Potential Health Risks of Micro-Nanoplastics and Persistent Organic Pollutants: A Review of Exposure Pathways and Toxic Effects

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Abstract: Human exposure to micro-nanoplastics (MNPs) and persistent organic pollutants (POPs) occurs concurrently via ingestion, inhalation, and dermal contact. Once inside the body, MNPs may act as carriers for POPs due to their adsorption capacity, potentially enhancing the bioavailability and tissue distribution of these toxic compounds through a "Trojan horse" effect. This interaction can lead to combined toxicological effects—such as inflammatory responses, cellular dysfunction, and metabolic disturbances—that threaten human health. This review critically assesses the combined health impacts of MNP–POP co-exposure, evaluates advanced methodological approaches including in vitro organoid models and multi-omics integration, and identifies key research priorities such as intracellular transport mechanisms and the development of human-relevant risk assessment frameworks. Our goal is to provide a scientific basis for improved health risk assessment and preventive health strategies related to mixed pollutant exposure.

Keywords: Micro-Nanoplastics; Persistent Organic Pollutants; Combined Toxicity; Health Risk; Toxic Mechanisms

1. Introduction

1.1 Definition and Sources of Micro-Nanoplastics

In 2004, scholars such as Thompson first proposed the concept of "Microplastics", MPs [1]. In 2008, the U.S. National Oceanic and Atmospheric Administration clearly defined microplastics as plastic particles or fragments with a diameter of less than 5 mm [2], with those smaller than 1000 nm classified as Nanoplastics, NPs [3]. This study collectively refers to both as Micro-nano Plastics, MNPs.

The massive production and improper disposal of plastic products have led to severe environmental pollution. Over the past 50 years, global cumulative plastic production has reached 9.2 billion metric tons [4], with approximately 79% of single-use plastics being difficult to recycle and ultimately becoming waste [5]. Plastics are resistant to degradation in natural environments and can gradually fragment through physical (e.g., erosion, abrasion), chemical (e.g., UV photolysis), and biological (e.g., microbial biofilm attachment) processes, forming MNPs. These MNPs are widely distributed in water bodies, soil, and the atmosphere, posing potential threats to ecosystems and human health [6,7].

Based on their sources, MNPs can be classified into primary and secondary types. Primary microplastics originate directly from human activities and products, including textile fibers [8], cosmetic microbeads [9], personal care product exfoliating particles [10], medical devices [11], and industrial raw materials [12]. Secondary microplastics are formed when larger plastic items break down in the environment due to UV exposure, mechanical action, etc. [13,14]. Common plastic types in the environment include Polystyrene (PS), Polyamide (PA), Polyethylene (PE), Polyethylene terephthalate (PET), Polypropylene (PP), Polyvinyl chloride (PVC), and Polycarbonate (PC). The surface chemical properties of these materials (e.g., oxygen-containing functional groups) directly influence their interaction behaviors with coexisting chemicals in the environment [15].

1.2 Definition and Classification of Persistent Organic Pollutants

Persistent Organic Pollutants (POPs) are organic compounds characterized by their persistence,

high toxicity, bioaccumulation potential, and long-range transport capacity [16]. Due to their stable chemical structures and resistance to degradation, POPs are widely dispersed through the atmosphere and water bodies, persisting in ecosystems over extended periods while exhibiting biomagnification and accumulation effects [17]. These properties pose severe threats to ecosystems and have become a global environmental concern [18].

POPs are generated through natural processes (such as volcanic eruptions and forest fires) and human activities, with industrial production being the primary source [19]. For example, pesticides like dichlorodiphenyltrichloroethane (DDTs) and industrial materials such as polychlorinated biphenyls (PCBs) enter the environment during use and discharge [20], spreading globally through wastewater, runoff, and atmospheric transport to various media, where they can even be detected in polar regions [21,22]. POPs can trigger immunotoxicity, neurotoxicity, carcinogenicity, and endocrine disruption in organisms [23]. The number of regulated POPs continues to grow [24], primarily including organochlorine pesticides such as DDTs and hexachlorocyclohexane (HCH); industrial chemicals like PCBs, perfluorooctane sulfonate (PFOS), and per- and polyfluoroalkyl substances (PFAS); as well as industrial byproducts such as polychlorinated dibenzo-p-dioxins (PCDDs), furans, and polycyclic aromatic hydrocarbons (PAHs). This article will subsequently focus on several high-concern POPs.

1.3 The Concept of Combined Toxic Effects and Its Relevance to Human Health

Combined toxic effects occur when multiple pollutants are present simultaneously within a biological system, interacting in ways that cause the overall health impact to deviate from the simple sum of their individual effects [25]. These interactions are generally categorized as additive, synergistic, or antagonistic [26,27].

While the health risks of single pollutants are relatively well-studied, their behavior can change significantly when combined inside the body [28]. Co-exposure may alter the absorption, distribution, metabolism, and excretion of these substances, thereby modulating their toxicity [29]. Therefore, understanding combined toxicity is essential for accurate health risk assessment.

Combined toxicity effects can manifest in several types, including additive effects, synergistic effects, antagonistic effects, and independent effects [30]. The expression of combined toxicity effects is regulated by multiple factors, including environmental parameters and the types of coexisting pollutants [31]. Micro- and nanoplastics (MNPs) can act as carriers for other pollutants, such as persistent organic pollutants (POPs), due to their high adsorption capacity. Through a "Trojan horse" mechanism, MNPs may enhance the bioaccumulation and tissue distribution of POPs in the human body, potentially increasing toxicity. However, under certain conditions, MNPs might also reduce the bioavailability of other contaminants, leading to antagonistic effects [32]. Given the widespread human exposure to both MNPs and POPs—substances known for their environmental persistence and potential health hazards [33]. There is an urgent need to clarify their combined health impacts. Systematic research in this area is critical to support evidence-based public health guidelines and preventive strategies.

2. Human Exposure Pathways and Health Implications of Micro-Nanoplastics

2.1 Human Exposure Pathways to Micro-Nanoplastics

Organisms are primarily exposed to MNPs through three pathways: ingestion, inhalation, and dermal contact.

2.1.1 Ingestion

Gastrointestinal intake is recognized as the primary route of human exposure to MNPs. Contaminated aquatic products are a significant source, with MNPs detected in hundreds of aquatic species, confirming their transfer and accumulation through the food chain [34]. Additionally, atmospheric deposition can contaminate the surfaces of crops and other food products with MNPs, which are then ingested by humans [35]. MNPs have been detected in various daily consumer goods and beverages [36,37]. Human studies provide direct evidence: the concentration of PET in infant feces is significantly higher than in adults, and MNPs have even been detected in meconium [38], placenta, and breast milk [39], demonstrating that MNPs can be exposed early in life through maternal-infant pathways.

2.1.2 Inhalation

MNPs are widespread in the atmospheric environment. Inhaled MNPs can reach the lower respiratory tract and cause respiratory irritation, with studies having detected MNPs in human lung tissues [40]. MNP exposure is associated with respiratory diseases, including symptoms of airway and interstitial lung diseases [41]. Data show that individuals can inhale 13-26 MNPs daily from indoor and outdoor air [42].

2.1.3 Dermal contact

MNPs are widely present in personal care products and cosmetics, increasing the likelihood of skin exposure during use. Existing evidence indicates that NPs can penetrate the skin barrier [43]and induce oxidative stress in epithelial cells [44], suggesting that skin contact is a potential pathway for MNPs to enter the human body.

2.2 Toxic Effects of Micro-Nanoplastics

In vivo and in vitro studies have confirmed that the accumulation of MNPs in organisms can lead to various health damages, including physical injuries and toxicity at the cellular and molecular levels [45,46]. MNPs can be transported to multiple systems via the circulatory system, causing corresponding functional impairments. The severity of their toxic effects depends on the dose, particle size, and chemical properties of MNPs [47].

2.2.1 Digestive system

The gastrointestinal tract is the primary site of exposure and a toxicological target organ for MNPs following oral ingestion. Although most MNPs are excreted in feces, residual portions accumulate in the digestive tract, causing damage such as gastrointestinal obstruction and digestive dysfunction [48]. Studies have confirmed that MNPs can exacerbate cellular inflammatory responses, significantly impair intestinal function, reduce intestinal mucus secretion, cause gut microbiota dysbiosis, and disrupt intestinal barrier function and metabolic homeostasis [49,50]. MNP exposure also interferes with liver function, indicating oxidative stress and disruptions in energy/lipid metabolism [51]. Notably, MNPs have a high potential to penetrate intestinal epithelial cells and translocate across barriers, entering systemic circulation and leading to systemic exposure in organisms and damage to other organ systems [52].

2.2.2 Immune system

MNP exposure can lead to immune dysfunction, manifested as immune cell death, abnormal expression of surface receptors, and dysregulated cytokine secretion [53]. After phagocytes ingest MNPs, immune-stimulatory or immunosuppressive responses are triggered, mediating inflammation, autoimmune disorders, increased susceptibility to host infection, and elevated carcinogenic risk. The immune system recognizes MNPs as foreign substances, initiating multi-level immune responses that ultimately result in host toxicity. Among these, the activation of immune cells associated with inflammatory responses is one of the primary effects of MNP exposure [54]. In vitro studies have confirmed that PP particles can stimulate immune cells, induce elevated cytokine levels, and enhance potential hypersensitivity reactions [55].

2.2.3 Respiratory system

The lung, as a major target organ for MNPs exposure, has its gas exchange function particularly vulnerable to toxic damage. Occupational exposure evidence indicates that industrial workers in synthetic textile manufacturing, due to long-term exposure to high concentrations of MNPs, face a significantly elevated risk of developing respiratory symptoms associated with airway and interstitial lung diseases. Cellular-level studies reveal that MNPs can inhibit the viability of human lung epithelial cells, induce cell cycle arrest, activate inflammatory gene transcription, and alter the expression of cell cycle and pro-apoptotic related proteins [56].

2.2.4 Reproductive system

MNPs can disrupt testicular structure through various mechanisms including oxidative stress [57], immune response [58], mitophagy [59], and apoptosis [60], directly affecting testosterone synthesis, compromising blood-testis barrier integrity, and impairing spermatogenesis. Research confirms that MNP exposure damages spermatogenic cell structure, leading to seminiferous tubule atrophy and germ cell loss [61]. The harm of MNPs to female reproductive health is equally significant, potentially inducing ovarian inflammation, oxidative stress-induced ovarian atrophy [62], and disrupting placental immune homeostasis, with markedly adverse effects on offspring health [63].

2.2.5 Nervous system

Studies have confirmed that MNPs can induce neurotoxicity in organisms. MNPs can enter the

central nervous system through the respiratory or circulatory systems [64], and subsequently reach the brain via pathways such as the olfactory or trigeminal nerves [65]. Long-term MNP exposure can induce significant neurotoxic effects in mice, including blood-brain barrier dysfunction, hippocampal inflammation, and cognitive deficits [66]. There is controversy regarding the neurotoxic effects of short-term MNP exposure [67], and their migration to the central nervous system as well as their direct neurotoxicity still require further clarification.

3. Human Exposure Pathways and Health Implications of Persistent Organic Pollutants

3.1 Exposure Pathways of POPs

Humans are primarily exposed to POPs through dietary intake, drinking water consumption, and environmental contact [68]. This multi-pathway exposure pattern makes the accumulation of POPs in the human body a complex public health issue.

3.1.1 Dietary intake

Dietary intake is the main route of human exposure to POPs, accounting for over 90% of total exposure [69]. Animal-derived foods, particularly fatty fish, meat, and dairy products, generally contain higher concentrations of POPs [70]. Among plant-based foods, certain vegetables and fruits may also test positive for POPs, mainly due to soil absorption or atmospheric deposition [71].

3.1.2 Drinking water consumption

Drinking water intake is generally not a primary route of POPs exposure, but it can become a significant source in areas with severe localized pollution. For instance, in regions with industrial contamination or intensive agricultural activities, groundwater can be polluted by POPs [72]. In recent years, newly identified POPs frequently detected in drinking water, such as PFAS [73]and 1,4-dioxane [74], have also emerged as major concerns.

3.1.3 Occupational exposure

Occupational exposure is another important pathway for POPs contact. Workers in specific industries face higher risks of POPs exposure. For example, the concentration of brominated flame retardants in the blood of e-waste dismantling workers is significantly higher than in the general population [75], and 1,4-dioxane has also been identified by the U.S. Environmental Protection Agency as posing an unreasonable risk to workers in certain occupational settings [76].

3.1.4 Breastfeeding

Breastfeeding is a unique route of infant exposure to POPs. The detection of POPs in breast milk not only reflects the maternal accumulation levels but also poses potential impacts on infant health. Although concentrations of traditional POPs in breast milk have shown a declining trend in some countries, the detection rates of emerging POPs remain high [77].

3.2 Toxic Effects of Persistent Pollutants

The impact of POPs on human health is long-term and complex, with their toxic effects extensively affecting multiple physiological systems and organs.

3.2.1 Endocrine disrupting effects

Multiple POPs are typical endocrine-disrupting chemicals (EDCs) that can interfere with hormone synthesis, secretion, and transport, leading to endocrine and metabolic system disorders and increasing the risk of specific cancers [78]. Studies have shown that triclosan (TCS) can significantly alter fish sex hormone levels and related gene expression [79]. Population studies have found that environmental PAH exposure is significantly associated with changes in male reproductive hormone levels [80].

3.2.2 Neurological effects

Some POPs exhibit neurodevelopmental toxicity. PAHs can cross the blood-brain barrier, exerting direct neurotoxic effects on the central nervous system, potentially leading to neurodevelopmental disorders and cognitive impairment in children. Vulnerable populations such as children and the elderly show higher sensitivity to these effects [81]. Additionally, low-dose CS can induce oxidative stress, DNA damage, and histopathological changes in the liver and brain of adult zebrafish [82].

3.2.3 Immunosuppression

Long-term exposure to POPs can lead to suppression of immune system function, increasing susceptibility to infections and the risk of autoimmune diseases. Studies have revealed that PAHs may contribute to the pathogenic mechanisms of autoimmune diseases such as rheumatoid arthritis through interactions with the aryl hydrocarbon receptor [83]. Additionally, PAHs exposure can interfere with the body's effective immune response to

infections and tumors by inhibiting the activity of immune cells [84].

3.2.4 Carcinogenicity

Several POPs have been identified as human carcinogens (Group 1) or probable human carcinogens (Group 2A). For example, PCDD, as a Group 1 carcinogen, is significantly associated with an increased risk of various cancers [85]. Large-scale epidemiological studies have shown a positive correlation between dietary intake of Benzo [a]pyrene (BaP) and the risk of breast cancer [86].

3.2.5 Metabolic disorders

Numerous studies have confirmed that POPs exposure can interfere with lipid metabolism and glucose homeostasis regulation, increasing the risk of obesity, type 2 diabetes, and cardiovascular diseases [87]. Recent research has found that POPs can directly affect the overall metabolic function of the gut microbiota [88], alter its composition and function, and thereby participate in the development and progression of obesity or diabetes [89].

3.2.6 Reproductive and developmental toxicity

POPs can induce epigenetic changes in reproductive tissues, affecting gene expression regulation and cellular function; they can also trigger inflammatory and immune responses, further impairing reproductive capacity [90]. Studies indicate that PAH exposure can damage oocyte DNA integrity, disrupt ovarian function, and is associated with adverse reproductive outcomes [90]. Semen omics analysis shows a significant correlation between abnormal sperm function in male infertility patients and elevated urinary PAH concentrations [91].

The impact of POPs on human health exhibits significant chronic cumulative characteristics, with health damage often becoming apparent only after years of exposure. More notably, POPs in the environment often exist as mixtures, and different pollutants can produce combined exposure effects, which greatly complicates the comprehensive assessment of their health risks.

4. Interactions Between Micro-Nanoplastics and Persistent Organic Pollutants

The complex interactions between MNPs and POPs are a research hotspot in environmental science and toxicology. MNPs not only pose environmental threats themselves but also act as carriers, adsorbing and enriching pollutants such as POPs, thereby exacerbating environmental risks through combined exposure effects.

4.1 Adsorption and Desorption Mechanisms of Micro-Nanoplastics and Persistent Organic Pollutants

Due to their small size and large specific surface area, MNPs exhibit strong adsorption capabilities and can adsorb POPs through various mechanisms such as hydrophobic interactions, electrostatic attraction, and hydrogen bonding [92]. The adsorption process is influenced by environmental parameters and the intrinsic properties of MNPs [93,94].

The strong adsorption capacity of MNPs for hydrophobic organic pollutants mainly stems from the inherent hydrophobicity of POPs and the high specific surface area of MNPs [95]. Therefore, in the marine environment, POPs can significantly accumulate on suspended particulate matter [96]. Numerous studies have confirmed that the adsorption capacity of MNPs for organic pollutants is approximately 1-2 orders of magnitude higher than that in natural sediments and soil environments [97], highlighting their potential environmental risks as efficient pollutant carriers.

Desorption is the process by which pollutants are released from the surface of MNPs, driven by environmental conditions [96]. Under specific conditions, previously adsorbed pollutants may desorb and re-enter the environment, forming a secondary source of pollution.

4.2 Influence of Micro-Nanoplastics as Carriers on the Transport of Persistent Organic Pollutants

MNPs can act as "Trojan horses" for POPs, significantly promoting their transport and diffusion in the environment. Due to their small size, MNPs can penetrate environmental barriers and transport adsorbed pollutants to areas that are otherwise difficult to reach [98]. This carrier effect not only alters the spatial distribution and environmental behavior of pollutants but also potentially affects their bioavailability and ecological risks.

Moreover, MNPs can transfer through the food chain, transporting adsorbed pollutants from lower trophic levels to higher ones, causing bioaccumulation and magnification effects. This ultimately increases the exposure levels and health risks of pollutants to higher trophic organisms.

4.3 Combined Toxic Effects and Mechanisms of Micro-Nanoplastics and Persistent Organic Pollutants

The coexistence of MNPs and POPs in the environment leads to complex combined toxic effects, with their interaction patterns highly dependent on factors such as pollutant combinations, concentration ratios, exposure duration, and biological receptors [87]. Current research has revealed the following key mechanisms and effect patterns:

1). MNP carrier effects enhance the bioavailability and toxicity of POPs: Both laboratory studies and field investigations have confirmed that MNPs can effectively adsorb chemical pollutants in the environment, exhibiting strong adsorption capacity for hydrophobic organic pollutants [99,100]. Research provides typical evidence: low-dose PS increases the bioaccumulation of PCBs in benthic organisms, directly confirming that MNPs exacerbate the bioaccumulation and potential toxicity of POPs [101]. Combined exposure to MNPs and POPs results in more oxidative damage, indicating that MNPs can increase the absorption of pollutants by acting as an additional exposure pathway [102]. These results suggest that MNPs play a "Trojan horse" role, enhancing the delivery efficiency of POPs to biological targets, which is one of the key mechanisms underlying their synergistic toxicity.

2). Adsorption Reduces Bioavailability and Potential Antagonistic Effects: Conversely, the strong adsorption of POPs by MNPs may reduce their bioavailability in environmental media or organisms, thereby causing antagonistic effects [103]. This "passivation" effect typically occurs under specific conditions and may be counteracted by subsequent digestive desorption processes; its environmental relevance and persistence still require careful evaluation. Additionally, the toxicity of adsorbed POPs varies with the diameter of MNPs, with smaller-diameter MNPs exhibiting more significant biotoxicity [104].

3). Synergistic Effects of Physical Damage and Chemical Stress: MNPs themselves can cause physical damage and induce oxidative stress. Physical damage can compromise the integrity of biological barriers, providing more entry pathways for POPs. Meanwhile, MNP-induced oxidative stress and the chemical toxicity of POPs can produce additive or synergistic effects, exacerbating cellular damage, inflammatory responses, and organ dysfunction [105]. Studies have found that MNPs adsorbed with BaP are more toxic than MNPs alone, with smaller-diameter MNPs causing higher DNA damage toxicity [106]. Combined exposure to MNPs and BaP can result in severe colon barrier damage and inflammation in mice, producing synergistic toxic effects [107].

4.Interference with Pollutant Metabolism and Detoxification Processes: Preliminary studies indicate that MNPs may interfere with the metabolic transformation and detoxification pathways of POPs in organisms. For example, MNP exposure can reduce sperm-egg collision probability, enhancing the fertilization toxicity of TCS [108]. MNPs can also inhibit lipid metabolism activity in the liver, leading to prolonged retention of TCS in the liver and intestines, accumulation of toxic metabolites, and consequently amplifying its toxic effects [109].

5. Research Methods for Combined Toxicity Effects

Since these two types of pollutants commonly coexist in the environment, their combined effects may lead to more complex and severe ecological risks than individual pollutants. To comprehensively assess their joint toxicity, researchers have employed various methods and technical approaches.

In vitro and in vivo experiments are the two primary methods for studying the combined toxicity of microplastics and POPs, each with its own advantages and disadvantages. In vitro experiments are simple to perform, highly reproducible, and allow rapid screening of large numbers of samples while enabling in-depth investigation of toxicity mechanisms. However, they struggle to simulate complex physiological processes and organ interactions. In vivo experiments better reflect the actual behavior and effects of pollutants in organisms, including long-term chronic effects, but are operationally complex, time-consuming, costly, and involve ethical concerns regarding animal use.

In recent years, researchers have increasingly favored combining in vitro and in vivo experiments to obtain more comprehensive toxicity assessment results. For example, zebrafish embryo in vivo experiments and human liver cell in vitro experiments were integrated to evaluate combined toxicity [110].

Additionally, researchers have begun exploring the integration of in vitro-in vivo coupled methods with other advanced techniques to gain deeper mechanistic insights. Several approaches have been utilized, including enzymatic assays, histological analysis, and fluorescence tracking [111,112], which demonstrate that exposure to POPs associated with MNPs can impact the health of aquatic organisms.

Furthermore, innovative applications of in vivo imaging systems (IVIS), radioisotope tracing, and histological staining have been employed to reveal pollutant uptake, biological effects, and interactions, illustrating the distribution and biological effects of typical pollutants in marine organisms [113]. This multidimensional research approach provides critical clues for unraveling the mechanisms of combined pollutant effects.

It is noteworthy that some studies have used zebrafish larvae as model organisms to evaluate the impact of MNPs on the bioavailability of these pollutants [114]. The results showed that while MNPs can adsorb these pollutants, the adsorption does not always align with predictions based on physicochemical properties. The research highlights the unique perspective of biological measurement methods in assessing the co-pollutant bioavailability of MNPs.

6. Research Challenges and Future Directions in Health Risk Assessment

The co-exposure of micro-nanoplastics (MNPs) and persistent organic pollutants (POPs) presents a growing concern for public health. While the individual toxicities of these pollutants are increasingly recognized, their combined effects within the human body may lead to unexpected health risks due to potential synergistic interactions. Recent evidence suggests that these co-pollutants can disrupt biological systems in complex ways, potentially altering cellular responses and exacerbating toxicity.

Current research on the combined health effects of MNPs and POPs remains in its infancy, with a critical shortage of human-relevant data. This review has synthesized existing knowledge on their individual and joint toxicological pathways and evaluated prevailing methodological approaches. Moving forward, research must prioritize elucidating the molecular mechanisms of MNP-POP interactions within biological systems, focusing on their co-transport, cellular uptake, and collective fate inside human tissues. Establishing a definitive link between co-exposure doses and adverse health outcomes is essential.

Furthermore, there is an urgent need to develop advanced human organoids and multi-cellular tissue models that can more accurately predict human-specific toxicological responses. In conclusion, resolving the combined health risks posed by MNPs and POPs is a pressing public health challenge that demands interdisciplinary collaboration. A deeper understanding of the intracellular behavior and synergistic toxicity of these pollutant complexes will provide a scientific foundation for developing effective exposure guidelines and preventive health measures.

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