



Recent advances in toxicological research and potential health impact of microplastics and nanoplastics in vivo

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Abstract

As emerging pollutants, direct and indirect adverse impacts of micro(nano)plastics (MPs/NPs) are raising an increasing environmental concern in recent years due to their poor biodegradability and difficulty in recycling. MPs/NPs can act as carriers of bacteria, viruses, or pollutants (such as heavy metals and toxic organic compounds), and may potentially change the toxicity and bioavailability of pollutants. Ingested or attached MPs/NPs can also be transferred from low-trophic level organisms to high-nutrient organisms or even the human body through the food chain transfer process. This article reviews the emerging field of micro- and nanoplastics on organisms, including the separate toxicity and toxicity of compound after the adsorption of organic pollutants or heavy metals, as well as possible mechanism of toxicological effects and evaluate the nano- and microplastics potential adverse effects on human health. The inherent toxic effects MPs/NPs mainly include the following: physical injury, growth performance decrease and behavioral alteration, lipid metabolic disorder, induced gut microbiota dysbiosis and disruption of the gut's epithelial permeability, neurotoxicity, damage of reproductive system and offspring, oxidative stress, immunotoxicity, etc. Additionally, MPs/NPs may release harmful plastic additives and toxic monomers such as bisphenol A, phthalates, and toluene diisocyanate. The vectors' effect also points out the potential interaction of MPs/NPs with pollutants such as heavy metals, polycyclic aromatic hydrocarbons, organochlorine pesticides, polychlorinated biphenyls, perfluorinated compounds, pharmaceuticals, and polybrominated diphenyl ethers. Nevertheless, these potential consequences of MPs/NPs being vectors for contaminants are controversial.

Keywords Microplastics · Nanoplastics · Toxicity · Human health · Composite pollutant · Implications

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Introduction

Micro(nano)plastics, as emerging contaminants, attract the increasing interest of researchers due to their accumulation and biological persistence in environment and undoubtedly wide distribution in all the compartments causing ineluctable human exposure. The term of microplastics (MPs) was first proposed by Thompson et al. (2004), generally with the size range of 100 nm to 5 mm in diameters (Alimi et al., 2018). Microplastics in the environment are a kind of compound pollutants with uneven spatial distribution owing to their unique physical and chemical properties (such as size, shape, color, weathered, and density) and multiple dynamic characteristics because of continuous changes of various environmental conditions in nature, and the chemical stability and high heterogeneity of these compounds which make the characterization and environmental analysis unreliable (Browne et al. 2011). In the human body, the inhaled microplastic fibers (polyester) were taken up by lung tissue and

may be related to tumors (Pauly et al. 1998). The disperse blue dyes of polyester and acrylic fibers had been shown to cause dermatitis (Pratt and Taraska. 2000). The bioavailability of release monomers, dispersive dyes, mordants, and plasticizers from manufacture and sorbed contaminants from sewage is likely to be greater from fibers of polyester and acrylic, compared to the more hydrophobic microplastics (e.g., polyethylene, polypropylene) that have more heterogenic atoms (Browne et al. 2008). Nanoplastics (NPs) are the particles unintentionally produced (i.e., from the degradation and the manufacturing of the plastic objects) of size range from 1 to 1000 nm and with a colloidal behavior (Gigault et al. 2018). The presence of microplastics with size of 1.6 μm confirmed the possibility of the decomposition of microplastics into nanoplastics (Galgani et al. 2010). The clear evidence for the toxicological potential of microplastics (nanoplastics) is complex and multifaceted, encompassing primarily physical damage, chemical, biological, and ecological toxicity. Microplastics ingested by microorganisms can decrease ingestion rates (Kaposi et al. 2014; Sikdokur et al. 2020), cut the internal organs of the organism, and lead to intestinal inflammation (Provencher et al. 2010). NPs can be transferred through the digestive tract of organisms to the circulatory and immune system, even visceral and tissue cells, and affect innate immune system (Elizalde-Velázquez et al. 2020).

Aside from causing adverse implications per se, micro(nano)plastics (MPs/NPs) can release additives and monomers to the organisms or biota, which represent more toxic sources of pollution than the MPs (or NPs) themselves (Wardrop et al. 2016; Liu et al. 2020). Moreover, MPs/NPs can act as carriers of chemical pollutants, and transfer pollutants to organisms through enrichment, transport, diffusion, and biological absorption, posing a great threat to aquatic and terrestrial organisms. The toxicological interaction between microplastics, nanoplastics, and other environmental pollutants is of great concern. MPs/NPs are well-known to interact with heavy metals (Zhou et al. 2019; Khan et al. 2015; Luís et al. 2015; Rochman et al. 2014), polycyclic aromatic hydrocarbons (Oliveira et al. 2013; Avio et al. 2015; Kleinteich et al. 2018; Karami et al. 2016; Ma et al. 2016), organochlorine pesticides (Ogata et al. 2009), polybrominated diphenyl ethers (PBDEs) (Wardrop et al. 2016) and pharmaceuticals (Fonte et al. 2016; Guilhermino et al. 2018), etc. Contaminants initially adsorbed on the surface of microplastics are released when microplastics are ingested and remain in the human body with lower pH, higher temperatures, and the presence of digestive surfactants. Furthermore, among these contaminants, some are toxic, mutagens, endocrine disruptors, and bio-amplifiers transferred through nutrients (Cole et al. 2011). A recent study found that pigmented microplastic fragments (5–10 μm in size) were detected in human placenta samples collected from six

consenting women with uneventful pregnancies by Raman microspectroscopy (Ragusa et al. 2021), which may trigger immune responses (Wright and Kelly. 2017) and the release of toxic contaminants causing adverse pregnancy and fetus outcomes (Jiang et al. 2020). In addition to adversely affecting individual organisms, ingested or adhering MPs/NPs can be transferred from low-nutrient organisms to high-nutrient organisms and even humans through food chain transfer processes, causing a potential menace to organisms and human health (Catarino et al. 2018). Nevertheless, to date, the impact of MPs/NPs on environmental pollution and human health remains controversial. This may be that the dose effectiveness or time effectiveness concerning MPs/NPs has not yet been explored. Moreover, the sorption behaviors of bacteria, viruses, or chemicals on MPs/NPs have a bearing on plastic size, types, and other chemical or physical properties as well as ambient environment (Endo et al. 2005; Kang et al. 2021; Moresco et al. 2021; Mughini-Gras et al. 2021). However, together with poor biodegradability and ubiquitousness, research of nano- and microplastics influence in this field is realistic and urgent. Although there have been few reports of direct relevance to humans, this review brings together increasing evidence that exposure to nano- or microplastics can directly or indirectly interfere with various biological functions of organisms. In this study, toxic effects of nano- and microplastics on organisms are reviewed, including the separate toxicity and toxicity of compound after the adsorption of organic pollutants, heavy metals or pathogens, and the potential adverse effects of MPs/NPs on human health, as well as possible mechanism of toxicological effects from the perspectives of laboratory exposure, field observation, or model simulation.

The inherent toxic effects of microplastics/nanoplastics

The accumulation of ingested or adhered microplastics in organisms will lead to various physical and chemical damages, and ultimately may result in unpredictable risks to the ecosystem. Exposed microplastics can cause change of predation behavior, obstruction of the digestive tract, and induced satiety, which may lead to decreased growth and development and even survival rates (Wright et al. 2013; Luís et al. 2015). For mussels (*Mytilus edulis*), microplastics may affect their growth and development, and have immunotoxicity (Canesi et al. 2015; Détrée and Gallardo-Escárate, 2018), genotoxicity (Avio et al. 2015) and neurotoxicity (Avio et al. 2015; Magni et al. 2018). After a period of exposure to water containing PS, the filtration rate decreased (Wegner et al. 2012) and energy expenditure increased by 25% in mussels (Van Cauwenberghe et al. 2015). In addition, exposure to microplastics induced a significant increase

of granulocytes then a strong inflammatory response, and caused the lysosomal membrane less stability as the exposure time increased in mussel (von Moos et al. 2012). PE and PS could damage mussels' immune system and the stability of lysosomal membrane, and have toxic effects of immune system and nervous system (Avio et al. 2015). For fish common goby *Pomatoschistus microps* (*P. microps*), poor predatory performance was found when exposed to microplastics (Fonte et al. 2016). The accumulation of microplastics in medaka can also lead to liver glycogen depletion and intrahepatic fat vacuoles (Rochman et al. 2013a). However, it has also been reported that goldfish (*Carassius auratus*) can quickly excrete microplastics, so that microplastics will not accumulate in their gut (Grigorakis et al. 2017), suggesting that microplastics have different effects on fish. Nevertheless, the presence of micro(nano)plastics may benefit organisms. With the presence of microplastics, algae (*Raphidocelis subcapitata*) in the exposed medium grew more (Canniff and Hoang 2018). Microplastics had a negative effect on the reproduction of cladoceran *Daphnia magna* at low algal concentrations, while a positive effect at high algal concentrations (Ogonowski et al. 2016). Li et al. (2020a, b) reported low concentrations of nanoplastics (5 mg/L) may enhance the viability of juvenile shrimp, whereas high concentrations (10, 20, 40 mg/L) had inhibitory and/or toxic effects.

Nanoplastics can be absorbed by living organisms and accumulated in the body and transferred along the food chain. Nanoplastics can penetrate through cell membranes and get into the circulatory system and lymphatic tissue system of the organisms, leading to stunted growth and development, decreased reproductive capacity, genetic toxicity, immunotoxicity, decreased survival rate, increased mortality, etc. The algal species *Pseudokirchneriella subcapitata* (Nolte et al. 2017), *Chlorella* spp., and *Scenedesmus* spp. (Bhattacharya et al. 2010) can adsorb nanoplastics on their surface due to electrostatic interaction. This hindered the absorption and utilization of carbon dioxide and photons, thereby decreasing the photosynthetic efficiency and thus inhibiting algal growth (Bhattacharya et al. 2010). Toxicity to organisms largely relied on the particle size and surface chemical properties of the nanoplastics. Nanoplastics with positive charge have more significant effect on normal physiological activities of cells than those with negative charge. Nanoplastics can lead to oxidative damage though decreasing antioxidant capacity and/or increasing reactive oxygen species (ROS) production (Bhattacharya et al. 2010). The toxicity of polystyrene nanoplastics (Nano-PS) is variable but is related with feeding behavior (Wegner et al. 2012; Cedervall et al. 2012), oxidative stress, neurotoxicity, immunotoxicity, and energy imbalance in aquatic species (Liu et al. 2021, 2018; Pitt et al. 2018a, 2018b; Veneman et al. 2017). Previous data have shown that Nano-PS (34–40 nm) can accumulate in zebrafish embryos under environmental

exposures or maternal transplantation and affect the developing heart, the antioxidant system, and the locomotor activity of the larvae (Pitt et al. 2018a, 2018b). Nano-PS can have longer intestinal residence time than polystyrene microparticles (Ward and Kach, 2009). Polystyrene microparticles (PS-MPs, 45 µm) exhibited no obvious effects; however, Nano-PS (50 nm) caused neurotoxicity to zebrafish (*Danio rerio*) larvae regarding the locomotor activity (Chen et al. 2017b). Exposure of Nano-PS can cause zebrafish (*Danio rerio*) embryos accumulate nanoplastics mainly in lipid-rich areas like the yolk sac, and then transfer to the digestive organs, heart, and brain (Pitt et al. 2018b). Exposing primary producers such as algae to Nano-PS can cause the nutrient transfer of nanoplastics to fish and crustaceans (Chae et al. 2018), and Nano-PS can also be inherited to offspring (Brun et al. 2017; Pitt et al. 2018a). Plastics with particle size can influence their tissue distribution pattern in mice. Xu et al. (2021) reported that in mice exposed to 1 mg/day 100-nm Nano-PS by oral gavage once a day for 28 days, Nano-PS were highly detected in the stomach, small intestine, and large intestine, and were less detected in other tissues with the order of testis > brain > kidney > lung. Compared to Nano-PS, PS-MPs were mainly detected in the liver, gut, kidney, and testis (Jin et al., 2021; Deng et al., 2017). Nano-PS could penetrate blood–brain barrier of the adult fish medaka (*Oryzias latipes*) and mice and reach the brain (Kashiwada 2006; Xu et al. 2021). Nano-PS can affect the feeding behavior and lipid metabolism of top consumers through the aquatic food chain from algae through zooplankton to Crucian carp (*Carassius carassius*) (Cedervall et al. 2012). Overview of the literature involved in the inherent toxic effects of micro- and nanoplastics in vivo are shown in Table 1.

Block the feeding organs and digestive tract, reduce growth performance, and alter behavior

Exposure to MPs (or NPs) can obstruct the feeding organs and digestive tract (AU et al. 2015; Besseling et al. 2014; Blarer and Burkhardt-Holm 2016; Nasser and Lynch 2016; Rehse et al. 2016; Huang et al. 2020), decrease the feeding rate (Nasser and Lynch 2016), or disturb the feeding process directly (AU et al. 2015; Blarer and Burkhardt-Holm 2016), reduce filtration rate (Oliveira et al. 2018; Sıkdokur et al. 2020), and change predatory performance (Yin et al. 2018), leading to energy deficiency and developmental anomaly (e.g., growth, molting) (Cole et al. 2019), reduced activities or reproductive capacity (AU et al. 2015; Besseling et al. 2014; Casado et al. 2013; Rehse et al. 2016), and even individual death (AU et al. 2015; Besseling et al. 2014; Blarer and Burkhardt-Holm 2016; Casado et al. 2013). After exposure to PE microparticles (PE-MPs), the Mediterranean mussel *Mytilus galloprovincialis*' filtration rate was decreased with the concentration increase of PE-MPs

Table 1 Overview of the literature involved in the inherent toxic effects of micro- and nanoplastics in aquatic organisms in vivo

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
1	European seabass (<i>Dicentrarchus labrax</i>)	Polymer microspheres	1–5 µm	0.26, 0.69 mg/L	96 h	Neurotoxicity through AChE inhibition, increased LPO in brain and muscle, altered energy-related enzymes LDH and IDH activities	Barboza et al. 2018a
2	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	0.14 mg/L	96 h	Reduced post-exposure predatory performance and AChE activity	Miranda et al. 2019
3	Zebrafish (<i>Danio rerio</i>)	PS	5 µm, 70 nm	20, 200, 2000 µg/L	3 w	Both caused lipid accumulation and inflammation in liver; induced increased activities of SOD and CAT and alterations of metabolic profiles, and disordered the energy and lipid metabolism	Lu et al. 2016
4	Zebrafish (<i>Danio rerio</i>)	PS	500 nm	20 mg/L	48 h	DNA damage in the gill cells, enhanced the length and proportion of tail DNA of the comet	Cai et al. 2017
5	Bivalve <i>Corbicula fluminea</i>	Polymer microspheres	1–5 µm	0.2, 0.7 mg/L	96 h	ChE activity inhibition at the lower concentration tested but not at the higher one; 0.7 mg/L caused 17% of feeding inhibition	Guilhermino et al. 2018
7	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	18.4, 184 µg/L	96 h	Neurotoxic effects by reducing AChE activity	Oliveira et al. 2013
8	Bivalve <i>Corbicula fluminea</i>	Polymer microspheres	1, 5 µm	0.13 mg/L	8 d	Decreased filtration rate and increased LPO levels; reduction of adductor muscle ChE activity, indicating neurotoxicity	Oliveira et al. 2018
9	Mice (male ICR)	PS	0.5, 50 µm	1000 µg/L	5 w	Decreased the body, liver, and lipid weights; hepatic lipid metabolism disorder (hepatic TG and TC decreased); caused gut microbiota dysbiosis and reduced mucus secretion in the colon	Lu et al. 2018a

Table 1 (continued)

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
10	Mussels <i>Mytilus</i> spp.	PS	Mix of 2 and 6 µm	32 µg/L/d	7 d	Enhanced hemocyte mortality and led to regulation of cellular oxidation balance: increased production of reactive oxygen species in blood cells and antioxidants and glutathione-related enzymes	Paul-Pont et al. 2016
11	Zebrafish (<i>Danio rerio</i>) larvae	PS	45 µm, 50 nm	1 mg/L	48, 72 h	MPs caused no significant effects except for the upregulated zfh1 whereas NPs inhibited the larval locomotion, and decreased body length, inhibited the AChE activity, upregulated gfap, zfh1, and zfh1, α 1-tubulin gene expression	Chen et al. 2017b
12	Crucian carp (<i>Carassius carassius</i>)	PS	28 nm	0.01% (w/v)	3 d	Transported from algae through an aquatic food chain, through zooplankton to fish, affected lipid metabolism and behavior of the top consumer; fish: the weight loss, affected TG/TC ratio in serum and TC distribution between liver and muscle; hunted and moved more slowly	Cedervall et al. 2012
13	Zebrafish embryos and larvae	PS	44 nm	0.1–10 ppm	24, 48, 72, or 96 h	Exposed to NPs did not show developmental defects, but increased NADH production and reduced the efficiency of mitochondrial coupling	Trevisan et al. 2019

Table 1 (continued)

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
14	Discus fish (<i>Symphysodon aequifasciatus</i>)	PS	32–40 µm	50, 500 µg/L	30 d	Increased the activities of SOD, CAT and glutathione peroxidase, glutathione levels; MDA content was effected by MPs and raised with elevated MPs; increased the activities of both alkaline phosphatase and acid phosphatase	Wen et al. 2018
15	Pacific oyster <i>Crassostrea gigas</i>	PS	2, 6 µm	0.023 mg/L	2 m	Decreased oocyte diameter, number, and sperm velocity; reduced the larval yield and offspring development	Sussarellu et al. 2016
16	Common goby (<i>Pomatoschistus microps</i>) juveniles	PE	1–5 µm	0.184 mg/L	96 h	At 20 °C, induced mortality (8%), inhibition of the post-exposure predatory performance (PEPP) (23%) and AChE (21%); at 25 °C, showed mortality (33%) and PEPP inhibition (28%)	Fonte et al. 2016
17	<i>Arenicola marina</i> (L.) (lugworm)	PS	400–1300 µm	0.074, 0.74, and 7.4%	28 d	Decrease in feeding activity (dose of 7.4%), positive relation between microplastics concentration in the sediment and both weight loss and uptake of MPs	Besseling et al. 2013
18	Blue mussel <i>Mytilus edulis</i> L	HDPE (free of any additives)	0–80 µm	2.5 g/L	96 h	Adsorbed into the stomach and transported into the digestive gland where they accumulated in the lysosomal system; enhanced granulocytomas and decreased stability of lysosomal membrane	von Moos et al. 2012

Table 1 (continued)

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
19	Larval zebrafish (<i>Danio rerio</i>)	PS	5, 50 µm	100, 1000 µg/L	7 d	Alterations in the microbiome at the genus and phylum levels and metabolic profiles, and lipid metabolism-related and glycolysis-related genes; decreased CAT activities and glutathione content	Wan et al. 2019
20	Mussels <i>Mytilus galloprovincialis</i>	PE, PS	< 100 µm	20 g/L	7 d	Alterations of immunological responses, antioxidant system, lysosomal compartment, peroxisomal proliferation, neurotoxic effects, onset of genotoxicity	Avio et al. 2015
21	Muscle <i>Mytilus galloprovincialis</i>	PE	40–48 µm	1, 10, 100, 1000 µg/L	14 d	Reduced filtration rate, induced oxidative damage (LPO) at 1 and 10 µg/L with a significant reduction in females of 1000 µg/L treated group and inactivate antioxidant system (CAT and GST) at 100 and 1000 µg/L	Abidli et al. 2021
22	Gilthead seabream (<i>Sparus aurata</i>)	LDPE	100–500 µm	10% feed	21 d	Increased cellular stress, triggered the activation of antioxidant enzymes; showed bolder during social interactions and more active during feeding	Rios-Fuster et al. 2021
23	Jacopever (<i>Sebastes schlegelii</i>)	PS	15 µm	1 × 10 ⁶ MPs/L	14 d	Lowered sensitivity toward the food, increased foraging time; reduced swimming speed and range of movement; lowered growth, protein, and lipid contents	Yin et al. 2018

Table 1 (continued)

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
24	Copepod <i>Calanus finmarchicus</i>	Nylon	10–30 μm , 10 \times 30 μm	50 MPs/mL	6 h	Prey selectivity was altered exposed to nylon fibers; triggered premature molting in juvenile copepods	Cole et al. 2019
25	<i>Daphnia magna</i>	PE	17.23, 34.43 μm	5 mg/L	21 d	Reduced survival; small-sized MP fragments reduced algal feeding, body length, and the number of offspring	An et al. 2021
26	Guppy (<i>Poecilia reticulata</i>)	PS	32–40 μm	100, 1000 $\mu\text{g/L}$	28 d	Existed in gut and induced enlargement of goblet cells; reduced activities of digestive enzymes in gut; stimulated the expression of gut immune cytokines; decreases in diversity and evenness and changed composition of microbiota in gut	Huang et al. 2020
27	Crab (<i>Eriocheir sinensis</i>)	PS	5 μm	0.04, 0.4, 4, 40 mg/L	7, 14, 21 d	Provoked different levels of immune inhibition in the hemolymph and hepatopancreas; changed the diversity and composition of the intestinal microflora	Liu et al. 2019
28	Mice (ICR)	PE	0.4–5 μm	100 mg/kg bw	30 d	Decreased sperm number, disturbed the spermatogenesis, induced higher levels of SOD and MDA in the testis	Deng et al. 2021
29	Mice (ICR)	PS	0.5 and 5 μm	100 and 1000 $\mu\text{g/L}$	During gestation	Had no significant effect on growth, caused blood and liver lipids disorder, changed amino acid metabolism and carnitine metabolism homeostasis of F1 offspring, 5 μm MPs were more pronounced	Luo et al. 2019

Table 1 (continued)

No	Organism	Types	Particle Size	Exposure doses	Exposure duration	Toxicity effect	Reference
30	<i>Artemia Parthenica</i> larvae	PS	10 µm	10 particles/mL	14 d	Lipid droplets appeared among epithelia. intestinal epithelia were deformed, arranged disorderly and discharged into the lumen	Wang et al. 2019
31	Maale fathead minnow (<i>Pimephales promelas</i>)	PS	50 nm	i.p. 0.1 mL (5 µg/L); exposure to contaminated <i>Daphnia</i> (5 µg/L PS)	48 h	Both affected the innate immune system by downregulating the gene expression ncf, mst1, and c3 in liver and kidney	Elizalde-Velázquez et al. 2020
32	Male BALB/c mice	PS	100 nm	Gavage, 10 mg/mL, 100 µL	28 d	Accumulated in spleen, lung, kidney, small intestine, large intestine, testis, and brain; induced cell apoptosis, inflammation, and pulmonary fibrosis, kidney injury, and liver damage, caused hematological system injury, lipid metabolism disorder	Xu et al. 2021
33	Orange-spotted groupers <i>Epinephelus coioides</i>	PS	Nano	300,3000 µg/ml	14 d	Reduced the activities of digestive enzymes lipase, trypsin, and lysozyme and the specific growth rate, altered microbial community composition, and increased harmful bacteria (<i>Vibrio</i> and <i>Aliivibrio</i>)	Wang et al. 2021b

The reported particle size reflects the diameter of primary particles. Every study included a control group that was not exposed to micro- and nanoplastics, or measurements were taken at time-point 0, before exposure

Abbreviations: HDPE high-density poly ethylene, LDPE low-density polyethylene, PE polystyrene, PS polystyrene, PE polyethylene, h hour, d day, w week, m month, LPO lipid peroxidation, SOD superoxide dismutase, CAT catalase, MDA malondialdehyde, ChE cholinesterase, AChE acetylcholinesterase, LPO lipid oxidation, LDH lactate dehydrogenase, IDH isocitrate dehydrogenase, TG triglyceride, TC total cholesterol, i.p. intraperitoneal injection, ncf neutrophil cytosolic factors, mst1 macrophage stimulating 1, c3 complement component 3; in vivo: taking place in a living body, vs. in vitro (of a process) performed or taking place in a test tube, culture dish, or elsewhere outside a living organism

(Abidli et al. 2021). However, studies with the cladoceran *Daphnia magna* (*D. magna*), a non-selective filter feeder, have shown that in exposure to 25, 50, and 100 mg/L PE-MPs (63–75 µm), no significant effect on survival and reproduction in of *D. magna* was found although the gut was filled with PE microbeads (Canniff and Hoang 2018).

In mammals, microplastics are currently thought to be unable to penetrate deep into the organs and therefore only cause localized inflammatory responses, although negative surface charges and smaller sizes can cause increased uptake. A 28-day study in male mice showed that PS-MPs did not cause histologically detectable damage or inflammatory responses, and did not interfere with human macrophage model's differentiation and activation (Stock et al. 2019).

The potential influence of microplastics exposure on lipid metabolism

In addition to physical damage, the accumulation of microplastics can also lead to liver glycogen consumption, lipid vacuoles, and lipid accumulation in fish (Rochman et al. 2013a; Lu et al. 2016). When brine shrimp *Artemia Parthenitica* larvae were exposed to 10 µm PS-MPs at a concentration of 10 particles/mL for 24 h, a greater abundance of lipid droplets appeared among the epithelia (Wang et al. 2019). In the gut tissue of fish, zebrafish (*Danio rerio*) and European sea bass (*Dicentrarchus labrax*), similar histopathological changes (vacuolation of enterocytes) may occur when chronically exposed to microplastics through ingestion (Qiao et al. 2019; Pedà et al. 2016). For male mice, oral administration of PS-MPs can cause inflammation and lipids droplets in livers (Deng et al. 2017) and reduce liver mass and cause lipid disorders (hepatic TG and TC decreased) (Lu et al. 2018a; Deng et al. 2017).

Adverse effects on the gut epithelium and intestinal microbiota

Exposure of nano- and microplastics can disrupt the intestinal microbiota and key intestinal functions include dysbiosis and destruction of intestinal epithelial permeability. Lu et al. proved that 0.5-µm and 50-µm PS-MPs with a concentration of 1000 µg/L for 5 weeks can reduce the secretion of intestinal mucus and change the composition of the intestinal microbiota (Lu et al. 2018a). Exposure to PS-MPs reduced the activities of digestive enzymes in the intestinal tract, stimulated the expression of intestinal immune responses, and induced imbalance of the intestinal microbiota of juvenile guppy (*Poecilia reticulata*) (Huang et al. 2020). Microplastics can alter the diversity and composition of the gut microflora of Chinese mitten crabs *Eriocheir sinensis* (Liu et al. 2019). Wang et al. (2021c) studied Nano-PS toxicity

in intestines of juvenile orange-spotted groupers *Epinephelus coioides* and found that Nano-PSs at exposure concentrations of 300 and 3000 µg/ml, respectively, for 14 days decreased the specific growth rate; reduced the activities of digestive enzymes lipase, trypsin, and lysozyme; altered microbial community composition; and increased harmful bacteria (*Vibrio* and *Aliivibrio*).

Inhibition of brain AChE activity indicates neurotoxicity

Significant microplastic-induced inhibition of brain acetylcholinesterase (AChE) activity was found in fish, suggesting an adverse effect on cholinergic neurotransmission, therefore, potentially on neurological and neuromuscular function (Avio et al. 2015; Luís et al. 2015; Oliveira et al. 2013, 2018; Barboza et al. 2018a; Miranda et al. 2019). Polyethylene microplastics (1–5 µm) caused the AChE activity inhibition by 22% in common goby *Pomatoschistus microps* (Oliveira et al. 2013). Bivalve *Corbicula fluminea* exposed to microplastics showed inhibition of cholinesterase (CHE) activity, indicating neurotoxicity (Guilhermino et al. 2018; Oliveira et al. 2018). Microplastics can cause juvenile European seabass (*Dicentrarchus labrax*) neurotoxicity by inducing brain AChE inhibition and lipid peroxidation (Barboza et al. 2018a).

Impacts on reproduction and offspring

The main impacts of MP exposure include reproductive system damage, decrease in the number and quality of oocytes and gametes, fertility, testicular spermatogenesis, sperm quality, sperm speed, testosterone level, and offspring quality (Martínez-Gómez et al. 2017; Sussarellu et al. 2016; Sharifinia et al. 2020; Deng et al. 2021). Nano-PS could cross rats' placental barrier and deposit in fetal placenta, fetal liver, lungs, heart, kidney, and brain and reduce fetal and placental weights (7 and 8%, respectively) and increase number of fetal reabsorptions after an acute maternal pulmonary exposure to 20-nm Nano-PS during late-stage pregnancy (Fournier et al. 2020). Exposure to 100 · ml⁻¹ 1-µm and 10-µm microplastics to larvae of Pacific oyster (*C. gigas*) for 8 days had no significant effect on growth, however caused reproductive damage of adult Pacific oysters (*C. gigas*) (Cole and Galloway 2015). Adult oysters (*C. gigas*) were exposed to virgin PS-MPs (2 and 6 µm, 0.023 mg·L⁻¹) for 2 months in one reproductive cycle, and oocyte diameter, number, and sperm speed decreased significantly, and larval production and larval development of progenies from exposed parents reduced (Sussarellu et al. 2016). PS or PE-MPs could reduce the sperm number and quality and testosterone level, and induce abnormal testicular spermatogenesis in mouse testis (Deng et al. 2021; Jin et al. 2021; Hou et al.

2021). Smaller-sized PE MP fragments ($17.23 \pm 3.43 \mu\text{m}$) decreased the number of offspring in *D. magna* when compared with MP beads ($39.54 \pm 9.74 \mu\text{m}$) (An et al. 2021). Maternal mice PS-MP exposure (0.5 and 5 μm with 100 and 1000 $\mu\text{g/L}$ in drinking water) during gestation had no significant effect on growth of F1 offspring, but caused blood and liver lipid disorder, and changed amino acid metabolism and carnitine metabolism homeostasis, and 5- μm MPs were more pronounced (Luo et al. 2019).

Effects on oxidative stress and lipid oxidative damage

Microplastics induced oxidative stress in some species (Oliveira et al. 2013; Avio et al. 2015; Barboza et al., 2018a, 2018b; Wan et al. 2019; Wang et al. 2021c). Marine fish European seabass (*Dicentrarchus labrax*) exposed to microplastics showed induction of oxidative stress in both the liver and gills, and lipid oxidation in muscle and brain (Barboza et al. 2018a, 2018b). Polyethylene microplastics (40–48 μm) induced oxidative damage (LPO) in mussels (*Mytilus galloprovincialis*) at low concentrations (1 and 10 $\mu\text{g/L}$) and significantly decrease of LPO in 1000 $\mu\text{g/L}$ treated group of females, and inactivation of antioxidant systems (CAT and GST) in the ampholytic digestive glands at high concentrations (100 and 1000 $\mu\text{g/L}$) (Abidli et al. 2021). Su et al. demonstrated that microplastics can serve as an external stressor on dinoflagellate *Cladocodium goreau* (*C. goreau*), with enhancing oxidative stress through increasing the activity of superoxide dismutase and caspase 3, and reducing the activity of glutathione S-transferase (Su et al. 2020). Juvenile gilthead seabream *Sparus aurata* exposed to virgin and weathered MPs showed the activation of antioxidant enzymes (Rios-Fuster et al. 2021). PS-MPs induced endoplasmic reticulum (ER) stress via mitochondrial ROS production in the mice (Wang et al. 2021c).

Adverse impacts on immune system

In mussels *Mytilus galloprovincialis*, MPs can cause blood cell immunotoxicity, lysosomal membrane instability, and reduced phagocytic activity (von Moos et al. 2012; Avio et al. 2015; Détrée and Gallardo-Escárate, 2018). High-density polyethylene (HDPE, < 80 μm) plastic particles can be enriched in the digestive system of mussels, leading to blood flow granulocytosis, instability of lysosomal membrane, and inflammation of the body's immune system after only 3 h of exposure (von Moos et al. 2012). For crabs *Eriocheir sinensis*, low concentrations (0.040 and 0.4 mg/L) or short periods of exposure to microplastics can enhance immune enzymes' activities, while negative effects were found in high concentrations (4 and 40 mg/L) or long periods of exposure on all aspects of innate immunity (Liu et al. 2019). Nano-PS

particles can activate complement system in fish (Veneman et al. 2017; Elizalde-Velázquez et al. 2020), and can also be phagocytized by neutrophils and macrophages and activated macrophages, and enhance the recruitment of neutrophils to release interferon gamma and interleukin 1 beta (Brun et al. 2018; Lu et al. 2018a, b). Alterations in the innate immune response in adult fish were found after exposure to nanoplastics through the ingestion of species from a lower trophic level; the gene expression of neutrophil cytosolic factor (ncf), macrophage stimulating 1 (mst1), and complement component 3 (c3) were downregulated in the kidney and liver (Elizalde-Velázquez et al. 2020).

Leaching of plastic additives and toxic monomers

Microplastics can also leach out chemicals such as residual toxic monomers and plastic additives, which can have toxic effects on human health and the environment. Plastic additives are chemical compounds that are used primarily as stabilizers, plasticizers, flame retardants, pigments, and antioxidants. It has been reported that plastic particles may contain up to 4% by weight as additives, such as plasticizers (Andrady and Neal 2009). Different types of plastics, depending on their purpose, use different types of additives, such as plasticizers, which increase the flexibility, durability, and tensile properties of the plastic polymer. Bisphenol A (BPA), the monomer of polycarbonate (PC), is a stabilizer for other polymers, and can be released from MPs, and has carcinogenic, teratogenic, mutagenic, and reproductive effects on organisms (Hu et al. 2021; Seachrist et al. 2016; Harnett et al. 2021). The chemical substances leaching from polyvinyl chloride (PVC) and polyurethane could produce acute toxic effects (immobility) for *Daphnia magna* (Lithner et al. 2009). Plasticizers do not chemically bind to the polymer and therefore can leach from the plastics (OECD 2004). Phthalates, as a kind of endocrine-disrupting chemicals, account for 95% of all plasticizers (OECD 2004) and are widely spread in the environment today, some of which may cause developmental and/or reproductive toxicity concerns even at environmental concentrations (Zhang et al. 2021). Plasticizers butylbenzyl phthalate and dibutyl phthalate (DBP) can disrupt the antioxidant system of human erythrocytes that causes eryptosis (Sicińska 2018; Sicińska et al. 2020). Monomer toluene diisocyanate reacting with polyether or polyester to form polyurethane usually along with catalysts (Harper and Petrie 2003) is an allergenic, has very high acute toxicity, and is environmentally hazardous with long-term effects (Ott 2002; Zhuang et al. 2020). The leachates of polymer PS and HDPE fluff were more toxic to sea urchin embryos than the virgin materials or the aging materials themselves. The raw material microplastics may release unknown chemicals, such as residual toxic monomers or additives, which seems to be the main cause of the

seen sea urchin embryo toxicity (Martínez-Gómez et al. 2017).

Combined toxic effects of micro(nano) plastics and persistent, bioaccumulative, and toxic substances

In addition to the hazards of microplastics per se or leachates, micro(nano)plastics can also alter the form, local concentration, environmental persistence, environmental behavior, and ecological risks by adsorption and desorption of coexisting organic pollutants (Tanaka et al. 2013; Wright et al. 2013; Llorca et al. 2018) because of their small particle size (<5 mm) and large specific surface area (Law and Thompson 2014). Toxicological interactions between MPs/NPs and persistent, bioaccumulative, and toxic substances are of grave concern, as MPs/NPs can cause a “Trojan Horse” effect by transferring other environmental pollutants to organisms and the environment that are directly exposed, or indirectly, through the long-distance transport of particulate matter and food webs (Avio et al. 2017). This vector effect also points out the potential interaction of microplastics with pollutants such as heavy metals (Ashton et al. 2010; Wen et al. 2018; Massos and Turner 2017; Kim et al. 2017; Khan et al. 2015; Kang et al. 2021), polycyclic aromatic hydrocarbons (PAHs) (Oliveira et al. 2012, 2013; Guven et al. 2018; Sørensen et al. 2020; Avio et al. 2015; Trevisan et al. 2019), organochlorine pesticides (Ogata et al. 2009), polychlorinated biphenyls (PCBs) (Engler 2012; Velzeboer et al. 2014), perfluorinated compounds (Wang et al. 2015; Bakir et al. 2014), pharmaceuticals (Wei et al. 2019; Wang et al. 2018; Li et al. 2019a, b; Xu et al. 2018a; Zhang et al. 2019), and personal care products (Wu et al. 2016), PBDEs (Wardrop et al. 2016). MPs may change these chemicals’ bioavailability, environmental behavior, and toxicity in the environment, for example, increasing their concentration to 100 times that in sediments, six orders of magnitude higher than the background concentration in surrounding seawater (Lee et al. 2014; Rochman et al. 2013b), and may modulate targets and patterns of action of plastic particles and related compounds at the molecular level. PS and PE microplastics are considered to be the plastic polymers of the highest adsorption capacity for hydrophobic organic pollutants (Sørensen et al. 2020). Black or aged MPs can absorb more pollutants that are colored or white ones (Verla et al. 2019). Toxicological interactions between micro(nano)plastics and heavy metals in vivo are shown in Table 2. Overview of in vivo studies of toxicological interactions between micro(nano)plastics and organic environmental pollutants are summarized in Table 3.

Heavy metals and MPs/NPS

Heavy metals and MPs/NPS are two types of persistent contaminants in the water environment owing to their persistence and poor biodegradability, bioaccumulation, and possible biological amplification in the food chain (Abdolahpur Monikh et al. 2013; Grigorakis et al. 2017; Gu et al. 2015; Vendel et al. 2017). MPs/NPS and heavy metals both can get into the food web (chain) by direct or indirect exposure (Hosseini et al. 2015; Vendel et al. 2017). In the field scenario, lead (Pb) and cadmium (Cd) are more abundant in microplastics than in other metallic elements (Ashton et al. 2010; Massos and Turner 2017). Akhbarizadeh et al. (2018) investigated the relationship between MPs and some metals (As, Cr, Cu, Mn, Ni, Pb, Zn, V, Fe, Se, and Hg) in different species fish muscles; a positive linear relationship was observed between MPs and metal content in shrimp scad *Alepes djedaba* and bartail flathead *Platycephalus indicus*, respectively, while the relationship between MPs and metal pollution index (MPI) in orange-spotted grouper *Epinephelus coioides* was negative in northeastern Persian Gulf. The desorption rate of zinc by microplastics in the intestinal tract of earthworms is much higher than that of soil, indicating that microplastics may increase metal elements’ bioavailability (Hodson et al. 2017). MPs may absorb metallic elements from the aquatic environment and the concentrations of metals absorbed on MPs were much higher than those of local estuary sediments (Rochman et al. 2014; Turner and Holmes 2015). There is also growing concern in regard to the potential role of MPs as transport carriers of heavy metals and transport of metals into fish, which may change the bioavailability and uptake route of metals in fish tissues. Silver-incubated MPs could increase the biological accumulation of silver in zebrafish (*Danio rerio*) intestines (Khan et al. 2015). The presence of MPs in water environment influenced the acute toxicity (96 h) of Cr(VI) on early juvenile gobies, such as enhanced oxidative damage, and reduced the predation performance in fish (Luís et al. 2015). When co-exposed to 20–200 $\mu\text{g L}^{-1}$ PS-MPs (5 μm) and 10 $\mu\text{g L}^{-1}$ CdCl_2 , the accumulation of Cd and toxic effects increased in *D. rerio* compared to the effect of CdCl_2 exposure alone (Lu et al. 2018b). Lang et al. (2020) reported that compared with the pristine PS, the adsorption capacity of Cd^{2+} after aging was significantly enhanced. Aging will not only increase the specific surface area of PS, but also oxidize the functional groups on the surface of PS and form surface microcracks, resulting in a significant increase in the content of carbonyl and carboxyl groups. The adsorption process of Cd^{2+} by pristine PS mainly occurs on the surface, but with the continuous aging of PS, the adsorption mechanism of Cd^{2+} by PS is the coexistence of physics and chemistry. MP can absorb mercury from surrounding water and increase the degradation of mercury in water with increasing concentrations of

Table 2 Toxicological interactions between micro(nano)plastics and heavy metals in vivo

No	Species	Compositions	Particle size	Concentrations	Chemical substances	Exposure duration	Toxicological interactions	References
1	European seabass (<i>Dicentrarchus labrax</i>)	Polymer microspheres	1–5 µm	0.26, 0.69 mg/L	Mercury, 0.010, 0.016 mg/L	96 h	Increased the decay of mercury in the water and the bioaccumulation of mercury	Barboza et al. 2018a
2	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	0.14 mg/L	Cadmium (Cd), 3–13 mg/L	96 h	Antagonism, MPs changed the sub-lethal toxic effects of Cd, especially neurotoxicity	Miranda et al. 2019
3	Discus fish (<i>Symphysodon aequifasciatus</i>)	PS	32–40 µm	50, 500 µg/L	Cd, 50 µg/L	30 d	Decreased accumulation of Cd in fish body; co-exposure stimulated innate immunity, induced severe oxidative stress	Wen et al. 2018
4	Zebrafish (<i>Danio rerio</i>)	PS breads	5 mm	20, 200 µg/L	Cd, 10 µg/L	3 w	The presence of MPs increased the toxicity of Cd; the co-exposure caused inflammation and oxidative damage	Lu et al. 2018b
5	Zebrafish (<i>Danio rerio</i>)	PE	10–106 µm	10, 100, 1000 MPBS/mL	Silver (Ag) 1 µg/L	4, 24 h	No effect on the uptake or localization of Ag; reduced Ag uptake, increased the proportion of intestinal Ag	Khan et al. 2015
6	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	0.184 mg/L	Chromium (VI) 5.6–28.4 mg/L	96 h	Coexposure decreased of the predatory performance and inhibition of AChE activity, higher than the inhibition caused by MP alone and that was not observed in Cr(VI) alone; increased LPO levels that were not observed under Cr(VI) or MP single exposures	Luis et al. 2015
7	<i>Daphnia magna</i>	PS, PS-COOH	201.5, 191.3 nm	1, 5, 10, 20, 30 mg/L	Nickel, 1, 2.5 mg/L	48 h	Antagonistic effect on PS and Ni toxicity, synergistic effect between PS-COOH and Ni	Kim et al. 2017

Table 2 (continued)

No	Species	Compositions	Particle size	Concentrations	Chemical substances	Exposure duration	Toxicological interactions	References
8	Bivalve <i>Corbicula fluminea</i>	Polymer microspheres	1, 5 µm	0.13 mg/L	Mercury, 30 µg/L	8 d	Reduced mercury bio-concentration; antagonism in filtration rate, ChE enzymes activity, glutathione S-transferases activity and LPO levels	Oliveira et al. 2018
10	Clam <i>Ruditapes philippinarum</i>	PE	10–45 µm	25 µg/L	Mercury, 10 µg/L	7 d	Contaminated MPs showed a negligible vector for mercury bioaccumulation	Sikdokur et al. 2020
11	Zebrafish (<i>Danio rerio</i>)	PS	50, 200 nm	0.1 mg/mL	Gold (III) chloride trihydrate, 0.5, 1, 2 µg/mL	24 h	Nano-PS had no toxicity but exacerbated Au ions mortality, deformation, reduced hatching rate, synergized by the production of reactive oxygen species, mitochondrial damage, and the proinflammatory responses	Lee et al. 2019

The reported particle size reflects the diameter of primary particles. Every study included a control group that was not exposed to micro- and nanoplastics or heavy metal, or measurements were taken at timepoint 0, before exposure

Abbreviations: PS polystyrene, PE polyethylene, h hour, d day, w week, LPO lipid peroxidation, ChE cholinesterase, AChE acetylcholinesterase; in vivo: taking place in a living body, vs. in vitro (of a process) performed or taking place in a test tube, culture dish, or elsewhere outside a living organism

Table 3 Overview of in vivo studies of toxicological interactions between micro(nano)plastics and organic environmental pollutants

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological interactions	References
1	Mussels <i>Mytilus</i> spp.	PS	Mix of 2 and 6 μm	32 $\mu\text{g/L/d}$	Fluoranthene, 30 $\mu\text{g/L}$	7d exposure, 7d depuration	Altered fluoranthene depuration (detoxification), regulated fluoranthene kinetics and toxicity: after depuration, a higher fluoranthene concentration was shown exposed to MPs and fluoranthene	Paul-Pont et al. 2016
2	Zebrafish embryos and larvae	PS	44 nm	0.1–10 ppm	PAH (Elizabeth River Sediment Extract, ERSE, comprised of 36 detected PAHs), 5.07–25.36 ppb	24, 48, 72, or 96 h	Increased the sorption of PAHs; decreased the bioaccumulation and bioavailability of PAHs; impaired vascular development and decreased the developmental deformities caused by ERSE	Trevisan et al. 2019
3	Zebrafish (<i>Danio rerio</i>)	PS	500 nm	20 mg/L	Anthracene, 200 $\mu\text{g/L}$	48 h	The presence of plastic particles reduced the DNA damage of anthracene to zebrafish gill cells, reduced the tail length, tail moment, and tail DNA ratio of comets	Cai et al. 2017

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter- actions	References
4	<i>Daphnia magna</i>	PS	50, 500 nm, 5, 10, 15 μ m	5 mg/L	Phenanthrene, 0.1 mg/L	14 d	The combined toxicity of 50-nm NPs and phenanthrene showed an additive effect; 50-nm NPs enhanced bioaccumulation of phenanthrene-derived residues and suppressed the dissipation and transformation of phenanthrene, whereas 10-nm MPs not showed this effects	Ma et al. 2016
5	Barramundi (<i>Lates calcarifer</i>)	MPs	97 μ m	100 particles/L	Pyrene, 100 nM	24 h	MPs alone showed no influence feeding performance, while pyrene showed strong effect on behavior; combined exposure, no effect on feeding while swimming speed decreased; pyrene impacted the performance, while additional exposure to MPs effected their activity only and not their feeding rate	Guvven et al. 2018

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter-actions	References
6	Mice (<i>Mus musculus</i> , CD-1)	PE, PS	0.5–1.0 µm	2 mg/L	Organophosphorus flame retardants (OPFRs) [tris (2-chloroethoxy) phosphate, 10 µg/L, tris (1,3-dichloro-2-propyl) phosphate, 100 µg/L]	90 d	Aggravated the toxicity of OPFRs; induced greater oxidative stress (increase SOD and CAT); greater neurotoxicity (lower AChE); disruption of amino acid metabolism and energy metabolism	Deng et al. 2018
7	Bivalve <i>Corbicula fluminea</i>	Polymer microspheres	1–5 µm	0.2, 0.7 mg/L	Florfenicol, 1.8, 7.1 mg/L	96 h	Florfenicol caused ChE activity inhibition (~32%), exposed to MPs showed ChE activity inhibition (31%), and no other significant alterations. mixtures led to feeding inhibition (57–83%), inhibition of ChE (44–57%) and IDH activity, and enhanced lipid peroxidation levels and antioxidant enzymes activity; mixtures being more toxic	Guilhermino et al. 2018

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter- actions	References
8	Zebrafish (<i>Danio rerio</i>)	PS	41 µm, 47 nm	1 mg/L	17α-Ethinylestradiol (EE2), 2.20 µg/L	48, 72 h	Co-exposed with 2 µg/L EE2, alleviated EE2's inhibition effect on locomotion, NPs showed stronger adsorption ability for EE2; co-exposed with 20 µg/L EE2, both plastics increased effect on oxidative damage, hypoactivity, inhibition of AChE by 9% (MPs), 40% (NPs), 21% (MP and NP co-exposed with EE2); locomotor hypoactivity 22% (NPs) and 18–36% (co-exposed with EE2)	Chen et al. 2017b
9	Loach <i>Misgurnus anguillicaudatus</i> (<i>M. anguillicaudatus</i>)	PVC	< 10 µm	50 mg/L	Chiral antidepressant venlafaxine and its metabolite O-desmethylvenlafaxine, 500 µg/L	40 d	Played a carrier role to increase venlafaxine and O-desmethylvenlafaxine accumulate; with MPs, the bioaccumulation factor of venlafaxine and O-desmethylvenlafaxine in loach tissue magnified more than 10 times; in liver subcellular structure, MPs may help to transport more compounds into subtle areas and delay the contaminants metabolism	Qu et al. 2019

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological interactions	References
10	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	0.184 mg/L	Cefalexin 1.3, 2.5, 5, 10 mg/L	96 h	In the presence of MPs increased EC50; 25 °C the presence of MPs reduced the toxicity of cefalexin; toxic interaction of cefalexin and MPs increased with the rise of temperature from 20 to 25 °C	Fonte et al. 2016
11	<i>Arenicola marina</i> (L.) (lugworm)	PS	400–1300 µm	0.074, 0.74, 7.4%	19 polychlorinated biphenyls (PCBs)	28 d	0.074% PS enhanced bioaccumulation of PCBs, higher doses, bioaccumulation decreased compared to the low dose, which, however, was only significant for PCB105; the impact of PS on PCB transfer to <i>A. marina</i> can be considered small	Besseling et al. 2013

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter- actions	References
12	<i>Daphnia magna</i>	PE, PET/PA	2.09 µm, 10 × 2 µm	2.2 × 10 ⁶ /mL, 10 to 30/mL	Glyphosate acid, glyphosate-monoisopropylamine salt, and Roundup Gran	1 w	Glyphosatemonoisopropylamine salt caused the highest mortality, whereas glyphosate acid the lowest, in the absence of MPs, these results were inverted, however, when the individuals were exposed in combination with the PE or the PET/PA fibers; the mortality in the Roundup Gran also increased when combined with the two MPs	Zocchi and Sommaruga 2019
13	Natural freshwater sediment bacterial communities	PE	2, 20 mg/g sediment	212–250 µm	Phenanthrene (0.12 µM), anthracene (0.14 µM)	14 d	High concentrations decreased the effect of PAHs; reduced biodegradation and bioavailability of the PAHs by the sorption to microplastics	Kleinteich et al. 2018
14	Mussels <i>Mytilus galloprovincialis</i>	PE, PS	< 100 µm	20 g/L	Pyrene, 0.5, 5, 50 µg/L	6 d	Adsorbed pyrene with a dose- and time-dependent relationship; increased bioavailability of these chemicals	Avio et al. 2015

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter-actions	References
15	Common goby (<i>Pomatoschistus microps</i>)	PE	1–5 µm	18.4, 184 µg/L	Pyrene, 20, 200 µg/L	96 h	Postponed pyrene-induced fish mortality and increased the concentration of bile pyrene metabolites; simultaneous exposure reduced the energy available and IDH activity, not seen following exposure to the two stressors alone	Oliveira et al. 2013
16	Red tilapia (<i>Oreochromis niloticus</i>)	PS	0.1 µm	100 µg/L	Roxithromycin (ROX), 50 µg/L	14 d	Increased ROX bioaccumulation in various tissues, alleviated the neurotoxicity (AChE activity) and oxidative damage caused by ROX	Zhang et al. 2019
17	Mice (male ICR)	PE	0.4–5 µm	100 mg/kg bw	Phthalate esters (DEHP, DBP, DEP, and DMP), 5, 50 µg/L	30 d	Aggravated reproductive toxicities (sperm physiological alterations, spermatogenesis disorders, oxidative stress in the testis)	Deng et al. 2021
18	Copepod <i>Acartia tonsa</i>	PE	10–90 µm	500 MP/ml	Triclosan (TCS, 0–300 µg/L)	48 h	MP potentiated the toxicity of TCS (lower LC ₅₀)	Syberg et al. 2017

Table 3 (continued)

No	Species	Types	Size	Concentrations	Chemical substances	Exposure duration	Toxicological inter- actions	References
19	Zebrafish (<i>Danio rerio</i>) larvae	PS	0.5 µm	200 µg/L	TCS (0.6 µg/L)	7 d	Formation of PS-TCS complex greatly changed the toxicological behavior of the single pollutant, opposite behaviors in swimming activity and modulation of diverse protein classes, TCS increased MN frequency and GST and GPx activity, while significant decreases were found in PS-TCS compared to TCS alone	Parenti et al. 2020

The reported particle size reflects the diameter of primary particles. Every study included a control group that was not exposed to micro- and nanoparticles or any other substance, or measurements were taken at timepoint 0, before exposure

Abbreviations: PS polystyrene, PVC polyvinylchloride, PE polyethylene, PET/PA polyethylene terephthalate/polyamide, AChE acetylcholinesterase, SOD superoxide dismutase, CAT catalase, IDH isocitrate dehydrogenase, GPx glutathione peroxidase, GST glutathione S-transferase, MN micronuclei, h hour, d day, w week; in vivo: taking place in a living body, vs. in vitro (of a process) performed or taking place in a test tube, culture dish, or elsewhere outside a living organism

microplastics, thus influencing the mercury accumulation in the European seabass (*Dicentrarchus labrax*) (Barboza et al. 2018a). The inhibition rate of the combination of nickel and carboxylated polystyrene (PS-COOH) on *Daphnia magna* was higher than that of nickel alone. PS-MPs caused a slight antagonistic effect on nickel (Ni) toxicity, while PS-COOH MPs had a slight synergistic effect with Ni (Kim et al. 2017). Exposure to nano-scale plastics (50 nm) intensified arsenic (As) toxicity of rotifer *Brachionus plicatilis* in marine, while As toxicity was mitigated by micro-scale ones (6 μm) (Kang et al. 2021).

However, other studies showed that microplastics had no significant effect on the bioavailability and toxicity of heavy metal copper (Davaranpanah and Guilhermino 2015). Therefore, the impacts of different types of microplastics and heavy metals on different organisms may be very different. These findings indicated that MPs could not necessarily increase the bioavailability of heavy metals, which might rely on the physical and chemical properties of MPs (size, color, and concentrations) and the type and content of metals. Moreover, the long-term toxicological interactions between MPs and heavy metals are largely unclear.

Polycyclic aromatic hydrocarbons and MPs/NPS

Fish co-exposed to microplastics and PAHs have shown impaired swimming ability in young gobies (Oliveira et al. 2012). In mussels (*Mytilus galloprovincialis*), exposed to pyrene contaminated of polyethylene and polystyrene plastics, obvious biological accumulation of these chemicals was observed in gills, digestive gland, and blood lymphatic (Avio et al. 2015), and PE and PS microplastics can adsorb pyrene with a dose- and time-dependent relationship and augment pyrene's bioavailability and toxicity in *Mytilus galloprovincialis* (Avio et al. 2015). PS-MPs had little effect on the absorption and bioaccumulation of fluoranthene, but could change its purification (detoxification) and regulate the kinetics and toxicity of fluoranthene. After purification, compared with mussels exposed to fluoranthene alone, higher concentrations of fluoranthene were detected in mussels when co-exposed to PS-MPs and fluoranthene, because the micro-plastics can weaken metabolic transformation of polycyclic aromatic hydrocarbons by inhibiting metabolic enzymes (Paul-Pont et al. 2016). The Nano-PS (50 nm) can increase the accumulation of phenanthrene and have synergistic toxic effects with phenanthrene in *Daphnia magna*. Meantime, Nano-PS can also inhibit the degradation of phenanthrene and its metabolites to augment the accumulation of phenanthrene in *Daphnia magna* (Ma et al. 2016). However, studies have found that exposure to PE microplastics (1–5 μm) can delay pyrene-induced death in marine fish *P. microps* juveniles and increase the concentration of pyrene metabolites in the bile of fish (Oliveira et al. 2013).

The presence of microplastics can decrease the damage of toxic organic pollutants to the DNA of zebrafish gill cells. This may be due to the strong adsorption of anthracene by polystyrene particles, which can prevent anthracene from being completely desorbed on the gill surface after entering the zebrafish tissue, thereby reducing anthracene toxicity (Cai et al. 2017).

Pharmaceuticals and MPs/NPS

Some studies have reported several new types of ionizable organic pollutants (such as antibiotics) can be adsorbed on the surface of microplastics (Wei et al. 2019; Wang et al. 2018; Li et al. 2019a, b; Xu et al. 2018a, 2018b; Zhang et al. 2019; Guilhermino et al. 2018). Antibiotics with ion form of the pH 6 to 9 in natural water can also be accumulated on microplastics surface. For instance, aromatic antibiotics tetracycline and oxytetracycline containing hydroxyl and amino groups have maximum adsorption at neutral pH (with minimal electrostatic repulsion) (Xu et al. 2018b; Zhang et al. 2018). Changes in oxytetracycline adsorption on the PS-MP foams with changing pH were more prominent for the beached samples than the virgin samples owing to higher surface area, micropore area, and oxidation degree of the former (Zhang et al. 2018). The inhibition of ChE activity (32%) when bivalve *Corbicula fluminea* (*C. fluminea*) was exposed to florfenicol (1.8 and 7.1 mg/L) and ChE activity inhibition of 31% when exposed to 0.2 mg/L of microplastics was found, and no other significant alterations were observed, whereas mixtures led to feeding inhibition (57–83%), significant suppression of ChE (44–57%) and isocitrate dehydrogenase activities, and increased lipid peroxidation levels and anti-oxidant enzyme activities, suggesting that mixtures of florfenicol (low ppm range) and microplastics (ppb range) were much more toxic to *C. fluminea* (Guilhermino et al., 2018). PVC microplastics raised the antidepressant drug venlafaxine's accumulation in fish mitochondria of *M. anguillicaudatus*, and magnified venlafaxine's bioaccumulation factor of tissue by more than 10 times (Qu et al. 2019). The presence of PS-MPs significantly increased the bioaccumulation of roxithromycin (ROX) in the gut, gills, brain, and liver of red tilapia, whereas the inhibition of AChE activity and oxidative damage caused by ROX was alleviated in the presence of PS-MPs after 14 days of exposure (Zhang et al. 2019).

PCBs and MPs/NPS

It has been reported that discolored MPs can adsorb more PCBs than non-discolored ones (Endo et al. 2005). The adsorption capacity of PE for environmental pollutants was generally higher than that of other plastics (Alimi et al. 2018). The sorption of PCBs to Nano-PS was 1–2

orders of magnitude higher than that of PE-MPs because of greater aromaticity and surface area/volume ratio of Nano-PS (Nano-PE was not available, but the relative effect of surface adsorption and volume distribution can still be deduced by comparing Nano-PS and PE-MPs) (Velzeboer et al. 2014). Previous study showed that low doses of PS (0.074%) increased biological accumulation of PCBs with the coefficient of 1.1–3.6, the influence of which was significant for ΣPCBs and a couple of separate homologs; however, at higher doses, biological accumulation reduced when compared with the low dose, but which only PCB105 was significant (Besseling et al. 2013).

Polybrominated diphenyl ethers and MPs/NPS

The detritivorous marine amphipod *Allorchestes compressa*'s body tissue can take in PBDEs from the microplastics, while environmental MPs may reduce the uptake of PBDEs compared to unabsorbed free chemicals, which can transfer PBDEs into marine organisms (Chua et al. 2014). On the contrary, when rainbow fish (*Melania fluviatilis*) absorbed PBDEs, the accumulation of PBDEs in its tissues was greater, and low-bromine homologs were easier to accumulate in its tissues, while the high-bromine homologs were not easy to transfer to the organs due to the stronger binding power of microplastics (Wardrop et al. 2016).

Phthalate esters & MPs/NPS

Polyethylene (PE) MPs (45–53 μm) could absorb four phthalate esters (PAEs) (DEHP > DBP > DEP > DMP) and transport PAEs into mice gut and induce aggravated intestinal inflammation and metabolic disorders (Deng et al. 2020). PAE-contaminated PE-MPs (0.4–5 μm) aggravated male mice reproductive toxicities manifested by greater alterations in sperm physiological alterations, spermatogenesis disorders, and oxidative stress in the testis (Deng et al. 2021). In contrast, adsorption to PS-MPs led to decreased bioavailability of DBP, resulting in reduced toxicity of DBP, and antagonistic toxicity between the two pollutants was observed in acute and chronic trials in marine copepod *Tigriopus japonicus* (Li et al. 2020a, b).

Microplastics (nanoplastics) and other toxic substances

Adsorption of Nano-PS increased the concentration of BPA in zebrafish viscera and head by 2.6 times and 2 times, respectively, and aggravated BPA neurotoxicity to central nervous system and dopaminergic system (Chen et al. 2017a). PS (or PE) microplastics increased the toxicity of organophosphorus flame retardants, and induced higher oxidative stress (greater superoxide dismutase (SOD) and

catalase (CAT)) and neurotoxicity in mice (*Mus musculus*) (lowered AChE) (Deng et al. 2018).

Micro(nano)plastics as vectors of microorganisms or invasive substances

Micro(nano)plastics in the environment can be used as carriers for selection and transmission of animal and human pathogens such as Vibrionaceae, Flavobacteriaceae, Campylobacteraceae, and Aeromonadaceae (Frère et al. 2018; Kirstein et al. 2016; Viršek et al. 2017; He et al. 2018); invasive species; and harmful algae (Wright and Kelly. 2017; Keswani et al. 2016). Meanwhile, pathogens such as bacteria and viruses by the ingestion or direct contact with organisms through micro(nano)plastics can also cause toxicological effects (Mughini-Gras et al. 2021; Moresco et al. 2021; Wang et al. 2021a). Moreover, antibiotic resistance genes (ARGs) and antibiotic-resistant bacteria were found on microplastic surfaces (Lu et al. 2020). Micro(nano)plastics not only accelerate the spread of organisms in the environment, leading to biological invasion, but also increase the gene exchange between attached biofilm groups, leading to the transfer of pathogenic genes and ARGs (Arias-Andres et al. 2018; Mughini-Gras et al. 2021). In free-living or naturally aggregated bacteria, microplastics can increase the frequency of plasmid transfer. Microplastic biofilms serve as new hot spots for the transmission of ARGs through horizontal gene transfer (Arias-Andres et al. 2018). On microplastic particles of polyethylene, polystyrene, and polypropylene, pathogenic *Vibrio parahaemolyticus* was detected in the North/Baltic Sea (Kirstein et al. 2016). Viršek et al. (2017) reported that 28 bacterial species were identified on the microplastics particles in the North Adriatic including *Aeromonas* spp. and hydrocarbon-degrading bacterial species. These studies showed that potential pathogenic microorganisms in the ocean may catch up with micro(nano)plastic particles and spread around the world through water or air currents. The potential harm caused by this is unclear and needs further scientific verification.

Nevertheless, there is controversy regarding this potential consequence, as some researchers object to MPs (or NPs) as pollutant carriers. According to Gouin et al. (2011) and Beckingham and Ghosh (2017), the transfer of organic contaminants into biological organisms by dietary MPs may be a small or limited contribution compared to other natural routes of exposure in most cases. It was reported that contaminated PE microplastics displayed a negligible vector role in terms of mercury bioaccumulation in the clams (Sıkdokur et al. 2020). The presence of polyethylene plastic microspheres in artificial sea water of a salinity of 18 ± 1 g/L test media did not significantly change the toxic effects of gold nanoparticles (ppb range)

to *P. microps* juveniles (Ferreira et al. 2016). Therefore, MPs can introduce these harmful chemicals into organisms only when fugacity of a chemical in microplastics is greater than that in organism, which may result in an exposure risk. Moreover, the sorption behavior of chemicals on MPs is related to polymer type, particle size, color, temperature, salinity, the degree and typology of plastic aging (mechanical, UV or biological degradations), and other physical and chemical properties (Endo et al. 2005; Sørensen et al. 2020; Binda et al. 2021) and biofilms (Guan et al. 2020). In addition, the presence of other sorbents is also important. In exposures more relevant to the environment, modeling studies showed the total organic contaminant fraction or metals absorbed by plastic was much smaller than that adsorbed by other media like dissolved organic carbon and colloids in the ocean (Koelmans et al. 2016; Lohmann 2017) or freshwater environments (Guan et al. 2020). Seidensticker et al. (2017) found that the concentration of dissolved organic matter may alter the distribution of pollutants between MPs and water. In addition, the increase of MP concentration will increase the adsorption of chemical substances.

Urgency and challenges

Lack of effective indicator organisms and biomarker

Although a large number of studies have confirmed the widespread presence of micro(nano)plastics in various marine media, there is no uniform international technical method for marine micro(nano)plastics monitoring and ecological risk assessment. Seabirds and turtles have been widely used to monitor plastic debris with a size of more than 1 mm. It is also reported that mussels are suitable bioindicator for microplastic pollution because of their wide distribution, vital ecological niches, susceptibility to microplastic uptake, and close connection with marine predators and human health (Li et al. 2019a, b). However, there is a lack of effective indicator organisms for the monitoring of smaller size microplastics. Further studies are needed on efficient biomarker screening and ecological risk assessment techniques to indicate toxicological effects of micro(nano)plastics.

Effects of seafood cooking and/or processing on micro(nano)plastics toxicity

Thus far, available data on the toxicokinetics of micro(nano)plastics mainly include absorption and distribution, with less information on metabolism or excretion. There is no data on the potential effects of cooking and/or processing seafood at

high temperatures on micro(nano)plastics toxicity. The toxic effect of micro(nano)plastics on human body must be first digested by digestive tract and then absorbed by intestinal wall cells to enter the circulatory system. It has been documented that ingested microplastics in Antarctic krill turned into nanoplastics through digestive fragmentation (Dawson et al. 2018); however, whether the micro(nano)plastics will be destroyed in the process of digestion, how much is the absorption and utilization rate in the process of absorption, and what factors (food matrix/digestion environment/particle size of microplastics) will lead to the decrease of its digestibility and utilization are also worthy of further study.

Lack of direct evidence of micro(nano)plastics affecting organisms in the field

Over the past decade, it is an indisputable fact that micro(nano)plastics are ubiquitous in the environment and the quantity keeps increasing rapidly. However, in the field, there have been few direct evidence that micro(nano)plastics have an impact on the organisms. Although laboratory experiments showed that micro(nano)plastics can produce a variety of toxicological effects on organisms, the real conditions and intrinsic dynamic evolution characterizing the phenomena in natural ecosystems cannot be easily reproduced at laboratory or pilot scale. For instance, unpredictable factors as climatic variations causing modifications of the current regime in sea and lakes cannot be totally investigated in lab experiments involving MPs/NPs. Therefore, the data cannot be applied to the ecological and health risk assessment of micro(nano)plastics because of the great difference between indoor research and field environment in aspects of weathering, and adsorption of organic environmental pollutants and organisms, etc. Moreover, in these laboratory experiments, the concentration of micro(nano)plastics tested was not environmentally relevant (de Sá et al. 2018; Zocchi and Sommaruga 2019), even several orders of magnitude higher than would be found in the environment.

Limitation of the methods of sample collection, separation, and identification of micro(nano)plastics

To date, only a part of the microplastics, especially nanoplastics information in the environment, are obtained due to the limitations of current sample collection, separation, and identification methods. The characterization index of microplastics in the environment, mainly including abundance, size, shape, and color, is often characterized by rough ranges or proportions. Despite some recent comments on microplastic sampling and analysis (Campanale et al. 2020; Bellasi et al. 2021), it is still difficult to properly quantify dispersed particles in sediments. Due

to the lack of consistent and standardized methods and protocols for evaluating and quantifying microplastics present in sediment or aqueous phase systems, appropriate comparisons between different sites are not possible, which hinders the current knowledge of the environmental and toxicological effects of microplastics. In the aqueous phase, characterization methods that only refer to the concentration of chemical pollutants are not feasible for micro(nano)plastics, and establishing a “characteristic spectrum of microplastics” may be an effective method for more comprehensive characterization of micro(nano)plastics in the environment.

Occasionality and contradiction in studies on the toxicity of micro(nano)plastics

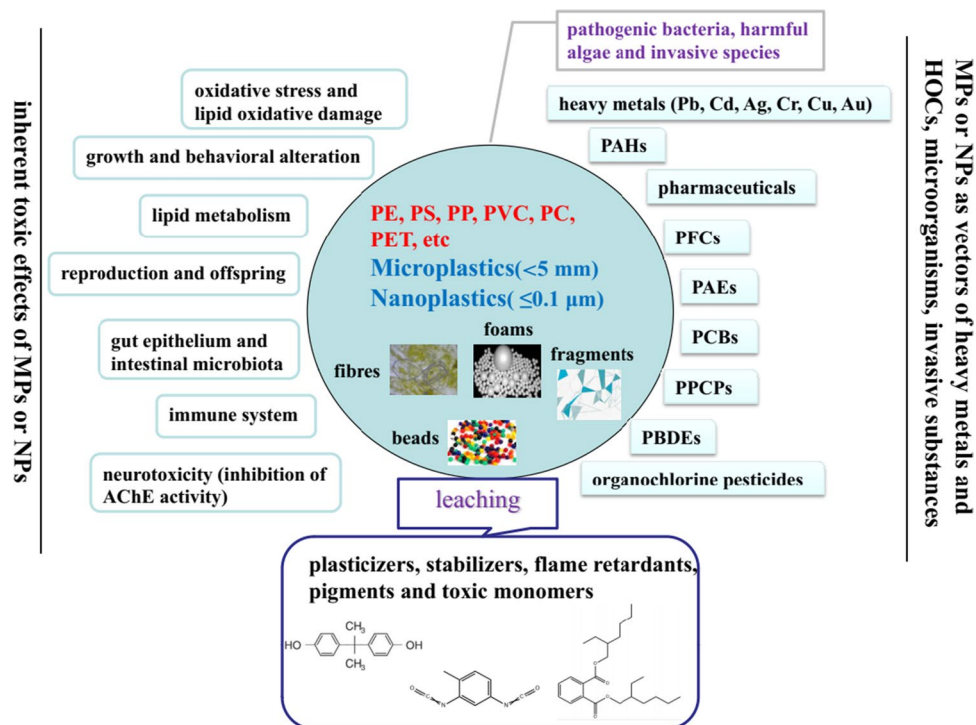
Uncertainties remain regarding the extent of harm caused to organisms directly by ingestion of micro(nano)plastics, and over the effect they make to overall exposures to hazardous chemicals. Although current studies have reported that micro(nano)plastics will have a series of adverse effects on organisms, the toxic effects of these reports are sometimes uncertain and contradictory, and different results may be obtained in different studies and different biological tissues. Several studies have reported that microplastics caused little or no physical or chemical harm to marine biota (Koe-lmans et al. 2014), and had limited function as carriers of hydrophobic pollutants compared to natural phytoplankton,

bacterioplankton, and yeasts (Frydkjær et al. 2017). In terms of the toxicity of microplastics to organisms, some conditions or factors such as species, the size, shape, polymer type, exposure time, and concentration of microplastics used in exposure, and environmental factors, such as food abundance (Chae and An 2020), may affect the corresponding experimental results. The toxic changes caused by the adsorption of pollutants on micro- and nanoplastics are still controversial, which depends on the chemical and physical interaction, the corresponding changes in bioavailability; the changes in intake, transport, and accumulation in organisms; and the characteristics of pollutants. When pollutants are combined with microplastics or nanoplastics, their toxicity may undergo various modification, rather than simple additive, synergistic, or competitive effects. Future research still needs to explore different biological indicators to find specific indicators that are sensitive to microplastics.

Lack of long-term and systematic toxicity studies

The current studies on microplastics or nanoplastics are mainly acute and short-term toxicity, but there is a lack of long-term and systematic toxicity studies. Therefore, there is an urgent need for future long-term and systematic toxicity studies related to micro- and nanoplastics.

Fig. 1 Summary of toxicity pathways of microplastics and nanoplastics



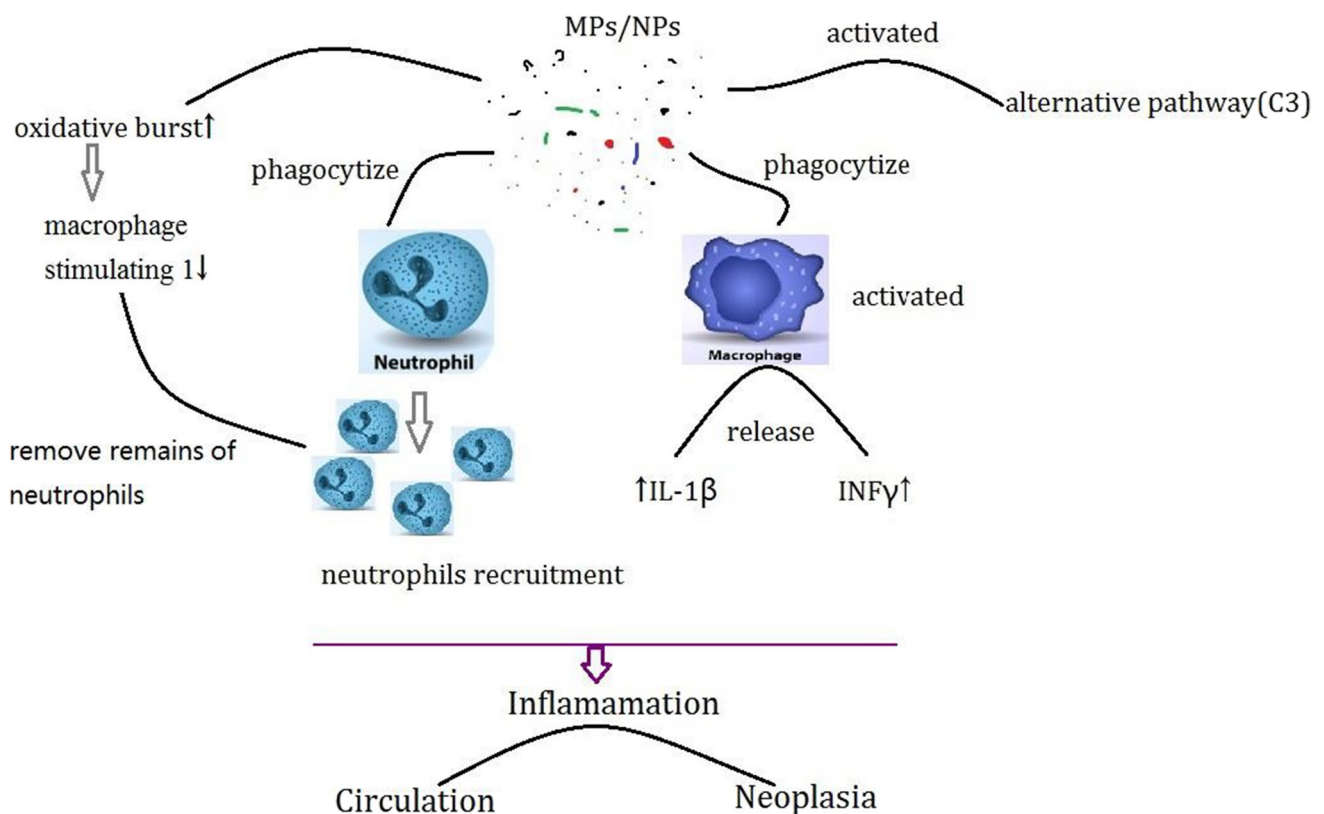


Fig. 2 The potential mechanism of toxicological effect for MPs/NPs in the body

Conclusions

This review summarized inherent toxic effects of micro- and nanoplastics in vivo (shown in Fig. 1), which mainly include the following implications: physical injury (block the feeding organs and digestive tract), reduced growth performance and behavioral alteration, induced lipid metabolic disorder, induced gut microbiota dysbiosis and disruption of the gut's epithelial permeability, neurotoxicity (inhibition of AChE activity), damage of reproductive system and offspring, oxidative stress, immunotoxicity, etc. We also outline the potential mechanism of toxicological effect for MPs/NPs in the body (Fig. 2). Additionally, besides hazardous consequences related to MPs/NPs themselves, plastics additives and residual and toxic monomers are diverse and complex, and the harm caused by their release cannot be ignored. Moreover, we generalize simultaneous toxic effects of micro- and nanoplastics with persistent, bioaccumulative, and toxic substances (heavy metals and organic environmental pollutants), as well as adverse effect as vectors of microorganisms, and invasive substances. Nevertheless, these potential consequences are controversial because some researchers object the idea that

MPs (NPs) act as a vector for contaminants. Finally given the facts laid out above, we put forward the existing problems in the toxicity research of micro(nano)plastics and the direction of future efforts.

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Declarations

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