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Review article

Unraveling the potential human health risks from used disposable face mask-derived micro/nanoplastics during the COVID-19 pandemic scenario: A critical review

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ABSTRACT

With the global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), disposable face masks (DFMs) have caused negative environmental impacts. DFMs will release microplastics (MPs) and nanoplastics (NPs) during environmental degradation. However, few studies reveal the release process of MPs/NPs from masks in the natural environment. This review presents the current knowledge on the abiotic and biotic degradation of DFMs. Though MPs and NPs have raised serious concerns about their potentially detrimental effects on human health, little attention was paid to their impacts on human health from DFM-derived MPs and NPs. The potential toxicity of mask-derived MPs/NPs, such as gastrointestinal toxicity, pneumotoxicity, neurotoxicity, hepatotoxicity, reproductive and transgenerational toxicity, and the underlying mechanism will be discussed in the present study. MPs/NPs serve as carriers of toxic chemicals and pathogens, leading to their bioaccumulation and adverse effects of biomagnification by food chains. Given human experiments are facing ethical issues and animal studies cannot completely reveal human characteristics, advanced human organoids will provide promising models for MP/NP risk assessment. Moreover, in-depth investigations are required to identify the release of MPs/NPs from discarded face masks and characterize their transportation through the food chains. More importantly, innovative approaches and eco-friendly strategies are urgently demanded to reduce DFM-derived MP/NP pollution.

1. Introduction

The global outbreak of Coronavirus Disease-2019 (COVID-19) has caused serious human health concerns. Globally, as of 22 July 2022, confirmed cases of COVID-19 have passed more than 565 million, including over 6 million deaths, were reported by World Health Organization (WHO) (WHO 2022). Since the wide spread of COVID-19, the demand for medical equipment is drastically increased, ultimately increasing medical and healthcare waste at an alarming rate (Al-Omran et al. 2021; Chowdhury et al. 2022). Wearing face masks in public transport and spaces is a feasible way to curb the infection and transmission of the virus, leading to increasing demand for face masks (Cheng et al. 2020; Tesfaldet et al. 2022). To date, the use and production of face masks have gradually increased to an unprecedented level. The WHO estimated that roughly 89 million medical masks will be required globally per month (WHO 2020). However, inadequate management of these used masks has posed threats to public health and environment, especially in developing countries (Chen et al. 2021b; Kwak and An 2021; Liang et al. 2021; Morgana et al. 2021). Discarded masks have been widely observed in our surrounding environments, such as urban spaces (streets, parks, and gardens), fresh water (lakes and rivers), and marine environments (beaches and oceans) (Aragaw et al. 2022; Cordova et al. 2021; De-la-Torre et al. 2022; Gunasekaran et al. 2022; Kwak and An 2021; Tesfaldet et al. 2022; Wang et al. 2021a). It was estimated that 10 million masks (equal to 30,000–40,000 kg) will be dispersed in the environment per day even considering only 1 % of disposable face masks (DFMs) (World Wildlife Fund 2020). Therefore, approximately 15 years would be needed to degrade half of marine masks (Chen et al. 2023). However, limited studies reported the degradation of DFMs in natural environment.

The materials commonly used in DFMs are plastic polymers such as polycarbonate (PC), polypropylene (PP), polystyrene (PS), polyurethane

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(PU), polyacrylonitrile (PAN), polyethylene (PE), or polyester (PES) (Fadare and Okoffo 2020; Potluri and Needham 2005). In the natural environment (weathering, temperature, solar ultraviolet (UV) radiation, pH, and biological degradation), discarded face masks can be gradually degraded into smaller plastics, such as microplastics (MPs) and nanoplastics (NPs), and give rise to a new environmental challenge (Chen et al. 2021b; Kwak and An 2021). Moreover, plastic residue (tubes, pipet tips, falcon tubes, buffer bottles, and medical globes) wastes after polymerase chain reaction testing for COVID-19 diagnosis also are potential sources of plastic waste (Aragaw and Mekonnen 2022). MPs are often defined as plastic particles smaller than 5 mm in dimension, and NPs are ranging from 1 nm to 1 μm (Gigault et al. 2018). However, there is yet no universally accepted definition of the relevant plastic size range. DFM-derived MPs/NPs could readily get into waterways from where they were released and reach the aquatic ecosystem. Aquatic MP/NP issues are of particular concern since they can be transported over a long distance to diverse aquatic biota and ultimately transferred along the food chain (Chowdhury et al. 2021). For instance, MPs/NPs have already been observed in shellfish and fish consumption (Barboza et al. 2018; Clere et al. 2022; Smith et al. 2018). Thus, the bioaccumulation of and biomagnification of MPs in aquatic products could cause detrimental effects on human health. Not surprisingly, recently published studies detected MPs/NPs in human feces and revealed the level of MPs was closely associated with inflammatory bowel disease (IBD) status (Schwabl et al. 2019; Yan et al. 2020b; Yan et al. 2021).

Given the physical properties of plastics, the negative effects of MPs/NPs on organism are closely associated with their types, sizes, shapes, and concentrations (Qin et al. 2021; Schwarzer et al. 2022; Xu et al. 2021b; Zhang et al. 2022a). Moreover, various additives used in masks, such as plasticizers, pigments, and dyes, might also pose direct risks to environmental and public health (Lellis et al. 2019; Xie et al. 2022). The toxic effects of MPs/NPs also can be enhanced by their ability to adsorb chemical toxicants from the surrounding water (Bakir et al. 2014; He et al. 2022; Suzuki et al. 2020). MPs/NPs can not only act as carries of pollutants, such as persistent organic pollutants (POPs) (e.g. cpolycyclic aromatic hydrocarbons [PAHs], perfluorooctanoic acid [PFOA], polychlorinated biphenyls [PCBs], and polybrominated diphenyl ethers [PBDEs]) and heavy metals (e.g., arsenic [As], chromium [Cr], copper [Cu], cadmium [Cd], and lead [Pb]), but also transfer pathogenic bacteria and viruses through the food chain to humans (Bakir et al. 2014; Herrera et al. 2022; Li et al. 2022d; Qin et al. 2022; Wang et al. 2021a; Wang et al. 2021c; Zhang et al. 2022b; Zhang et al. 2022b; Zhou et al. 2022a). More recently, MPs/NPs also serve as an "antibiotic-resistant reef" providing an interface for the enrichment of antibiotic resistance genes (Liu et al. 2021b; Wang et al. 2022a; Zhou et al. 2022b). Although there are growing studies on DFM-derived MP/NP pollution, limited data on the potentially toxic effects they might have on aquatic animals, how they transfer through the food chain, and their direct or indirect impacts on human health.

In general, human exposure to face mask-derived MPs/NPs often happen through dermal contact (skin), inhalation (air), and ingestion (food and water). Therefore, it is urgent to estimate their potential adverse effects on humans, especially developing fetuses. Aiming at this case, our study provides an overview of the potential source of MPs/NPs from DFMs in detail about their types (surgical, N95, and cotton masks) and natural degradation (abiotic and biotic processes). Moreover, previously published reports about their toxic effects on different organs (gastrointestinal toxicity, pulmonary toxicity, neurotoxicity, hepatotoxicity, cardiovascular toxicity, kidney toxicity, skin toxicity, and reproductive toxicity) will be consulted and studied. The potential mechanism, directly or indirectly, is also needed to explain the impacts on humans brought by MPs/NPs. Given ethical issues and species difference between humans and animals, more studies combined with novel *in vitro* models need to be conducted to evaluate the potential risks of face mask-derived MPs/NPs. Moreover, in-depth investigations are demanded to identify the release of MPs/NPs from abandoned DFMs and characterize the transport of MPs/NPs in the food chains. At last, innovative methods and sustainable strategies to reduce DFM-derived MP/NP pollution will be discussed.

2. The release of MPs/NPs from disposable face masks

2.1. Diverse types of face masks

COVID-19 disease has made a profound impact across the world. The spread of the deadly coronavirus can be optimally prevented or avoided by using personal protective equipment (PPE) including protective clothing, helmets, gloves, face shields, goggles, and face masks. Face masks are the most widely used type of PPE due to their effectiveness and low cost. Governments and public health agencies across the world have passed legislation requiring the use of masks when taking public transportation and going to public areas. This has brought about a phenomenal rise in the worldwide production of face masks. Wearing face masks has gradually become a habit of people. The most commonly available face masks include medical or surgical masks, respirators, and cotton face masks (Fig. 1). However, controversy remains on the proper type of face masks and the situation in which they need to be used in community and health care settings to prevent SARS-CoV-2 infection (Qaseem et al. 2020).

Medical or surgical masks are highly recommended by WHO for nurses, doctors, and patients to protect themselves from COVID-19 exposure. Increasing evidence suggests that SARS-CoV-2 can be transmitted via respiratory droplets and aerosols (Jayaweera et al. 2020; van Doremalen et al. 2020). Surgical face masks can protect healthcare workers against droplet communication. Although Milton et al. showed that surgical masks might not be able to effectively limit the emission of small droplets, more researchers have shown that no significant difference was found between the surgical masks and N95 masks in the protection from viral pathogens (Chua et al. 2020; Johnson et al. 2009; Milton et al. 2013). The common surgical masks consist of four parts (Long et al. 2020; Shen et al. 2021; Smith et al. 2016). The outer most superficial layer is composed of non-woven fibers (e.g., PES) that are water-resistant and normally colored. The middle layer is made up melt-blown filters (e.g., PP and PS), which are the core material for virus rejection. The inner layer and ear band are made of fiber materials. Therefore, MPs/NPs will be generated during the degradation of face masks (Aragaw 2020; Fadare and Okoffo 2020).

The N95 respirator is a respiratory protective device designed to achieve a very close facial fit and is the most common of the particulate filtering facepiece respirators (FFRs). The N95 designation is certified by the United States National Institute for Occupational Safety and Health (NIOSH), meaning that it removes at least 95 % of airborne particles. The N95 four-layer respirator consists of the inner, support layer, filter, and outer filter layer from inside to outside (Zhou et al. 2018). The innermost layer is constructed of non-woven PP which minimizes moisture from breathing into the mask materials. The support layer is composed of modacrylic that provides rigidity and adds thickness to the mask, giving it more structure and adding to the feel of comfort. The filter layer is made up non-woven PP and melt-blown to capture oil and non-oil based particles. The outer filter layer is constructed of hydrophobic non-woven PP that prevents external moisture from entering the mask. It was reported that the N95 respirator prevented air leakage more effectively than the surgical mask (Dbouk and Drikakis 2020).

Cloth face masks are made of cloth materials, including cotton, gauze, silk, or muslin. During the outbreak of SARS in 2002, cotton cloth masks were reported to effectively protect Health Care Workers and the general public in China (Pang et al. 2003). After the coronavirus outbreak, cloth masks might be the only viable option if the medical masks are unavailable in stock. However, cloth masks may provide a greater opportunity for air leakage around the sides, which may decrease their filtration efficiency, compared to surgical masks and N95 respirators (Jain et al. 2020). Ma et al. demonstrated that cloth

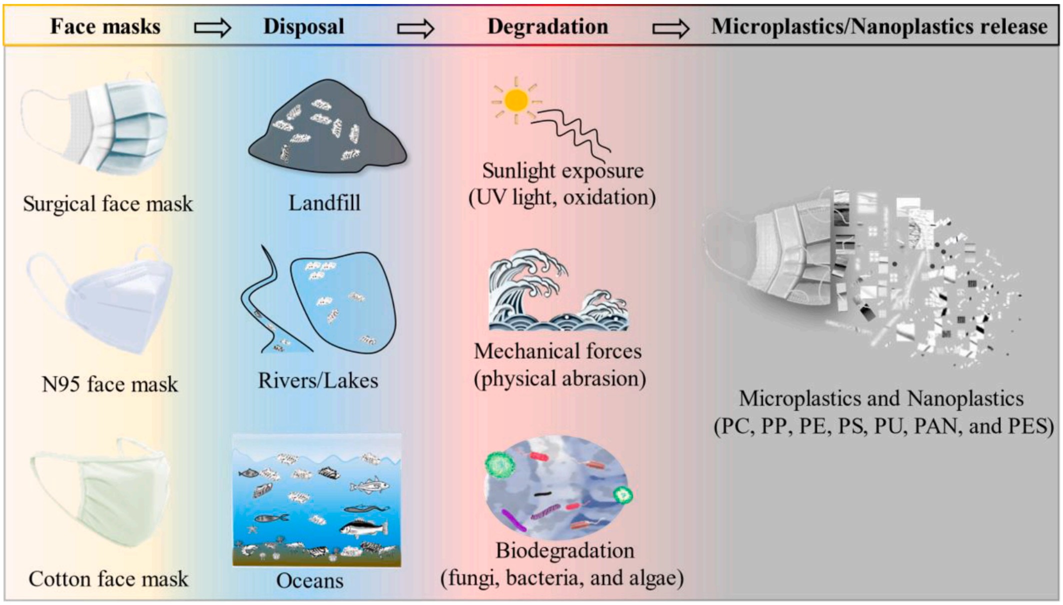

Fig. 1. Microplastics and nanoplastics are released from face masks. There are three commonly used face masks include surgical, N95, and cotton face masks. Improper waste management has caused used face masks to appear in landfill, rivers and lakes, and oceans. Once in the natural environment, face masks could release numerous MPs and NPs under sunlight exposure, mechanical forces, and biodegradation.

homemade masks blocked 95.15 % of avian influenza virus, while surgical masks and N95 respirators were comparable (97.14 % and 99.98 %, respectively) (Ma et al. 2020). Although cloth masks exhibit less effective degree of protection than surgical masks and N95 respirators, to some extent, more research should be conducted to assess the effectiveness of cloth masks for virus prevention. Moreover, unlike surgical masks and N95 respirators, cloth masks can be reused after being sterilized and decontaminated contributing to pro-environment and sustainability. However, cloth mask users may put themselves at risk of contamination during washing and decontaminating of used masks (Chughtai et al. 2019; MacIntyre et al. 2017). Although the material of cloth masks may be unlike to degrade from normal degradation procedures, previous study also proved that fibers could be released from washing cloth masks (Chughtai et al. 2020; Das et al. 2021; Li et al. 2021a).

2.2. The degradation of disposable face masks

The massive use of face masks caused environmental disorder both in the terrestrial environment and aquatic medium during the COVID-19 scenario (Du et al. 2022). Once in the environment (disposal in landfill or discarded in public places, rivers, lakes, and oceans), discarded face masks can be gradually degraded or break down into numerous smaller plastic debris under environmental weathering, such as abiotic and biotic processes, becoming a new source of MPs/NPs (Fig. 1). The abiotic processes refer to the physicochemical and mechanical factors, such as sunlight exposure, temperature, and mechanical forces, while the biotic processes are related to the participation of animals, plants, fungi, and bacteria (Zhang et al. 2021c). Notably, biotic and abiotic processes often work in tandem in the natural environment.

Sunlight (UV-radiation) and oxygen are vital factors of abiotic plastic degradation in the environments (Chubarenko et al. 2020; Gewert et al. 2015; Mao et al. 2020). Plenty of synthetic polymers could absorb solar UV radiation and free radicals can react with oxygen to produce peroxy radicals that mediate oxidative reactions, leading to the initial degradation of polymers with C—C and C—H bonds (Chamas et al. 2020; Zhang et al. 2021c). Smaller polymer fragments formed by chain scission are more susceptible to degradation (Gewert et al. 2015; Wang et al. 2016). Light-induced oxidative degradation of polymers was found to be orders of magnitude faster compared to other types of degradation processes. However, the rate of degradation of plastics in the ocean was much slower than that of in the terrestrial environment due to the deficiency of oxygen and lower temperature (Anderson et al. 2016; Andrady 2011; Chubarenko et al. 2020; Wang et al. 2016). Moreover, other factors include the differences in polymer structure and component are closely associated with the photodegradation processes (Min et al. 2020; Zhang et al. 2021c). A recent study showed that the middle layer (the melt-blown cloth) of masks was the most sensitive part to UV radiation and could release numerous MPs into the aqueous environment (Wang et al. 2021a). These data suggest that photo-oxidation of abandoned masks contributes to plastic degradation in the environment.

It has been widely recognized that mechanical degradation was the primary and critical process for the generation of MPs/NPs, especially on the beaches due to the wind and wave action, and tidal currents (Chubarenko et al. 2020; Song et al. 2017). Mechanical forces (wave action and abrasion with sand) can cause the flaking of weathered or oxidized surfaces, leading to ablation (Andrady 2017; Chamas et al. 2020). To investigate the behavior of face masks in shoreline conditions, the masks were put into the water in the presence of sand (Wang et al. 2021a). The study showed that the physical abrasion from sand promoted the release of plastics in the aquatic environment. Coupled with UV radiation, physical abrasion could accelerate the fragmentation and photodegradation of abandoned masks (Song et al. 2017). A recent study demonstrated that MPs could be detected in artificial seawater with shaken continuously using a mechanical shaker for nine days (Sun et al. 2021a). Moreover, a surgical mask may release approximately 173,000 fibers/day in artificial seawater with 180 h of UV-light radiation combined with vigorous stirring (Saliu et al. 2021).

Biotic degradation of plastics refers to the deterioration of plastics caused by living microorganisms, such as fungi, bacteria, and algae (Gautam et al. 2007; Kyrikou and Briassoulis 2007; Zeenat et al. 2021). Previous studies have shown that microbial strains could cause the weight loss of polymers and fractures and pores on the polymer surface (Harshvardhan and Jha 2013; Wang et al. 2016; Zettler et al. 2013). Plastic biodegradation can be categorized as aerobic and anaerobic biodegradation based on the presence or absence of oxygen. In aerobic biodegradation, aerobic microbes break down large matter into smaller molecules with CO_2 and water by using oxygen as an electron acceptor

(Fesseha and Abebe 2019; Priyanka and Archana 2011; Zeenat et al. 2021). In anaerobic biodegradation, nitrate, iron, sulfate, manganese, and CO_2 are used as electron acceptors by anaerobic bacteria to break down organic chemicals. Biodegradation of polymers entails three steps: (a) attachment of the microorganism to the surface of the polymer; (b) using the polymer as a carbon source for the growth of the microorganism; and (c) degradation of the polymer (Gu 2003; Singh and Rawat 2020). It was reported that the formation and development of biofilms onto MPs/NPs from microorganisms including pathogens, will influence plastic fragmentation and degradation (Jiang 2018; Tu et al. 2020). Nonetheless, the biodegradation mechanism of plastics has yet to be fully elucidated. Furthermore, the biodegradation of plastics might be influenced by the physicochemical characteristics of plastics, including molecular types, weight, crystallinity, and hydrophobicity, as well as plasticizers or additives used in plastics (Lin et al. 2022; Yuan et al. 2020). Therefore, a full investigation is necessary to determine the biodegradation of discarded masks by microorganisms.

3. Potential toxicity of microplastics on human organs

In recent years, increasing studies have reported that MPs/NPs accumulated in animal intestine, lung, brain, live, kidney, and testis after exposure, and induced cell apoptosis, acute or chronic inflammation, and functional abnormality in multi-organs (Kwon et al. 2022; Liu et al. 2022c; Xu et al. 2021a; Zheng et al. 2021). These studies provide evidence regarding the risk of human exposure to MPs/NPs and help us to predict the possible adverse effects of DFM-derived MPs/NPs on humans (Fig. 2).

3.1. Gastrointestinal toxicity

The gut is one of the most important tissues which could be affected by DFM-derived MPs/NPs directly. Existing literature revealed that there was a median of 20 pieces of MPs per 10 g of human stool (Schwabl et al. 2019). Moreover, MPs were observed in human colectomy specimens, showing that PC was most abundant in colonic tissue samples (Ibrahim et al. 2021). However, it was different from Schwabl's study, which found that PP was the most frequent polymer detected (Schwabl et al. 2019). The study indicated that the increased intestinal permeability, such as in IBD, may have a higher risk of MP translocation into deeper tissues and even the circulatory system which could lead to unpredictable adverse effects on human patients (Schmidt et al. 2013). Although studies in marine species showed that MPs induced aberrant intestinal permeability and dysbiosis, which may associate with intestinal inflammation, the relationship between MP exposure and intestinal toxicity in humans remains speculative due to the species differences (Qiao et al. 2019b). Obviously, gut microbiota plays a critical role in maintaining the host's metabolic homeostasis and health (Qin et al. 2022). Previous studies have shown that exposure to MPs caused intestinal microbiota dysbiosis in zebrafish and mice (Hu et al. 2022; Jin et al. 2018; Lu et al. 2018b). The decreased diversity of gut microbiota was closely correlated with the aberrant lipid metabolism (Karlsson et al. 2013; Qiao et al. 2019b). Therefore, exposure to DFM-derived MPs from food chains could cause human gastrointestinal toxicity.

3.2. Pneumotoxicity

Although studies speculated that humans may exposure to MPs/NPs through food and drinking water, MPs have been detected in human nasal mucus after wearing a mask (Ma et al. 2021; Nelms et al. 2018; Yan et al. 2020b). Similarly, MPs were detected in all regions of the human lung, indicating that MPs/NPs might translocate into the human body through inhalation (Jenner et al. 2022). Therefore, it is urgent to investigate whether DFM-derived MPs/NPs by inhalation cound cause

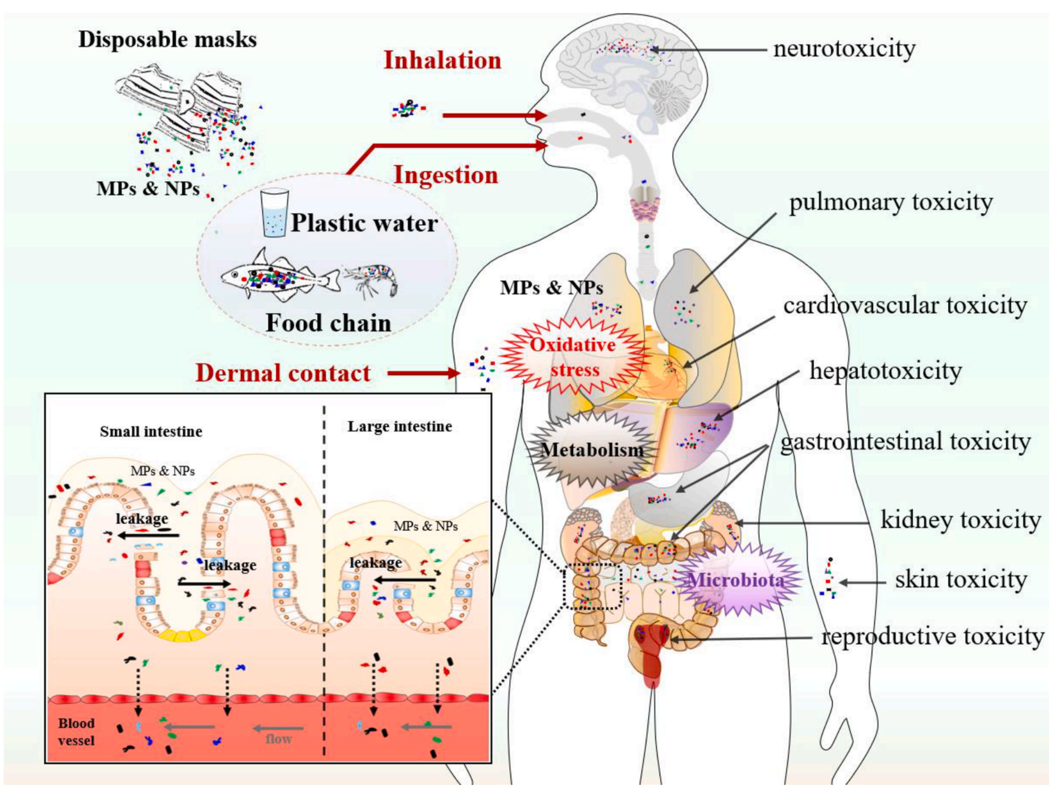

Fig. 2. Potential toxicity of disposable face mask-derived microplastics and nanoplastics on human organs. Human exposure to MPs/NPs may happen through dermal contact, inhalation, and ingestion (for instance, MPs/NPs cross the leakage of intestinal barriers and induce endothelial leakiness in vessels (Wei et al. 2022)). MPs/NPs could cause gastrointestinal toxicity, pulmonary toxicity, neurotoxicity, hepatotoxicity, cardiovascular toxicity, kidney toxicity, skin toxicity, and reproductive toxicity through oxidative stress, aberrant metabolism, and microbiota dysbiosis.

adverse effects on lung tissues. For instance, Shi and colleagues showed that PS-MPs affected the interfacial properties of lung surfactants, including phase behavior, surface tension, and membrane structure (Shi et al. 2022). Moreover, PS-MP exposure accelerated conversion between ascorbic acid and deoxyascorbic acid, as well as increased the production of the level of hydroxyl radicals. Exposure to PS-MPs was also found to reduce the permeability of airway epithelium and impair lung barrier function (Dong et al. 2020). A similar result was observed by Yang's group, showing that PS-NPs disrupted the alveolar epithelial barrier and lung function (Yang et al. 2021). PS-MPs induced alveolar destruction, bronchial epithelium disarrangement, and lung inflammation may be closely associated with altered expression of long noncoding RNAs and circular RNAs (Fan et al. 2022). Although a growing number of studies demonstrated the existence of MPs in the air, it remains unclear whether inhaled MPs/NPs are from DFMs following occupational exposure. There are limited studies reported human exposure to MPs/NPs through inhalation during the wearing of face masks (Li et al. 2021a). Furthermore, following intestinal absorption, research on the transportation of MPs/NPs into the circulation and finally deposited in the lung tissue is very scarce (Deng et al. 2017).

3.3. Neurotoxicity

The central nervous system has been identified as a sensitive target for nanoparticles (Prust et al. 2020; Teleanu et al. 2019). In recent studies, MPs/NPs absorbed by the gut can cross the blood–brain barrier (BBB) and exert neurotoxic effects (Kogel et al. 2020; Lusher et al. 2017; Prust et al. 2020). The accumulation of PS-MPs in mice brains was found after oral and intraperitoneal administration (Estrela et al. 2021; Kwon et al. 2022). *In vitro* study showed that the internalization of MPs/NPs was observed in neuronal cells (Hoelting et al. 2013; Murali et al. 2015). Existent evidence showed that short- and long-term PS exposure disrupted neuronal development in nematodes (Chen et al. 2021a; Qu et al. 2019; Qu and Wang 2020). Recently, in the neurons, RNAi knockdown of *eat-4* could induce resistance to PS-NPs toxicity in *Caenorhabditis elegans* (Wang et al. 2021b). Alteration regulation of cholinergic nervous transmission, particularly acetylcholinesterase (AchE) activity, was also found in fish after MP exposure (Bhagat et al. 2020). The inhibition of AchE caused by MPs/NPs could increase acetyl choline levels, leading to the disruption of the nervous system, such as motor dysfunction and behavioral abnormalities (Kim et al. 2021). Meanwhile, the visual system was also affected by MPs as illustrated by the upregulated visual-related gene expression (Chen et al. 2017a). Moreover, PS-NP exposure was found to induce defective neural tube morphogenesis during mice embryogenesis (Nie et al. 2021). However, whether DFM-derived MPs/NPs could cross the BBB by circulation and exert toxic effects on the nervous system of humans, remains to be determined.

3.4. Hepatotoxicity

The liver is a large and critical detoxifying organ in the human body. It was well accepted that MPs can accumulate in the living organism's liver and cause hepatotoxic effects (Araujo et al. 2020; Shen et al. 2022; Zitouni et al. 2022). For instance, PS-MPs were observed in zebrafish liver and induced oxidative stress (Lu et al. 2016). PS-MPs were also found to induce inflammation and lipid accumulation in the liver as illustrated by the high levels of necrosis, infiltration, and lipid droplets (Lu et al. 2016). Moreover, PS-MP exposure disrupted the lipid and energy metabolism in the liver (Deng et al. 2017; Lu et al. 2018b; Zhao et al. 2020; Zheng et al. 2021). The hepatotoxicity of MPs was closely associated with the activation of cGAS/STING (cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon gene) and Keap1-Nrf2 (kelch-like ECH-associated protein 1-nuclear factor-E2-related factor) signaling pathway (Li et al. 2021b; Shen et al. 2022). MP-induced liver injury was also evidenced by activating pyroptosis and ferroptosis, which were caused by intense oxidative stress and inflammation in mice (Mu et al. 2022). Furthermore, PS-MPs-induced the hepatotoxicity, such as hepatocyte apoptosis and abnormal glycolytic flux, could be caused by reactive oxygen species (ROS)-driven calcium overload (Li et al. 2021a). These findings provide new insights for uncovering the potential hepatotoxicity of DFM-derived MPs/NPs.

3.5. Others

The deposition and accumulation of MPs in the kidneys could induce kidney damage (Deng et al. 2017; Wang et al. 2021d; Yang et al. 2019). *In vivo* study, Meng et al. demonstrated that the intake and bio-accumulation of PS-MPs/NPs in the kidneys induced oxidative stress and kidney inflammation in mice (Meng et al. 2022). *In vitro* study, uptake of PS-MPs by human kidney proximal tubular epithelial cells (HK-2 cells) caused mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation (Wang et al. 2021d). Moreover, it has been speculated that particles (< 100 nm) could penetrate the skin barrier and cause potential skin toxicity (Revel et al. 2018; Schirinzi et al. 2017).

The possible mechanisms on cardiovascular toxicity of NPs were investigated by Sun's group (Sun et al. 2021b). Exposure to NPs caused severe pericardial edema and significantly decreased cardiac output and blood flow velocity, ultimately affecting thrombosis in zebrafish embryos. Similarly, MP exposure was found to cause cardiotoxicity in chicken and rats (Li et al. 2020c; Wei et al. 2021; Zhang et al. 2022d). Recently, plastic particles were detected in human blood and even accumulated in human thrombi (Leslie et al. 2022; Wu et al. 2022). These studies provide an essential clue for the potential toxicity of DFM-derived MPs/NPs on human cardiovascular systems.

More recently, researchers have explored the potential toxicity of DFM-derived MPs/NPs on reproductive toxic effects (Ferrante et al. 2022; Park et al. 2020; Sendra et al. 2022; Yan et al. 2020a). For instance, Sendra et al. found that face mask degradation fibers strongly impacted different steps of reproduction of *Danio rerio*, including gametogenesis, sperm-egg recognition and binding or fertilization (Sendra et al. 2022). Similarly, PS-MP exposure caused sperm deformity, promoted testicular inflammation, and disrupted the blood-testis barrier of male mice (Hou et al. 2021; Jin et al. 2021). In female mice, PS-MPs were found in uterus and decreased the levels of glutathione, mitochondrial membrane potential and endoplasmic reticulum calcium, and increased ROS in oocytes of mice (Li et al. 2022e). These studies indicated that DFM-derived MP/NP exposure could disrupt the function of the reproductive organ.

Recently, plastics were found in the placentas and could be maternally delivered to the next generation, causing detrimental effects on fetal development and offspring (Aghaei et al. 2022; Fournier et al. 2020; Huang et al. 2022; Pitt et al. 2018). It was found that maternal exposure to PS-MPs and PS-NPs brought about fetal growth restriction in mice (Aghaei et al. 2022). Jeong and colleagues proved that maternally ingested PS-NPs reached the developing brain of next-generation mice through maternal breast milk and caused brain dysfunction and impairment in cognition (Jeong et al. 2022). Similarly, Fournier et al. observed the transfer of PS from the maternal lung, crossed the placenta to the fetal circulation, and deposited in fetal tissues, such as the liver, lung, kidney, heart, and brain after maternal pulmonary exposure (Fournier et al. 2020). These data present a crucial first step toward evaluating the *trans*-generational toxicity of maternal exposure to DFM-derived MP/NPs.

4. The underlying toxic mechanism of discarded mask-derived MPs/NPs

4.1. Directly toxic effects

The directly detrimental effects of MPs/NPs can be categorized into physical and chemical injuries (Campanale et al. 2020). The former effects are associated with the type, size, shape, and level of MPs/NPs released from discarded masks, and the latter is associated with hazardous additives used in masks. Different types, sizes, shapes, and concentrations of MPs/NPs from DFMs have been characterized by atomic force microscopy, energy dispersive X-ray detector, scanning electron microscope, and fourier transform infrared spectroscopy (Chen et al. 2021b; Kwak and An 2021; Liang et al. 2021; Ma et al. 2021; Morgana et al. 2021; Shen et al. 2021). It has been well accepted that MPs/NPs exerted toxicity in type-, size-, shape-, and dose-dependent manners (Fig. 3) (Qin et al. 2021; Schwarzer et al. 2022; Xu et al. 2021b; Zhang et al. 2022a). For instance, Brehm et al. conducted an in-depth characterization of fragments in the same level and size range, and explored the polymer type and chemical content-specific effects of MPs on *Dreissena bugensis* (Brehm et al. 2022). Lei et al. compared the adverse influences of five common types of MPs: polyamides (PA), PE, PP, polyvinyl chloride (PVC), and PS on *Danio rerio* (Lei et al. 2018). The study found that the intestinal toxicity of MPs is closely associated with their sizes, rather than their chemical constituents. However, different polymer types of MPs were reported to impact the distribution, accumulation, and toxic effects of pollutants on contamination (Sheng et al. 2021). Therefore, it is necessary to consider the influence of polymer types when evaluating the environmental risk of MPs.

As DFMs degrade in the natural environment, they are commonly decomposed into MPs/NPs with different sizes and concentrations, showing size- and concentration-dependent toxicity (Chen et al. 2020; Zhang et al. 2022a). The study conducted by Zhang's group showed that the early developmental toxicity of PS-MPs exhibited a size-dependent manner, smaller MPs exerted more toxicity (Zhang et al. 2022a). Bigger plastics have lower bioreactivity than smaller plastics due to their lower surface-to-volume ratio, resulting in they cannot being internalized by cells (Deng et al. 2017; Gautam et al. 2022; Stock et al. 2019). Therefore, it was speculated that NPs could cross the barrier, such as the BBB, to some extent (Zhang et al. 2022a). Nonetheless, MPs with bigger sizes could directly interact with tissues or cells by surface cellular membrane contact (Hwang et al. 2019; Prata et al. 2020). Such size-dependent toxicity of MPs has also been reported in the *Daphnia magna*, showing that small spherical PS-MPs reduced neonatal body length and count compared to larger size PS-MPs (Schwarzer et al. 2022). Likewise, more studies have proved that the potential toxic effects of plastics could tend to increase with decreasing plastic size (An et al. 2021; Gonzalez-Soto et al. 2019; Rist et al. 2017). Except for shape-dependent PS-MPs toxicity, Zhang et al. demonstrated the concentration-dependent toxicity of MPs on hybrid snakeheads (Zhang et al. 2022a). This study showed that high levels of MPs (2 mg/L and 20 mg/L) induced more severe immune responses and shortened intestinal villi of hybrid snakeheads. Expectedly, the toxic effects were positively associated with the level of exposure, the higher level of MPs caused greater toxicity (Sun et al. 2021c; Tunali et al. 2020). Moreover, the accumulation of MPs in tissues was found to be closely associated with exposure time (Cappello et al. 2021; Dolar et al. 2022; Lackmann et al. 2022). Further studies are needed to focus on the toxic effects of MPs at environmentally relevant levels (Sun et al. 2021c). To better assess the size- and dose-dependent toxicity of MPs/NPs, the size and level ranges need to be determinated in diverse species of different developmental stages and different tissues (Kogel et al. 2020).

To elucidate whether the effects exhibit a shape-dependent manner, Qiao et al. conducted a study on zebrafish that were exposed to three main shapes (beads, fibers, and fragments) of MPs (Qiao et al. 2019a). The data showed that the accumulation of MPs in the gut exhibited shape-dependent manners with the order of fibers > fragments > beads. Similar results were also reported by Gray et al., where it was found that the shape of the MPs significantly affected the number of MPs ingested by the shrimp (Gray and Weinstein 2017). MP fibers caused more severe harm to the intestine than MP fragments and beads did (Qiao et al. 2019a). However, the shape-dependent toxicity of MPs is still a controversial issue. For instance, Schwarzer et al. pointed toward spherical particles likely to induce more toxicity on daphnids than PS fragments and fibers (Schwarzer et al. 2022). Moreover, studies

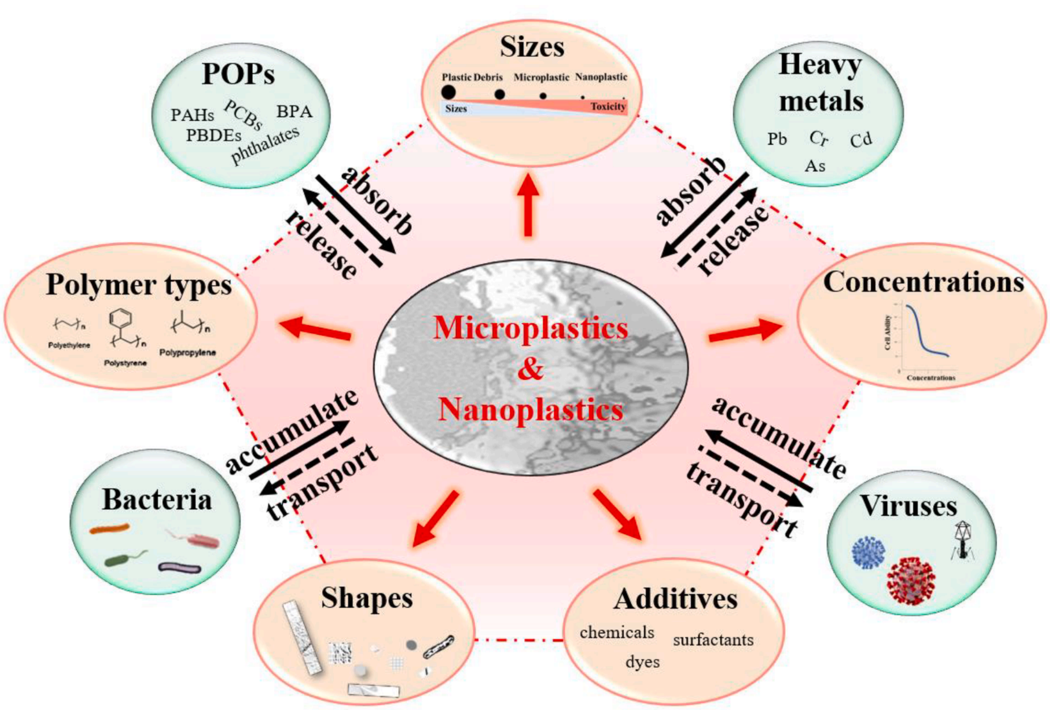

Fig. 3. The potential source of toxicity from microplastics and nanoplastics. The toxic influences of MPs/NPs are closely related to the polymer types, sizes, shapes, and concentrations of MPs/NPs and the usage of commercial additives. MPs/NPs can sorb environmental contaminants including POPs (persistent organic pollutants), heavy metals, bacteria, and viruses, and act as vectors to transport contaminants, resulting in the bioaccumulation and biomagnification of toxic substances.

compared the effects of spherically against irregularly shaped MPs, showing that spherical MPs caused fewer toxicity on daphnids than irregular MPs (Frydkjaer et al. 2017; Yokota and Mehlrose 2020). Nevertheless, Jaikumar and colleagues demonstrated that spherical MPs exerted greater toxic potential as compared to irregular particles on daphnids (Jaikumar et al. 2019). Therefore, more studies are needed to be conducted to elucidate the shape-dependent toxicity of MPs.

Like commercial plastics, the additives and chemicals in face masks could be released into the environment during degradation due to additives are not chemically bound to the plastic polymers (Aragaw 2020; Smith et al. 2018; Sullivan et al. 2021). Organic chemicals, surfactant molecules, dye-like molecules, plastic oligomers, and heavy metals (Pb, Cd, and antimony [Sb]) were identified in the leachates of DFMs (Sullivan et al. 2021). For instance, multiple phthalates, such as bis(2-ethylhexyl)phthalate (DEHP), dimethyl phthalate (DMP), diethyl phthalate (DEP), diisobutyl phthalate (DiBP), di-*n*-butyl phthalate (DBP), diamyl phthalate (DPP), diphenyl phthalate (DPhP), and dinonyl phthalate (DNP), have been detected in the face masks (Xie et al. 2022). The total phthalate level in the masks ranged from 115 ng/g to 37.700 μg/g (median 1.950 μg/g). Similarly, phthalate esters were frequently detected in a surgical mask and N95/*P*1/*P*2 masks, their levels summed up at $55 \pm 35 \sim 1700 \pm 140$ ng and $2300 \pm 150 \sim 5200 \pm 800$ ng per mask, respectively (Wang et al. 2022b). These studies suggest that face mask is a potential source of phthalate exposure. Moreover, previous studies have demonstrated that increased toxicity was found in the combination of MPs/NPs and associated chemicals (Lu et al. 2022b; Smith et al. 2018). However, the toxicity of 10 μg/mL perfluorooctane sulfonate (PFOS) was reduced in the presence of PS due to the decreased bioavailability of PFOS after absorption (Liu et al. 2022b). Therefore, a full investigation is necessary to determine the toxicity of MPs/NPs modified by the additives and chemicals.

4.2. Combined adverse effects of MPs/NPs and environmental contaminations

Given MPs/NPs can sorb environmental contaminants such as POPs, heavy metals, bacteria, and viruses, due to their physicochemical properties, specific surface area, and hydrophobic nature, DFM-derived plastics may act as vectors of these toxic substances (Fig. 3) (Brennecke et al. 2016; Kutralam-Muniasamy et al. 2021; Noro and Yabuki 2021; Wang et al. 2021a). Adsorption is a reversible process; thus, the adsorbed toxics could be leached with time (Sharma et al. 2020). Therefore, the processes of absorption and release affect the toxicity and vectoring effects of MPs. Moreover, toxic contaminants may be concentrated and transferred into the human body through the food chain upon accidental ingestion by marine organisms, leading to unpredictable ecological effects for bioaccumulation and biomagnification of the toxic substances (Jiang 2018; Noro and Yabuki 2021).

MPs/NPs possess a vital property as they can adsorb POPs, such as PAHs, PCBs, PBDEs, phthalates, organochlorine pesticides, and bisphenol A (BPA) from the surrounding environment, and serve as vectors to transport these chemicals into aquatic animals and continuously release into the local tissues (Bakir et al. 2012, 2014; Deng et al. 2020; Deng et al. 2021; Liao et al. 2022; Liu et al. 2022a; Wang et al. 2016; Wang et al. 2021a; Wang et al. 2020; Zhang et al. 2021a). Recently, the occurrence of carcinogenic PAHs in water and food has become a global problem (Sharma et al. 2020). A previous study showed that PAHs could be efficiently absorbed by MPs as illustrated that tissue localization of MPs was integrated with the measurement of PAHs bioaccumulation (Avio et al. 2015). This study showed that PAH-contaminated MPs entered the marine mussels and caused adverse effects. Benzo[*a*]pyrene (BaP) is one of the most toxic PAHs and was found to strongly sorb to MPs. Therefore, MPs with absorbed BaP exerted more toxicity than MPs alone as indicated by altered hemocyte viability and CAT activity (Gonzalez-Soto et al. 2019). Similarly, MPs/NPs can adsorb PBDEs and BPA and exacerbate their adverse effects on organisms (Chen et al. 2017b; Gu et al. 2020b).

Numerous studies have explored the role of MPs/NPs as carriers of heavy metals, including As, Cr, Cu, Cd, and Pb, in aquatic environments (Kutralam-Muniasamy et al. 2021; Naqash et al. 2020). Therefore, ingested MPs and NPs could exert more toxic than MP/NP or heavy metal exposure alone resulting from the combined effects of co-exposure (Cao et al. 2022; Eom et al. 2021; Jiang et al. 2022; Zhang et al. 2022a). For instance, MPs enhanced Cd accumulation in the livers, guts, and gills of zebrafish after MPs and Cd co-exposure for three weeks (Lu et al. 2018a). Therefore, MPs strengthened Cd toxicity on zebrafish as evidenced by increased oxidative damage and inflammation. Similarly, the combination of MPs and Pb enhanced Pb bioaccumulation in Chinese mitten crabs compared to Pb exposure alone and accelerated Pb toxicity on antioxidant performance and lipid metabolism (Yang et al. 2022). However, the level of adsorbed heavy metal in DFM-derived MPs/NPs and their re-release have not been well established yet. More studies are needed to establish a valid method to assess the combined effects of DFM-derived MPs/NPs and heavy metals.

Although face masks can effectively reduce the transmission of microbes, they could be rapidly contaminated during wear (Kalaiselvan et al. 2022). Highly bacterial contamination was found on the outside area of the used masks by hospital personnel (Luksamijarulkul et al. 2014). Bacteria and fungi have been found on the inside and outside areas of the used masks. Moreover, Gund et al. confirmed that surgical masks are contaminated after aerosol-producing dental treatment procedures (Gund et al. 2021). Compared with pathogenic bacteria and fungi, less attention has been paid to viruses on the discarded mask surface. Recently, viruses have been detected on plastic surfaces, and the used masks from the patients diagnosed with COVID-19 could be considered the primary transmission route of SARS-CoV-2 into water and wastewater (Chin et al. 2020; Tran et al. 2021; van Doremalen et al. 2020). Therefore, discarded face masks will be rapidly colonized by diverse groups of microbes including potentially pathogenic species after exposure to environment (Wright et al. 2020). Moreover, microbial contact transmission can occur by touching the tainted masks (Tunon-Molina et al. 2021). Released plastics provided a perfect habitat for microbes, such as algae, protists, viruses, fungi, and bacteria (Gkoutselis et al. 2021; Joo et al. 2021; Mammo et al. 2020; Meng et al. 2021; Oberbeckmann et al. 2015); thus, it is expected that DFM-derived MPs/NPs may act as reservoirs and carriers in pathogen transmission through food chains and enhance the detrimental influences of MPs/NPs. For example, a study of Banihashemi and colleagues showed that co-exposure to MPs and *Yersinia ruckeri* could synergistically affect infection in rainbow trout (Banihashemi et al. 2022). Therefore, discarded contaminated facemask-derived MPs/NPs may increase the risk of new infections in wildlife and humans. However, it is still unknown whether DFM-derived MPs/NPs would participate in pathogens transmission and increase the spread of diseases in humans due to the limited data.

4.3. Pathways of MP/NP toxicity

The generation of ROS, such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl ($OH\bullet$), peroxyl ($RO\bullet_2$), and alkoxyl ($RO\bullet$) radicals, has been proposed as the main mechanism of MPs- and NPs-induced toxicity (Hu and Palic 2020; Li et al. 2022c; Solomando et al. 2020). Reports showed that MPs/NPs can induce extracellular and intracellular ROS production (Hu and Palic 2020; Li et al. 2022c). The generation of extracellular ROS could be triggered by the weathering processes of plastic polymers and promote the degradation of environmental DFMs. Upon photo-oxidation and UV radiation, free radicals on plastic surfaces could be generated by chain scission of polymers. This could be one possible explanation as to why the aging process enhanced the oxidative stress after the cellular entrance of MPs (Wang et al. 2021b).

Intracellular ROS generation commonly occurs after the internalization of MPs. MPs and NPs enter the cell possibly through passive penetration or active endocytosis after adhesion to the cell membrane (Liu et al. 2021a). When intercellular oxidative stress occurs, endogenic antioxidant enzymes and molecules, including superoxide dismutase (SOD), catalase (CAT), glutathione-s-transferase (GST), glutathione (GSH), glutathione peroxidase (GPX), and glutathione reductase (GR), are synthesized to maintain the redox homeostasis. Although several studies have shown that low-dose MP exposure enhanced the activity of SOD, CAT, and GST, excessive production of ROS caused by MPs cannot be scavenged by the cellular antioxidant system resulting in redox imbalance (Huang et al. 2020; Kim et al. 2021; Li et al. 2022e; Lu et al. 2016; Solomando et al. 2020). Therefore, the imbalance between antioxidant defenses and ROS production could cause cellular oxidative injuries, such as protein oxidation, lipid peroxidation, and DNA damage. Moreover, since MPs act as a carrier for environmental contaminants, the combined effects of toxins and MPs could enhance oxidative injury.

In organisms, MPs and NPs are generally recognized as xenobiotics by the immune system and can directly affect the immune responses. Once MPs are absorbed into the body, innate immune cellular effectors can interact frequently with MPs/NPs (Browne et al. 2008; Hirt and Body-Malapel 2020; Hu and Palic 2020). Previous studies have shown that the immune system including lysozyme, neutrophil, phagocytosis, and immunoglobulin could be activated after fish exposure to MPs (Ahmadifar et al. 2021; Greven et al. 2016; Limonta et al. 2019). Lysozyme, a proteolytic enzyme contributing to innate immunity, plays bactericidal roles *in vivo* in fish and mammalians (Gu et al. 2020a; Luo et al. 2018; Saurabh and Sahoo 2008). It was found that the expression of the lysozyme gene was upregulated in the fish after 28-day 9 μm PS-MP exposure (Ahmadifar et al. 2021). Lysozyme was observed to be present in human neutrophil granules (Lollike et al. 1995). Neutrophil activation is critical for resisting the invasion of various foreign substances. It has been shown that an increased number of neutrophils gathered in the larval blood after PS-MPs (50–350 μm) exposure, exhibit a dose-dependent manner (Qin et al. 2021). Furthermore, more neutrophils were observed after the 100 nm PS exposure than of micro-PS. The activated neutrophil function was found after exposure to both PE and PC in the fish model as evidenced by phagocytosis, degranulation, neutrophil extracellular trap release, and a slight increase in the oxidative burst (Greven et al. 2016). These data suggest that MPs are capable of phagocyte activation and act as a potential stressor of innate immunity.

Phagocytosis, the cellular ingestion and digestion of particulate matter, is the central effector mechanism of innate immunity (MacArthur and Fletcher 1985). *In vitro* study showed that PS-MPs could be absorbed by the intestinal epithelial Caco-2 cells via macropinocytosis and clathrin-mediated endocytosis, resulting in the tight junctions between cells being disrupted (Xu et al. 2021a). Oral small-sized PS-MP ($<$ 2 μm) exposure could cause brain accumulation by microglial phagocytosis and activated microglia, leading to apoptosis (Kwon et al. 2022). The phagocytic capacity of microglia for PS-MPs corresponded with that of macrophages. Macrophages are the primary phagocytes that occur in the intestinal tract, lungs, and liver and act as a first-line defense against contaminants (Merkley et al. 2022). The internalization of MPs by murine macrophages did not cause MP degradation while inducing a rewriting of metabolism with a shift toward glycolysis and reduction of mitochondrial respiration (Merkley et al. 2022). The study indicated that the phagocytosis of MPs caused an immune-metabolic active state in macrophages. On the contrary, MP accumulation was found to suppress immune responses as illustrated by the reduction of lysozyme, immunoglobulin, and neutrophil levels (Banaee et al. 2019; Gu et al. 2020a; Hamed et al. 2019; Kim et al. 2021). These data suggest that MPs can cause the stimulation and suppression of immune responses by inducing immune toxicity, which exhibits gene expression variability across cells and species shape innate immunity (Hagai et al. 2018). However, considering the complexity of immune response and species differences, more precise studies on the human immune responses to MP exposure are urgently demanded.

It has been widely accepted that intestinal microorganism plays a critical role in maintaining host biological homeostasis and is a toxicity target due to plastics offer a habit for microbes and their interaction (Lu et al. 2019). Previous studies proved that PS-MP exposure altered gut microbiota composition, resulting in gut inflammation of zebrafish (Lu et al. 2019). Similarly, Kang et al. showed that MPs disrupted gut microbiota composition at both phylum and genus levels in the marine medaka (Kang et al. 2021). Alteration of gut microbiota was observed after mussels were exposed to MPs (Li et al. 2020b). These data suggest that digested MPs could cause adverse effects on gut microbiota within aquatic organisms (Li et al. 2022d). Moreover, MP exposure was found to induce gut microbiota dysbiosis in mammals (Djouina et al. 2022; Lu et al. 2018b). For instance, 5 μm PS-MPs induced gut microbiota dysbiosis in mice, as evidenced by the decreased content of *Actinobacteria* at the phylum level or the alteration of 15 types of bacteria at the genus level (Jin et al. 2019). Chronic exposure to PVC-MPs reduced the relative abundance of probiotics while increasing the abundance of conditionally pathogenic bacteria in mice (Chen et al. 2022b). According to existing studies, alterations or dysbiosis of the gut microbiota were closely related to the host metabolic disorders (Wu et al. 2018; Xia et al. 2018). The gut microbiota can directly impact the brain and behavior via the brain-gut axis (Cryan and Dinan 2012; Valles-Colomer et al. 2019). Therefore, MPs/NPs might cause behavioral toxicities via the brain-gut-microbiota axis (Chen et al. 2022a; Guo et al. 2022). Although there is growing concern regarding the interaction between MPs and gut microorganisms, limited data show the relationship of MPs/NPs with human gut microbiota and their impacts on human health.

5. Challenges and future opportunities

The SARS-CoV-2 outbreak has increased face mask waste all around the world. Considering tremendous numbers of masks will be dispersed in the environment, further in-depth investigations are required to clear the degradation of abandoned face masks, the detection and characterization of MPs/NPs from abandoned DFMs, the transport of DFM-derived MPs/NPs in the food chains, and how they interact with human biological tissues. Moreover, possible strategies to reduce DFM-derived MP/NP pollution are urgently demanded.

5.1. Identification and characterization of MPs/NPs from abandon face masks

As mentioned above, discarded face masks can be broken down and decomposed into massive MPs and NPs, leading to the omnipresent presence of MPs/NPs in our surrounding environments. Although face masks are new sources of environmental MPs/NPs, the recognized sources of MPs and NPs are food containers, teabags, cigarette butts, and disposable cups (Hernandez et al. 2019; Xu et al. 2021c). Hence, it is imperative to clear the released characteristics of MPs and NPs from discarded face masks for potential risk assessment (Liang et al. 2021). However, few studies are available identifying the release kinetics of MPs from DFMs into the natural environment. Liang et al. revealed that the release process of MPs from DFMs was mainly divided into two steps, including the release of MPs on the surface of the masks and the migration of MPs inside the masks to the surface (Liang et al. 2021). The study also identified the length (fine groups: $<$ 100, 500–1000, 1000–2000, and greater than 2000 μm), the shape (fibers and debris), and the color (transparent, black, blue, yellow, brown, and red) of released MPs. Among them, fiber and transparent MPs were the dominant MPs released from masks, and the number of released MPs increased with time (Liang et al. 2021). A previous study reported that the greatest difference between masks was in the middle layer (Chen et al. 2021b). Therefore, the number of MPs released did not differ from the type of mask (N95, surgical masks, and cotton masks) due to the broken state of the inner and outer layers (Liang et al. 2021). A previous study showed that N95 masks released more and smaller NPs than surgical masks (Ma et al. 2021). A potential reason for this may be two more layers of melt-blown fibers in N95 masks in comparison with the common surgical masks.

Nonetheless, the release process of MPs from DFMs was closely associated with the extent of DFM degradation due to complex environmental factors including sunlight exposure, temperature, mechanical forces, and microbe biofilm (Saliu et al. 2021). Currently, artificial weathering experiments have been carried out to recapitulate the environmental release process of MPs from DFMs. For instance, Saliu et al. reported that a surgical mask with UV-light exposure combined with stirring in artificial seawater released up to 173,000 fibers/day (Saliu et al. 2021). Consistently, a study by Wang's group showed that DFMs released MPs to the aqueous environment could be exacerbated in the presence of sand (Wang et al. 2021a). Moreover, exposure to different levels of mechanical stress forces, mimicking conditions of realistic mechanical deterioration, has been demonstrated effective in breaking and fragmenting face mask nonwoven textiles into MPs and NPs (Morgana et al. 2021). These studies suggest that the release quantity of MPs from the weathered masks will be higher than that of virgin masks (Saliu et al. 2021; Wang et al. 2021a). Therefore, the combined effects of natural weathering are needed to be considered in the release of MPs/NPs in further studies. In addition, a previous study has proved that chronic low-level aged PS-MP exposure induced more severe neurotoxicity compared to original PS-MPs (Chen et al. 2021a). Compared with the pristine MPs, Qu's team also showed that chemical modifications of MPs, such as sulfonate modification, leading to increased neurotoxicity on locomotion behaviors and sensory perception behaviors, as well as the development of dopaminergic neurons in exposed nematodes (Qu and Wang 2020).

Despite the ubiquitous distribution, the quantification and characterization of MPs and NPs in environmental and food matrices are still challenging (Ivleva 2021). Studies have suggested that the toxicity of MPs depends on exposure times, routes and concentrations, and plastic sizes, shapes, and types (Kogel et al. 2020). However, a precise study on the identification of MPs/NPs in the human body is rare because of ethical constraints and technical bottlenecks (Yan et al. 2020b). Recently, Yan et al. developed a feasible and efficient method for extracting MPs with a high recovery rate from feces of different species, including zebrafish, chicken, and humans (Yan et al. 2020b). With this method, different polymer types and shapes of MPs have been identified in chicken and IBD patient feces. Remarkably, MPs and NPs exerted dose- and time-dependent toxicity manners. However, current experimental exposure levels may higher as well as the exposure duration is shorter than human-relevant exposure (Prust et al. 2020). Moreover, most of the studies used plastic materials that were quite unlike those found in the environment (Guo et al. 2022; Lim 2021). In the natural environment, organisms are commonly exposed to a mixture rather than one type of MPs, of a specific size and shape (Koelmans et al. 2019; Lim 2021). Therefore, innovative methods are urgently required for the detection and characterization of MPs/NPs in environmental matrices. Foetisch et al. have developed a new method to extract and characterize NPs in environmental and food matrices by combining scanning transmission X-ray spectro-microscopy (STXM) with near-edge X-ray absorption fine-structure spectroscopy (NEXAFS) (Foetisch et al. 2022). STXM with a high spatial and spectral resolution will provide a promising tool to deliver a full chemical, size, and shape characterizations of the MPs and NPs in different types of matrices. More recently, the pyrolysis and gas chromatography-mass spectrometry (GC/MS) method was also established to identify the level of MPs in environmental samples (Wang et al. 2022a).

5.2. *The transport of MPs/NPs in the food chains*

Although the fate, transport, mechanistic behavior, and biological uptake of MPs/NPs can be investigated using artificial materials labeled with metals, fluorescent dyes, or enriched stable isotopes, they are not pre-labeled in the natural environment and transportation of DFM-derived MPs/NPs through the food chain is often difficult to trace (Foetisch et al. 2022; Li et al. 2020a; Mitrano et al. 2019; Wagner and Reemtsma 2019). A previous study presented that MPs can be transported across trophic levels, from fish to a marine mammal top predator, which has implications for human health (Nelms et al. 2018). Moreover, it is not yet known the retention time of MPs/NPs in animals and the human body (Smith et al. 2018). To date, there are insufficient epidemiological studies that determined the human-relevant levels of MPs/NPs via food chains. It could be an efficient way to monitor the exposure level in human consumption, especially in aquatic foods. In fact, the detrimental influences of MPs/NPs on human health depend on exposure levels. Current approaches for toxicity assessment failed to capture the features of low-dose exposure or co-exposure of MPs/NPs. Moreover, chronic exposure could also produce cumulative effects. More recently, a harmonized *in vitro* static and dynamic gastrointestinal simgi® model was created to mimic the digestive process of polyethylene terephthalate (PET) in the gastrointestinal tract (Tamargo et al. 2022). The study showed that MPs presented structural differences during the biotransformation in the gastrointestinal tract. Therefore, it is indispensable to elucidate the process of MPs biodegradation in the human body.

Considering that plastics serve as carriers of toxins and cause the bioaccumulation and biomagnification of toxic substances, both adsorption capacity and adsorption/desorption rates of adverse substances to and from plastics may be influenced by several factors, such as the size of plastics (Gonzalez-Soto et al. 2019; Xu et al. 2021b). For instance, smaller plastics with a larger surface area and a shorter diffusion pathway were found to adsorb higher toxin levels and exchange with the surrounding environment more rapidly (Gonzalez-Soto et al. 2019; Velzeboer et al. 2014). Moreover, investigating the sorption and leachates of environmental toxins to/from MPs/NPs under diverse environmental conditions is also poorly understood. Therefore, determining the final distribution, impacts, and fate of DFM-derived MPs/NPs is an extremely arduous task.

5.3. *Advanced human organoid models for MPs/NPs risk assessment*

Zebrafish is s a successful model to evaluate the potentially adverse effects of MPs/NPs owing to the transparent embryo and larvae providing advantages for studying the localization by live imaging of fluorescent-labeled MPs/NPs (Bhagat et al. 2020). However, conventional animal models cannot mimic the human actual responses to MP/NP exposure due to the variations in species. Although animal models, such as *Caenorhabditis elegans* (*C. elegans*), have been commonly utilized to evaluate the neurotoxicity of MPs, it is hard to extrapolate the effects of plastics on human health owing to insufficient data demonstrating whether MPs/NPs could accumulate in human brains and differences in the nervous system (Chen et al. 2021a; Qu et al. 2019; Qu and Wang 2020). Therefore, a proper model that enables a comprehensive assessment of possible human health risks caused by MPs/NPs remains to be developed.

More recently, advanced human stem cell-derived three-dimensional (3D) organoids are of particular concern since they are sophisticated and multicellular organotypic models, which recapitulate organogenesis, morphogenesis, and cellular processes of human early development. To data, diverse 3D organoids have been successfully generated *in vitro*, such as neural, kidney, gastrointestinal, and lung organoids. With the rapid development of organoid technology, human organoids have been applied in toxicity assessment (Fig. 4) (Li et al. 2022a; Li et al. 2022b; Li et al. 2022c). In our previous study, human induced pluripotent stem cell (hiPSC)-derived intestinal organoids were established to analyze the uptake and toxic effects of PS-NPs on the human intestine (Hou et al. 2022). PS-NP accumulation was observed in the goblet, endocrine, Paneth, and enterocyte cells after 2-day PS-NP exposure (100 μg/mL) and induced cell apoptosis and triggered an inflammatory response (Hou et al. 2022). Recently, Cheng et al. developed human liver organoids to

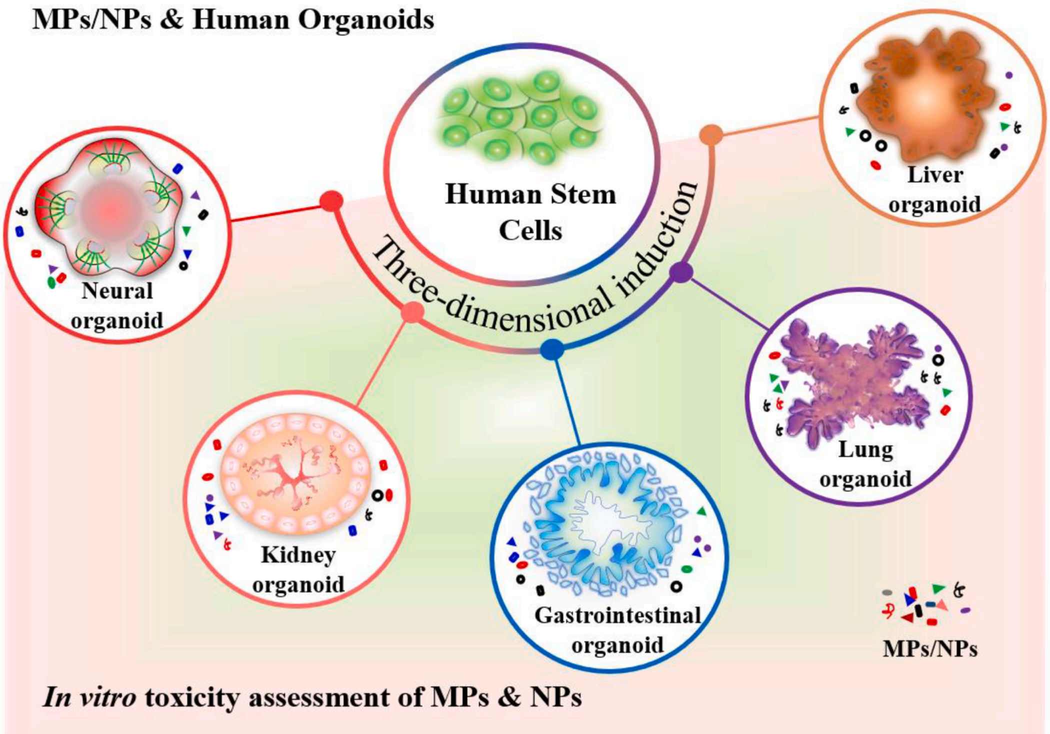

Fig. 4. The novel human organoids can be applied in toxicity assessments of microplastics and nanoplastics. Human stem cells are induced into tissue-specific organoids, such as neural organoids, kidney organoids, gastrointestinal organoids, lung organoids, and liver organoids, providing a promising model for in-depth study to explore the possible adverse effects of MPs/NPs on humans and their underlying mechanism.

evaluate the hepatotoxicity of PS-MPs on humans due to previous studies showed that MP-caused hepatic disturbance in animal models (Cheng et al. 2022; Deng et al. 2017; Lu et al. 2018b; Zheng et al. 2021). Consistently, PS-MPs were found to disrupt lipid metabolism and caused hepatotoxicity in liver organoids (Cheng et al. 2022).

Given MPs have been detected in the human placenta and meconium, MPs/NPs might pose threats to embryonic development (Braun et al. 2021; Ragusa et al. 2021; Zhang et al. 2021b). Human stem cell-derived embryoid bodies (EBs) display a propensity to yield three primary germ layers, including ectoderm, mesoderm, and endoderm, which recapitulates human early embryogenesis (Itskovitz-Eldor et al. 2000). Hence, EBs have been applied to predict embryotoxicity and developmental toxicity of toxic substances *in vitro* (Faiola et al. 2015; Li et al. 2022a; Seiler and Spielmann 2011). For instance, EB-derived forebrain cerebral spheroids were generated to investigate the potential influences of PS-MPs on the human developing brain owing to MPs were reported to be accumulated in the brain (Estrela et al. 2021; Hua et al. 2022; Kwon et al. 2022). The study showed the size- and dose-dependent manner of PS-MP toxicity on cortical layer differentiation (Hua et al. 2022).

Recently, Winkler et al. employed human airway organoids for toxicity assessment of inhaled and deposited MP fibers (MPFs) (Winkler et al. 2022). In our previous study, retinal organoids from human embryonic stem cell (hESC)-derived EBs were used to evaluate the adverse effects of low-level PBDE on human early retinal development (Li et al. 2022c). PBDE exposure was found to cause abnormal neural retinal development in human retinal organoid model. Considering the adverse effects on the visual system caused by MPs, human retinal organoids might be a promising tool for retinal toxicity assessment of DFM-derived MPs/NPs in the future (Chen et al. 2017a). Therefore, human organoids will provide ideal systems for the toxicity assessment of DFM-derived MPs/NPs on human health, even though the application of organoids for predictive toxicology is still in its infancy. Multi-organoids on a chip could be used to assess the systemic toxicity of MPs and NPs *in vitro*. Moreover, human organoids combined with single-cell RNA sequencing (scRNA-seq) would be a promising method for targeting cell population identification and corresponding adverse effects of DFM-derived MPs/NPs (Yu et al. 2022).

5.4. Possible strategies to reduce DFM-derived MP/NP pollution

Considering the high consumption rate of face masks that poses a severe environmental threat, it is critical to scale up innovation and technology to use bio-based and eco-friendly materials to produce biodegradable surgical face masks (Babaahmadi et al. 2021; Pandit et al. 2021). Furthermore, it is feasible to plan the sustainable management and treatment technology (e.g., recycling, recovery, and reuse) for used face masks to avoid entering the environment directly (Aragaw 2021; Aragaw and Mekonnen 2021; Mekonnen and Aragaw 2021; Pourebrahimi 2022). The controllable degradation process of DFMs is an environmentally safe action that could reduce the environmental contaminations of MPs/NPs. Moreover, advanced methods are required to decontaminate and sterilize the masks for multiple reuses (Lee et al. 2021; Pandit et al. 2021). However, it remains unclear whether MPs/NPs will be released from masks during the process of sterilization, disinfection, and antisepsis. Once in the environment, more efforts are needed to address the issues of the sorption capacity of discarded facemask-derived MPs/NPs to environmental toxins and their transportation through food chains.

Currently, great efforts have been made in developing innovative and promise approaches to promote the degradation of plastics (Conk et al. 2022; DelRe et al. 2021; Tournier et al. 2020). For instance, Conk et al. showed that mild catalysis with ethylene could be applied to deconstruct waste PE to form propylene (Conk et al. 2022). The catalytic latency can be regulated by thermal treatment and/or operation temperature (DelRe et al. 2021). More recently, a bacterial strain isolated from the gut of insect larvae can depolymerize PVC, which is potentially associated with catalase peroxidase (Zhang et al. 2022a). In chemical degradation, sodium dodecyl sulfate assisted electrochemical advanced oxidation process technology was found to cause obvious changes in the particle size, morphology, and functional groups of the PS MPs (Lu et al. 2022a). These studies suggest that abovementioned strategies could be applied to reduce DFM-derived MP/NP pollution.

6. Conclusions

Given global discarded face mask issues, aquatic face mask-derived MPs/NPs may pose a particular concern because they can be accumulated and retained in food consumption. To date, the influence of discarded face mask-derived MPs and NPs on human health has not been well understood yet. The novel human stem cell-derived 3D organoid will provide a promising model to evaluate the toxic effects of face mask-derived MPs/NPs on humans and reveal their potential mechanism. Moreover, the combination of environmental science and epidemiology is urgently needed in future studies. More importantly, innovative approaches and eco-friendly strategies are greatly demanded to reduce DFM-derived MP/NP pollution.

CRediT authorship contribution statement

Minghui Li: . **Zongkun Hou:** . **Run Meng:** . **Shilei Hao:** Supervision. **Bochu Wang:** .

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.

Data availability

No data was used for the research described in the article.

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