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Recent advances in toxicological research of nanoplastics in the environment: A review☆

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ABSTRACT

Nanoplastics have attracted increasing attention in recent years due to their widespread existence in the environment and the potential adverse effects on living organisms. In this paper, the toxic effects of nanoplastics on organisms were systematically reviewed. The translocation and absorption of nanoplastics, as well as the release of additives and contaminants adsorbed on nanoplastics in the organism body were discussed, and the potential adverse effects of nanoplastics on human health were evaluated. Nanoplastics can be ingested by organisms, be accumulated in their body and be transferred along the food chains. Nanoplastics showed effects on the growth, development and reproduction of organisms, and disturbing the normal metabolism. The toxic effects on living organisms mainly depended on the surface chemical properties and the particle size of nanoplastics. Positively charged nanoplastics showed more significant effects on the normal physiological activity of cells than negatively charged nanoplastics, and smaller particle sized nanoplastics could more easily penetrate the cell membranes, hence, accumulated in tissues and cells. Additionally, the release of additives and contaminants adsorbed on nanoplastics in organism body poses more significant threats to organisms than nanoplastics themselves. However, there are still knowledge gaps in the determination and quantification of nanoplastics, as well as their contaminant release mechanisms, degradation rates and process from large plastics to nanoplastics, and the transportation of nanoplastics along food chains. These challenges would hinder the risk assessment of nanoplastics in the environment. It is necessary to further develop the risk assessment of nanoplastics and deeply investigate its toxicological effects.

1. Introduction

Nowadays, the production and application of plastics are increasing. In 2015, the global amount of plastic production has reached 322 million tons (PlasticsEurope, 2016). Due to the chemical stability, persistence, bioaccumulation of plastics, the problem of plastic pollution in the environment is becoming increasingly prominent (Barnes et al., 2009; Fossi et al., 2016; Hu et al., 2019; Shen et al., 2019). Up to now, plastics wastes have been detected in soils (Zhang and Liu, 2018), lakes (Xiong et al., 2018b), sediments (Abidli et al., 2018; Rodrigues et al., 2018; Wen et al., 2018), oceans (Keswani et al., 2016; Mendoza et al., 2018), and even in places with rare human activities, such as Antarctic (Munari et al., 2017) and Arctic (Cózar et al., 2017; Peeken et al., 2018). Plastic wastes can be degraded into small fragments or particles due to weathering, sunlight radiation and biodegradation. The plastic species with the particle sizes less than 5 mm were defined as microplastics (Thompson et al., 2004). Cosmetics and detergents that contains small plastic particles are the major sources of microplastics (Duis and Coors, 2016; Lei et al., 2017). The characteristics of small particle size and low density enable microplastics to escape the traditional wastewater treatment process and enter into the marine systems (Carr et al., 2016; Murphy et al., 2016). Microplastics can be further degraded to nanoplastics, which have the particle size between 1 nm and 100 nm (Jambeck et al., 2015). The commercial application of nanoplastics is also an important source of nanoplastics in the environment.

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Compared with other nanomaterials, such as carbon nanomaterials (Gong et al., 2009; He et al., 2018b; Xiong et al., 2018a; Yi et al., 2018) and metal nanomaterials (He et al., 2018a; Qin et al., 2018; Xu et al., 2012; Yang et al., 2018), the research of nanoplastics is still in its infancy. Due to the limitation of technology, the degradation processes and degradation rates of microplastics to nanoplastics are not yet clear. But it is certain that the decomposition processes will not stop and the microplastics will continue to form nanoplastics (Mattsson et al., 2015). It is a long-term and lasting process in the environment. The amount of nanoplastics in the environment is not yet known, because there are no effective methods for the determination, quantification and assessment. Due to the considerably small particle size, nanoplastics are widely distributed in the aquatic environment and can be easily ingested by organisms. Lu et al. showed that polystyrene (PS) nanoplastics (70 nm) could be ingested and accumulated in the body of zebrafish (*Danio rerio*) (Lu et al., 2016). The authors further found that PS nanoplastics with a concentration of 20 $\mu g\,L^{-1}$ (1.1×10^8 particles/mL) could cause local infection and lipid aggregation in the liver, resulting in metabolic disorders and energy cycling disruption. Kashiwada et al. studied the uptake and accumulation of PS nanoplastics in medaka (*Oryzias latipes*) (Kashiwada, 2006), and found that PS nanoplastics (39.4 nm, 10 $mg\,L^{-1}$) were mainly distributed in gills and viscera, but also in testis, liver and blood. More seriously, PS nanoplastics could pass through the blood-brain barrier, a highly selective barrier that can prevent the entry of potential neurotoxins via an active transport mechanism mediated by P-glycoprotein, and enter into the brain tissues, posing profound effects on organisms. On the other hand, nanoplastics could be transported along the food chain, eventually accumulated in the higher trophic levels, such as fish, birds, and even human beings. Cedervall et al. showed that PS nanoplastics (28 nm) at a concentration of 0.01% (w/v) could transfer along the food chain from algae to zooplankton and fish, and the feeding behavior and lipid metabolism of fish were noticeably affected (Cedervall et al., 2012). Nanoplastic particles can adsorb chemical substances from water (heavy metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, etc.), which may aggravate the adverse effects of nanoplastics on living organisms (Koelmans et al., 2016). Once these nanoplastic-contaminant complexes were ingested, contaminants can be simultaneously absorbed by organisms. Plastic additives and polymer monomers, such as bisphenol A, anti-ultraviolet radiation stabilizers, polybrominated diphenyl ethers and phthalates, can be released during degradation process. Many of these additives and polymer monomers are toxic to organisms, and can bring about acute poisoning symptoms, endocrine disorders, and reproduction toxicity (Bejgarn et al., 2015). Consequently, nanoplastic contamination should be seriously considered, and the ecotoxicity and environmental risks of nanoplastics need to be well studied.

Although some studies have been carried out on the toxicity of nanoplastics, further efforts are still needed. For example, to date, toxicological studies on nanoplastics mostly focused on model organisms, such as zebrafish and earthworm, but few experimental studies on toxicity of nanoplastics in mammals were carried out. Although nanoplastics could enter the cell membranes and blood circulation of organisms, the metabolic system of lower trophic levels is different from that of human beings and the ability of clearance and resistance to nanoplastics is also different. The release of toxic pollutants from nanoplastics was affected by many factors, so it was not certain whether or not toxic substances would be released in the human body. In this paper, in order to provide valuable reference for the biological safety assessment and potential toxicity studies of nanoplastics, sources and environment behaviors of nanoplastics, toxic effects of nanoplastics on organisms, toxic effects of pollutants brought about by nanoplastics, and potential human health risks are comprehensively reviewed, and some future research needs are proposed.

2. Sources and environmental behaviors of nanoplastics

The sources of microplastics in marine environment were mainly from land-based input, aquatic aquaculture and fishing, and coastal tourism (Browne et al., 2011). It has been reported that about 800 million tons of plastic wastes in the ocean from the land (Jambeck et al., 2015). Due to small particle size, traditional wastewater treatment processes could not thoroughly remove such plastic particles, which cause huge amount of microplastic particles entering the marine environment (Vance et al., 2015). Loss or erosion of soil polluted by microplastics is another way of the land-based source of microplastics to the marine environment (Horton et al., 2017). In addition, shipping industry and coastal tourism cause the release of a large number of plastic products and wastes into the beach and ocean, which is an important reason for the increase of marine plastic pollution. According to the estimation issued by the United Nations Environment Program, the amount of waste plastics was about 275 million tons in 2010, and approximately 4.8–12.7 million tons entered the marine system (Mattsson et al., 2015).

Compared with terrestrial ecosystem, plastic wastes are more easily decomposed into smaller plastic fragments because of the effects of high salinity and microorganisms in the marine environment (Sudhakar et al., 2007; Watters et al., 2010). The mechanism of degradation can be divided into two pathways: non-biodegradation and biodegradation (Fig. 1). Non-biodegradation of plastics mainly includes thermal degradation, physical degradation, photodegradation, thermos-oxidative degradation and hydrolysis (Andrady, 2011). Thermal degradation of plastics is a commercial degradation process and do not occur in the environment. Physical degradation is an important process of large plastic wastes into fragments, and this process is mainly controlled by weathering and sea waves. Hydrolysis, a bond breaking reaction, is an efficient process contributing to the degradation of plastics in aquatic environment, changing the high polymer to low polymer. Photodegradation is a very efficient non-biodegradation method of plastic degradation in the environment. These types of plastic degradation would decompose the structure, change the mechanical properties of high polymers, and increase the effective surface area of plastics during their physical-chemical reactions and their interactions with microorganisms (Nathalie et al., 2008). Biodegradation is another important pathway that further degrades plastic fragments into nanoplastics in the environment (Trishul and Mukesh, 2010). During the biodegradation, plastics are often degraded outside the bacteria. Extracellular enzymes excreted by living microorganisms can breakdown the polymer chains. This process produces smaller plastic particles of different structure, eventually forming nanoplastics. Once reaching to the nanoscale level, the specific surface area will extensively increase. For example, the specific surface area of a common plastic bag (0.2 m^2) would become of 2600 m^2 after being totally decomposed into nanoplastic particles with the average diameters of 40 nm (Mattsson et al., 2015). With the extensive plastic wastes entering the marine environment, large amount of nanoplastics would be generated.

Furthermore, nanoplastics can act as carriers of chemical and biological contaminants (Hodson et al., 2017; Koelmans et al., 2016; Lagana et al., 2019). Nanoplastics can adsorb chemical contaminants due to their low polarity and high roughness surface characters. The accumulation of chemical contaminants on the surface of nanoplastics increased their potential of transport and uptake by organisms, because of the ubiquitous existence of nanoplastics

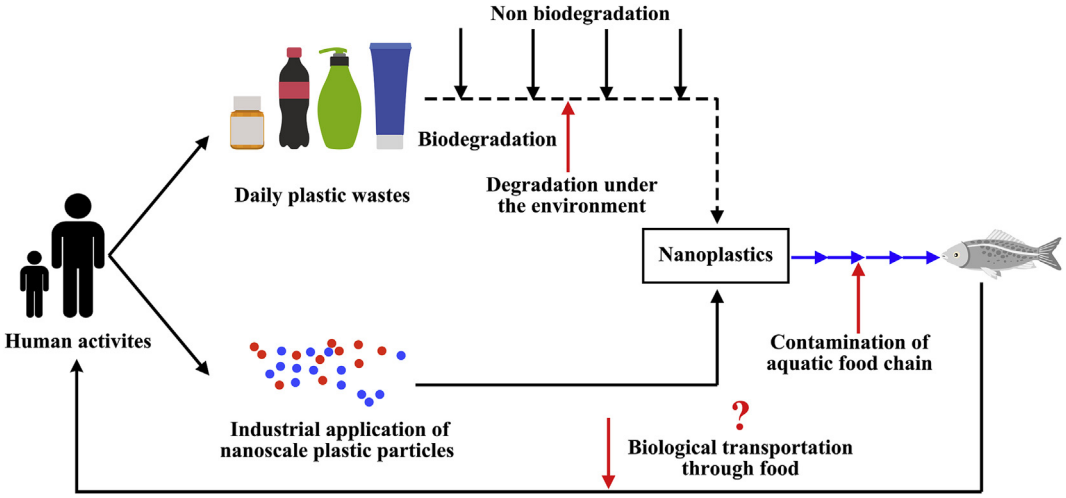

Fig. 1. Sources of nanoplastics in the environment. Nanoplastic particles can enter the aquatic food chain/web via low trophic level organisms such as algae and bacteria, which then are predated by high trophic level organisms such filter feeders and fish. However, whether nanopalstics can enter human body through food chain/web and pose threats to human health still need further exploration.

(Pittura et al., 2018). Contaminants can enter the food chain via ingestion of these nanoplastics by organisms, thereby increasing the bioavailability of chemical contaminants to the organisms. Nanoplastics can also adsorb harmful algae, bacteria and viruses. The aggregation of these harmful species may induce gene exchange among different species and promote the diffusion ability of drug resistant bacteria and pathogenic bacteria, which may aggravate toxicological and pathological responses to organisms. New bacteria may be produced during the gene exchange. In particular, pathogenic and antibiotic resistance bacteria contain abundant pathogenic and antibiotic resistance genes, which may be transferred by multi pathways between communities on biofilms (Arias-Andres et al., 2018; Parthasarathy et al., 2019; Schmidt et al., 2014). The presence of nanoplastics may enhance the migration of antibiotic resistance genes because of their strong floatability and mobility. Antibiotic resistance genes may be transferred to different areas. The exchange of antibiotic resistance genes between communities or the surrounding environment and the presence of antibiotic resistance bacteria may result in huge uncontrollable disasters.

3. Toxic effects of nanoplastics on organisms

Research on the impacts of nanoplastics to organisms showed that nanoplastics could be ingested and accumulated by various organisms. They can enter the circulatory system through enteric tissues, causing toxic effects at cellular and molecular levels. The adverse effects of nanoplastics on organisms are closely associated with the particle size, composition, morphology, aging time and surface properties. Some examples of toxicity evaluations of nanoplastics to organisms are shown in Table 1.

Bhattacharya et al. showed that charged PS nanoplastics (20 nm) can be easily adsorbed on the surface of green algae (2–10 μm) and affect its photosynthesis process (Bhattacharjee et al., 2014). The authors further showed that the absorption capacity of nanoplastics on the surface of these algae by scallops was greatly enhanced. Another research performed by Della et al. reported that charged PS nanoplastic particles (40 nm) were easily accumulated in the digestive tract of sea urchin; as compared with negatively charged particles (PS–COOH), positively charged particles ($PS–NH_2$) showed more obvious toxicity to sea urchin (Della et al., 2014). $PS\text{-}NH_2$ nanoplastics could bind to lipid bilayers on the cell membrane with high affinity, which promotes the cell absorption through endocytosis. Canesi et al. suggested that $PS\text{-}NH_2$ could decrease lysosomal membrane stabilization, significantly increase oxyradical production in hemolymph serum, and induce rapid cellular damage such as membrane blebbing and loss of filopodia (Canesi et al., 2016). The generation of $PS\text{-}NH_2$ protein corona in hemolymph serum was observed with the existence of $PS\text{-}NH_2$. Micro-scale aggregates of PS-COOH nanoplastics occurred in the media, which may efficiently reduce the bioavailability of PS-COOH nanoplastics and decrease its toxicity. Actually, $PS\text{-}NH_2$ nanoplastics could exist as nanoparticles in the environment for a long time, which greatly increases their bioavailability, exposure risk, and the ability of penetrating cells and tissues.

Composition and particle size of nanoplastic polymers would also have significant effects on the toxicity of nanoplastics to organisms. Smaller nanoplastics may more easily enter the body tissues and cells. The remove of these nanoplastic particles is even more difficult, thereby increasing their exposure period and risks to organisms. The nanoplastics toxic effects on various test subjects, including different polymers used in experiments and different toxic endpoints, were summarized based on previously published literature (Fig. 2). Compared with other nanoplastics, PS and polymethylmethacrylate (PMMA) nanoplastics were more commonly used. This may be due to the difficulty in the synthesis of other polymers. Ward et al. reported that mussels (*Mytilus edulis*) could directly absorb PS nanoplastic particles (30 and 100 nm) through the intestine (Ward and Kach, 2009). Evidence showed that bioaccumulation of PMMA nanoplastics occurred in barnacles at even low concentrations (1 ppm) in chronic exposure tests (Bhargava et al., 2018). PMMA nanoplastics could persist in the body throughout the whole stage of growth and development from Nauplius to juvenile barnacle, posing a potential long-term threat on invertebrate communities. The abundance of mRNA transcript was obviously increased and the immune system might be impaired after exposure to PMMA nanoplastics. Nanoplastics could change molecular signaling pathway and potentially interfere with the metabolism of lipids.

The coexistence of nanoplastics and other nanoparticles or chemical substances would significantly affect their toxic effects on organisms. Dong et al. studied the combined toxicity of PS nanoplastics and titanium dioxide (TiO_2) nanoparticles on nematode (*Caenorhabditis elegans*) (Dong et al., 2018). The authors found that

Table 1
Toxicity evaluation of nanoplastics to organisms.

Test object	Particle type	Particle size (nm)	Concentration	Exposure time	Adverse effect	Reference
Daphnia pulex	Polystyrene PS	75	0.1 mg/L 1 mg/L	1–21d	The expression of the gene encoding the energy-sensing enzyme AMPK α, β and γ were significant difference among all age groups. Age affects the sensitivity of its individuals to pollution of nanoplastic via altering vital physiological and biochemical processes such as cellular energy homeostasis and oxidation in vivo.	Liu et al. (2018)
Oyster gametes (*Crassostrea gigas*)	PS PS-COOH PS-NH_2	100	0.1–100 mg/L	1–5 h	Nanoplastic exposure can cause an increase in relative cell size and complexity of oyster spermatozoa. A significant dose-response increase in reactive oxygen species production was observed after exposure to PS-COOH, but no to PS-NH_2. Conversely, oocytes were less influenced after exposure to both nanoplastics. Toxic effects to two gamete cells might be related with different cell membranes.	Gonzálezfernández et al. (2018)
Nematode (*Caenorhabditis elegans*)	PS and TiO_2 nanoparticle	108.2 ± 4.5 10 ± 2	0.01–1 μg/L	Prolonged exposure	Combinational exposure to PS and TiO_2 nanoparticle could change the molecular basis of oxidative stress. Additionally, the presence of nanoplastics further enhanced the toxicity of TiO_2 nanoparticle such as inducing intestinal reactive oxygen species production and decreasing locomotion behavior in sod-3 mutant nematodes.	Dong et al. (2018)
Rotifer (*Brachionus plicatilis*)	PS-COOH PS-NH_2	40 50	0.5–50 mg/L	24–48 h	PS-NH_2 nanoplastics showed a high mortality PS-COOH showed no obviously acute toxicity in rotifers. Compared to be exposed in natural seawater (6.62 ± 0.87 mg/L), LC50 values were lower exposed in reconstituted seawater (2.75 ± 0.67 mg/L) in rotifers.	Manfra et al. (2017)
Mussel (*Mytilus galloprovincialis*)	PS	110 ± 6.9	0.5–50 mg/L Carbamazepine 6.3 μg/L	96 h	Mussels are sensitive to PS nanoplastics exposure even at low concentrations. PS can change the expression of gene, decrease enzymatic activity, induced effects on neurotransmission, increase the oxidative status and result in peroxidative damage.	Brandts et al. (2018)
Dicentrarchus labrax	Poly (methyl methacrylate) PMMA	45	0–20 mg/L	96 h	Abundance of mRNA transcript was obviously increased and the immune system might be impaired after exposed to nanoplastics. Nanoplastics can change molecular signaling pathway and potentially interfere with the metabolism of lipids.	Brandts et al. (2018b)
Zebrafish (*Danio rerio*)	PS	50	1 mg/L	3 d	Both bisphenol A and nanoplastics could result in myelin basic protein or gene up-regulation in the central nervous system, and significant inhibit acetylcholinesterase activity. Additionally, the existence of nanoplastics obviously enhanced neurotoxic effects in central nervous system and dopaminergic system.	Chen et al. (2017b)
Acorn barnacles (*Amphibalanus amphitrite*)	PMMA	45	5–25 ppm	24 h	Chronic exposure test suggested that bioaccumulation of nanoplastics occurred in barnacles even at low concentrations of the particles. Nanoplastics could persist in the body of throughout stage of growth and development from Nauplius to juvenile barnacle, which posed a potential long-term effect of nanoplastics on invertebrate communities.	Bhargava et al. (2018)
Mussel hemocytes (*Mytilus galloprovincialis*)	PS-NH_2	50	1–50 mg/L	0.5 h	PS-NH_2 could decrease lysosomal membrane stabilization and significantly increase oxyradical production in hemolymph serum, and induce rapid cellular damage such as membrane blebbing and loss of filopodia. Moreover, the generation of PS-NH_2 protein corona in hemolymph serum was observed at the existence of PS-NH_2.	Canesi et al. (2016)
Zebrafish (*Danio rerio*)	PS	42	5 mg/L	7 d	PS nanoplastics modulated the antioxidant system by decreasing the activity of glutathione reductase. Furthermore, PS nanoplastics can be transferred from mothers to the offspring via accumulation in the eggs due to interaction of nanoplastics with plasma proteins of oocytes.	Pitt et al. (2018)
Nematode (*Caenorhabditis elegans*)	PS	100 500	1 mg/L	3 d	Nanoplastics inhibited the growth and development of nematode individuals, altered locomotor behavior such as accelerating the frequency of head thrashing and body bending, induce significantly oxidative damage, and led to neurotoxicity.	Lei et al. (2018)
Daphnia pulex	PS	75	0.1–2 mg/L	48 h	Nanoplastics obviously induced and inhibit the expression of stress defense genes. Growth and reproduction were affected. The clutch time was delayed, offspring numbers of clutches were decreased and the female numbers of per clutch were also decreased.	Liu et al. (2011)
Crustacean (*Daphnia galeata*)	PS	52	5 mg/L	5 d	Nanoplastics can significantly inhibit the survival and reproduction of crustaceans. The abnormal development of embryos was observed after exposed to PS nanoplastics, including a low hatching rate.	Cui et al. (2017)
Zebrafish (*Danio rerio*)	PS	50	1 mg/L	120 h	Nanoplastics significantly inhibited the acetylcholinesterase activity, upregulated rhodopsin and blue opsin gene expression, reduced the length of larvae body and limited the larvae locomotion.	Chen et al. (2017)
Bacterium (Halomonas alkaliphila)	PS PS-NH_2	50 55	0–320 mg/L	0–2 h	Naoplastics showed growth inhabitation in high concentrations and induced oxidative stress. Further, positively charged nanoplastics induced higher oxidative stress than the non-charged nanoplastics and interrupted the NH_4^+ conversion efficiencies. In addition, under the action of electrostatic activity, positively charged nanoplastics attached to the cell surface and showed higher toxicity.	Sun et al. (2018)

Zebrafish (*Danio rerio*)	PS	70	20 mg/L	7 d	Nanoplastics could result in local infection and accumulation of lipids in the liver. Furthermore, exposure of nanoplastics also could cause changes in metabolites, disrupt some mechanisms and energy metabolism of the liver of fish.	Li et al. (2016)
Algae (*Scenedesmus obliquus*)	PS	70 nm	44–1100 mg/L	72 h	Growth and development of algae were inhibited. Photosynthesis was also affected and the content of chlorophyll synthesis decreased significantly. Oxidative damage of algae caused by nanoplastics was observed.	Besseling et al. (2014)
Zooplankton (*Tigriopus japonicus*)	PS	50	0.125–25 mg/L	96 h	Fecundity significantly decreased after exposed to nanoplastics. Moreover, malformation of embryo development and high mortality of larvae were observed. Parents were dead as exposure to high concentrations of nanoplastics.	Lee et al. (2013)

co-exposure to PS and TiO_2 nanoparticles changed the molecular basis of oxidative stress. The presence of PS nanoplastics further enhanced the toxicity of TiO_2 nanoparticle via inducing intestinal reactive oxygen species production and decreasing locomotion behaviors in sod-3 mutant nematodes. Another study showed that mussel (*Mytilus galloprovincialis*) was more sensitive to PS nanoplastics exposure even at low concentrations ($0.05\ mg\ L^{-1}$) (Brandts et al., 2018). PS nanoplastics changed the expression of gene, decreased the enzymatic activity, induced effects on neurotransmission, increased the oxidative status and finally resulted in peroxidative damage (Brandts et al., 2018). Chen et al. reported that both bisphenol A and PS nanoplastics (50 nm) could result in myelin basic protein or gene up-regulation in the central nervous system, and significantly inhibit acetylcholinesterase activity of zebrafish (*Danio rerio*) (Chen et al., 2017). The existence of PS nanoplastics obviously enhanced neurotoxic effects in central nervous system and dopaminergic system. Besides, PS nanoplastics could be transferred along the food chain (algae—zooplankton—-fish), the lipid metabolism and behavior of crucian were significantly affected (Cedervall et al., 2012).

At present, due to the small particle size of nanoplastics, the detection methods of nanoplastics in biological tissues are few, and there are relatively few studies on the composition, distribution of nanoplastics and their impact on the environment and organisms. Although the growth, development and reproductive toxicity of living organisms by nanoplastics has been revealed, huge concentrations of nanoplastics were used to test the effects within short periods (Table 1), and these concentrations cannot occur in the environment. More tests are needed to examine the impacts of lower dosage or environmental dosage and long-term exposure to nanoplastics. Moreover, to date, most researches on toxicity and risk assessments of nanoplastics were performed using PS materials. We expect that more studies are needed using other nanoplastic materials such as polypropylene (PP), polyethylene (PE), polyvinyl chloride (PVC), polyethylene terephthalate (PET), etc. Many conclusions and phenomena of nanoplastics in organisms need to be further explored.

4. Toxic effects of pollutants brought about by nanoplastics

4.1. Additives

Some chemical compounds are often used in the production of plastics, such as anti-ultraviolet radiation stabilizers, phthalates and bisphenol A (Hirai et al., 2011). It is worth mentioning that plastic polymer monomers, such as styrene monomers, and phthalates can be easily released from plastic matrices during decomposition and degradation. Evidence showed that these additives and polymer monomers have estrogenic or anti-androgenic (Fries et al., 2013), reduction of reproductive rate and endocrine disrupting effects on organisms (Iguchi et al., 2006). The release of additives from microplastics or nanoplastics was affected by many factors, such as ionic strength of leaching solution, aging time, surface roughness, polymer type, etc. The mortality, growth inhabitation and abnormal embryo of organisms caused by the exposure to micro (nano)plastic leaching solution have been revealed. We summarized recent toxicity tests of plastic leachates of different polymer types. According to these studies (as seen in Table 2), manufacturing process, polymer type, aging time and particle size had obvious influences on the toxicity of leaching solution. However, there are few data on the toxicity of leaching solution to nanoplastics. Further researches on release mechanism of polymer monomer and additives from nanoplastics and toxicity exposure of leaching solution are needed.

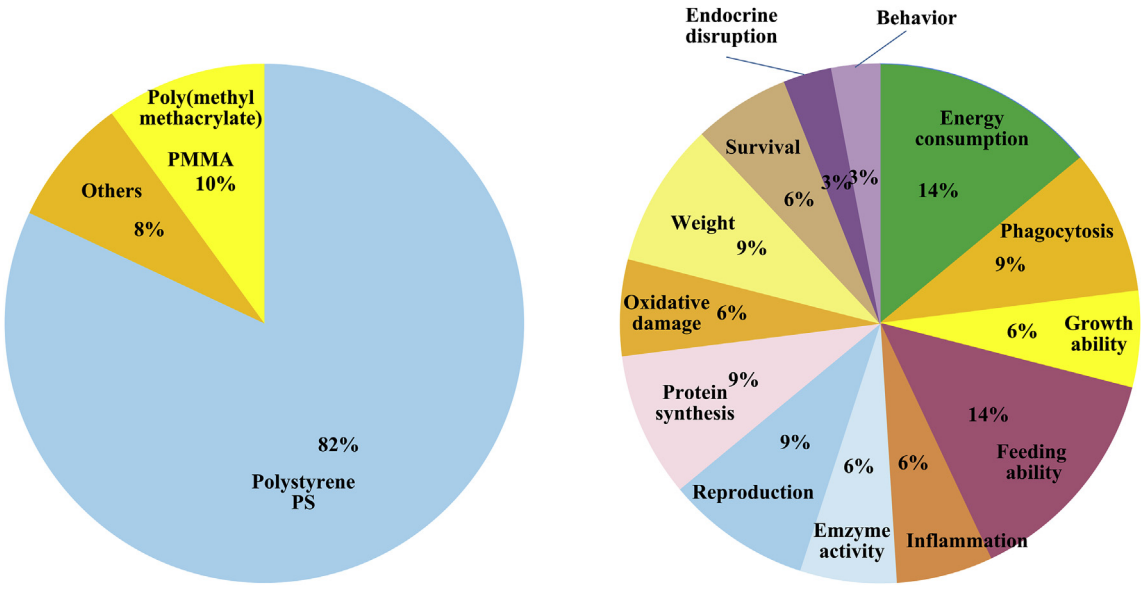

Fig. 2. Analysis of nanoplastics toxic effects to test subjects. The left refers different polymers used in experiments, and the right refers different toxic endpoints observed in tests. Polystyrene nanoplastic particles were commonly used in tests, and the toxic effects of nanoplastics were mainly evaluated at sub-lethal levels, such as energy consumption, feeding ability, reproduction, growth rate, oxidative damage, oviposition, enzyme activity and behavioral abnormalities.

Table 2
Toxicity test of various polymer types of plastic leachates.

Test object	Plastic type	Exposure time (h)	Exposure concentration	Ecological assessment methods	Toxicity effect	Reference
Daphnia magna	ABS, Epoxy resin, HDPE and PP	24 48	250 g/L	Mortality	PVC showed significant acute toxicity, while the acute toxicity observed by epoxy resin was no obvious.	Lithner et al. (2012)
Daphnia magna	ABS, HDPE, LDPE, MDPE, PC, PE, PET, PMMA, PP, PTFE, PU, PVC	24 48	70–100 g/L	Mortality	The leachate of various materials showed acute toxicity to the *Daphnia magna* and semi inhibitory effective concentration was measured to be 5 −80 g/L.	D et al. (2009)
Mussel (*Perna perna*)	Primitive PP and waste PP	48	25% (v/v)	Embryo development	Primitive PP plastics and waste PP plastics led to 23.5% and 100% embryo mortality and deformity of brown mussel respectively, implying that the toxicity of plastics extract depended largely on the compounds loaded on the plastics.	Silva et al. (2016)
Marine copepods (*Nitocra spinipes*)	ABS, HDPE, LDPE, PET, PLA, PP, PS, PUR and PVC	96	100 g/L	Mortality	38% of the leaching solution of plastics showed acute toxicity to test objects, and its toxicity mainly depended on the manufacturing process of plastics and the aged level.	Bejgarn et al. (2015)
Fish (*Pseudochromis fridmani*)	Two kinds of PE with different sources	48	–	Mortality	The toxic effects of the leaching liquor of plastics differed greatly because of the difference of the additives content of the same plastics from different processing and different sources.	Hamlin et al. (2015)
Acorn barnacles (*Amphibalanus amphitrite*)	HDPE, LDPE, PC, PET, PP, PS and PVC	24 48 72 96	0.1–0.5 m^2/L	Settlement	The leaching solution of all types of plastics would significantly reduce the survival rate under the concentration of high osmotic filtrate. Among them, PCV was the most toxic.	Lu et al. (2016)

Note: ABS, Acryloniterle butadiene styrene; HDPE, High density polyethylene; LDPE, Low density polyethylene; MDPE, Medium density polyethylene; PC, polycarbonate; PE, polyethylene; PET, polyethylene terephthalate; PMMA, Polymethyl methacrylate; PP, polypropylene; PTFE, polytetrafluororthylene; PU, polyurethane; PVC, polyvinyl chloride.

4.2. Attached contaminants

Due to large specific surface area and inherent hydrophobicity, persistent organic pollutants (such as polychlorinated biphenyls (PCBs) (Ren et al., 2018b; Velzeboer et al., 2014) and polybrominated diphenyl ethers (PBDEs) (Ren et al., 2018a; Ye et al., 2017a; Ye et al., 2017b)) and heavy metals (Tang et al., 2018) can be easily adsorbed on the surface of plastic particles. Mato et al.

reported that concentrations of PCBs and dichloro-diphenyl-trichloroethane (DDT) in plastic particles were significant higher than in surrounding sea waters, demonstrating strong affinity of plastics for these chemicals (Mato et al., 2001). Polymer type, particle size and surface structure of nanoplastics are important factors affecting the surface bound contaminants (Guo et al., 2012). Nowadays, few studies are conducted on the adsorption of pollutants by nanoplastics, however, researches on the adsorption of pollutants by microplastics have been carried out.

Laboratory studies generally suggested that pollutants adsorbed on the surface of micro (nano)plastics can be transported and accumulated into organisms via feeding behaviors. Nevertheless, there is no clear conclusion of whether a linear relationship exists between the concentrations of micro (nano)plastics and the residual concentrations of pollutants. For instance, Browne et al. showed that the contents of pollutants in the abdominal wall and intestine of *Arenicola marina* increased significantly after being fed with microplastics and gravel (Browne et al., 2013). The authors further showed that there was no clear judgment whether pollutants were adsorbed on gravel or onto microplastics. Besseling et al. reported that the relationship between concentrations of microplastics and content of ingested pollutants was complex in *Arenicola marina* after being exposed to soils containing microplastics and PCBs (Besseling et al., 2013). The study found that when the concentration of microplastics was low, the accumulation of PCBs in the organisms increased obviously; however, when the concentration of microplastics rose to a higher level, the aggregation of PCBs slightly decreased. Another study also reported that no significant influence on the concentration of PBDEs in earthworms (*Eisenia fetida*) by the addition of microplastics was observed (Gaylor et al., 2013). Chua et al. showed that microplastics and nanoplastics could serve as vectors for pollutants when entering marine organisms, while the transport and absorption efficiency of pollutants was related to their inherent properties (Chua et al., 2014).

On the other hand, some simulation experiments showed that the migration ability of pollutants on the surface of microplastics was limited (Gouin et al., 2011; Koelmans et al., 2013). Gouin et al. studied the effects of different temperature, pH and intestinal surfactants on the accumulation of pollutants on the surface of microplatics using a single storehouse model (Gouin et al., 2011). The results showed that microplastics had little effect on the intake of pollutants via the organism intestinal. Meanwhile, according to the research on thermodynamic food web model, pollutants on the surface of microplastics also had less contribution to the total amount of transfer and accumulation of pollutants in organisms. Another simulation study on North Sea cod (*Gadus morhua*) also suggested that microplastics had less effect on the aggregation of pollutants in organisms (Koelmans et al., 2013). However, some complicated factors were not taken into account in these models, such as the accumulation of pollutants in lipids and the existence of absorption and distribution dynamics. These factors would lead to the gradual dissociation of pollutants from microplastics and consequently the absorption and accumulation of pollutants in the intestinal tract of organisms. Therefore, more reasonable and explicit models should be established in further researches to simulate the release and accumulation of pollutants attached on microplastics in organisms.

5. Potential human health risks of nanoplastics

5.1. Translocation and absorption in the body

Evidences showed that these tiny particles can be transferred along the food chain to higher trophic level organisms, or into the human food chain through other pathways (such as via sea salt or animal feed) (Yang et al., 2015). It is of great value to investigate and evaluate the transportation, absorption and toxic effects of nanoplastics in the human body. More recently, the studies on the toxic effects of nanoplastics were mainly focused on their transportation and absorption efficiency in the intestine, and their accumulation in tissues of various model animals. We here reviewed the endocytosis mechanism and toxicity evaluation of micro (nano)plastics in various animals and in vitro models (Table 3).

Whether nanoplastics can break the intestinal barrier and enter other parts after being ingested is an important basis for studying whether nanoplastics can be accumulated in organisms. This would be an important starting point for analyzing and assessing the toxic effects of nanoplastics. For example, in vivo and in vitro tests are important methods to investigate the endocytosis and absorption mechanisms of nanoplastics. Studies on a series of different types of nanoplastics suggested that they can cross the intestinal barrier into the circulatory system and eventually lead to systemic exposure (Bouwmeester et al., 2015). Magrì et al. simulated that the interaction between PET nanoplastics and cells using in vitro Transwell model of the intestinal epithelium (Magri et al., 2018). The authors reported that PET nanoplastics (26.7 nm) showed small size and long-term stability in various biological media, which increase the possibility of living organism exposure. No obvious toxic effects were observed during the evaluation of the biological impact of PET nanoplastics on ingestion on human intestinal cells, but they can efficiently pass through an in vitro Transwell model of the intestinal epithelium. The absorption and transportation in vivo of nanoplastics was depended on their own structure and properties, such as chemical composition and surface modification. The oral bioavailability of 50 nm PS nanoplastics was in the range of 0.2%–7% (Jani et al., 2011). However, some studies reported that the bioavailability of 60 nm PS nanoplastics was relatively high, ranging from 1.5% to 10% (Hillery et al., 2008; Mishra et al., 2019). The possible reasons for such variation may be related to the aging time and surface modification of nanoplastics. Due to the difference of surface modification, the bioavailability of different sized nanoplastics (50–500 nm) showed a significant difference (0.2%–10%) (Kulkarni and Feng, 2013; Walczak et al., 2015a; Walczak et al., 2015b). Due to their large surface area and complex surface structure, nanoparticles can interact with various molecules, such as lipid, protein, water, ions etc. For example, the interaction of proteins and nanoparticles can lead to the generation of coronal protein rings (Huang et al., 2018; Lundqvist et al., 2008). These protein rings show a significant effect on the endocytosis of nanoparticles of cells. Coronal protein rings on the surface of nanoplastics would have similar chemical effects on the endocytosis and can promote the translocation efficiency of 50 nm nanoplastics during digestion. Also, the interaction of nanoplastics and iron ions could promote the uptake of irons (Mahler et al., 2012), the presence of nanoplastics would affect the transporting function of cell membrane to induce toxic effects at cellular and molecular level.

5.2. Potential toxic effects on human health

Generally, smaller nanoplastics are easier to enter and accumulate into tissues and cell organisms, the positively charged nanoplastics showed a significant impact on cell physiological activities. Xia et al. found 60 nm cationic PS nanoplastics had being significantly toxic to macrophages and epithelial cells (Xia et al., 2008). Forte et al. studied the role of PS nanoplastic particle sizes on its toxicity effects (Forte et al., 2016). The authors suggested that, as compared with 100 nm nanoplastics, 44 nm nanoplastics could enter gastric cancer cells more quickly and efficiently, and further affect the cell morphology, the expression of genes and cell

Table 3
Endocytosis mechanism and toxicity evaluation of micro (nano)plastics in various animals and in vitro models.

Test object	Particle type	Particle size (nm)	Concentration	Exposure time	Adverse effect	Reference
Biomembrane model	PS	7	0–12% (mass ratio)	0–270 μs	Nanoplastics can penetrate into membranes, change membrane structure, reduce molecular diffusion rate, weaken membrane rigidity and eventually affect the function of membrane protein activator cells.	Rossi et al. (2014)
Lung cancer cells	PS	40–50	25 mg/L	0–4 h	Nanoplastics irreversibly entered into human lung cancer cells, increased with incubation time and accumulated in lysosomes.	Salvati et al. (2011)
Medaka (*Oryzias latipes*)	PS	39.4 474 932	1 mg/L 10 mg/L	24 h 3 d	Nanoplastics can penetrate the blood-brain barrier and eventually reach the brain of fish. Biocompatibility and toxicity of nanoplastics were related to the physical and chemical properties.	Kashiwada (2006)
Gastric adenocarcinoma cells	PS	4 100	0–10 mg/L	0–24 h	Nanoplastics can affect the survival rate, the expression of inflammatory factors and the morphology of cells. Meanwhile, the cytotoxicity of nanoplastics was closely related to its particle size, concentration and reaction time.	Forte et al. (2016)
Human cervical cancer cells & Mouse embryonic fibroblasts	PS-COOH PS-NH_2	50 100 500	0–100 mg/L	0–72 h	PS-NH_2 showed higher toxicity than PS-COOH. Additionally, 50 nm PS-NH_2 destroyed the cell membrane integrity, delayed G1 phase and decreased the expression of cyclin.	Liu et al. (2011)
Macrophage	PS-COO^-PS-NH_3^+	50 100	1–100 mg/L	0–24 h	Positively and negatively charged nanoplastics on the surface increased the surface roughness of cell membrane. Small particle and positively charged nanoplastics increased reactive oxygen stress and calcium content in cells, decreased phagocytic index, mitochondrial membrane potential and ATP content, thereby affecting cell viability and proliferation.	Bhattacharjee et al. (2014)
Caco-2 human intestinal epithelial cells	PET	26.7	1–30 mg/L	0–96 h	PET nanoplastics showed small size and long-term stability in various biological media, two important factors that increase the possibility of living organism exposure. No obvious toxic effects were observed during the evaluation of the biological impact of PET nanoplastics on ingestion on human intestinal cells, but they can efficiently pass through an in vitro Transwell model of the intestinal epithelium.	Magri et al. (2018)

proliferation by inducing up-regulation of some gene expression levels. Bhattacharjee et al. showed that different modification of nanoplastics' surface had different effects on cell membrane and cell oxidative stress (Bhattacharjee et al., 2014). Compared with anionic PS nanoplastics, cationic PS nanoplastics significantly increased the concentration of free Ca^{2+} and the content of intracellular reactive oxygen species. Meanwhile, mitochondrial membrane potential and the content of adenosine triphosphate decreased. Another research done by Liu et al. reported that 50 nm NH_2-PS nanoplastics could obviously destroy cell integrity, as well as the proliferation of cervical cancer cells and mouse embryonic fibroblasts (Liu et al., 2011). The reorganization of cytoskeleton and chromosomes during cell mitosis was also directly affected, including prolongation of division cycle and decrease in expression of cyclin.

Due to the stable properties and difficulty of degradation, nanoplastics can be accumulated in tissues and cells easily, causing metabolic disorders and local inflammation. Especially in patients with intestinal diseases, changes of tissue permeability caused by inflammatory infection would significantly increase the transportation and absorption of nanoplastics, thereby further increasing the exposure risk. More recently, it is noteworthy that researchers and scientists have begun to be conscious of the potential impact of nanoplastics on human health. Researches on the direct and indirect effects of nanoplastics on organisms have been gradually preformed. However, test subjects of these studies are limited to model cells and organisms, the shape and composition of nanoplastics investigated are comparatively single. Consequently, further studies should focus on nanoplastic contamination in ordinary organisms or in the food chain to accurately and comprehensively assess the impact of nanoplastics on ecosystem and human health.

6. Perspectives and challenges

As plastic products are widely used and difficult to be degraded, plastic pollution will continue to affect the health of the ecological environment. The large-scale growth of plastic production causes the continuous increase in the number of plastic fragments in the environments, leading to the accumulation of nanoplastics in different media. Although researches on the effects of nanoplastics on wildlife are limited, the adverse effects of nanoplastics on organisms will surely damage the ecosystem, sometimes even affecting human health. In order to obtain more information on the toxicity consequence of nanoplastics, further studies should focus on:

a. Efficient methods for determination, quantification and assessment of nanoplastics in the environment.
b. Degradation rates from large plastic particles to nanoplastics and mechanisms of degradation process.

c. Transmission and toxicological effects of nanoplastics on different trophic layers in marine representative ecosystems.
d. Using environmental concentrations of nanoplastics to test.

6.1. Determination of nanoplastics in the environment

Detection and quantification techniques of nanoplastics in the environment are limited. This analytical challenge has bogged the obtainment of data on the occurrence, fate, assessment and ecotoxicology of nanoplastics. There are few methods for detection of nanoplastics in the environment. Due to their small particle size, most existing sampling methods for microplastics have artificially neglected the detection of nanoplastics, and these methods were not applicable to nanoplastics. Consequently, establishment of new technologies and approaches for nanoplastic detection and quantification in the environment are urgent. Separation of organic materials and nanoplastics in samples is necessary. Based on our knowledge, chemical solvents, such as strong acids, would affect organic materials and probably also the nanoplastics. Thus, enzyme separation could be a better option.

6.2. The process from plastics to nanoplastics and degradation rates

Due to technologies and methods limits, it is difficult to obtain nanoplastics from the environmental samples. Exploration on the degradation processes and rates of large plastic particles being decomposed to nanoplastics is necessary and urgent. Laboratory experiments of stable isotope labeling to study the process are feasible. For example, large plastic particles are exposed to natural conditions under experimental simulation where the temperature, pH, sunlight and other forces can be easily controlled. Under controlled conditions, the separation of degraded plastics based on particle sized can be achieved, as well as the determination of the fragments content at nanoscale. This procedure can probably reflect the existence of plastics with different particle sizes in the natural environment, and estimate the formation amount of nanoscale size after degradation, thereby approximately assessing its ecological effects. Moreover, the degradation processes not only reduce particle size, but also change the chemical properties on the surface of nanoplastic particles. However, the characterization techniques of nanoplastics have not been reported yet, new methods and technologies need to be developed and applied to the characterization of nanoplastics.

6.3. Transmission via food chain/web and toxicological effects

More recently, evidences showed that nanoplastics not only have adverse effects on organisms, but also accumulate in organism bodies. However, most of researches on the accumulation and toxicity of nanoplastics were only at individual level of organisms. Studies on the mechanisms of transmission of nanoplastics via the food chain/web should be strengthened. Before that, two important factors need to be considered: origin and particle size. Nanoplastics in the environment can originate from the degradation of large waste plastics and the direct release of commercial applications. The properties of nanoplastics from these two sources are quite different. In order to accurately evaluate the environment effects, nanoplastics used in tests need to be originated from the accordingly sources. The size of nanoplastics adopted in experiments should be set according to the size range of nanoplastics in real environment. Additionally, biological experiments should not be limited to single organisms or individual level, but along the food chains or webs. For instance, phytoplankton, zooplankton, protozoa, metazoan, fish or higher trophic levels need to be exposed to the same nanoplastics containing environments. Survival, development, reproduction, behavior changes and toxicity need to be characterized. It is important to describe the effect of exposure time, composition and size of nanoplastics on organisms. Although laboratory experiments can obtain data on the toxicity of nanoplastics to organisms by food chain, its extension to real environment conditions can be very complicated. Therefore, achievable way forward still needs to be explored. The low trophic level bears different metabolic system with human beings, their ability of clearance and resistance to nanoplastics is also variated. Data on exposure experiments of nanoplastics may not be suitable for human. Whether nanoplastics can enter the human body via the food chain and the trigger of adverse effects on human also needs further investigation.

6.4. Using environmental concentrations of nanoplastics to test

Facts proved that everyone was using huge concentrations of nanoplastics to test the effects within short periods (Table 1). These concentrations cannot occur in the environment at all. More tests are needed to examine the impacts of lower dosage or environmental dosage and long-term exposure to nanoplastics. Most researches on toxicity and risk assessments of nanoplastics were often performed using PS materials. This will lead to misunderstand of the toxicity of nanoplastics to the ecosystems. Therefore, the establishment of new technologies and approaches for nanoplastic detection in the environment is needed. The impact on organisms and human health should be further developed in conjunction with the current status of nanoplastic pollution in the environment.

Declaration of interest

The authors have no conflict of interest to declare regarding this article.

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