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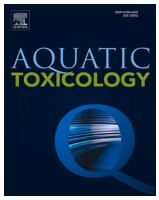

Interactive effects of micro/nanoplastics and nanomaterials/ pharmaceuticals: Their ecotoxicological consequences in the aquatic systems

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ABSTRACT

Micro/nanoplastics are ubiquitous in the environment and cause pollution of the aquatic ecosystem, in particular, which is a serious concern worldwide. Micro/nanoplastics can act as a vector for multiple co-contaminants that co-exist in the aquatic environment. Apart from micro/nanoplastics, nanomaterials and pharmaceuticals are other emerging contaminants that can also raise severe problems. Thus, in this review, the physicochemical interactions occurring between micro/nanoplastics and nanomaterials and pharmaceuticals and the factors (chemical and environmental) affecting the sorption efficiency of nanomaterials and pharmaceuticals have been addressed. Furthermore, the influence of micro/nanoplastics on the bioavailability and toxic effects of nanomaterials and pharmaceuticals on both freshwater and marine species has been highlighted. Additional focus has also been given to study the mechanism of toxicity of the micro/nanoplastics–nanomaterials and pharmaceuticals complex on the different species of different trophic levels. Finally, this review addresses the knowledge gaps and provides insights into the future research strategies to better understand the interactive mechanisms between the binary contaminants and also the toxicity mechanisms of micro/nanoplastics and nanomaterials and pharmaceuticals.

1. Introduction

Plastics have been the material of choice for many years owing to their omnipresence, low cost, lightweight, durability, and versatility (Nielsen et al., 2020). The most commonly manufactured and used plastic polymers include polyamide (PA), polystyrene (PS), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), and polyethylene terephthalate (PET) (Rochman et al., 2013). A considerable percentage of the manufactured plastics are accumulated in the aquatic environment as a result of the inconsiderate human activity, waste mismanagement, and their accidental discharge (Fig. 1) (Peng et al., 2020). Their predicted levels in the ocean are expected to reach 250 million tonnes by 2025 (Alimi et al., 2018), and thus, the assessment of their toxicological effects on aquatic species is necessary. In recent years, the number of studies on plastic toxicity has substantially increased owing to their ubiquity and potential threat to aquatic biota.

Plastics of interest for toxicological risk evaluation are classified based on their size as nanoplastics (< 1 μm) and microplastics (< 5 mm) (Frias and Nash, 2019). However, based on the source, microplastics are further categorized into primary and secondary microplastics. Primary microplastics represent the directly manufactured plastics, which include small plastic beads used in cosmetics, face wash, and toothpaste, while secondary microplastics are the fragmented products of larger plastics that break via weathering processes such as photo-oxidation and physical stress (Lehtiniemi et al., 2018). The impact of micro/nanoplastics (MNPs) is both physical and chemical because of their ability to adsorb and accumulate co-contaminants. However, the vector effect of MNPs (i.e. the ability of metals or organic pollutants to adhere to microplastics and get transported in the animal gut) depends on the sorption mechanisms, which are primarily regulated by the physicochemical properties of MNPs, nature of co-contaminants, and solution chemistry (Wang et al., 2018). Several studies have reported the role of MNPs as a vector for emerging contaminants such as pharmaceuticals (Zhou et al., 2020), nanomaterials (Yu et al., 2019), heavy metals

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(Brennecke et al., 2016), and organic contaminants (Rodrigues et al., 2019). At present, the most frequently discussed emerging contaminants include nanomaterials (Hassanpour et al., 2020; Khoshnamvand et al., 2020; Rezaei Tavabe et al., 2020) and pharmaceuticals (Fu et al., 2020; Kergaravat et al., 2021; Ruan et al., 2020). Both nanomaterials and pharmaceuticals are constantly released into the aquatic environment and their concentrations can vary between ng/L and mg/L (Balakrishna et al., 2017; Zhang et al., 2019a). Their release into water bodies (as depicted in Fig. 1) has been attributed to arise from wastewater treatment plants, aquaculture practices, hospital and industrial waste discharges, consumer products, and surface runoffs (Klatte et al., 2017; Williams et al., 2019; Yang et al., 2017). Following their release into the water bodies, the sorption efficiency of nanomaterials/pharmaceuticals (NM/PC) on MNPs decides their fate (augment or alleviate) and toxic effects on aquatic organisms.

Investigations on the mixture effects of MNPs and NM/PC are of particular interest. Both nanomaterials and pharmaceuticals are common secondary contaminants that are particularly noted in the industrialized and urbanized sectors, and the aquatic biota is constantly exposed to them. Moreover, nanomaterials and pharmaceuticals vary in their mechanisms of sorption on MNPs, which further prompts the researchers in pursuit of the exact mechanisms. Finally, the presence of these contaminants (MNPs, nanomaterials, and pharmaceuticals) in the aquatic environment is of great concern with respect to the seafood safety and public health. Hence, the interactive effects of MNPs and NM/PC and their ecotoxicological implications to aquatic organisms (both freshwater and marine) have been reviewed. Additionally, the mechanism of toxicity of the MNP–NM/PC complex on the various species of different trophic levels have been discussed elaborately. Finally, the uncertainties and knowledge gaps in understanding the fate, transport, distribution, and toxic mechanism of MNPs and NM/PC have also been focused.

2. Physicochemical interaction between the MNPs and NM/PC

The interaction between MNPs and NM/PC (Fig. 2) has been known to occur through sorption processes. Sorption is a transfer phenomenon, in which the molecules move from an aqueous phase to a solid phase. It typically includes both adsorption and absorption. Adsorption is the phenomenon, in which the molecules remain intact on the interface between the aqueous and the solid phases through a wide range of interactive forces; whereas during absorption, the dissolved molecules are retained within the solid phase of the sorbent via a weak van-der-Waals forces (Endo and Koelmans, 2019). The sorption kinetics includes three mass transfer rate-limiting steps: (i) external mass transfer, in which the NM/PC diffuse into the aqueous phase surrounding the MNPs; (ii) internal mass transfer, in which the NM/PC diffuse into the MNPs; and (iii) adsorption of NM/PC on active sites (Abdolahpur Monikh et al., 2020; Guo et al., 2019; Hu et al., 2019; Lin et al., 2020).

The sorption of pharmaceuticals on MNPs is driven by various interactive forces that include hydrophobic, van-der-Waals, electrostatic, π–π interactions, and hydrogen bonding. Hydrophobicity is an important property for the sorption of pharmaceuticals and is measured in terms of the octanol–water partition coefficient (log K_{ow}). Pharmaceuticals having a high log K_{ow} value (> 4) readily absorbs onto hydrophobic MNPs as they have a low affinity for water molecules (O'Connor et al., 2016). On the other hand, the sorption of hydrophilic pharmaceuticals on non-aromatic/aliphatic MNPs is governed by non-bond forces such as the van-der-Waals or the electrostatic interaction (Guo et al., 2019; Xu et al., 2018a). However, the major interactive force existing between aromatic MNPs and pharmaceuticals is the π–π interaction (Hüffer and Hofmann, 2016; Liu et al., 2020a). Besides these interactions, the least commonly occurring interaction is the hydrogen bonding. It is a specific attractive force occurring between a hydrogen atom covalently bonded to a very electronegative atom (N, O, or F atom) and another very electronegative atom (Li et al., 2018; van der Lubbe and Fonseca Guerra, 2019).

On the other hand, only a handful of reports have investigated the interactions of nanomaterials with MNPs in the aquatic environment. The sorption profiles of metallic ions involve either a period of rapid sorption followed by an approach towards equilibrium or a more prolonged period of slower sorption (Holmes et al., 2012). The reactivity of MNPs to metals can be ascribed to the short-term sorption of organic matter and the long-term ageing and surface modification of the MNPs (Holmes et al., 2014). For example, divalent cations such as Cu^{2+} released from copper nanoparticles interacted either with the charged/polar sites of the virgin PE pellets or indicated a non-specific interaction between neutral metal–organic complexes and the hydrophobic surface of the virgin PE pellets (Ashton et al., 2010; Holmes et al., 2012). Besides, the presence of phenyl group in MNPs might increase their polarity that promotes the sorption of nanomaterial over MNPs through electrostatic attraction (Li et al., 2020a). Other

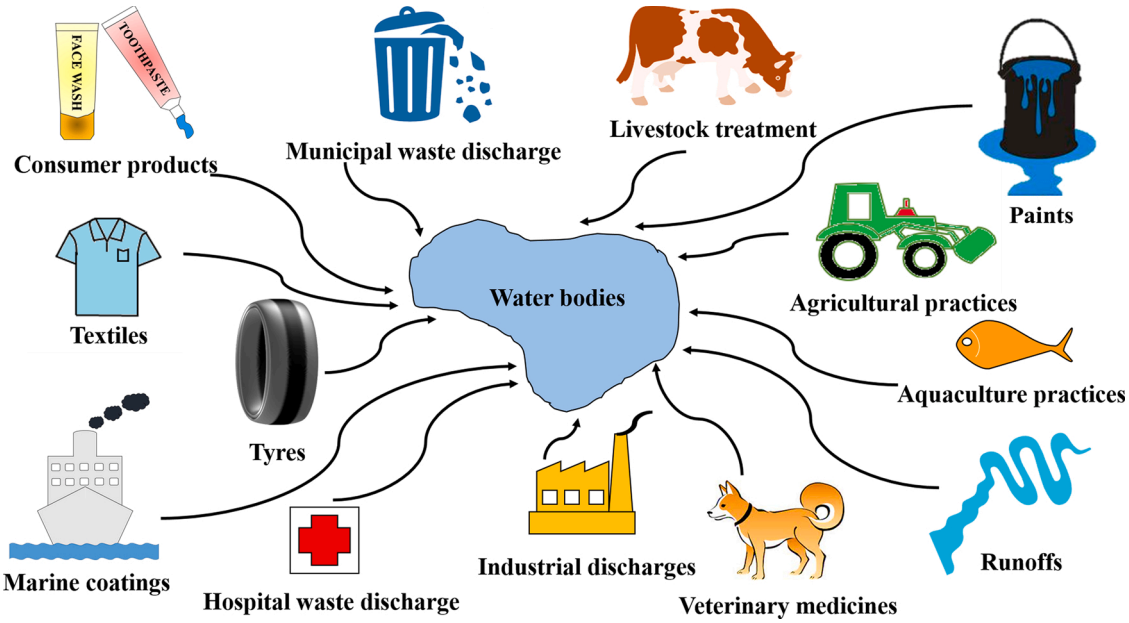

Fig. 1. Release of MNPs, pharmaceuticals, and nanomaterials into the waterbodies indicating aquatic pollution.

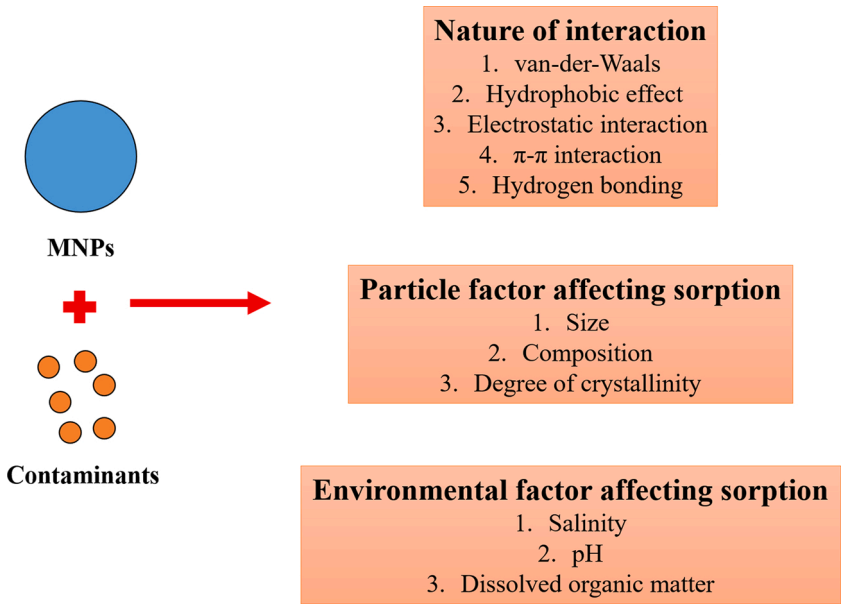

Fig. 2. Nature of interaction between MNPs and contaminants as well as the factors affecting the sorption process.

non-electrostatic interactions such as π–π interaction can also contribute to the adsorption of nanomaterials onto MNPs (Li et al., 2020b).

3. Factors affecting the sorption phenomenon

Although MNPs are assumed to be relatively inert, the sorption kinetics of NM/PC can be altered by factors involving the particle, i.e. MNPs (size, composition, and degree of crystallinity) and environment (salinity, pH, and dissolved organic matter). The following subsections deal with the factors influencing sorption (Fig. 2) in the aquatic environment.

3.1. Particle (MNPs) factor: particle size, composition, and degree of crystallinity

The sorption of contaminants on MNPs has mainly been associated with physical properties such as the size and composition of MNPs (Ašmonaite et al., 2018). Nanosized plastic particles have a larger surface-area-to-volume-ratio than micron-sized particles that adsorb contaminants (Zhang and Goss, 2020). The reason is that with a decrease in particle size, the number of accessible binding sites for the contaminants increases, which eventually increases the sorption rate. For instance, Lin et al. (2020) reported that the sorption of tetracycline hydrochloride was faster with nylon microplastics of length 1 mm rather than nylon microplastics with 5 and 10 mm length. Likewise, Lee et al. (2019) reported two-fold higher sorption of Au metal ions over smaller-sized PS nanoplastics (50 nm) compared to larger-sized PS nanoplastics (500 nm). Given that the size of MNPs plays a major role in the sorption process, this factor must necessarily be taken into account during the toxicity assessment of a mixture of contaminants in the aquatic environment.

In addition to the size effects, the differences in the polymeric composition and their structures can lead to diverse interactive mechanisms (Guo et al., 2018). Studies suggest that polymers with a rich rubbery domain have high mobility and high accessibility to organic contaminants such as pharmaceuticals (Guo et al., 2012; Liu et al., 2019a). Rubbery plastics such as PE have greater sorption efficiency than glassier plastics such as PS, PVC, and PET. Among different types of MNPs, PE has a rich source of rubbery domains (Hu et al., 2017; Rochman et al., 2013). It was found to exhibit greater affinity to three nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, diclofenac) in comparison to PS and PP microplastics (Elizalde-Velázquez et al., 2020). Nanomaterials, on the other hand, are inorganic and their sorption depends on the structure and the functional groups present in the MNPs. For example, the presence of phenyl group in PS microplastics increased the polarity, that lead to the electrostatic attraction of citrate coated-Ag nanoparticles onto their surface (Li et al., 2020a). Thus, the difference in the sorption onto MNPs does not depend merely on the polymer type, but also on the type of NM/PC under study.

Furthermore, the degree of crystallinity of plastic materials can also affect the sorption of NM/PC on MNPs. Crystallinity is an important property of a polymer as the crystalline region contains well-ordered and compactly structured molecular chains. Thus, based on the arrangement of the polymeric chains, polymers are classified as crystalline, semi-crystalline, and amorphous. The degree of crystallinity ranges from 0 to 90 %, and MNPs possessing a lower degree of crystallinity adsorb more contaminants onto their surface (Velez et al., 2018). In this regard, Li et al. (2020a) reported that the PS microplastics had a very low degree of crystallinity than PP and PE microplastics, and was able to strongly capture the Ag nanoparticles onto their surface. This was due to the amorphous nature of PS containing randomly arranged polymeric chains, which can be readily accessed by the sorbate (Syberg et al., 2015). On the contrary, in the report by Liu et al. (2019b), though the PS microplastics used were crystalline, they did not favour the sorption of ciprofloxacin due to the high energy requirement for the destabilization of the compactly structured molecular chains. Based on the above reports, it could be inferred that the fate of sorption of NM/PC on MNPs also depends on the crystallinity of MNPs.

3.2. Environmental factors: salinity, pH, and dissolved organic matter

An increase in the salinity increases the number of ions in the medium that compete with the cation exchange interactions of NM/PC for the free binding sites on MNPs. The same was observed by Zhang et al. (2020b), wherein the increase in salinity (0.035–35%) decreased the sorption efficiency of norfloxacin and levofloxacin to bind with nano-PS and carboxylated nano-PS. Likewise, Yuan et al. (2020) reported a decrease in the sorption of three-dimensional reduced graphene oxide (3D RGO) to bind with PS microplastics, which was corresponding to the increase in the ionic concentration (0.005, 0.01, 0.05, 0.1, and 0.5 mol/L). Besides, the increase in salinity also promotes the aggregation of MNPs in the medium; thus, making them unfavourable for sorption (Li

et al., 2017). Wan et al. (2019) demonstrated rapid aggregation of nano-PS in a medium containing 10 mM of $MgCl_2$, and this inhibited the sorption of tetracycline on nano-PS. Furthermore, the effect of salinity on the sorption efficiency can also be influenced by the behaviour of adsorbate (pharmaceuticals). Hydrophobic pharmaceuticals have very low water solubility that further decreases with increasing salinity, resulting in greater salting-out and increased sorption onto MNPs. In support of this, Ma et al. (2019) observed salting-out of triclosan that resulted in its increased sorption onto PVC microplastics as the salinity approached from 8.75 % to 35 %. Thus, based on the above discussion, the sorption efficiency under the influence of salinity could depend on the nature and behaviour of both the adsorbent (MNPs) and the adsorbate (NM/PC) under study.

Factors such as the dissociation constant (pK_a) of a pharmaceutical, the zeta potential of MNPs, and pH values of the medium play an important role in the sorption process, among which the change in the solution pH will affect the dissociation of pharmaceuticals and the surface potential of MNPs (Ma et al., 2019). For instance, three pharmaceuticals, namely ibuprofen, naproxen, diclofenac, were noted to have a pK_a value close to 4 and existed in their non-ionized form at pH 2 that resulted in an increased sorption when compared to pH 6.9 and 10 (Elizalde-Velázquez et al., 2020). Besides, the surface potential of MNPs can also change with pH, which can be determined by the point of zero charge (pzc). MNPs have positively charged surfaces below pzc and negatively charged surfaces above pzc. For instance, tetracycline had three pK_a values: 3.30, 7.68, and 9.69, and as the pH went below 4.0, tetracycline existed in the cationic form, and the three microplastics studied were also positively charged. However, at pH greater than 8.0, tetracycline existed in its anionic form, and PS, PP, and PE microplastics were also negatively charged. Thus, the presence of similar charges on tetracycline and microplastics at acidic (lower than 4) and alkaline (greater than 8) pH electrostatically repelled the particles that decreased the sorption process (Xu et al., 2018b). Altogether, the relation between the pK_a of a pharmaceutical, pzc of MNPs, and pH of the medium controls the electrostatic interactions and subsequently affects the sorption process between pharmaceuticals and MNPs. Similarly, in the case of nanomaterials also, pzc of MNPs along with the pH of the medium can control the electrostatic interactions. Yuan et al. (2020) reported that with an increase in the pH from 2 to 6, the sorption capacity of the 3D RGO on PS microplastics increased, and subsequently decreased, when the pH increased from 6 to 10. In the case of metal ions such as Cu^{2+} and Zn^{2+}, the sorption efficiency on PET microplastics increased with an increase in the initial pH value (Wang et al., 2020b). At a pH value of 7, an increase in the number of charged sites on the microplastics lead to the effective sorption of positively charged cations, while at acidic conditions, the presence of H^+ ions in the medium competed with Cu^{2+} and Zn^{2+} cations for the binding sites on the microplastics, which decreased the sorption efficacy. When the pH crosses above 7, the cations interacted with the OH^- ions in the medium and formed hydroxides, resulting in their precipitation. When considering the nanomaterial as a whole instead of their released metal ions, the stability and mobility of the nanomaterial will be significantly increased under alkaline conditions (far from pzc); thus, favouring the sorption process (Qiao et al., 2019). Thus, the sorption of nanomaterials or their metal ions under the influence of pH depends on mechanisms, such as electrostatic affinity and competitive sorption as well as the stability of the nanomaterials.

Dissolved organic matter (DOM) is another important component in water that affects the sorption behaviour of NM/PC. The impact of DOM on the sorption of organic pharmaceuticals on MNPs can involve different mechanisms. In one type, the interaction of organic pharmaceuticals with DOM via hydrophobic interaction or complexation decreases the capture of pharmaceuticals by MNPs. For example, increasing concentrations of fulvic acid significantly reduced the sorption of tetracycline on PS, PE, and PP microplastics (by more than 90 %), indicating the higher affinity of tetracycline to fulvic acid when compared to microplastics (Xu et al., 2018b). In another type of mechanism, DOM could be sorbed over the MNPs first and then interact with the pharmaceutical. In support of this, Zhang et al. (2018) reported that humic acid acted as a bridge between oxytetracycline and aged PS microplastics that promoted the significant sorption of oxytetracycline onto aged PS microplastics. Moreover, the structure of MNPs also plays a decisive role in the interaction with DOM. Humic acid, being hydrophilic, had negligible affinity to PE debris (Wang et al., 2020b), while the aromatic structure of humic acid interacted with PS microplastics containing benzene rings and a large section of condensed domains through π–π conjugation that electrostatically attracted the cationic or zwitterionic form of pharmaceuticals (Chen et al., 2018). Qiao et al. (2019) also reported similar interactions of PS microplastics with DOM that significantly increased the sorption of Cu on PS microplastics within a pH range of 6–8. Also, the presence of amine-containing groups on DOM favours the sorption of metal ions (Cabaniss, 2011). In another study, Tang et al. (2021) reported that fulvic acid formed complexes with metal ions and affected the adsorption of metals onto MNPs. The formation of a small number of bidentate complexes between fulvic acid and Zn^{2+} inhibited the adsorption of Zn^{2+} onto nylon microplastics.

4. Influence on the aquatic species

The vector effect of MNP-mediated transport could be categorized into three types: environmental, organismal, and cellular vector effect. With respect to the environmental vector effect, the adsorption capacity of MNPs serves as an advantage to the aquatic environment as the hetero-agglomerates sediment down as precipitates in the test medium and decreases their bioavailable concentration (Deng et al., 2017). A few bioaccumulation and modelling studies reported that the uptake of microplastics did not contribute substantially to the transfer of sorbed contaminants from the water into the organism (Bakir et al., 2016; Koelmans et al., 2016). This was observed in the work of Zhu et al. (2019), wherein the adsorption of triclosan increased the hydrophobicity of microplastics and resulted in their precipitation in the water column and subsequently reduced the bioavailability and direct toxic effects of triclosan to the marine microalgae, *Skeletonema costatum*. In the study conducted by Ferreira et al. (2016), no significant interaction between microplastics and Au nanoparticles was documented in the test medium, and thus, the toxic effects of Au nanoparticles were not altered significantly when observed in the fish, *Pomatoschistus microps* juveniles. Thus, though MNPs can serve as a toxic substance, they also act as a vector in decreasing the accumulation and toxicity of contaminants to the aquatic biota (Mato et al., 2001). The following sections discuss both the positive and negative influence of MNPs on NM/PC toxicity.

4.1. Effect of MNPs on the NM/PC toxicity to microalgae

In an aquatic ecosystem, primary producers (microalgae) form the basis of the food web and are considered to be the most sensitive taxonomic groups, and hence, have been used by several researchers in the ecotoxicological testing of MNPs and NM/PC (Sjollema et al., 2016). Tables 1 and 2 summarize the toxic effects of mixtures containing MNPs and NM/PC on aquatic organisms. According to Huang et al. (2019), a 24-h exposure to Ag nanoparticles (~10 nm)–sorbed carboxylated PS nanoparticles (~20 nm) synergistically stimulated the toxicity in freshwater microalgae, *Chlamydomonas reinhardtii* and *Ochromonas danica*, irrespective of Ag bioaccumulation, structural property, and physiology of algal species. While testing the hypothesis that stated 'microplastics increase the toxic effects of gold nanoparticles', Davarpanah and Guilhermino (2019) found that the mixtures containing the lowest and intermediate concentrations of Au nanoparticles and microplastics did not induce a significant reduction in the specific growth rate, while the mixtures containing high concentrations of Au nanoparticles and microplastics were toxic and significantly reduced the specific growth rate of marine microalgae, *Tetraselmis chuii*. Another study by Zhu et al. (2020) reported that the adsorption of copper

Table 1
Effect of mixture of MNPs and MN/PC on aquatic organisms. Note: ↑ indicates an increase in toxicity, ↓ indicates a decrease in toxic effects, and = indicates no significant change in toxicity.

Test species	Plastic composition	Size	Test concentration of MNPs	Co-contaminant	Exposure period	Effect of MNPs (↑ or ↓ toxicity)	Major findings	Reference
Danio rerio	PE	10–106 μm	10, 100, or 1000 beads/mL	Radiolabelled silver	96 h	NA	Microplastics had no effect on the uptake or localization of Ag while Ag incubated microplastics significantly decreased uptake and increased the amount of intestinal Ag	(Khan et al., 2015)
Pomatoschistus microps	Fluorescent PE	1–5 μm	0.184 mg/L	Gold nanoparticles	96 h	=	Microplastics insignificantly altered the uptake and toxic effects of low concentration of Au nanoparticles	(Ferreira et al., 2016)
Oncorhynchus mykiss (*in vitro*)	PE	10–106 μm	1000 beads/mL	Radiolabelled silver	3 h	NA	Uptake of the radiolabelled Ag in the anterior/mid intestine region remain unaffected in the presence of microplastics	(Khan et al., 2017)
Daphnia magna	Red fluorescent microspheres	1–5 μm	0.02, and 0.2 mg/L	Gold nanoparticles	21 days	↑ - High mixture concentration↓ - Low mixture concentration	Co-exposure induced greater toxicity in terms of mortality, growth and reproduction	(Pacheco et al., 2018)
Danio rerio (embryo)	Plain and fluorescent PS	50, 200, and 500 nm	0.1 mg/mL	Au ions	24 h	↑	Nanoplastics synergistically aggravated a dose and size-dependent abnormalities, survival, and hatching rate	(Lee et al., 2019)
Chlamydomonas reinhardtii and *Ochromonas danica*	PS	~20 nm	3, and 30 mg C/L	Silver nanoparticles	24 h	↑	Nanoplastics synergistically stimulated the toxicity irrespective of Ag bioaccumulation	(Huang et al., 2019)
Tetraselmis chuii	Fluorescent microplastics	1–5 μm	0.3, 0.9, and 4 mg/L	Gold nanoparticles	96 h	= - Low mixture concentration↑ - High mixture concentration	Co-exposure induced greater toxicity and reduced the average specific growth rate	(Davarpanah and Guilhermino, 2019)
Chlorella sp.	Plain, aminated, and carboxylated PS	6 μm	3, 6, and 9 mg/L	Titanium dioxide nanoparticles	72 h	↑ - Plain and aminated PS microplastics↓ - Carboxylated PS microplastics	Plain and aminated PS microplastics additively stimulated the toxicity and oxidative stress while the carboxylated microplastics antagonistically diminished the same	(Thiagarajan et al., 2019)
Chlorella pyrenoidosa and *Daphnia magna*	Aminated iron oxide doped PS Carboxylated iron oxide doped PS	1 μm	0.09, and 0.19 mg/L 0.45, and 0.47 mg/L	Iron oxide nanoparticles	72 h for algae, and 48 h for daphnids	↑ - Aminated iron oxide doped PS microplastics↓ - Carboxylated iron oxide doped PS microplastics	Toxicity of aminated iron oxide doped PS was greater than carboxylated iron oxide doped PS in both species, particles contributed to the toxicity rather than their dissolved fraction	(Zhang et al., 2020a)
Skeletonema costatum	PVC	1 μm	3, 6, 10, 15, 20, and 30 mg/L	Copper nanoparticles	96 h	↓	Toxicity of copper nanoparticles was reduced in the presence of PVC microplastics	(Zhu et al., 2020)
Dunaliella salina	Plain PS	6 μm	1 mg/L	ZnO nanoparticles (<50 nm), and Bulk ZnO (<5 μm)	72 h	↓	The harmful effects such as toxicity, ROS generation and lipid peroxidation were reduced upon the treatment of bulk ZnO or ZnO nanoparticles with plain PS microplastics.	(Gunasekaran et al., 2020)

Table 2
Effect of mixture of MNPs and pharmaceuticals on aquatic organisms. Note: ↑ indicates an increase in toxicity, ↓ indicates a decrease in toxic effects, and = indicates no significant change in toxicity.

Test species	Plastic composition	Size	Test concentration of MNPs	Co-contaminant	Exposure period	Effect of MNPs (↑ or ↓ toxicity)	Major findings	Reference
Pomatoschistus microps	Red fluorescent PE	1–5 μm	0.184 mg/L	Cefalexin	96 h	↓- 20 °C↑- 25 °C	Presence of microplastics (20 °C) decreased cefalexin toxicity by small extent; and induced neurotoxicity, altered the levels of enzyme activity and post-exposure predatory behaviour at 25 °C	(Fonte et al., 2016)
Tetraselmis chuii	Red fluorescent polymer microspheres	1–5 μm	1.5 mg/L	Procainamide/ doxycycline	96 h	↑	Microplastics favoured the uptake of doxycycline/ procainamide, as well as decreased the growth rate and chlorophyll levels	(Prata et al., 2018)
Mytilus galloprovincialis	PS	110 ± 6.9 nm	0.05 mg/L	Carbamazepine	96 h	↓	Co-exposure downregulated the genes responsible for biotransformation, DNA damage, and cell-tissue repair	(Brandts et al., 2018)
Corbicula fluminea	Red fluorescent polymer microspheres	1–5 μm	0.2, and 0.7 mg/L	Florfenicol	96 h	↑	Co-exposure inhibited the feeding, cholinesterase activity and isocitrate dehydrogenase activity as well as enhanced the MDA levels and anti-oxidant enzyme activity	(Guilhermino et al., 2018)
Misgurnus anguillicaudatus	PVC	< 10 μm	50 mg/L	Venlafaxine and its metabolite	40 days	↑	PVC increased the bioaccumulation, metabolism, distribution, and toxicity of venlafaxine and its metabolite and elevated the levels of MDA and SOD	(Qu et al., 2019)
Skeletonema costatum	PE, PS, and PVC PVC 800	74 μm 1 μm	0.05 g/L	Triclosan	96 h	↓	Antagonistic decrease in toxicity of PVC/PVC800 with triclosan was greater than PE/PS with triclosan, increase in MDA and decrease in SOD levels	(Zhu et al., 2019)
Daphnia magna	PS	1 and 10 μm	0.1 mg/L	Roxithromycin	48 h	↑	Co-exposure altered the oxidative stress and reduced the activities of glutathione peroxidase and glutathione S-transferase	(Zhang et al., 2019b)
Oreochromis niloticus	Green fluorescent PS	0.1 μm	1, 10, and 100 μg/L	Roxithromycin	14 day	↓	Microplastics mitigated roxithromycin-induced neurotoxicity, decreased MDA content and increased SOD activity	(Zhang et al., 2019c)
Tegillarca granosa	PS	500 nm and 30 μm	0.29 mg/L	Sertraline	14 days	↑	Nanosized PS induced immunotoxic effects of sertraline, hampered detoxification and altered the fatty acid and lipid metabolic processes	(Shi et al., 2020)
Chlorella pyrenoidosa	Red fluorescent PS	600 nm	1 mg/L	Ibuprofen	96 h	↓	Nanoplastics reduced the inhibitory effect, bioaccumulation, ROS and MDA levels, also enhanced the degradation of ibuprofen	(Wang et al., 2020a)
Chlorella pyrenoidosa and *Cipangopaludian cathayensis*	Non-functionalized fluorescent PS	700 nm	20 mg/L	Methamphetamine	96 h	↑	Microplastics increased the acute toxicity and oxidative damage of methamphetamine in algae, increased the apoptosis and filtration rate in snails, and also altered the BCF, BMF and bio distribution of methamphetamine	(Qu et al., 2020)
Skeletonema costatum	Amino-modified PS	86.05 nm	20 mg/L 200 mg/L	Tetracycline	24 h	↓ - Amino-modified PS nanoplastics↑ -	Toxicity changes attributed to the surface characteristics (hydrophobicity and	(Feng et al., 2020)

(*continued on next page*)

Table 2 (*continued*)

Test species	Plastic composition	Size	Test concentration of MNPs	Co-contaminant	Exposure period	Effect of MNPs (↑ or ↓ toxicity)	Major findings	Reference
	Negatively charged PS Sulfonic acid-modified PS	79.96 nm 80.05 nm	200 mg/L			Negatively charged PS and sulfonic acid-modified PS nanoplastics	charges) of tetracycline incubated nanoplastics	

nanoparticles over PVC microplastics alleviated the toxic effect of nano-Cu and Cu^{2+} to microalgae, *Skeletonema costatum*. Thiagarajan et al. (2019) studied the impact of differently functionalized PS microplastics (~6 μm) on the toxic effects of TiO_2 nanoparticles on marine microalgae, *Chlorella* sp. The addition of plain and aminated PS microplastics additively stimulated the toxicity of TiO_2 nanoparticles, while carboxylated PS microplastics antagonistically diminished the toxicity of TiO_2 nanoparticles. Similarly, in a recent study reported by Zhang et al. (2020a), the iron-oxide-doped aminated PS microplastics induced greater toxic effects on two freshwater species, *Chlorella pyrenoidosa* and *Daphnia magna*, when compared to iron-oxide-doped carboxylated PS microplastics. The particle as a whole was responsible for exerting toxicity rather than the dissolved Fe ions. Very recently, our research group found that the plain PS microplastics (6 μm) were capable of decreasing the toxic effects of both bulk ZnO and ZnO nanoparticles on marine microalgae, *Dunaliella salina* (Gunasekaran et al., 2020). Under both the light conditions (UV-A and dark), plain PS played a mitigating effect on the toxicity of ZnO particles that was corroborated by the reduced responses in toxicity, ROS production, and lipid peroxidation.

Similar to the nanomaterial interaction with MNPs, pharmaceuticals are also constantly exposed to MNPs, which alters their fate, distribution, and toxicity in the aquatic environment (Table 2). Several authors have investigated the combined toxicity of MNPs and pharmaceuticals on microalgae. Prata et al. (2018) reported that polymeric microspheres (1–5 μm) increased the uptake of doxycycline/procainamide as well as decreased the growth rate and chlorophyll levels in marine microalgae, *Tetraselmis chuii*. Moreover, the concentration of microplastic and doxycycline that induced toxicity to *Tetraselmis chuii* was greater than their environmentally relevant levels in marine water. With the availability of various types of microplastics (PS, PE, PVC, PVC800), Zhu et al. (2019) documented that the co-exposure of PVC/PVC800 with triclosan exhibited a greater decrease in the toxicity of microalgae, *Skeletonema costatum*, when compared to the joint toxicity of PE/PS and triclosan. Moreover, all the co-exposures studied exhibited antagonistic effects on the toxicity. Recently, Feng et al. (2020) suggested that the changes in toxic effects noted in marine microalgae, *Skeletonema costatum*, were attributed to the surface characteristics (hydrophobicity and charges) of the tetracycline-incubated nanoplastics. In the study by Wang et al. (2020a), PS nanoplastics (1 mg/L) reduced the inhibitory effect and bioaccumulation as well as enhanced the degradation of ibuprofen (5–100 mg/L) in the freshwater algae, *Chlorella pyrenoidosa*. Moreover, the presence of nanoplastics did not enantioselectively affect the toxicity, accumulation, and degradation of ibuprofen. In the study conducted by Qu et al. (2020), non-functionalized PS microplastics (700 nm) enantioselectivity induced acute toxicity of methamphetamine by increasing the oxidative damage in green algae, *Chlorella pyrenoidosa*.

The toxicity mechanism of the mixture containing MNPs and NM/PC in microalgae can be summarized as follows and is also depicted in Fig. 3. The binding of MNPs to the cell wall of microalgae damaged the membrane structure that triggered a toxic response (ROS generation) and facilitated the entry of NM/PC into the cells (Bhattacharya et al., 2010; Mao et al., 2018). However, this binding of MNPs on the cellular surface was dependent on their surface charge. The cellular membrane of microalgae is a rich source of carboxyl and phosphate groups, which

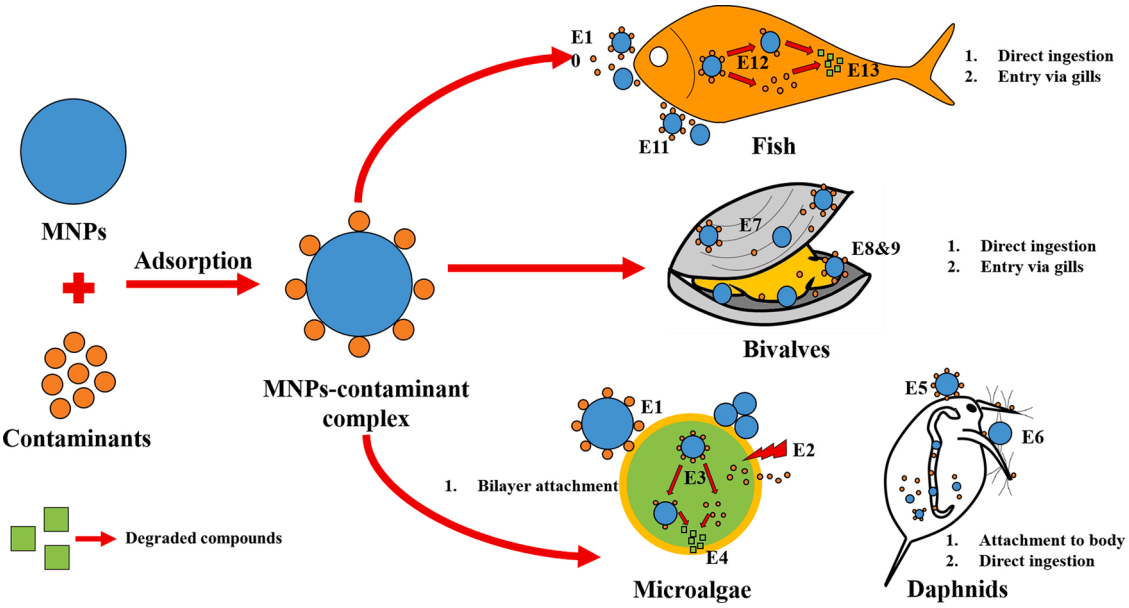

Fig. 3. Overview of the entry of MNPs–contaminant complex into different trophic levels of the species. (E1 indicates the binding of MNPs–contaminant complex to the lipid bilayer of the algal cell membrane; E2 indicates the entry of contaminants through damage induced by MNPs; E3and E12 indicate the desorption of MNPs–contaminant complex into individual products; E4 and E13 indicate the degraded components of the contaminants; E5 indicates the binding of contaminants to the body of the daphnids; E6, E8, and E10 indicate the direct ingestion of the contaminants; E7 indicates the binding to the shell; E9 and E11 indicate the entry of contaminants via gills).

can provide them with a net negative charge (Kim et al., 2006). These negatively charged lipid bilayers on the cellular membrane have a greater affinity to positively charged MNPs that favoured their intake via endocytosis and induced toxicity (Zhang et al., 2020a). On the other hand, the negatively charged MNPs have weaker interaction with the cellular membrane that lessened the toxic effects (Thiagarajan et al., 2019). However, the internalization of MNPs and contaminants following the membrane damage might not be a prerequisite for the reduced growth/toxic effects. Two other proposed mechanisms are as follows. The attachment of MNPs and NM/PC to the cell walls of microalgae restricted the movement of nutrients and energy from the external environment and reduced algal growth (Davarpanah and Guilhermino, 2019). Besides, the toxic metabolites trapped inside the microalgae also affected the normal cellular functioning (Zhang et al., 2017). Finally, the direct physical damages to the cellular membrane by the binding of MNPs generated ROS-mediated oxidative stress in microalgae, which created an imbalance in the antioxidant defence mechanisms (Jeong and Choi, 2019).

4.2. Effect of MNPs on the NM/PC toxicity to daphnids

Daphnia magna is the most commonly used crustacean species for testing of environmental contaminants and is also included as the prerequisite test organism in toxicity testing guidelines such as Organisation for Economic Co-operation and Development (OECD) and International Organization for Standardization (Baun et al., 2008). Co-exposure of Au nanoparticles (~5 nm) and microplastics (1–5 μm) during a 21-day chronic test on *Daphnia magna* produced higher toxicity in terms of mortality, growth, and reproduction when compared to their individual counterparts (Pacheco et al., 2018). This higher toxicity exhibited by the mixture was a result of the concentration-dependent interaction between Au nanoparticles and microplastics. High concentrations of both the contaminants in the mixture (2 mg/L AuNP +0.2 mg/L of MP) produced a synergistic effect. On the other hand, low concentrations of one or both contaminants in the mixture (0.2 mg/L AuNP +0.02 mg/L of MP/ 0.2 mg/L AuNP +0.2 mg/L of MP/ 2 mg/L AuNP +0.02 mg/L of MP) produced antagonistic effect. Based on the integrated biomarker response index, Zhang et al. (2019b) reported that the stress response in *Daphnia magna* was greater for PS microplastics (1 μm) incubated with roxithromycin when compared with roxithromycin alone, 1 μm PS microplastics alone, PS microplastics (10 μm) incubated with roxithromycin, and 10 μm PS microplastics alone. This stress response to the co-exposure increased the activity of SOD and CAT and decreased the activity of MDA, glutathione peroxidase, and glutathione S-transferase in *Daphnia magna*.

Similar to microalgae, the entry and accumulation of the contaminant mixture in daphnids depend on the surface functionalization of the MNPs (Fig. 3). Positively charged MNPs had a greater attraction towards negatively charged daphnids that restricted normal physiology such as swimming, filtering, and feeding. Besides, this could also mean that the toxicity could be induced by the direct physical damage posed by MNPs. On the other hand, negatively charged MNPs exhibited weaker interaction with the body and entered the daphnids through direct ingestion (Zhang et al., 2020a). Upon ingestion, non-aggregated MNPs and NM/PC are retained in the gut of the daphnids and subsequently absorbed through the gastrointestinal epithelia, which later entered the circulatory system and induced toxic effects in various organs and tissues. Besides, the entry of MNPs and NM/PC through the gills of the organism can make breathing and respiration more difficult, resulting in tissue hypoxia and ultimately leading to cell death (Pacheco et al., 2018).

4.3. Effect of MNPs on the NM/PC toxicity to fish

The differential sensitivity of species to chemical contaminants leads back to the view that risk assessment requires the intervention of organisms from several trophic levels (Saaristo et al., 2018). Fishes being a secondary consumer form the base for higher trophic level species in the aquatic ecosystem. However, only a few researchers have reported the uptake and mixture toxicity of MNPs and nanomaterials in aquatic fishes. Khan et al. (2015) were the first ever to document how microplastics influence the uptake and localization of a metal contaminant in an aquatic fish. The co-exposure to radiolabelled silver ^{110m}Ag (1 μg/L) and PE microplastic beads (10, 100, or 1000 beads/mL) did not affect the uptake and localization of Ag in *Danio rerio*, while the exposure to Ag-incubated PE microplastic beads significantly decreased the Ag uptake and increased the proportion of intestinal Ag as well. Similarly, the uptake of radiolabelled silver ^{110m}Ag in the anterior/mid intestine region of rainbow trout, *Oncorhynchus mykiss*, in an *in vitro* experiment was unaffected after a 3-h co-exposure of PE microplastic beads and Ag or Ag-incubated PE microplastic beads (Khan et al., 2017). Lee et al. (2019) reported that PS nanoplastics in the presence of Ag ions synergistically aggravated dose- and size-dependent abnormalities, mortality, hatching rate, and oxidative stress in *Danio rerio* embryos. Through his investigations, Ferreira et al. (2016) reported that the decay of PE microplastics (1–5 μm) in the test medium insignificantly altered the uptake and toxic effects of lower concentrations of Au nanoparticles (~5 nm) in marine fish, *Pomatoschistus microps* juveniles.

To date, only a limited number of reports have demonstrated the toxic impacts of MNPs and pharmaceuticals on aquatic fish. Zhang et al. (2019c) documented that 0.1 μm PS microplastics (1–100 μg/L) facilitated the bioaccumulation of roxithromycin (50 μg/L) in various tissues of red tilapia (*Oreochromis niloticus*) and subsequently mitigated roxithromycin-induced neurotoxicity by altering the oxidative stress response (decrease in MDA content and increase in SOD activity). Fonte et al. (2016) reported that the significant interaction between PE microplastics and cefalexin at 25 °C resulted in a range of effects, such as neurotoxicity, changes in enzyme activity, and post-exposure predatory performance in juveniles of the common goby, *Pomatoschistus microps*; however, at 20 °C, microplastics decreased the toxicity of cefalexin to a relatively lower extent. PVC microplastics (< 10 μm) enhanced the enantiomeric bioaccumulation, metabolism, distribution, and toxicity (MDA and SOD levels) of venlafaxine and its metabolite, O-desmethylvenlafaxine in the loach, *Misgurnus anguillicaudatus* (Qu et al., 2019).

The toxicity mechanism of a mixture of MNPs and NM/PC on fishes are poorly understood (Fig. 3). MNPs help in the localization of nanomaterials in the lipid bilayer, which disrupted the membrane fluidity and provoked a toxic response resulting in cell death (Lee et al., 2019). Oxidative stress was marked by an increase in the levels of reactive oxygen species. The generation of reactive oxygen species induced lipid peroxidation that damaged the tissues surrounding it. Similarly, the co-exposure with MNPs and pharmaceuticals induced the production of reactive oxygen radicals as evidenced by an increase in the levels of MDA and SOD (Qu et al., 2019). The enhanced oxidative stress was overcome by the activation of antioxidant defence mechanisms, such as SOD and CAT (Zhang et al., 2019c). Besides, the production of intracellular ROS and lipid peroxidation activated the apoptotic pathway such as caspase-3, which suggested stronger cellular damage (Qu et al., 2020).

4.4. Effect of MNPs on the NM/PC toxicity to molluscs

MNPs in the presence of NM/PC can settle down as precipitates and present a long-term risk to benthic organisms. Molluscs, being a diverse family among benthos, are a filter feeder that has a high propensity for bioaccumulation (Moreno-González et al., 2016). Such reported bioaccumulation of contaminants in molluscs through MNPs is alarming. Shi et al. (2020) studied co-exposure of sertraline and PS microplastics on the bivalve mollusc, *Tegillarca granosa*, which revealed that the 30-μm PS microplastics produced no impact on the immunotoxicity of sertraline, while the 500-nm PS microplastics induced immunotoxic effects of sertraline, hindered the detoxification of sertraline, and altered

the fatty acid and lipid metabolic processes. In the genotoxic studies conducted by Brandts et al. (2018), the co-exposure of PS nanoplastics (0.05 mg/L) and carbamazepine (6.3 μg/L) in the gills of the Mediterranean mussel, *Mytilus galloprovincialis*, resulted in a significant down-regulation of the genes responsible for biotransformation, DNA damage, and cell-tissue repair. In another study, Guilhermino et al. (2018) demonstrated that the adverse effects induced by the mixtures containing florfenicol (1.8 and 7.1 mg/L) and microplastics (0.2 and 0.7 mg/L) on freshwater bivalve, *Corbicula fluninea,* were diverse and dependent on the concentrations of both the contaminants in the mixture. The adverse effects include inhibition of feeding, cholinesterase activity, and isocitrate dehydrogenase activity as well as enhanced MDA levels and anti-oxidant enzyme activity.

In bivalves, the entry of contaminant-sorbed MNPs occured either by direct ingestion or gill adsorption (Fig. 3). Upon direct ingestion, the complex reached the gut and the contaminant desorbed from the surface of the MNPs, provided the contaminants are either organic (pharmaceuticals such as atorvastatin, amlodipine, etc.) (Liu et al., 2020b) or must undergo dissolution (nanomaterials such as gold, silver, etc.) (Khan et al., 2017). Toxic effects related to the mixtures of MNPs and pharmaceuticals were related to the feeding inhibition (Guilhermino et al., 2018). Feeding inhibition was directly correlated with the enzyme levels such as cholinesterase (ChE) and isocitrate dehydrogenase (IDH). A decrease in the levels of isocitrate dehydrogenase reduced the energy required for feeding, while the inhibition of ChE in the adductor muscle interfered with shell closing and opening, which ultimately inhibited the uptake of food from the surrounding water. Also, the mixture significantly induced the GST activity in the gills and LPO levels in the foot, suggesting oxidative stress. Increasing levels of ROS and MDA have also been reported to have adverse immune effects such as the activation of caspase-3-mediated apoptosis of haemocytes (Shi et al., 2020).

4.5. Critical assessment

A critical assessment of the mixture toxicity of MNPs and NM/PC indicated the predominant use of PS and PE MNPs in toxicity testing. Almost all studies evaluated the acute toxicity of both the individual and mixture contaminants by assessing the toxicological endpoints, such as the growth inhibition, survival rate, reproduction, hatching rate, predatory behaviour, feeding rate, and oxidative stress. In most of the studies, positively charged MNPs were served as a trigger for intensifying the toxic effects caused by NM/PC. On the other hand, few studies have recorded the decreased toxic effects of NM/PC in the presence of negatively charged MNPs, which can be attributed to the concentration, surface functionalization, and fate of MNPs in the medium. The mechanistic pathways involved are complex and not clearly understood. The interaction between MNPs and NM/PC *in vivo* can be completely different from that of the test medium. Moreover, the mechanism of mixture toxicity on aquatic organisms can also be inter-species dependent and can vary based on the accumulation and translocation within the tissues, the capability of the organisms to eliminate NM/PC, and the potential for trophic transfer. Overall, the environmental threats and toxic effects of a mixture of dissimilar contaminants need to be precisely assessed.

5. Artifact effects

5.1. MNPs

Diverse outcomes associated with ecotoxicity testing might be due to modifications in the protocol (dispersion procedure, exposure period, and concentration), differences in MNPs (manufacturer, surface functionalization, and particle size), and inappropriate controls that can result in artifacts (Petersen et al., 2014). Artifacts produce erroneous results, and thus, a proper design of control tests is essential. Several commercially available formulations of MNPs contain preservatives, surfactants, or additives that could introduce artifacts during toxicity evaluation. Pikuda et al. (2018) reported that the acute toxicity of commercial PS nanoplastics on *Daphnia magna* was due to the preservative (sodium azide) rather than the plastics themselves. Likewise, Boyle et al. (2020) demonstrated that the toxic response elicited by PVC microplastics on *Danio rerio* was indirect and governed by the desorption of a chemical additive (lead) from PVC microplastics. Substances that leach from MNPs could absorb onto nanomaterials and alter their properties. In support of this, Li et al. (2020a) revealed the aggregation of Ag nanoparticles with time, possibly due to the leaching of additives from the PS microplastics. Interestingly, colours added as additives to MNPs can alter the toxic effects and sorption of co-contaminants (Antunes et al., 2013; Chen et al., 2020). Moreover, the use of fluorescently labelled MNPs can also be susceptible to introduce artifacts. Schür et al. (2019) demonstrated that the fluorescence observed in the daphnid tissue was a result of the leaching of the fluorescent dye from the plastic particles to the lipid droplets rather than the translocation of microplastics into the tissues. Thus, the use of a fluorescent label as a substitute for particles could produce artifacts, and it would need the confirmation of the stability of labels before their use. Another possible artifact related to the MNPs toxicity assessment is the formation of hetero-aggregates with food souce. Studies involving the chronic toxicity assessment and trophic transfer are usually conducted in the presence of a food source. Any alterations to the feeding habit during the course of the study can affect the toxicity results. During chronic exposure studies, Aljaibachi and Callaghan (2018) reported a decrease in the uptake of microplastics by *Daphnia magna* in the presence of microalgae *Chlorella vulgaris* as a feed, possibly due to the formation of hetero-aggregates between microplastics and microalgae. Likewise, Rist et al. (2017) also reported the formation of aggregates between nanoplastics and microalgae (*Raphidocelis subcapitata*) that increased the feed size as well as decreased the feeding rate and body burdens of nanoplastics in *Daphnia magna*. Hence, a protocol must be developed for adding food during the experiments to prevent such artifacts. In the aquatic environment, MNPs have irregular shapes, whereas particles used in toxicity testing are mostly spherical. Since shape might decide the fate of sorption efficiency, the use of irregularly shaped MNPs must be encouraged to achieve a more realistic effect (Phuong et al., 2016).

5.2. Nanomaterials

Similar to MNPs, nanomaterials are also likely to induce artifacts in the absence of a careful experimental plan. Artifacts might arise from the interaction of nanomaterial with a test reagent/biomolecules, interference with the light absorption or fluorescence, physicochemical alterations in the medium (aggregation, dissolution, and alterations to the surface coatings), and sorption of contaminant to the nanomaterial surface (Oh et al., 2014). The interaction of nanomaterial with a test reagent/biomolecules can introduce artifacts during the following assays: MTT, MTS, neutral red, and lactate dehydrogenase assays (Petersen et al., 2014). For example, Shinohara et al. (2009) reported that fullerenes are capable of inducing lipid peroxidation in the brain of *Cyprinus carpio* if the LPO assay is performed under illumination conditions (600 lx, 30 min). To study the physicochemical alterations, Shen et al. (2015) documented that the occurrence of an uncontrollable and consistent physicochemical transformation of silver nanoparticles in the OECD medium impedes the identification of Ag species that are accountable for the toxicity in *Daphnia magna*. Interactions between nanomaterials and test species could cause unexpected alterations in the test species that might also result in artifacts. Hartmann et al. (2013) reported that TiO_2 nanoparticles were capable of agglomerating algal cells that hindered the measurement of biomass using a hemocytometer as it was difficult to count the number of cells that were in contact to or inside the TiO_2 NP agglomerates.

6. Scope of research, uncertainties, and knowledge gap

This review provides an insight into the interactive effects of MNPs and emerging contaminants (NM/PC), their associated risk, and mechanistic actions in aquatic species. The ability of MNPs to adsorb NM/PC depends on the spatial distribution, size, type, and chemical composition of MNPs. Moreover, the risk assessment of NM/PC-sorbed MNPs in the aquatic environment is complex as it requires knowledge regarding the exposure organism, contaminant concentration, exposure time, and the mechanism of action. Although the systematic understanding regarding the fate and transport of contaminants in the aquatic environment is rising, there still exists uncertainties and knowledge gaps in understanding the exact mechanism of toxic effects of MNPs and co-contaminants. A few of the uncertainties and gaps in mixture toxicity are given below.

Uncertainties

Uncertainties related to mixture toxicity include the following:

- Uncertainty as to which characteristics of the MNPs and NM/PC must be assessed before and during ecotoxicological testing.
- Increased ambiguity arises when as-manufactured MNPs and nanomaterials are used to assess the environmental behaviour and effects.
- Uncertainty when trying to relate dose and species response as techniques used to characterize and quantify mixture contaminants in the test medium require specialized equipment and are time consuming.
- Ambiguity can arise in the route of exposure, mode of action, interactions between mixture components, and exposure period.

Knowledge gaps

- Laboratory experiments which are a common means of toxicity assessment have resulted in the poor understanding of actual toxicity in the real environment.
- The uptake of contaminant-sorbed MNPs may impact the well-being of aquatic species in the long term.
- There is a lack of understanding on the effect of multi-stressors on the mixture toxicity as the aquatic species are also vulnerable to additional stressors such as changes in temperature, nutrient level, and salinity.

Therefore, for an effective and thorough risk assessment, filling the knowledge gap is crucial, and the plans for the same are listed below:

- Use of environmentally relevant concentrations of MNPs and co-contaminants in the toxicity studies to assess the actual level of risk.
- Designing mesocosm and microcosm experiments that offer a chance to assess the toxic effects of the mixture in realistic exposure conditions.
- Designing chronic studies to better understand the long term effects of MNPs/contaminant mixtures on aquatic species.
- Assessing the impact of concurring factors such as pH, temperature, dissolved organic matter, etc., on the mixture toxicity.

CRediT authorship contribution statement

Vignesh Thiagarajan: Investigation, Methodology, Visualization, Formal analysis, Writing - original draft. **Sruthi Ann Alex:** Writing - review & editing. **R. Seenivasan:** Conceptualization, Supervision. **N. Chandrasekaran:** Formal analysis, Resources. **Amitava Mukherjee:** Conceptualization, Methodology, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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