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Micro(nano)plastic toxicity and health effects: Special issue guest editorial

1. Background

Microplastics (MPs) and nanoplastics (NPs), collectively termed "Micro(nano)plastics [MNPs]" in the special issue, compose the vast majority of plastic contaminants. MPs have become ubiquitous in the global environment (Walker, 2021; Allen et al., 2022) and NPs have also been reported in environmental samples (Cai et al., 2021). MPs have been widely detected in hundreds of animal and plant species (Karbalaei et al., 2019; Litterbase, 2022), including human placentas and blood (Leslie and Depledge, 2020; Prata et al., 2020; Ragusa et al., 2021; Leslie et al., 2022) as MPs are inhaled or consumed via food products and drinking water (Danopoulos et al., 2020; Sequeira et al., 2020; Zhang et al., 2020; Adib et al., 2022). Due to their small sizes, ubiquitous and persistent nature, the potential toxicity and health effects of MNPs have attracted significant attention and spurring rapidly-increasing research efforts (e.g., Guo, et al., 2020; Castro-Castellon et al., 2021; Karbalaei et al., 2021; Khoshnamvand et al., 2021; Lahive et al., 2022; Palacio-Cortés et al., 2022).

Studies on laboratory animals have mostly focused on aquatic species and have shown accumulation of MNPs in tissues and organs, causing intestinal injuries, increasing oxidative stress, triggering inflammation, neurotoxicity, and impaired development (Castro-Castellon et al., 2021; Karbalaei et al., 2021; Kukkola et al., 2021; Matthews et al., 2021). However, the actual ecological and human health impacts of MNPs are still largely unknown and few published studies have directly investigated the effects of MNPs on humans (Weber et al., 2022). Evaluating the potential adverse ecological and human health effects of MNPs across levels of biological organization has become highly imperative but challenging due to the high heterogeneity of MNPs, unknown environmental concentrations, debated vector effects for associated chemicals, and co-impact with other environmental stressors, such as climate change and other chemical contaminants (Thornton Hampton et al., 2022). Currently, the concentrations of MNPs in the environment may be low, but their increasing inputs are inevitable based on current and projected plastic production data (Borrelle et al., 2020). Therefore, it has become imperative to evaluate the potential ecological and human health impacts of MNPs.

2. Aim of the special issue

Environment International has a very strong reputation as a multidisciplinary, Open Access journal publishing high-quality and novel studies within the broad field of 'Public and Environmental Health Sciences'. Even before this special issue, Micro(nano)plastic toxicity and health effects, *Environment International* had published some ground-breaking studies related to the human and ecological health impacts of MNPs. For example, a study by Leslie et al. (2022) published in *Environment International*, reported on the discovery and quantification of plastic particle pollution in human blood. Another ground-breaking study by Ragusa et al. (2021) published in *Environment International*, reported on the discovery of microplastics in the human placenta. These and other ground-breaking studies published in *Environment International* (e.g., Leslie and Depledge, 2020; Kukkola et al., 2021) encouraged the guest editors to lead this special issue, Micro(nano)plastic toxicity and health effects, to further advance our understanding of the toxicity and ecological and human health effects posed by MNPs.

This special issue aimed to compile cutting-edge experimental and modeling studies that evaluate the toxicity and health effects of MNPs. This special issue was edited by Tony R. Walker, Alice Horton, Lei Wang, and Elvis Genbo Xu based on the editor's expertise on MNP toxicity and effects on human and ecological health (e.g., Karbalaei et al., 2019; Xu et al., 2020; Castro-Castellon et al., 2021; Karbalaei et al., 2021; Khoshnamvand et al., 2021; Matthews et al., 2021; Allen et al., 2022; Lahive et al., 2022; Palacio-Cortés et al., 2022). In particular, this special issue encouraged submissions that included: 1) environmentally-relevant exposures, considering different shapes, sizes, and surface charge of MNPs, low-concentrations, and chronic exposures; 2) multiple stressors such as association with other chemicals and environmental factors; and, 3) human toxicological or human health-relevant studies. Submissions that were excluded included: microbead-only acute exposures, particle behavior in lab-scale experiments, adsorption or desorption-only testing, solely animal ingestion studies, or review articles.

3. Content overview of the special issue

This special issue attracted international submissions from a wide variety of interdisciplinary MNPs researchers (over 100 submissions). Following the rigor of peer-review (a minimum of three peer-reviewers are required for *Environment International*) and editorial judgment, a total of 14 papers were published. This represents a substantial collection of all microplastics or nanoplastics papers ever published in *Environment International*. The 14 published articles included scholars from China, Norway, France, Germany, Croatia, Republic of Korea, and Italy, addressing several MNP research frontiers that included experimental and modeling studies to evaluate the toxicity and health effects of MNPs. For example, research on cell lines and animal models included human monocytes and dendritic cells (Weber et al., 2022), human lung carcinoma cells (H. Zhang et al., 2022), porcine coronary artery endothelial cells (Shiwakoti et al., 2022), soil invertebrates (*Eisenia Andrei*, *Eisenia*

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fetida, and *Amynthas cortices*) (Lackmann et al., 2022; Liu et al., 2022; Jiang et al., 2022), arthropods (*Daphnia magna*) (De Felice et al., 2022), zebrafish (*Danio rerio*) (Cheng et al., 2022), rodents (mice and rats) (Jing et al., 2022; Fan et al., 2022; Y. Li et al., 2022; N. Li et al., 2022), and bacteria (J. Zhang et al., 2022). The main studied effects and mechanisms of MNPs toxicity included immunotoxicity, hepatotoxicity, pulmonary toxicology, oxidative stress, as well as interaction with metals and microbes. In addition to *in vivo* and *in vitro* toxicological studies, this special issue also included multiple types of studies which included environmental occurrence, as well as machine learning (N. Li et al., 2022) and MP detection methods (Xie et al., 2022).

4. Key findings of the special issue

The occurrence of MPs has been long reported in aquatic environments and increasing studies have confirmed the wide distribution of MPs in terrestrial environments. Jiang et al. (2022) investigated seasonal variation and correlation of MPs and cadmium in farmland soils of Taihu Lake, China. It was found that MPs were mainly polyethylene MPs derived from mulching films. Microplastic abundance reached 890 particles/kg soil, with most MPs (>72.5 %) in the 0–500 μm size range. The response of *in situ* earthworms (*Amynthas cortices*) to MP–cadmium pollution was also measured, showing that MPs can act as a vector to transfer metals from soil into the bodies of soil organisms. Multiomics techniques demonstrated bacterial community structure dysbiosis and metabolic changes of *in situ* earthworms under MP metal-contaminated soils. The abundance of MP in earthworm casts and intestines was higher than in soil samples (Jiang et al., 2022). In another study, Liu et al. (2022) investigated the toxicity of polystyrene MP (PS-MP) to earthworms (*Eisenia fetida*) along with assessing aging effects. Liu et al. (2022) showed that the 28 d-LC_{50} (50 % lethal concentration) of PS-MP decreased with age. PS-MP toxicity was believed to be due to PS-MP ingestion by earthworms and physical damage from epidermis abrasion and setae loss by PS-MP. Levels of reactive oxygen species, antioxidant enzyme activities, and malondialdehyde content increased with PS-MP concentrations from 0.1 to 1.5 g kg^{-1} but decreased with age from 7 to 28 days. SEM found that PS-MP were progressively covered by soil particles during soil aging, inducing the formation of protective layers and increasing particle PS-MP sizes, which prevented direct contact with earthworms and decreased PS-MP ingestion which subsequently decreased PS-MP toxicity (Liu et al., 2022). Soil biota using earthworms was again the focus of a study by Lackmann et al. (2022), who attempted to gain insight into the effects of environmentally relevant concentrations of MPs on *E. andrei* based on different exposure periods. Earthworms were exposed to polystyrene-HBCD and car tire abrasion MPs in natural soil for 2, 7, 14, and 28 d. Subcellular endpoint biomarkers included enzymatic biomarker responses, namely, carboxylesterase, glutathione peroxidase, acetylcholinesterase, glutathione reductase, glutathione S-transferase and catalase activities, as well as fluorescence-based measurements of oxidative stress-related markers and multixenobiotic resistance activity. Multiple biomarkers showed significant changes in activity, but a recovery of most enzymatic activities could be observed after 28 d. Only minor effects were observed at the subcellular level, showing that environmentally relevant concentrations (based on typical soil MPs concentrations from Germany), posed a low risk to soil biota (Lackmann et al., 2022).

Two studies investigated the aquatic toxicity of MNPs. Cheng et al. (2022) investigated the hepatic inflammatory effects of polystyrene (PS) NPs (100 and 50 nm) and PS-MPs on transgenic zebrafish (*Danio rerio*) larvae using fluorescent-labeled neutrophils, macrophages, and liver-type inflammatory binding protein (fabp10a). It was found that smaller-sized particles induced higher aggregations of neutrophils and apoptosis of macrophages in the larvae's abdomen, corresponding to greater larvae hepatic inflammation. NPs increased the expression of fabp10a in larval livers in a dose- and size-dependent manner. Metabolic pathways of catabolic processes, amino acids, and purines were promoted by NPs, compared to MPs. NPs also activated steroid hormone biosynthesis in zebrafish larvae, which resulted in immune-related diseases (Cheng et al., 2022). De Felice et al. (2022) investigated sub-individual (i.e., molecular and biochemical) and individual (i.e., behavioral) adverse effects induced by a 21-day exposure to two sub-lethal concentrations of PS-NPs (0.05 and 0.5 μg/mL) on *Daphnia magna*. PS-NPs induced modulation of genes involved in oxidative stress response but biochemical analyses (i.e., the amount of pro-oxidants, the activity of antioxidant and detoxifying enzymes, and lipid peroxidation) did not show an oxidative stress condition. De Felice et al. (2022) also observed ssignificant changes in energy reserves of *D. magna* but the swimming activity was not affected by PS-NPs.

Mice or rat models were used in 4 studies in the special issue to reveal important toxicity mechanisms of MNPs, such as metabolism disorder, changing gut microbiota, immunotoxicity, and pulmonary toxicity. Hematopoietic toxicity in mice induced by 42-d exposure to PS MP and NP particles was identified by 16S rRNA, metabolomics, and cytokine chips (Jing et al., 2022). MNP exposures disturbed the gut microbiota, increased metabolism, and cytokine of inflammation, all of which were related to the hematopoietic function. N. Li et al. (2022) also found that 28-d exposure to PS-MPs (5 μm) induced gut microbiota dysbiosis, disrupted amino synthesis in mice, and enhanced the Th2 inflammatory response leading to immune toxicity. However, *Bifidobacterium breve* M-16 V, an important probiotic bacterial strain, could significantly reduce immune damage caused by PS-MPs via inhibiting Th2 and Th17 lymphocyte subset, activating MyD88 expression and promoting the production of Th1-related cytokine IL-12, and decreasing the abundance of gut flora. Although gut bacteria could be stimulated by MNPs to disorder metabolite and cytokine composition activating toxicity, this effect was not irreversible. Also in mice (C57BL/6), Y. Li et al. (2022) showed that tire wear microplastic particles (TWMPs) inhalation-induced pulmonary toxic effects and its epigenetic mechanisms. Restricted ventilatory dysfunction and fibrotic pathological changes were observed in TWMP-treated mice. It was further tested that miR-1a-3p played an important role in TWMP-induced lung injury. Mechanistically, miR-1a-3p inhibited the F-actin formation by targeting cytoskeletal regulatory proteins twinfilin-1, leading to TWMP-induced pulmonary fibrotic injury. Besides miRNA, the roles of other non-coding RNA (lncRNAs and circRNAs) in the pulmonary toxicity of MNPs were explored by Fan et al. (2022). In this study, rats were treated with 100 nm, 500 nm, 1 μm, and 2.5 μm PS-MNPs, and these particles were deposited in the lungs, and 100 nm PS-MPs with the dose of 0.5, 1or 2 mg of PS-MPs under intra-tracheal instillation in the saline induced lung injury. Sequencing results showed that several novel circRNAs and lncRNAs may play an important role in the development of lung inflammation caused by PS-MNPs.

Cytotoxicity of MNPs and molecular mechanisms were investigated by using both human and animal cell lines *in vitro*. H. Zhang et al. (2022) used nanoparticles of polyethylene terephthalate (nano-PET), to measure the toxicity of nano-PET at environmentally relevant concentrations on human lung carcinoma cells. They found that nano-PET exhibited low toxicity on mitochondrial membrane potential levels and cell apoptosis. At low concentrations of 0.10 and 0.98 μg/mL, the nano-PET had a slight promotion effect on cell viability, while an inhibitory effect on cell viability was presented at higher nano-PET concentrations of 98.40 and 196.79 μg/mL, and significant oxidative stress in cells caused by the nano-PET exposure at 49.2 μg/mL was observed. H. Zhang et al. (2022) suggested the cytotoxicity may be due to the increase of reactive oxygen species caused by oxidative stress, which in turn induced a decrease in the mitochondrial membrane potential. Weber et al. (2022) showed whether NPs of different types induce inflammatory processes in primary human monocytes and monocyte-derived dendritic cells. Cells were exposed to NPs of different shapes (irregular vs spherical), sizes (50–310 nm and polydisperse mixtures), and polymer types (polystyrene; polymethyl methacrylate; polyvinyl chloride, PVC) using concentrations of 30–300 particles per cell. Irregular PVC-

NPs induced the strongest cytokine release of these plastic particles. Irregular PS-NPs triggered a significantly higher pro-inflammatory response compared to spherical NPs. The contribution of chemicals leaching from the particles was minor. The effects were concentration-dependent but varied markedly between cell donors. The study concluded that NP exposure can provoke human immune cells to secrete cytokines as key initiators of inflammation, and NPs cannot be considered one homogenous entity when assessing their health implications. Shiwakoti et al. (2022) assessed the possibility that NP exposure promotes premature endothelial cell (EC) senescence in porcine coronary artery ECs. Treatment of ECs with NPs promoted the acquisition of senescence markers, senescence-associated β-galactosidase activity, and p53, p21, and p16 protein expression, resulting in the inhibition of proliferation. In addition, NPs impaired endothelium-dependent vasorelaxation associated with decreased endothelial nitric oxide synthase (eNOS) expression. NPs enhanced reactive oxygen species formation in ECs and increased oxidative stress levels were associated with the induction of NADPH oxidases expression, followed by the subsequent downregulation of Sirt1 expression. The characteristics of EC senescence and dysfunction caused by NPs were prevented by an antioxidant (*N*-acetylcysteine), an NADPH oxidase inhibitor (apocynin), and a Sirt1 activator (resveratrol). These findings indicate that NPs induced premature EC senescence, at least in part, through the redox-sensitive eNOS/Sirt1 signaling pathway.

MNP contamination has become an increasingly serious environmental problem, including the atmosphere (Allen et al., 2019; Allen et al., 2022), but the environmental and health risks of MNPs remain unclear due to detection methodological challenges, lacking quantitative monitoring data, the complexity of exposures, and high heterogeneity of MNPs. To address some of the gaps, the present special issue also included a methodological study for MP detection in air and a machine learning approach. Currently, the size detection limit in measuring airborne MPs makes it difficult to assess human MP exposure levels via inhalation and limits our understanding of airborne MP pollution. Xie et al. (2022) assessed MP pollution in indoor and outdoor air samples from eight sampling sites in Shanghai, China using Raman microscopy and characterized suspended atmospheric MPs down to 1 μm. Inhalable MPs were detected in all samples but indoor samples had the highest concentrations demonstrating potential human exposure via inhalation. Xie et al. (2022) found that polyethylene, polyester, phenolic resin, and polyvinyl chloride were the dominant MPs measured in indoor and outdoor air samples. J. Zhang et al. (2022) established a multi-feature superposition analysis boosting (MFAB) machine learning (ML) approach to identify and predict the importance, interaction networks, and superposition effects of multiple features, including 34 characteristic variables (e.g., MP contamination and climatic and geographic variables), from 1354 samples distributed globally. MFAB-ML analysis achieved realistic and significant results, in some cases even opposite to those obtained using a single or a few features, revealing the importance of considering complicated scenarios. J. Zhang et al. (2022) predicted that the microbial diversity in East Asian seas would continually decrease due to the superposition effects of MPs with ocean warming; for example, the Chao1 index will decrease by 10.32 % by 2065. Given the fast-accumulating exposure data of MNPs, the ML approach provides a good potential to predict the multi-feature superposition effects of MNPs on realistic environments.

5. Conclusions

The 14 articles published in this special issue help advance our understanding of the toxicity and health effects of MNPs. These articles provide evidence showing that MNPs are detrimental to both ecosystem and individual species' health, including human cells. Although there has been a dramatic increase in MNP research in recent years, our understanding of the toxicity and health effects of environmental MNPs has not yet been fully understood, the articles published in this special issue help guide future research which needs to focus on the identification of acute and chronic exposure thresholds and advancing the quantitative understanding of environmental MNPs. Given the toxic nature of MNP particles, their plastic additives, and adsorbed contaminants, environmentally relevant toxicity and health effect studies that consider multi-generational effects are required, including bioaccumulation studies across multiple species and environmental compartments. The need to better understand the toxicity and health effects of MNPs remains of vital importance.

Declaration of Competing Interest

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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