Chapter

Micro(Nano)Plastics as Carriers of Toxic Agents and Their Impact on Human Health

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Abstract

Currently, globally the demand and production of plastic items are increasing exorbitantly, generating a large amount of waste, and polluting the ecosystem, a site in which degradation processes are triggered, which give rise to smaller particles such as micro(nano)plastics (MNP). Continuous human exposure to these particles generates negative alterations in the host's health. Three routes of MNP exposure or contact have been established: inhalation, ingestion of particles, and dermal absorption. Recently, it has been pointed out that microplastics (MP) can even be found in the human placenta. This chapter aims to compile and provide information on their role as conveyor vectors of agents potentially toxic to humans, mechanisms by which they enter the human body, their bioaccumulation, and health human effects.

Keywords: microplastics, nanoplastics, conveyor, gut, microbiota, inflammation, health

1. Introduction

At present, globally, there is an important and relevant environmental and public health problem; 8300 million metric tons of plastic were manufactured worldwide between 1950 and 2017, and this production continues to increase, reaching 390.7 million metric tons only in 2021, and is expected to increase to 34,000 million metric tons by 2050 [1, 2]. Degradation resistance is one of the most critical characteristics that initially gave an advantage to the use of plastics; however, now, it is a significant disadvantage since they are resistant to chemical, biological, and corrosive degradation; therefore, their durability in the environment is greater [3]. Plastics are widely used in various consumer products because of their low density and costs; there are about 30,000 types of plastics, being the most widely used polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), polystyrene (PS), polyurethane (PU), polyvinyl chloride (PVC), and polycarbonate (PC) [4]. Plastic residues are transported by rivers, storms, and strong winds or are discarded directly into

terrestrial or aquatic ecosystems. Plastic residue pieces are classified according to their size into mesoplastics (50–200 mm), macroplastics (200–1000 mm), and mega-plastics (>1000 mm) [5]. These residues undergo physical changes due to environmental interactions, such as fragmentation, and changes in their physicochemical properties, generating new types of micropollutants such as microplastics (MP (less than 5 mm)) and nanoplastics (NP (<1 μm)) [6]. These tiny plastic particles are ubiquitous worldwide and generate great concern for environmental and human health damage. The impact on human health may be due to their small size, specific surface, and high biological penetrability [7].

Micro(nano)plastics absorbs and transports external toxic pollutants; these plastic particles harm human and wild health, altering the physiological functions of immunity and metabolism and modifying the intestinal microbiota, thereby facilitating exposure to pathogens [8]. In fact, according to morphology, size, and concentration, MP can trigger ecotoxicological problems in different organisms [6]. Exposure to MNP causes local inflammation, oxidative stress, metabolic alteration, gastrointestinal toxicity, hepatotoxicity, reproductive disorders, and neurotoxic effects [9]. Humans are subjected to prolonged exposure to this type of particle in low concentrations; however, these effects on the organism need to be profoundly and widely studied, mainly in the case of NP [9]. So far, eradicating plastic waste remains challenging, and its impact on health is becoming increasingly evident. Despite the increase in recent research on plastic waste, it is still in the early stage; therefore, more research is required. This chapter presents and discusses the role of these particles as carriers of different molecules or microorganisms that directly impact health. Besides, it presents the current knowledge about MNP human exposure pathways and the toxicological effects on the intestinal microbiota-immunity, reproductive and neurotoxic.

2. From plastics to micro- and nanoplastics

The term "plastic" refers to any material with high polymer content as the ingredient; this discovery dates from the beginning of the twentieth century [10, 11]. Plastics are formed by a set of polymers such as polypropylene (PP), polyethylene (PE), polyethylene terephthalate (PET), polystyrene (PS), polyurethane (PU), polyvinyl chloride (PVC), polycarbonate (PC), polymethyl methacrylate (PMMA), polyamide (PA), polylactic (PL) and additives such as stabilizers, flame retardants, plasticizers, and pigments [12].

Plastic presence is ubiquitous in the environment due to its excessive use and polymeric materials' long permanence in plastic residues. When exposed to the environment, plastic undergoes an abiotic degradation, either by a physical or by a chemical weathering process; in the physical weathering process, it suffers from mechanical wear due to water and wind or photodegradation processes, and in the chemical weathering process, hydrolysis or oxidation of polymers takes place [3]. As regards biotic degradation, it is essential to mention that plastic debris in the aquatic ecosystem is usually resistant to corrosion and degradation by microorganisms, being fragmented into smaller-sized plastic particles by the already mentioned abiotic factors [13]. The impressions of the abiotic physical process led to the wear of the plastic parts forming smaller particles, the microplastics (MP) and the nanoplastics (NP). Nowadays, plastic pollution is a global problem that has caused the generation of massive amounts of such MNP, which can be transported through rivers, seas, air, and rain; the last one causes the particles in the air to fall into different areas [14, 15].

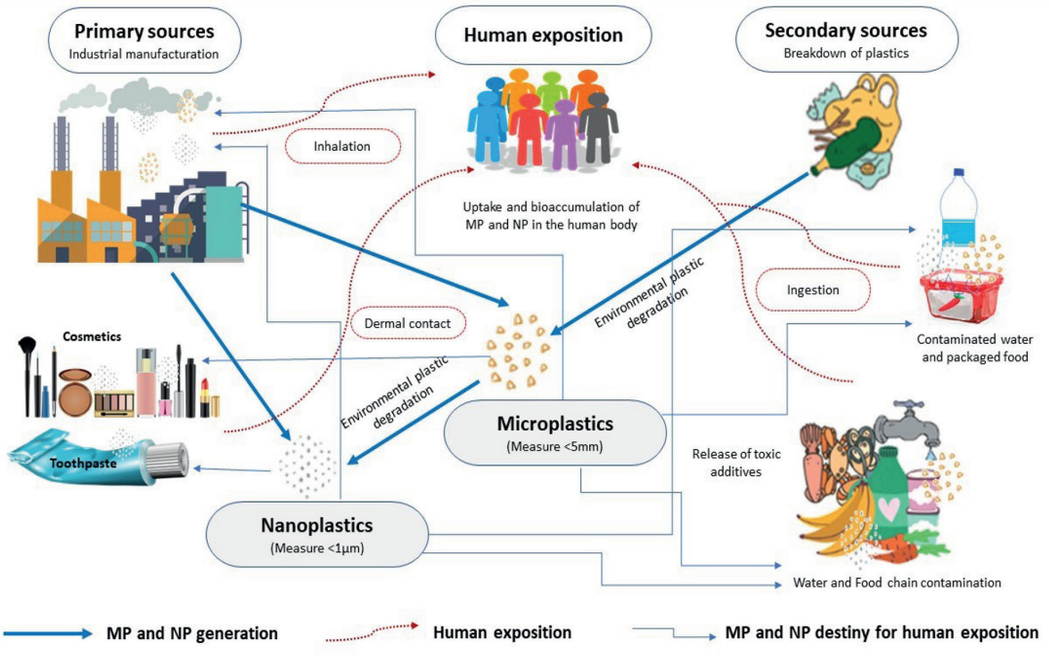

Figure 1.
Microplastics (MP) and nanoplastics (NP) generation and human exposition to these plastic particles.

Based on the source, MNP can be classified as primary and secondary. Primary are particles manufactured for indirect or direct use of raw materials with a size between 0.001 and 5 mm. In contrast, secondary are particles that have been manufactured from macroplastic degradation, defined as plastic material of less than 0.001 mm (<1 μm). Both particles are part of cleaning products, coating, cosmetics, and medical applications; these particles are also generated when bottles, clothing, tires, and containers begin their decomposition by the action of the environment [16–18] (**Figure 1**).

Due to the characteristics of MNP, mainly their size, they become difficult to detect. Indeed, there are still methodological problems with regard to standardization in the characterization and quantification of plastic particles in different materials, media, ecosystems, and the human body [19].

3. Plastic particles as conveyor vectors

The fate of plastic, once discarded, is to follow a long journey. Ultimately, they flow into local, regional, or global ocean currents and usually travel to the ocean gyres, where large amounts of debris accumulate [20, 21]. Indeed, plastic pollution has been found in rivers such as those of the tropical Andes or Germany. Given the above, plastic has the quality of being able to move through great distances and transport different plastic additives used for their manufactures, such as flame retardants, vinyl acetates, styrenes, phthalates, plasticizers, and phenols, which are related to carcinogenic or mutagenic effects as shown in the examples in **Table 1** [27].

Additionally, besides their size, plastic characteristics change because of weathering; this is a change in the microtopography of plastic; for example, smooth areas can become rougher, and cracks, bumps, and bumps cavities are formed, changing to irregular particles with a greater contact surface. These characteristics, together with hydrophobicity, provide a non-polar surface where various pollutants, such as heavy metals, pesticides,

Chemical	Function	Possible effects	Authors
Bisphenol A (BPA)	It is used in polycarbonate plastic and epoxy resin production	Endocrine disrupter	[22]
Ester phthalates (di(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate (DBP), and diethyl phthalate (DEP))	Plasticizers Increase plastic flexibility, especially PVC Solvents Fixatives of essences (perfumes and cosmetics)	Some are toxic for reproduction. Others can cause damage in high doses.	[23]
Nonylphenol (NP)	Antioxidant Plasticizer Stabilizer	Highly toxic to marine life. Endocrine disruptor in fish, where it can cause feminization. Toxicity to reproduction and development of other animals.	[24]
Polybrominated diphenyl ether (PBDE)	Flame retardant in plastics, foams, and textiles	Possible endocrine disruptor, especially for thyroid function. Toxic effects on neurodevelopment behavior, immune system, and blood in humans.	[25]
Biphenyls (Polychlorinated biphenyl (PCB))	Flame retardants Plasticizers Insulators	Toxic effects on neurodevelopment, immune system, and reproduction in humans It can produce certain cancer types.	[26]

Table 1.
Main additives in plastics and their effects.

polyaromatic hydrocarbons, antibiotics, fertilizers, and microorganisms, can adhere to and can be harmful to living beings when they are absorbed (**Table 2**) [5, 31, 32].

Indeed, MNP are substrates for colonization by microorganisms and the formation of biofilms [33–36]. These biofilms are communities of microorganisms that adhere to the surface of the plastic and form an extracellular matrix that protects them from adverse environmental conditions, changing the chemical characteristics of the piece, as we will explain widely in the next section. In conclusion, weathering processes change physical and chemical properties of MNP, leading to changes in the environmental behavior of MNP. It is essential to know that these changes in MNP affect the transport and end up in large amounts of toxic contaminants. In addition, weathering affects sedimentation, ingestion by other organisms, and pathogen transportation [15]. Considering this behavior, MNP can be transport vectors for different toxic agents [37].

3.1 Toxic agents carried by plastic particles

Micro(nano)plastics with various functional groups have been considered to interact with organic and inorganic pollutants; size and electrically neutral surfaces allow

Pollutant	Function	Possible effects	Authors
Polycyclic aromatic hydrocarbons (PAHs)	Result of incomplete burning of fossil fuels Ingredients of fuels and tar	All are persistent and bioaccumulated; some are carcinogenic, mutagenic, and toxic to reproduction.	[28]
Pesticide residues	Control various pests and disease carriers Insecticides in agriculture and urban area. DDT use is limited to malaria control.	DDT is highly toxic to aquatic life, a possible endocrine disruptor, and toxic to reproduction. Hexachlorocyclohexane (HCH) is toxic to the liver and kidneys and may act as an endocrine disruptor and a human carcinogen.	[29]
Metals and metalloids	Many uses for the construction industry. Electronics and area of medicine . Machinery, refractory, and automobile industries. Decorative products.	Suppress the immune system, damage the endocrine system, and cause reproductive dysfunction.	[29]
Microorganisms	Play a leading role in countless natural processes, e.g.; they help produce foods, treat wastewater, creating biofuels and a wide range of chemicals and enzymes. Still, they can also cause many essential diseases.	Harmful to health, such as *Escherichia coli* and *Enterococci*.	[30]

Table 2.
Plastic particles transport the main toxic agents.

these particles to be easily transported in aqueous media, which allows MNP to be considered vehicles of importance in the long-range transport of pollutants. In recent years, several research have been developed to evaluate the impact of MNP absorption on human and animal health; being essential to know the distribution and transport mechanism in marine environments, in freshwater, as well as in food chains [38–40]. However, the environmental and biological toxicity of MNP is the genesis of current studies because, to some extent, there are pollutants, which are toxic agents that are adsorbed on the surface of MNP [15, 41].

Rodrigues and coworkers describe that the sorption of a compound can refer to two separate processes: absorption and adsorption. On the one hand, absorption refers to the coupling between a compound and a sorbent mediated by low Van-Der-Waals forces, which allows dissolved molecules to be retained by the sorbent. On the other hand, adsorption needs gamma forces, from Van-Der-Waals forces to ionic or covalent bonds concerning the adsorbent surface [33, 35, 36, 42]. On the one hand, the physical and structural characteristics of MNP are determinants for their transport; however, they also allow the development of absorption and adsorption processes of organic and inorganic compounds on the plastic particle, as well as interfere with the bioavailability of contaminants and their effects on organisms [43, 44]. On the other hand, the characteristics of the contaminants,

such as heavy metals, present in plasticizers, stabilizers, pigments, fillers, diluents, solvents, and other additives, as well as in the medium where the MNP particles lie, should also be considered, which may ultimately influence the absorption and adsorption behavior [45, 46].

Furthermore, the characteristics of plastic residues such as size, shape, and polymorphism, as well as environmental conditions (pH of medium, ionic strength, organic matter, microorganisms, and temperature) are involved in MNP pollutant interactions, as well as in hydrophobic and electrostatic interactions [47]. When trying to remove MNP particulate debris by membrane filtration, particle size, biofilm formation, and the interactions described above influence the final fate of these environmental elements [47, 48]. So, MNP undergoing physical, chemical, and biological interactions are released into the environment with the sorption capacity of contaminants that eventually accumulate in the environment in the form of metabolic by-products, degradation by-products, or residual MP [49].

Relevant studies that distinguish between the effects of the synthetic polymer itself and the incorporated additives or chemicals in the polymer itself are still scarce [50]. As we mentioned above, MNP have other constituents (e.g., plasticizers, stabilizers, pigments, fillers, extenders, solvents, and other additives), which have the potential to influence their absorption/adsorption behavior [45, 46, 51]. The following section describes how MNP carries the environment's most frequently encountered toxic agents.

3.2 Microorganisms

The chemical qualities already mentioned of MP, their size, and their physical changes brought about by weathering cause different organisms to adhere to the surface of microplastics. Cracks in the pieces and the hydrophobicity of MP give rise to the adhesion of microorganisms and, consequently, to the formation of glued microorganism biofilms; this ecosystem developed in MP has been named the plastisphere [52]. Plastisphere causes changes in the physicochemical properties of plastic, having a higher level of adsorption pollutants that can be transported using the currents reaching other sites. It should be noted that these biofilms increase the probability of MP ingestion by animals since they attract organisms that depend on chemoreceptors to select prey through olfactory and taste cues [5, 53].

Since the discovery of biofilm-forming microorganisms on MP in marine ecosystems by Carpenter and Smith [54], little research has been done to describe the named plastisphere in 2013. From this date, the research on the microbiota associated with plastic debris has started to receive attention. In the beginning, the marine plastisphere was described, which comprised diverse microbial communities, including opportunistic pathogens transported through MNP worldwide [13, 55].

Marine plastisphere differs from the surrounding water, natural and artificial substrates, and within the plastic types [13, 52]. For example, the microbiota colonizing MP and NP from different polymers in the Bay of Brest (France) presents a prevalence of *Pseudomonadales* and *Oceanospirillales* on PE, alpha-*Proteobacteria* on PP, and *Rhodospirillaceae* on PS [56]. *Pseudomonas* predominate on fresh and marine water microbiota associated with MP and NP; now, n their capability to degrade a wide array of plastics is well known [57]. In addition, *Firmicutes* and *Proteobacteria* were also detected, confirming that some microorganisms may use MP as a raft to migrate from one ecosystem to another [58, 59]. A little research has been done on fungal communities associated with MNP.

The potential role of MNP in dispersing pathogenic species such as *Vibrio*, *Pseudomonas*, *Acinetobacter*, and even the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has been reported [58, 60]. For the last case, interaction mechanisms between MNP and the SARS-CoV-2 RNA fragment involve electrostatic and hydrophobic forces, and the interaction affinity is associated with the inherent structural parameters of the MNP. Humans are exposed to SARS-CoV-2-contaminated MNP via their lungs [60].

The transportation feasibility of pollutants and pathogenic microorganisms needs to be better understood by MNP across the waters and their introduction into the food web. Nonetheless, aquatic organisms' ingestion of MNP has been described as a possible transport mechanism of hazardous substances and microbial communities associated with MNP [61].

3.3 Heavy metals (HM)

Not only can microorganisms be transported by MNP, but they can also transport other hydrophobic organic contaminants due to their hydrophobic nature and increased available sites on their contact surface. They can also adsorb heavy metals [62]. Although the mechanisms are being studied, it is observed that the biofilms formed in the MP increase the adsorption of heavy metals through electrostatic interaction, cationic ion exchange, and the formation of complex groups with the functional ones in the biofilms [63, 64].

The first reported interaction between plastics and heavy metals (HM) took place as early as in 2010. Later, some studies proved that HM (Cr, Co, Ni, Cu, Zn, Cd, Pb, Ag, and Hg) could be enriched in MP from different polymers such as PE, PP, PS, PA, PVC, and polyformaldehyde (POM). Interestingly, the adsorption of heavy metals on pristine MP without surface modification is almost negligible, while the eroded/weathering MP, as well as those modified through the attachment of organic matter, accumulate HM [41].

Heavy metals, non-biodegradable inorganic pollutants, cause direct toxicity in the organism; exposure to these pollutants has been linked to the development of cancer and chronic diseases due to their bioaccumulation [65, 66]. As both pollutants (MP and HM) are persistent in environmental degradation and transformation, being resistant and challenging to eliminate, the threat posed by their combined exposure to ecosystems and human beings can be worrisome. A limited number of studies have been conducted on the combined effects of MP and HM, suggesting that the interaction between the two types of pollutants may trigger synergistic, antagonistic, or potentiating effects on organisms. However, since assessment of co-exposure risks in organisms is complex, their effects on humans still need to be determined [41].

3.4 Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons are a class of chemicals that occur naturally in coal, crude oil, and gasoline. PAHs have been detected in surface water, drinking water, and wastewater treatment plants, thus representing a risk to public health and the environment [67–71]. Epidemiological studies have demonstrated that exposure to polycyclic aromatic hydrocarbons (PAH) causes damage to human health, ranging from decreased immune response, altered thyroid function, liver, and kidney disease, altered lipid and insulin metabolism, involvement in the development of cancer and non-Hodgkin's lymphoma, and may even negatively influence reproduction and

human development. They also have a high carcinogenicity and mutagenicity index, and some cases have been reported where the descendants of mothers exposed to these pollutants have alterations in neuronal development. Therefore, it is crucial to determine the mechanisms of PAH adhesion or absorption in MNP [72, 73].

The interaction of MNP with emerging contaminants of clinical interest and importance for their health effects (per- and polyfluorinated substances (PFAS), PAHs, and BCP) are recalcitrant to environmental degradation. Industrialization development and anthropogenic activities are the primary sources of PAHs in the environment. There are three principal anthropogenic sources of PAH emissions. One is pyrolysis, which includes the incomplete combustion of coal, wood, petroleum, and organic polymer compounds. Another is the leakage and discharge of oil during the mining, transportation, production, and use of crude oil, coal tar, asphalt, shale oil, carbon ink, and industrial mineral oils. The third includes food cooking processes, municipal waste incineration, and agricultural surface emissions (sewage discharge, use of pesticides and herbicides during agricultural irrigation) [2, 74].

Polycyclic aromatic hydrocarbons are transported in the environment in different ways, including leakage, volatilization, and biosynthesis. Like MNP, PAH can also migrate through rivers, precipitation, and air [2, 74]. The main factors affecting the adsorption of PAH by MNP are related to their physical characteristics, including spatial structure, particle size, specific surface area, crystallinity, and glass transition. As regards the chemical interaction between MP and PAH, the major forces are π-π interaction and halogen or hydrogen bonding [75].

Another point of biological and environmental importance to consider in the case of PAHs is their phototoxicity, as the PAH organism exposure in the environment is inevitably accompanied by sunlight. Studies based on various aquatic organisms and mammals have shown that ultraviolet (UV) light amplifies the toxicity of PAH and cannot be neglected [2, 74]. The phototoxicity of PAH in humans has been done *in vitro* at the cellular level, where benzo (*a*) pyrene (BaP) is a hot research topic. Under ultraviolet A (UVA) and ultraviolet B (UVB) irradiation, BaP significantly promoted the production of hydrogen peroxide (H_2O_2) from human epidermoid carcinoma cells (A431) and human primary keratinocytes in a dose-dependent manner [76]. UVA and BaP showed a 7-fold increase in synergy in comparison to UVB. Another study also proved that BaP and its metabolites induced the production of reactive oxygen species (ROS) in human skin keratinocytes (HaCaT) under UVA irradiation, which mediated the formation of intracellular lipid peroxides in a low dose-response manner [77].

3.5 Pesticides

Pesticides have favored the generation of economic income from commercializing agricultural products; however, they are potentially harmful to the environment and human health [78]. These pesticides can bind to organic matter, to PE (polyethylene) agricultural films, or to the soil's clay mineral fraction, making their eradication in the ecosystem difficult. Carbofuran and carbendazim (CBD) are pesticides that are potentially harmful to human health by inhibiting the acetylcholinesterase (AChE) activity, damaging the parasympathetic nervous system, and causing bradycardia, abnormalities in blood pressure, bronchoconstriction, gastrointestinal hypermotility, among other disorders. Unfortunately, these pesticides can adsorb on the surface of MNP, thus becoming internalized in the human organism and increasing the toxicological risk [79]. The pH, ionic strength, and temperature are parameters that are considered to evaluate the interactions between plastic particles and pesticides [80].

It has been considered that the interactions between these compounds with plastic particles start in the farmland and thus are maintained during transport to the ocean. Therefore, it is necessary to consider the search for new strategies to reduce the presence of MNP in the environment since they are vectors that can affect human and animal health and irreparably damage our ecosystems.

3.6 Antibiotics

As mentioned above, in the aquatic environment, MNP are colonized by microorganisms, mainly bacteria that form dynamic biofilms. These biofilms promote antibiotic resistome (AR) in the plastisphere. AR is conformed mainly by antibiotic-resistant bacteria (ARB) and antibiotic or multi-drug-resistant genes. MP have a specific function in the enrichment and transportation of AR through processes such as horizontal gene transfer, conjugation, gene transduction, and transformation. The levels and types of mobile genetic element (MGE), especially integrase genes (*intI1* and *intI2*), besides the structure and density of bacterial communities, the incubation period, and anthropogenic chemicals promoting the co-selection are all significant factors in the development, enrichment, and transportation of plastisphere-associated AR and pathogens in the aquatic environment [81].

Several studies have reported that tetracyclines, macrolides, fluoroquinolones, sulfonamides, aminoglycosides, chloramphenicol, and beta-lactams are frequently encountered antibiotics adhered to MP detected in worldwide marine environments [82]. AR associated with MP (AR-MP) can be a vector for bioaccumulation of these antibiotics and have higher lethality than MP [83].

Exposure to AR-MP and pathogens could be linked to disruption in food chain, enzymatic and genetic toxicity, oxidative stress, altered feeding behavior, gut microbiota dysbiosis, metabolic disorders, pathogen-induced diseases, and drug resistance [81].

The adsorption of antibiotics on microplastics can span a very wide transport range and cause a large combination of effects. One study investigated the adsorption of mainly five types of antibiotics (sulfadiazine (SDZ), amoxicillin (AMX), tetracycline (TC), ciprofloxacin (CIP), and trimethoprim (TMP)) on five types of microplastics (polyethylene (PE), polystyrene (PS), polypropylene (PP), polyamide (PA), and polyvinyl chloride (PVC)) in freshwater and seawater systems. It was shown that PA had higher adsorption capacity for antibiotics in the freshwater system, which can be attributed to its porous structure and the ability to form many hydrogen bonds [83].

In resume, from the time we used plastic products, they have had a journey through tributaries, suffered weathering in the sea, they journeyed through the chain trophic and the air, which causes them to absorb contaminants on the way, becoming a conveyor vector.

4. Human exposure to plastic particles

Plastic particles, as mentioned above, have become a multifactorial and far-reaching problem; this does focus not only on the nutritional consequences or damage to aquatic systems but also on the epidemiological consequences [84, 85]. Microplastics and nanoplastics (MNP) are ubiquitous in the environment, and the effects of human exposure to these particles have not been fully described, representing a challenge and point of studies related to human health [86]. Even exposure to low concentrations

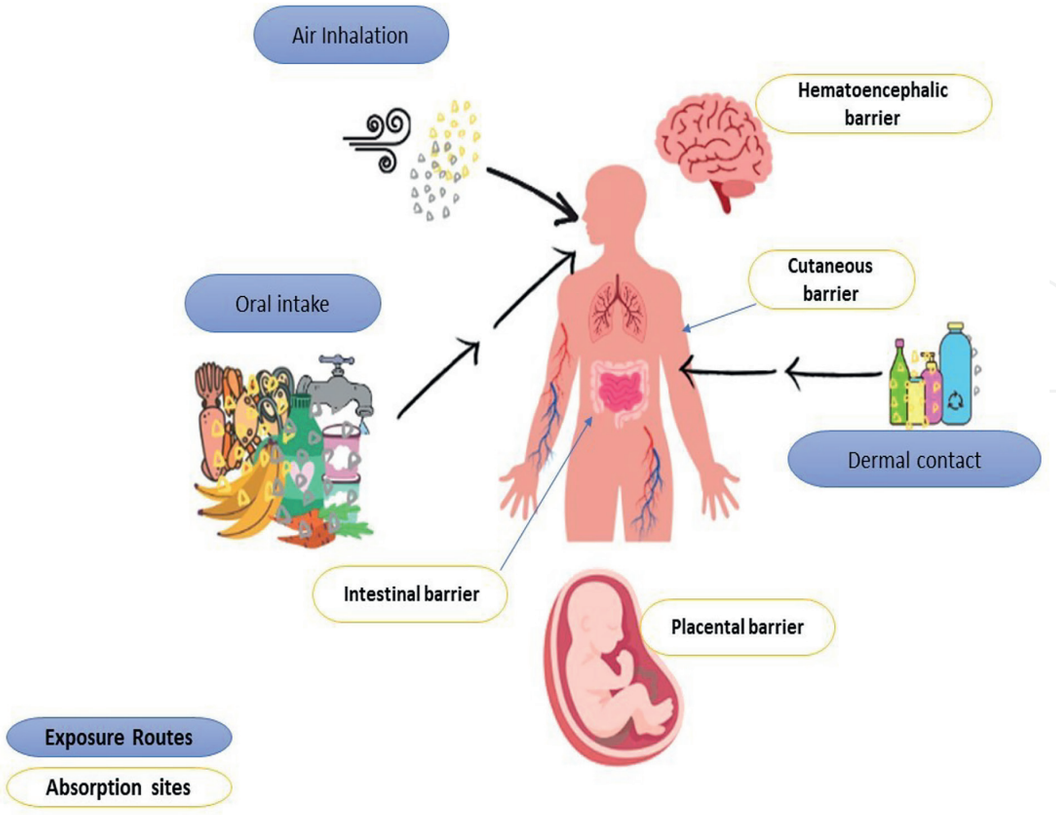

Figure 2.
Human exposure routes to plastic particles and sites where their absorption occurs.

of these particles for prolonged periods is a worrying situation, as they are present in food and drinking water [87].

The Center for Diseases Control and Prevention (CDC), in [88], verified that the main routes of exposure to MNP for humans are inhalation, ingestion, and dermal contact (**Figure 2**). According to data reported by Cai and coworkers in [89], marine animals ingest MNP contained in water, and as they are eaten, they can be passed mainly in this way to humans; likewise, MNP have been found in table salt [90]. Moreover, other MNP exposition vias also occur by ingestion of food and plastic packaged consumer goods, which can become contaminated by package degradation or by ingestion of contaminated food or water and inhaling contaminated air; for all vias, it has been determined that they impact negatively human health [91] (**Figure 2**).

The main absorption sites are related to the principal body barriers (**Figure 2**). Contact exposure begins with penetration through the pores of the skin, ingestion through the consumption of MNP-contaminated water or food, articles of personal use, etc., which pass the intestinal barrier. Exposure via area or inhalation is brought about by the presence of MNP in the air, and through breathing, enters the body and accumulates in the respiratory system. The three main routes of exposure to MNP are described in more detail below.

4.1 Exposure by ingestion

The most evaluated and common route by which humans are continuously exposed to MNP is the oral route; it occurs through the intake of contaminated

water, food, and personal cleaning items such as toothpaste. Extensive use of plastic components in drinking water networks and filtration of particles from water pipes under long-term use can lead to high exposure to large concentrations of MNP that can impact health [92]. Several studies have proven that humans consume hundreds of millions of MNP particles from packaging tea bags, seafood, table salt, honey, beer, and bottled beverages. In food, MNP can be present in animals that become contaminated through their environment or food chains, such as shellfish. MNP absorbed by microorganisms lower in the food chain are ingested by higher organisms in it and are finally ingested by humans affecting human health through bioaccumulation [93, 94]. MNP can also be present in contaminated food during its production or packaging processes [95–98].

Deng et al. [99] used pristine particles of fluorescent polystyrene microplastics with two diameters, 5 and 20 μm, to evaluate their distribution in the tissues, their accumulation, and the specific effect on the health of the mice that formed both experimental groups. The results indicated an accumulation of particles in the liver, kidneys, and intestine; the distribution of these particles depends on the size. It was determined that the intake of MP alters energy and lipid metabolism and intervenes in oxidative stress. It has also been determined that particles up to 150 μm can move through the mammalian intestinal barrier and that the absorption rate is <0.3% [100]. On the other hand, Campanale et al. [101] report that most particles down to 10 μm can penetrate all organs, including the brain; however, the consequences have not been established.

Due to the permanence and accumulation of MNP in the food chain and in wildlife, whose resources are destined for human consumption, they are of great relevance because, as we depict above, they act as transporters of pathogens, pollutants, and potential toxins with negative impacts on health [102]. In addition, the accumulation of plastic particles at all trophic levels potentially exposes humans [103]. The European Food Safety Authority (EFSA) and World Health Organization (WHO) suggest that exposure to MNP in humans has low adverse effects; however, more evidence is needed on the preliminary signs, which propose better analytical methods to assess this problem. Auta and collaborators [104] studied the toxic effects of exposure to MNP in marine organisms, observing that depending on the type of organism, there is bioaccumulation of particles, metabolic changes, inflammatory processes, reproductive problems, changes in behavior between others, and all of this will determine the ability to survive in nature.

The lack of an established and validated method providing non-destructive evidence of the presence of MNP in the tissue limits estimates of the degree and effect of their exposure [103]. Ultra-thin tissue fractions are used in medical research, making assessment of the possible presence of MNP and their influence on disease processes even more challenging. It is essential to deepen studies on the possible immunological effects, gastrointestinal alterations derived from modifying the intestinal microbiota due to exposure to these particles, and the damage they generate. Murine models are a tool of choice to evaluate these processes, which allow us to know the risk to health in animals and humans and evaluate the sensitivity of specific pathologies to such exposure.

4.2 Inhalation exposure

Inhalation itself is considered one of the main human exposures to MNP; it also occurs because these particles are found in the air, some of the sources of which can

be synthetic textiles, tire erosion, and some types of polymeric fibers such as PP, PE, PS, and PET. The exposure per individual has been estimated at 26,130 airborne plastic particles daily [105].

Once inhaled, MNPs reach the respiratory epithelium, causing their translocation by diffusion, penetrating the cell directly or by uptake of MNPs by endocytosis or phagocytosis. In the alveoli, phagocytosis is carried out for particles between 1 and 3 μm in size, being this mechanism the main one for this route of exposure. Smaller particles could be passively transported by diffusion across the membrane [106]. However, the number of studies evaluating MNP in indoor and external environments is scarce [107].

After studying MNP presence in the air of private residences and public offices, it was reported that indoor air contains a higher concentration of MNP than outdoor air, implying that exposure in humans is higher [108]. Likewise, MNP can be inhaled through fine dust suspended in the air and then release chemical additives [109]. Plastic fragments and fibers are the most common means that favor the inhalation of MNP [46].

Removal of inhaled particles can be done through mucociliary transport, resulting in minimal MNP concentration in the airways or phagocytosis by macrophages. However, it has been reported that MNP can circumvent these mechanisms by accumulating in the lungs and entering the systemic circulation [110]. Another conduit through which inhaled nanoparticles can reach the central nervous system (CNS) is the olfactory bulb [111]. Some studies indicate that in some neurological diseases, the absorption of plastics in neonates (plasticenta) and its consequences are associated with inhalation to MPN [112]. One of the studies by Fournier and collaborators [110] shows that an intratracheal dose of microplastics during gestation undergoes maternal-fetal translocation, generating secondary damage to fetal development.

4.3 Dermal exposure

Topical exposure to MNP contained in personal hygiene products and contaminated water affects skin health, and epidermal cells have shown stress in oxidative experiments *in vitro* [113]. Tiny synthetic fibers (<25 μm) penetrate skin pores measuring around 40–80 μm and will bypass the stratum [114, 115]. However, nanoparticles smaller than 100 nm can be exclusively absorbed in the stratum corneum [100]. Exposure by this means is based on individual susceptibility because the pores of human skin have different characteristics between one living being and another.

The nanotoxicology of nanoengineered materials indicates that nanoparticles (NPs) with a size <40 nm can enter the body through the epidermal barrier [116, 117]. This exposure occurs when there is contact between the dermis and NP in the environment, which can occur when showering with water or using personal care products containing, for example, nanopolystyrene [31, 118]. Indeed, the Food and Drug Administration (FDA) passed the microsphere-free water law that went into effect for products manufactured after the 2017–2018 law that restricts the use of MP in exfoliating products, toothpaste, and other cosmetics to reduce dermal exposure and decrease residues in water systems. In the medical field, there is also a wide use of MP for drug administration; it is considered that people may have been exposed to 4594–94,500 MP particles in just 5 mL of the product [35].

Considering the seriousness of plastic pollution in recent decades, it is necessary to act and raise awareness about its effects on the human body. More research is currently needed to analyze whether there is a risk of absorption of MNP through the

dermal exposure route in humans. For example, it has not been determined whether rigid MNP cross the subcutaneous barrier under normal conditions; however, it has been shown that they accumulate in hair follicles, and it was observed that Langerhans cells absorbed them [119]. The following section describes the most critical effects of MNP exposure on human health.

5. Human digestion of toxic agent-contaminated MP and NP

When we eat food with MNP contaminants, they can be released into the digestive system. The contaminants can then be absorbed through the lining of the gastrointestinal tract (GIT) and transported through the circulatory system to various organs in the body [120]. The exact process has yet to be fully understood, but it is believed that contaminants are released by the action of stomach acids and digestive enzymes, as well as by interaction with gut microbiota. So far, research on MP digestion is scarce; it has been performed *in vitro* and using single-batch models, and studies of MP with adsorbed toxicants are even scarcer.

An example is the study on MP with Chromium (Cr) in a human static *in vitro* digestion model, including mouth, gastric, small intestinal, and large intestinal digestive phases where no microbiota was included. The results showed high desorption under acidic conditions, which means that Cr adsorbed on MP with different polymers, such as PE, PP, PVC, PS, and PLA, 150 μm, was more bioaccessible due to acidic conditions favoring the desorption of anionic Cr species from the MP surface. At the same time, no release was observed in the oral phase. Additionally, PLA exhibited the highest oral bioaccessibility compared to other polymer types, probably due to its degradation enhanced by the action of enzymes in simulated digestive juices [121].

Moreover, it has been reported that there is no striking alteration in the physicochemical characteristics of the five types of MP (PE, PP, PVC, PET, and PS) by artificial digestive juices mimicking the saliva, gastric, and intestinal phases of human digestion. However, corona formation on the MP surface due to the adsorption of organic compounds, such as proteins, mucins, and lipids during digestion, should be considered [122].

Increasing attention is paid to the gastrointestinal tract (GIT) as the first barrier and a portal of entry and target for MP. As we have reviewed above, MP harbors a unique microbiome shaped by polymer type and environmental factors. After MP ingestion, several human pathogenic microbial species associated with MPs represent a potential risk for humans. In addition, ingestion of AR-MP could enhance the antibiotic release and the development of antibiotic-resistant bacteria in the human gut acting as vehicles for transferring antimicrobial resistance genes to the intestinal microbiome and favoring human infection related to resistant bacteria. However, reliable *in vitro* gut models could then be made relevant to mimic such exposure scenarios considering the consequences on at-risk populations (children and elderly) and, ultimately, pathophysiological conditions (obese patients and inflammatory bowel disease patients) [123].

6. Principal health effects associated with plastic particles' exposure

As mentioned before, there is still a lack of definitive evidence linking the consumption of MNP with human health; in correlation studies on people exposed to

high concentrations of microplastics, experiments with animal models and cell cultures have shown that microplastics can cause the activation of the immune response, stress and induce increased or developed toxicity.

6.1 Effects on physical barriers

Ingestion is considered the main route of exposure to MNP, so the tissues of the human gastrointestinal tract are considered the most exposed, data supported by changes in the intestinal microbiota. Information has been found on morphological alterations in Peyer's plaques, which are part of the lymphoid tissues associated with the intestine, leading to the activation of inflammatory processes. Other cells that undergo morphological and functional changes are the M cells responsible for the absorption of particles from the intestinal lumen to the basolateral region, where many lymphocytes and others are found. Cells of the immune system; These, in turn, transport antigens in an integral way because on their surface, there are receptors for specific antigens, proteins, viruses, and bacteria incorporated into endocytic vesicles in the luminal plasma membrane and transported to pre-lysosomes and lysosomes; site of presentation of antigens and their epitopes to dendritic cells, macrophages, and lymphocytes present in the epithelium of lymphoid follicles or in the mucosa; this feature of a carrier cell also allows it to transport plastic nanoparticles from the intestine to lymphoid tissues; therefore, it is associated with pro-inflammatory processes in humans [31, 101, 124]. These particles can sometimes concentrate and disrupt immunity processes in the intestinal barrier.

The persorption process for larger particles up to 130 μm in diameter, performed by the epithelial cells of the gastrointestinal tract, is another pathway of uptake but not absorption of MNP.

In addition to the particle size of MNP, their chemical composition, shape, and hydrophobicity are other factors that affect absorption and translocation to other organs. However, it has been determined that hydrophobic surfaces can be transported more efficiently through the intestinal mucosa. These characteristics allow corona formation by the adhesion of microorganisms, proteins, and other biomolecules [125]. MNP, after being internalized in the intestinal epithelium, can be released into the intestinal lumen due to tissue cell renewal that occurs approximately every other day; therefore, it has been determined that they do not reach the bloodstream. Some studies assume that the continuous accumulation of particles in the liver and digestive tract generates toxic effects [126]. Li et al. [127], in a mouse model, fed PE particles, reported increased inflammation in the small intestine, followed by changes in the microbiota and an increase in systemic pro-inflammatory markers.

6.2 Effects on gut microbiota (GM)

The gut microbiota plays a vital role in human health; this term refers to the microbial ecosystem that colonizes the gastrointestinal tract. The relevance and impact of resident bacteria on host physiology and pathology are documented, as are the main functions of GM ranging from metabolic activities to their translation into metabolic activities, in the recovery of energy and nutrients, protection of the host against foreign microorganisms; trophic functions essential for the development and homeostasis of the immune system; absorption of vitamins, etc. On the other hand, evidence implicates the intestinal microbiota in pathological processes such as

multiorgan failure, colon cancer, inflammatory bowel disease, obesity, neurocognitive disorders, and even personality disorders. Variations in GM after *in vivo* exposure to microplastics are being investigated in several contexts. Metagenomic studies have been developed to explore changes in GM; for example, in the springtail *Folsomia candida*, exposed to PVC microspheres of 80 to 250 μm, 1 μg/kg of dry soil for 56 days, intestinal microbial diversity was significantly higher, and its composition showed a significant decrease in *Bacteroidetes* and an increase in *Firmicutes* [128]. On the other hand, in the *crab Eriocheir sinensis*, during 21 days of exposure to PS microspheres of 5 μm at doses of 40 mg/L, a decrease in the relative abundance of *Firmicutes* and *Bacteroidetes* was reported, and an increase in the relative abundance of *Fusobacteria* and *Proteobacteria* [129].

Within the studies carried out in murine models, a large number of significant modifications have been found in the composition of the bacterial phyla of the GM after chronic exposure to PS microspheres of 5 μm at a concentration of 100 μg/ day for 5–6 weeks, the relative abundance of the phylum α-*Proteobacteria* decreased, the relative abundance of the phyla *Actinobacteria* and *Firmicutes* was also reduced [38, 130, 131]. In the study by Luo et al. [132], they used a protocol with similar exposure, used PS beads of 5 μm and a dose of 1000 μg/L for 6 weeks, exposure was performed in pregnant and lactating mice, some transcriptome studies and 16 s RNA sequencing indicated that MP caused metabolic disorder in pregnant mice associated with dysbiosis and intestinal barrier dysfunction. Simultaneously, maternal exposure to MP triggered intergenerational effects and even caused long-term metabolic consequences in generations 1 and 2. MP and PN influence the development of intestinal dysbiosis; these variations can, in turn, cause functional alterations in the immune system.

6.3 Effects on immune response

Plastic particle accumulation has been demonstrated in the liver, kidneys, brain, spleen, and reproductive organs (**Figure 2**) [40, 113, 133]. The intestinal immune system interacts with non-pathogenic commensal microorganisms and harmless food antigens that generally must be immunologically tolerated. In turn, the immune system must retain the ability to respond quickly to infectious toxins. This event depends on the different mechanisms involving myeloid, lymphoid, innate, and T cells found in the intestinal lamina propria and mesenteric lymph node. The immunotoxicity of MNP has yet to be thoroughly evaluated; however, until now, it is known that the immune system is compromised by exposure to these.

There are several examples of immune response after MP exposure. One of this is the exposure in *Daphnia magna* to carboxylate-modified PS-NP with a size of 500 nm at a concentration of 85 mg/L for 1 year, which increases the number of hemocytes. Studies on invertebrates have determined that exposure to PS alters the immune system [134]. After exposure to amino-modified nanoplastics with a particle size of 50 nm at 10 μg/L after 24 h, hemocytes presented mitochondrial and lysosomal alterations; after 72 h, the levels of bactericidal activity and transcription of genes related to the immune system were elevated, and after 96 h of exposure, hemolymphatic phagocytosis, oxidative stress levels, and microbiota were modified [135]. On the other hand, a specific dysregulation of proteins involved in the immune response in the hemolymph of mussels exposed to PE and PA-MP at doses of 845 and 1296 particles/L, respectively, for 52 days was observed. Finally, exposing mollusks of *Mytilus* spp. to a mixture of PE and PS microspheres with a size <400 μm, 10 μg/L,

for 10 days, improves the activity of acid phosphatase in hemolymph and causes DNA damage, as published by Revel et al. [136].

After *in vivo* evaluation of the effects of exposure to PS-NP (41 nm, 0.025–0.2 μg/μL) in fish, *Pimephales promelas* modify their neutrophil function. This activity is dose-dependently administered, and myeloperoxidase activity is also modified [137].

As mentioned above, there are intergenerational effects of exposure to MNP, for example, after a 90-day administration of 2 mg/day/mouse of PE particles. In mice, exposure to PE-MP for 5 weeks at administered doses of 20 and 200 μg/g modifies serum interleukin 1α (IL1α) and granulocyte colony-stimulating factor (G-CSF), decreases regulatory T-cell count, and increases the proportion of Th17 cells in splenocytes [83]. In a mouse model of pregnant and lactating female, it has also been reported that blood neutrophil counts and immunoglobulin A (IgA) levels were elevated in mothers and spleen lymphocytes in mothers and offspring [138].

The presence of macroplastics in the gastrointestinal tract of the shark *Scyliorhinus canicula* was associated with a significant upregulation in the expression of T-cell receptor beta (TCRß) and T-cell receptor delta (TCRδ) and immunoglobulin M (IGM) cell receptors in the spleen [139].

Secretory IgA is one of the main components of the immune barrier present on the surface of the intestinal mucosa, so it interacts with symbiotic bacteria to protect against pathogens. On the other hand, under the intestinal epithelium are located different cells of the immune system such as T, B, dendritic cells, and macrophages, which coordinate and are responsible for the presentation of antigen-producing antibodies and secretors of cytokines in the intestinal barrier [140]. Within the research that have been carried out to evaluate the immunotoxicity caused by MNP, it is estimated that in immune cells, they are the target and where toxic effects are present [139].

As the production of plastics increases, so does pollution in the air, water, and food chain, increasing their permanence and exposure in living beings. It is estimated that every 10 g of human feces contains at least 20 particles of MP or NP [141]. In 1 g of tissue obtained from adult colectomy samples, 28 ± 15 particles were determined, and approximately 331 MP particles were sampled [142]. Confirming that MP can enter the gastrointestinal tract and the intestinal permeability caused by MNP allows commensal and pathogenic bacteria to penetrate, causing pro-inflammatory immune responses [143]. The transcription of genes related to cell proliferation, metabolism, and immunity in epithelial cells is regulated by GM [144], so it is necessary to monitor and determine damage to the intestinal barrier as the impact of microplastics on GM cannot be ignored. In addition to the intestinal barrier, studying the effects on the intestinal-vascular barrier (IVB) is relevant, an additional cellular barrier located under epithelial cells, which controls access to circulation and the liver [145]. Suppose any molecule or microorganism crosses the epithelial barrier. In that case, they will remain in the lamina propria, and when the IVB is damaged or exposed, intestinal pathogens can enter the systemic circulation and cause further damage [146]. The damage caused in IVB is brought about by bacterial translocation and MP and NP, thus participating in the pathogenesis of non-alcoholic steatohepatatis (NASH) [147]. However, there is still not enough evidence on the effects of MP and NP on the intestinal-vascular barrier, remembering that the intestinal system is a complex and multifunctional organ. The damage exerted by these particles is not limited to the intestines; they are also causes of inflammation and metabolic dysfunction through intestinal injuries. It remains to be clarified whether acute, long-term toxic effects are triggered in humans.

6.4 Effects on the respiratory tract

Plastic particles are widely distributed in the atmosphere and can be inhaled directly and continuously, posing a potential risk to the respiratory system [148]. The translocation vias of MNP into body compartments have been previously described. Most research to determine the effects of MNP on the respiratory system have been conducted *in vitro* to determine lung cell viability, finding that exposure to these particles and the pollutants they can carry increases cell death, induces oxidative stress and inflammatory response, and increases epithelial barrier destruction. Specific NPs have been reported to reduce the repair capacity of the lungs, leading to tissue damage and lung disease after prolonged exposures [149].

Lu and coworkers [130] administered microplastic droplets (1–5 μm, 300 μ/20 μl) into the nasal passage of mice, where they reported the presence of MP in the airways, alveoli, and interstitial, indicating that particulate matter (PM) can cross the alveolar epithelial barrier. In other studies with animal models, pathological examination showed alveolar structural alteration and disorganized arrangement of the bronchial epithelium because of tracheal administration of PM at a concentration of 2 mg/200 μl [150]. The translocation of MPs and NPs to the pulmonary level activates the immune response by releasing secretory signals (cytokines) because it is estimated that the airway epithelium detects them in the same way as if they were allergens or other irritants. The cytokines whose expression is increased are tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β), and transforming growth factor beta (TGF-β) [149–151]. These underlying mechanisms are related to refractory asthma; the aggregate of these data suggests that PMs can differentiate alveolar cells, activate fibroblasts and extracellular matrix organization, events related to fibrosis and pulmonary emphysema and even to lung cancer. Therefore, it is necessary to show the potential risk posed by inhaled MNP.

6.5 Effects on the liver and lipid metabolism

As mentioned above, when responding to oral exposure to MP and NP, multiple groups showed that the gut microbiota is altered, as well as serum and hepatic markers of amino acid and lipid synthesis and metabolism, as well as liver inflammation [38, 83, 127]. Exposure to these particles produces hepatocellular edema and infiltration of inflammatory cells with increased production of IL-1β and TNF-α; hepatotoxic injury also occurs, whose elevation of serum markers of liver function depends on concentration, exposure time, and particle size; mice exposed to 250 nm Polyurethane (PUR) particles for 10 days showed elevated serum levels of alanine transferase (ALT), alkaline phosphatase (ALP), IL-6, and TNF-α, hepatic vascular congestion, and hepatocyte vacuolization [152]. Subsequently, the exposure was brought about with a mixture of PS particles of 1.4 and 10 μm by the oral probe in triple transgenic reporter mice (HOTT) with heme oxygenase-1 (HO-1), which expressed a LacZ indicator sensitive to oxidative stress and pro-inflammatory processes.

Effects that depend on the concentration of particles [122]. The liver is the main site where lipid metabolism occurs; it is sensitive to pathologies such as NASH, which manifests as an accumulation of fatty vesicles combined with cholesterol and high-circulation triglycerides. The MP and NP alter these performances in rodents. Hepatic distension increased hepatic triglycerides, total cholesterol,

and decreased expression of peroxisome proliferator-activated receptor alpha (PPARα) and peroxisome proliferator-activated receptor gamma (PPARɣ) has been observed. The lipid-sensitive nuclear receptor PPARα regulates catabolism and fatty acid elimination, and some studies concluded that it may have anti-inflammatory effects by suppressing the nuclear factor-kappa B (NF-κB) [153, 154]. Thus, the regulation of PPARα is reduced, predicting the potential development of NASH. It is understood that changes in lipid metabolism depend on particle size, as mentioned above.

7. Conclusion

When evaluating the effects of MNP in humans, routes of exposure such as absorption, ingestion, and inhalation have been established; however, a few research have described the gastrointestinal and pulmonary toxicity that develops oxidative stress, inflammatory response, and metabolic disorders.

In addition, it is essential to understand whether MNP can be further degraded after ingestion under acidic conditions of the stomach or within cell lysosomes—the long-term occurrence and fate of ingested MP and NP in the human body warrant further investigation.

Given the wide variety of particle sizes, shapes, and chemical compositions of plastics, the potentially dangerous effects of different types of MNP on human health remain largely unknown. Therefore, we recommend that future research focus on understanding the potential hazards and risks of chronic exposure to various types of MNP at relevant concentrations.

Both MP and NP can significantly affect marine organisms and human health. Since MP are small and lightweight, human-consumed marine species can ingest them quickly, accumulating this debris in tissues, circulatory systems, and the brain. Research on MP bioaccumulation and biomagnification through the food web is scarce; efforts should be directed toward clarification.

Compared to MP, NPs can spread even more efficiently in animal bodies and translocate between various organs. They also offer more effective adsorbents, transport of contaminants, and proven threats to human and animal health. However, NPs have yet to be noticed in most studies due to their enigmatic existence, limits on sampling and analysis protocols, and non-standardized basic parameter units, such as particulate matter abundance.

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Conflict of interest

No conflicts to declare.

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