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Review

Resolving the effects of environmental micro- and nanoplastics exposure in biota: A knowledge gap analysis

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ABSTRACT

The pervasive spread of microplastics (MPs) and nanoplastics (NPs) has raised significant concerns on their toxicity in both aquatic and terrestrial environments. These polymer-based materials have implications for plants, wildlife and human health, threatening food chain integrity and ultimate ecosystem resilience. An extensive – and growing – body of literature is available on MP- and NP-associated effects, including in a number of aquatic biota, with as yet limited reports in terrestrial environments. Effects range from no detectable, or very low level, biological effects to more severe outcomes such as (but not limited to) increased mortality rates, altered immune and inflammatory responses, oxidative stress, genetic damage and dysmetabolic changes. A well-established exposure route to MPs and NPs involves ingestion with subsequent incorporation into tissues. MP and NP exposures have also been found to lead to genetic damage, including effects related to mitotic anomalies, or to transmissible damage from sperm cells to their offspring, especially in echinoderms. Effects on the proteome, transcriptome and metabolome warrant ad hoc investigations as these integrated "omics" workflows could provide greater insight into molecular pathways of effect. Given their different physical structures, chemical identity and presumably different modes of action, exposure to different types of MPs and NPs may result in different biological effects in biota, thus comparative investigations of different MPs and NPs are required to ascertain the respective effects. Furthermore, research on MP and NP should also consider their ability to act as vectors for other toxicants, and possible outcomes of exposure may even include effects at the community level, thus requiring investigations in mesocosm models.

1. Introduction

Micro- and nano-plastics (MPs and NPs) are novel environmental contaminants of emerging international interest due to their increasing levels in aquatic and terrestrial environments with demonstrable effects at numerous biological levels. MP and NP pollution is an emerging threat to ecosystem health and integrity as reported in earlier reviews (Ryan et al., 1988; Moore, 2008; Zarfl et al., 2011; Guzzetti et al., 2018). Beyond the biological effects resulting from exposure and uptake of MPs and NPs in the environment, macroscopic plastic debris represents another environmental threat to biota through impacts on increased frequency of suffocation, entanglement, and ingestion, especially in marine wildlife such as birds, sea turtles, marine mammals, invertebrates and fish (Kühn and Franeker, 2020). These effects are often translated into impacts on movement, feeding and reproduction, skin ulcerations and necrosis, and even death (Provencher et al., 2017, 2018; Rezani et al., 2018; de Souza Machado et al., 2018). A growing body of literature in recent years has been devoted to understanding the biological effects of exposure to MP/NPs in biota, including spatial and temporal patterns of exposure and effect (see for example: Alimba and Faggio, 2019; Alimi et al., 2018; Chae and An, 2018, Chae et al., 2019; Foley et al., 2018; Saleem et al., 2018; Wang et al., 2018; Ferreira et al., 2019; Rochman et al., 2019;

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Wu et al., 2019; Barbosa et al., 2020). The present review aims at providing a synthesised update on the reported effects from exposure to MP/NPs in biota, if any, and will outline some knowledge gaps that could inform future research and monitoring priorities.

As a preliminary step, a comprehensive literature review was undertaken to extract relevant manuscripts published in the last 10 years using search terms such as “microplastics” and “nanoplastics” with “toxicity”, “embryo”, “gene”, “growth”, and “oxidative stress”. Databases such as PubMed, Scopus, Google Scholar and Web of Science were queried. That search provided a set of peer-reviewed works that were evaluated against a set of inclusion and exclusion criteria. Studies that reported MP/NP exposure and uptake with effects (or no effect reported) at the molecular to the organismal and community levels (about 8% of the identified studies) were retained for analysis. Studies that did not quantify exposure levels, or doses, or biological effects were not retained for analysis. Further, quality control and quality assurance data in manuscripts needed to include the use of procedural blanks and/or positive controls, duplicates (or triplicates) and industry-recognised chemical analysis procedures for retention and inclusion in our database. Presence and absence of effects were noted, as well as the nature and/or level of reported biological effect, including: impacts on behaviour, mortality and reproduction, molecular-level effects (such as cytotoxicity, biotransformation enzymes, neurotoxicity, hematological changes, oxidative stress, immunity, genotoxicity, metabolic changes) and other organismal-level effects (including physical effects, malformations, etc.). Any biological effects assessment of plastic pollution should include the well-known feeding impairment effect due to obstruction of the digestive tract (Besseling et al., 2014, 2015). However, this review is not aimed at evaluating the effects of macroplastic ingestion, but rather is focused on other MP- and/or NP-associated biological effects, including those molecular initiating events.

As shown in Fig. 1, a steady increase in MP-focused reports up to 2020 is evident while studies on NPs have picked up recently with a greater number of publications in 2019–2020 (It should be noted that the 2020 data are confined to the first six months of the calendar year . An extensive body of evidence was accumulated showing a number of more or less severe effects associated with MP/NP exposures in a number of different biota including aquatic and terrestrial animals, plants, bacteria and cell cultures.

Altogether, the present review aims to outline different MP/NP types, sizes and concentrations tested in the peer-reviewed literature in order to identify differing size-, type- or concentration-dependent toxicities, allowing us to suggest potentially important biological effect pathways among different polymers or different sizes.

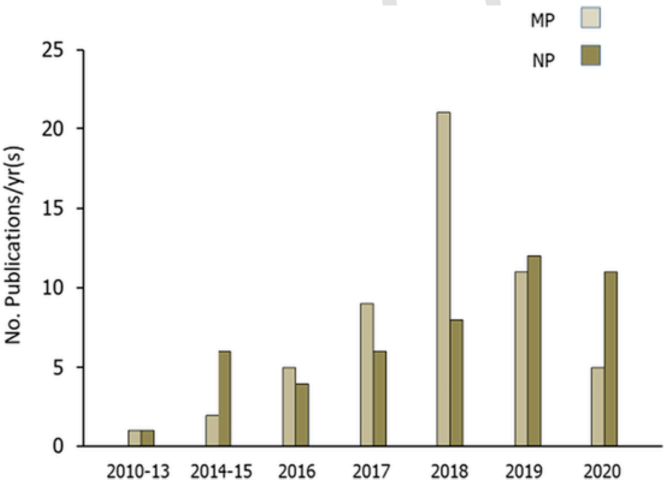

Fig. 1. Annual publications on MP- and NP-induced toxicity data.

2. MP ingestion without relevant adverse effects

From the 94 studies identified and retained for analysis, only 15% (14/94) measured and detected MP ingestion without reporting any major resultant biological effect (Table 1). This was the case in some reports on exposures to either micro-polyethylene (mPE), virgin micro-polyvinylchloride (mPVC), micro-polyethylene terephthalate (mPET), or MP mixtures in fish *Sparus aurata* or sea urchins *Tripneustes gratilla* and *Paracentrotus lividus* which showed microparticle ingestion, yet without any major effects on embryonic development, growth rates or stress (Kaposi et al., 2014; Beiras et al., 2018; Beiras and Tato, 2019; Jovanović et al., 2018).

Other studies on crustaceans were conducted using *Aristeus antennatus*, *Daphnia magna*, *Artemia franciscana*, *Gammarus fossarum*, *Gammarus pulex* and *Macrobrachium nipponense* to test the effects, if any, of MP exposures including mPE, and several other MPs and MP mixtures. The findings confirmed exposure through ingestion of MPs, yet without any major discernable adverse effects (Frydkjær et al., 2017; Straub et al., 2017; Carreras-Colom et al., 2018; Kokalj et al., 2018; Weber et al., 2018; Li et al., 2020a). Similar results were reported in two other studies of MP-associated effects in mussels *Dreissena polymorpha* and *Mytilus galloprovincialis* which, again, failed to show any relevant adverse outcomes (Magni et al., 2018; Gonçalves et al., 2019). Rochman et al. (2017) evaluated the effects of four different MPs in a clam and sturgeon model (*Corbicula fluminea* and *Acipenser transmontanus*, respectively), failing to find pertinent adverse outcomes except for slight bioaccumulation in clams, but a lack thereof in sturgeons. Other fish species were tested for MP-associated effects using several MP types; beyond ingestion and bioaccumulation in lower trophic aquatic biota (i.e. clams), no effects were detected in early life stages or on lipid peroxidation (Jovanović et al., 2018; Rainieri et al., 2018).

Altogether, the negative results summarised in Table 1 suggest that some biota failed to exhibit, or some laboratory bioassays failed to induce detectable MP-associated damage. These lack of effects do not extend to all biota as demonstrated in the studies presented in Table 2.

3. MP-associated adverse effects in biota

The toxicity of various MP/NPs across different organisms, expressed through a number of adverse effects, are summarised in Fig. 2 and Table 2. The top three most commonly observed changes were related to physical effects, oxidative stress and reproduction. Moreover, there is a large amount of literature investigating the toxicity of MP/NPs in aquatic biota, whereas research in terrestrial models (such as humans and rodents) is currently more limited (Fig. 3). This represents a significant knowledge gap considering that MPs are present in terrestrial ecosystems due to accidental loss and poor waste management (de Souza Machado et al., 2018; Dris et al., 2016). Furthermore, the toxic effects of PS are more commonly explored with significantly less attention paid to other MPs/NPs. This clearly indicates the need for further targeted investigations based on polymer type as there is a broad variety of plastic particles present in the environment, including PE, PET, PVC and PMMA.

It has been reported that exposures to MPs can lead to altered behaviour and subsequent impacts on survivorship and mortality rates. For example, a recent report by Mak et al. (2019) found that zebrafish, *Danio rerio*, exposed to mPE, underwent altered gene expression (cyp1a and vtg1) and abnormal behaviour. Further, Lei et al. (2018) provided evidence of MP-associated toxicity in *D. rerio* and in a nematode (*Caenorhabditis elegans*) exposed to five different MPs. In their study, changes in development, heart rate, swimming activity, body length and reproduction were pronounced (Lei et al., 2018). Ex-

Table 1
Reports finding limited effects, as ingestion or bioaccumulation, following microplastic exposures, without further organismal or molecular effects.

Authors	Test Species	Plastic Type (Concentration)	Evaluated and detected effects
Beiras and Tato (2019)	*Paracentrotus lividus* (echinoderm)	PE (1 to 10 mg/L)	No acute toxicity - MP is no vector of a hydrophobic organic compound
Beiras et al. (2018)	*Brachionus plicatilis* (rotifer)	PE (0.01 to 10 mg/L)	No acute toxicity at early life stages
	Tigriopus fulvus (crustacean)	PE (0.01 to 10 mg/L)	No acute toxicity at early life stages
	Acartia clausi (crustacean)	PE (1 to 30 mg/L)	No acute toxicity at early life stages
	Mytilus galloprovincialis (mollusc)	PE (20 to 100 mg/L)	No acute toxicity at early life stages
	Oryzias melastigma (fish)	PE (1 to 10 mg)	No acute toxicity at early life stages
Carreras-Colom et al. (2018)	*Aristeus antennatus* (crustacean)	MP mixture	Spatial occurrence of MP; MP ingestion
Chen et al. (2017)	*Danio rerio* (fish)	PS (1 mg/L)	Decreased larval locomotor activity; oxidative stress; decreased body length;
Frydkjær et al. (2017)	*Daphnia magna* (crustacean)	PE (0.01 to 5 g/L)	PE as a vector for hydrophobic organic compounds; morphology affects egestion
Gambardella et al. (2018)	*Vibrio anguillarum* (bacterium)	PS (0.001 to 10 mg/L)	Decreased culturability
Gonçalves et al. (2019)	*Mytilus galloprovincialis*	PS (10 to 1000 μspheres/mL)	Decreased MP filtration; infiltration in the digestive tract
Jovanović et al. (2018)	*Sparus aurata* (fish)	PVC; PA; PS; PE (0.1 g/kg body mass)	Accumulation in blood, gut, liver, muscles
Kokalj et al. (2018)	*Daphnia magna*	PE (two facial cleansers, a plastic bag, PE textile fleece) 100 mg/L	Uptake and tissue distribution; feeding behaviour
	Artemia franciscana (crustacean)	PE (two facial cleansers, a plastic bag, PE textile fleece) 100 mg/L	Uptake and tissue distribution; feeding behaviour
Le Bihanic et al. (2020)	*Oryzias melastigma* (fish)	PE (1 to 10 mg/L)	No effect on embryonic development, unless combined with benzo(*a*)pyrene or benzophenone-3
Magni et al. (2018)	*Dreissena polymorpha* (mollusc)	PS (5×10^5 to 2×10^6 μspheres/mL)	MP uptake; cell stress, oxidative damage, genetic damage
Rainieri et al. (2018)	*Danio rerio*	low density PE (2% to 4% of feed)	Affected organ homeostasis (liver, gut, muscle, brain)
Rochman et al. (2017)	*Acipenser transmontanus* (fish)	PET, PE, PVC, PS (0.2 g/mL)	Bioaccumulation; trophic transfer; affected endocrine function; tissue morphology
Santana et al. (2018)	*Perna perna* (mollusc)	PVC (0.125 g/L)	Ingestion of MP, effect on metabolism; feeding activity

Abbreviations: PS: polystyrene; PE: polyethylene; PET: polyethylene terephthalate; PVC: polyvinylchloride; MP: microplastic.

posure to virgin and aged MPs was also found to affect behaviour in *Sparus aurata*, with fish more active during feeding and bolder in their interactions with other individuals (Rios-Fustera et al., 2021). In contrast, exposure of European bass *Dicentrarchus labrax* over 90 days to mPVC (<300 μm) added to feed at concentrations of 0.1% *w*/w was not found to result in altered behaviour although caused significant histopathological alterations in the distal intestine which could with time affect feeding patterns (Pedà et al., 2016).

Studies in echinoderms (e.g. sea urchin bioassays) reported similar developmental toxicity in several MP types, including mPE, mPS and mPVC, and their leachates. In some instances, these leachates displayed more severe effects compared to mPS alone such as in *Paracentrotus lividus* (Martínez-Gómez et al., 2017; Oliviero et al., 2019) and in the mussel *Perna perna* (Gandara e Silva et al., 2016), whereas the opposite effect was detected in *Lytechinus variegatus* by Nobre et al. (2015). Other research teams documented decreased larval size in mPS-exposed *P. lividus* larvae, along with growth inhibition or developmental defects in other tested aquatic biota (ascidians, insects, corals, bacteria, microalgae, and rotifers) (Chapron et al., 2018; Messinetti et al., 2018; Gambardella et al., 2018; Mouchi et al., 2019; Natarajan et al., 2020; Parenti et al., 2020). In a recent study, urchin *Sphaerechinus granularis* displayed significantly increased developmental defects in pluteus larvae either exposed during embryogenesis or in the offspring of mPS and mPMMA-exposed sperm (Trifuoggi et al., 2019). Additionally, cytogenetic anomalies and mitotoxicity were also observed in *S. granularis* embryos exposed to these MPs (Trifuoggi et al., 2019).

These types of physical effects (including developmental defects) were not constrained to echinoderm models, but were also detected in crustacean *D. magna* where growth inhibition was prominent (Martins and Guilhermino, 2018). In their study, Martins and Guilhermino made the remarkable discovery that exposure to these microplastic polymers not only affected parental mortality and growth inhibition, but these effects were even detectable across four generations of offspring, suggesting transmissible damage to the offspring as similarly observed in echinoderms. Growth inhibition was also commonly reported in crustacean models (*Artemia parthenogenetica* and *Eriocheir sinensis*) along with other related developmental effects such as abnormal ultrastructures of intestinal epithelial cells and increased number of mitochondria and autophagosomes (Wang et al., 2019; Yu et al., 2018).

Table 2
Studies reporting microplastic and nanoplastic-associated adverse effects in biota.

Authors	Test species	Plastic type (concentration)	Evaluated and detected effects
Ašmonaite et al. (2018)	*Oncorhynchus mykiss* (fish)	mPS (500–700 particles/fish/day; 226–2411 particles/fish/day)	Hepatic stress (oxidative stress; endocrine regulation and detoxification)
Auclair et al. (2020)	*Hydra attenuata* (cnidarian)	nPS (1.25 to 80 mg/L)	Morphological changes; bioaccumulation; oxidative stress; viscosity changes
Balbi et al. (2017)	*Mytilus galloprovincialis* (mollusc)	n(NH_2-PS) (0.001 to 20 mg/L)	Affected embryonic development; gene expression; antioxidant defense; autophagy; immune response
Batel et al. (2018)	*Danio rerio* (fish)	mPE (1.2 to 5×10^6 μspheres/L)	Accumulation; BaP transfer from MP to tissues; EROD activity; embryo morphology
Bergami et al. (2016)	*Artemia franciscana* (crustacean)	nPS (5 to 10 mg/L) (COOH- and NH_2-PS)	Increased mortality; uptake and adsorption; feeding behaviour; motility
Bergami et al. (2017)	*Dunaliella tertiolecta* (algae) *Artemia franciscana*	n(COOH- and NH_2-PS) (0.5 to 50 mg/L)	Growth inhibition; mortality; gene modulation growth inhibition; mortality
Bergami et al. (2019)	*Sterechinus neumayeri* (echinoderm)	n(COOH- and NH_2-PS) (1 to 5 mg/L)	Affected cell morphology; gene expression; oxidative stress; apoptosis
Brandts et al. (2018)	*Dicentrarchus labrax* (fish)	nPMMA (0.02 to 20 mg/L)	Affected gene expression of targets related to lipid metabolism, immune system, liver cell stress
Brun et al. (2019)	*Danio rerio*	nPS (2 to 100 mg/L)	Affected cortisol levels; glucose metabolism; swimming behaviour
Canesi et al. (2015, 2016)	*Mytilus galloprovincialis*	nNH_2-PS (1 to 50 mg/L)	Cytotoxicity; cell functional parameters
Chen et al. (2017)	*Danio rerio*	nPS (1 mg/L)	Affected larval locomotor activity; oxidative stress; body length
Della Torre et al. (2014)	*Paracentrotus lividus* (echinoderm)	n(COOH-PS) (25 mg/L) n(NH_2-PS) (3 mg/L)	Embryotoxicity; decreased cell viability; altered gene expression
Deng et al. (2017)	*Mus musculus* (rodent)	mPS (0.05 to 0.5 mg/day)	Oxidative stress; neurotoxic response; altered energy metabolism
Ding et al. (2020)	*Oreochromis niloticus* (fish)	nPS (100 to 10,000 mg/L)	Oxidative stress; CYP enzymes; neurotoxicity; metabolomics changes
	Oreochromis niloticus	mPS (100 to 10,000 mg/L)	Oxidative stress; CYP enzymes; neurotoxicity; metabolomics changes
Duan et al. (2020)	*Danio rerio*	mPS (250 items μ-PS/50 mL)	Embryotoxicity; oxidative stress
	Danio rerio	nPS (2×10^4 items μ-PS/50 mL)	Affected embryonic development; oxidative stress
Elizalde-Velázquez et al. (2020)	*Pimephales promelas*	nPS (intraperitoneal injection or ingestion)	Downregulating ncf, mst1, and c3 gene expression in liver and kidney
Espinosa et al. (2019)	*Sparus aurata* (fish)	mPVC (100 to 500 mg/kg feed)	Decreased growth and immune activity; stress-related gene expression
Gandara e Silva et al. (2016)	*Perna perna* (mollusc)	mPP (0.5 to 2 mL pellets)	Impaired development
González-Fernández et al. (2018)	*Crassostrea gigas* (mollusc)	n(COOH-PS); n(NH_2-PS) (0.1 to 100 mg/L)	Decreased sperm motility; oxidative stress
Granby et al. (2018)	*Dicentrarchus labrax* (fish)	mPE (2% of feed)	Decreased growth; altered gene expression in the liver
Greven et al. (2016)	*Pimephales promelas* (fish)	nPC; nPS (0.025 to 0.2 mg/L)	Altered stress response of immune system; neutrophil function
Jeong et al. (2016)	*Brachionus koreanus* (rotifer)	mPS (0.1 to 20 mg/L)	Reproductive toxicity; altered growth rate, lifespan, body size; oxidative stress
Jeong et al. (2017)	*Paracyclopina nana* (crustacean)	mPS; nPS (0.1 to 20 mg/L)	Ingestion; egestion; oxidative stress; altered development and fecundity
Jeong et al. (2018)	*Brachionus koreanus*	nPS (0.1 to 20 mg/L)	Oxidative stress; altered xenobiotic resistance, growth and reproduction
Jin et al. (2018)	*Danio rerio*	mPS (0.1 to 1 mg/L)	Gut histopathology; effects on gut microbiota; gene expression
Jin et al. (2019)	*Mus musculus*	mPS (0.1 to 1 mg/L)	Gut barrier dysfunction; bile acids metabolism disorder; gene expression & protein levels
Kaposi et al. (2014)	*Tripneustes gratilla* (echinoderm)	mPE (1000 to 300,000 MP/L)	Impaired larval growth and survival; MP retention
Karami et al. (2016)	*Clarias gariepinus* (fish)	mPE (0.05 to 0.5 mg/L) (LD-PE and phenanthrene-loaded PE)	tissue changes; glycogen stores; blood biochemistry changes
Kim et al. (2019)	*Caenorhabditis elegans* (nematode)	nPS (1 to 10 μg/L)	Altered locomotion; reproduction; oxidative stress

Authors	Test species	Plastic type (concentration)	Evaluated and detected effects
Lee et al. (2019)	*Danio rerio*	nPS (100 mg/L)	Impaired embryo survival, hatching, development, increased Au ion toxicity
Lei et al. (2018)	*Caenorhabditis elegans*	m(PA, PE, PP, PVC, PS) (0.05 to 100 mg/L)	Decreased body length; reproduction; gut calcium levels; oxidative stress
	Danio rerio	m(PA, PE, PP, PVC, PS) (0.001 to 10 mg/L)	Survival; morphological changes; histopathological changes
LeMoine et al. (2018)	*Danio rerio*	mPE (5 to 20 mg/L)	Decreased growth; hatching and oxygen consumption rates
Li et al. (2020b)	*Corbicula fluminea* (mollusc)	nPS (0.1 to 5 mg/L)	Oxidative stress and damage
Liu et al. (2019a, 2019b)	*Daphnia pulex*	nPS (0.1 to 400 mg/L)	Oxidative stress; heat shock proteins
Liu et al. (2019a, 2019b)	*Scenedesmus obliquus* (alga)	n(COOH-PS); n(NH$_2$-PS) (0.001 to 1 mg/L)	Growth inhibition; oxidative stress; mitochondrial dysfunction
Liu et al. (2020a, 2020b)	*Daphnia pulex*	nPS (0.1 to 2 mg/L)	Oxidative stress
Lu et al. (2016)	*Danio rerio*	mPS (0.02 to 20 mg/L)	Oxidative stress; metabolomics change
Luo et al. (2019a, 2019b)	*Mus musculus*	mPS (0.1 to 1000 mg/L)	Maternal exposure in gestation; altered offspring metabolic parameters
Magara et al. (2018)	*Mytilus edulis*	mPE (10^{5} to 10^{6} μspheres/L)	Oxidative stress & response in gills and digestive glands
Mak et al. (2019)	*Danio rerio*	mPE (11 to 1100 μspheres/L)	Behavioural changes; neurotoxicity; changes in gene expression in liver, gut and gills
Malafaia et al. (2020)	*Danio rerio*	mPE (6.2 to 100 mg/L)	Mortality; impaired hatching success; morphological changes; neurotoxicity
Mao et al. (2018)	*Chlorella pyrenoidosa* (alga)	mPS (10 to 100 mg/L)	Impaired growth; photosynthetic activity; oxidative stress
Marques-Santos et al. (2018)	*Paracentrotus lividus*	nNH$_2$-PS (1 to 25 mg/L)	Protein corona formation; loss of viability; DNA damage; affected multi-xenobiotic resistance
Martins and Guilhermino (2018)	*Daphnia magna*	pristine polymer (0.1 mg/L)	Transmissible offspring damage; altered reproductive parameters
Mattsson et al. (2017)	*Scenedesmus sp.* (alga) *Daphnia magna* *Carassius carassius* *Ciona robusta* *Paracentrotus lividus*	mPS and nPS (0.05 to 0.15 mg/L)	Transfer of MP/NP through the food chain; neurotoxicity; behaviour alterations; embryotoxicity
Nasser and Lynch (2016)	*Daphnia magna*	n(COOH-PS); n(NH$_2$-PS) (0.01 to 1 mg/L)	Interaction of NP with biomolecules; altered feeding behaviour
Nobre et al. (2015)	*Lytechinus variegatus* (echinoderm)	mPE; MP leachate (2 to 200 mL pellets)	Embryotoxicity
Oliviero et al. (2019)	*Paracentrotus lividus*	mPVC (0.3 to 30 mg/L)	Embryotoxicity
Parenti et al. (2019)	*Danio rerio*	nPS (1 mg/L)	Oxidative stress; protein carbonylation; altered swimming behaviour;
Parenti et al. (2020)	*Bombyx mori*	0.5 μm nPS	Accumulation in larval midgut, malpighian tubules and hemocytes
Park et al. (2020)	*Mus musculus*	mPE (0.125 to 2 mg/day/mouse)	Changed body weight; hematological and immune response; reproduction in pups: growth rate; body weight; hematological changes
Paul-Pont et al. (2016)	*Mytilus galloprovincialis*	mPS (32 μg/L)	Oxidative stress; altered gene expression
Pinsino et al. (2017)	*Paracentrotus lividus*	nNH$_2$-PS (3 to 4 mg/L)	Embryotoxicity; oxidative stress; altered gene expression
Pitt et al. (2018a, 2018b)	*Danio rerio*	nPS (10% of food by mass)	Oxidative stress; parental transfer
Poma et al. (2019)	Human Fibroblast Line Hs27	nPS (5 to 75 mg/L)	Oxidative stress; DNA damage;
Qi et al. (2018)	*Triticum aestivum* (wheat)	mPE (1% in soil)	Decreased wheat development, plant biomass and chlorophyll content
Qiu et al. (2020)	*Caenorhabditis elegans*	nPS (1 to 1000 μg/L)	Decreased lifespan; altered locomotion behaviour; oxidative stress
Qu et al. (2018)	*Caenorhabditis elegans*	nPS (0.1 to 10 μg/L)	Gut barrier function; oxidative stress
Ribeiro et al. (2017)	*Scrobicularia plana* (mollusc)	mPS (1 mg/L)	Oxidative stress and response; neurotoxicity; DNA damage
Rist et al. (2019)	*Mytilus galloprovincialis*	mPS and nPS (0.7 to 1.4 mg/L)	Ingestion, larval development

Authors	Test species	Plastic type (concentration)	Evaluated and detected effects
Rochman et al. (2017)	*Corbicula fluminea* (mollusc)	m(PET; PE; PVC; PS) + PCB (200 g/L)	Bioaccumulation among polymers; trophic transfer; protein expression for metabolism, endocrine function
Rubio et al. (2020)	3 human leukocytic cell lines	50 nm nPS	Cytotoxicity; oxidative stress; genotoxicity
Sarasamma et al. (2020)	*Danio rerio*	nPS (0.5 to 5 mg/L)	Neurobehavioral alterations; tissue accumulation; oxidative stress
Sendra et al. (2019)	*Phaeodactylum tricornutum* (alga)	nPS (0.1 to 50 mg/L)	Decreased growth population; oxidative stress; mitochondrial dysfunction; DNA damage
Straub et al. (2017)	*Gammarus fossarum* (crustacean)	m(PHB and PMMA) (10 to 100,000 μspheres/animal)	Ingestion and egestion; feeding rate; decreased growth
Sun et al. (2018)	*Halomonas alkaliphila* (bacterium)	nPS (20 to 320 mg/L)	Growth inhibition; oxidative stress
Sussarellu et al. (2016)	*Crassostrea gigas*	mPS (0.023 mg/L)	Offspring development; hemocytological parameters; feeding behaviour/energy uptake
Tallec et al. (2018)	*Crassostrea gigas*	nPS; nPS-COOH; nPS-NH_2 (0.1 to 25 mg/L)	Altered fertilisation, embryogenesis, metamorphosis
Thomas et al. (2020)	*Paracentrotus lividus*	mPS; mPMMA; MP leachate (0.1 to 10 mg/L)	Spermiotoxicity; offspring quality following sperm exposure; ingestion
Trifuoggi et al. (2019)	*Sphaerechinus granularis* (echinoderm)	mPS; mPMMA (0.1 to 50 mg/L)	Embryotoxicity; offspring quality following sperm exposure; cytogenetic damage and genotoxicity
van Weert et al. (2019)	*Myriophyllum spicatum* (plants) *Elodea sp*	nPS; mPS (0.1 to 10% sediment dry weight)	Changes in root and shoot dry weight; relative growth rate; shoot:root ratio
Varó et al. (2019)	*Artemia franciscana*	nPS (0.1 to 10 mg/L)	Ingestion/filtration; larval survival, development; oxidative stress
Wan et al. (2019)	*Danio rerio*	mPS (0.1 to 1 mg/L)	Abundance/diversity of microbiome; inflammatory and neurotoxic response; oxidative stress
Wang et al. (2019)	*Artemia franciscana*	mPS (1 to 10,000 μspheres/mL)	Ingestion, bioaccumulation; survival; decreased development; changes to ultrastructure of digestive tract cells
Wen et al. (2018)	*Symphysodon aequifasciatus* (fish)	mPS (0.05 to 0.5 mg/L)	Decreased growth; oxidative stress; metallothionein content
Xie et al. (2020)	*Mus musculus*	mPS (0.01 to 1 mg/day/animal)	Reproductive toxicity; oxidative stress
Yu et al. (2018)	*Eriocheir sinensis* (crustacean)	mPS (0.04 to 40 mg/L)	Decreased growth rate; increased markers of liver damage; neurotoxicity; oxidative stress
Zhang et al. (2019)	*Daphnia magna*	nPS (10 mg/L) (3 types of PS latex nanoparticles)	Toxicity under varying particle surface modification and solution chemistry parameters
Zhang et al. (2020)	*Daphnia magna*	nPS (1 mg/L)	Changed expression profile of key genes
Zhao et al. (2019)	*Karenia mikimotoi* (alga)	mPVC (5 to 100 mg/L)	Decreased algal growth; chlorophyll content and photosynthetic efficiency
Zheng et al. (2019)	*Mus musculus*	nPS (1 to 30 × 10^{-6} mol/L)	Oxidative stress; response to SOD and deoxyribonucleic acid

Abbreviations: PS: polystyrene; PE: polyethylene; PET: polyethylene terephthalate; PVC: polyvinylchloride; PMMA: polymethyl-metacrylate; PC: polycarbonate; PP: polypropylene; PHB: polyhydroxybutyrate; MP/NP: micro/nanoplastics.

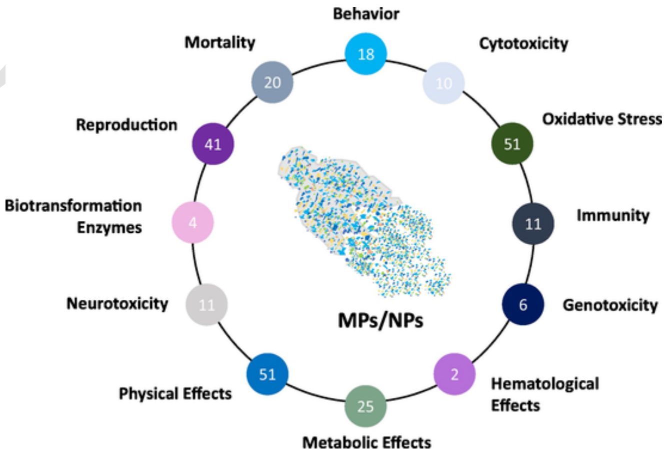

Fig. 2. Summary of MP- and NP-associated adverse effects reported in the available literature. *N* = 94 studies retained for analysis. Sum of endpoint is higher than 94 due to some studies considering more than one possible biological outcome.

Microalgal (*Chlorella pyrenoidosa, Karenia mikimotoi*, *Skeletonema costatum* and *Chlorella vulgaris*) and plant models (*Triticum aestivum* and *Cucumis sativus*) were tested for adverse effects of MPs in a number of studies. Biological effects in plant models included reduced photosynthesis and again, growth inhibition following exposures to mPS, mPE or mPVC (Mao et al., 2018; Zhao et al., 2019; Qi et al., 2018; Zhu et al., 2019; Hazeem et al., 2020; Li et al., 2020c).

Altogether, the data on MP-associated toxicity, obtained in a number of biota, support the hypothesis that exposure to MPs can result in several negative biological outcomes tied to physical development, essential to life and survival.

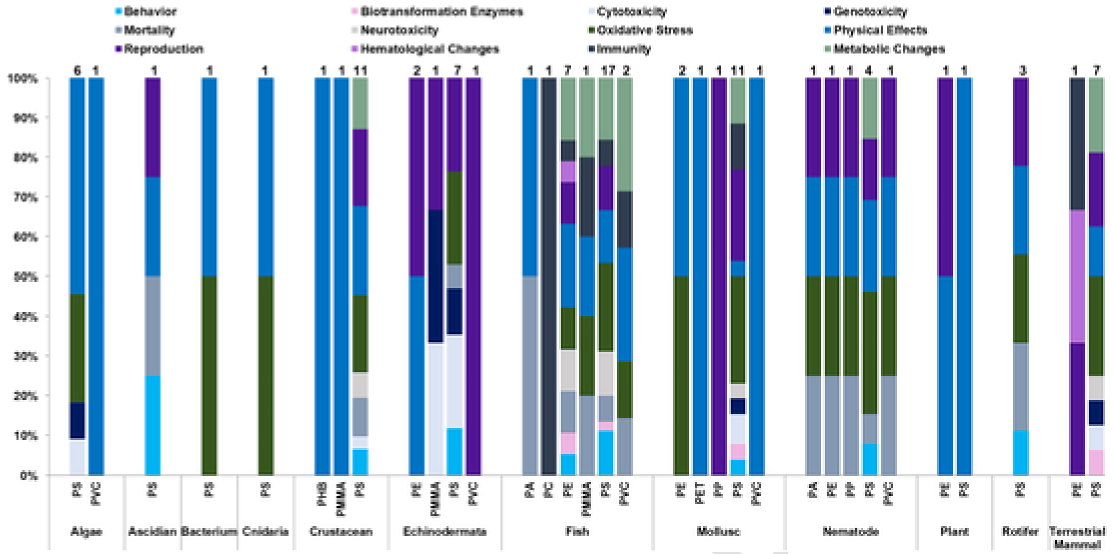

Fig. 3. Toxicity associated with different micro-(MP) and nano-(NP) plastics across different groups of species. The numbers at the top of each bar represents the number of studies that contributed to the observed MP/NP-associated toxicological effect.

4. MP-associated molecular effects

There is a growing body of literature published on the effects of MP exposures in vertebrate models including mouse, fish and other test models as shown in Table 2.

Terrestrial mammals (including mice) exposed to mPS underwent a number of metabolic disorders including altered energy and lipid metabolism, oxidative stress, neurotoxicity, and intestinal barrier dysfunction (Deng et al., 2017; Jin et al., 2018, 2019). Luo et al. (2019a, 2019b) submitted pregnant and lactating mice to mPS exposures, and found transmissible damage in their F1 and F2 offspring in terms of altered metabolic parameters including, for example, alterations in serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL—C) and low-density lipoprotein cholesterol (LDL-C) levels. In zebrafish *D. rerio*, MP-induced gut microbiome dysbiosis affected energy metabolism, glucose metabolism and lipid metabolism (Wan et al., 2019). The same mechanistic pathway of effect could also be true in terrestrial mammals, warranting further investigation.

A series of studies on *D. rerio* provided some important mechanistic information on MP-associated molecular effects (Table 2). These effects included dysmetabolic events such as excess expression of proinflammatory cytokines, glutathione S-transferase, cytochrome P4501A1 induction, and oxidative stress (Jin et al., 2018; Lei et al., 2018; Batel et al., 2018; Wan et al., 2019). Other fish models, including *Clarias gariepinus*, *D. labrax*, *Symphysodon aequifasciatus* and *S. aurata*, were used to test the effects of MP exposures and yielded similar results to those obtained in earlier studies in *D. rerio*, namely increase in proinflammatory markers and oxidative stress response evaluated through the activities of superoxide dismutase and glutathione peroxidase enzymes, as well as the over-expression of a number of dysmetabolic markers (Karami et al., 2016; Espinosa et al., 2019; Granby et al., 2018; Wen et al., 2018; Solomando et al., 2020). In some cases, these effects were explained as the result of MP exposure that could lead to covalent binding with DNA or inhibition of DNA synthesis, contributing to genotoxicity and altered gene expression profiles resulting in altered cell division or DNA replication (Ribeiro et al., 2017). As a result it has been hypothesised that the oxidative stress responses in those cases could be a defense mechanism in response to MP-induced genotoxicity. Other aquatic invertebrate studies in molluscs *Scrobicularia plana* and *Mytilus* spp. corroborated these findings by linking the oxidative stress response to DNA damage and neurotoxicity (Ribeiro et al., 2017; Paul-Pont et al., 2016; Magara et al., 2018). Mao et al. (2018) reported that these findings extended to an algal model (*C. pyrenoidosa*) suggesting that the effects of MP-induced genotoxicity, inflammatory and oxidative stress responses extend beyond the animal kingdom.

The available literature focuses primarily on mPS, with far fewer reports on the other types of MPs (redox homeostasis, particularly for mPS and molluscs, was recently reviewed by Trestrail et al., 2020); by considering the extensive number of different polymer types, much work needs to be done on testing other MP particles.

5. Impacts of NP-exposure on biota

Unlike the literature focused on MP-associated effects, the currently available literature on NP-associated effects is almost confined to nanopolystyrene (nPS), with two exceptions to the best of our knowledge; Brandts et al. (2018) investigated exposure to nPMMA in a *D. labrax*, while Greven et al. (2016) determined the impacts of nano-polycarbonate (nPC) particles in fathead minnow *Pimephales promelas*.

Table 2 also summarises the reported effects induced by NPs in a number of test organisms and cell models, including fish, sea urchins, crustaceans, bivalves, nematodes, plants, diatoms, bacteria, and human cell lines (Poma et al., 2019; Xu et al., 2019; Rubio et al., 2020). In each of the NP-focused studies, biological effects were detected, suggesting that a wide array of organisms are sensitive to NP-exposure to the same polymer types, at similar concentrations [see, for example, Chen et al., 2017; Ding et al., 2020; Duan et al., 2020; Sökmen et al., 2020; Jeong et al., 2017].

nPS-associated toxicity in fish (*D. rerio*) was for example demonstrated through developmental abnormalities and maternal transfer to offspring in a study investigating five different NPs, with biological consequences on heart rate, swimming activity, body length and reproduction (Pitt et al., 2018a, 2018b). Other studies of nPS-induced effects in *D. rerio* found dysmetabolic damage including oxidative stress (superoxide-dismutase and glutathione peroxidase enzymatic activity), disrupted glucose metabolism and cortisol levels, and disturbed membrane function (Brun et al., 2019; Parenti et al., 2019; Liu et al., 2019a, 2019b). Investigations in crustacean *D. pulex* revealed that genes involved in metabolism, growth regulation, ROS metabolism, and sex difference changed after NP exposure (Zhang et al., 2020). Consistently, NPs had significant effects pertaining to development, fecundity, oxidative stress and response compared to larger particle sizes

(MP) of the respective polymers (Jeong et al., 2016, 2018). It was suggested that surface charges (cationic vs. anionic) may lead to different uptake and biodistribution, potentially disrupting these physiological processes (Bergami et al., 2016, 2017). A number of other crustacean studies were conducted to probe NP-induced effects, including *Daphnia* and *Artemia*. Altogether, these studies found NP-induced anomalies in protein and gene expression, oxidative damage, and delayed larval development, similar to what has been observed in MP exposure studies, but often at lower concentrations (Nasser and Lynch, 2016; Bergami et al., 2016, 2017; Zhang et al., 2019, 2020; Liu et al., 2018, 2019a, 2019b; Varó et al., 2019; Kelpsiene et al., 2020). These findings are most likely due to increased distribution of these smaller plastic polymers in the organisms' tissues.

A report by Della Torre et al. (2014) focused on the comparative effects of two nPS (with carboxylate and amine–functionalised surfaces) in the sea urchin *P. lividus*, and found embryotoxicity in larvae exposed to NH_2-PS, but not to COOH-PS, while both nPS preparations induced different changes in gene regulation. Other studies focused on nPS-induced damage in sea urchin *P. lividus*, reporting on a series of dysmetabolic effects including decreased lysosomal membrane stability, modulated protein and gene profile, and affected cellular phagocytosis (Marques-Santos et al., 2018; Pinsino et al., 2017). These functional effects were not only reported in echinoderm models, but were also observed in mollusc *Crassostrea gigas* (González-Fernández et al., 2018).

A set of studies of NP-induced effects in bivalves *Crassostrea* and *Mytilus* resulted in damage to fertilisation, embryogenesis and metamorphosis, and oxidative stress (Canesi et al., 2015, 2016; Balbi et al., 2017; Tallec et al., 2018; González-Fernández et al., 2018; Rist et al., 2019).

Other studies focused on the nematode *C. elegans* and on the rotifer *Brachionus koreanus*; when exposed to nPS, these organisms exhibited oxidative stress and inhibition of multi-drug resistance proteins and dysregulated gene expression (Qu et al., 2018; Jeong et al., 2018). Multiple species representing important links in food chains were tested for mPS and nPS exposure; for example, histopathological changes were noted in *D. rerio* liver after treatment with 5 μm PS particles, including necrosis, infiltration and presence of lipid droplets in hepatocytes, in addition to significant changes to the hepatic metabolome (Lu et al., 2016). Furthermore, lipid accumulation and inflammation were accompanied by oxidative stress, as indicated by increased catalase and superoxide dismutase activity, after exposure to both 70 nm and 5 μm particles. In addition, nPS (30–35 nm hydrodynamic diameters) was found able to penetrate embryo walls in *D. rerio* and accumulate in the yolk sac of hatched juveniles, testifying to increased tissue distribution and impacts deriving from maternal transfer to eggs and/or embryos (Pitt et al., 2018a). Altogether, nPS induced multiple adverse effects in the food chains (Mattsson et al., 2017; Chae and An, 2018), including on lower trophic levels such as in plants, diatoms and bacteria (e.g. *Myriophyllum spicatum* and *Elodea* sp., *Phaeodactylum tricornutum* and *Halomonas alkaliphila*, respectively) where decreased photosynthesis, growth inhibition and induction of oxidative stress were commonly reported (Bhattacharya et al., 2010; van Weert et al., 2019; Sendra et al., 2019; Sun et al., 2018).

6. Knowledge gaps and concluding remarks

The current and growing body of peer-reviewed literature on the effects of MP and NP pollution raises significant environmental concern on a global level. The present review evaluated the multiple outcomes of MP/NP exposures, ranging from a general lack of detectable effects at the organismal level to strong adverse effects ranging from the sub-cellular to the whole organism level. While broad consensus has yet to form on the degree of risk, it is increasingly acknowledged that MP/NPs are materials of concern in the environment and their potential to cause deleterious effects in biota is clearly an issue which should inform environmental policy. Their persistence in the environment and toxicity at environmentally relevant levels are concerning. Nevertheless, it should be recognised that there are still substantial knowledge gaps in the ever growing MP/NP-toxicity field. An important aspect relates to the relative toxicities of the different MPs; this question is more cogently raised for NPs, whose dataset is mostly confined, as yet, to nPS. The imbalance between the number of studies of nPS and those on the broad spectrum of other NPs clearly indicates that much work has yet to be accomplished. Further, gathering such comparative data may help in refining current risk assessment models to establish relative environmental concern when evaluating MP/NP-associated toxicities in the environment (e.g. Lithner et al., 2011). These open questions warrant ad hoc investigations.

Relevant, yet limited information is available concerning MP- and NP-induced effects in plants, agro-ecosystems and algae, which would have important implications for their possible impact on food webs (Ng et al., 2018; Rillig et al., 2019). The bioavailability of plastics for marine plants should be investigated as well as their accumulation in plant cells in the marine environment in order to extend the currently scarce literature (Bhattacharya et al., 2010; Nolte et al., 2017a, 2017b).

The physical shape of MPs encompasses another area of relatively little study but which may be important as an additional driver of toxicity (Jemec et al., 2016). Specifically, most research has focused on MP/NPs that are broadly spherical in shape. However, the degradation of plastics in the environment may produce fibres of various aspect ratios or 'jagged'-edged particles which might not physically or biologically impact in the same way as spherical particles, for example in terms of uptake and accumulation in biota or leaching of chemicals (Choi et al., 2021). Moreover, replacements for traditional plastics such as biodegradable polymers, though catching the public imagination as a means to reduce human impact on the environment, also have not been investigated in sufficient detail, particularly as the polymer degradation products may themselves form MP fragments and particles and become available to biota (Senga Green et al., 2016). In addition, while microparticulate plastics remain the focus of much research, the potential degradation of polymer-based textiles to also release even finer plastic fragments and secondary chemicals such as dyes and plasticisers during use and laundering has received insufficient attention to date (Dalla Fontana et al., 2020; Klein et al., 2021).

MP/NPs have most regularly been investigated in isolation from other contaminants which may be concomitantly present in the environment (Rainieri et al., 2018). Recent studies of mPS as a vector for certain hydrophobic contaminants have shown that interaction between plastic polymers and pollutants such as PCBs for example exhibit complex behaviour in simulated gut fluid of worms and fish (Mohamed Nor and Koelmans, 2019). MPs may also even act as a vector for pathogenic fish bacteria (Viršek et al., 2017). Similarly, nPS showed bioaccumulation in *D. rerio* by modulating Au toxicity (Lee et al., 2019). The relatively scarce knowledge in this area and the enormous potential for synergistic, additive or antagonistic effects of pollutants adsorbed on MPs – and presumably NPs - indicates a relatively unmet need for research to understand the ability of MPs/NPs to act as carriers of harmful substances. In addition, impacts deriving from a range of other multi-stressors concomitantly present including, for example, engineered nanoparticles and abiotic parameters such as temperature, UV intensity etc., which may modulate the physico-chemical behaviour of MP/NPs in the environment and the co-transport of pollutants in organisms, present a significant risk in terms of potential toxicity (Ferreira et al., 2016). However, studies on such aspects remain relatively limited in number.

Another important knowledge gap to consider stems from the fact that the overwhelming majority of literature is based on aquatic biota, in spite of the fact that MP pollution extends to terrestrial locations (see for example Dris et al., 2016) such as landfills. This may be regarded as an under-investigated source of MP and NP contamination (He et al., 2019) and it will be important in the future to verify the impact of MP/NP pollution on terrestrial biota, and by extension on human health, due to potential trophic transfer.

Overall, research on deleterious effects of MP/NPs in biota has focused to a great degree on specific organisms, with relatively few studies taking a broader perspective, for example considering trophic transfer of these materials in simplified food webs. This represents a weak point in current approaches as the significance of negative biological impacts, e.g. oxidative stress, energetic deficiencies affecting growth, or transmissible damage to offspring, in organisms has oftentimes not been translated into a deeper understanding of the wider ecological consequences at community or ecosystem levels. Furthermore, the tests used for probing the biological effects of MPs might themselves not be fit for purpose in every case, and there is inadequate focus on using appropriate controls (Catarino et al., 2019). In terms of widely used biochemical tests, it is clear that they present only one facet of the toxicological profile of MP/NPs, and future research in this area will need to focus greater attention on '-omics' approaches which may uncover deeper or more subtle effects on, for example, the transcriptome. This is further highlighted by the fact that many chemicals that may leach from polymer particles do not give rise to acute toxicity (most common type of test conducted) but rather may have low level, though important, chronic effects such as seen with endocrine disrupting chemicals.

Another important issue is that MP/NPs must be characterised such that their physical properties can be related to the effects they induce in biota. In particular, completing the matrix of particle property versus biological effect may eventually permit read-across, allowing predictions to be made about the potential effects of new MPs based on the properties of similar particles already tested. While progress is being made in this regard, we are still some way from being able to implement the adverse outcome pathway paradigm, relating biological effects at cellular or sub-cellular level to impacts at the whole organism level which become relevant for risk assessment. Of course, it must be borne in mind that there are currently important limitations to the analytical chemistry toolbox in terms of being able to characterise very small polymer particles, with microparticles of diameter ~ 1 μm typically representing the lower limit. Thus, characterising polymer particles with diameters in the nano-scale range, or tracking their transport in biota or uptake in cells and tissues, remains an enormous challenge which still remains to be met.

It is clear that significant strides have been made over the past several years in understanding the potential threat MP/NPs may present, and interest in this area as a topic of research is growing rapidly. Even though there are a number of important aspects outlined herein which have not received sufficient attention to date, and unaddressed would hinder further advances in the area, the increasing body of literature in this field may be viewed as a measure of the scientific community's resolve to answer these questions, ultimately relating materials' physical and chemical properties to an organism's biological response and eventually to broader ecological effects.

Uncited reference

Li et al., 2020

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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