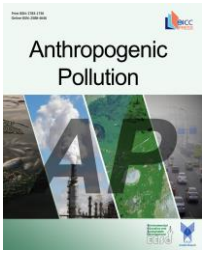

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Review Article

Nanoplastics as Epigenetic Disruptors: A Biochemical Review of Environmental Pollutants and Gene Regulation

Tahereh Navaei Diva[1*], Ali Taleshtabar Dolaty [2]

[1]*Department of Chemistry, Sava.C., Islamic Azad University, Savadkooh, Iran*
[2]*Department of Biology Education, Farhangian University, P.O. Box 14665-889, Tehran, Iran*

***Corresponding author:** Tahereh.Navai@iau.ac.ir

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Abstract

Nanoplastics (NPLs), emerging environmental contaminants, have been found to perturb cellular homeostasis through biochemical and epigenetic mechanisms. Due to their small size and high surface reactivity, NPLs can pierce biological systems where they induce oxidative stress, inflammation, and endocrine disruption. Recent studies propose that NPLs have the ability to alter DNA methylation patterns, histone changes, and non-coding RNA expression, leading to persistent alterations in gene regulation. Such epigenetic changes correlate with the development of cancer, neurological diseases, and metabolic disorders with possible heritable effects crosswise through generations. In spite of rising evidence, considerable deficiencies remain in current research, especially regarding human epidemiological experiments and standardized detection assays. Lack of longitudinal experiments with accredited biomarkers limits our data about chronic exposure as well as transgenerational impacts. Multi-omics approaches, such as transcriptomics, proteomics, and metabolomics, hold viable methodologies to establish molecular pathways induced by NPLs. Integration of biochemical data with environmental toxicity is critical to enable accurate risk assessment as well as policy construction. Our review highlights an imperative for interdisciplinary collaboration to address the complex health and environmental implications of nanoplastics. Improvement of detection technologies, standardizing exposure protocols, and incorporating epigenetic endpoints into regulatory protocols are critical steps to reduce NPLs' molecular legacy.

Keywords: Nanoplastics; Epigenetic disruption; Oxidative stress; Multi-omics; Environmental toxicology; Regulatory challenges

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1. Introduction

Nanoplastics (NPLs) are described as plastic particles typically with sizes in the range of 1 to 1000 nanometers (nm), although certain definitions limit this range to 100 nm, depending on the application and detection procedures used (Gigault et al., 2018; Hartmann et al., 2019). The particles may be distinguished into primary nanoplastics—prepared on purpose with certain industry applications—or secondary nanoplastics produced by the breakdown of larger chunks of plastic litter like nanoplastics (Figure 1) (Sharma et al., 2023; Kochanek et

al., 2025; Allen et al., 2022). Due to their smaller size and high surface area-to-volume ratio, nanoplastics have unique physicochemical properties that allow their mobility, reactivity, and biological uptake (Yu et al., 2023). Their largest contributor is the degradation of microplastics within the environment through physical, chemical, and biological processes, including UV radiation, mechanical fragmentation, and microbial activity (Karbalaei et al., 2022; Allen et al., 2022). The biggest sources are industrial activities, specifically the manufacturing process of plastics, as well as packaging and recycling processes by industries, through the release of nanospheres by mistake (Kochanek et al., 2025). Moreover, a combination of consumer products, including cosmetics, paints, and detergents, is intentionally formulated with engineered nanoplastics that will end up in wastewater treatment plants and indirectly affect aquatic ecosystems (Zimmermann et al., 2025; Kochanek et al., 2021). Nanoplastics were discovered to be found in various environmental compartments such as air, freshwater ecosystems, soils in terrestrial environments, as well as in living organisms, indicating their pervasive distribution (Yu et al., 2023; Kochanek et al., 2025). Their occurrence in urban runoff, farm soils, and estuarine sediments suggests the intricate character of their environmental transport and difficulty in tracing their sources and destinies (Allen et al., 2022; Gündoğdu et al., 2023). Moreover, fragments from tire deterioration, synthetic fibers from clothing wear, and plastic coatings employed in packaging food are increasingly identified as significant sources of the growth of nanoplastic pollution (Karbalaei et al., 2022; Zimmermann et al., 2025). Identification of their sources is central to an evaluation of their associated environmental and health effects. Due to their size, they can permeate through biological membranes, interact at a cellular level, and potentially cause adverse effects such as oxidative stress as well as inflammation (Kochanec et al., 2025; Gigault et al., 2018). As scientific knowledge has improved over time, it has increasingly been evident that nanoplastics cannot be considered a subset of microplastic pollution; they represent their own class of harmful compounds that deserve unique detection protocols as well as regulatory interest (Hartmann et al., 2019; Yu et al., 2023). Epigenetics refers to gene expression changes that can be inherited but that take place in the absence of concomitant DNA sequence alterations. These changes are mediated by a host of different mechanisms such as DNA methylation, histone modification, chromatin remodeling, and non-coding RNA (Soles & Shi, 2021; Greer & Shi, 2022).

As compared to mutations that arise at a gene's DNA sequence, epigenetic alterations share a characterization by virtue of their reversal alongside their increased responsiveness to environmental and developmental signals. For instance, DNA methylation tends to suppress gene expression by the addition of methyl groups to cytosine bases, whereas histone acetylation tends to activate gene expression by relaxing the chromatin complex (Song et al., 2025). These transactions represent a central aspect of developmental cell fate regulation, embryogenesis, and tissue-specific gene expression. Epigenetic regulation is also crucial in maintaining cell identity and has been associated with different diseases, including cancer, neurodegenerative diseases, and diseases involving the immune system (Bird, 2002; Cavalli & Heard, 2019). The recent advances in epigenomic profiling, in addition to CRISPR-based editing technologies, have opened up possibilities to edit epigenetic marks in a defined manner and hence unveiled novel therapy options (Song et al., 2025). Again, the crosstalk between epigenetic processes and RNA processing, like alternative polyadenylation and splicing, adds another level of complexity to the regulation of genes (Soles & Shi, 2021; Tian & Manley, 2017). Collectively, epigenetics plays the role of an active interface to connect genotype and phenotype by correspondingly regulating gene expression to internal and external stimuli. The objective of this review is to provide an in-depth analysis of the biochemical mechanisms by which nanoplastics cause epigenetic changes. It specifically summarizes the interactions of nanoplastics with cellular systems to bring about DNA methylation shifts, post-translational histone modifications, chromatin structure, and non-coding RNA expression. Through an integration of the latest experimental results and theory-based paradigms, this review tries to establish the molecular mechanisms by which these epigenetic transitions are governed and their likely impacts on gene expression, illness vulnerability, and intergenerational inheritance. This research will advance our understanding of nanoplastic toxicity at the organismal level and bring to light novel areas of study in environmental health.

2. Research methodology

This study is a narrative review aimed at synthesizing current knowledge on the biochemical and epigenetic impacts of NPLs as emerging environmental pollutants affecting biological systems. To achieve this, a comprehensive and systematic search was conducted across reputable scientific databases, including PubMed, Scopus, Web of Science, and ScienceDirect. Keywords such as “nanoplastics”, “epigenetic disruption”, “oxidative stress”, “multi-omics”, “Environmental toxicology”, and “Regulatory challenges” were used to

identify relevant peer-reviewed articles. Although the search covered a broad range of publications, the majority of selected studies were published between 2020 and 2025, reflecting the recent surge in research addressing pollution-related health risks and molecular disruptions caused by NPLs. This time frame also coincides with the advancement of multi-omics technologies and growing awareness of epigenetic consequences linked to environmental contamination.

3. Results and Discussion

The research findings are presented in several separate sections

3.1. Nanoplastics: Properties and Biological Entry Routes

3.1.1.*Physicochemical Characteristics of Nanoplastics*

NPLs, in general characteristically less than 1000 nm in size, possess physicochemical features that profoundly impact their mobility in the environment and biological interactivity. The minute size allows penetration through biological barriers like intestinal epithelium and even the blood–brain barrier to invoke concerns over systemic exposure (Yong et al., 2020). Surface charge, usually assessed through zeta potential, regulates colloidal stability and biomolecule interactivity. Positively charged NPLs are prone to greater adsorption to negatively charged cell membranes and nucleic acids and are likely to increase cellular uptake and cytotoxicity (Ducoli et al., 2025). Further, aging processes in the environment, like UV irradiance and oxidation, may change surface charge and property governing the preference of NPLs for biological structures rich in lipids and hydrophobic pollutants. Hydrophobic NPLs have the potential to adsorb persistent organic pollutants (POPs) and act as transporters, enhancing adverse toxicological effects (Alimi et al., 2018). Weathering processes like photodegradation and biofilms may increase the polarity of NPLs and alter their interactions with aquatic systems (Hartmann et al., 2019). Additionally, the form and stiffness of NPLs, in being spherical, fibrous, or fragmented, affect their kinetics of aggregation and routes of cellular internalization (Mattsson et al., 2017). These physicochemical properties indirectly determine the environmental behavior, bioavailability, and toxicological properties of nanoplastics and so justify standardized characterization in risk assessment protocols.

3.1.2. *Routes of Human Exposure*

Nanoplastics may be incorporated into the human body through inhalation and ingestion. Air-based nanoplastics produced by tire wear, polyester clothing, and urban dust are presented in the atmosphere and, upon inhalation, may avoid mucociliary clearance and so come to rest in the alveolar zone (the region of the lungs where gas exchange occurs between alveoli—tiny air sacs—and pulmonary capillaries) and possibly translocate through the air–blood barrier into systemic circulation (Bhardwaj et al., 2025). Exposure through diet is achieved by ingestion of contaminated seafood, table salt, pre-packaged foods, and bottled drinking water stored in clear plastics. After ingestion, nanoplastics may penetrate the intestinal epithelium through transcellular uptake or by paracellular diffusion and so gain entry into portal circulation and be deposited in organs like the liver and kidney (Thapliyal et al., 2025). Dermal exposure is a third mode of contact because nanoplastics from consumer products and personal care products, and industrial particulate, as well as soil, entail direct contact with the dermis. An intact stratum corneum effectively excludes the vast bulk of particles; however, wet or broken skin admits nanoplastics through intercellular paths or hair follicles. When the epidermal cover is compromised, these particles have the possibility of entering dermal capillaries and then achieving systemic circulation.

3.1.3. *Systemic Distribution and Toxicological Effects*

NPLs represent an important risk with the potential to accumulate in multiple tissues after exposure through either environmental or occupational routes. After internalization of these particles, they can permeate through biological barriers like the epithelial lining of the intestine and alveolar membrane and possibly the blood-brain barrier to achieve systemic distribution and organ retention in the liver, kidneys, spleen, and brain (Lee et al., 2023; Schirinzi et al., 2025).

Animal studies have determined that once in the blood system, nanoplastics are deposited in tissues like the liver and kidney and cause oxidative stress and enzymatic dysfunction, and inflammation (Vogel et al., 2024; Deng et al., 2023). Studies on gold-doped polymeric nanotoxicants have shown significant accumulation within aquatic organisms reflective of possible trophic transfer and ecological persistence (Schirinzi et al., 2025). With the application of mammalian surrogates in experimental investigations, long-duration exposure has been associated with oxidative damage and mitochondrial impairment, and immune activation, and hence implicatesthe possibility of NPLs to accumulate and perturb cellular homeostasis (Deng et al., 2023; Leslie et al., 2022).

3.1.4. *Cellular Internalization and Subcellular Responses*

The cellular internalization of nanoplastics occurs principally through endocytic processes such as clathrin-mediated and caveolae-mediated processes (two cellular mechanisms for internalizing substances: one using clathrin protein-coated pits, and the other involving small invaginations called caveolae) and through passive diffusion as a function of particle size, surface charge, and functionalization (Hua & Wang, 2022). Within the cellular environment, nanoplastics are carried by endosomes, lysosomes, and autophagosomes and are likely to elicit organelle-specific stress responses. In vitro cell experiments have been capable of demonstrating mitochondrial fragmentation, endoplasmic reticulum stress, and cytoskeleton disruption, and imply subcellular modes of cellular injury (Lee et al., 2023). The long-term cellular residence of nanoplastics and their capacity to engender disturbances in the expression of genes and signal transduction processes are of significant concern and possess considerable potential for long-lasting detrimental health consequences, such as carcinogenesis and developmental/metabolic disturbances (Leslie et al., 2022; Hua & Wang, 2022). Table 1 qualitatively summarizes how nanoplastics affect different environmental compartments (water, soil, air, marine ecosystems, and living organisms), highlighting their pathways of entry, ecological consequences, and potential risks to human health.

3.2. Biochemical Mechanisms of Epigenetic Alteration

3.2.1. *DNA methylation: how nanoplastics may alter methylation patterns*

Methylation of DNA is one such epigenetic phenomenon that regulates gene expression, cell differentiation, and maintains genomic integrity. Environmental contaminants, including NPLs, have been implicated as potential disruptors of such a regulatory mechanism. In particular, polystyrene-based nanoplastics embody the capability to cause oxidative stress alongside inflammatory responses that have been demonstrated to impact DNA Methyltransferase (DNMT) activity with subsequent methylation pattern changes (Leslie et al., 2022; Zeng et al., 2024).

These changes could lead either to a global hypomethylation (a general reduction of chemical markers called methyl groups attached to DNA, leading to the activation of genes) or specific hypermethylation (an increase of such markers at specific regions, leading to the suppression of specific genes). These changes of gene action are of vital importance in protecting cells from programmed cell death (apoptosis), supporting immune systems, and assisting in tissue renewal (Wade et al., 2025; Poma et al., 2023). Mechanistically, the NPLs might alter methylation through ROS-mediated mechanisms. The reactive oxygen species could repress or induce overexpression of DNMTs based on cell context and consequently cause epigenetic instability (Bogan & Yi, 2024). The NPLs might equally act as delivery vehicles for endocrine-disrupting chemicals (EDCs), whose individual action is to alter DNMT expression and reorganization of the chromatin (Poma et al., 2023). The combined actions might have transgenerational consequences with a proven aquatic model in which the change in the methylation is retained across generations (Wade et al., 2025). NPLs in plant systems have been demonstrated to affect microRNA and long non-coding RNA (lncRNA) expression, critical DNA methylation, and chromatin structure regulators (Aloisi et al.,2025; Poma et al., 2023) (Figure 2). Epigenetic alterations of this sort may affect stress response, growth, and fertility. Similarly, in animal systems, we have found exposure to NPLs to be correlated with differentially methylated regions (DMRs) within genes related to metabolism, neurodevelopment, and detoxification (Hua & Wang, 2022; Zeng et al., 2024). These findings suggest NPC-mediated epigenetic alteration is evolutionarily conserved and may be an ecosystem-wide hazard.

With nanoplastics so ubiquitously present in environmental contexts and having the capacity to induce long-lasting epigenetic transformations, greater investigation is needed. The simultaneous application of epigenomic profiling and assessments of toxicity might be beneficial in the identification of biomarkers of susceptibility and exposure. An examination of nanoplastic-mediated methylation change reversibility might likewise provide routes to treatment strategies or ecological restoration. Accordingly, the science of epigenetics provides an exemplary framework by which to illuminate the fragile but significant biological outcomes of nanoplastics.

3.2.2. *Histone modifications: changes in acetylation, methylation, and chromatin structure*

Histone modifications are an important characteristic of epigenetic regulation and affect the structure of chromatin and the accessibility of genes.

Figure 1. Common sources of primary and secondary NPLs

Table 1. Environmental Impacts of Nanoplastics Across Different Contexts

Environment	Main Source of Nanoplastics	Qualitative Effects	Example Outcomes
Surface and drinking water	Water treatment plants, plastic packaging	Entry into the food chain	Contamination of water, risks to human health
Agricultural and urban soils	Organic fertilizers, compost, tire wear particles	Altered microbial activity	Reduced nutrient uptake in plants
Air and urban dust	Tire abrasion, synthetic fibers	Inhalation and respiratory exposure	Inflammation, respiratory dysfunction
Marine ecosystems	Breakdown of macroplastics	Disruption of photosynthesis and aquatic balance	Harm to algae and aquatic organisms
Living organisms (humans and biota)	Packaged foods, cosmetics, personal care products	Tissue penetration and systemic distribution	Oxidative stress, epigenetic alterations

Significantly, acetylation and methylation of histone tails—specifically of H3 and H4- are instrumental in both activation and repression of transcription. Research reveals NPLs exposure is capable of perturbing histone-modifying enzymes, specifically histone acetyltransferases (HATs) and histone deacetylases (HDACs), causing perturbed acetylation patterns and ensuing acetylation-associated gene expression of stress response, apoptosis, and inflammation (Poma et al., 2023). Under human epithelial lung cell experiments, the addition of polystyrene nanoplastics has been found to diminish global acetylation of H3 and be associated with antioxidant gene transcriptional behavior (Wade et al., 2025). Histone methylation, specifically at lysine residues like H3K4, H3K9, and H3K27, is another important mechanism influenced by NP exposure. The marks are either associated with activation or repression of gene expression, depending on their context and position. Research using zebrafish and mammalian systems has demonstrated nanoplastic exposure to modulate histone methyltransferase activity and result in alterations in levels of H3K27me3 and H3K9me2—epigenetic modifications correlated with chromatin condensation and repression of genes (Cho et al., 2025; Hua & Wang, 2022). Altered histone methylation has been correlated with developmental regression, dysregulated immune systems, and neurotoxicity, and implies the possibility of disruption in chromatin remodeling at crucial points in developmental life. Along with discrete histone modifications, nanoplastics may influence higher-order chromatin structure. Findings show nucleosome positioning and chromatin compaction aberrations in nanoplastic-treated cells as a consequence of altered chromatin remodelers' expression, such as SWI/SNF complexes (Bogan & Yi, 2024). These structural distortions may impede DNA repair processes, hinder replication fidelity, and modulate long-distance gene regulatory processes. Interestingly, some of these epigenetic alterations appear to be transmissible, posing considerable epigenetic concern in regard to nanoplastic exposure, inducing transgenerational alterations in chromatin structure and gene function (Wade et al., 2025). As analysis moves forward, histone modifications represent a sensitive and dynamic biomarker of cellular stress and nanoplastic-mediated epigenetic reprogramming.

3.2.3. *Non-coding RNAs: impact on miRNAs and lncRNAs involved in gene silencing or activation*

Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are critically involved in gene expression regulation by post-transcriptional silencing and chromatin regulation. As depicted from available literature, NPLs exposure has been discovered to alter expression profiles and functional attributes of such ncRNAs with subsequent epigenetic reprogramming. miRNAs commonly interact with 3′ untranslated regions (3′ UTRs) of their own mRNAs with a consequent translation inhibition or degradation. Studies have found that polystyrene nanoplastics are capable of altering miRNA expression patterns in the human and aquatic systems, and then modulating genes connected to oxidative stress, apoptosis, and immune regulation (Chen et al., 2024; Poma et al., 2023). lncRNAs greater than 200 nucleotides in length operate by interacting with chromatin modifiers, transcription factors, and miRNAs themselves to direct gene expression. Nanoplastics may injure lncRNA-mediated epigenetic complex scaffolding such as PRC2, and thus influence histone methylation and DNA accessibility (Aloisi & Poma, 2025). For example, lncRNA expression, such as MALAT1 and HOTAIR, has been discovered to be disrupted in cells subjected to NP and correlates with modifications in chromatin structure and transcriptional profile (Prabhakaran et al., 2024). These modifications may have long-lasting phenotypic consequences and increased susceptibility to disease. Significantly, nanoplastic-induced dysregulation of ncRNAs has the potential to have transgenerational effects. There is evidence in zebrafish and plant systems demonstrating that miRNA and lncRNA dysregulation is maintained over time, possibly through processes of epigenetic inheritance (Wade et al., 2025; Cavalieri & Kathrein, 2022). This is relevant to the ecological and public health effects of low-dose and long-duration exposure to NPLs. As epigenetic biomarkers, ncRNAs are valuable resources in tracing environmental toxicity and guiding regulatory processes. Future studies must be on mapping responsive ncRNA networks to NPLs and interfacing them into predicted models of gene-environment interplays. Table 2 provides a qualitative overview of the major biological mechanisms disrupted by nanoplastic exposure, including DNA methylation, histone modifications, non-coding RNA dysregulation, oxidative stress, and inflammation. It highlights how nanoplastics interfere with gene regulation, cellular homeostasis, and immune responses, thereby contributing to long-term health risks and potential transgenerational effects.

3.3. Experimental Evidence from In Vitro and In Vivo Studies

3.3.1. *Cytotoxic and Genotoxic Effects*

Exposure to NPLs in cell culture models always causes cytotoxic and genotoxic effects in several cell types. Polystyrene NPLs decreased cell viability and increased DNA strand break and micronucleus formation markers in human lymphocyte lines, suggesting chromosomal instability. Human epithelial lung cells treated with 50–200 nm polystyrene NPLs demonstrated dose-dependent apoptosis, increased reactive oxygen species (ROS), and lipid peroxidation, emphasizing oxidative stress–related toxicity (Milillo et al., 2024). Ninety percent 80 nm NPLs triggered human keratinocytes to form single- and double-strand DNA breaks and upregulated γ-H2AX foci formation (Bu et al., 2024).

3.3.2. *Epigenetic Reprogramming and Transgenerational Effects*

The in vivo zebrafish (Danio rerio) system has emerged as a standard reference system to assess NP-induced epigenetic alterations in intact organisms. Background reviews emphasize zebrafish embryo applications to observe in real time by confocal microscopy the dynamics of chromatin after exposure to NPLs and show dose-dependent modifications in DNA methyltransferase expression and histone methylation (Cavalieri & Kathrein, 2022). Exposure to fluorescently stained PS-NPLs directly led to dysrhythmic heartbeat and neurodevelopmental impairment with concomitant decreases in global 5-mC and increases in histone H3K4me3 in neural tissues (Sun et al., 2023). Concurrent studies demonstrated the inability of chronically exposed developing animals to perturb methylation profiles at essential morphogenetic gene loci. Transgenerational and multigenerational aquatic organism experiments highlight long-term nanoplastic epigenetic inheritance. Parent PS-NPLs exposure of the organism Pimephales promelas (fathead minnow) produced offspring miRNA profile shifts directed toward immune-regulatory genes concomitantly with DNA methylation shifts at cytokine promoter regions (Wade et al., 2025). The in vitro animal experiments scoping review at a broad and in-depth level characterized frequent epigenomic shifts of relevance to NPLs in gill and intestinal cell lines of fish and crustaceans, respectively, and therefore highlighted the ecological significance of chromatin-based biomarkers (Viana, Tonin, & Ladeira, 2025). The in vivo findings signify wider organismal shifts in toxicity highlighted in

broad reviews (Xie et al., 2023). Besides direct cytotoxicity results, NPLs cause epigenetic reprogramming in cell culture. Polystyrene NPLs in human keratinocytes caused differential global DNA methylation patterns by bringing about hypomethylation in LINE-1 elements and hypermethylation in tumor suppressor gene promoters (Bu et al., 2024) (Figure 3). Toxicity-driven analyses unveiled dysregulation of miRNA biogenesis enzymes DROSHA and DICER by NPLs to bring about aberrant miRNA expression in pathways of oxidative stress (Chen, Lin, Gong, Zhao, & Peng, 2024). Exposure to 50 nm PS-NPLs also regulated levels of histone H3K9 trimethylation and acetylation of H3K27 in hepatocyte lines, suggesting direct disruption of chromatin-remodeling complexes (Prabhakaran et al., 2024).

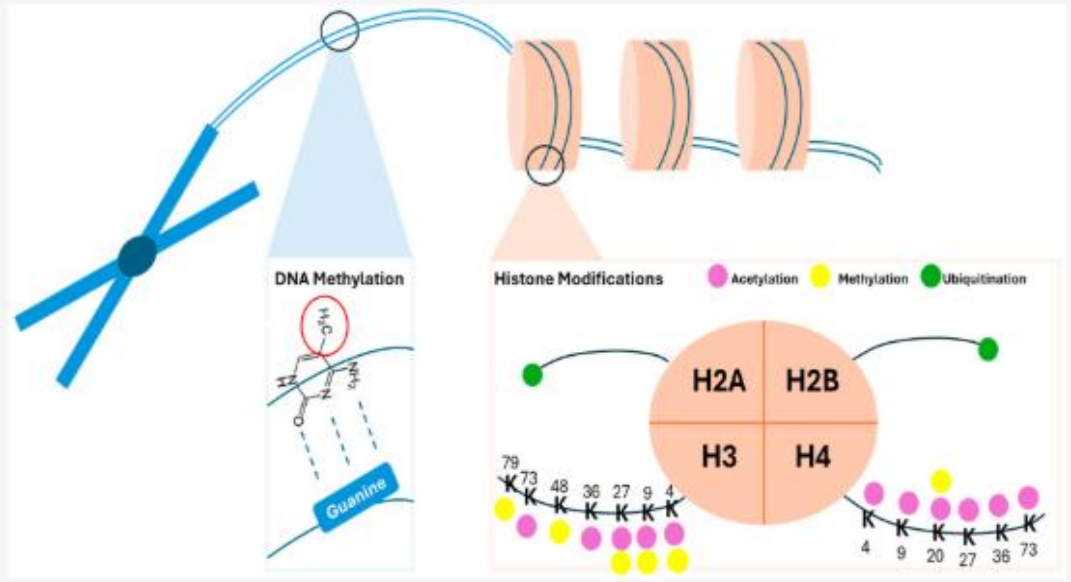

Figure 2. Epigenetic modifications in plants. DNA methylation consists of the addition of a -CH3 molecule to a cysteine residue. Main histone modifications include acetylation and methylation of lysine (K) residues of the histones. A nucleosome (the protein core around which DNA wraps itself) is composed of four proteins called H2A, H2B, H3, and H4 (H = histone)
Source: (Aloisi and Poma, 2025)

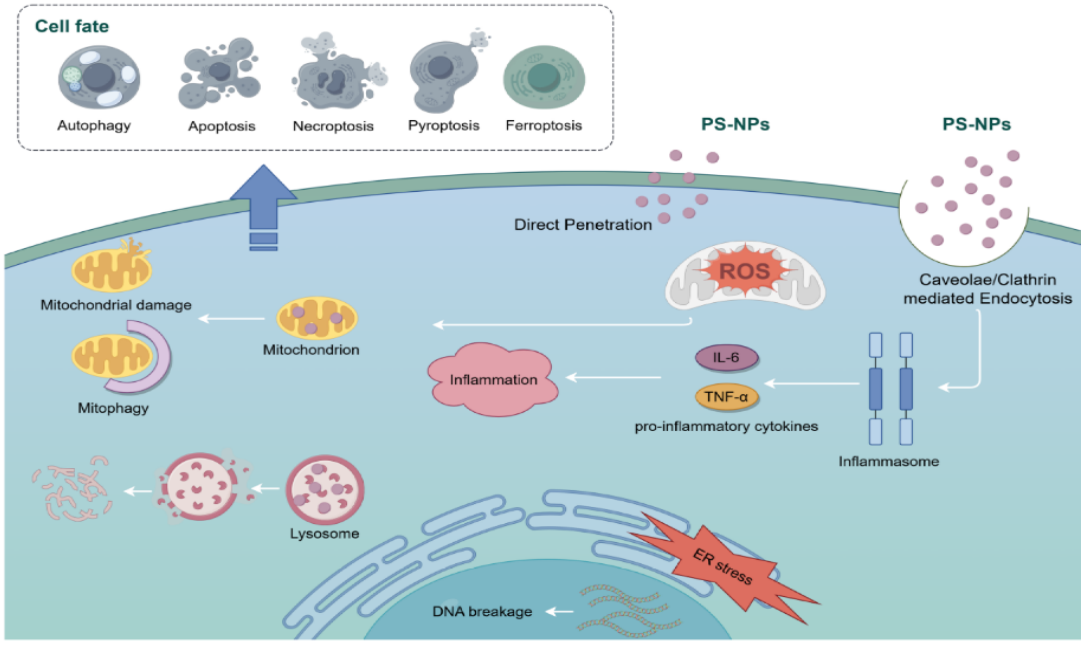

Figure 3. Mechanistic overview of PS-NP-induced cellular impacts. This figure illustrates the key biological impacts of PS-NPLs on cellular systems, including oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, autophagy disruption, and various forms of cell death
Source: (Bu et al., 2024)

Table 2. Epigenetic and Biochemical Impacts of Nanoplastics

Biological Mechanism	Example Nanoplastic Interaction	Qualitative Impact	References
DNA Methylation	Altered DNMT activity via ROS	Global hypo-/hypermethylation; gene regulation instability	Leslie et al., 2022; Zeng et al., 2024
Histone Modification	Disruption of HATs/HDACs	Aberrant acetylation/methylation; chromatin remodeling defects	Wade et al., 2025; Cho et al., 2025
Non-coding RNAs	Dysregulation of miRNAs/lncRNAs	Gene silencing disruption; immune and stress response alteration	Chen et al., 2024; Prabhakaran et al., 2024
Oxidative Stress	ROS generation by PS-NPLs	Mitochondrial dysfunction; apoptosis	Bu et al., 2024; Deng et al., 2023
Inflammation	Cytokine dysregulation	Chronic immune activation; tissue damage	Wu et al., 2024; Wade et al., 2025

3.3.3. *Renal Toxicity*

Renal cell cultures have presented strong evidence of nanoplasticic toxicity, specifically to polystyrene nanoplastics (PS-NPLs). Zhu et al. (2023) showed PS-NPLs induce apoptosis in human proximal tubular epithelial cells through oxidation and activation of MAPK signaling processes. He et al. (2024) further showed UV-aged PS-NPLs adsorbing transferrin and causing ferroptosis in renal cells, indicating a hitherto unknown mode of iron-dependent cell death. Employing a kidney–testis microfluidic device, Xiao et al. (2023) established dysregulation of cancerous signaling processes upon PS-NP exposure and posited long-term oncogenic consequences. Li et al. (2023) further presented evidence of particle size and Pb ion enrichment having significant modulating effects on PS-NP cytotoxicity to human embryonic kidney cells in vitro, wherein Pb^{2+} co-pollutant and reduced particle sizes enhanced cellular injury. Together, these investigations underscore the susceptibility of renal tissues to nanoplastic exposure and illustrate a necessity to investigate mechanisms of nephrotoxicity under environmentally relevant regimes.

3.3.4. *Respiratory Toxicity*

Respiratory cell culture systems have been increasingly employed to assess lung toxicity induced by nanoplastics in mouse, fish, as well as human models. Scientific findings from human lung epithelial lines, including A549, BEAS-2B, NHBE, as well as a number of nasal epithelial lines, verified that polystyrene nanoplastics as well as polyethylene terephthalate nanoplastics induced oxidative stress, apoptosis, ferroptosis, as well as epithelial-to-mesenchymal transition invariably mediated by ROS-dependent endoplasmic reticulum stress as well as through MAPK signal transduction cascades (Lim et al., 2019; Yang et al., 2021; Zhang et al., 2022; Wu et al., 2024). In fish cell lines dosed with PS-NPLs accompanied by copollutants, including TBBPA, copoisoning effects with additional membrane disruption were found to be observed (Soto-Bielicka et al., 2023).

Mouse models dosed intranasally with nanoplastics presented lung inflammation, ferroptosis, as well as genotoxic effects, where antioxidants, including N-acetylcysteine, only showed partial protective effects (Wu et al., 2023; Huang et al., 2022). Individually, such data indicate that respiratory tissues continue to be susceptible to treatment with nanoplastics, as well as indicate a critical need for standardized lung-based testing from lung-based toxicity among various species. Lung three-dimensional in vitro cultures and cell cultures of airway epithelial cells have also confirmed nanoplastic-mediated epigenetic reprogramming. Chronic exposure to 100 nm PS-NPLs in alveolar organoids downregulated let-7 family miRNAs critical in cell differentiation and immune response (Milillo et al., 2024). The outcomes are in accordance with the report of Toxics, suggesting surface charge and particle size to be crucial in regulating the level of ncRNA dysregulation of the airway cells (Chen et al., 2024).

3.3.5. *Gastrointestinal Toxicity*

The epithelial lining of the gut is a key site of nanoplastic uptake, and several in vitro experiments have established it to be sensitive to polystyrene and polyethylene terephthalate nanoplastics. The well-established system to simulate human intestinal uptake, Caco-2 cells, shows strong bioenergetic disruption, oxidative damage, and DNA lesions upon treatment with pristine and UV-weathered NPLs (Peng et al., 2024; Domenech et al., 2021). Size-dependent genotoxicity and presumed carcinogenicity were presented by Ding et al. (2024) in gastrointestinal cells, whereas Xu et al. (2023) and Chen et al. (2021) presented activation of autophagy as an antioxidant cell response. Translocation of orally ingested

NPLs into the nuclei of intestinal models has been shown by DeLoid et al. (2021), and Brandts et al. (2023) presented lysosome targeting and lipid biosynthesis disruption through the PPAR system. These reports collectively indicate the possibility of nanoplastics to breach the intestinal barrier and perturb metabolic homeostasis. More studies have been conducted on the interactions of gastric epithelial cells and intestinal organoids with NPLs. Ding et al. (2021) tracked PS-NPLs' cytotoxicity and tissue distribution in GES-1 cells, and He et al. (2022) revealed duodenal tissue inflammation and permeability breakdown by ROS-mediated NF-κB/NLRP3 signaling. Magrì et al. (2021) and Banaei et al. (2023) investigated real-world sources of NPLs, such as PET and PLA, by teabag packaging and confirmed their intestinal bioactivity. Moreover, uptake enhancement by co-pollutants such as PFOS (Liu et al., 2022) and transition and heavy metals (Li et al., 2023) increased the NPLs' toxicity. Intestinal organoids and triple-culture systems-based advanced investigations further established NPLs' accumulation and inflammatory actions (Hou et al., 2022; Busch et al., 2021). These findings highlight nanoplastics' multiple dangers to digestive health and their justification to be listed as emergent environmental toxicants.

3.3.6. *Immunotoxicity Across Vertebrate and Invertebrate Models*

Immunocompetent cell systems have shown an array of reactions to nanoplastic exposure that are diverse and species-specific. Treatment with polystyrene nanoplastics (PS-NPLs) has been demonstrated to induce oxidative stress, DNA damage, as well as cytokine dysregulation in human hematopoietic cells, as well as peripheral blood mononuclear cells with size- as well as charge-specific cell toxicity (Rubio et al., 2020; Djapovic et al., 2023; Ballesteros et al., 2020; Babonaite et al., 2023). Exposures utilizing $CD34^+$ stem/progenitor cells as well as immortalized lymphocytes have been discovered to induce changes in metabolomic markers as well as genotoxity, notably with concurrent treatment utilizing heavy metals or with silver nanoplastics (Guo et al., 2023; Ilić et al., 2022; Li et al., 2023). In cell-based models with RAW264.7 macrophages, internalization utilizing PS-NP has been accompanied by disturbed lipid metabolism, upregulated pro-inflammatory signaling, as well as lysosomal damage, with cell reactions determined by both surface functionalization as well as protein corona makeup (Chen et al., 2023; Florance et al., 2021, 2022; Brandts et al., 2023; Wang et al., 2023). Aside from human models, charge-dependent cytotoxicity and inflammation have been noted among murine lymphocytes as well as murine splenic macrophages, and disruptions within IL-1 signals have been associated with gut–brain axis dysregulation (Yang et al., 2023; Li et al., 2022). PS-NP invasion into aquatic animals disrupts immune homeostasis among fish macrophages as well as sea urchin coelomocytes and impacts phagocytosis, redox homeostasis, as well as genes that contribute to inflammation (Brandts et al., 2023; Murano et al., 2021). In general, these results indicate the immunotoxic effect of nanoplastics among both vertebrate as well as invertebrate animals and underscore cross-species comparative analysis to distinguish conserved as well as divergent immune pathways. Reviews and meta-analyses collectively offer a holistic description of NPLs-mediated epigenetic disruptions ranging from single cells to entire organisms. Xie et al. (2023) combined over 100 articles that recorded NPA-triggered changes in DNA methylation, histone alterations, together with non-coding RNA (ncRNA) gene expression within terrestrial and freshwater ecosystems. Viana et al. (2025) also point to the necessary standardized exposure protocols to minimize observed variability among the epigenetic endpoints being measured. Pioneering studies also recommend integrating multi-omics data—made up of epigenomic, transcriptomic, and metabolomic components—to develop predictive models for NPA toxicity and to inform environmental hazard evaluations (Hua & Wang, 2022; Poma, Morciano, & Aloisi, 2023; Prabhakaran et al., 2024).

3.4. Dose-dependent effects and tissue-specific responses

NPLs, and in particular polystyrene-based particles, have emerged with well-documented dose-dependent toxicity in some biological systems. Sarma et al. (2022) demonstrated that human lymphocytes exposed to PS-NPLs (50-2,000 µg/mL) exhibited chromosomal aberrations and reduced viability and thus established genotoxicity at higher dosages. The hepatic models further confirm dose-dependent cytotoxicity. Bu et al. (2024) confirmed PS-NPLs to dismantle autophagy and induce ferroptosis in liver cells in an effect whose intensity is amplified at concentrations above 50 µg/mL. These findings establish particle size and dose to be significant predictors of hepatotoxicity. The in vivo experiments have robust evidence to demonstrate tissue-specific damage and accumulation. Deng et al. (2017) orally gave PS-NPLs to mice at a dose of 20 mg/kg/day once daily for 28 days and recorded particle deposition in the liver, kidney, and spleen. The liver tissues showed elevated ALT/AST levels and inflammatory cytokines, while renal tissues showed glomerular damage.

Respiratory tissues are seemingly responsive to nanoplastic exposure. Milillo et al. (2024) established that human alveolar epithelial cells treated with 800 nm PS-NPLs displayed greater senescence and apoptosis and upregulated IL-6 and CXCL8. Inhalation experiments in vivo in rodents demonstrated particle localization in alveolar sacs and bronchioles and dose-dependent inflammation and epithelial thickening (Xie et al., 2023). These findings suggest that the respiratory epithelium is potentially an earlier target of airborne nanoplastics. The immune and reproductive systems are dose-responsive as well. Treatment of PS-NPLs by Wade et al. (2025) in Pimephales promelas modulated immune cell miRNA expression and induced cytokine promoter methylation. Long-term dosing of a murine system with NPLs led to impaired spermatogenesis and reduced levels of testosterone in a dose-dependent fashion, with histopathological lesions in testicular tissue. These are system endpoints and show the broad biological range of nanoplastics, besides sites of key accumulation. Viana et al. (2025) performed a systematic review and concluded from an analysis of 108 in vitro experiments that respiratory and neural cell lines are specifically more sensitive to cytotoxicity induced by NPLs compared to hepatic or digestive lines. Smaller and positively charged particles (<100 nm) were always correlated with increased toxicity. The review highlighted the fact that tissue-specificity is governed by dose and size as well as by surface chemistry and duration of exposure.

Individually, these findings indicate a necessity for characterization of dose-response and tissue-specific investigation for the field of nanoplastic toxicology. In future research, standardized protocols of exposure should be established, and multi-omics approaches should be combined to understand organ-specific vulnerability. As nanoplastics spread increasingly into environmental matrices, knowledge about their differential effects throughout tissues will be crucial to precise risk assessment as well as effective regulatory action.

3.5. Limitations and gaps in current experimental designs

3.5.1. *Methodological and Analytical Constraints*

Despite the growing level of academic investigation on NPLs, current experimental systems used in in vitro and in vivo experiments are faced with significant limitations hindering accurate risk assessment. One overriding issue is the over-reliance on commercially available polystyrene nanoplastics that cannot be representative of the chemical diversity, surface degradation, and additive properties of environmental NPLs (Cunningham et al., 2023). The bulk of the investigations is on pristine, spherical PS-NPLs, while ignoring the rough morphologies and inhomogeneous polymer compositions characteristic of real samples (Xie et al., 2023). Another important gap is the non-uniform procedures of characterizing and exposing the NPLs. Particle size and surface charge, and aggregation property are highly variable across experiments, so it is very hard to make inter-comparison (Bu et al., 2024). Most in vitro experiments do not report important physicochemical parameters like zeta potential or the dispersity index, and these are needed to interpret biological interactions. Further, the concentration of exposure is often too high and bears no relevance to the environment (Viana et al., 2025). In vivo systems vary in duration and routes of exposure. Oral gavage, injection, and immersion are employed frequently but cannot simulate the chronic low-dose environmental exposure (Deng et al., 2017). Short-term effects are again overrepresented in the vast majority of animal-based research at the expense of long-term effects such as epigenetic inheritance, reproductive toxicity, and immune modulation (Wade et al., 2025). The restriction to a non-multigenerational study design precludes us from gaining insight into transgenerational risk.

3.5.2. *Biological Scope and Predictive Limitations*

Another limitation is the extremely narrow focus on limited organ systems—it is primarily the liver, gut, and brain—to the neglect of other sensitive tissues such as endocrine glands, bone marrow, and placenta (Milillo et al., 2024). Most experiments are even carried out in monocultures or using a single-cell line and cannot portray tissue–tissue complexity and system-wide effects. The newer sophisticated systems, such as organoids and co-culture systems, are yet to be utilized in NP toxicology. Analytical hurdles also hinder progress in experimental studies. The measurement and quantification of NPLs in biological matrices pose considerable technical challenges due to their small size and low mass concentration (Cunningham et al., 2023). Techniques such as electron microscopy, Raman spectroscopy, and nanoparticle tracking analysis require specialized instrumentation and personnel and, hence, limit availability to many research groups (Xie et al., 2023). This has therefore led to the underreporting of NP buildup and incorrect interpretations of endpoints of toxicity. Conversely, an insufficient amount of combining experimental outcomes with simulation results is available. Not many papers make predictions using toxicokinetic or systems biology methods to forecast nanoparticle behavior at several biological levels. Without

such a combination, it is hard to extrapolate results from animal systems or cellular cultures to scenarios important to human health. Bridging the gap will involve interdisciplinary effort and funding to standardize and validate data and simulations.

3.6. Clinical and Environmental Implications

3.6.1. *Disease Associations and Mechanistic Pathways*

NPLs have increasingly been highlighted as new pollutants with significant risk to human health. Due to their submicrometric size (<1 μm), high coverage area, and chemical activity, NPLs can potentially permeate through biological barriers such as epithelial coverings of the gastrointestinal tract as well as through the blood-brain barrier for systemic delivery. When they become internalized, they interact with cell structures or their components with resultant oxidative stress, inflammation, and genotoxically-induced effects—processes that comprise the emergence of various chronic ailments (Yong et al., 2020). Due to their capability to adsorb environmental pollutants, their further biological effects represent an intricate as well as multi-dimensional threat. NPLs also pose a significant risk to neurological health. Due to their ability to cross through the blood-brain barrier, they are capable of accumulating within neural tissues, where they have the specific ability to impair synaptic transmission as well as evoke neuroinflammation. Urani et al. (2024) reported NPLs to induce β-amyloid accumulation, indicative of Alzheimer's disease. Moreover, Kumari et al. (2025) also highlighted NPLs' ability to impair the gut-brain axis, leading to cognitive impairments as well as behavioral changes. These findings support that NPLs can be implicated to induce a sequence of events leading to a series of events culminating in neurodegenerative diseases.

3.6.2. *Environmental Persistence and Systemic Exposure*

Environmental persistence, together with bioaccumulation of nanoparticles, increases their clinical significance. There is direct evidence by Leslie et al. (2022) of the occurrence of plastic particles in human blood, and hence, proving systemic exposure. The occurrence of the nanoparticles in edible organisms and their transfer through trophic levels emphasize the need for comprehensive risk assessments and diet monitoring.

3.6.3. *Combined Toxicity and Regulatory Challenges*

They are also characterized by the "Trojan Horse" effect through which other toxicants are carried by them to improve their cell entry and their resultant toxicity. Research in Environmental Science & Technology has found cadmium uptake to be facilitated by NPLs with consequent imbalance in the levels of calcium and inflammatory reactions (Li et al., 2025). This combined or synergistic toxicity renders classical toxicological paradigms obsolete and requires combined approaches to hazard assessment. Although awareness of the issue has been on the rise, the regulatory framework and analysis of NPLs are still insufficiently developed. Koelmans et al. (2022) highlighted the lack of standardized methods of detection and biomarkers of exposure to NP. The lack of coordinated protocols affects risk assessment and epidemiological analysis. As exposure to humans is becoming increasingly obvious, regulatory steps are needed critically, sophisticated analytical processes, and longitudinal analyses to establish long-lasting health outcomes associated with nanoplastics.

3.6.4. *Epigenetic Mechanisms and Multigenerational Effects*

NPLs, owing to their smaller size and high reactive surface, can permeate through barriers of a living being and come into contact with cell components such as DNA and chromatin. Recent findings confirm that NPLs can facilitate epigenetic alterations such as DNA methylation, histone acetylation, and non-coding RNA regulation disruption with relevance to acute toxicity and potentially be transmitted to future generations (Poma et al., 2023). These alterations have the prospective to change gene expression while keeping the DNA sequence unchanged and hence potentially affect developmental and disease outcomes in offspring. Animal modeling research has begun to clarify transgenerational consequences of nanoplastic (NP) exposure. Long-term exposure of zebrafishes (Danio rerio) to polystyrene nanoparticles led to alterations to methylation patterns among germ cells, with developmental anomalies found among F1 and F2 generations (Aloisi & Poma, 2025). Similar results were recorded among Daphnia magna, where DNA lesions and oxidative stress caused by nanoparticles were associated with epigenetic changes manifesting throughout various generations. Such results indicate that nanoparticles can disrupt reproductive development as well as embryonic growth through epigenetic inheritance.

3.6.5. *Endocrine Disruption and Human Health Implications*

The endocrine system is particularly vulnerable to epigenetic perturbations caused by NPLs. Studies have shown that NPLs are capable of perturbing estrogenic and

thyroid hormone signaling and causing modifications in gene expression in reproductive tissues (Aloisi & Poma, 2025). They are often mediated by hyper- or hypomethylation of genes related to hormone receptors and may be passed on to offspring and influence fertility, sexual maturation, and hormone-driven cancers (Bhagat et al., 2020). Further evidence to support the possibility of exposure at both the prenatal and postnatal levels is given by the finding of NPLs in placental tissue and in breast milk (Leslie et al., 2022). Mechanistic research has characterized multiple ways in which NPLs induce epigenetic alterations. Activation of inflammatory cascades, production of oxidative stress, and inhibition of chromatin remodeling enzymes are some of the involved factors (Urani et al., 2024). For example, nanoparticles have been related to epigenetic changes of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which represent key controllers of chromatin accessibility to gene transcription (Kumari et al., 2025). These interferences may impact only directly exposed subjects but may leave epigenetic imprints on the germ cells and induce transgenerational transmission. Although these results exist, limited human data are available to date. Findings from the presence of microplastic particles in blood throughout humans, placental tissue, and breast milk constitute adequate evidence to confirm that exposure is ubiquitous and has the potential to affect fetal development and future health outcomes (Leslie et al., 2022; Pulusu et al., 2025). Epigenetic biomarkers, including miRNA profiles and methylation signature changes, represent prospective avenues to quantify nanoparticle exposure effects and heritable results (Li et al., 2023). More longitudinal and multi-generational experiments should be conducted to validate such correlations and to inform public health strategies. Nanoplastics represent a novel category of environmental epimutagens possessing a further ability to induce gene expression changes that are inheritable. As a function of their prospective capability to interfere with endocrine signaling, embryonal growth, and germline integrity, risk assessments should include epigenetic endpoints as a central aspect. Future investigations should be directed towards mechanistic evaluations, standardized exposure regimens, and epidemiologic correlations with human surrogates to delineate comprehensively the transgenerational hazard of nanoplastics.

3.7. Broader environmental health concerns and regulatory challenges

3.7.1. *Environmental Persistence and Systemic Exposure*

NPLs have been commonly recognized as pervasive environmental contaminants that can theoretically affect ecosystems and human health. As a result of their small size, high surface area, and chemically reactive properties, they can permeate through biological membranes, adsorb contaminants, and persist within atmospheric, aquatic, and terrestrial environments (Khanna et al., 2024). In comparison to their larger counterpart, microplastics, NPLs have the potential to permeate distant habitats and cell architectures with unique toxicological problems.

The environmental health effects of NPLs go even beyond direct toxicity. Their carrier function to retain heavy elements, persistent organic pollutants (POPs), and pathogens enhances their environmental effect even further. This "Trojan Horse" action allows simultaneous co-delivery of harmful agents into organisms to enhance bioavailability as well as toxicity (Sharma et al., 2023). Research has established that nanoparticles can disrupt communities of microbes, their nutrient cycle functions, as well as their trophic relationship within an aqueous solution (Cunningham et al., 2023).

3.7.2. *Human Exposure Routes and Regulatory Challenges*

Human exposures to nanoparticles take place through various routes such as intake of contaminated drinking water and foods, inhalation of particulate matter from air, and dermatological exposure (Rajaei et al., 2020). Recent work has verified the presence of microplastic particles in humans' blood, placental tissues, and breast milk and thus raised more concerns regarding systemic and developmental toxicity (Leslie et al., 2022). Persistent exposure has a probability of inflammation and oxidative stress alongside endocrine disruption with a prospective effect on cancer, neurological diseases, and metabolic diseases (Yong et al., 2020). Regulations of NPLs are still patchy and immature despite burgeoning evidence. Current policies are mostly interested in macro- and microplastics with sparse consideration of nanoscale particles owing to analytical difficulty and gaps in information (Koelmans et al., 2022). Nonavailability of universally accepted detection procedures and certified biomarkers impedes risk analysis and policy making. Again, lab experiments mostly involve pure polystyrene spheres, while in the real-world environment, the NPLs are highly heterogeneous (Cunningham et al., 2023).
International endeavors to regulate plastic pollution have been receiving more support; however, related discussions concerning nanoplastics are limited. EU's Chemicals Strategy for Sustainability and United Nations

Global Plastics Treaty negotiations pinpoint a threshold-based decision with evidence-based backing as well as monitoring strategies (Vethaak & Legler, 2021). Nonetheless, non-concurrence concerning definitions, evaluations for exposure, as well as metrics for toxin effects continues to deter regulatory measures. Further, adaptive management strategies should incorporate novel results on nanoplastic fate and transport and health consequences.

3.8. Research Gaps and Future Directions

3.8.1. *Lack of Human Epidemiological Data and Biomonitoring Limitations*

Despite the intensified alarm over the health impacts of NPLs, a lingering shortfall remains in the epidemiologic data on humans. The vast majority of the current knowledge comes from in vitro experiments and animal systems, and though these are enlightening, they are incapable of capturing the in vivo actuality of real-world human exposure and disease progression. The lack of comprehensive long-term experiments on human volunteers restricts our capacity to establish causal links between long-standing pathologies like cancer, neurodegenerative diseases, and metabolic disturbances (Cunningham et al., 2023). One important limitation is the inability to have standard procedures to identify and quantify the levels of nanoparticles in body fluids and human tissues. For microplastics, these might be characterized by spectroscopy and microscopy, but need sophisticated methods such as nanoparticle tracking analysis and mass spectrometry to be performed on these particles by sophisticated facilities located in clinical areas (Zarate-Bermudez et al., 2025). The limitation has been impeding biomonitoring programs and formulating exposure biomarkers crucial in conducting epidemiological studies (Koelmans et al., 2022). Subsequent pilot studies have indeed established the presence of microplastic particles in human blood, placenta, and breast milk and hinted at general exposure (Leslie et al., 2022). These are limited by low numbers of samples, shortcomings in long-term longitudinal follow-up, and insufficient confounding factor control. Lacking strong paradigms of epidemiology, one cannot determine dose–response relations or vulnerable populations like infants and children, pregnant and post-parturition women, and immunocompromised subjects (Jayavel et al., 2024).

3.8.2. *Disconnect Between Environmental Exposure and Clinical Outcomes*

There is also a gap between linking environmental exposure data with clinical outcomes. Despite environmental monitoring's observation that nanoparticles have been found to be suspended within the atmosphere's air, watershed supplies of foods, and water supplies, few investigations have tied these findings to health profiles or disease databases (Ebrahimzadeh, 2023; Fekri et al., 2022). The absence of geospatial and time-based exposure mapping infringes on scientists' capacity to connect levels of concentration of NPLs to local levels of disease occurrence or trends (Mitrano et al., 2021). This divide between public health information and environmental science delays sound risk assessment and policy-making.

3.8.3. *Need for Multidisciplinary Collaboration and Regulatory Reform*

Multidisciplinary collaboration is also necessary to close these gaps. It is necessary that epidemiologists, clinicians, environmental scientists, and toxicologists coordinate to design studies with realistic scenarios of exposure, qualified biomarkers, and standardized protocols. Toxicologists, epidemiologists, environmental scientists, and clinicians must join forces in the planning of investigations involving genuine exposure scenarios, (certified) biomarkers, and consistent protocols. The establishment of worldwide databases and consistent reporting criteria would make meta-analyses easier and improve the overall generalizability of results (Khanna et al., 2024). Ethical frameworks must be established to guide human sampling and data sharing. It even impedes regulatory decision-making. Quantitative risk analyses are employed by authorities to define levels of exposure and levels of safety, but are currently calibrated with extrapolated animal results and assumed scenarios of exposure. As a consequence of the absence of human-specific information, regulatory authorities are in doubt in quantifying the true health burden of NPLs and defining effective mitigative measures (Pradel, 2021).

3.9. Need for advanced detection methods for nanoplastics in biological samples

3.9.1. *Analytical Limitations and Imaging Challenges*

NPLs are a formidable challenge to characterization in biological matrices because they have low size, chemical variability, and a tendency to form aggregates.

In contrast to microplastics that can be detected by standard microscopy and spectroscopy methodologies, NPLs demand highly sensitive as well as specific

analytical protocols. Detection of such particles within tissues, blood, and cell compartments is important for establishing exposure routes and corresponding health impacts, but is limited by losses in resolution, throughput, as well as reproducibility (Mariano et al., 2021). Standard procedures, including Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy, were modified to characterize nanoparticles, but their sensitivity is dramatically reduced if the scale is decreased to submicron dimensions (Fekri et al., 2021; Arjaghi et al., 2021). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) offer high-resolution imaging, but they require extensive labor to implement and extensive sample preparation (Ivleva et al., 2017). Moreover, they frequently cannot discriminate NPLs from other nanoparticles or cell debris, resulting in false positives or subrepresentation of particle enumeration (Schwaferts et al., 2019). Recent advancements in hyperspectral microscopy and fluorescent imaging have improved the visualization of NPLs in biological tissues. For instance, fluorescent labeling with Nile Red or with BODIPY can qualitatively tag plastic particles to enable their identification within tissues or cells (Maes et al., 2017). These fluorescent dyes might, however, bind to lipids as well, with a resultant loss of specificity.

3.9.2. *Emerging Technologies and Standardization Needs*

Emerging biosensing technologies present some encouraging alternatives. Rivera-Rivera et al. (2025) discussed optical biosensors, microfluidic platforms, and surface-enhanced Raman scattering (SERS) as high-tech instruments for nanoparticle detection within biological liquids. These technologies enable real-time measurement, low volumes of samples, and the choice to be implemented into portable systems. Nonetheless, their integration within clinical applications is currently early-stage, warranting a confirmation with certified reference materials (Mintenig et al., 2018). Notable lacunae present in the present literature include a lack of consistent protocols to extract and purify nanoparticles from complex biological matrices. Enzyme digestion, density-based separation, and filtration vary significantly among experiments, with effects on comparability as well as reproducibility (Prata et al., 2020). In the absence of standardized sample preparation protocols, derivations of reliable exposure metrics or conduct of epidemiological assessments become problematic. Koelmans et al. (2022) noted that interlaboratory experiments and standard reference materials were necessary to serve as yardsticks against detection protocols. Research development is also contingent upon interdisciplinary collaboration. To interface with biological systems, detection platforms would be developed collectively by analytical chemists, biomedical engineers, and toxicologists. An integration of omics technologies with tracing of NPLs could yield mechanistic details regarding bioaccumulation as well as toxicity (Mitrano et al., 2021).

Aside from that, regulatory authorities should invest in development as well as method validation to support risk assessment, together with public health surveillance. The key limitations in nanoplastics research are shown in Figure 4.

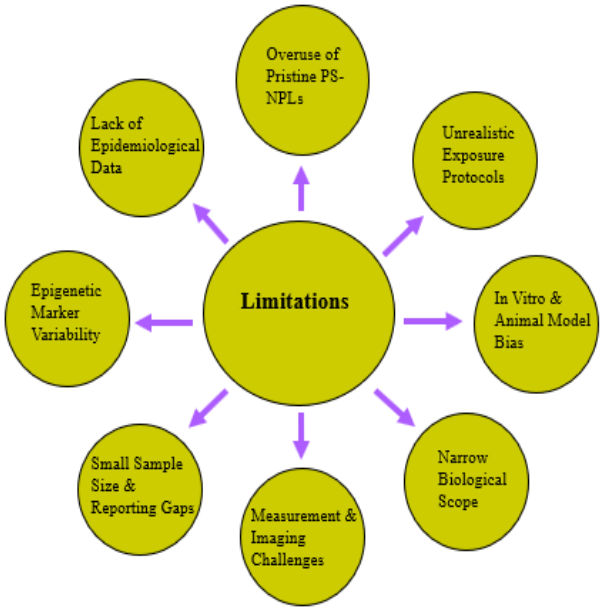

Figure 4. Schematic representation of key limitations in nanoplastics research

3.10. Suggestions for longitudinal studies and multi-omics approaches

3.10.1. *Long-Term Monitoring and Vulnerable Populations*

Understanding the long-term health and ecological impacts of NPLs requires thorough longitudinal studies examining exposure and outcomes over the long term. For the most part, current literature is founded on short-term lab experiments that insufficiently consider long-term effects, latency periods, and total toxicity. Longitudinal cohort study approaches—with special emphasis on combining environmental monitoring with clinical endpoints- are essential in examining real-world exposure scenarios and disease progression (Yu et al., 2023). Studies should emphasize vulnerable groups such as children, expectant mothers, and individuals exposed through their workplaces.

3.10.2. *Integrating Multi-Omics for Mechanistic Insights*

Multi-omics approaches offer a powerful system for interpreting the molecular processes underlying NP toxicity. Through the combination of transcriptomics, proteomics, metabolomics, and epigenomics, researchers can reveal exposure biomarkers, detect signals before disease onset, and evaluate disturbed biological processes. Helal et al. (2024) performed a review of 37 omics evaluations among aquatic organisms with an emphasis on recurring changes to responses associated with oxidative stress, immune signal cascade events, and metabolic energy events. The application of similar approaches in mammalian systems has the promise to unveil conserved signatures of toxicity and improve human risk assessment processes. Integration of longitudinal studies with multi-omics analysis makes it possible to track biological response over time. For instance, frequent sampling of blood, urine, or saliva from chemically exposed subjects might identify time-dependent alterations in gene expression or levels of metabolites associated with NP burden. Rivera-Rivera et al. (2025) highlighted biosensor-based platforms of omics to achieve real-time measurement of exposure to NPLs. The devices could be used in epidemiologic research to establish correlations among molecular alterations and clinical endpoints, and environmental parameters.

3.10.3. Standardization, *Environmental Mapping, and Collaborative Networks*

Multi-omics research has great potential but is plagued by high expense, complex data, and non-standard protocols. The standardization of sampling, processing, and analysis is necessary to enable comparability and replicability across investigations. There is a need to standardize metabolomic analysis in environmental toxicology, as it has poor and inconsistent annotation and few reference databases (Bedia 2022). There is a critical need for community-based activities to establish open-access omic repositories and calibrated workflows to drive forward NP research. Longitudinal multi-omic analyses are also in need of integration with environmental exposure information. Geospatial mapping of air, water, and food source concentrations of NP may be correlated with individual exposure profiles through wearable devices or personal monitors. Environment-based surveillance has been suggested by Khanna et al. (2024) to be combined with biological sampling to develop exposure–response relationships. This systems biology approach may be used to determine areas of high concentration of NP and direct specific interventions. Efficiency can be enhanced by using interdisciplinary and international projects to inform future work. Interdisciplinary integration among epidemiologists, toxicologists, policy experts, and bioinformaticians will boost data interpretation as well as methodological development. Yu et al. (2023) cited international webs of studies together with bibliometric analysis as being important in discerning emerging trends as well as knowledge gaps. There is an urgent need to encourage funding agencies and regulatory authorities to facilitate longitudinal multi-omics investigations as a necessary component of nanoplastic risk assessment and public health safety.

4. Conclusion

Biochemical explorations of nanoplastics have discovered their ability to disrupt fundamental epigenetic processes such as DNA methylation, histone modification, and non-coding RNA regulation. These molecular alterations are not temporary reactions to environmental insults but represent durable gene expression changes that can be maintained throughout cell division and sometimes throughout generations. Such discoveries promote nanoplastics from being passive contaminants to dynamic regulators of genomic activity.

Research establishes that nanoplastics have been found to induce oxidative stress and inflammation with an activation or inhibition of various core epigenetic enzymes, including DNA methyltransferases and histone deacetylases. Such changes parallel aberrant cellular differentiation, immune impairment, as well as an escalated susceptibility to chronic diseases. Interestingly, such biochemical impacts take place with reduced exposure levels to nanoplastics to indicate their effects

could be acting via subtle cumulative rather than direct cytotoxicity avenues. Because nanoplastics permeate air, water, foods, and tissues, including human blood, placenta, and breast milk—both in house dust and the external environment—the urgency to bring biochemical knowledge together with environmental toxin science is imperative. Conventional models of toxicity, with their emphasis on acute organ-level injury, fail to account for subtle molecular results resulting from chronic nanoplastic exposure. Epigenetic markers represent a novel opportunity for early identification as well as mechanistic characterization of such effects. Interdisciplinary paradigms to complex epigenetic transformations induced by nanoplastics would call for an interplay among molecular biologists, toxin researchers, environmentalists, and clinicians to generate holistic models realistically portraying scenarios of exposure. Such holistic models would entail multi-omics types of data, longitudinal profiles of sampling, and standardized detection procedures to allow for reproducibility as well as relevance to various populations as well as ecosystems. Policy adjustments should progress concomitantly with scientific discoveries. Current regulatory systems often forego nanoscale contaminants because analytical methods fall short or because complete risk hazard has yet to be properly assessed. The inclusion of epigenetic endpoints within environmental health assessments would allow for more sensitive and predictive evaluations regarding nanoplastic toxicity. Such a shift would require investments in analytical protocols, validations of biomarkers, and intersectoral collaboration. In addition, public health programs should include considerations related to transgenerational effects of nanoplastic exposure. In the event that epigenetic alterations induced by nanoplastics prove to be inheritable traits, their effects would transcend the individual directly exposed, extending to future generations. Such a reality serves to highlight an imperative for regulation based upon a Precautionary Principle, close monitoring among high-risk groups, and outreach programs to convey molecular risks in communicable language. Lastly, investigation of nanoplastics through a biochemical prism serves to reveal a latent yet influential mode of environmental disruption—one that alters the very essence of the genome. Addressing such a problem will require scientific rigor but also institutional flexibility, ethical foresight, and repeated interdisciplinarity. The molecular effects of nanoplastics reveal themselves increasingly, and our response should be as meticulous and unforgiving as their respective mechanisms.

Authors Contribution
All authors have contributed equally to prepare the paper.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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