

Perspective

Nanoplastics: An Emerging Threat to Human Health—A Perspective Review

José Gonçalves ¹, João Pequeno ¹, Davor Krzisnik ^{1,2}, Paula Sobral ¹ and Joana Antunes ^{1,3,*}

¹ MARE—Marine and Environmental Sciences Centre, ARNET—Aquatic Research Network, NOVA School of Science and Technology, NOVA University of Lisbon, 2829-516 Caparica, Portugal

² Department of Wood Sciences and Technology, Biotechnical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia

³ LAQV—Associate Laboratory for Green Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, 2829-516 Caparica, Portugal

* Correspondence: jcsantunes@fct.unl.pt

Abstract

Nanoplastics (NPs, <100 nm) have emerged as nano-scale contaminants with superior mobility and biological barrier-crossing capacity, yet risk assessment fails due to unstandardized analytical methods and a lack of realistic exposure data. This perspective proposes an “Exposome–Microbiome–Immune” (EMI) framework as a One Health paradigm to integrate detection, toxicokinetics, and systemic effects. We prioritize the following actions: (i) validated nano–Fourier transform infrared spectroscopy (nanoFTIR) and surface-enhanced Raman spectroscopy (SERS) for environmental/human monitoring; (ii) multi-generational studies in zebrafish and organoids; (iii) longitudinal cohorts for biomonitoring. Without shifting from descriptive reviews to systems toxicology, NP risk will remain underestimated.

Keywords: nanoplastics; human health; emergent contaminants

1. The Challenge: Nanoplastics as a Multiscale Stressor

The global plastic life cycle generates vast quantities of plastic debris that fragment over time into progressively smaller particles, including nanoscale plastic fragments referred to as nanoplastics. These arise from the degradation of macro- and microplastic waste through environmental weathering and mechanical abrasion, as well as from certain industrial applications at the nanoscale [1,2]. Nanoplastics are defined here as plastic particles smaller than 100 nm, consistent with European Food Safety Authority (EFSA) recommendations, whereas larger particles are referred to as microplastics or sub-micron plastics.

While microplastics have received substantial scientific and public attention, nanoplastics pose distinct concerns because their small dimensions confer higher surface area-to-volume ratios, altered surface chemistry, and enhanced mobility in both environmental and biological systems [3,4]. These properties, well documented in nanomaterials and nanomedicine research, can increase reactivity, facilitate the sorption of co-contaminants, and modify interactions with biological macromolecules relative to larger particles [5].

These physicochemical properties also promote interactions with proteins, membranes, and other cellular components, and enable translocation across physiological barriers that are less permeable to larger particles, such as the intestinal epithelium, blood–brain barrier, and placental interface [5,6]. Several controlled studies have reported nanoplastic-sized particles in human blood, placenta, and post-mortem brain tissue, demonstrating



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that exposure can be systemic and capable of reaching sensitive organs, including the developing fetus and central nervous system [4,6].

However, the field also faces significant analytical challenges, as detection methods are still under development and subject to debate over specificity and contamination controls [1,2].

Quantitative environmental data on nanoplastics are particularly scarce due to the absence of reliable, harmonized methods for detection and quantification [7]. Existing reviews highlight that only a small number of studies have actually measured nanoplastics in real field samples (e.g., seawater, snow, air, sand, soil), and that most analytical work is focused on spiked standards or laboratory-prepared samples rather than genuine background environmental levels [8]. Detection approaches are under active development and remain subject to debate regarding specificity, size resolution, and contamination control, thereby limiting robust exposure assessment.

Authoritative bodies, including the EFSA and other expert panels, emphasize that current data are insufficient for a full quantitative risk assessment, particularly for nanoplastics, due to major gaps in occurrence, toxicokinetics, and toxicity data [9–11]. In particular, the available evidence does not yet allow the derivation of robust exposure–response relationships or well-constrained environmental exposure scenarios for nanoplastics, especially with respect to environmentally realistic concentrations, size distributions and polymer types.

Nevertheless, converging lines of evidence, including the continuous fragmentation of the global plastic stock, the detection of micro- and nanosized plastic fractions across multiple environmental compartments, and modeling studies of particle transport and fate, support the view that nanoplastics are likely to be widespread, even though their exact prevalence and spatio-temporal trends remain poorly characterized [12]. In this sense, nanoplastics are increasingly regarded as a candidate emerging contaminant class with a high potential for widespread occurrence, rather than being categorically labeled as pervasive. It is therefore essential to acknowledge that this appraisal is based largely on indirect and still limited occurrence data, and that nanoplastics are of emerging concern precisely because they are plausibly ubiquitous while remaining analytically under characterized, which currently precludes a comprehensive, quantitative risk assessment [13].

Research on nanoplastics is rapidly evolving but remains limited. Studies have demonstrated the presence of plastic particles, predominantly in the microplastic and sub-micrometer size ranges, in human-relevant matrices such as blood, placenta, and post-mortem brain tissue, indicating that exposure can be systemic [10–12]. While these findings support the plausibility of systemic exposure to nanoscale plastics, direct evidence for nanoplastics in human tissues is still scarce and requires more sensitive, size-resolved analytical methods. Experimental work on plastic particles, predominantly in the microplastic and sub-micromere size ranges and, to a lesser extent, on nanoplastics, has revealed potential cellular and organ-level toxicity, including oxidative stress, inflammatory responses, endocrine disruption, and neurodevelopmental perturbations [14–17]. Studies using well-characterized nanoplastics further suggest that these endpoints are also relevant at the nanoscale, although the number of such investigations remains comparatively small. However, controversies exist regarding the environmental relevance of laboratory exposures, the relative importance of nanoplastics compared to microplastics in environmental and biological systems, and the interpretation of human tissue detection data [18,19]. Analytical challenges further complicate robust quantification, with no standardized methods yet available for routine detection at environmentally relevant concentrations [20,21].

Against this backdrop, the present study aims to systematically review the current evidence on the sources, exposure pathways, cellular mechanisms, systemic toxicity, and

human health implications of nanoplastics. By synthesizing in vitro and in vivo data, this work seeks to clarify where consensus exists, identify major uncertainties, and highlight critical knowledge gaps for future research. Principal conclusions suggest that nanoplastics are a highly mobile, barrier-crossing pollutant with the potential to affect multiple organ systems, and that precautionary measures may be warranted, while scientific understanding continues to develop [7,15,18].

This perspective advances a central thesis: NPs represent not “small microplastics” but a multiscale systems toxicology challenge engaging the exposome–microbiome–immune (EMI) triad. Conventional toxicology’s focus on isolated endpoints (reactive oxygen species (ROS), inflammation) fails to capture emergent effects propagating from nano-scale interactions to population-level One Health outcomes. We propose the EMI framework (Figure 1) as an integrative roadmap, synthesizing current evidence while charting priority research and policy action.

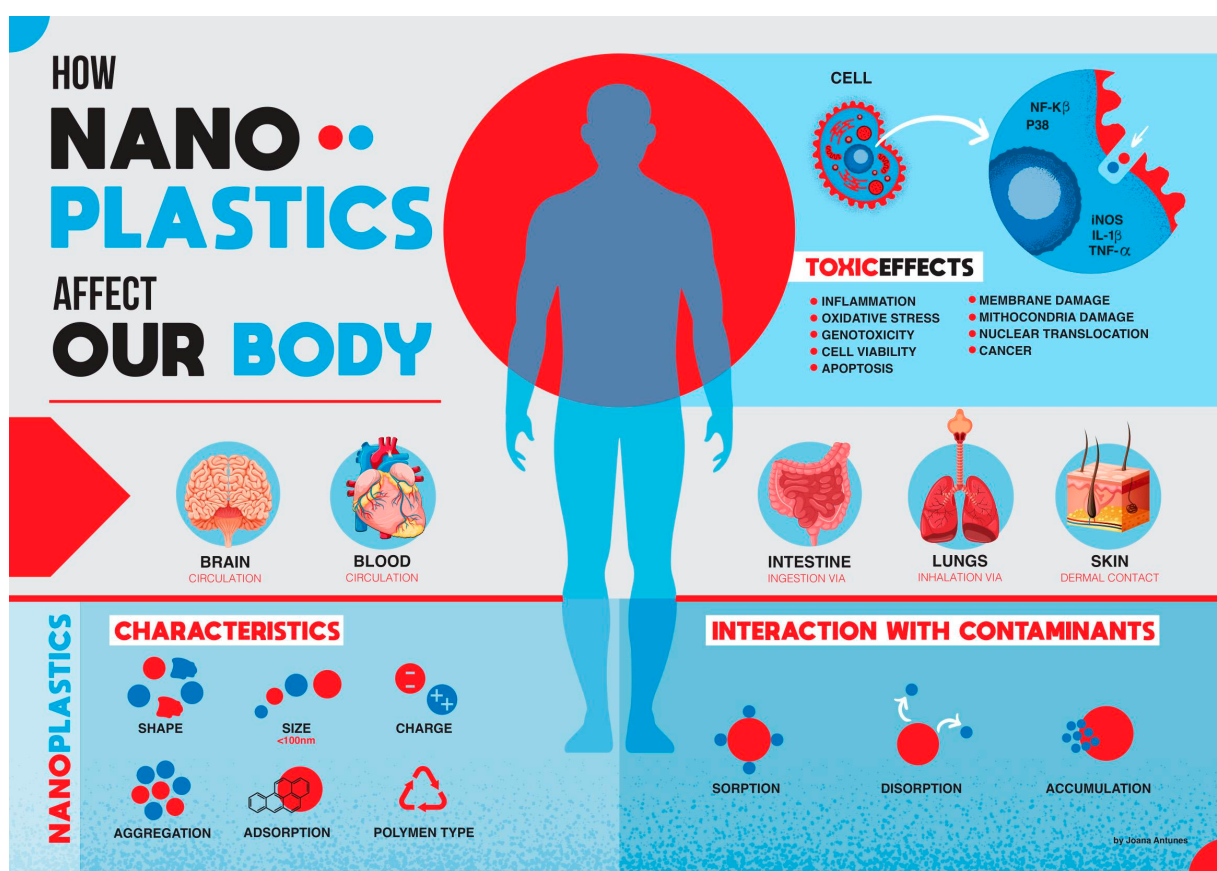


Figure 1. Overview of key sources, environmental pathways, and human exposure routes of nanoplastics, highlighting their potential interactions with biological systems and implications for human health. In the “Nanoplastic characteristics” section, blue and red spheres depict nanoplastics with different physicochemical properties. In the “Interaction with contaminants” section, blue dots indicate chemical contaminants (e.g., plastic additives or environmental pollutants), while arrows represent transportation processes.

2. Nanoplastics in the Environment and Human Body

2.1. Origin, Properties and Environmental Occurrence

Nanoplastics originate from two primary sources: (i) secondary nanoplastics generated by fragmentation, weathering, and mechanical abrasion of larger plastic items, and (ii) primary nanoplastics intentionally manufactured for commercial or industrial applications [1,2]. These particles represent a broad continuum in size (from a few nanometers

up to <100 nm) and encompass a broad range of polymer chemistries (e.g., polystyrene, polypropylene, polyethylene terephthalate) and morphologies (spheres, fragments, fibers), often co-occurring within complex aggregates [15].

Their small size and high surface area enhance the adsorption of environmental pollutants, interaction with dissolved organic matter, and release of embedded additives such as plasticizers and flame retardants, thereby modifying both their own behavior and that of associated chemicals. In biological fluids, nanoplastics may acquire biomolecular coronas composed of proteins, lipids, and other macromolecules, which dynamically alter surface properties, are recognized by cells, and influence cellular uptake, biodistribution, and potential toxicity [3,16].

Environmental occurrence of nanoplastics is now documented for marine, freshwater, soil, and (indirectly) atmospheric compartments, but is often inferred from MNP-focused studies and hampered by analytical limits [13,22]. Field observations in the North Atlantic, for instance, have revealed nanoplastic concentrations on the order of tens of mg m^{-3} throughout the water column, with elevated levels at coastal and subtropical gyre stations and a dominance of polystyrene and polyethylene terephthalate in intermediate waters [23]. Freshwater and soil reviews highlight soils and sediments as major reservoirs of nanoplastics, receiving inputs from wastewater, sludge, and biosolid applications, plastic mulches, and atmospheric deposition, and acting as long-term sources to biota and adjacent aquatic systems. Despite growing evidence of their ubiquity, most available data rely on indirect approaches and a limited set of polymers, underscoring the need for improved detection methods and standardized monitoring strategies for environmental nanoplastics [24,25].

Nanoplastics thus represent a quintessential One Health challenge, linking environmental contamination, ecosystem integrity, animal exposure, and human health outcomes. Their generation from global plastic production results in continuous release into terrestrial, freshwater, marine, and atmospheric compartments, while the nanoscale size range facilitates atmospheric transport, translocation across biological barriers, and trophic transfer.

From a One Health perspective, environmental reservoirs act simultaneously as sources of human exposure and as sites where ecological effects may alter ecosystem services (e.g., soil fertility, microbial cycling, and food-web stability). Wildlife studies increasingly demonstrate uptake of nanoscale plastic fractions in aquatic and terrestrial organisms, suggesting potential bioaccumulation and biomagnification processes that remain poorly quantified.

Integrating environmental monitoring, veterinary toxicology, and human biomonitoring is therefore essential for understanding cumulative exposure and systemic risk. Future surveillance programs should include coordinated environmental, occupational, and clinical sampling strategies using harmonized analytical workflows.

2.2. Human Exposure Pathways

Humans are exposed to nanoplastics through multiple, overlapping pathways, including ingestion, inhalation, and, in specific contexts, dermal contact. Ingestion occurs via contaminated drinking water and food—although direct quantification of nano-sized plastic particles remains analytically challenging, numerous studies demonstrate ubiquitous contamination and infer smaller fractions from modeling and indirect measurements [15,17].

Inhalation of airborne nanoscale plastics from indoor dust, synthetic textiles, tire wear, and industrial emissions represents another important exposure route, especially in urban or occupational settings [3]. Experimental studies show that inhaled or orally administered plastic particles, predominantly in the microplastic and sub-micrometer size ranges, can cross pulmonary or gastrointestinal barriers and reach systemic circulation [18,20]. These findings, together with emerging data from studies using well-characterized nanoplastics,

support the plausibility that nanoscale plastics can also undergo systemic translocation, although direct *in vivo* evidence remains limited [26,27].

Maternal–fetal exposure is of particular concern. Animal studies have demonstrated that polystyrene and polypropylene nanoplastics administered to pregnant rodents can cross maternal barriers, reach the placenta, and accumulate in fetal organs, including the developing brain [17,21]. Recent work further shows that gestational exposure to nanoplastics disrupts fetal development by promoting placental aging via ferroptosis of syncytiotrophoblasts [28]. Human observational data reporting nanoplastic-sized particles in placenta, fetal tissues, and meconium support the plausibility of *in utero* exposure in real-world settings [4,6].

Once internalized, nanoplastics may traverse epithelial and endothelial barriers and distribute to multiple organs such as the liver, kidney, spleen, and brain, as observed in both animal models and post-mortem human tissues [4,9].

3. Biological Effects and Toxicity of Nanoplastics

3.1. Cellular Mechanisms

In vitro studies using nanosized polystyrene (PS), polypropylene (PP), polyethylene (PE), and other model nanoplastics consistently demonstrate that smaller particles, particularly those below ~100–200 nm, elicit stronger and more diverse cellular responses than larger microplastic counterparts. These responses include increased production of reactive oxygen species (ROS), mitochondrial structural damage and dysfunction, impaired ATP generation, lipid peroxidation, and plasma membrane damage across a wide range of human and animal cell lines, including epithelial, neuronal, immune, and reproductive cells [4,29–31].

Nanoplastics are efficiently internalized via energy-dependent endocytic pathways, including clathrin- and caveolin-mediated endocytosis and macropinocytosis, after which they can accumulate in lysosomes and mitochondria. This intracellular localization promotes lysosomal destabilization, mitochondrial dysfunction, oxidative stress, and activation of apoptotic and inflammatory signaling pathways, accompanied by widespread transcriptional reprogramming affecting stress response, metabolism, and cell-cycle regulation [32–34].

In placental and reproductive models, PS nanoplastics impair trophoblast viability, disrupt mitochondrial metabolism, induce pro-inflammatory cytokine release, and interfere with steroid hormone synthesis at concentrations approaching those reported in human-relevant biological fluids [6,15,21].

Neuronal cultures and human brain organoids exposed to nanoplastics exhibit reduced neurite outgrowth, altered synaptic protein expression (e.g., synapsin-1, PSD-95—Postsynaptic Density Protein-95), calcium signaling disturbances, and dysregulation of neuroactive ligand–receptor pathways, indicating that nanoplastics can perturb key neurodevelopmental processes *in vitro* [35,36].

3.2. *In Vivo* Toxicity, Neurodevelopment, and Barrier Crossing

Mouse and rodent studies provide critical insight into systemic responses and barrier-crossing behavior that cannot be captured in isolated cell systems. Rodents exposed to PS or PP nanoplastics via oral or inhalation routes exhibit systemic distribution and accumulation in the liver, kidney, spleen, lung, and brain, accompanied by oxidative stress, inflammatory responses, metabolic disruption, and histopathological alterations in exposed organs [3,18,20].

Maternal exposure to nanoplastics during gestation has been shown to impair fetal neurodevelopment. In mouse models, prenatal exposure to PP or PS nanoplastics reduces

markers of cortical neurogenesis (e.g., Sox2, Ki67), disrupts neuronal migration, and results in persistent behavioral deficits in offspring, including impaired learning and memory, increased anxiety-like behavior, and altered social interactions [21,37,38].

Multiple experimental studies demonstrate that nanoscale plastic particles can cross the blood–brain barrier, accumulate in brain tissue, and exacerbate neuroinflammatory signaling, oxidative stress, and pathways implicated in neurodegeneration [3,15,39]. Supporting human relevance, analyses of post-mortem tissues have reported the presence of micro- to nanoscale plastic particles in the human brain, in some cases at higher concentrations than in the liver or kidney, suggesting preferential accumulation or retention of smaller plastic fractions in the central nervous system [4,6]. Although direct causal links to neurological disease remain unproven, these findings raise concern about chronic nanoplastic exposure as a potential contributor to neurodegenerative and neurodevelopmental disorders.

3.3. Immune and Systemic Effects

Nanoplastics interact with the immune system at multiple levels. In vitro studies show that nanoscale plastics are readily internalized by macrophages, dendritic cells, and neutrophils, where they induce lysosomal stress, NLRP3 inflammasome activation, and altered secretion of pro- and anti-inflammatory cytokines, including IL-1 β , TNF- α , and IL-10 [32].

In vivo, chronic nanoplastic exposure in rodents is associated with systemic low-grade inflammation, altered immune cell populations, and modulation of lymphoid tissues, including gut-associated lymphoid structures [39].

The gut microbiota appears particularly sensitive: several animal studies report that oral nanoplastic exposure alters microbial community composition, reduces diversity, impairs short-chain fatty acid production, and compromises intestinal barrier integrity, with downstream effects on host metabolism and inflammatory tone [18,19].

Whether these immune- and microbiome-mediated effects are reversible, and how they translate to long-term human disease risk, remains largely unknown and represents a major research gap.

4. Key Knowledge Gaps for Nanoplastics

4.1. Definitions and Analytical Limitations

Despite increasing concern, there is no universally accepted operational definition of nanoplastics. Some authors restrict the term to particles < 100 nm, consistent with engineered nanomaterial terminology, whereas others define nanoplastics as plastic particles ranging from ~1 nm to <1 μ m to reflect environmental fragmentation processes and current analytical limits [31,32]. This lack of consensus complicates inter-study comparison, exposure assessment, and regulatory integration.

Analytical detection and characterization of nanoplastics in complex environmental and biological matrices remain major challenges. Conventional optical methods are inadequate at the nanoscale, and while advanced approaches combining field-flow fractionation, electron or atomic force microscopy, Raman or FTIR spectroscopy, and thermal analysis are emerging, no standardized, validated workflows exist for routine quantification at environmentally relevant concentrations [10,11,14].

4.2. Chronic Exposure, Dose–Response, and Real-World Relevance

Most experimental studies employ short-term exposures and concentrations that are orders of magnitude higher than current best estimates of human exposure, limiting real-world relevance. Chronic low-dose exposure scenarios, cumulative internal burdens,

and latent outcomes such as carcinogenesis, neurodegeneration, or chronic inflammatory disease remain poorly characterized. Dose–response relationships and toxicity thresholds at which nanoplastics overwhelm physiological defense mechanisms are largely undefined, hampering quantitative risk assessment [3,4].

Real-world exposure pathways are also insufficiently understood. Few studies explicitly distinguish nanoplastics from the broader microplastic fraction, and the relative importance of ingestion versus inhalation for nanoscale particles likely varies across age groups, occupations, and environments. Occupational settings such as textile production, plastic recycling, and manufacturing may involve substantially elevated nanoplastic exposures, yet remain under-studied.

4.3. Epidemiology and Human Health Outcomes

To date, no large-scale epidemiological studies have quantified nanoplastic body burdens using validated methods and linked them to health outcomes in humans. Existing human evidence is largely indirect, based on tissue detection studies and extrapolation from *in vitro* and animal data, which is insufficient to establish causality. Without well-designed observational studies incorporating reliable nanoplastic exposure metrics, associations with outcomes such as asthma, inflammatory bowel disease, infertility, metabolic disorders, or neurodegenerative disease cannot be robustly evaluated. The development of biomonitoring tools and longitudinal cohorts that explicitly address nanoplastics is therefore a critical priority.

5. Regulatory and Policy Implications Focused on Nanoplastics

Regulatory agencies increasingly recognize nanoplastics as an emerging concern but largely address them alongside microplastics due to shared sources and data gaps, while emphasizing that nanoplastics warrant particular attention because of their small size, barrier-crossing capacity, and potential for bioaccumulation [10,11,14]. Given that secondary nanoplastics arise predominantly from the fragmentation of macro- and microplastics already in circulation, upstream interventions that reduce fragmentation-prone plastic flows are directly relevant to future nanoplastic burdens. To date, no jurisdiction has established nanoplastic-specific exposure limits, health-based guidance values, or standardized toxicity testing requirements.

Nanoplastics challenge conventional risk-assessment paradigms because they are heterogeneous particle mixtures rather than discrete chemicals, can cross biological barriers, may accumulate in tissues, and can act as carriers for co-contaminants, leading to combined particle- and chemical-mediated toxicity [3,34]. Existing regulatory frameworks, developed primarily for soluble chemicals or engineered nanomaterials, may therefore be inadequate.

In the near term, regulators can promote the development of nanoplastic-specific analytical methods, explicitly integrate nanoplastics into environmental and food monitoring programs, and apply precautionary measures targeting upstream drivers such as plastic production, product design, and waste management to limit environmental generation of nanoplastics.

6. A Next-Generation Research Framework for Nanoplastics

To advance beyond current limitations in nanoplastics research, a systems toxicology paradigm is required, one that integrates multiple biological scales while reflecting realistic exposure conditions. Conventional particle toxicology approaches, which emphasize isolated endpoints such as oxidative stress or inflammation, are insufficient to capture the complexity of nanoplastic interactions. Instead, future research should focus on network-level responses, enabling the identification of emergent effects that arise across molecular,

cellular, organ, and ecosystem scales, an approach increasingly advocated for complex environmental contaminants using network biology and multi-omics integration [40,41]. This shift is essential for understanding how subtle perturbations propagate through biological systems and contribute to long-term adverse outcomes.

Central to this framework is the integration of the exposome–microbiome–immunology triad. Nanoplastic exposures should be evaluated within the broader exposome, incorporating size-fractionated, environmentally weathered particles and associated chemical mixtures at field-realistic ratios. At the same time, soil and aquatic microbiomes must be recognized both as sensitive sentinels of environmental disturbance and as active modifiers of nanoplastic behavior and toxicity, as chronic nano-/microplastic exposure has been shown to alter gut microbial communities and oxidative stress responses in zebrafish [42].

Immune system interactions, particularly those associated with barrier crossing and immune modulation, warrant focused investigation, supported by experimental evidence demonstrating inflammatory signaling pathway activation following low-dose nanoplastic exposure in organoid and animal models [43].

Equally important is the prioritization of environmentally realistic exposure scenarios. Research designs should emphasize chronic, low-dose exposures representative of environmental conditions, as numerous laboratory studies still employ concentrations orders of magnitude higher than those typically measured in soils and natural systems [15]. Particular attention should be given to secondary nanoplastics generated through environmental fragmentation, which exhibit irregular morphology, altered surface chemistry, and potentially greater biological reactivity. Incorporating polymer-diverse mixtures is critical to accurately reflect the compositional heterogeneity and gradients observed in real-world environments.

To ensure relevance to both human and ecological health, advanced human-relevant *in vitro* platforms should be combined with ecological validation. Microphysiological systems and iPSC-derived organoids representing key biological interfaces, including the intestine–liver axis, blood–brain barrier, and placenta, have demonstrated value for mechanistic toxicology, including the investigation of combined stressor effects at low nanoplastic doses [44]. These findings should be validated using environmentally relevant sentinel species such as zebrafish and earthworms, given evidence that nanoplastics can accumulate in tissues, induce oxidative stress, disrupt neurobehavioral and reproductive endpoints, and produce size-dependent toxicity across life stages [45,46]. Integration of multi-layer omics approaches, including transcriptomics and metabolomics, can further reveal pathway-level responses and mechanistic convergence across biological scales.

Together, this next-generation framework bridges the gap between laboratory experimentation and ecosystem complexity, supporting robust, quantitative risk assessment across the One Health continuum. By aligning mechanistic insight with environmental realism and ecological validation, this approach provides a coherent roadmap for addressing the multifaceted risks posed by nanoplastics and for translating scientific evidence into meaningful environmental and public health protection.

7. Conclusions and Future Directions

Nanoplastics have emerged as a distinct and concerning component of plastic pollution, characterized by high mobility, the ability to cross biological barriers, and the capacity to induce oxidative stress, inflammation, endocrine disruption, and neurodevelopmental toxicity in experimental systems. Despite growing awareness, major uncertainties persist regarding definitions, analytical capabilities, chronic low-dose toxicity, real-world exposure patterns, and human health outcomes. Addressing these gaps will require coordinated advances across multiple disciplines, including analytical chemistry, ecotoxicology, exposure

science, epidemiology, and regulatory science, supported by international harmonization and data-sharing efforts.

Specifically, future research priorities include the following: analytical standardization, with harmonized protocols for detecting particles below 100 nm across environmental matrices, validation of single-particle techniques such as nano-FTIR, SERS, and Atomic Force Microscopy (AFM) at environmentally realistic concentrations, and development of size-fractionated exposure scenarios to distinguish nano- versus microplastic effects; environmental fate and transfer, including long-term field studies quantifying nano/microplastic ratios in soils amended with biosolids, trophic transfer experiments using environmentally weathered nanoplastics, and assessment of atmospheric deposition to remote ecosystems; ecotoxicology and risk assessment, prioritizing chronic, multi-generational studies in soil and aquatic species (including zebrafish), evaluation of mixture effects with plastic additives and co-contaminants at realistic ratios, and development of quantitative exposure–response models bridging laboratory and field conditions; and finally, a One Health approach, integrating coordinated human biomonitoring with environmental surveillance, alongside the establishment of size-specific regulatory thresholds for nanoplastics.

In parallel, precautionary measures targeting upstream drivers, including reducing the production of high-fragmentation plastics, improving product design for durability and recyclability, and strengthening waste sorting and recycling systems, can limit the generation and environmental release of secondary nanoplastics while scientific understanding continues to evolve. Nanoplastics thus exemplify a 21st-century environmental health challenge: complex, uncertain, and cross-disciplinary, yet sufficiently concerning to justify proactive action rather than delayed response. By combining methodological rigor, cross-disciplinary research, and precautionary policy, the scientific community can generate the knowledge necessary to assess risk, guide management, and ultimately safeguard ecosystem and human health.

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