceramides, glutathione pathway metabolites	Urine, plasma	Oxidative stress pathways

4.2. Inflammatory Cytokines

Environmental pollutants induce a sterile inflammatory response through activation of pattern recognition receptors (e.g., TLR4, NLRP3) and redox-sensitive transcription factors (notably NF-κB), leading to the release of pro-inflammatory cytokines [63] [64]. C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and fibrinogen are the most extensively studied systemic inflammatory biomarkers in environmental epidemiology [65].

A comprehensive meta-analysis of 38 studies comprising over 210,000 participants demonstrated significant positive associations between short-term exposure to gaseous air pollutants (O_3, NO_2, SO_2) and circulating CRP levels. Specifically, a 10 μg/m^3 increase in O_3, NO_2, and SO_2 was associated with 1.05%, 1.60%, and 10.44% increases in CRP, respectively. Moreover, NO_2 exposure correlated with a 4.85% increase in TNF-α [65]. These findings confirm that even brief elevations in ambient pollutants activate a systemic inflammatory state, providing a mechanistic link to increased cardiovascular risk.

Beyond traditional cytokines, high-mobility group box 1 (HMGB1) has emerged as a key damage-associated molecular pattern (DAMP) molecule that amplifies inflammation via TLR4 signaling. Extracellular HMGB1 exists in multiple redox-dependent isoforms: the disulfide form (cysteines 23 and 45 linked, cysteine 106 reduced) acts as a potent cytokine inducer, while the all-thiol form directs chemotaxis [63] [66] [67]. Elevated serum HMGB1 levels have been documented in malignant mesothelioma patients with asbestos exposure, and specific isoforms (hyper-acetylated and disulfide) are increasingly recognized as sensitive disease biomarkers [67] [68]. The NLRP3 inflammasome, a central mediator of PANoptosis

(concurrent pyroptosis, apoptosis, and necroptosis), is also activated by diverse environmental toxicants, including trichloroethylene and chlorinated phenols, leading to robust IL-1β and IL-18 release [64] [69] [70].

4.3. Tissue-Specific Damage Markers

While oxidative stress and inflammation reflect global responses, tissue-specific biomarkers offer the advantage of localizing injury to a particular organ, thereby increasing diagnostic precision.

1) Lung: Club cell secretory protein (CC16) is a sensitive indicator of bronchiolar epithelial integrity, and its decline in serum correlates with air pollution-induced lung barrier disruption. Surfactant protein D (SP-D) reflects alveolar damage [56]. These markers have been successfully implemented in the HBM4EU occupational studies.

2) Kidney: Traditional metrics (serum creatinine, blood urea nitrogen) are late and non-specific indicators of acute kidney injury (AKI). Next-generation biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and microalbuminuria, enable earlier detection of proximal tubular injury, often within hours of toxicant exposure [61] [71]. The Predictive Safety Testing Consortium (PSTC) has validated KIM-1 and NGAL as safety biomarkers for regulatory decision-making, significantly improving the preclinical detection of nephrotoxic potential [61].

3) Liver: Although not covered in detail in the provided references, established liver injury markers such as alanine aminotransferase (ALT) and more novel apoptosis markers (e.g., cytokeratin-18 fragments) are commonly used in environmental hepatotoxicity studies.

4.4. Molecular Biomarkers (Genes, Proteins, Metabolites)

The advent of high-throughput omics technologies has revolutionized biomarker discovery, allowing simultaneous assessment of hundreds to thousands of molecular features. These approaches are central to the exposome paradigm, which seeks to comprehensively characterize the totality of environmental exposures and their biological consequences [57] [72] [73].

1) Epigenetic biomarkers: DNA methylation at specific loci can serve as an integrator of past exposures and a predictor of future disease risk. In the HBM4EU project, the methylation status of the BDNF (brain-derived neurotrophic factor) and KISS1 (kisspeptin) genes was evaluated as molecular markers of neurological and reproductive health, respectively [56]. A classic example is the demonstration that infant bisphenol A (BPA) exposure was longitudinally associated with adolescent behavioral dysfunction, a relationship mediated by altered BDNF methylation [56]. More broadly, environmental chemicals, including metals, air pollutants, and persistent organic pollutants, have been shown to induce aberrant DNA methylation, histone modifications, and microRNA expression, which may persist across generations [74] [75].

2) Transcriptomic and proteomic biomarkers: Although less routinely applied in surveillance programs, transcriptomic signatures (e.g., altered expression of oxidative stress and inflammatory genes) and proteomic panels are increasingly used in mechanistic studies. The HELIX (Human Early-Life Exposome) project has combined multi-omic profiling (transcriptome, proteome, epigenome, metabolome) with detailed exposure assessment in mother-child cohorts to identify molecular pathways linking environmental exposures to child health outcomes [57].

3) Metabolomic biomarkers: Untargeted metabolomics provides a global readout of metabolic perturbations induced by pollutant exposure. A systematic review of PM exposure and multi-omics signatures reported consistent alterations in pro-oxidant metabolites (e.g., eicosanoids, ceramides) and disruption of antioxidant pathways (e.g., glutathione, vitamins C and E metabolism), alongside changes in energy metabolism and fatty acid oxidation [61]. The HBM4EU occupational studies have successfully incorporated untargeted urinary metabolomics to detect biological changes in response to Cr (VI) exposure [56].

4) Novel cell death-related biomarkers: Recent research has identified biomarkers associated with non-apoptotic regulated cell death pathways, particularly ferroptosis and PANoptosis. Ferroptosis, an iron-dependent lipid peroxidation process, is implicated in cadmium and other heavy metal toxicities, and markers such as lipid hydroperoxides, altered glutathione peroxidase 4 (GPX4) activity, and malondialdehyde accumulation are being explored as exposure-specific effect markers [76]-[80]. Similarly, PANoptosis (integration of pyroptosis, apoptosis, and necroptosis) can be monitored through detection of cleaved gasdermin D, caspase-8, and mixed lineage kinase domain-like protein (MLKL) [64] [69]. Although these markers are currently confined to mechanistic studies, they hold promise for future translation into population-based biomonitoring.

A tiered approach to effect biomarker implementation is recommended: i) first-line markers of oxidative stress and inflammation for routine surveillance; ii) tissue-specific markers when organ injury is suspected; and iii) high-dimensional omics signatures for hypothesis-generating exposomic research. The ongoing validation of these biomarkers within large-scale HBM frameworks (e.g., HBM4EU, HELIX) will continue to refine their application in environmental and occupational health practice [56] [57].

5. Exposure Assessment and Epidemiological Evidence

Accurate characterization of both external and internal exposures is foundational to understanding the health effects of environmental and occupational pollutants. This section synthesizes current approaches to exposure assessment, synthesizes key population-based epidemiological evidence, and examines the characterization of dose-response relationships.

5.1. Environmental and Occupational Exposure Assessment

Traditional exposure assessment has relied on environmental monitoring (ambient

air, water, soil) and biological monitoring (blood, urine, hair, nails) of specific pollutants. However, these methods often capture only a fraction of the total exposure burden. The exposome paradigm—conceptualized as the totality of environmental exposures from conception to death—offers a more holistic framework [81]. Recent advances in high-resolution mass spectrometry and non-targeted analysis have enabled the simultaneous detection of hundreds of chemicals, including emerging contaminants such as per- and polyfluoroalkyl substances (PFAS), microplastics, and halogenated by-products [82]. For occupational settings, the assessment of engineered nanomaterials remains challenging; effect biomarkers measured in exhaled breath condensate or urine are increasingly used to monitor subclinical physiological changes in exposed workers [83]. Integrating wearable sensors with multi-omics platforms is now expanding the capacity to capture personal exposure dynamics in real time [82]. Despite these advances, critical gaps persist in low- and middle-income countries, where conventional monitoring infrastructure is often lacking [81].

5.2. Population-Based Epidemiological Studies

Long-term cohort studies have provided the most robust evidence linking air pollution exposure to mortality and morbidity. Over 25 years of follow-up of diverse cohorts—including the Harvard Six Cities study, the American Cancer Society Cancer Prevention Study II, and more recent administrative cohorts—has consistently demonstrated that long-term exposure to fine particulate matter ($PM_{2.5}$) increases the risk of all-cause, cardiopulmonary, and lung cancer mortality [84]. Meta-analyses of these studies have substantially strengthened causal inferences [84] [85]. Short-term panel studies further show that daily variations in $PM_{2.5}$ and ozone are associated with increased hospital admissions for respiratory and cardiovascular diseases, with effects observed even at concentrations below current regulatory standards [85]. The 2022 Lancet Countdown report extends this evidence by documenting that climate change-induced heatwaves and wildfires are amplifying the health burden of air pollution, particularly among vulnerable populations such as older adults and young children [86]. Meanwhile, the integration of intersectionality frameworks into exposome research has begun to reveal how racial and socioeconomic factors modify exposure-effect relationships, as illustrated by work on uterine fibroids in Black women [81].

5.3. Dose-Response Relationships

A key finding from epidemiological studies is the absence of an identifiable safe threshold for several pollutants. For $PM_{2.5}$, concentration-response functions are steeper at lower concentrations, implying that public health benefits accrue from reducing even already-low levels of exposure [84] [85]. Benchmark dose modeling has largely replaced the traditional no-observed-adverse-effect level (NOAEL) approach in environmental risk assessment, as it makes fuller use of the dose-response curve [85]. However, characterizing dose-response relationships for complex

mixtures—such as occupational dusts containing multiple metals and organic compounds—remains methodologically challenging [83]. Emerging evidence from multi-omics studies suggests that low-dose exposures may activate adaptive pathways (e.g., Nrf2-mediated antioxidant responses) before overt toxicity appears, indicating a hormetic zone that must be carefully distinguished from adverse effects [82] [87]. **Table 4** summarises key exposure assessment methods and their epidemiological applications.

Table 4. The key exposure assessment methods and their epidemiological applications in population studies.

Assessment Method	Examples	Epidemiological Application
Environmental Monitoring	Ambient $PM_{2.5}$, water heavy metals	Linking spatial exposure to health outcomes
Biological Monitoring	Blood lead, urinary cadmium	Internal dose metrics; used in cohort studies
Exposomics (Non-Targeted HRMS)	PFAS, microplastics, unknown contaminants	Discovery-based associations; early warning
Wearable Sensors + Omics	Personal exposure monitoring with multi-omics	Real-time exposure-response in panel studies
Biomarkers of Effect	8-OHdG, cytokines, KIM-1	Mechanistic confirmation of exposure-effect chains

Modern exposure assessment has evolved from single-pollutant monitoring towards multi-dimensional exposome characterization. Epidemiological evidence from long-term cohorts has firmly established dose-dependent adverse effects of air pollution, with no clear threshold. Translating these insights into regulatory action requires continued refinement of exposure assessment tools, particularly for vulnerable populations and emerging contaminants [81] [82].

6. Prevention, Intervention, and Future Perspectives

6.1. Prevention and Control Strategies

Primary prevention—source reduction, engineering controls, and regulatory standards—remains the cornerstone of mitigating exposure risks. A systematic review of air pollution control strategies found that nearly 70% of studies reported economic benefits outweighing costs, primarily through reduced morbidity and mortality from particulate matter [88]. For metal mixtures, enhanced monitoring and stricter occupational safety regulations are urgently needed, especially for vulnerable populations [89].

Beyond exposure reduction, pharmacological interventions targeting core toxic mechanisms have gained traction. N-Acetylcysteine reduced mortality in acute copper poisoning in mice, though it was ineffective against thallium and cadmium [90]. Activation of the Nrf2 signaling pathway—a master regulator of antioxidative enzymes—attenuates toxicity from electrophilic insults, with several Nrf2

activators in clinical development [91] [92]. Antioxidant nanoformulations using biodegradable carriers overcome the poor bioavailability of free antioxidants [93]. Natural products such as curcumin, resveratrol, and glycyrrhizin also show promise; glycyrrhizin directly inhibits HMGB1-mediated NF-κB signaling and ER stress in particulate matter-induced lung injury [94].

6.2. Challenges in Current Research

Several obstacles hinder progress. First, real-world exposures involve complex mixtures, yet most studies focus on single agents. The exposome concept offers a systematic framework but remains in early operational stages [95]. Second, gene-environment interactions are poorly understood; although genome-wide studies have identified susceptibility variants, these await mechanistic validation [96]. Third, even promising interventions show limited efficacy in complex models—Fer-1, a ferroptosis inhibitor, did not substantially alleviate major toxic outcomes in rats exposed to 1-nitropyrene [97]. Fourth, translating nanomedicines and small-molecule inhibitors faces bioavailability and off-target hurdles [98]. Traditional risk assessment frameworks have also been criticized for using incomplete or biased data [99]. Finally, advanced models such as microphysiological systems (MPS) and adverse outcome pathways (AOPs) have not been widely adopted by regulators due to qualification gaps and insufficient stakeholder communication [100].

6.3. Future Directions: High-Throughput Detection, Multi-Omics, and Targeted Intervention

High-resolution mass spectrometry and network science now enable comprehensive exposome assessment at a scale comparable to the human genome [100]. The environment-wide association study (EWAS) paradigm has identified environmental factors associated with type 2 diabetes with effect sizes comparable to genetic loci [101]. High-throughput in vitro screening and in silico toxicology are gradually being incorporated into regulatory practice [102].

Multi-omics integration—combining transcriptomics, proteomics, metabolomics, and metagenomics—provides mechanistic insights into host-microbial metabolic disruptions caused by pollutants [97]. Organ-on-a-chip and MPS technologies recapitulate physiologically relevant tissue environments, reducing animal testing while improving human predictivity [100] [103]. AOP frameworks systematically link molecular initiating events to adverse outcomes, supporting cross-chemical extrapolation [104]. Machine learning models for toxicity prediction from chemical structures are advancing, though success depends on careful validation [105].

On the therapeutic front, targeted interventions are shifting from broad antioxidants to pathway-specific modulators, including NRF2-KEAP1-targeted agents, ferroptosis inhibitors, and RIPK1 inhibitors for inflammatory and neurodegenerative diseases [105] [106]. A systems-based, agnostic approach to the exposome, combined

with precision intervention strategies, promises to transform the prevention and management of pollutant-induced diseases.

7. Conclusion

Environmental and occupational pollutants exert their deleterious health effects through a set of conserved mechanisms—oxidative stress, inflammation, mitochondrial damage, and disrupted cell death pathways—leading to multi-organ toxicity in the lung, brain, liver, and kidney. Early biomarkers of effect, ranging from oxidized DNA bases to tissue-specific proteins and molecular omics signatures, provide a powerful toolkit for detecting harm before irreversible injury occurs. Epidemiological evidence, particularly from well-designed cohort studies with robust exposure assessment, continues to refine our understanding of dose-response relationships, often demonstrating effects below traditional safety thresholds. Moving forward, the integration of high-resolution exposomics with multi-omics and mechanistic in vitro models promises to usher in an era of precision environmental health. For public health and occupational protection, the priority remains clear: primary prevention through regulation and engineering controls, complemented by biomarker-based surveillance to protect the most vulnerable.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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