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Review

Bridging the Gaps between Microplastics and Human Health

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Abstract: Given the broad and intense use of plastic, society is being increasingly affected by its degradation and by-products, particularly by microplastics (MPs), fragments smaller than 5 mm in size, and nanoplastics (NPs), with sizes less than 1 µm. MPs and NPs may enter the body primarily through inhalation, consumption, and skin contact. Once ingested, MPs can penetrate tissues, deviating to other parts of the body and potentially affecting important cellular pathways such as nonconforming chemokine receptors that control the communication between the fetus and the mother. Consequently, the potential health harm induced via MP internalization is a major issue, evidenced by multiple studies demonstrating harmful consequences in diverse animal models and human cells. Here, an overview of the various modes of exposure to MPs and NPs is presented, including inhalation, placental transfer, ingestion, breastmilk consumption, and skin absorption, as well as placental and fetal toxicity due to plastic particles based on animal and in vitro studies. Though MPs in our environment are becoming more recognized, their developmental toxicity is still scarcely known. Besides negatively affecting pregnancy, MPs and NPs have been shown to potentially harm the developing fetus, given their ability to cross the placental barrier. Still, considerable gaps remain in our understanding of the dispersion and toxicity of these particles in the environment and the precise types of NPs and MPs bearing the greatest dangers. As a result, we advocate for larger-scale epidemiological investigations, the development of novel approaches for measuring NP and MP exposures, and the necessity of understanding the toxicity of various kinds of NPs to guide future research efforts.

Keywords: exposure routes; human breast milk; human placenta; microplastics; nanoplastics

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1. Introduction

The production of plastics worldwide has increased from just two million tons in 1950 to over 390 million tons in 2021. This is due to the high demand for the material, commonly believed to be the best choice for durability, adaptability, and usage in consumer products [1]. Hence, plastic products can be found everywhere in our modern lives and are a very popular material in construction, textiles, consumer goods, transportation, electronics, and machine parts. The largest application for plastics, though, is as packaging material. One of the biggest concerns and challenges with plastics is that they can degrade to microplastics through weathering, e.g., via mechanical, microbial, or photodegradation. The term "microplastics" (MPs) refers to particles that are smaller than 5 mm, and it is estimated that over 170 trillion of these microplastic particles are afloat in the world's oceans [2]. Marine animals can ingest MPs found in the sea, accumulate, and end up in

humans through the food chain. Indeed, there are several reports of MPs in the environment and food [3], predominantly in sea salt, seafood [4], and drinking water [5]. Their effect on human health is yet unknown, but plastics often contain additives, such as stabilizers or flame retardants, and other possibly toxic chemical substances that may be harmful to the organism ingesting them [6,7]. Because MPs are pervasive in the environment, human exposure is unavoidable, mostly through three major paths: consumption, breathing, and skin contact. MPs can traverse cell membranes after being internalized. They are seen as unknown substances by the body and hence generate regional immune responses [8]. Given that the amount, incertitude, and variations of MP exposure concentrations and its associated incorporation kinetics remain uncertain, the potential risks that MPs pose to human health can result in controversy [9].

A previous review [9] reported on human exposure assessments for MPs by estimating the total MP intake in different sources (i.e., table salt, drinking water, and air). Nonetheless, the analytical detection approach has proven to be challenging, as the distribution of global MP intake rates is not necessarily well represented when using only single-exposure estimates based on average exposure rates.

MPs in the atmosphere have drawn attention lately, and several sample techniques, such as dust collection and wet/dry deposition, have been utilized. The weather has an impact on MP levels, which are higher in urban locations and lower in indoor settings. The main causes are rubber tire wear, wind-dispersed synthetic materials, and road dust; horticulture operations also have a role. Analytical methods such as air sampling to estimate human inhalation and wet/dry deposition for total MP monitoring are selected based on study aims. Scenarios involving dust intake necessitate specialized sampling, with subsequent treatment procedures according to sample kinds. MP identification is aided using analytical techniques such as μ-FTIR, SEM-EDX, fluorescence microscopy, and μ-Raman. Although there has been progress, a greater understanding of this pervasive environmental problem still requires standardized methodologies and further research into MP–environment interactions [9]. The exposure of MPs' respiratory system was also considered, and for the calculations, only atmospheric MP abundance data with a unit of item·m^{-3} were utilized. High MP concentrations (1.3×10^4–1.7×10^4 items·m^{-3}) in outdoor air samples from busy roadways and low MP concentrations (0–1.37 items·m^{-3}) in atmospheric MPs from seas were disregarded since they are not the primary locations for human activity. There is a 14.3 m^3 day^{-1} inhalation rate [10]. According to reports, the range of inhalable MP abundances is 0–19.6 items·m^{-3} [11,12]. Human MP intakes from indoor and outdoor air inhalation were computed separately since MP abundance is often higher indoors than outdoors [9]. The review provides solid quantitative data highlighting that the most significant MP intake is through inhalation (estimated to be 1.9×10^3 to 1.0×10^5 items·year^{-1} indoor air; compared to $0 - 3.0 \times 10^7$ items·year^{-1} outdoor air). Furthermore, they conclude that long-term MP exposure in humans and the fate and transport of MPs upon entering an organism through absorption and excretion are vague [13].

2. Characteristics of Micro- and Nanoplastics

Common plastic polymers like high- and low-density polyethylene, polyvinyl chloride, polyethylene terephthalate, polypropylene, and polystyrene are widely used [4]. Industries produce primary plastic particles used as essential components, e.g., in manufacturing plastic goods, for biomedical applications, and as cosmetic additives. Secondary plastic particles are formed from the degradation of larger plastics in natural environments, e.g., via mechanical, microbial, and/or photodegradation, as mentioned above. Primary MPs are intentionally produced for specific purposes, including preproduction resin pellets, microbeads in personal care products, powders for textile coatings, and drug delivery systems. Similarly, nanoplastics (NPs) are increasingly manufactured for products such as paints, adhesives, drug delivery vehicles, and electronics. These fragmented particles are the main source of MPs/NPs found in terrestrial and aquatic environments. Due to

their limited biodegradability, they can persist for extended periods, spanning hundreds of years, in marine and terrestrial environments [14].

Defining the size of MPs and NPs has lacked universal agreement. MPs are generally smaller than 5 mm, while NPs have less defined boundaries but are typically below 1 µm or even below 100 nm [15]. MPs and NPs exist in various shapes, including spherical, angular, irregular, and fibrous forms [15]. Recent findings suggest that MPs can travel up to 100 km in the atmosphere, maybe even farther, exhibiting true free tropospheric MP transport and high-altitude MP particles < 50 µm [16,17]. Therefore, it should not come as a surprise that MP particles are now found in a large variety of ecosystems, including in Arctic Sea ice [18].

3. Routes of Exposure

As both MPs and NPs are present widely in food, water, and air, the most common routes of exposure are ingestion and inhalation. Bottled water is a prevalent exposure source, potentially originating from both the water itself and the plastic packaging it comes in [19]. According to a study on human consumption, between 74,000 and 121,000 microplastic particles are consumed yearly per person in the United States [20]. MPs have been found in human feces, which is strong proof that they were consumed through the food chain and exposed to the stomach [21]. MPs and NPs can be incorporated into the lungs and gastrointestinal tract through processes including endocytosis and persorption after being inhaled or ingested and eventually reaching circulation [22]. An important development is the recent detection and quantification of plastic polymer particles even in human blood [23,24].

Thus far, only a limited number of studies have assessed these MP/NP exposures to humans. Based on the consumption of foods and drinking water in the United States, a study estimated daily MP exposure to 203 particles for girls and 223 for boys. Furthermore, the combination of ingestion and inhalation of MPs yields total exposure estimates of approximately 81,000 and 74,000 particles $\cdot$ year^{-1} for boys and girls, respectively. Nonetheless, a thorough description of the children population is missing, only to be inferred that individuals are less than 18 years old [25]. However, these figures may be "dramatic underestimates". Cox et al.'s (2019) analysis of estimates of American consumption of MPs could be underestimated by a factor of at least 1×10^5 [25]. They state that around 15% of an average male adult's caloric intake is interrelated with the consumption of up to 52,000 MP particles per year; unfortunately, the remaining 85% of calories cannot be extrapolated to a specific number of MPs consumed. The authors used different analytical methods, including Fourier-transform infrared spectroscopy (FTIR), inductively coupled plasma mass spectrometry (ICP-MS), Raman spectroscopy, and Rose Bengal stain, to determine the MP concentration in several samples, including seafood, honey, salt, sugar, and water. Another research study assessed the daily consumption rates of 553 particles for children and projected the lifelong accumulation of MPs using a physiologically based pharmacokinetic model [7]. Furthermore, in another example, Li et al. [26] examined the potential exposure of infants to MPs from consuming formula prepared in polypropylene infant feeding bottles. The bottles were able to release up to 16.2×10^6 MPs per liter. This wide range underscores the significant uncertainty surrounding human exposure to both NPs and MPs, especially during infancy, and the difficult analytical tasks involved in quantifying them [26].

Recent studies have expanded the analysis of MPs and NPs to include various food products such as honey, chicken, beer, sugar, salt, teabags, milk, seaweed, and certain fruits and vegetables. Plastic teabags, bottled water, and seafood are major exposure sources for MPs/NPs. Particularly high levels of MPs have been reported in fruits and vegetables. Although some estimates of daily exposure to MPs/NPs are known, its linkage to direct human health effects is still missing. It is agreed that studies in humans are prioritized, and the following questions can be categorized as challenging as they have not been fully addressed, e.g., what is the daily exposure of MP/NP in humans? Which populations bear low and high exposures? What main MP/NP characteristics are present in humans? When

will advanced, sophisticated, and standardized fast throughput analytical tools be available to quantify MPs/NPs in environmental and human samples? [14].

Most MPs and NPs that have the potential to be harmful to humans are primarily made of polyethylene terephthalate (PET), polystyrene (PS), and polyvinyl chloride (PVC) [27]. In laboratory studies, these plastics have been found to negatively affect cell viability and trigger the expression of inflammatory genes by releasing compounds that could potentially cause cancer. Plastics, including MPs/NPs, can contain hazardous substances and endocrine-disrupting compounds like phthalates and bisphenol A. These substances have been associated with various health issues in humans, such as epigenetic changes, reproductive toxicity, insulin resistance, type II diabetes, obesity, skeletal abnormalities, allergies, asthma, and cancer [28]. MPs/NPs may consist of different types of plastics and other chemicals, and their combined effects could lead to more severe health risks [14].

4. Transport Routes for MPs in the Human Body

Inhalation, cutaneous contact, and ingestion are the three main ways that MPs can be exposed, as recorded in the literature; the latter is the most important and is thought to result in annual intakes in the range of 39,000–52,000 mg per individual [7,29]. After being swallowed or breathed, MPs can be incorporated into tissues. In the digestive tract, they can bypass the epithelial tissue through either endocytosis processes or via diffusion paracellularly before being transported by means of dendritic cells into both the circulatory and lymphatic systems [25]. According to reports, once MPs enter the body, they might gather and cause localized damage by triggering or amplifying immune reactions, weakening the body's defenses against infections [19]. These MPs may enter the placenta through paracellular or M-cell-mediated endocytosis pathways from the respiratory or digestive systems. The most plausible method of transport for MPs is through particle absorption and translocation, which has already been described as internalization from the gastrointestinal system [19]. A recent study showed that MPs were at higher concentrations in indoor air and dust (from homes and offices) compared to outdoors [30]. As an example, in a coastal area of California, airborne MPs in indoor air (3.3 ± 2.9 fibers and 12.6 ± 8.0 fragments per m^3) were higher than in outdoor air (0.6 ± 0.6 fibers and 5.6 ± 3.2 fragments per m^3). This was ascribed to several potential factors, such as interior MP sources (such as furniture and textiles), greater atmospheric MP deposition indoors, and less atmospheric mixing and dilution compared to outdoor air [30].

Figure 1 summarizes the different pathways that MPs may encounter with the human body. The following subsections will expand our understanding of specific transport routes involving the placenta and breast milking, inhalation, ingestion, cutaneous contact, circulatory system, and brain.

4.1. Placenta and Breastmilk

As with other foreign substances, MPs can enter the tissue in depth once they have achieved the maternal side of the placenta through several yet poorly known active and passive transport modes. The trans-placental transit of MPs sized 5–10 µm can be influenced by various physiological factors and inherited traits. This may help to explain the various locations and properties of the particles found in the current investigation, as well as the patients' varied dietary and lifestyle habits and the lack of MPs in two out of six placentas that were examined in a recent study by Ragusa et al. [31]. Nonconforming chemokine receptors that control the communication between the fetus and the mother, motioning between the womb and the embryo, as well as the transferring of uterine immune cells like the dendritic, natural killer, T cells, and macrophages during a characteristic gestation are just a few of the cellular regulatory pathways that MPs may potentially alter in the placenta. Preeclampsia and fetal growth restriction are two possible unfavorable pregnancy outcomes that might result as a consequence [20]. Breastmilk also serves as the finest nutritional standard for newborns, providing nutrients and strengthening their immune system; hence, it is crucial to ensure that breastfeeding is as pure as possible. The occurrence

of MPs in the placenta, which symbolizes interactions between the fetuses and the mothers that are exposed to the environment, was confirmed by Braun et al. [32]. Recent research has shown that MPs circulate throughout every region of the body due to the existence of plastic particles in the blood [33]. Both immune cell-dependent pathways and mammary epithelial cell-dependent pathways have been proposed as potential routes for exogenous particles to go from circulation to breast milk in the mammary glands, with the latter being more pertinent in inhaled particles [34–37].

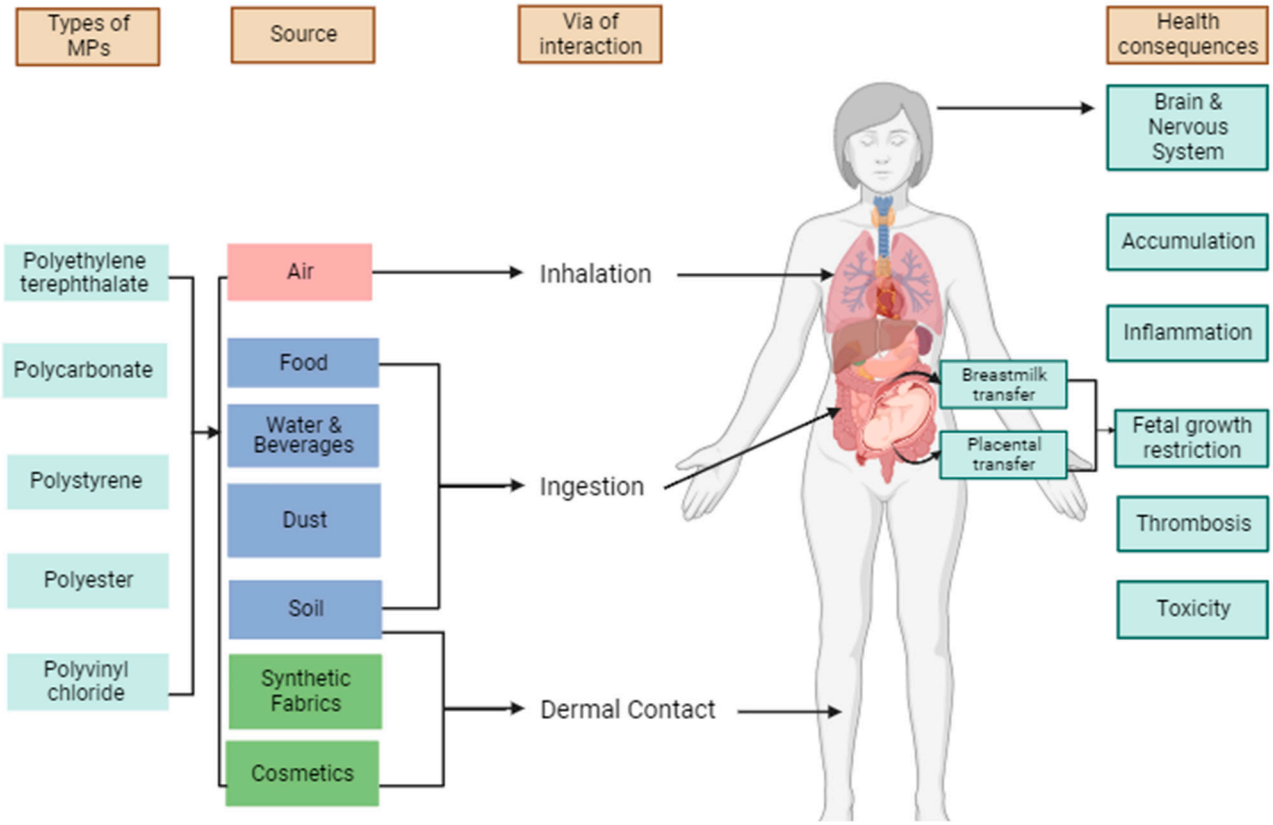

Figure 1. Pathways of human exposure to microplastics and their types, modes of interactions, and possible associated health consequences.

4.2. Inhalation

Since MPs are consistently found in high quantities in indoor and outdoor air, inhalation has become a significant pathway for human exposure to MPs [38,39]. Considering the physiological aspect, MPs widely present in the atmosphere interact with lung fluid and cells [40]. Inhaling MPs can trigger inflammatory cascade responses, causing acute and chronic respiratory diseases like asthma, dyspnea, and chronic obstructive pulmonary disease (COPD). The loss of epithelial integrity in airway epithelial cells is a pivotal event in COPD development, as these cells constitute the initial defense barrier in the respiratory tract [41,42]. Studies indicate that the uptake of polystyrene NPs by human alveolar epithelial cells leads to cellular toxicity, elevated secretion of proinflammatory cytokines, and disruption of tight junctions, potentially contributing to COPD [42]. Damage to the epithelium is caused by inflammation and oxidative stress, manifesting as increased permeability and decreased expression of tight junctions, ultimately resulting in epithelial barrier dysfunction [41].

Cox et al. (2019) underlined the importance of the inhalation route in a meta-analysis of 26 research articles on human exposure to MPs with a special focus on the American population [25]. Based on the findings, the average concentration was determined to be 9.8 MPs per m^3. Adult males and females were estimated to inhale 170 and 132 MPs daily, respectively, while children inhaled 110 and 97 MPs daily. These estimates accounted for approximately 50% or more of the total daily exposure to MPs through all routes, indicating that inhalation is the primary pathway of human exposure to MPs. Another recent study conducted in Australian homes reported an average inhalation intake of 0.2 mg per kg of body weight per year, equivalent to approximately 12,891 MP fibers per year, with higher intake observed in young children ($\leq$0.5 years of age) at 0.31 mg per kg of body weight per year [43]. Previous studies estimated individual inhalation exposure to be between 26 and 132 MPs per day [29], while a study by Vianello et al. [44] reported an average inhalation of 272 MPs per day for adult males engaged in light activity. Notably, a recent study highlighted the increased risk of MP inhalation associated with wearing various types of face masks during the COVID-19 pandemic. Fibers and spheres were the most commonly detected types of MPs, with activated carbon masks showing the highest levels of MPs inhalation and N95 masks the lowest [30]. Another significant matrix for human exposure to MPs has emerged as indoor dust. High concentrations of MPs in indoor dust samples were found, with children being more sensitive due to increased rates of dust consumption. Higher exposure was noted inside compared to outdoors, with an estimated daily intake of MPs via indoor dust ranging from 6500 to 89,700 ng per kg of body weight per day. Adults were found to have lower exposure levels due to variations in body weight and dust intake rates, whilst infants were found to have the greatest exposure levels. This emphasizes how important it is to consider indoor dust as a possible cause of exposure, especially for children [30].

4.3. Ingestion

MPs are primarily exposed to humans through the digestive tract, as they have been found in the digestive systems of various organisms [45]. In the intestine, M cells facilitate the absorption of MPs, leading them to the lymphoid tissue [46]. Intestinal epithelium secretes cytokines and chemokines as a response to MPs. Gut barrier cells, such as colon cells, cause phagocytosis, leading to intestinal barrier damage as an interaction with MPs [47]. By directly and indirectly interacting with the gut, MPs lead to disturbances with microecology, which can affect energy metabolism and cause adverse health effects. Larger MPs are not efficiently captured, but they are cleared by mucus and excreted with stool [48]. It is essential to understand the impact of MPs on the function of the gut microbiota as it is crucial for assessing MP toxicity and its effects on human health [49].

Recent research has shown the paths through which people are exposed to MPs, revealing the importance of both nutrition and indoor dust as channels. MPs have been identified in a variety of foods, including fish, shellfish, table salt, sugar, honey, milk, and beer; therefore, diet is a crucial factor. According to studies calculating food exposure, daily MP consumption for various demographic groups ranged from 106 to 142 particles per day [25]. Another recognized source of exposure is the release of MPs from plastic packaging, such as teabags [50] and baby feeding bottles, as discussed earlier. MPs have also been discovered in branded milk containers, meat items [51], and bottled drinks. These results highlight the necessity of thorough research to comprehend the scope and dangers of food exposure. Another significant matrix for human exposure to MPs has emerged as indoor dust. Studies have found high concentrations of MPs in samples of indoor dust, with children being more sensitive due to increased rates of dust consumption.

4.4. Dermal Contact

As summarized in Figure 1, dermal contact includes cosmetic use and synthetic fibers. Studies explicitly evaluating human skin exposure to MPs and its dangers are scarce. However, it is logical to think about dermal contact as a potential route for human exposure to MPs, given the widespread presence of MPs in indoor dust, atmospheric deposition from both indoor and outdoor air, the use of microbeads in cosmetics, and the ongoing degradation of microfibers from textiles, as discussed earlier. Microbeads generally have a diameter of less than 1 mm and are frequently found in toothpaste, denture fillings, and treatments for washing and exfoliating the skin. A limited number of studies tried to calculate the amount of microbeads each person uses in various personal care products [52]. For instance, research on face scrubs conducted in the UK discovered that the MP content ranged from 10 to 100 g per liter, translating to an intake of 40.5 to 215 mg per capita per day [53]. Another study calculated that the US population has an average intake of 2.4 mg of MPs per person per day using liquid soaps [54].

These few studies do not offer a thorough knowledge of human cutaneous exposure to MPs, but they do show that it is important to consider this route of exposure. Research indicates that NPs may immediately overcome the dermal barrier, even though human skin serves as an efficient barrier against the entry of bigger particles. However, the transdermal penetration of bigger particles may also occur via other pathways, including hair follicles, sweat glands, or open skin wounds. Additionally, skin damage brought on by inflammation and oxidative stress has been linked to dermal exposure to MPs. Determining human skin exposure to MPs through interaction with cosmetics, settling dust particles, fabric fibers, and other sources requires more investigation. The relevance of this exposure pathway and any potential health concerns involved must be further considered [30].

4.5. Circulatory System and Brain

Regarding the circulatory system, inhaled MPs are more likely to pass via the lower respirational region, which has a fine coating of secretion, and diffuse into the circulation via both cellular absorption and paracellular distribution [55]. Growing scientific evidence supports the existence of MPs in individuals. Ibrahim et al. revealed the predominance of MPs in specimens from colectomy, whereas Schwabl et al. stated the occurrence of MPs in feces from humans, demonstrating that they can only partially cut across the intestinal membrane [48,56]. Medical studies on both rodents and humans have shown that particles of PVC [57] and PS [58] less than 150 μm translocated from the gut cavity to their lymph and circulatory systems. The mussel *Mytilus edulis* was used to investigate the ingestion, translocation, and accumulation of MPs. After ingestion, MPs accumulated in the gut, then translocated to the circulatory system within 3 days and persisted for over 48 days. This long persistence of MP particles in the hemolymph of *M. edulis* has further implications for predators (i.e., birds, crabs, starfish, and humans) [59]. Another publication shows NPs can induce thrombosis; here, hamsters were injected with 60 nm polystyrene particles, showing up later in the blood stream [60]. Consequently, MPs in the circulatory system can potentially restrict blood flow, ergo damaging vascular tissues and causing changes in cardiac activity [61].

As stated by Persiani et al. [61], different MP types have been demonstrated to accumulate in the heart, explained by a trophic transfer via the bloodstream. It has been shown in mammals that MP presence impairs heart contractility, neonatal cardiomyocyte apoptosis, and the activation of fibrotic processes. MPs/NPs negatively interact with developing hearts, impairing cardiac function (including loss of function, failure of cardiac morphogenesis in early stages, arrhythmia, or reduced contractility in developing and likely adult hearts).

In another study by Yang et al. [62], the existence of MPs in the human heart and its surrounding tissues was examined using laser-based infrared chemical imaging and scanning electron microscopy. Microplastic samples, comprising diverse tissue types and blood samples, were gathered from a range of heart surgery patients. Even while not all tissue samples had MPs, nine different forms were found in five distinct types of tissues, with the biggest being 469 µm in diameter. Blood samples taken before and after surgery revealed the presence of MPs, the largest of which had a diameter of 184 µm. After surgery, there was a shift in the kinds and sizes of MPs in the blood. The study demonstrated conclusive proof of MPs in heart surgery patients' tissues, excluding surgical accidents as the source. Further study is necessary to understand how certain types of MPs are introduced during surgery and their possible impact on human health [62].

MP particles may easily pass through biological barriers and settle in the digestive system due to their small size. From there, they can go to various regions of the body, including the liver, blood, kidneys, and brain [63]. The transgenerational neurotoxicology of MPs has emerged as a novel avenue for toxicity research. The transgenerational neurotoxicology of nanoparticles (NPs) originating from the food chain, or microplastics (MPs), has been the subject of recent research. These particles cross the embryonic blood–brain barrier and are inherited, which affects the activity of neurotransmitters and genes linked to neurodevelopment [64–66]. MPs/NPs have the capacity to pass the blood–brain barrier and elicit neurotoxic effects in a variety of species [67]. The placental barrier is crossed by NPs when they are given to a fetus via the trachea or breast milk, which affects neurodevelopment and results in cognitive deficits [65,68].

Furthermore, during the early embryonic stage, there is a larger concentration of NPs in the blood–brain barrier, possibly as a result of the fetal blood–brain barrier not developing, which enables NPs to cause neurological dysfunction [68]. Further study is necessary to understand the processes behind the interaction between MPs/NPs and the blood–brain barrier during transfer or transgenerational transport, even if these findings highlight the transgenerational neurotoxicity risk from MPs/NPs exposure. Likewise, the findings from various studies investigating the neurotoxic effects of polystyrene and polyethylene micro- and nanoplastics on different aquatic organisms were performed [69]. Spherical polystyrene MP exposure caused excitatory toxicity in *Caenorhabditis elegans* (nematodes), which resulted in decreased survival rates, shortened average lifetimes, and impaired locomotor activity. In addition, this exposure resulted in downregulated neural genes, oxidative stress, and compromised GABAergic and cholinergic neurons [69]. Low-density polyethylene particles in artificial soil induced skin damage in *Eisenia fetida* (earthworms), verified particle ingestion, changed acetylcholinesterase activity, and elevated oxidative stress markers [70]. Freshwater zebra mussels, *Dreissena polymorpha*, were found to have polystyrene microbeads in their tissues. The gut had the highest concentration of these beads, suggesting cellular stress and elevated dopamine levels but no genotoxicity [71]. Similarly, when exposed to polystyrene microplastics, the bivalves *Scrobicularia plana* showed signs of oxidative stress in their gills, elevated activity of glutathione-S-transferase and superoxide dismutase, and decreased levels of acetylcholinesterase and lipid peroxidation in their digestive glands and gills [72]. The exposure of *Mytilus galloprovincialis* (Mediterranean mussels) led to a decrease in cholinesterase activity, alterations in gene expression in the gills and digestive gland, and increased DNA damage, all of which may have neurotoxic effects [73].

On the other hand, *Corbicula fluminea* (Asian freshwater clams) exposed to polymer microspheres experienced cholinesterase activity inhibition, oxidative damage, and irreversible effects, which were made worse when florfenicol was also present [74]. Conversely, shrimp and striped barnacle larvae of *Artemia franciscana* and *Amphibalanu ampitrite* exposed to microplastics showed changed swimming patterns and enzyme activity, such as elevated catalase and dose-independent effects on cholinesterase [75]. Finally, when *Artemia franciscana* larvae were exposed to amino-modified polystyrene nanoparticles, they

showed reduced oxidative stress indicators such as GST and catalase activity as well as higher concentrations of inhibition for cholinesterase and carboxylesterase [76].

MP exposure causes oxidative stress, inflammation, and decreased cell viability, according to early research on marine species [77]. Although it is recognized that these particles might travel through the environment and perhaps build up in human tissues, little is known about how they affect health, particularly in mammals. The biological and cognitive consequences of MP exposure were investigated in a rat model study. Age-dependent changes in immunological markers and behavior in liver and brain tissues were found in C57BL/6J mice, both young and old, that were exposed to water containing fluorescently labeled pristine polystyrene MPs for three weeks. The behavioral experiments included open-field and light–dark preference tests. The changing effects of age suggest aging's influence. These findings underscore the necessity for additional research to elucidate the precise pathways through which microplastics may influence physiology and cognition [78].

Researchers delved into how MPs affected mammalian systems as they aged. U-2 OS cells treated with 0.1 and 2 μm polystyrene microplastic particles (PS-MPs) showed decreased viability in vitro, suggesting cytotoxicity. For three weeks, C57BL/6J mice given PS-MPs in their drinking water had behavioral modifications; these changes were more pronounced in older mice. Tissue presence, systemic circulation, hepatic inflammation, and a disrupted blood–brain barrier were all indicated by the evidence. Neuroinflammatory patterns related to age were noted. These results highlight how MPs might affect behavior, tissue accumulation, and inflammatory responses as people age, underscoring the necessity for more investigation into MPs' effects on human health [79].

In recent work, researchers used short-term absorption tests in mice using various-sized polystyrene particles to examine the blood–brain barrier (BBB). Larger particles were shown to lack this capacity to penetrate the brain efficiently within two hours, but nanoscale-sized particles did. The crucial function of the biomolecular corona in enabling particle passage through the blood–brain barrier was demonstrated using molecular dynamics simulations examining the interaction between lipid layers and polystyrene nanoparticles. It was discovered that cholesterol molecules promoted uptake, but the protein model inhibited it, offering information on the passive entry of particles into the brain [80].

To better understand the cytotoxicity of MPs/NPs at a cellular level (by evaluating the effect of reactive oxygen species and cell viability), polyethylene and polystyrene MPs were used to demonstrate the cytotoxic effects induced on T98G and HeLa cell lines (human brain and epithelial cells) [81,82]. The MP interaction with humans can produce cytotoxicity, hypersensitivity, unwanted immune responses, and acute responses like hemolysis, and, therefore, constitutes a potential risk to human health [82]. The EC_{50} values for the exposure of PE and PS to cerebral (T98G) human cells for 24 h were reported to be 41.22 and 9.61 mg/L, respectively, measured using high-content analysis (HCA) [81].

5. Placental Translocation and Effect on Fetus

According to research conducted over the past few decades, the windows of sensitivity to environmental toxins are during pregnancy and childhood [83]. Even small amounts of early exposure to harmful substances can have long-term effects on a person's health because of child-specific activities, including crawling and hand-to-mouth action [84]. Children are exposed to the world differently than adults [85]. The key development of the immunological, metabolic, cardiovascular, and other vital bodily systems coincides with these greater exposures.

The placenta carefully controls the fetal–maternal milieu and, indirectly, the external environment, operating as a critical interface through several complex systems [23,86]. Additionally, a special protective biological structure known as the chorion surrounding the embryo of oviparous organisms prevents contaminants from interacting with the embryo [87]. MPs adhering to this chorionic membrane block gas exchange pores and

create a hypoxic microenvironment. This, in turn, diminishes oxygen utilization and prolongs the incubation time of the embryo [88].

MPs may harm embryo development by affecting the ability to distinguish self from non-self. Knowledge in this area is limited, and clarification is needed regarding the associated effects [89]. In a study performed by Ragusa et al. [37], MPs were found inside the placental cord of healthy females with a normal gestation and childbirth; therefore, it is most likely that the mothers inhaled or ingested the particles. MPs were also discovered in the barrier that the fetus develops inside the placenta, as well as on the maternal and fetal sides of the placenta [37].

In another study by Ragusa et al., Raman microspectroscopy revealed 58 MP particles in samples from human placentas taken from six individuals [31]. A total of 12 MP pieces were discovered in four placentas (three in the chorioamniotic membranes, four on the maternal side, and five on the fetal side). Furthermore, milk samples from 34 patients were collected and evaluated using Raman microspectroscopy to verify the existence of microplastic contamination in breast milk and to evaluate a different MP exposure pathway in the particularly sensitive subset of babies. Out of the 34 breast milk samples analyzed by Ragusa et al. [31], 26 exhibited MP contamination. The types of MPs identified in the breast milk samples included polyethylene, polyvinyl chloride, polypropylene, polyvinyl alcohol, poly (ethylene-co-vinyl acetate), poly (ethyl methacrylate), polyester, and polycarbonate [37]. Additionally, most of the detected MPs were colored (~90%), with orange/yellow and blue being the highly prevalent hues (about 36% and 17%, respectively).

Age, usage of hygiene items containing plastic (such as lotions, cleansers, and toothpaste), consumption of seafood, drinks in plastic containers, and meals in plastic containers in the seven days prior to and seven days after the expected delivery date were all reflected.

6. Microplastics in Our Daily Life

The feasting of seafood, drinks in plastics, plastic-wrapped food, and the practice of using hygiene products encompassing plastic particles in the seven days formerly and subsequently the anticipated day of delivery were evaluated as possible relationships between the occurrence of MPs in the breastmilk and data about moms' lifestyles. However, no links were discovered between MP existence or amount and any of the aforementioned facts [90].

The lack of an association between utilizing personal care products and exposure to contaminants is mostly justified by the fact that dermal touch has little influence as an exposure pathway since only particles smaller than 100 nm may move through the dermal barrier [91]. Contrarily, it is more difficult to explain why there is no connection between the absence of a lima relationship and mothers' dietary preferences, given that ingesting food is the main way MPs are exposed. Fish, shellfish, and essential everyday items for humans such as bottled water, honey, milk, salt, sugar, teabags, and, to a lesser amount, synthetic kitchenware, plates, and containers have all been shown to contain MPs [92]. Furthermore, as per a study by Liu et al. [93], sixteen varieties of MPs were detected, where polyamide and polyurethane dominated. It was shown that the intake of water and the use of toothpaste or soap can be exposure sources for expectant females. Additionally, nursing, the use of nursing bottles, and the use of synthetic toys may expose babies. Due to MPs' ubiquitous presence in the environment and inherent vulnerability, it is difficult to pinpoint their particular origin amid the complex array of confronted interactions.

7. Crossing the Blood–Brain Barrier

The function of the biomolecular corona in the blood–brain barrier (BBB) breaching of MPs and NPs has been discussed in the work by Kopatz et al. [80]. A critical defensive system, the BBB works to keep dangerous chemicals from entering the brain. In the study, mice were given oral doses of polystyrene micro/nanoparticles of different sizes (9.55, 1.14, and 0.293 μm) for short-term uptake tests. The findings demonstrated that whereas bigger particles could not cross the BBB, nanometer-sized particles could do so

within two hours after consumption. In another study by Shan et al. [94], the effects of PS-NPs (polystyrene nanoparticles) were investigated. When administered to mice, PS-NPs increased the permeability of the blood–brain barrier (BBB) and accumulated in the brain in a dose-dependent manner. PS-NPs were found to activate microglia and cause damage to neurons. In vitro studies using human brain endothelial cells showed that PS-NPs were internalized by the cells, leading to the production of reactive oxygen species, inflammation, disruption of tight junctions, and cell death. PS-NPs also activated murine microglia cells, and their culture medium caused damage to murine neurons. Overall, these findings suggest that PS-NPs can cross the BBB, induce neurotoxicity, and activate microglia.

Since rodents and humans share many genetic and biological traits, they are frequently employed as study models. After oral or intravenous injection, these investigations have demonstrated that MPs/NPs bioaccumulate in several organs, including the liver, spleen, kidney, brain, gut, and placenta. The size of the particles ranged from 40 nm to 50 µm; however, due to the dearth of investigations, there is little knowledge regarding the link between particle size and results [14]. Upcoming studies must, however, account for field circumstances and evaluate a wide variety of plastic compositions, forms, and sizes.

8. Abiotic Factors

Humans primarily encounter MPs through air, soil, and water exposure. These MPs originate from various sources and tend to accumulate in the ocean and soil. While there is extensive research on the distribution and levels of MPs in the ocean and soil, less attention has been given to their presence in the atmosphere [95].

MPs such as synthetic, mixed, and natural fibers originating mainly from industries are transferred into the atmosphere through human activities and air currents [19]. Approximately 26–74% of MPs originated from tire rubber [96] and possess a significant source of hazardous MPs in the atmosphere. In addition, a significant number of MPs are released into the atmosphere from face masks used during the COVID-19 pandemic [39]. Airborne MPs have the capability to infiltrate the human lungs, where fibers ranging in size from 15 to 20 µm encounter limited clearance by alveolar macrophages and the mucociliary escalator. Consequently, these airborne particles deposit within the small and epithelial airways, triggering an inflammatory response in both the airway and interstitium. It is significant to mention that fibers measuring 0.3–10.0 µm in length, as emphasized by Wright et al. (2017) [19], present a particular risk of causing cancer, emphasizing the health risks associated with the inhalation of MPs. These emerging sources of MPs have raised concerns about their potential adverse health effects.

Human activities such as industrial production, disposal in landfills, and the increased utilization of waterproofing membranes and geomembranes allowed the spread of plastic in terrestrial environments [97,98]. According to this context, the small size of MPs leads to increased absorption by plants, allowing penetration and accumulation in the food chain and posing a risk to human health [99].

Furthermore, extensive research has been conducted on the distribution and biotoxicity of MPs in marine and aquatic environments. The majority of marine MPs (70–80%) are introduced into rivers [100], with key sources being industries, degraded plastic waste, and additives in daily human consumables [101]. MPs persist in sediments, oceans, and rivers as they continuously migrate through tidal and ocean flows, impacting aquatic ecosystems [100]. The ingestion of MPs and associated environmental chemicals causes physical damage and toxicity to marine life, leading to bioaccumulation and potential health impacts for humans. Inland freshwater environments, more exposed to human activities, require urgent research on MP pollution and associated risks as gaps exist in understanding the extent of MP pollution in freshwater [102].

9. Towards the Potential Standardization of Techniques for Quantifying Microplastics in Biological Samples

There are currently no established techniques for calculating the amount of MPs present in biological samples. This makes it difficult to compare study results and restricts our ability to draw generalizations about the health concerns associated with exposure to MP. Another gap is the dearth of epidemiological research on the possible consequences of MPs on human health. Animal models or in vitro studies have been used for most research up to this point. More extensive epidemiological studies are required to comprehend the possible health consequences linked to human exposure to MP. Furthermore, we still have a limited understanding of the degree and modes of human exposure to MPs.

Most environmental toxicology tests involving MPs use procedures that involve the chemical digestion of biological samples to extract, identify, and quantify the MPs. Various methods have been employed using alkaline agents, acids, oxidants, enzymes, or combinations of these agents. These procedures aim to remove organic matter and separate it from plastic particles. The specific concentrations of reagents, digestion time, and temperature can affect extraction efficiency, making some protocols more suitable than others based on study conditions. After digestion, post-digestion procedures commonly involve the filtration of the digested solution using filters like fiberglass, cellulose nitrate, or cellulose acetate membranes, followed by washing to identify and quantify MPs. Some studies have also reported scraping membranes post-filtration to isolate plastic particles for further analysis [103]. The success of these procedures relies on the effectiveness of reagents in detaching particles from the filtered membranes. Their subsequent identification and quantification may be underestimated if MPs remain attached to the membranes. Inefficiencies in the washing procedures for these membranes can compromise the accuracy of MP identification and quantification. It has been observed that small fragments may attach to the membrane pores, and pellets can aggregate within the membrane's layers after filtration. Therefore, thorough washing of the membranes is crucial to ensure analytical accuracy in detecting and quantifying MPs.

An increase in the diversity of methods and techniques for the identification and quantification of MPs has also been remarked [104], both in environmental samples (e.g., water [104,105], soil [106,107], sediment [108], and air [109]) and in biological samples [103,110]. However, the comparison between the various studies has become more difficult, with analytical accuracy being a key issue in recent publications [81,111], which can be attributed to the lack of standardization of the methods and techniques used [112]. Table 1 summarizes the most common techniques used, their action range, and major advantages and drawbacks [113]. In an effort to standardize the analysis of MP in water samples, the ISO/DIS 16090-2 is currently under development, employing a microscopy technique coupled with vibrational spectroscopy. The data thus generated should be reliable and comparable when examining the presence of MPs in clean waters with micro-Fourier-transform infrared spectroscopy (μFTIR) and micro-Raman spectroscopy [15].

Table 1. Summary of key techniques used for the detection of micro- and nanoplastics and their major advantages and drawbacks.

Major Techniques	Particle Size	Types of Samples Examined	Advantages	Drawbacks	Refs.
Fourier-transform infrared spectroscopy (FTIR)	(a) ATR-FTIR particle size > 500 µm (b) Microscopy coupled FTIR ~20 µm	Air Wastewater Food	Non-destructive technique; fast and reliable	Not all analytes are IR-active; Absorbance spectra from samples below 20 µm might not be interpretable; Environmental matrices effect detection.	[80,114–116]
Inductively coupled plasma mass spectrometry (ICP-MS)	1–2.5 µm	Marine environments River water	Allows characterization of subsurface layers	Occurrence of spectral and non-spectral interferences; High costs.	[117–119]
Raman spectroscopy	>1 µm	Stomach contents of fish	Small particle analysis (1–20 µm)	Interference by fluorescence induced by inorganic (e.g., clay minerals and dust particles), organic (e.g., humic substances), and (micro)biological impurities in the matrix.	[86,120,121]
In Vitro using human cerebral microvascular endothelial cells (hCMEC/D3)	40–50 nm	Mice (hCMEC/D3)	Allows detection of internalized MPs and NPs into cells	Little knowledge regarding the link between particle size and results; Must account for field circumstances and evaluate a wide variety of plastic compositions, forms, and sizes.	[94]
Laser infrared imaging spectrometer	>74% of the MPs were 20–50 µm	Placenta, breastmilk, meconium, feces, infant formula	Non-destructive, non-invasive; Provides detailed spectral information	Significant data processing requirements; Limited spatial resolution.	[93]

10. Current Legislation and Future Targets

On 25 September 2023, the European Commission (EC) announced the adoption of measures that restrict MPs from being intentionally added to products under the EU chemical legislation REACH [122]. The new rules will prohibit the sale of MPs and products to which MPs have been added on purpose during manufacture and aim to prevent the release of an estimated 500,000 tons of MPs to the environment. Products that are used at industrial sites or do not release MPs during use are exempt from the sales ban, but manufacturers must provide instructions on how to use and dispose of the product to avoid microplastic releases. This new, important announcement is part of a larger strategy known as the Zero Pollution Action Plan, where the EC set the target to reduce MP pollution by 30% by 2030 [123], one of the key deliverables of the European Green Deal and the new Circular Economy Action Plan that was adopted in March 2020.

Given the potentially severe negative effects of (micro)plastics, tackling plastic pollution and accelerating the transition to a circular, resource-efficient economy [124]. Although plastics are a very important material in our economy and daily lives, we can support legislation and governmental guidelines by reducing, e.g., single-use plastics and plastic packaging in our households and recycling as many plastic end-of-life products as possible.

11. Bridging Gaps

According to a recent report by the World Health Organization (WHO) on plastic particles in drinking water, there is currently no conclusive evidence available in the public domain that directly associates plastic particles with negative health effects in humans [125]. However, the report emphasizes that this conclusion is primarily due to a lack of extensive research rather than concrete evidence supporting the safety of plastic particles. It underscores the urgent need for rigorous research focused on human populations to better understand the potential risks associated with plastic particles [14]. However, not only are the potential health impacts from MPs and NPs poorly identified so far, but it is also unclear what effect they could have on pollutants that adhere to them. Previous research has shown that heavy metals can easily attach to MPs, a combination that can potentially harm aquatic life and, eventually, human health by contaminating the food web [126–131]. Recent studies further indicated that UV filters used, for example, in sunscreens, can increase the toxicity of chromium metal by altering the oxidation state of MP-bound metals [132]. Generally, MPs and NPs can contain numerous toxic chemicals, as recently reviewed by the United Nations Environment Programme (UNEP) [133] and by others (e.g., [81,134]). The UNEP report identified ten groups of chemicals as being of major concern due to their high toxicity and potential to migrate from plastics, including specific flame retardants, certain UV stabilizers, per- and polyfluoroalkyl substances (PFASs), phthalates, bisphenols, alkylphenols and alkylphenol ethoxylates, biocides, certain metals and metalloids, polycyclic aromatic hydrocarbons (PAHs), and many other non-intentionally added substances (NIAS). Potential hazards from MP polymers were also ranked recently in a semi-quantitative risk assessment model, highlighting polyurethane (PUR), polyvinyl chloride (PVC), polyacrylonitrile (PAN), acrylonitrile-butadiene-styrene terpolymer (ABS), poly(methyl methylacrylate) (PMMA), styrene acrylonitrile copolymer (SAN), thermoplastic polyurethanes (TPU), unsaturated polyester (UP), polyethylene terephthalate (PET), polystyrene (PS), and high-density polyethylene (HDPE) as the top-ranking polymers of concern [135].

The standardization of techniques for calculating and quantifying the presence of MPs in biological samples is an additional key research gap. Although some scientists have demonstrated that MPs can have harmful impacts on animal models' health, we are yet unsure exactly how much of a risk MP exposure poses to human health. Finally, there is a significant lack of long-term research on how MPs could affect human health. Further studies are required to understand the possible health hazards linked to chronic, long-term exposure to MPs because most studies have concentrated on short-term exposure so far. To safeguard human health and guide policy decisions, it is essential to fill in

these knowledge gaps about the possible dangers linked to exposure to MPs. In 2019, the Norwegian Food Safety Authority conducted a systematic analysis and discovered just three studies that were pertinent to human health, concluding that it was presently impossible to evaluate the health hazards of MPs/NPs [136]. This is consistent with past evaluations made by the European Food Safety Authority [137], the United Nations Food and Agriculture Organization [138], and the European Academies' Science Advice for Policy [139]. One final element to consider is education and incorporating topics related to MPs/NPs in the syllabus. As a valuable example, the importance of incorporating citizen science to assist in data collection and environmental education in MP research must increase. A higher societal inclusion in science through education projects results in the involvement of volunteers and increases the science capital in individuals with fewer science experiences [140].

12. Conclusions and Future Perspectives

The prevalence of MPs in maternal breastmilk and placenta is especially problematic as it impacts a vulnerable population of neonates. Chemicals present in foodstuff, drinks, and items for personal hygiene consumed by nursing mothers might well be transferred on to their infants, possibly harming them. Increasing scientific research efforts are needed to increase consciousness about the possible health implications of MP internalization and buildup, particularly in infants and the placenta. It is also important to assess innovative, effective methods for minimizing exposure to these contaminants during lactation and pregnancy.

The effects of plastic pollution on the environment have been well researched, but it is still unclear how ingesting plastic by mammals, including humans, may affect their health. These latest discoveries about the mechanics of plastic particle transfer provide a crucial foundation for further study and regulatory measures intended to lessen their harmful impact on human health. We can create practical methods and recommendations to reduce the dangers associated with plastic use and protect human health by better understanding the underlying processes of plastic particle toxicity.

MPs are pervasive in the environment and have several entry points into the body, including ingestion, inhalation, and skin contact (Figure 1). It is crucial to understand the extent and modes of human exposure to MPs to assess their health risks. These plastic fragments may include dangerous materials and pathogens that have a detrimental impact on human health. Determining the long-term health impacts of MP exposure may be done by studying the biopersistence of MPs and their possible accumulation in different tissues. To limit exposure to MPs and promote ecologically sustainable practices, legislative changes and consumer behavior may be influenced by raising public knowledge of the possible health hazards related to MPs. Because the health of ecosystems is directly correlated with human health, microplastic contamination can have serious negative effects on the environment.

Every effort should be made to minimize the manufacture and use of plastics, as well as to boost recycling and ecologically safe disposal of plastics, together with the development of technologies that remove MPs from our environment. This should be performed until these issues are overcome to restrict the potential damage that MPs and NPs might cause to our health.

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