



A metabolomics perspective on the effect of environmental micro and nanoplastics on living organisms: A review

Leilei Zhang^a, Pascual García-Pérez^{a,*}, Barbara Muñoz-Palazon^{b,*},
Alejandro Gonzalez-Martinez^{c,d}, Luigi Lucini^a, Alejandro Rodriguez-Sanchez^{c,d}

^a Department for Sustainable Food Process, Università Cattolica del Sacro Cuore, Piacenza, Italy

^b Department of Ecology and Biology, Tuscia University, Viterbo, Italy

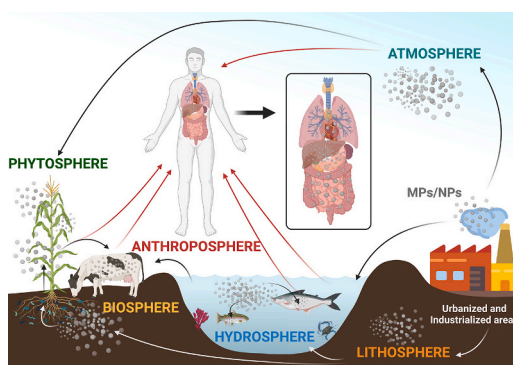
^c Department of Microbiology, Campus Universitario de Fuentenueva s/n, 18071, University of Granada, Spain

^d Institute of Water Research, Calle Ramon y Cajal 4, 18001, University of Granada, Spain

HIGHLIGHTS

- Micro- and nanoplastics (MNPs) are considered relevant environmental contaminants.
- The MNPs spread from industrialized areas reaches all environmental interfaces.
- MNPs-associated pollution finally impacts both the phytosphere and anthrosphere.
- Metabolomics is required to elucidate the real impact of MNPs on living organisms.

GRAPHICAL ABSTRACT



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ABSTRACT

The increasing trend regarding the use of plastics has arisen an exponential concern on the fate of their derived products to the environment. Among these derivatives, microplastics and nanoplastics (MNPs) have been featured for their associated environmental impact due to their low molecular size and high surface area, which has prompted their ubiquitous transference among all environmental interfaces. Due to the heterogenous chemical composition of MNPs, the study of these particles has focused a high number of studies, as a result of the myriad of associated physicochemical properties that contribute to the co-transference of a wide range of contaminants, thus becoming a major challenge for the scientific community. In this sense, both primary and secondary MNPs are well-known to be adscribed to industrial and urbanized areas, from which they are massively released to the environment through a multiscale level, involving the atmosphere, hydrosphere, and lithosphere. Consequently, much research has been conducted on the understanding of the interconnection between those interfaces, that motivate the spread of these contaminants to biological systems, being mostly represented by the biosphere, especially phytosphere and, finally, the anthrosphere. These findings have highlighted the potential hazardous risk for human health through different mechanisms from the environment,

* Corresponding authors.

E-mail addresses: pasgarcia@uvigo.gal (P. García-Pérez), bmp@ugr.es (B. Muñoz-Palazon).

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requiring a much deeper approach to define the real risk of MNPs exposure. As a result, there is a gap of knowledge regarding the environmental impact of MNPs from a high-throughput perspective. In this review, a metabolomics-based overview on the impact of MNPs to all environmental interfaces was proposed, considering this technology a highly valuable tool to decipher the real impact of MNPs on biological systems, thus opening a novel perspective on the study of these contaminants.

1. Introduction

Plastics are synthetic organic polymers characterized by surprising physical and chemical properties. Due to their durability and affordability, they are widely employed in daily human life, either alone or in conjunction with other materials (Dube and Okuthe, 2023). Global plastic production has been exponentially increasing, reaching over 350 million cubic tons in 2021 (Schiavi et al., 2023). Most quantities of plastic production are concentrated in industrialized countries, where approximately 10,000 different types of plastics are employed to manufacture various products, particularly in the clothing and packaging industries. The growth in the manufacture of plastic materials and products implies the growth in the composition of plastic wastes. Around 350 million tonnes of plastic waste have been generated so far and are projected to be doubled by 2040 (Pathak et al., 2023). The recycled percentage remains disappointingly low, close to 12 %, even in plastic products' recycling, reusing, and/or remanufacturing process. In developing countries, it typically ranges from 15 % to 35 %, with even lower rates of 8 % in Asia and 4 % in Africa. The general low recycling rate, combined with the continuous growth in plastic production, contributes to the escalation of final waste streams and the illegal disposal of plastics into the environment, including rivers, oceans, roadways, and lakes (D'ambrières, 2019). This production process contributes to the dispersion of microplastics (MPs) and nanoplastics (NPs) into terrestrial and aquatic environments (White and Winchester, 2023).

Plastics play an extensive role in diverse sectors of the economy, encompassing agriculture, construction, healthcare, and consumer goods, which include the packaging of food items, pharmaceuticals, detergents, and cosmetics (Mihai et al., 2021). In the agricultural sector, plastic deposition in soil results from mulch films, nets, and the application of sewage sludge and composts. Once plastics enter the agricultural ground, they can interact with other soil contaminants, including heavy metals (HMs), persistent organic pollutants (POPs), antibiotics, and various other toxic substances, determining additional detrimental impacts on soil quality, as well as the surrounding flora and fauna (Ansari et al., 2022).

In recent years, the scientific community has expressed increasing concerns regarding releasing MPs ranging from 100 nm to 5 mm in size and NPs, measuring <100 nm, into the environment. These particles are obtained from the breakdown of plastics and can pose risks to ecosystems and all living beings, including humans (Amobonye et al., 2021). NPs are primarily attributed to the plastic harmful potential due to their small particle size, which allows them to enter into living organisms, including plants (Shi et al., 2023a, 2023b). Furthermore, their extensive plastic surface area enhances their potential interactions with environmental pollutants and specific microorganisms, thereby facilitating specific chemical enrichment and a reduction in microbial diversity within the areas directly affected by the presence of plastics (Nath et al., 2023). Despite several studies investigating the effects of small-size NPs on different living organisms, a significant knowledge gap exists concerning the specific mechanisms of action following their exposure, hindering the development of strategies to mitigate their detrimental effects.

Comprehending the mechanisms of action of plastic particles in biological samples is crucial for health risk assessment, and omics approaches, such as metabolomics, can play a fundamental role in achieving this objective. Metabolomics is an analytical technique that can provide a picture of the functional status of an organism. This

approach has been previously used in different fields of research, including ecotoxicology interactions between aquatic organisms and environment (Cappello, 2020), early diagnosis of cancer (Danzi et al., 2023; Wang et al., 2023b), chronic obstructive pulmonary disease (Song et al., 2023), early pregnancy metabolic disorders (Zhu et al., 2023), mechanistic understanding of plant-microbe interactions for plant disease control (Ramlal et al., 2023), relationships between gut microbiome and depression diseases (Refisch et al., 2023), or cattle production (Kaur et al., 2023), among others. In recent years, the potential impact of micro- and nanoplastics (MNPs) on the metabolic processes of living organisms has emerged as an urgent concern across various research and productive sectors, spanning biotechnology, horticulture, and plant science. In this sense, the search "metabolom* AND microplastic* AND nanoplastic*" on Scopus (accessed April 19, 2024) provides only 84 results, all presenting a recent publication date starting from 2020 to 2024. This exponential awakening underscores the importance of characterising the chemical fingerprint associated with MPs on living organisms, as metabolomics constitutes the area of systems biology reflecting the closest phenotype-associated response (García-Pérez et al., 2023). An overview of the most recent metabolomics research conducted on MNPs exposure to different environmental interfaces is provided in Table 1, which will be further described in the subsequent sections. The widespread presence of MNPs in the environment raise concerns about their impact on biological systems, thus prompting the application of metabolomics approaches to comprehensively investigate the effect of MNPs exposure on the biochemical composition of organisms. It is noteworthy that metabolomics is a relatively young technology, which is currently evolving following an exponential growth to provide an integrated profiling of small molecules in biological tissues (García-Pérez et al., 2024). In the case of MNPs-based studies, the scope of metabolomics is devoted to the determination of the abundance of cellular end products, conferring a holistic view of the physiological alterations induced by MNPs exposure. As a result, metabolomics has been considered highly valuable to detect subtle and systemic changes that can undergo to adverse physiological responses in living organisms. On these bases, metabolomics can be considered as a promising technology in achieving the toxicity assessment of MNPs, facilitating the elucidation of the underlying mechanisms of action. However, due to the rapid evolution of metabolomics in the field of MNP research, there is still a lack of consensus on the identification of exposure biomarkers, which is recognized as one of the fundamental advantages of metabolomics workflows (García-Pérez et al., 2024). In this regard, much research is still required to achieve a clear identification of specific biomarkers, considering the heterogeneous record found for organisms, which ranges from either aquatic or terrestrial animal models, to microbiological and plant species. Moreover, in analytical terms, different approaches have been applied in metabolomics workflows with this purpose, expanding the chemical coverage of identified metabolites. This review provides a comprehensive framework of the existing knowledge surrounding the presence of MNPs in different ecosystems, including the hydrosphere, lithosphere, and atmosphere, and the associated risks on the metabolic functions of the biosphere, mainly represented by the phytosphere and anthroposphere, as a function of two paramount physicochemical features of MNPs: molecular composition, particle size, and concentration. This information will prove valuable for guiding future research in MNPs and will contribute to a deeper understanding of the metabolic impact of MNPs on the functional implications of these materials for living

Table 1
Metabolomics overview of the impact of MNPs on different environmental interfaces.

Environment	Organism	MNPs	Concentration	Time	Metabolite up-regulation	Metabolite down-regulation	References
Anthroposphere	Human	PS NPs	1-20 µg/mL	2–28 day	Glycolysis, TCA cycle, and pentose phosphate pathway		Bonanomi et al. (2022)
Anthroposphere	Human CD34+ hematopoietic stem/progenitor cells	PS NPs	0.1–0.6 mg/mL	1 day	Glucose 6-phosphate, dimethylglycine 2,2-dimethyl adipic, linoelaidic, nonanoic, oxoglutaric, octanoic, propionic, ethylmethylacetic and isocaproic acids		Guo et al. (2023)
Anthroposphere	Human bronchial epithelial cells	PS NPs	0-220 µg/mL	12–24 h	ROS, innate immunity pathways		Xuan et al. (2023)
Anthroposphere	Human liver cells	PS NPs	0–0.25 mg/mL	2 day	ROS at mitochondrial levels	Energy production, Arg, Ala, Asp, and Gln metabolisms	Lin et al. (2022)
Anthroposphere	Human lung cells	PS NPs	0–0.125 mg/mL		ROS at mitochondrial levels	Energy production, nicotinate and nicotinamide metabolisms	Lin et al. (2022)
Biosphere	Mouse	PS MPs	0.5 mg/day	60 day	ABC transporters, tropane, piperidine, and pyridine alkaloid biosynthesis, phenylpropanoid biosynthesis, and bile secretion		Chen et al. (2023a)
Biosphere	Mouse	PS NMPs	50 mg/kg	28 days	Adenosine triphosphate	Cytidine, alanine, acetic acid, fumaric acid, glycine, glutamate, xanthine, creatine, leucine, uridine, lactic acid, trimethylamine, adenosine, valine, acetic acid and isoleucine, hypoxanthine, choline, succinic acid, inosine, cysteine and glutamine	(He et al., 2024)
Biosphere	Mouse	PS NMPs	2–5 mg/mL	45 days	mTOR signaling pathway, D-glutamine and D-glutamate metabolism, pancreatic cancer and PPAR signaling pathway, central carbon metabolism in cancer, glycerophospholipid metabolism		(Zha et al., 2024)
Biosphere	Mouse	PS NMPs	10 ⁶ ng/L	18.5 days		GABA, creatine and glucose, and asparagine	(Mercer et al., 2023)
Biosphere	Mouse	PS NMPs	10 mg/L	21 days	Amino acids such as glutamate, aspartate, alanine, glycine, serine, threonine, taurine, and serotonin. Retinal neurotransmission related processes were also dysregulated, including synaptic vesicle cycle, glutamatergic synapse, GABAergic synapse and retrograde endocannabinoid signaling		(Xiong et al., 2024)
Biosphere	Mouse	PS, PTFE, PMMA NMPs	50 µg/mL	3 days	Ethyl hexadecanoate levels, L-lactic acid, PC(24:1 (15Z)/P-16:0), nicotine, PI(20:0/16:0), PC(20:0/14:0), PE (20:0/18:4 (6Z,9Z,12Z,15Z)), 2-Methylpiperidine, PC (18:2(9Z,12Z)/15:0), PC (18:3(6Z,9Z,12Z)/20:2(11Z,14Z)), stearoyl sphingomyelin, SM(s18:0/18:1 (9Z)), PE(20:0/14:1 (9Z))	Amino acids (L-Glutamic acid, Pyroglutamic acid, L-Asparagine, and L-Proline, L-Valine, L-Threonine and L-Glutamine), nervonic acid and myristic acid, SM (d16:1/24:1 (15Z)), PC(20:4 (5Z,8Z,11Z,14Z)/P-18:0), oxypurinol, 1-beta-D-arabinofuranosyluracil	(Xuan et al., 2024)
Biosphere	Mouse	PS NPs	100–1,000,000 ng/L	17.5 day		Biotin, glycolysis/gluconeogenesis	Aghaei et al. (2023)
Biosphere	Mouse	PS NPs	1–10 mg/L	17 day		Steroid, cholesterol, cholesterol transporter APOA4	Chen et al. (2023b)
Biosphere	Mouse	PS NPs	3–15 mg/kg	30 day		Deoxy-erythronic acid, apo-10'-violaxanthin, β-D-glucosamine, oxoadipic acid	Fu et al. (2023)
Biosphere	Mouse	PS NPs	25 mg/kg/day	42 days	Total cholesterol, triglycerides	Phosphatidylcholine	Tang et al. (2023a)
Hydrosphere	<i>Phaeodactylum tricornutum</i>	PS NPs	0.01–10 mg/L	120 h	Mitochondrial damage, ROS	Chlorophyll content	Yao et al. (2023)
Hydrosphere	Fujian oyster	PS NPs	10–10,000 particles/L	14 day	Adenosine, 3-(4-hydroxyphenyl) pyruvate, sorbitol, mannose, unsaturated fatty acids, Pro, Lys		Lu et al. (2023)
Hydrosphere	Marine rotifer	PS NPs	20–2000 µg/L	7 days	Cytidine, uridine monophosphate	Adenine diphosphate ribose, citrulline, Ala, Asp, Glu metabolisms, oxidative phosphorylation, TCA cycle	(Xuan Li et al., 2023)
Hydrosphere	Mussel	PS-MNPs	50 particles/mL	3 days	Amino acids, osmolytes, GSH	Hypotaurine, cetoacetate, succinate, malonate, dimethylglycine, glycine	Cappello et al. (2021)

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Table 1 (continued)

Environment	Organism	MNPs	Concentration	Time	Metabolite up-regulation	Metabolite down-regulation	References
Hydrosphere	<i>Chlorella sorokiniana</i>	PS NPs	3.5–10 mg/L	7 days	Arachidonic acid metabolism and ABC transporters. The arginine and proline metabolic pathway, carbohydrate cycling		(M. Xu et al., 2024b)
Hydrosphere	<i>Chlorella vulgaris</i>	PS NPs	1–10 mg/L	96 h	Fatty acid metabolism, malic acid, nonanoic acid and terephthalic acid. Small-molecule acid (e.g. nonanoic acid, terephthalic acid)	Amino acid metabolism (glutamate, lysine and serine, alanine, aspartate, glutamate, and arginine biosynthesis), and tricarboxylic acid cycle cycle.	(Q. Wang et al., 2023a)
Hydrosphere	Mussel	PS-MNPs	50 particles/mL	3 days	Taurine, betaine, alanine, glutamate, hypotaurine, homarine, glucose, malonate, serotonin, acetoacetate, ATP/ADP and mytilitol	succinate, glycine, and acetylcholine	De Marco et al. (2023)
Hydrosphere	Zebrafish	PS	1–10 mg/L	144 h	Glutathione metabolism, N-acetyl-l-aspartic acid and arachidonic acid biosynthesis	Succinate semialdehyde biosynthesis	(Y. Wang et al., 2023c)
Hydrosphere	Zebrafish	PE	5–200 ppm	24 h	Fatty acids, cholesterol	Acetate, glucose, alanine, leucine, isoleucine, valine, glutamate, glutamine, cysteine, glycine, glutathione, ATP and NADH. Significant increase on the other hand was observed in the levels of lactate, choline, glycerophosphorylcholine and ethanolamine, tryptophan, phenylalanine and tyrosine	(Bashirova et al., 2023a, 2023b)
Hydrosphere	Zebrafish	Mask-derived MNPs	7.8×10^4 – 7.8×10^5 items/L	3 h		Acylcarnitines, amino acid and lipid metabolism. Biosynthesis of N-formylglycine, carnitine, 12-OxoETE, and Prostaglandin F2 α . Biosynthesis of amino acids, such as histidine, alanine, aspartate and glutamate, glycine, serine and threonine.	(Hu et al., 2024)
Hydrosphere	Zebrafish	PS NPs	0–100 μ g/L	30 days		3,4-dihydroxyphenylacetic acid, acetylcholine chloride, 5-hydroxyindoleacetic acid, serotonin, 5-hydroxytryptophan, norepinephrine	Teng et al. (2022a, 2022b)
Hydrosphere	Zebrafish	PS NPs	0–200 mg/L	100 h	Glycerophosphocholine, ethanolamine, cholesterol, choline, Trp, lactate, Phe, tyrosine	Ala, Leu, Ile, Val, Glu, Gln, Cys, Gly, glutathione, acetate, glucose, adenosine triphosphate, nicotinamide dinucleotide	Bashirova et al. (2023a, 2023b)
Hydrosphere	Zebrafish	PS NPs, Hg	10 mg/L	3 days		Ala/Asp/Glu metabolism and Val/Leu/Ile biosynthesis	Wang et al. (2022a)
Hydrosphere	Red drum	PS, PE, and PP MNPs	5 mg/L	7 days	Glycerophospholipid, purine, pyrimidine, and ABC transporters metabolisms. Within glycerophospholipid metabolism pathway, seven long-chain polyunsaturated fatty acids, i.e., PC (18:2(9Z,12Z)/22:6 (4Z,7Z,10Z,13Z,16Z,19Z)), PC(16:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)), PC (22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:0), PC(18:1(11Z)/22:6 (4Z,7Z,10Z,13Z,16Z,19Z)), PC(16:0/20:5(5Z,8Z,11Z,14Z,17Z)), PE(18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)), and PE(P-16:0/22:6)		(Sun et al., 2024)
Hydrosphere	<i>Oreochromis niloticus</i>	PS	100 μ g/L	28 days	Phosphagen and phosphocreatine biosynthetic and metabolic processes	Disrupting retrograde endocannabinoid signaling, linoleic acid metabolism, glycerophospholipid metabolism, and arachidonic acid metabolism	(Zheng et al., 2024)
Hydrosphere	<i>Monopterus albus</i>	PS	0.5–10 mg/L	28 days	ABC transporters, cAMP signaling pathway, neuroactive ligand-receptor interaction, and synaptic vesicle cycle		(Yao et al., 2024)
Hydrosphere	<i>Macquaria novemaculeata</i>	PS	20 μ L	7 days	Hypoxanthine, taurine, butyrate, l-lysine, glycerol, L-histidine, tyrosine, D-glucose, D-galactose, fumaric acid, glutamic acid, D-proline, L-ornithine, L-asparagine and butyrate	L-arginine, carnitine, and uracil	(Afrose et al., 2024)
Hydrosphere	<i>Gobiocypris rarus</i>	PS	1–10 mg/L	14 days	Arginine and proline metabolism, sphingolipid metabolism,		(Chu et al., 2024)

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Table 1 (continued)

Environment	Organism	MNPs	Concentration	Time	Metabolite up-regulation	Metabolite down-regulation	References
Lithosphere	Earthworm gut	PS NPs	1 g/L	14 days	aminobenzoate degradation, histidine metabolism, and primary and secondary bile acid biosynthesis	Ala, betaine, glucose, Ile, Leu, lactate, maltose, myo-inositol	Tang et al. (2023b)
Lithosphere	<i>Bombyx mori</i>	PS NPs	0.25–1.0 µg/mL	22 days	Amino acids, carbohydrates, lipids, nucleotides, vitamins and cofactors, carboxylic acids, and other biomolecules	Nucleosides and their intermediates such as 2'-deoxyguanosine, deoxycytidine, guanosine, L-dihydroorotic acid, ribose 1-phosphate, and urate-3-ribonucleoside	(Muhammad et al., 2024)
Lithosphere	Bacterial consortium	PS NPs	10–100 mg/L	6 days	Lipid metabolism, nucleotide metabolism, membrane transport, and carbohydrate metabolism	Phenylalanine metabolism, arginine and proline metabolism, and cyanoamino acid metabolism	(Zhai et al., 2024)
Lithosphere	Corn	PHBV NPs	0.01–10 % soil mass	56 days	Maltotriose, 6-deoxyglucose, ribose and xylulose		Brown et al. (2023)
Phytosphere	Corn	PS NPs	50 mg/L	15 days	Organic acids biosynthesis and Ala, Asp, and Glu metabolism		Zhang et al. (2022b)
Phytosphere	Corn	PS NPs, PP NPs, Cd	2 % soil mass	42 days	Glu, Ser, phenylpyruvic acid		Zhao et al. (2023a, 2023b)
Phytosphere	Cucumber	PS NPs	50–100 mg/L	21 days	Carbon fixation-related metabolism, pentose phosphate pathway, glyoxylate and glutathione metabolic pathways		Huang et al. (2023)
Phytosphere	Lettuce	PE NPs				Ile, Leu and Ser, benzoic acids, monosaccharides	Zeb et al. (2022)
Phytosphere	Lettuce	PE NPs, Cd	0.1–0.2 %	60 days		Leu, Ser, glyoxylate and dicarboxylate metabolism	Zeb et al. (2022)
Phytosphere	Lettuce	PS NPs	10–50 mg/L	18 days	Ascorbic acid, terpenoids, flavonoids, Ser, glucosylceramide		Wang et al. (2023a)
Phytosphere	Lettuce	PS-NPs	10-100 µg/d	10 day	ROS	β-Ala metabolism, glycerophospholipids, Met, Cys, photosynthetic pigments, purine metabolism	Wang et al. (2022e)
Phytosphere	Lettuce	PS-MNPs, heavy metals	100-1000 mg/kg	60 days	ATP-binding cassette transporters, ROS-mediated cell damage, linoleic acid, phenylpropanoid, pyrimidine and galactose metabolism		Xu et al. (2023)
Phytosphere	Lettuce	PE-MNPs	50–5000 mg/kg	18 days	Phenylpropanoids (cinnamates, ferulates, anthocyanins, and flavonols), alkaloids, and lipids (phospholipids and sterols)	N-containing compounds and phenylpropanoids (quinones, isoflavonoids, coumarins, and stilbenes classes), aliphatic glucosinolates, and serotonin amide compounds, and hormones (gibberellin, abscisic acids)	(Zhang et al., 2024)
Phytosphere	Lettuce	PS-MNPs	1–50 mg/kg	48 days	Styrene degradation, vitamin digestion and absorption, pantothenate and CoA biosynthesis, beta-alanine metabolism, nicotinate and nicotinamide metabolism		(Y. Li et al., 2024b)
Phytosphere	Lettuce	PS-MNPs	100–1000 mg/kg	60 days	Flavonoid biosynthesis, zeatin biosynthesis, circadian rhythm biosynthesis, nicotinate and nicotinamide metabolism, and amino acids biosynthesis		(G. Xu et al., 2024a)
Phytosphere	Spinach	Aged PS NPs	100 mg/L	21 days	ABC transporters, purine and pyrimidine metabolism, ABC transporters, aminoacyl-tRNA biosynthesis, pentose and glucuronate interconversions, valine, leucine and isoleucine biosynthesis, cyanoamino acid metabolism and galactose metabolism.		(Huang et al., 2024)
Phytosphere	<i>Taraxacum officinale</i>	PS MNPs	10 mg/L	14 days	Synthesis and metabolism of sugars, such as D-galactose, L-rhamnose, and D-xylose.	Galactose, fructose, mannose and amino sugar and nucleotide sugar metabolism, D-alanine and CO2 fixation metabolism. Glyoxylate and dicarboxylate metabolism, pyruvate metabolism, amino acid biosynthesis, and pentose phosphate metabolism pathway, dicarboxylate metabolism.	(Xingfan Li et al., 2023)

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organisms.

2. MNPs in the hydrosphere and aquatic organisms

Societies' increasing use of plastics has increased plastic debris accumulation in the aquatic food chain, including fresh and saltwater environments. Marine MNPs are ubiquitous, considering either industrialized areas, such as those found mainly in the Pacific (Isobe and Iwasaki, 2022) and the Atlantic coastlines (Pabortsava and Lampitt, 2020), or areas with a lower human impact, such as the Antarctic (Bessa et al., 2019) and Arctic regions (Bergmann et al., 2022). Indeed, recent reports predict that annual levels of worldwide manufactured plastics that enter aquatic systems as waste may reach 53 million metric tons by 2030, concerning 19–23 million metric tons estimated in 2016 (Borrelle et al., 2020). Recent research pointed out that between 0.013 and 25 million metric tons per year of MNPs are potentially being transported within the marine atmosphere and deposited in the oceans (Allen et al., 2020). As a result of the generation of MNPs by human activity, they are discarded and further incorporated into the sanitation networks up to the wastewater treatment plants (WWTPs). From this estimate, about 4–30 yearly tons, mostly represented by <500- μm MPs, escape the different physical, chemical, and biological treatments of WWTPs and are invariably released into the oceans due to their high persistence, density, mobility and low degradation rate (Kruglova et al., 2022). This way, greater efforts are required to better predict the impact of MNPs and associated contaminants in the hydrosphere.

MNPs can be incorporated into continental aquatic systems through different sources, including wastewater discharges, mostly from urban areas during street cleaning processes, where the accumulation of plastic waste and accidental spills of plastic microstructures occur. WWTPs discharge these particles into river basins and estuaries, distributing MNPs from continental waters (rivers and lakes) to oceans. Following WWTPs discharges to aquatic systems, MNPs are found to act as vectors for both pollutants and microorganisms (Stapleton et al., 2023). Thus, several pollutants in the water cycle, such as heavy metals (Dong et al., 2020; Tang et al., 2020), polycyclic aromatic carbon (Sørensen et al., 2020), or antibiotics (Stapleton et al., 2023;) constitute an additional concern for environmental pollution. In parallel, MPs could act as

vectors for the transport of microorganisms, providing a relatively stable habitat on their surface to accelerate the formation of biofilms in WWTPs. In this regard, the colonization of plastic surfaces by the microbial community has gained much attention in the last years, coining the term “plastisphere”. Communities of potential pathogenic microorganisms have been identified on the surfaces of MPs discharged by WWTP (Kruglova et al., 2022).

Concerning drinking water, most purification treatments are committed to avoiding the release of MPs particles. However, MPs have been reported in drinking water deriving from treatment plants, tap water and bottled drinking water (Pivokonsky et al., 2018). In this sense, much research is underway to investigate MPs' presence in different drinking water sources from various countries, becoming an important issue for public health systems (Zhang et al., 2020). The accumulation of MPs in aquatic organisms is influenced by the physical properties of the particles, essentially size and shape, since smaller MPs are easily ingested by both small and big organisms, as well as by the aquatic system since the ingestion of MNPs in freshwater aquatic organisms is much more limited than in marine organisms (Xu et al., 2020). For instance, studies on the phytoplankton *Daphnia magna* demonstrated its capability to ingest significantly larger amounts of <7.3- μm MPs with respect to >2- μm particles (Schwarzer et al., 2022). Furthermore, higher predators can ingest MPs directly through consumption or indirectly by feeding on prey that has previously ingested the MPs, affecting the whole food chain. Consequently, applying metabolomics approaches should be committed to studying the effects of MNPs consumption to decipher the effect of these particles on aquatic organisms.

2.1. Metabolic impact of MNPs in aquatic organisms

Several studies, around 20 % in the last years, focused on the application of metabolomic approaches to characterize the impact of MPs on microalgae and other aquatic species, suggesting the importance of shedding light on the consequences of MPs exposure in aquatic ecosystems (Jia et al., 2023; Li et al., 2023). In detail, MNPs may impact the development and reproductive processes, as well as the induction of oxidative stress and histological alterations (Li et al., 2023) of marine organisms upon ingestion. Xuan Li et al. (2023) reported that the degree

Table 1 (continued)

Environment	Organism	MNPs	Concentration	Time	Metabolite up-regulation	Metabolite down-regulation	References
Phytosphere	Maize	PS NPs	30 mmol/L	7 days	Amino acid biosynthesis, ABC transporters, cysteine and methionine metabolism.		(Q. Li et al., 2024a)
Phytosphere	Rice	PS NPs	0–500 mg/L	21 days		Biosynthesis of amino acids, nucleic acids, fatty acids	Wu et al. (2020)
Phytosphere	Rice	PS NPs	0.1–10 mg/L	14 days	Salicylic acid, Phe	Sugars	Wu et al. (2021)
Phytosphere	Rice	PS NPs				Arg, Ala, Asp, Glu, Val, Leu, Ile, Gly, Ser, and Thr	Wu et al. (2022a)
Phytosphere	Rice	PS NPs	0–0.5wt% /kg soil	142 days		Pentose phosphate pathway, starch and sucrose metabolism	Wu et al. (2022a, 2022b)
Phytosphere	Soybean	PE NPs	1 mg/L	49 days	Gly, Ile, Leu, Val	Galactose metabolism	Lian et al. (2022)
Phytosphere	Tomato	PE NPs PS NPs PP NPs	1 mg/L	14 days		Ala, aspartic acid, and glutamic acid metabolism	Shi et al. (2023a)
Phytosphere	Tomato	PS NPs PE NPs PP NPs	0-1000 mg/L	7 days	Citric, malic, and succinic acids	Glyoxylate and dicarboxylic acids pathways, glutathione metabolism	Shi et al. (2022)
Phytosphere	Wheat	PE NPs	1 mg/L	49 days	Glyoxylate and dicarboxylate metabolism, Gly, Ser, Thr, glutathione metabolism	Arg, Trp, and Pro metabolism	Lian et al. (2022)
Phytosphere	Wheat	PS NPs	1 mg/L	21 days	Glyoxylate and dicarboxylate metabolism, TCA cycle metabolism, Ala, Asp and Glu metabolism	Starch and sucrose metabolism	Lian et al. (2020)

Abbreviations: ROS: reactive oxygen species; TCA: tricarboxylic acid; PS: polystyrene; PE: polyethylene; NPs: nanoplastics; PHBV: poly(3-hydroxybutyrate-co-3-hydroxyvalerate).

of MNP ingestion was directly related to their harmful potential as a function of particle size, mainly affecting the tricarboxylic acid (TCA) cycle, hindering the energy provision capacity on marine rotifer (*Brachionus plicatilis*). This led to an impairment in population growth, life-history traits, nutrient accumulation, and metabolomic profiles only after 7 d of NP exposure. The metabolomic alterations induced by NPs consisted of increased levels of uridine monophosphate (UMP) and cytidine, and decreased contents of adenine diphosphate (ADP) ribose and citrulline, as well as the impairment of primary metabolic pathways involved in alanine, aspartate, and glutamate metabolism, and oxidative phosphorylation, and the TCA cycle.

Research based on a marine polychaete (*Hediste diversicolor*) revealed the effect of the presence of MNPs of diverse composition on this organism, in which were found MNPs <20 µm in connective and muscle tissues with a progressive increase over exposition time (Missawi et al., 2022). Authors highlighted the damage caused on the cytoskeleton and the induced autophagy pathway detected in immunohistochemical labeling of specifically targeted proteins, through Tubulin (Tub), Microtubule-associated protein light chain 3 (LC3), and p62g. Authors underlined the destabilization of the cytoskeleton as a consequence of the loss of Tub in the tissues. The results of metabolomics tools shed light on the increase of amino acids, energy metabolites and osmolytes metabolisms.

Cappello et al. (2021) and De Marco et al. (2023) studied the exposure to fragments of 3 µm of PS to the mussel (*Mytilus galloprovincialis*) chosen as filter-feeding specie with commercial interest. The studies described the effect of the time exposure on the organics, elucidating the quick uptake of microplastics in mussel digestive tubules in only 24 h, but authors described a drastic reduction of the numbers of MPs after 48 h, because mussels are able to active mechanisms of detoxification, whereas once the toxic effect decreased the number of MPs increased again at 72 h, demonstrating dynamics periods. The results threw serious perturbations in the physiological functions with modifications in energy metabolisms, disorders in amino acids metabolism, the onset of oxidative stress, and interferences in the osmoregulatory processes. Likewise, the study by De Marco et al. (2023) was carried out to extend the findings on the effects of PS MPs of 3 µm on the digestive glands branchial tissue. The metabolomic results to short-exposure demonstrate changes in the amino acids and energy metabolisms, alteration osmoregulatory, onset of oxidative stress corroborating the effect on digestive glands. The study finds shet on the modifications of cholinergic neurotransmission.

A study developed on larvae of *Danio rerio* (zebrafish) showed that exposition to polyethylene terephthalate (PET) NPs significantly reduced their rate of survival at >100 ppm, being accumulated in several organs including the intestines, liver, kidney, and brain (Bashirova et al., 2023a, 2023b). Metabolic profiles of larvae exposed to PET NPs reported a significant decrease in the levels of amino acids biosynthesis, e.g., alanine (Ala), leucine (Leu), isoleucine (Ile), valine (Val), glutamate (Glu), glutamine (Gln), cysteine (Cys), glycine (Gly), glutathione (GSH), and energetic molecules, e.g., acetate, glucose, adenosine triphosphate (ATP), and reduced nicotinamide dinucleotide (NADH). Moreover, a significant increase in the levels of lipids (glycerophosphocholine and ethanolamine) and free fatty acids was observed together with those of cholesterol, choline, tryptophan (Trp), lactate, phenylalanine (Phe), and tyrosine (Tyr), reflecting a detrimental effect to PET NPs exposition. In parallel, plastic concentration was reported to play a significant dysregulation of the brain–intestine–microbiota axis and embryo–larval development after 30 days of exposition with increased doses of polystyrene (PS) NPs (1, 10, and 100 µg/L). Metabolomics studies demonstrated the dysregulation of 42 specific metabolites involved in neurotransmission and their strict correlation with the changes of 3 gut microbial groups, including Proteobacteria, Firmicutes, and Bacteroidetes in one-month-old zebrafish after the ingestion of PS NPs. Specifically, the activities of 3,4-dihydroxyphenylacetic acid, acetylcholine chloride, 5-hydroxyindoleacetic acid, serotonin, 5-

hydroxytryptophan, and norepinephrine were significantly changed in a dose-dependent manner (Teng et al., 2022a, 2022b). The concentration factor was also confirmed by Yao et al. (2023) in a study on algal toxicity. Specifically, PS NP concentrations ranging 0.01–10 mg/L were shown to affect different physiological characteristics of *Phaeodactylum tricoratum* (diatoms), such as chlorophyll content, mitochondrial damage, and accumulation of reactive oxygen species (Yao et al., 2023). Metabolomics analysis clarified that the changes in chlorophyll content were linked to disruption of fatty acids biosynthesis. In contrast, mitochondrial damage was related to the increased TCA cycle activity. Finally, the accumulation of reactive oxygen species was correlated with the increase in tyrosine biosynthesis, suggesting a metabolome-wide effect attributed to PS NPs exposure. A thorough research on the effect of PS MNPs on aquatic organisms can be found in Eliso et al. (2024). In light of this, exposure of zebrafish to particles of PS MNPs in concentrations of 50 and 500 µg/L showed alteration to different metabolites such as proline, leucine, lysine, threonine, linoleic acid, palmitic acid, and triglycerides, among others (Qiao et al., 2019). The metabolic effects of MNPs of different sizes were also studied on zebrafish embryos. Reports concluded that PS microplastics affected the metabolisms of linoleic and saturated fatty acids, while PS nanoplastics affected the metabolisms of alanine, aspartate and glutamate (Duan et al., 2020). In the case of zebrafish larvae, PS MNPs of 5 to 50 µm at 100 and 1000 µg/L resulted in amino acids, nucleic acids, fatty acids and carbohydrate metabolisms (Wan et al., 2019b).

The liver of rare minnow (*Gobiocypris rarus*) exposed to 1 µm PS MNPs at 20 µg/L concentration resulted in significant upregulation of cytosine, fructose, glyceraldehyde, glucose and mannose metabolisms, and significant downregulation of acetyl-phenylalanine, mannitol 1-phosphate, and mannonate metabolisms (Wang et al., 2022). Medaka is another fish that has been researched for affection of MNPs exposure. Marine medaka (*Oryzias melastigma*) exposed to high concentrations of PS MNPs showed upregulation of disaccharides, ethyl esters, fatty acids, fatty acid methyl ester, and trisaccharides, and downregulation of monosaccharides, organic acids, amino acids in their liver metabolic profile (Ye et al., 2021). On the other hand, Javanese medaka (*Oryzias javanicus*) showed upregulation of alanine, anserine, creatine, glucose, glucuronate, glutamate, lactate, valine and 2-hydroxyvalerate when exposed to high concentrations of PS MNPs (Usman et al., 2022).

The presence of MNPs affected differently the metabolic profiles of gills and livers of adult zebrafish, according to a study developed by Kaloyianni et al. (2021). After exposure, the metabolic profile of the gills showed significant downregulation of carnitine, choline, lactic acid, phenylalanine, proline and salicylic acid. For the liver, significant upregulation of adenine, adenosine and glutamine, and significant downregulation of arginine, asparagine, deoxyadenosine, hypoxanthine, phenylalanine, proline, uridine and valine were observed. Furthermore, differences among metabolic profiles of different organs have also been found for other aquatic organisms, such as mussels. Exposure of Mediterranean mussels to 50 particles per mL of PS MNPs showed upregulation of acetoacetate, ATP/ADP, betaine, homarine, mytilitol and taurine in gills and alanine, betaine, dimethylglycine, glycogen, glucose, glutathione, homarine, isoleucine, lactate, leucine, tyrosine, taurine and valine in hepatopancreas, while downregulation of acetylcholine, alanine, glycine and succinate in gills and acetoacetate, glycine, hypotaurine, malonate and succinate in hepatopancreas, were reported (Cappello et al., 2021; De Marco et al., 2023).

Furthermore, Teng et al. (2022b) featured the importance of the electrochemical properties of MNPs in the process of plastic accumulation in the zebrafish brain and gastrointestinal tract. They reported that NPs with a positive charge (amino-modified) developed more toxicity, reducing spontaneous movement, heart rate, hatching rate, and length, compared to negatively charged NPs (carboxyl-modified). Additionally, MNPs induced higher levels of brain cell apoptosis due to the interaction with neurotransmitter receptor *N*-methyl-D-aspartate receptor 2B. Interestingly, metabolomics studies demonstrated the protective effect

of MNPs against the toxicity of mercury in the brain of zebrafish embryos by inhibiting different pathways related to Ala/aspartate (Asp)/Glu metabolism and Val/Leu/Ile biosynthesis (Wang et al., 2022). In contrast to the sensitivity of zebrafish larvae, developed specimens of *Crassostrea angulata* (Fujian oyster) reported an adaptation response to PS NPs (Lu et al., 2023). In this study, the metabolomics revealed that NP exposure boosted the antioxidant systems by increasing the enzyme antioxidant system as well as the accumulation of antioxidant compounds, such as adenosine, 3-(4-hydroxyphenyl)pyruvate, sorbitol, mannose, unsaturated fatty acids, as well as amino acids proline (Pro) and lysine (Lys).

Zitouni et al. (2022) studied the metabolomic disorders in wild fish (*Serranus scriba*) found in the Tunisian coast. The data obtained were very interesting because the effect of cytotoxicity at the hepatic level was linked with the collection site due to the MNP concentration. The MNPs in the fish tissue were also correlated with the MNPs pollution. The predominant accumulation was found in the liver, especially in the blood vessels and the surrounding area, indicating their role in the MNPs translocation via the circulatory system. The hepatic consequences in the fish were corroborated by modifications in malondialdehyde (MDA) content, the presence of reactive oxygen species (ROS) expressed by the altered level of catalase (CAT) and glutathione-S-transferase (GST) activities and in the content of metallothioneins (MTs), as well as genotoxicity by changes in the amount of micronucleus (MN), and neurotoxicity by altered activity of acetylcholinesterase (AChE). Moreover, the metabolomics results demonstrated that the incorporation of MNPs <3 μm significantly affected 36 metabolites involved in the energy, corroborating the affections suffered by mussels by the incorporation of MNPs as reported by Cappello et al. (2021) and De Marco et al. (2023). Metabolic profiles of *S. scriba* reported elevated levels of amino acids including Ala, proline, Glu, methionine, aspartate, Gly, tyrosine and phenylalanine. Interesting results obtained from the metabolomic profile showed that environmental pollutants induce a rise of anaerobic metabolisms with an increase of lactate as a strategy to recover energy. Therefore, this could modify the energy metabolisms in fish as reported Cappello et al. (2016).

3. MPs in the atmosphere and related environmental systems

The ubiquitous presence of MNPs, even in remote areas, suggests a relevant atmospheric mobilization of these pollutants, thus diversifying their environmental fate (Kung et al., 2023). Therefore, depicting the fate of airborne MNPs is fundamental for understanding their environmental dynamics and the eventual development of remediation mechanisms. Airborne MNPs can be divided into outdoor and indoor, with higher concentrations (Liao et al., 2021), which might indicate higher potential risks for human health. Accordingly, industrialized urban areas exhibit much higher concentrations of airborne MNPs than natural areas (Wang et al., 2022b). However, there are increasing reports about the occurrence of MNPs in natural environments, referring to MNPs contamination in the Atlantic Ocean's atmosphere (Caracci et al., 2023) and the Alps (Materić et al., 2021).

The ubiquitous presence of airborne MNPs motivates their association with the other intersectional environmental components, including the hydrosphere, lithosphere, phytosphere and biosphere, mostly having deleterious effects. Recent reports in lettuce plants (*Lactuca sativa*) grown under airborne MNPs-containing atmosphere for one month showed a reduction in growth and photosynthetic activity, coupled with a significant increase in electrolyte leakage rate and a decrease in their antioxidant capacity, highlighting the phytotoxic effect of MNPs particles (Lian et al., 2021). As explained later, maize plants (*Zea mais*) can uptake airborne MNP particles through leaves, causing further detrimental effects on plant growth, health, and productivity (Sun et al., 2021). In parallel, several studies have highlighted a direct interaction of humans with these atmospheric contaminants (De-la-Torre, 2020; Shao et al., 2022), suggesting that breathing MNPs induced deleterious

effects on the human respiratory system, depending on particle size, shape, surface charge, attached pathogenic organisms and/or toxic substances, absorption to cell tissue and bio-persistence of the plastic particle (Wieland et al., 2022). In this regard, the breathable characteristics of airborne MNPs constitute one of the principal hazards to human health compared to those present in soil and water, which can only be ingested (Zhao et al., 2023a). This risk could also be extended to all plants and breathing animals that promote an active gas exchange with the atmosphere in the presence of airborne MNPs.

4. MNPs in the lithosphere and soil-related organisms

In recent years, the presence of MNPs in the lithosphere has become an important environmental issue since MNP concentrations in soil can range from 4- to 23-fold higher than those found in marine environments (Horton et al., 2017), suggesting that marine MNP pollution is a consequence of prior soil contamination (Sheela et al., 2022). Therefore, addressing MNP pollution in the lithosphere and its potential effects on soil, plants, and terrestrial wildlife health becomes pivotal (Yang et al., 2023).

The presence of MNPs in soil potentially affects both the chemical and physical properties of soil (Moeck et al., 2023) as a function of plastic size, shape, polymer composition, biodegradability, additives, surface properties and degree of weathering (Mbachu et al., 2021). Concerning physical properties, MNPs generally decrease soil bulk density (De Souza Machado et al., 2019), making polluted soil more prone to erosion. Therefore, the presence of MNPs was correlated to a reduction in soil micropores and an increase in soil macropores (Zhang et al., 2019). Moreover, MNPs were found to decrease soil aggregation (Zhang et al., 2019), thus reducing soil biological activity by impairing air and water exchange. Besides water exchange, MNPs directly affect soil structure by reducing its water-holding capacity and increasing hydraulic conductivity, mainly associated with soil evaporation and evapotranspiration (Wan et al., 2019a). With respect to chemical soil properties, MNPs can influence the microbial population diversity, further affecting soil chemical composition. In this regard, as defined earlier for the aquatic environment, the term *plastisphere* can be equally associated with soil systems, since MNPs can create a specific environment for the microbe-colonizing plastic particles, influencing the soil microbial population (Rillig et al., 2023). Besides, the influence of MNPs on soil microbial communities is highly dependent on plastic concentration, exposure time and composition (Mbachu et al., 2021). Thus, the microbial soil activity was increased in the presence of polyamide (PA) and polyethylene (PE), while decreased in the presence of polymethyl methacrylate (PMMA) and polyethersulfone (PES) (De Souza Machado et al., 2018, 2019). Beyond soil microbiota, other microorganisms are affected by MNPs, as is the case of protists (Kanold et al., 2021; Zhang et al., 2022a) and nematodes, the last showing a reduction in fertility and offspring by increasing MNPs concentrations (Fajardo et al., 2022).

To date, limited research has been conducted on the metabolome of soil systems to determine the effect of MNP pollution in soil-associated organisms. Recently, Tang et al. (2023a, 2023b) concluded that soil NPs can affect the metabolome of earthworm gut: *Eisenia fetida* grown in soil with 0.02 % w/w PS NPs showed strong changes in gut microbiome population coupled with an accumulation of 2-hexyl-5-ethyl-furan-3-sulfonic acid, dimethylglycine, choline, malonate and succinate and a decrease in Ala, betaine, glucose (Glc), Ile, Leu, lactate, maltose and myoinositol levels (Tang et al., 2023b). Other study showed the impact of PS MNPs on *Eisenia fetida*, resulting in increased levels of adenylsuccinic, argininosuccinic and oxoglutaric acid, adenine, oxidized glutathione, avocadenyne acetate, 4-ene-valproic acid, acetyl-L-carnitine, tiglylcarnitine, capsianoside I, and ethyl hydrogen fumarate (Xu et al., 2021). The effect that different MNPs have on *Eisenia fetida* showed differences regarding nature of the plastic (Zhao et al., 2024). Under pressure of PVC MNPs, earthworms were subjected to increased linoleic and α -linoleic metabolisms, as well as increased

glycosaminoglycan biosynthesis-chondroitin sulfate/dermatan sulfate activity. For low density PE MNPs, mainly mTOR, PI3k-Akt, cGMP-PKG and FoxO signaling pathways were affected. In the case of polylactic acid MNPs, the metabolic profile of earthworms only showed increase in linoleic and α -linoleic metabolisms. The effect that the age of the MNPs has on the metabolism of *Eisenia fetida* has also been investigated recently (Jiang et al., 2023). It was found that the effect of aged PE MNPs was more severe than the effect of pristine PE MNPs on earthworms. Specifically, aged PE MNPs affected more severely the energy metabolism of earthworms. The short-term effects that MNPs exposure has on another species of earthworm, *Eudrilus euganiae*, has been also investigated, reporting significant effects on cardiolipin, cholesterol ester, diacyl glycerol, phosphatidylcholine, phosphatidylethanolamine, tetradecenoylcarnitine, and triglyceride, among other metabolites (Chan et al., 2023). Another earthworm species, *Amyntas corticis*, showed metabolite profile affection due to presence of MNPs in agricultural soil, with significant difference of γ -phenylalanine and succinic acid (Jiang et al., 2022). These observations highlight that MNP pollution reduces soil quality and impairs nutrient availability for associated organisms, ranging from the soil microbiota to terrestrial plants, including crops for food safety.

5. MNPs in the phytosphere

As sessile organisms, terrestrial plants are directly affected by a wide range of environmental threads, including MNP pollution. For that reason, plants are closely related to the rest of the environmental interfaces. As a result, studying the phytosphere is critical in deciphering the environmental impact of MNPs pollution, as they can finally pass into the food chain to humans, causing an significant risk to human health (Tympa et al., 2021).

Due to their close association with water, soil and air systems, terrestrial plants show heterogeneous absorption mechanisms involving NPs absorption through both root and leaf surfaces (Sun et al., 2021). Considering the root absorption, NPs may be incorporated into the root apoplastic transport pathway and then be translocated into other organs (Dong et al., 2021a, 2021b). Among the different mechanisms, it is well-known that NPs could undergo either endocytosis or mediated membrane transport involving aquaporins and ion channels (Wu et al., 2021; Zhou et al., 2021a, 2021b). On the other hand, the leaf-mediated MNP absorption is mainly found to be carried out through stomatal apertures from the aerial environment, reaching the apoplastic pathway prior to being translocated throughout the plant (Lian et al., 2021; Luo et al., 2022).

Once incorporated into plant systems, MNPs may play different phytotoxic effects (Mateos-Cárdenas et al., 2021; Gan et al., 2023). In this sense, larger-size MNPs are easily adsorbed to surfaces of plant roots and seeds (Bosker et al., 2019; Jiang et al., 2019), where they can physically block the transport of water and nutrients (Roy et al., 2023). This effect was reported in rice and soybean seeds, where surface-adsorbed MNPs reduce seed water uptake by blocking water pores, thus hindering the development of root hairs and slowing germination (Bosker et al., 2019)(Wang et al., 2021a, 2021b, 2021c; Zhou et al., 2021a, 2021b). However, Lian and co-workers (2020) indicated that PS MNPs promoted wheat germination, leading to controversial results that merit further research (Lian et al., 2020).

MNPs integrally affect plant organisms, involving all tissues at all developmental stages, from germination to vegetative growth, thus causing homeostatic imbalances. Recent evidence reports that MPs play both a direct and indirect role in plant physiology, following a species-dependent behavior. Among the most studied species subjected to the influence of MPs, crop plants such as tomato, wheat, and rice have been mostly selected because of the important implications for the agricultural sector, as they have been reported to affect horticultural productivity and the nutritional properties of derived foods (Wang et al., 2022c). This effect has been associated with the evidence about the

direct induction of abiotic stress under the presence of MPs and with the increase in susceptibility towards other stress-derived factors, such as heavy metals toxicity (Xu et al., 2023). Nevertheless, to date, there is not a universal consensus on the vast effect of MPs on plant physiology since contradictory results have been reported according to their administration, ranging from deleterious responses when incorporated in aqueous solutions to negligible effects when MPs were directly incorporated in soils (Brown et al., 2022). In the same way, exposure time and particle size constitute additional factors that significantly affect the impact of these materials, as different physiological outcomes were observed between micro- and NPs (Wang et al., 2022c).

5.1. Metabolic impact of MNPs in terrestrial plants

Among the most recent findings on the effect of MNP exposure on plant metabolome, cucumber leaves showed a dose-dependent metabolic modulation by polystyrene NPs treatment (<100 nm). Thus, at low concentrations (50 mg/L), leaves showed modulation of carbohydrate metabolism, as shown for the up-regulation of carbon fixation-related metabolism and pentose phosphate pathway. The exposure to the highest concentration (100 mg/L) promoted a more substantial effect combining TCA cycle and starch metabolism impairment with that of nitrogen metabolism, being represented by the differential modulation of amino acid biosynthesis, as well as the induction of antioxidant responses through the imbalances observed on glyoxylate and glutathione metabolic pathways (Huang et al., 2023). In the case of tomato, hydroponic cultures showed a reduction in their growth under PS, PE, and PP MPs exposure, exhibiting a type-dependent negative effect on photosynthetic parameters and inducing antioxidant enzyme activities, motivated by the MPs-driven oxidative stress (Shi et al., 2023a, 2023b). Moreover, PS and PE MPs caused a metabolic reprogramming, the latter mostly impacting amino acid biosynthesis, especially the pathways involved in alanine, aspartic acid, and glutamic acid metabolism. In contrast, PS and PP MPs also affected TCA cycle by inhibiting the accumulation of organic acids like citric acid, malic acid, and succinic acid, and modulating glyoxylate and dicarboxylic acids pathways, as well as glutathione metabolism on both roots and leaves. In contrast, PE MPs did not provoke a phytotoxic effect on soil-cultured soybean seedlings. However, 0.1 % polylactic acid (PLA) MNPs generated adverse effects that were more evident at the root level, where Lian et al. (2022) reported a decrease in length. However, soybean leaves reflected a significant metabolism-wide response under PLA soil administration through the up-regulation of amino acid biosynthesis, as found for Gly, Ile, Leu, and Val, combined with a down-regulation of galactose metabolism that was linked to a decrease in monosaccharide accumulation, thus suggesting a harsh impairment of primary metabolism involving nitrogen and carbon metabolism.

Much attention has been paid to other relevant crops like lettuce, maize, wheat, and rice, deepening into the effect of MPs on plant physiology. Thus, concerning lettuce, the foliar administration of charged MPs (PS-NH₃⁺ and PS-COO⁻) under flask-based cultivation led to a higher PS-NH₃⁺ accumulation in leaves via stomata uptake showing a decrease in photosynthetic activity and associated pigments coupled with the stimulation of ROS production and antioxidant activities (Wang et al., 2022d). These responses were accompanied by the impairment of β -alanine metabolism by positively charged PS, and glycerophospholipids and sulfur-containing metabolism (methionine and cysteine) by negatively-charged PS. In contrast, purine metabolism was found harshly repressed in both cases, suggesting a key role of purines associated with PS administration in lettuce. In parallel, lettuce cultured in PS-contaminated soil showed a dose-dependent effect in roots, promoting a dual mechanism to facilitate heavy metal bioaccessibility by accumulating ATP-binding cassette (ABC) transporters and modulating the rhizosphere soil microbiota, especially increasing the presence of metal-activation bacteria, such as *Clostridium* (Xu et al., 2023). The MP-assisted heavy metal uptake motivated ROS-mediated cell damage on

both leaf and root tissues, and roots exhibited an up-regulation of several pathways involved in linoleic acid, phenylpropanoid, pyrimidine and galactose metabolism, as reported by the same authors. Accordingly, PE microfibers were reported to impact rhizosphere soil microbiota in soil-grown lettuce plants under cadmium contamination, featuring the presence of *Proteobacteria* as responsible for regulating the assimilation of cadmium, as they can degrade polyester biogenic derivatives (Zeb et al., 2022). Indeed, PE drove a down-regulation of amino acids, as recorded for Ile, Leu and Ser, as well as a decrease in benzoic acids and monosaccharides, thus pointing to those metabolites as responsible for the decrease in shoot length and photosynthetic performance of lettuce plants under PE (Zhang et al., 2024). When treated with the combination of PE and Cd, a more severe metabolic impairment was reported, promoting a decrease in Leu and Ser while accumulating Glu and negatively affecting the carbohydrate metabolism through the down-regulation of glyoxylate and dicarboxylate metabolism. Following hydroponic cultivation, lettuce seedlings grown under different PS concentrations (0–50 mg/L, 0.2 μm particle size) were found to accumulate PS particles preferentially in root tips and leaf veins, thus causing the activation of stress-related genes involved in different biosynthetic metabolic pathways (Wang et al., 2023a, 2023b, 2023c, 2023d). From a metabolomic perspective, the MPs-derived stress response was characterized by an accumulation of antioxidant metabolites like ascorbic acid, terpenoids, and flavonoids, which was combined with an increased presence of Ser and glucosylceramide, being both closely related with sphingolipids metabolism.

In the case of maize, corn seedlings grown in hydroponic culture under 50 mg/L PS with different particle sizes (100–500 μm diameter) were not affected in terms of photosynthetic performance, although root microstructure was damaged following oxidative stress induction. With respect to metabolic modulation, PS caused a general up-regulation of key metabolic pathways, especially those involved in organic acids biosynthesis and Ala, Asp, and Glu metabolism, the latter being highlighted as major mediators of PS tolerance and/or detoxification (Zhang et al., 2022b). Furthermore, Brown et al. (2023) evaluated the impact of the bioplastic polymer poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) in soil-cultured corn seedlings, reporting an accumulation of TCA intermediaries ascribed to inefficient energetic management, as it was combined with the accumulation of different saccharides, such as the osmotic regulator maltotriose, the glycolysis inhibitor 6-deoxyglucose, and the signaling molecules ribose and xylulose. In parallel, the same authors reported a PS concentration-dependent response towards the soil-plant metabolome, referring to plant organisms as holobiont systems that co-exist with the surrounding environment, especially the soil and the associated microbiota. The deficient carbohydrate metabolism found in maize seedlings under PHBV presence was hypothesized to be a consequence of the rapid influx of labile carbon substrate into the soil, which was further symbolized by the enrichment of *Betaproteobacteria* within the soil microbiota (Brown et al., 2023). As was observed for lettuce, the co-existence of PS and PP with heavy metals like Cd was also studied in soil-culture maize plants, showing similar results since MPs enhanced Cd root absorption and improved its bioavailability towards soil-associated microbiota (Zhao et al., 2023a, 2023b). These authors also deciphered that the only administration of PS and PP slightly promoted maize plant growth, mediated by the accumulation of Glu, involved in nitrogen and carbon metabolism; Ser, related to the biosynthesis of chlorophyll; phenylpyruvic acid, a precursor of the endogenous phytohormone indole-3-acetic acid; and 3-dehydroquinone, found to promote key physiological processes, such as seed germination.

With respect to the research on MP administration to wheat, some authors have focused on the effects of these contaminants on wheat germination (Bao et al., 2022). Interestingly, Bao et al. (2022) demonstrated that PE administration promotes synergistic effects with other contaminants like the antibiotic oxytetracycline, showing a delay in germination and negatively affecting the germination rate associated with the onset of oxidative stress. The metabolomic signatures

associated with the observed results involved six pathways related to amino acid metabolism and four pathways related to carbohydrate and lipid metabolism, respectively. Thus, the combined exposure promoted the repression of pyruvate and nitrogen metabolism, the latter being mostly represented by Arg, Trp, and Pro metabolism, while boosting glyoxylate and dicarboxylate metabolism, as well as Gly, Ser, Thr, and glutathione metabolism, following concentration-dependent effects. Conversely, the exclusive administration of PS NPs at different concentrations (0.01–10 mg/L) on wheat seeds was found not only to have a negligible effect on the germination rate but also enhance root elongation, carbon and nitrogen contents, plant biomass and chlorophyll contents (Lian et al., 2020). These observations were justified by the metabolic shift associated with an efficient mobilization of carbohydrate and amino acid metabolism found through the up-regulation of glyoxylate and dicarboxylate metabolism and TCA cycle metabolism together with Ala, Asp, Glu metabolism while down-regulating starch and sucrose metabolism. However, despite the phytotoxicity absence of PS in wheat seedlings, the same authors are alert about the long-term consequences of MP exposure (Lian et al., 2020). Following these results, the field application of a wide range of PE (0–10,000 kg ha⁻¹) did not significantly affect wheat crop growth and yield in the short term (Brown et al., 2022) due to the maintenance of soil biological quality. In metabolic terms, nitrogen metabolism was slightly affected, with no significant differences among biogenic amines, thus also playing a negligible effect on the soil microbial community. Overall, these results suggest a resilient behavior attributed to wheat to cope with microplastic contamination effectively, eventually supported by the presence of an efficient soil microbiota associated with a short term, requiring the development of long-term studies to determine such an adaptive response.

Rice has also been considered an important crop to decipher the metabolic impact of MPs, especially under PS presence. Different PS particle sizes (0.1–1 μm diameter) and concentrations (0–10 mg/L) were administered to rice seedlings cultured hydroponically, reporting a clear dose-dependent phytotoxic effect (Wu et al., 2021), mainly attributed to the largest particles, although the smallest ones presented the highest internalization rates. The phenotypical traits observed, mainly characterized by the induction of oxidative stress and the impairment of nutrient uptake, were consistent with the results from the metabolic profiling, with the leaves showing a stronger impairment than the roots. Thus, PS promoted the accumulation of salicylic acid, considered a marker of plant abiotic stress induction, together with the accumulation of Phe at the root level combined with the reduction of sugars, which may indicate a shift from primary metabolism to secondary metabolism, as Phe is recognized as the universal precursor for specialized metabolites, especially polyphenols with associated antioxidant activity (Wu et al., 2021). The toxicity of PS was also reported in soil-cultured rice plants, reinforcing the global effects of these MPs on rice metabolome. Thus, Wu et al. (2020) indicated that PS decreased shoot biomass in a dose-dependent manner coupled with an increase in antioxidant enzyme system induction, motivated by a harsh metabolic impairment where the biosynthesis of amino acids, nucleic acids, fatty acids, and secondary metabolism were decreased against an increase in energy expenditure-related pathways that surpassed substance accumulation, resulting in a $\approx 26\%$ decrease in crop biomass under long-term cultivation in farmland in the presence of PS. Nevertheless, further field studies performed by the same authors indicated that the phytotoxicity attributed to PS (Wu et al., 2022a, 2022b) is dependent on the rice subspecies since *Oryza sativa* L. II Y900 genotype showed a rice yield decrease of 10.6% while the X5123 genotype showed an increase of 6.35% under PS exposure, also affecting rice nutritional quality. These findings were explained based on the distinctive metabolic profiles reported for both genotypes: while Y900 showed an impairment in carbohydrate metabolism involving the pentose phosphate pathway and starch and sucrose metabolism, X123 showed a significant modulation of amino acid metabolism, affecting mainly Arg, Ala, Asp, Glu, Val, Leu, Ile, Gly, Ser, and Thr biosynthesis. These rice genotype-dependent diversified

responses towards PS exposure open a broad perspective that requires in-depth research to better determine the causes underlying MPs' effect in plant organisms.

6. MNPs in the anthroposphere

The evaluation of MNPs' effects on human health remains a pivotal aspect when assessing their hazards, translocation, and exposure levels, primarily due to the ethical consideration of conducting experimental procedures on humans, thus limiting potential studies. Nevertheless, existing evidence from in vitro studies involving human cells and in vivo studies conducted on animal models, such as mice and rats, indicate that exposure to MNPs may lead to deleterious events, including inflammation, oxidative stress, cytotoxicity, and respiratory diseases (Li et al., 2022).

The three MNP exposure pathways in the anthroposphere consist of inhaling airborne plastics suspended in the atmosphere, ingesting MNPs-polluted foods and beverages, and dermal contact using cosmetic products (Domenech and Marcos, 2021). However, aerial exposure to MNPs is likely the most probable way to enter the human body, found in different compositions in the respiratory systems with a mean size of 75.43 μm and ranging abundances of 1.87–9.17 particles/mL (Huang et al., 2022). This way, MNP accumulation in the respiratory tract could lead to lung and respiratory damage. Metabolomic studies on human bronchial epithelial cells reported toxicity after exposure to 60 $\mu\text{g/L}$ of PS NPs, resulting in the impairment of mitochondrial membrane potential, a rise of ROS levels, and the induction of pathways related to innate immunity (Xuan et al., 2023). Accordingly, Lin et al. (2022) proved the damaging effect of PS NP exposure on human lung and liver cells, involving the accumulation of ROS at mitochondrial levels, leading to loss of membrane potential, thus impairing energy production. These effects were associated with a metabolic modulation of nicotinate and nicotinamide metabolisms in lung cells and amino acid metabolism (Arg, Ala, Asp, and Gln) in liver cells.

Beyond the respiratory tract, the presence of MNPs further affects other tissues and organs through the bloodstream, which suggests a systemic response at the whole-body level. Studies on mice (*Mus musculus*) after PS NP ingestion reported nephrotoxicity attributed to a modulation of the metabolic profiles (Tang et al., 2023a, 2023b). Metabolomics study validated the dysfunctional effect of NP exposure in the kidney phospholipid metabolism, reporting the decrease of phosphatidylcholine and the increase of total cholesterol and triglycerides. Moreover, this approach suggested that docosahexaenoic acid-enriched phosphatidylserine can ameliorate the nephrotoxic effects (Tang et al., 2023a, 2023b). Other studies on pregnant mice treated with increasing doses of PS NP (0.1 to 1000 mg/L) showed modulation on vitamins (biotin), amino acids, and energetic metabolic (glycolysis/gluconeogenesis) pathways, lowering fetal weight (Aghaei et al., 2023), as well as lipid metabolisms (steroid and cholesterol), caused by the abnormal regulation of the cholesterol transporter *APOA4* (Chen et al., 2023b).

Furthermore, PS NP-exposed male mice exhibited altered reproductive parameters, such as sperm count, viability, abnormality, and testosterone levels as well (Fu et al., 2023). At the metabolic level, metabolites like deoxy-erythronic acid, apo-10'-violaxanthin, beta-D-glucosamine, and oxoadipic acid correlate with reproductive parameters. On the other hand, exposition to MNPs has been reported to affect mice's mental health and behavior. Accordingly, Kang et al. (2023) showed a clear penetration of PS NPs into mice brain tissues, representing the leading cause of neurotoxicity and neuronal damage in the hippocampus and reducing memory and learning capacities (Kang et al., 2023).

The digestive tract has also been found to be affected by MNP exposure, requiring extensive metabolomics studies to decipher the effects found, with a special insight into the gut microbiota. A study conducted on mice ingesting PS MNPs at 0.5 mg/day for 60 days concluded that exposition changed the gut microbial communities, as

well as its metabolic profile, affecting the levels of carnitine, dodecanoic, myristic, myristoleic, oleic, and palmitoleic acids (Chen et al., 2023a). The changes in gut communities involved a significant decrease in the relative abundance of beneficial gut microbes, such as *Lactobacillus* and *Lachnospirillum*, while increasing the abundance of pathogenic and *Mirobactulaceae* bacteria. Furthermore, the effect of PS MNPs on human colon cells has been analyzed by Bonanomi et al. (2022), observing a similar metabolic response pattern between NPs and a carcinogenic compound incubation. The main pathways modulated were related to glutamate and glutathione metabolisms and the Warburg effect. Moreover, high energetic metabolisms were affected after NP incubation, including the upregulation of glycolysis, TCA cycle, and pentose phosphate pathway. Finally, exposure analysis was conducted on human CD34+ hematopoietic stem/progenitor cells with PS NPs. Metabolomics data showed a significant influence in lipid and energetic metabolisms, reporting the modulation of metabolites accumulation, for instance, glucose 6-phosphate, dimethylglycine, 2,2-dimethyl adipic, linoleic, nonanoic, oxoglutaric, octanoic, propionic, ethylmethylacetic and isocaproic acid (Guo et al., 2023). All these results suggested that the primary metabolic pathways, represented by those biosynthetic pathways involved in cell growth, maintenance and reproduction, were affected by MNP exposure.

7. Conclusion

MNPs are pollutants of emerging concern that have high mobility and are now present in the hydrosphere, lithosphere and atmosphere and their cross-interaction with the biosphere. In addition to their actual presence, they are difficult to degrade and remove from the environment; therefore, living beings inhabiting our planet will surely face their effects over their lives. Recent research has demonstrated that MNPs can have severe detrimental consequences on organisms existing on land and aquatic ecosystems and that those affections account for toxicity in organs, reproductive problems, and changes in behavior. Moreover, since living beings ingest most MNPs, the gut microbiome of higher organisms will also be affected, leading to corresponding effects on their host organisms. The variety of all these effects is vast due to the many different materials and shape nature of MNPs and the boundless diversity of organisms that could be affected. In light of this, limitless research could be conducted to understand and alleviate the detrimental effects of MNPs on living organisms on Earth. One of the most potent tools for discerning these effects is metabolomics. Recent and current research focusing on metabolomics has demonstrated to elucidate the exact effect, at the metabolite level, that exposure to MNP particles has over different organs of living beings. This accurate information can be exploited for a better understanding of the mechanistic interaction between organisms and MNPs and could lead to focused and efficient solutions to inhibit these detrimental effects by targeting key metabolic compounds. This review provides a global vision of the ubiquity of MNPs in the environment, the risks they pose to living beings on Earth, and a revision of the recent studies that have analyzed the effects of MNPs on different organisms through metabolomics. Due to the heterogeneous metabolomics-based perspectives of the currently available scientific literature, novel perspectives are predicted to be addressed to the discovery of robust biomarkers, in order to evaluate the toxicity and further physiological processes affected by MNPs. As well, the establishment of a solid normalized methodology to efficiently determine the metabolome-wide profile attributed to MNPs exposure is required to achieve an standardized analyzing platform, taking advantage of the recent advances in the field of machine learning to assist in this challenging task.

CRedit authorship contribution statement

Leilei Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal

analysis, Data curation, Conceptualization. **Pascual García-Pérez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Barbara Muñoz-Palazon:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Luigi Lucini:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition. **Alejandro Rodríguez-Sánchez:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

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

Data availability

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

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