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MORALITY BEFORE KNOWLEDGE

Beyond oxidative stress: Emerging molecular mechanisms and translational perspectives in environmental toxicant-induced hematotoxicity

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ABSTRACT

Background: Environmental toxicants, including heavy metals, pesticides, particulate air pollutants, per- and polyfluoroalkyl substances (PFAS), and microplastics, are increasingly recognized as major contributors to hematological disorders. Although oxidative stress has traditionally been regarded as the principal mechanism underlying environmental toxicant-induced hematotoxicity, emerging evidence suggests that additional molecular pathways contribute substantially to hematopoietic injury. This review examines the evolving molecular mechanisms of environmental toxicant-induced hematotoxicity beyond the conventional oxidative stress paradigm and explores their translational implications. **Methods:** Literature was retrieved from PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar and synthesized through a structured narrative review. Evidence published primarily between 2020 and 2026 was critically evaluated and organized into thematic areas including oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, hematopoietic stem-cell dysfunction, biomarker discovery, multi-omics technologies, artificial intelligence, and precision hematology. **Findings:** Environmental toxicant-induced hematotoxicity is mediated by a complex network of interacting molecular pathways rather than oxidative stress alone. Emerging evidence highlights important roles for mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and hematopoietic stem-cell (HSC) impairment in regulating blood-cell homeostasis and bone marrow integrity. These pathways interact extensively with oxidative stress and contribute to disease heterogeneity, chronic toxicity, and variable clinical outcomes. Advances in multi-omics technologies and artificial intelligence further provide opportunities for biomarker discovery, improved risk assessment, and early disease detection. **Conclusion:** Environmental toxicant-induced hematotoxicity should be viewed as a systems-level disorder arising from coordinated interactions among multiple molecular pathways. Integrating mechanistic insights with multi-omics technologies, artificial intelligence (AI), and precision hematology may improve disease prediction, biomarker development, early diagnosis, and targeted intervention strategies. **Novelty/Originality of this article:** This review moves beyond the traditional oxidative stress paradigm by integrating emerging molecular mechanisms into a systems hematotoxicology framework for understanding environmental toxicant-induced hematological injury.

KEYWORDS: environmental toxicants; hematopoietic stem cells; hematotoxicity.

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1. Introduction

Among the systems affected by environmental toxicants, the hematopoietic system is especially vulnerable owing to its rapid cellular turnover and the tightly regulated activity of hematopoietic stem cells (HSCs) (Ho & Takizawa, 2022). Exposure to these toxicants has been implicated in numerous hematological disorders, including anemia, immune dysfunction, bone marrow suppression, coagulation abnormalities, and hematological malignancies. Beyond impairing oxygen delivery and immune function, these conditions contribute substantially to morbidity and mortality (Cheng et al., 2025). Consequently, defining the molecular mechanisms responsible for toxicant-induced injury to the hematopoietic system remains essential for strengthening disease prevention, improving early diagnosis, refining risk assessment, and identifying effective therapeutic strategies (Li et al., 2026).

Oxidative stress has long been regarded as the predominant mechanism underlying environmental toxicant-induced hematotoxicity. Increased production of reactive oxygen species (ROS), together with weakened antioxidant defense systems, initiates lipid peroxidation, DNA damage, protein oxidation, mitochondrial injury, and disruption of cellular homeostasis within the blood and bone marrow (Khan et al., 2025). While this concept has provided an important framework for understanding toxicant-induced injury, it fails to fully explain the wide variation in hematological phenotypes, the persistence of chronic toxic effects, and the selective susceptibility of specific hematopoietic cell populations following environmental exposure (Germolec et al., 2022).

Environmental hematotoxicity is now recognized as a consequence of multiple interacting molecular pathways that extend beyond oxidative stress alone. Mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and HSC dysfunction are intricately linked with oxidative stress, collectively regulating cellular metabolism, inflammatory signaling, lineage commitment, and bone marrow homeostasis (Sinha, 2025). Instead of functioning as isolated processes, these mechanisms form an interconnected molecular network that ultimately governs cellular fate and disease progression. Nevertheless, the majority of current studies continue to evaluate these pathways individually, restricting a comprehensive understanding of how their coordinated interactions drive environmental toxicant-induced hematopoietic injury (Lemanowicz et al., 2026).

Although oxidative stress continues to be recognized as a key contributor to environmental toxicant-induced hematotoxicity, increasing evidence indicates that it represents only one facet of a far more complex molecular network (Sule et al., 2025). Comparable levels of oxidative stress may give rise to markedly different hematological manifestations depending on the contribution of mitochondrial dysfunction, ferroptosis, inflammatory cell death, epigenetic reprogramming, immunometabolic dysregulation, and HSC dysfunction. Moreover, traditional oxidative stress biomarkers often demonstrate limited sensitivity and specificity for predicting chronic toxicity and disease progression, underscoring the shortcomings of models that rely on a single pathogenic mechanism (Z. Zhang et al., 2025).

These limitations emphasize the need to move beyond conventional oxidative stress-focused paradigms towards an integrated systems-based framework capable of capturing the intricate molecular interactions that drive environmental hematotoxicity (Remigante & Morabito, 2023). In this review, we critically evaluate the emerging molecular mechanisms implicated in environmental toxicant-induced hematotoxicity, explore the extensive crosstalk among these interconnected pathways, highlight key gaps in current knowledge, and examine their translational relevance to biomarker discovery, multi-omics approaches, artificial intelligence, and precision hematology.

2. Methods

This review was conducted as a structured narrative literature review to critically examine the evolving molecular mechanisms underlying environmental toxicant-induced hematotoxicity beyond the conventional oxidative stress paradigm. A comprehensive search of the published literature was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar to identify relevant evidence. The search primarily focused on studies published between 2020 and 2026, while earlier landmark publications were included where necessary to provide historical context and support fundamental biological concepts. Search terms were used individually and in combination and included environmental toxicants, hematotoxicity, oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, hematopoietic stem cells, immunometabolism, multi-omics, artificial intelligence, precision hematology, heavy metals, microplastics, PFAS, pesticides, and air pollution.

Articles were selected on the basis of their scientific relevance, methodological quality, and contribution to understanding the molecular mechanisms, biological interactions, translational implications, and emerging diagnostic or therapeutic approaches associated with environmental toxicant-induced hematotoxicity. Priority was given to peer-reviewed original research articles, systematic reviews, meta-analyses, and authoritative review papers published in reputable international journals. Reference lists of key publications were also manually examined to identify additional relevant studies that were not retrieved during the initial database search. The retrieved evidence was critically evaluated and synthesized into thematic sections addressing oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, hematopoietic stem-cell dysfunction, systems hematotoxicology, biomarker discovery, multi-omics technologies, artificial intelligence, and future translational perspectives. As this work represents a structured narrative review, no formal risk-of-bias assessment or quantitative meta-analysis was undertaken.

3. Results and Discussion

3.1 Oxidative stress: The established paradigm

3.1.1 Environmental toxicants as drivers of oxidative stress

A wide range of environmental toxicants, including heavy metals, pesticides, particulate air pollutants, per- and polyfluoroalkyl substances (PFAS), and emerging contaminants such as microplastics, disrupt intracellular redox homeostasis by promoting excessive reactive oxygen species (ROS) generation while simultaneously impairing endogenous antioxidant defense systems (Zayani et al., 2025). The resulting imbalance between oxidant production and antioxidant capacity contributes substantially to cellular injury and has traditionally served as the principal mechanistic framework for explaining toxicant-induced hematological damage (Anwar et al., 2025). Oxidative stress has long served as the predominant mechanistic paradigm in environmental toxicology because it represents a common biological response to chemically diverse contaminants, irrespective of their physicochemical properties or primary molecular targets.

Although these agents initiate toxicity through distinct molecular interactions, many ultimately converge on excessive reactive oxygen species (ROS) production, disruption of intracellular redox homeostasis, and impairment of endogenous antioxidant defenses (Cardoso-Vera et al., 2024). This shared response has established redox imbalance as a unifying basis for investigating toxicant-induced cellular injury and has facilitated comparisons of toxicological responses across different classes of environmental contaminants. Consequently, biomarkers of oxidative stress are widely used in

experimental and epidemiological studies to assess exposure-related effects and evaluate toxicological risk (Hsu et al., 2025).

3.1.2 Molecular consequences of oxidative stress

Excessive ROS generation initiates a cascade of molecular events that jeopardise the structural and functional integrity of blood cells and bone marrow. One of the earliest consequences is lipid peroxidation, which occurs when reactive oxygen species attack polyunsaturated fatty acids within cellular membranes, resulting in reactive aldehydes that spread oxidative damage (Li Pomi et al., 2025). Membrane lipid oxidation changes membrane fluidity, increases permeability, and disturbs ion transport, reducing cellular survival and function. Oxidative stress also causes DNA damage by forming oxidized nucleotides, strand breaks, and chromosomal instability, which disrupts gene expression, cell cycle regulation, and genomic integrity. In addition, depletion of endogenous antioxidant defenses, including glutathione, superoxide dismutase, catalase, and glutathione peroxidase, compromises the ability of hematopoietic cells to neutralise reactive oxygen species, thereby exacerbating oxidative damage and increasing susceptibility to apoptosis and impaired cellular regeneration (Li et al., 2026).

Reactive oxygen species also serve as essential intracellular signaling mediators under physiological conditions, regulating cell proliferation, differentiation, immune activation, and adaptive stress responses. Within the hematopoietic system, tightly regulated redox homeostasis supports hematopoietic stem-cell maintenance, lineage commitment, and normal immune-cell development (Hong et al., 2024). Environmental toxicants disturb this delicate balance by inducing sustained or excessive ROS production that overwhelms endogenous antioxidant defenses, shifting normal redox signaling toward pathological cellular injury. Distinguishing between physiological and pathological redox states is therefore critical for understanding why comparable levels of ROS can produce markedly different biological outcomes depending on the toxicant, exposure duration, and cellular context (Afzal et al., 2023).

3.1.3 Hematopoietic consequences of oxidative injury

The hematopoietic system is especially sensitive to oxidative injury due to its high metabolic activity and constant cellular turnover. Erythrocytes are particularly vulnerable due to their frequent exposure to oxygen and the amount of membrane lipids, which serve as substrates for lipid peroxidation (Obeagu et al., 2024). Oxidative injury lowers membrane deformability, increases hemolysis, and shortens the lifespan of erythrocytes, all of which contribute to anemia and reduced oxygen delivery. Leukocytes exposed to high levels of reactive oxygen species demonstrate altered immunological signaling, decreased proliferative ability, and poor antimicrobial function, making them more susceptible to infection and immune dysregulation (Gwozdzinski et al., 2026). Platelets suffer oxidative changes that increase activation and aggregation, potentially leading to thrombotic problems and hemostasis disruptions. Chronic oxidative stress in the bone marrow impairs hematopoietic stem cell self-renewal and differentiation, threatening normal hematopoiesis and increasing the likelihood of bone marrow dysfunction (Arauna et al., 2024).

The extent of oxidative injury differs among blood-cell populations because of variations in metabolic activity, antioxidant capacity, proliferative potential, and lifespan. Hematopoietic stem cells maintain low intracellular ROS levels to preserve genomic stability and long-term self-renewal, whereas mature immune cells rely on tightly regulated ROS production to support host defense and intracellular communication (Rossin et al., 2025). Consequently, environmental toxicants can affect different blood-cell compartments through distinct molecular mechanisms, contributing to the diverse clinical manifestations associated with toxicant exposure. This cellular heterogeneity underscores the complexity

of hematotoxicity and highlights the importance of evaluating oxidative injury within the broader framework of blood-cell regulation (Koyama et al., 2024).

3.1.4 Limitations of the oxidative stress paradigm

Although oxidative stress remains a key mechanism of environmental hematotoxicity, it does not fully explain toxicant-induced hematological diseases. Individuals exposed to the same toxicants frequently have very varied clinical outcomes despite equivalent levels of oxidative damage, implying the participation of other regulatory processes (Sule et al., 2025). Furthermore, oxidative stress cannot fully explain chronic toxicity, disease-specific symptoms, or the selective vulnerability of different hematopoietic cell types. Increasing evidence suggests that mitochondrial dysfunction, regulated cell death, epigenetic reprogramming, and immunometabolic changes interact with oxidative stress to influence cellular fate and disease progression. Recognising these limitations has led a move toward a more comprehensive mechanistic paradigm that better captures the complexities of environmental toxicant-induced hematotoxicity (Garcia-Llorens et al., 2025).

Although decades of research have established oxidative stress as a central mechanism of toxicant-induced injury, antioxidant-based therapies have produced inconsistent results in both experimental and clinical settings (Ashok et al., 2022). These findings indicate that redox imbalance commonly occurs alongside multiple interconnected molecular disturbances rather than functioning as an isolated driver of disease. Consequently, growing emphasis has been placed on systems-based models that integrate oxidative stress with complementary pathogenic mechanisms, offering a more comprehensive perspective on environmental hematotoxicity while facilitating the identification of novel biomarkers and potential therapeutic targets (Balakrishnan et al., 2026).

3.2 From oxidative stress to systems hematotoxicology

Although oxidative stress remains a well-established mechanism of environmental toxicant-induced hematotoxicity, growing evidence suggests that it represents only one component of a broader and highly interconnected pathogenic network (Jomova et al., 2024). Recent studies have demonstrated that mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic alterations, and hematopoietic stem-cell dysfunction contribute significantly to toxicant-induced hematological injury and frequently interact with oxidative stress pathways rather than acting independently (Yang et al., 2026). These findings underscore the limitations of reductionist models and support the adoption of a systems-level framework capable of integrating multiple molecular mechanisms and their dynamic interactions in hematopoietic regulation. This emerging perspective provides the foundation for the Systems Hematotoxicology concept discussed below.

Recent advances in molecular toxicology suggest that environmental hematotoxicity is best understood as the consequence of coordinated interactions among multiple regulatory pathways rather than the activation of a single pathogenic mechanism. Instead of functioning independently, oxidative stress interacts extensively with mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and hematopoietic stem-cell (HSC) dysfunction to determine cellular fate and disease progression (Mafe & Büsselberg, 2025). Collectively, these mechanisms regulate mitochondrial bioenergetics, iron metabolism, inflammatory signaling, chromatin organization, cellular metabolism, and stem-cell maintenance, thereby shaping the hematopoietic response to environmental toxicants (Rojas-Lemus et al., 2026).

Importantly, the contribution of each pathway is unlikely to be static but may vary according to toxicant class, exposure dose, duration, and host-specific factors such as age, genetic susceptibility, nutritional status, and pre-existing disease. Recognizing these

context-dependent interactions is essential for accurately interpreting toxicological responses and improving individualized risk assessment (Matilla-Cabello et al., 2026).

This integrated perspective forms the basis of systems hematotoxicology, a framework that considers toxicant-induced injury as the result of dynamic molecular crosstalk occurring across interconnected biological networks (Moya-García et al., 2022). Rather than examining individual pathways in isolation, systems hematotoxicology emphasizes how alterations in one regulatory process influence multiple downstream mechanisms through coordinated signaling and feedback interactions. Such an approach provides a more comprehensive explanation for the diverse clinical manifestations associated with environmental toxicant exposure and better reflects the biological complexity of hematological disease (Bearth et al., 2025).

Furthermore, the rapid development of systems biology, network medicine, and high-throughput multi-omics technologies has transformed the investigation of environmental toxicology by enabling simultaneous characterization of genomic, transcriptomic, proteomic, metabolomic, and epigenomic alterations following toxicant exposure. Integrating these complementary datasets allows researchers to reconstruct molecular interaction networks, identify critical regulatory nodes, and distinguish toxicant-specific biological signatures that may not be evident using conventional reductionist approaches (Jiang et al., 2025). In parallel, advances in computational biology, artificial intelligence, and machine learning have strengthened systems-based analyzes by facilitating the integration of large and complex biological datasets into predictive models of disease susceptibility and progression. These technologies have accelerated the discovery of candidate biomarkers, improved mechanistic interpretation, and enhanced the potential for precision approaches to environmental risk assessment and therapeutic intervention (Shen et al., 2026). Consequently, systems hematotoxicology represents a significant conceptual shift from traditional single-pathway models toward an integrated network-based framework capable of capturing the molecular complexity of environmental toxicant-induced hematological disorders (Yang et al., 2026)

3.3 Emerging molecular mechanisms of hematotoxicity

Recent advances in molecular toxicology have demonstrated that environmental toxicant-induced hematotoxicity is driven by complex interactions among multiple molecular pathways rather than a single pathogenic mechanism. In addition to oxidative stress, processes governing energy metabolism, regulated cell death, immune signaling, epigenetic regulation, and hematopoietic stem-cell function collectively influence the onset and progression of hematological injury (Gao et al., 2025). The extensive crosstalk among these interconnected mechanisms contributes to disease heterogeneity while providing valuable opportunities for the identification of predictive biomarkers and the development of targeted therapeutic strategies (Molla & Bitew, 2025).

3.3.1 Mitochondrial dysfunction

Mitochondria regulate cellular energy production, redox balance, calcium homeostasis, and apoptotic signaling. Heavy metals, herbicides, particulate matter, and PFAS are examples of environmental toxicants that can accumulate within mitochondria, affecting electron transport chain activity and compromising oxidative phosphorylation (Neikirk et al., 2024). An early consequence is the depletion of adenosine triphosphate (ATP), which reduces the energy available for cellular upkeep, proliferation, and differentiation. Cells with high metabolic demands, such as hematopoietic stem cells and proliferative progenitor cells, are particularly vulnerable to these changes (Zhang et al., 2023).

Mitochondrial injury is usually associated with damage to mitochondrial DNA (mtDNA), which lacks the robust protective mechanisms found in nuclear DNA. Oxidative damages and mutations in mtDNA limit respiratory chain protein synthesis, reducing ATP

generation and prolonging mitochondrial dysfunction (Jauhari et al., 2026). Furthermore, disrupting mitochondrial metabolism disrupts the equilibrium between glycolysis and oxidative phosphorylation, causing metabolic reprogramming that affects cell survival, lineage commitment, and immunological responses. These metabolic changes go beyond basic oxidative injury and have been linked to bone marrow failure, poor erythropoiesis, and leukocyte dysfunction. Importantly, mitochondrial malfunction encourages excessive reactive oxygen species formation, resulting in a self-reinforcing cycle that links bioenergetic failure to oxidative stress (Kim et al., 2025).

3.3.2 Ferroptosis, pyroptosis, and inflammatory cell death

Ferroptosis is a novel type of controlled cell death characterized by iron-dependent lipid peroxidation and irreversible membrane damage. Unlike apoptosis or necrosis, ferroptosis is caused by dysregulated iron metabolism and the failure of cellular antioxidant systems that detoxify lipid peroxides. Environmental toxicants that disrupt iron homeostasis or glutathione metabolism may therefore cause ferroptotic cell death in the hematopoietic system (Dixon & Olzmann, 2024).

Erythrocytes are particularly vulnerable to ferroptotic injury because they contain abundant iron-rich haemoglobin and possess lipid-rich membranes that are highly susceptible to lipid peroxidation. Excessive lipid peroxidation impairs membrane integrity, reduces erythrocyte deformability, and promotes premature destruction, all of which contribute to anemia and decreased oxygen supply (Obeagu et al., 2024). Ferroptosis may potentially have an impact on bone marrow function by harming hematopoietic progenitor cells, which are crucial for sustaining normal blood cell generation. Although oxidative stress leads to lipid peroxidation, ferroptosis is a controlled biological process that involves iron metabolism, glutathione depletion, and the inactivation of glutathione peroxidase 4. Recognising ferroptosis thus broadens our understanding of environmental hematotoxicity beyond nonspecific oxidative damage and opens up possibilities for developing novel therapeutic approaches targeting iron metabolism and lipid peroxide detoxification (Kourti & Kontoghiorghes, 2026).

Persistent exposure to environmental toxicants may also cause inflammatory forms of programmed cell death, including pyroptosis, which has received increased attention (Rao et al., 2022). Pyroptosis is triggered by inflammasome activation, which results in the cleavage of inflammatory caspases and the creation of membrane holes, causing cellular swelling, membrane rupture, and the release of pro-inflammatory mediators. This procedure is essentially different from apoptosis because it actively stimulates inflammatory responses rather than promoting immunologically silent cell elimination (Liu et al., 2024).

Inflammasome activation promotes the maturation and production of cytokines such as IL-1β and IL-18, which are crucial for regulating the immune system and chronic inflammation. Elevated levels of these cytokines promote bone marrow inflammation, disrupt hematopoietic niches, and hamper blood cell development. Chronic inflammasome activation has also been linked to leukocyte dysfunction, aberrant platelet activation, and impaired hematopoietic stem cell regeneration (Panek et al., 2023). Increasing data reveals that oxidative stress commonly acts as an upstream trigger of inflammasome activation, demonstrating the complex interplay between oxidative injury and inflammatory cell death. As a result, pyroptosis provides an important mechanistic link between environmental exposure and chronic inflammatory hematological diseases (Tian et al., 2023).

3.3.3 Epigenetic reprogramming

Epigenetic regulation has emerged as another important mechanism by which environmental toxicants have long-term consequences on hematopoietic function. Unlike genetic mutations, epigenetic modifications change gene expression without altering the

underlying DNA sequence, allowing environmental exposures to have long-term biological impacts (Rubio et al., 2023). Environmental toxicants have an impact on a variety of epigenetic processes, including DNA methylation, histone changes, and non-coding RNA control.

Aberrant DNA methylation can silence genes involved in antioxidant defense, DNA repair, cell cycle regulation, and hematopoietic differentiation, increasing susceptibility to hematological diseases (Adegbola & Adetutu, 2024). Histone acetylation and methylation change chromatin accessibility, altering transcriptional programs that control cell proliferation, inflammatory signaling, and lineage specification. Furthermore, microRNAs and long non-coding RNAs have emerged as significant post-transcriptional regulators that influence apoptosis, immunological responses, mitochondrial function, and stem cell survival. Following exposure to a variety of environmental toxicants, altered expression of these regulatory RNAs has been seen, which may lead to long-term changes in hematopoietic homeostasis. Overall, these data suggest that epigenetic reprogramming is a fundamental pathway linking environmental exposure to chronic hematological dysfunction and may provide useful indicators for early detection of toxicant-induced harm (Oktar et al., 2026).

3.3.4 Hematopoietic stem cell dysfunction

Hematopoietic stem cells (HSCs) maintain lifelong blood cell production through tightly regulated self-renewal and multilineage differentiation. These functions are governed not only by intrinsic genetic programs but also by continuous interactions with the specialized bone marrow niche, a dynamic microenvironment composed of mesenchymal stromal cells, endothelial cells, osteoblasts, adipocytes, immune cells, and extracellular matrix components (Benam et al., 2025). Collectively, these cellular and structural elements preserve HSC quiescence, proliferation, differentiation, and survival. Environmental toxicants can disrupt this highly coordinated microenvironment by inducing oxidative stress, chronic inflammation, mitochondrial dysfunction, vascular injury, and aberrant intercellular signaling, thereby compromising both HSC function and the integrity of the niche that supports normal hematopoiesis (Ho & Takizawa, 2022).

Prolonged exposure to environmental toxicants may also accelerate stem-cell exhaustion, a state characterized by the gradual loss of self-renewal capacity and regenerative potential in response to persistent cellular stress (Rossin et al., 2025). Sustained production of reactive oxygen species, mitochondrial dysfunction, DNA damage, and chronic inflammatory signaling can force normally quiescent HSCs into repeated proliferative cycles, progressively depleting the functional stem-cell pool and disrupting long-term hematopoietic homeostasis. As a consequence, these alterations may impair blood cell production, compromise immune function, promote bone marrow failure, and diminish the capacity to recover from subsequent physiological or environmental challenges (Shevyrev et al., 2023).

Recent evidence also indicates that environmental toxicants may contribute to clonal hematopoiesis, particularly clonal hematopoiesis of indeterminate potential (CHIP), an age-related condition in which somatic mutations provide individual HSC clones with a selective growth advantage. Although CHIP is often clinically asymptomatic, it has been linked to an increased risk of cardiovascular disease, chronic inflammation, hematological malignancies, and all-cause mortality (Kallai et al., 2025). Through the induction of genomic instability, oxidative DNA damage, and persistent inflammatory signaling, environmental toxicants may facilitate clonal expansion or hasten the emergence of mutant HSC populations, although direct evidence supporting a causal relationship remains limited (Malkots et al., 2026).

These processes become increasingly important with ageing, when cumulative environmental exposures coincide with declining DNA repair capacity, mitochondrial dysfunction, and immunosenescence, collectively heightening HSC susceptibility to injury

(Anastasiou et al., 2026). Progressive impairment of HSC function together with ongoing clonal evolution may ultimately promote leukemogenesis, providing a plausible mechanistic link between environmental toxicant exposure and the development of hematological malignancies. Taken together, these findings position HSC dysfunction not merely as a consequence of environmental toxicant exposure but as a pivotal mechanism driving long-term hematopoietic decline and increased disease susceptibility (Wang et al., 2025).

3.3.5 Immune metabolic dysregulation

Recent advancements in immunology have shown that immune cell function is intricately connected to cellular metabolism. Leukocyte activation, differentiation, and survival need coordinated metabolic changes involving glycolysis, oxidative phosphorylation, amino acid metabolism, and lipid utilization. Environmental toxins can disrupt these metabolic pathways, affecting immune cell function independent of direct oxidative damage (Xu et al., 2024).

Table 1. Emerging molecular mechanisms involved in environmental toxicant-induced hematotoxicity.

Molecular Mechanism	Principal Molecular Features	Hematological Consequences	Translational Potential
Oxidative stress	Reactive oxygen species generation, antioxidant depletion, lipid peroxidation	DNA damage, impaired hematopoiesis, cellular dysfunction	Oxidative stress biomarkers and antioxidant-based therapeutic strategies
Mitochondrial dysfunction	ATP depletion, mitochondrial DNA damage, impaired oxidative phosphorylation	Bone marrow injury, stem cell dysfunction, defective energy metabolism	Mitochondrial biomarkers and targeted therapeutic interventions
Ferroptosis	Iron dysregulation, lipid peroxide accumulation, glutathione depletion, GPX4 inactivation	Erythrocyte injury, anemia, impaired bone marrow function	Ferroptosis inhibitors and therapies targeting iron metabolism
Pyroptosis	Inflammasome activation, caspase-1 activation, IL-1β and IL-18 release	Chronic inflammation, leukocyte dysfunction, impaired hematopoiesis	Inflammasome-targeted therapeutic strategies
Epigenetic reprogramming	DNA methylation, histone modifications, non-coding RNA regulation	Persistent alterations in gene expression and hematopoietic regulation	Epigenetic biomarkers and precision medicine approaches
Hematopoietic stem cell dysfunction	Impaired self-renewal, aberrant differentiation, disruption of the bone marrow niche	Bone marrow failure, hematopoietic imbalance, hematological malignancies	Stem cell biomarkers and regenerative therapeutic approaches
Immunometabolic dysregulation	Altered glycolysis, oxidative phosphorylation, mTOR and AMPK signaling	Immune dysfunction, chronic inflammation, disrupted hematopoiesis	Immunometabolic biomarkers and metabolism-targeted therapies

Metabolic reprogramming of immune cells contributes to pro-inflammatory cytokine production, poor pathogen clearance, and dysregulated immunological homeostasis. Chronic low-grade inflammation may eventually disrupt hematopoietic stem cell maintenance, induce aberrant myeloid differentiation, and impede adaptive immune

responses (Chronopoulos et al., 2026). Furthermore, reciprocal interactions between immune signaling and cellular metabolism result in self-perpetuating cycles of inflammation that persist even after toxicant exposure has subsided. Increasing data suggests that immunometabolic dysregulation plays a significant role in chronic hematological diseases related with environmental pollution (Chi, 2022).

These developing molecular mechanisms show that environmental toxicant-induced hematotoxicity is mediated by a complicated network of interacting biological pathways, not just oxidative stress (Fang et al., 2026). Integrating mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, hematopoietic stem cell dysfunction, and immunometabolic alterations into a single mechanistic framework provides a more complete understanding of hematological injury and lays the groundwork for the development of predictive biomarkers and precision-based therapeutic strategies (Diaconescu et al., 2025).

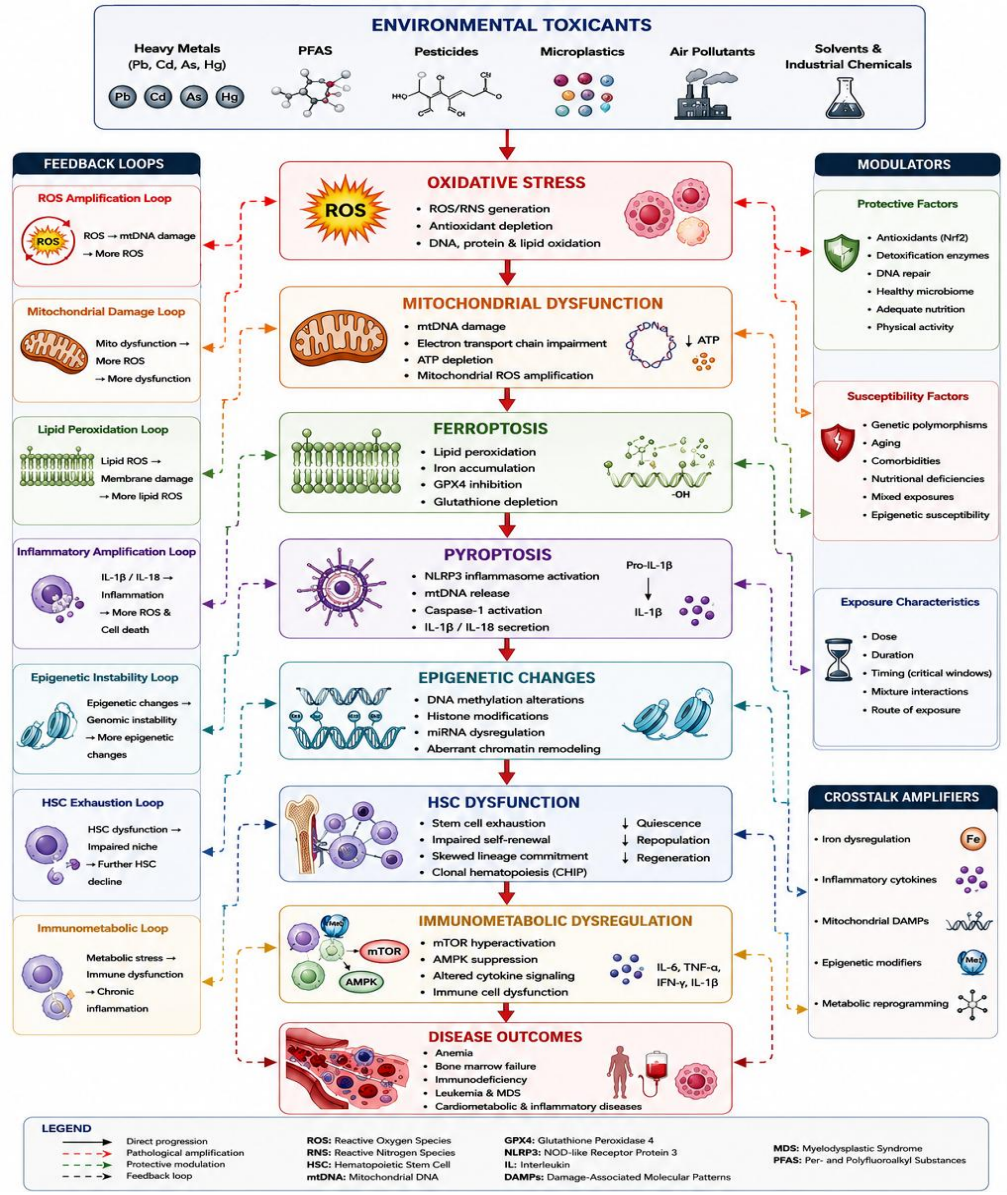

Fig. 1. Presents the proposed integrated molecular framework of environmental toxicant-induced hematotoxicity

Figure 1 proposed integrated molecular framework of environmental toxicant-induced hematotoxicity. Environmental toxicants initiate oxidative stress, which interacts with mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, and

hematopoietic stem cell dysfunction. These interconnected mechanisms converge to promote immunometabolic dysregulation, resulting in bone marrow dysfunction and ultimately contributing to hematological disorders, including anemia, immune dysfunction, thrombocytopenia, coagulopathies, bone marrow failure, and hematological malignancies.

3.3.6 The exposome and environmental hematotoxicity

The exposome provides a comprehensive framework for understanding how environmental factors collectively shape human health across the lifespan. In contrast to conventional toxicological approaches that examine individual chemicals separately, the exposome encompasses the full spectrum of environmental exposures including chemical pollutants, dietary influences, occupational hazards, lifestyle factors, psychosocial stressors, and endogenous biological processes from conception to the end of life (Wan et al., 2025). This broader perspective is particularly relevant to environmental hematotoxicity, where the cumulative and interactive effects of multiple exposures are likely to explain disease susceptibility more effectively than single-toxicant models (Sokan-Adeaga et al., 2023).

The cumulative burden of lifelong environmental exposure is increasingly recognized as a critical determinant of hematological health (Mesnage, 2025). Continuous or repeated exposure to low levels of environmental toxicants can result in cumulative biological injury characterized by persistent oxidative stress, mitochondrial dysfunction, chronic inflammation, epigenetic reprogramming, and impaired hematopoietic stem-cell function. Over time, these molecular disturbances may progressively accumulate, with clinically apparent hematological abnormalities developing only after years or even decades of exposure (Mafe & Büsselberg, 2025).

Another important consideration is that environmental exposures rarely occur in isolation. Individuals are routinely exposed to complex mixtures of heavy metals, air pollutants, pesticides, microplastics, endocrine-disrupting chemicals, and numerous other contaminants that may exert additive, synergistic, or antagonistic biological effects (Cannarella et al., 2026). Such interactions are difficult to capture using conventional toxicological models and highlight the need for integrative approaches that combine detailed exposure assessment with multi-omics technologies and advanced computational modeling (Kumbhar et al., 2026).

Applying exposome science to environmental hematotoxicity has considerable potential to advance precision environmental health. Integrating lifetime exposure histories with molecular biomarkers, multi-omics datasets, and artificial intelligence may improve individual risk stratification, facilitate the identification of susceptible populations, and support the development of more personalized prevention strategies (Sarigiannis et al., 2026). Consequently, an exposome-based approach is expected to provide a more comprehensive understanding of how environmental toxicants contribute to the initiation and progression of hematological disorders throughout life (Crépet et al., 2025)

3.4 Translational implications

3.4.1 Evidence from human studies

Although mechanistic investigations have greatly expanded our understanding of environmental toxicant-induced hematotoxicity, their clinical relevance ultimately depends on validation in human populations (Sarigiannis et al., 2026). Epidemiological and clinical studies increasingly support the involvement of oxidative stress, mitochondrial dysfunction, inflammatory signaling, epigenetic alterations, and hematopoietic stem-cell (HSC) impairment following exposure to diverse environmental toxicants. Nevertheless, the quality of evidence remains heterogeneous owing to differences in study design, exposure assessment, and biomarker selection (Pierro et al., 2025).

Human cohort studies, large prospective and cross-sectional cohort studies have associated chronic exposure to environmental toxicants including lead, cadmium, arsenic, particulate air pollution, PFAS, and microplastics with anemia, altered leukocyte profiles, platelet abnormalities, and impaired immune function (Shetty et al., 2023). These population-based investigations have also identified associations between cumulative toxicant exposure and biomarkers of oxidative stress, systemic inflammation, mitochondrial dysfunction, and epigenetic modification, suggesting that molecular perturbations may occur well before clinically apparent hematological disease develops (Okpoghono et al., 2026). Occupational exposure studies, evidence from occupational cohorts exposed to pesticides, industrial solvents, heavy metals, welding fumes, mining dust, and combustion-derived pollutants consistently demonstrates increased risks of bone marrow suppression, cytopenias, coagulation abnormalities, and hematological malignancies (La Torre et al., 2024). Biomarker analyzes within these populations frequently reveal enhanced oxidative stress, elevated inflammatory cytokines, mitochondrial injury, aberrant DNA methylation, and impaired antioxidant defenses, providing strong translational support for observations reported in experimental models (Dash et al., 2025).

Environmental exposure studies, investigations involving environmentally exposed communities have shown that individuals residing near industrial facilities, mining regions, agricultural settings, or areas with substantial air pollution often exhibit measurable hematological alterations despite relatively low levels of exposure (Ripanda et al., 2025). These findings suggest that prolonged low-dose exposure and complex toxicant mixtures can induce persistent molecular disturbances involving oxidative stress, immune activation, ferroptosis-associated pathways, and metabolic dysregulation, reinforcing concerns regarding the cumulative health effects of environmental pollution (Yang et al., 2025).

Biomarker studies, clinical biomarker studies increasingly utilise circulating microRNAs, extracellular vesicles, inflammatory cytokines, metabolomic signatures, and epigenetic markers to characterize toxicant-induced hematological injury (Zafar et al., 2025). Although no individual biomarker currently demonstrates sufficient sensitivity or specificity for routine clinical application, accumulating evidence indicates that integrated biomarker panels combining molecular, inflammatory, metabolic, and exposure-related indicators may substantially improve early diagnosis, disease monitoring, and precision risk assessment. Large longitudinal studies remain essential to validate these biomarkers and establish their clinical utility (Edwin & Jayaprakash, 2026).

3.4.2 Biomarker discovery and multi-omics technologies

Recognising that environmental toxicants induce hematotoxicity through multiple interconnected molecular mechanisms has transformed approaches to biomarker discovery. Conventional hematological assessments, including complete blood counts and routine biochemical analyzes, frequently detect toxicity only after substantial cellular injury has occurred (Grari et al., 2026). Consequently, considerable effort has focused on identifying molecular biomarkers capable of detecting early pathogenic changes before irreversible hematological dysfunction develops. Circulating microRNAs (miRNAs) have attracted particular interest because of their remarkable stability in biological fluids and their regulatory roles in oxidative stress, mitochondrial dysfunction, ferroptosis, inflammatory signaling, and HSC biology (Felekkis et al., 2023). Likewise, extracellular vesicles provide valuable insight into bone marrow injury and immune activation by transporting proteins, messenger RNAs, microRNAs, and other regulatory molecules that reflect the physiological state of their cells of origin. Circulating inflammatory cytokines associated with inflammasome activation further complement these biomarkers by capturing inflammatory processes underlying toxicant-induced hematological injury (Kumar et al., 2024).

Metabolomic profiling extends biomarker discovery by providing a functional overview of biochemical alterations associated with environmental toxicant exposure. Disturbances in glutathione metabolism may reflect impaired antioxidant capacity, whereas alterations in lipid metabolism indicate increased susceptibility to lipid peroxidation and ferroptosis (Liaqat et al., 2026). Similarly, disruption of iron metabolism provides insight into abnormalities in iron homeostasis that contribute to oxidative injury and ferroptotic cell death. Because many of these metabolic changes precede overt clinical manifestations, metabolomics offers valuable opportunities for early diagnosis, mechanistic characterisation, and improved clinical decision-making (Ru et al., 2025).

The integration of multi-omics technologies has further advanced environmental hematology by enabling systems-level characterisation of toxicant-induced molecular perturbations. Transcriptomic analyzes identify altered expression of oxidative stress-responsive genes, including NRF2 (NFE2L2), HMOX1, and NQO1, which serve as key indicators of cellular antioxidant defense. Complementary proteomic approaches characterize alterations in proteins involved in ferroptosis and inflammatory cell death, including glutathione peroxidase 4 (GPX4), caspase-1, and interleukin-1β (IL-1β) (Fan et al., 2025). In parallel, epigenomic profiling captures persistent regulatory changes through aberrant DNA methylation and histone acetylation that influence chromatin accessibility, inflammatory signaling, and hematopoietic differentiation. Integrating transcriptomic, proteomic, metabolomic, and epigenomic datasets therefore enables the identification of robust biomarker signatures, reveals interconnected regulatory networks, and provides mechanistic insights that cannot be achieved using individual omics platforms alone (Młynarska et al., 2026).

3.4.3 Artificial intelligence and precision hematology

Artificial intelligence (AI) is increasingly becoming an integral component of translational environmental toxicology by transforming complex biological datasets into clinically actionable information (Domingo, 2026). Conventional machine-learning algorithms, including Random Forest, Extreme Gradient Boosting (XGBoost), and Support Vector Machines (SVMs), are capable of integrating multi-omics, clinical, and environmental exposure data to identify biomarker signatures, classify toxicant exposures, and predict hematological outcomes. More recently, deep-learning models based on artificial neural networks have improved the analysis of high-dimensional datasets by identifying complex nonlinear relationships among molecular variables that may not be captured using conventional statistical approaches (Lin et al., 2025).

Alongside these advances, developments in systems toxicology and network biology have shifted analytical strategies from isolated biomarkers towards interconnected molecular networks. These approaches facilitate identification of regulatory pathways linking oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, and immunometabolic dysregulation, thereby providing a more comprehensive understanding of environmental hematotoxicity (Chowdhury et al., 2026). To enhance clinical confidence and support regulatory implementation, explainable artificial intelligence approaches, including SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME), are increasingly being adopted to improve model transparency by identifying the molecular features that contribute most strongly to predictive outcomes (Abbas et al., 2025).

Collectively, these developments are driving the emergence of precision hematology, where molecular biomarkers, multi-omics technologies, artificial intelligence, and environmental exposure data are integrated to enable personalized risk assessment, earlier diagnosis, and targeted intervention (Pathak et al., 2026). Rather than relying solely on population-based risk estimates, this integrated framework supports more accurate disease prediction, patient stratification, and mechanism-informed clinical decision-making. Although important challenges related to standardization, external validation, and clinical

implementation remain, the convergence of biomarker discovery, multi-omics technologies, and explainable artificial intelligence provides a promising foundation for improving the prevention, diagnosis, and management of environmental toxicant-induced hematological disorders (Greene et al., 2026).

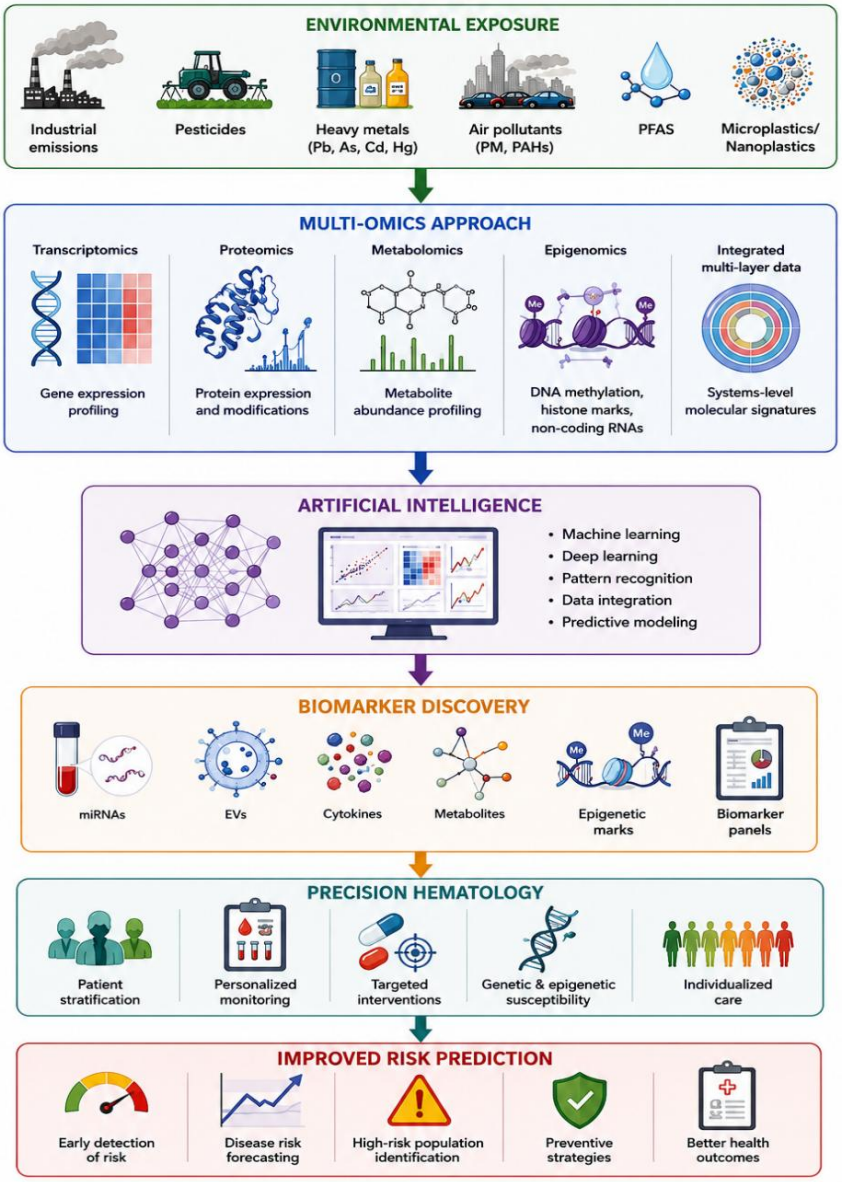

Fig. 2. Translational framework: From environmental exposure to precision hematology

Figure 2 presents a proposed translational roadmap illustrating this progression towards precision hematology. Then the roadmap linking into environmental exposure with multi-omics technologies and artificial intelligence for biomarker discovery. Integration of these approaches supports precision hematology by improving patient stratification, risk prediction, early diagnosis, and targeted interventions for environmental toxicant-induced hematological diseases.

3.4.4. Research gaps and future research priorities

Despite considerable progress in elucidating the molecular basis of environmental toxicant-induced hematotoxicity, important knowledge gaps continue to limit mechanistic understanding and clinical translation (Yang et al., 2026). Much of the current literature examines individual molecular pathways independently, whereas growing evidence

indicates that hematological injury arises from extensive interactions among oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and hematopoietic stem-cell (HSC) dysfunction. Addressing these unresolved questions will be critical for refining mechanistic models, identifying clinically relevant biomarkers, and advancing precision approaches in environmental hematology. Several research priorities warrant particular attention (Wang et al., 2025).

Priority research question first abour what determines pathway dominance following environmental toxicant exposure, although numerous molecular pathways contribute to environmental hematotoxicity, the factors governing pathway predominance under different exposure conditions remain poorly defined. Whether oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, or other mechanisms become the principal drivers of disease is likely influenced by toxicant characteristics, exposure duration, dose, and host susceptibility. Defining this mechanistic hierarchy would improve our understanding of disease pathogenesis and facilitate the development of more targeted therapeutic interventions (Koyama et al., 2024).

Priority research question second, which molecular events occur earliest during toxicant-induced hematological injury, current knowledge is derived largely from cross-sectional investigations and end-stage experimental models, making it difficult to distinguish initiating molecular events from secondary pathological responses. Longitudinal studies integrating temporal exposure assessment with molecular profiling are therefore needed to establish the sequence of pathogenic processes and identify early biomarkers of toxicant-induced hematological injury (Pognan et al., 2023). Priority research question third about how do mixed environmental toxicant exposures influence hematopoiesis, in real-world settings, individuals are exposed to complex mixtures of environmental toxicants rather than single contaminants. Nevertheless, most mechanistic studies continue to evaluate individual toxicants in isolation. Determining how combined exposures interact to influence hematopoietic function, molecular signaling, and disease susceptibility remains a major challenge for environmental toxicology and human health risk assessment (Fry et al., 2026).

Table 2. Current limitations and future research priorities in environmental toxicant-induced hematotoxicity

Current Limitation	Future Direction
Predominant focus on oxidative stress	Adoption of integrated molecular frameworks incorporating multiple pathogenic mechanisms
Predominantly acute exposure models	Long-term and environmentally relevant exposure studies
Use of high experimental toxicant concentrations	Environmentally realistic exposure concentrations
Heavy reliance on animal and in vitro models	Human cohort studies and translational research
Investigation of individual molecular pathways	Systems biology approaches integrating interconnected molecular mechanisms
Conventional biomarker assessment	Multi-omics approaches incorporating transcriptomics, proteomics, metabolomics, and epigenomics
Limited evaluation of epigenetic regulation	Comprehensive chromatin profiling and epigenomic analyzes
Minimal investigation of immunometabolic alterations	Integrated immunometabolomic profiling
Insufficient studies on hematopoietic stem cell biology	Investigation of bone marrow niche biology and stem cell programming
Limited application of artificial intelligence	Artificial intelligence-assisted toxicology and predictive risk modeling

Priority research question fourth, can hematopoietic stem-cell biomarkers predict future hematological diseaseubtle disturbances in HSC function may occur long before overt clinical manifestations become apparent, suggesting that HSC-associated biomarkers could provide sensitive indicators of early toxicant-induced injury. Identifying and validating reliable biomarkers of stem-cell dysfunction may improve early diagnosis, disease surveillance, and risk stratification while supporting more effective preventive interventions (Rix et al., 2022). Priority research question 5: can artificial intelligence improve prediction of environmental hematotoxicity, the integration of multi-omics datasets with environmental exposure histories and clinical information provides an ideal foundation for machine-learning approaches capable of identifying individuals at elevated risk of toxicant-induced hematological disease. Future research should also prioritize explainable artificial intelligence methods to improve model transparency, strengthen biological interpretation, and facilitate clinical implementation (Boini et al., 2025). Beyond the research priorities outlined above, several emerging technologies are expected to further transform the understanding, diagnosis, and management of environmental toxicant-induced hematotoxicity.

3.5 Future perspectives and emerging technologies

Building on the research priorities outlined above, future advances in environmental hematotoxicology are expected to be driven by the integration of mechanistic toxicology, systems biology, multi-omics technologies, and emerging computational approaches. While substantial progress has been made in identifying individual pathways involved in toxicant-induced hematological injury, future research should focus on elucidating the dynamic interactions among oxidative stress, mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and hematopoietic stem-cell dysfunction. Such efforts will be essential for developing comprehensive mechanistic models that more accurately reflect the complexity of environmental exposures and their biological consequences.

The increasing availability of multi-omics technologies, including transcriptomics, proteomics, metabolomics, and epigenomics, provides unprecedented opportunities to characterize molecular responses to environmental toxicants at multiple biological levels (Aslam et al., 2024). Integrating these datasets through systems-biology approaches may facilitate the identification of key regulatory networks, novel biomarkers, and previously unrecognized therapeutic targets associated with hematotoxicity (Amini & Wang, 2026). Artificial intelligence and machine-learning methodologies are expected to play an increasingly important role in environmental health research. By combining multi-omics data, environmental exposure histories, and clinical information, these approaches may improve risk prediction, patient stratification, biomarker discovery, and early disease detection. Particular emphasis should be placed on the development of explainable artificial intelligence models that enhance transparency, biological interpretability, and clinical applicability (Boini et al., 2025). Translating these advances into clinical practice will require large-scale longitudinal human studies, standardized biomarker validation frameworks, and stronger interdisciplinary collaboration among toxicologists, hematologists, epidemiologists, bioinformaticians, and data scientists (Liao et al., 2025). Such efforts will be critical for advancing precision hematology and improving the prevention, diagnosis, and management of environmental toxicant-induced hematological disorders (Salam et al., 2025).

4. Conclusions

Environmental toxicants remain a major challenge to hematological health by disrupting multiple interconnected molecular pathways that extend beyond the conventional oxidative stress paradigm. Although oxidative stress continues to play a

central role in toxicant-induced cellular injury, it represents only one element of a broader mechanistic network that includes mitochondrial dysfunction, ferroptosis, pyroptosis, epigenetic reprogramming, immunometabolic dysregulation, and hematopoietic stem-cell impairment. Considered together, these interacting mechanisms provide a more comprehensive explanation for the heterogeneity of clinical manifestations, chronic disease progression, and inter-individual differences observed in environmental toxicant-induced hematological disorders.

Appreciating the extensive interplay among these pathways shifts the emphasis from isolated molecular mechanisms towards a systems-level view of environmental hematotoxicity. This integrated perspective not only deepens mechanistic understanding but also strengthens opportunities for biomarker discovery, more accurate risk prediction, and the identification of targeted therapeutic strategies. In parallel, combining mechanistic insights with multi-omics technologies, artificial intelligence, and precision medicine offers a pathway towards transforming environmental hematology from a predominantly descriptive discipline into one focused on early detection, personalized risk assessment, and mechanism-informed clinical intervention.

Overall, environmental toxicant-induced hematotoxicity should be regarded as a systems-level disorder driven by dynamic interactions among multiple molecular pathways rather than as a consequence of oxidative stress alone. Continued integration of multi-omics technologies, longitudinal human cohort studies, and explainable artificial intelligence is expected to accelerate the transition from descriptive environmental toxicology to predictive precision hematology. Such an approach will strengthen biomarker discovery, improve causal inference, and support the development of more effective strategies for the prevention, early diagnosis, and management of environmental toxicant-induced hematological disorders..

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During the preparation of this work, the authors used Grammarly to assist in improving grammar, clarity, and academic tone of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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