

From Cradle to Grave: Microplastics—A Dangerous Legacy for Future Generations

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Abstract: Microplastics have become a ubiquitous pollutant that permeates every aspect of our environment—from the oceans to the soil to the elementary foundations of human life. New findings demonstrate that microplastic particles not only pose a latent threat to adult populations, but also play a serious role even before birth during the fetal stages of human development. Exposure to microplastics during the early childhood stages is another source of risk that is almost impossible to prevent. This comprehensive review examines the multiple aspects associated with microplastics during early human development, detailing the mechanisms by which these particles enter the adult body, their bioaccumulation in tissues throughout life and the inevitable re-entry of these particles into different ecosystems after death.

Keywords: microplastics; nanoplastics; particulate matter; environmental pollution



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1. Generation and Composition of Macro-, Micro- and Nanoplastic Particles

Macroplastic items like bottles, packages, toys and the like degrade through various biotic and abiotic processes, each involving different mechanisms and resulting in specific changes to the particles concerning size and composition [1]. Microplastics (MPs) are defined as plastic particles smaller than 5 mm, and nanoplastics (NPs) are defined as particles smaller than 1 μm [2]. Both are found in diverse forms, including spheres, fragments, and fibers with polyester being the most commonly detected polymer in humans, followed by polyamide (PA), polyurethane (PU), polypropylene (PP) and polyacrylate (PAC), as well as polyethylene (PE) and polyvinyl chloride (PVC) [3,4]. The two main categorizations for plastics are thermoplastics and thermoset plastics. While thermoplastics are defined as re-melted pellets used to assemble the final product, thermoset plastics are melted into their final shape using heat. The vast majority (80%) of plastics are thermoplastics which are also the major basis for primary MPs. The essential types of thermoplastics include PE, PP and PVC [5].

Most smaller particles that can be found in the environment arise from the mechanical deterioration of larger pieces of plastics over time, and it is estimated that such fragmentation processes could generate up to $>10^{14}$ times greater numbers of micro- and nanoplastic (MNP) particles [6]. To understand the fate and consequences of such particles in the environment, it is pivotal to measure their full range of sizes, shapes and composition thereof, and several reviews of MP detection methods have already been published [7,8]. The degradation of plastics involves the breakdown of plastic particles into smaller fragments, potentially reaching the nanoscale [9,10]. Besides mechanical and biological degradation, photo-degradation due to sunlight oxidizing the chemical structure and minimizing the molecular mass might even cause the polymers to become fragile and ultimately break down into the respective monomers [11]. The different processes that contribute to the degradation of macro- and MP particles, each influenced by environmental factors and the chemical nature of the plastic materials themselves, are summarized below (Table 1).

Table 1. Summary of different degradation processes for plastic materials.

	Degradation Process	Mechanism	Key Factors Involved	Resulting Changes	Ref.
BIOTIC	Biodegradation	Enzymatic breakdown	Microorganisms (fungal, multiple bacteria, algae)	Enzymatic oxidation, hydrolysis, chain scission, polymer fragmentation	[12,13]
	Chemical degradation	Chemical reactions catalyzed by environmental agents	Hydrolysis, oxidation, solubilization		[13]
ABIOTIC DEGRADATION	Thermal degradation	Slow thermal oxidation in combination with photodegradation	Thermal oxidation	Oxidation, dehydrochlorination, chain scission, cross-linking, polymer fragmentation	[11,14–16]
	Photo-degradation	Exposure to UV radiation	UV radiation, oxygen, temperature		[13,17,18]
	Mechanical degradation	Physical forces	Abrasion, friction, pressure	Ablation, particle fragmentation	[19,20]

2. Presence of Microplastics in the Environment

Inadequate management of plastic waste disposal procedures and poor recycling efforts have led to increased contamination of our environments, with global plastic waste production approaching an alarming 400 million metric tons (Mt) in 2021 [21,22]. It is estimated that approximately 8.3 billion tons of plastic have been generated globally since 1950 [23]. The unavoidable omnipresence of MNPs throughout different ecosystems and their potential impacts on human health have therefore raised substantial concerns [24,25]. One study suggests that up to 23 million Mt of plastic debris accumulated in the world's aquatic ecosystems in 2016 alone, which is equal to 11% of the worldwide plastic production in that year [26], while other studies estimate the global plastic production in 2016 to be as high as 335 million Mt [27]. If waste management is not optimized and current trends continue, it is predicted that by 2030 the amount of waste accumulating in global aquatic ecosystems could reach 90 million Mt/year [26]. Although the majority of research is currently focused on MP pollution in marine and freshwater environments [28]—mainly due to key analytical methods for the identification of MPs in soil still missing—several studies suggest a significant presence of MPs in soil environments [29,30]. A study focusing on the effect of MP on plant growth indicates that an increased concentration of these particles in soil may have detrimental consequences for the growth of grass and crop plants by reducing germination and altering the shoot length of the plants [31].

2.1. Drinking Water

MPs have been detected in drinking water across the globe with median concentrations in standard water sources of 2.2×10^3 particles/m³, predominantly with particle sizes exceeding 50 µm [32]. In addition, plastic bottles represent a significant source of MNP exposure for humans, particularly through PP and PET plastic particles released from the caps of such containers [33]. Individual MNP intake naturally varies greatly, depends mainly on the choice of drinking water and lifestyle habits, and has been calculated to be as high as 73,000 particles per year per person [34].

2.2. Food Products

A recent study shows the general exponential increase in MP accumulation in agricultural soils, which is partly due to the increased use of fertilizers [35]. Therefore, it is not

surprising that MNP contamination is also widespread in a variety of everyday agricultural food products [36]. The diffusion of MPs in the food supply chain is naturally an area of public concern, as their impact on human health is still largely unknown. Meat and dairy products are of course particularly noteworthy in this context, as the intake of MPs and their accumulation in farm animals can lead to particularly high concentrations in the final food products [37]. For example, particle concentrations between 0.03 and 1.19 particles per gram of meat have been reported, in unprocessed as well as processed products like hamburgers [38,39]. Not surprisingly, MNPs have also been detected in various dairy products such as skim-milk formulations, with average values reaching 40 particles per liter [40,41].

MNP contamination of seafood products is another area of concern. It has been suggested, that the main sources of plastic particles within marine systems result from the fragmentation of bigger plastic items and the application of plastic scrubbers in cleaning products [11]. They are also derived from household and cosmetic products entering aquatic systems via sewage discharge [10,42]. Furthermore, air-blasting technology also contributes to the accumulation of primary MPs [43]. The main principle of this technique involves blasting machines, engines or ship vessels with MP scrubbers to get rid of rust and other debris [44]. Subsequently, MNPs can pass into oceans via municipal drainage systems as well as rivers [45,46]. One study indicates that MP concentrations have increased in plankton samples, which were collected over a period of roughly 40 years in the northeast Atlantic. This would coincide with the steady increase in plastic production worldwide [47]. Aquatic as well as terrestrial animals ingest a huge amount of MNPs accidentally or by confusing plastic particles for food due to their small size [48]. Therefore, they have been found in a number of different animal species, such as fish [49], seals [50], marine worms [50] and seabirds [51].

2.3. Articles of Daily Use and (Leisure) Activities

MNPs are omnipresent in our environment today. We inevitably come into contact with all kinds of plastic particles during everyday activities. We are exposed to them when using individual and public transport vehicles, but also during various leisure activities carried out in indoor sports facilities, when using daily hygiene products or even when simply consuming food and liquids in general. It is now almost impossible to avoid contact with MNPs, which shows how widespread this problem is and how easily it is simultaneously ignored by every individual and society in general.

Concerning food intake, various packaging materials represent a rich source of plastic particles that should not be underestimated under any circumstances, which naturally raises concerns about the transfer of such MNPs into food and beverages. This includes, but is of course not limited to, take-out containers, plastic coffee bags, disposable drinking cups, and food packaging products [52–55]. Another alarming finding concerns recent reports that MNPs can be released from breastmilk storage bags and subsequently pose a potential health risk for infants [56]. We are also inevitably exposed to MNPs during various sports, recreational and leisure activities. Sports facilities are a rich source of MNPs, both in terms of the provided equipment and one's own sports- or footwear that is used, and high levels of indoor MNPs can be generated by abrasion [57–59]. Similarly, abrasion testing of various consumer items that come directly into contact with mucous membranes, such as female hygiene products and even sex toys, revealed the release of significant amounts of MNPs [60,61].

The problem of MNP generation also plays a major role in connection with individual road traffic, e.g., during commuting and, probably even more important, in connection with transportation via heavy-duty vehicles. Tire wear MPs originating from synthetic rubber tires are in the meantime among the most abundant MPs in the environment [62–65]. The particles that are released into the environment include tire wear particles, recycled tire crumb and tire repair-polished debris. More precisely, tire wear particles are generated as automobile tire treads wear down on roads, while recycled tire crumb is produced for

recycling purposes. This includes the creation of rubber granules for use in artificial turf, basketball courts and recreational areas, typically achieved by mechanically grinding or cryogenically freezing chipped or shredded whole tires [66,67]. It is estimated that there are approximately 21,000 full size pitches and 72,000 so-called mini pitches installed in the EU, most of them made of synthetic turfs from recycled tires, contributing significantly to the generation of sports-associated MNPs [66].

2.4. Leaching Chemicals and Additives

In addition to the physical presence of MNPs, the leaching of chemicals and release of absorbed heavy metals from these particles poses significant environmental and health concerns. Many MNPs contain additives such as Bisphenol A (BPA), phthalates and heavy metals, which can leach into food, beverages, biological tissues and the surrounding environment [68,69]. Especially, chemicals like BPA are known to be endocrine disruptors, which can interfere with normal hormonal functions and, therefore, potentially compromise different aspects of fertility by mimicking and/or blocking natural hormones in the body. The potential for these substances to disrupt endocrine function and negatively impact human health underscores the urgency of addressing the issue of chemical leaching alongside MP pollution [70,71].

3. Uptake and Accumulation of Microplastics in Human Tissues and Organs

3.1. Routes of Exposure

Living organisms are exposed to MNPs mainly through three routes, ingestion, inhalation and dermal contact. Therefore, such particles can be taken up through polluted water and food, by inhaling air contaminated by natural or anthropogenic sources with particulate matter and cutaneous exposure through, e.g., clothes, as well as personal care and hygiene items. Several tissues are especially prone to accumulation of MPs, as shown in Figure 1. In the colon, concentrations from 7.91 MP/g [72] to 28.1 MP/g [73] have been described. In the small intestine, 9.45 MP/g have been detected, while in lung tissue up to 14.19 MP/g have been found [72]. In the spleen, the reported concentration was 1.1 MP/g [74], and in the liver it reached 4.6 MP/g [74]. Notably, for brain tissue, MP accumulation of up to 8.861 $\mu\text{g/g}$ was reported [75].

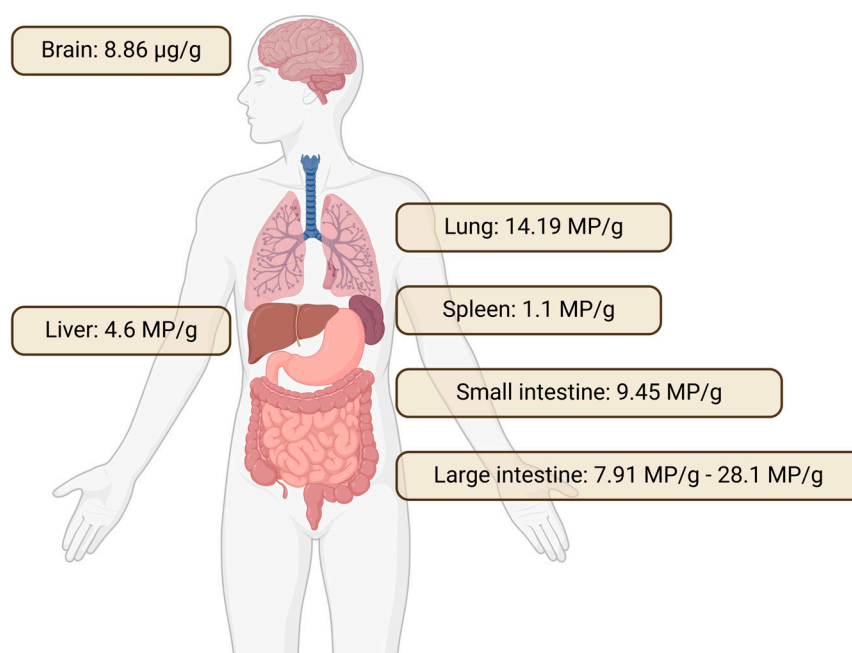


Figure 1. Accumulation of MPs in different tissues. (Created in BioRender. Lang, T. (2024) <https://BioRender.com/w89g368>, accessed on 17 November 2024).

3.1.1. Ingestion

Once ingested, MNPs pass through the esophagus into the stomach and can be absorbed by epithelial cells usually within 2–6 h [76]. Insoluble NPs smaller than 1.09 μm can pass through the gut epithelium and enter the bloodstream directly, while larger MPs are typically transported to the mid- and hindgut. MPs as large as 130 μm can move into human tissues through paracellular transport via desorption [77].

3.1.2. Inhalation

Inhalation represents one of the most significant pathways of MNP entry into the body. Airborne particles, depending on their size, can penetrate various regions in the respiratory system. Particles larger than 10 μm generally affect the upper airways, while those smaller than 10 μm can reach the bronchioles. Particles smaller than 2.5 μm in size, including ultrafine particles, are capable of penetrating down to the alveolar region [78]. It is not surprising that urban areas have a high presence of MNPs in the atmosphere, as anthropogenic sources such as industry and traffic are one of the main sources of these particles [79]. However, samples collected in remote areas (e.g., the alps/norther and southern polar ice regions) have also been reported to contain significant amounts of MNPs, highlighting the global threat of these contaminants [80,81].

3.1.3. Dermal Contact

The skin represents a fundamental barrier against most harmful substances from the environment. However, MNPs frequently come into contact with the skin due to topical agents such as cosmetics, hygiene products like tooth paste, pharmaceutical ointments and also medical devices like face masks [82,83]. Subsequently, MNPs might be absorbed in an unspecific way and ultimately accumulate in cells of the epi-/endodermal layers, keratinocytes or immune cells [84,85].

3.2. Particle Uptake and Transport Mechanisms Across Tissue Barriers

After ingestion by swallowing, inhalation or through the skin, different cell types can internalize particles such as MPs, fine dust and color particles in a largely unspecific manner. This process often leads to intracellular accumulation and—subsequently—also to the transfer of these substances to daughter cells following mitosis [86–88]. Cellular uptake of MNPs occurs primarily through two mechanisms: endocytosis-based uptake and direct cellular entry. Endocytosis involves several steps, beginning with specific ligands binding to the cell surface receptors resulting in the formation of a ligand-receptor complex. This is followed by nucleation of cytosolic proteins to form a coated pit. Next, the plasma membrane undergoes invagination, followed by the formation of intracellular vesicles. Finally, the coating is removed, and the endocytotic proteins are recovered from the vesicle [89–91]. Endocytosis-based cellular uptake includes clathrin-dependent uptake, caveolin-dependent uptake, clathrin- and caveolin-independent uptake, micropinocytosis and phagocytosis [92]. In contrast, some particles can enter cells directly, bypassing the need for these structured pathways, as will be discussed later in this text [92–95].

In specific tissues, the uptake processes can vary substantially. In the gut, smaller particles (size smaller than 150 μm) can penetrate the mucus layer and are absorbed via endocytosis by enterocytes, transcytosis through M-cells or by passing between cells through paracellular transport [96]. Inhaled MNPs can directly pass through the alveolar epithelium into the bloodstream [96]. Once MNPs enter the bloodstream, infiltration can occur on almost any tissue connected to the circulatory system [97].

Recent studies have demonstrated an additional mechanism of MNP transport via extracellular vesicles (EVs) [98]. These EVs, released by various cell types, play an important role in intercellular communication by transferring molecules such as proteins, nucleic acids, and also PS MNPs. A recent study demonstrated that such PS-MNPs can be encapsulated within EVs and transferred between cells through EV-mediated communication [98]. Through live-cell imaging, fusion of EVs containing PS-MNPs with recipient

cells was described, allowing the PS-MNPs to enter new cells. This shows that EVs can act as a transport mechanism for MNPs, facilitating their movement within tissues and possibly even across biological barriers such as those protecting, e.g., the brain and the placenta. This pathway could, therefore, represent a significant mean by which MNPs are distributed in the body, alongside traditional mechanisms like endocytosis and direct cellular entry [98].

The half-life of these particles in the circulation and therefore the uptake by cells varies based on the size and shape of the nanoparticles. Smaller particles generally demonstrate higher uptake efficiencies due to their ability to cross biological barriers more easily. For instance, in mice, PS particles sized 0.1–1 μm have a half-life of 1.4–4.9 min (with smaller particles persisting longer) [99], while acrylic particles under 1.8 μm last 44–84 min, with quicker clearance when coated in proteins like albumin [100]. In rats, polyacrylamide (PAA) particles sized 0.2–0.3 μm have a half-life of 40 min [101], whereas in rabbits, much smaller PS particles of 0.05–0.06 μm clear in just 0.9 min [102].

In addition to the previously discussed influences of size and protein coating, shape strongly dictates uptake efficiency. Molecular dynamics simulations have shown that spherical nano-sized particles typically internalize via clathrin-mediated endocytosis, while rod-like particles more commonly utilize caveolae-mediated pathways, which bypass lysosomal degradation and may allow more prolonged intracellular persistence [92]. Furthermore, rod-shaped and elongated particles tend to exhibit higher cellular uptake compared to spherical ones due to their ability to form stable adhesions on the membrane surface [92]. The lower uptake efficiency of elongated particles is likely due to the increased membrane tension required to engulf them fully, compared to the relatively simple internalization of spherical particles [94,95].

Additionally, the aspect ratio of rod-shaped nano-sized particles of different compositions has been shown to influence their cellular fate; particles with higher aspect ratios tend to localize preferentially in endosomal or lysosomal compartments [95,103]. Gold nanoparticles with sharp geometries, such as triangular or star-shaped forms, tend to penetrate cellular membranes more effectively. This is likely due to the ability of sharp edges to concentrate force on the membrane, facilitating membrane disruption and subsequent internalization [94]. Studies also suggest that non-spherical particles like nanodisks and nanorods demonstrate enhanced circulation times and reduced clearance rates in comparison to spherical particles, due to differences in their surface interactions with immune cells and serum proteins [95].

The orientation of the rod-shaped particle relative to the membrane is also important. In general, rod-like particles typically undergo stable endocytotic states with a small and high wrapping fraction. When the long axis of a particle aligns parallel to the membrane, it is referred to as the “submarine mode”, a configuration common for particles with high aspect ratios (long and thin shapes) and rounded tips. When the axis is oriented perpendicular to the membrane, it is known as the “rocket mode”, typically seen in particles with smaller aspect ratios and flat tips. Particles with a high aspect ratio often experience a “competition” between these two modes [93]. Studies have shown that particles with high aspect ratios (i.e., longer and thinner shapes) generally exhibit reduced uptake efficiency compared to spherical particles of similar size. This complex interplay of particle properties—such as size, shape and surface characteristics—ultimately determines how efficiently a particle is taken up by cells and how long it remains in circulation within the body [93].

4. Physiological Consequences of Microplastics Exposure During Human Development

4.1. Critical Stages During Early Human Development Affected by Microplastics

The potential health effects of MNPs during embryonal development are an emerging area of research, and while studies are still limited, there is growing concern about the possible far-reaching impact. The early development of all mammals, including humans, involves several critical stages where environmental influences by a multitude of different

factors and chemicals can have lasting impacts on health. Therefore, we have summarized possible effects during the fetal stage, the neonatal stage, and the prepubertal stage in more detail (see Figure 1). Each of these periods are characterized by rapid tissue growth, cellular differentiation, and critical biological processes that establish the foundation for future health and also disease susceptibility [104].

4.1.1. Fetal Exposure to Microplastic Particles via the Placental Route

During the fetal stage, development is highly sensitive to environmental influences, as this is when most tissues differentiate (including immune system cells) and cells are still in great plasticity. The blood–placenta barrier (BPB) is a vital structure in pregnancy that helps protect the developing fetus by controlling the exchange of substances between the maternal and fetal bloodstreams. However, recent research has indicated that MPs can cross this barrier, potentially affecting fetal development. For instance, a 2021 study detected MPs in human placentas, suggesting that these particles can be present in the womb and possibly affect embryonal development [105]. MPs can cause inflammation and trigger an immune response in tissues [106–108]. If MPs reach the embryonic environment, they could induce local inflammation, potentially disrupting normal development [104,109,110]. The potential health risks associated with such MNP exposure, coupled with the increased vulnerability of fetal development to environmental agents, highlight the critical need to study the maternal-to-fetal transfer of such particles via the placental route. While the placenta is responsible for facilitating the exchange of essential nutrients, gases and waste products for the fetus, it is not completely impermeable to environmental toxicants. The placental barrier is composed of the syncytiotrophoblast layer, cytotrophoblast cells and the endothelial cell layer of the fetal capillaries [111]. There are different ways of transplacental transfer: passive transfer, facilitated diffusion and active transport [112]; Grafmueller et al. stated that the transportation of nanoparticles such as nanoplastics is likely to involve an active, energy-dependent transport [111]. A recent study described MNP fragments with multiple shapes in human placental tissue. MNPs have been found in these samples either on the maternal side, the fetal side or on the chorioamniotic membranes [105]. This finding is significant because the placental barrier serves as a critical interface between the fetus and the external environment, ensuring safe conditions for embryonic development. Using an ex vivo human placenta perfusion model revealed that NPs up to 240 nm were taken up by the placenta and were able to cross the placental barrier without affecting the viability of the placental explant, being transported from the fetal to the maternal blood circulation [113]. This was further corroborated by animal studies that directly fed MP particles to pregnant mice, revealing that these particles were efficiently transported to embryonic tissues, significantly reducing their growth [114]. Additionally, an accumulation of PS beads was also observed in the syncytiotrophoblast layer of placental tissue using an ex vivo human placental perfusion model [111].

The maternal pulmonary exposure (intratracheal instillation) to nano-PS led to the translocation of such particles to placental and fetal tissues in pregnant Sprague Dawley rats making the fetoplacental unit susceptible to adverse effects. These particles were found in the maternal lung, heart and spleen as well as fetal liver, lungs, heart, kidneys and brain. Furthermore, 24 h after maternal exposure, fetal and placental weights were significantly lower (7% and 8%, respectively) compared to control groups [115]. Exposure to harmful substances during this time can disrupt cellular functions and epigenetic programming, potentially leading to long-term health issues. MNPs are considered potent vectors for other environmental pollutants such as heavy metals, organic pollutants and microorganisms, including pathogens and antibiotic-resistant bacteria, due to their adsorption properties. Heavy metals like arsenic, cadmium, chromium, copper, lead, nickel and zinc have been detected on MP surfaces [116]. The adverse effects of these pollutants are wide-ranging, including carcinogenicity, teratogenicity, genotoxicity, immunotoxicity, and neurotoxicity [68,117,118]. For example, research has shown that exposure to environmen-

tal contaminants during the fetal period can result in epigenetic modifications, affecting gene expression and increasing disease susceptibility later in life [104,110].

4.1.2. Microplastics and the Neonatal Stage

The neonatal stage, immediately following birth, is another window of heightened vulnerability. Newborns can be exposed to MNPs through various sources, similar to adults but with some specific considerations due to their unique environment and activities. After birth, infants continue to be exposed to plastic particles through various sources such as breast milk, toys, baby bottles, formula and household dust (see Table 2). As a consequence, the estimated daily exposure of MNPs by infants up to 12 months old ranges from 14,600 to 4,550,000 particles/d per infant [119].

Table 2. Routes of exposure during the neonatal stage. (Abbreviations: PP, Polypropylene; PC, Polycarbonate; BPA, Bisphenol A; TDI, Tolerable daily intake; PE, Polyethylene; PU, Polyurethane; PA, Polyacrylamide; PS, Polystyrene; MPs, Microplastic particles; MNPs, Micro-/Nanoplastic particles; PAH, Polycyclic aromatic hydrocarbon; BBzP, Butyl benzyl phthalate; DEHP, Bis(2-ethylhexyl) phthalate).

Source	Chemical	Amount	Detection via	Ref.
Baby bottles	PP	14,600–4,550,000 particles per person per day Or 16.2 million particles per liter especially after heating in microwave	Water incubated in baby bottles	[119]
	PC/BPA	0.8 to 23.8% of their safe TDI of BPA by using plastic bottles	Ethanol/water mixture in baby bottles	[120]
Baby formula	PP, PE	Not specified	Formula preparations in plastic bottles	[119]
	mostly PU	17.3 particles/g	Infant formula	[121]
Household dust → crawling/hand-to-mouth activities	PA, PS	20–60 particles/m ³	Indoor air sampling	[122]
Environmental dust	n.a.	15 MPs per day via inhalation	Street dust	[123]
Toys	n.a.	By friction, heat or light, MNPs may be released directly onto the hands, mouths and noses of children		[34]
Breastmilk	Various, mostly PU	20.2 particles/g	Breastmilk	[121]
Breastmilk	BPA	75% of breastmilk samples 0.4–1.4 µg/L	Breastmilk	[124]
Diverse sources	Various, mostly PA	18.0 particles/g	Placenta	[121]
Football pitches and playgrounds	PAH, phthalates, adipates	9–91 µg/g	Rubber samples	[125]
Children's toys	Bromine and antimony		Toy Samples	[126]
Vinyl Flooring	BBzP, DEHP	23.9 ng/m ³ BBzP in air samples (compared to 10.6 ng/m ³)	Indoor Air Sample	[127]
Pacifiers Toys	BPA	Below LOD—0.33 µg/L	11 Toy and Pacifier Samples	[128]

During this period, the infant's immune system is still developing, specific tissues are differentiating and the body undergoes crucial physiological adaptations to the external environment. The ingestion or inhalation of MNPs during this time could interfere with these processes, exacerbating the risk of immune system dysfunction or other developmental disorders. Considerable numbers of MNPs have been detected in this respect, highlighting the potential dangers of accumulation during early childhood development (see Table 3). Exposure to irregular MNPs shed from baby bottles was described to activate the ROS/NLRP3/Caspase-1 signaling pathway, causing intestinal inflammation [129]. Studies have demonstrated that neonatal exposure to environmental toxins can alter immune responses, increasing the likelihood of developing allergies or autoimmune diseases [130]. In addition, the commonly used stabilizer BPA as well as antioxidants in plastics have been shown to cause proliferation toxicity in human Caco-2 cells, highlighting the danger that is associated with MNP exposure [131].

Table 3. Composition of plastic particles detected in infants. (Abbreviations: PA, Polyacrylamide; MPs, Microplastic particles; BPA, Bisphenol A; MbzP, Monobenzyl phthalate).

Chemical	Amount	Detection via	Ref.
Various, mostly PA	54.1 particles/g	Meconium	[121]
Various, mostly PA	26.6 particles/g Correlation of exposure to plastic toys	Infant feces	[121]
MPs with 11 out of 15 plastic ingredients traced	1.2–3.3 µg/L In 93% of urine samples	Children (age 3–17) urine and blood samples	[132]
BPA	1.2–4.4 µg/L	Infant urine (3–15 months) without known BPA exposure	[124]
MBzP	32.6 ng/mL Urinary MBzP (compared to 18.3 ng/mL)	Urine metabolites from children living in homes with vinyl flooring	[127]

4.1.3. The Prepubertal Stage

Finally, the prepubertal stage is marked by continued growth and hormonal changes that prepare the body for adolescence and adulthood. The organs are maturing, and there is significant plasticity in specific hormone dependent tissues. Exposure to MNPs during this stage can disrupt endocrine functions, as first described in 1936 by Dodds et al. [133], which is critical for normal growth and reproductive health. Given that MNPs and associated chemicals have been found to possess endocrine-disrupting properties, their presence in the environment could pose significant risks during this sensitive developmental window. Research indicates that endocrine disruptors can interfere with hormone signaling during prepubertal development, leading to reproductive issues and increased cancer risk later in life [134,135].

However, while definitive evidence in humans is still emerging, the potential risks associated with plastic particle exposure during embryonal development and early childhood warrant further investigation. Given the critical nature of this developmental period and the known effects of related environmental toxins, understanding and mitigating exposure to MNPs is crucial for safeguarding fetal and maternal health (see Figure 2).

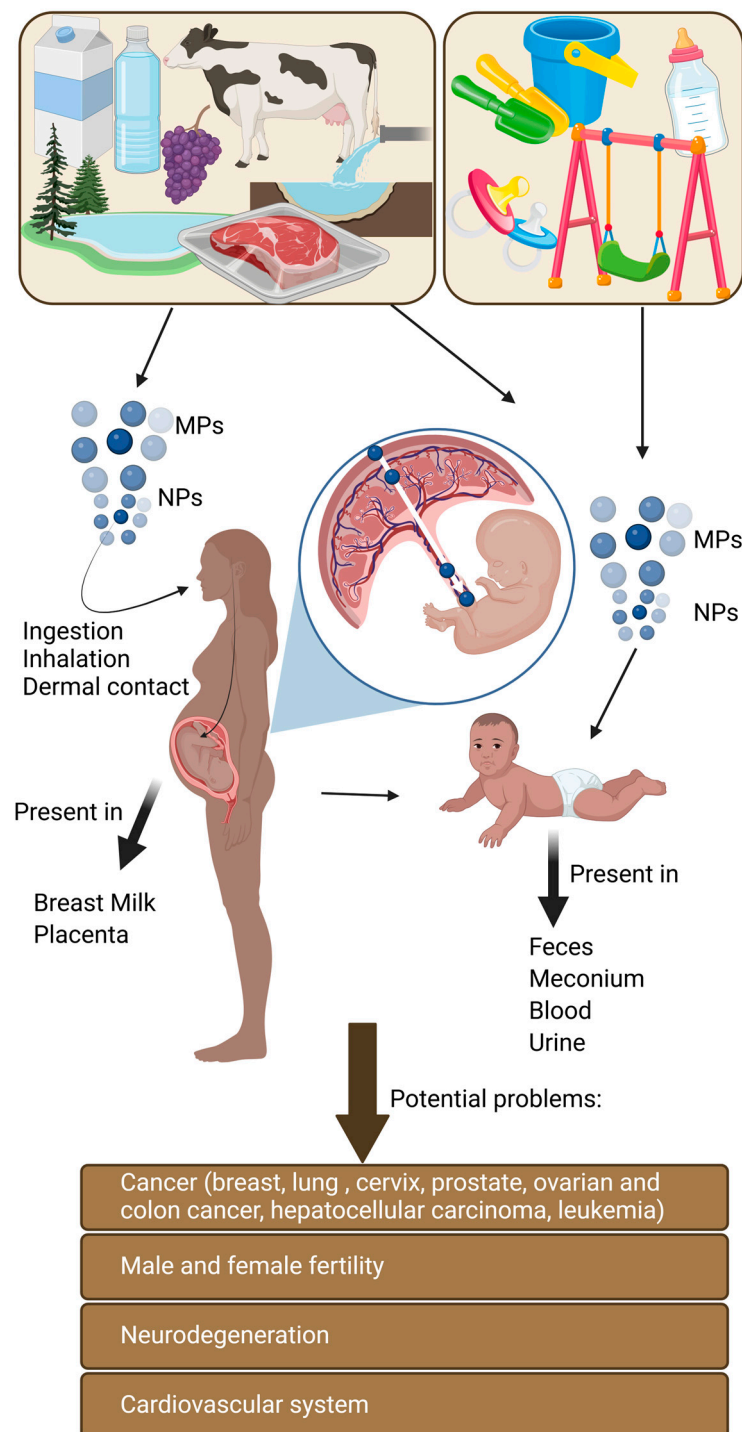


Figure 2. Microplastics uptake during different stages of human development. (Created in BioRender. Lang, T. (2024) <https://BioRender.com/d17c062>, accessed on 15 November 2024).

4.2. The Problem of Lifetime Accumulation of Microplastic Particles

4.2.1. Accumulation of Microplastics in Different Tissues of the Human Body

The potential for MNPs to affect critical periods of development raises concerns about long-term health effects, such as developmental disorders, reduced fertility and increased susceptibility to chronic diseases (see Table 4). The exposure to and accumulation of plastic particles in the human body begins early and continues throughout life. After MNPs enter the human body, it is a priority to understand the distribution of these particles in different tissues (see Table 4). Pristine MNPs, particularly those of ultrafine sizes, have the

potential to accumulate in various tissues and organs, leading to histological and biological changes [97]. The accumulation of MNPs in various tissues and organs, including lung, liver, spleen and even the brain, has been documented in several studies. For instance, significant accumulation of PS MPs with a size of 5 μm has been shown in the guts of rats with an average residence time of about 17 days [136].

Table 4. Distribution and consequences of plastic particle accumulation in different tissues.

Category	Affected Organs/Tissues	Key Findings	Ref.
Accumulation in tissues	Lung, spleen, liver, brain, intestine, etc.	Significant accumulation documented in animal studies; translocation to distant organs observed	[72–74,97,137–139]
Pathophysiology/toxicity and inflammation	Various tissues	Induces oxidative stress, inflammation and cytotoxicity; exacerbated by additives like BPA	[140–144]
Carcinogenic potential	Breast, lung, liver, cervical, prostate, colon, blood	Chronic exposure linked to cancer risk via inflammation and genotoxicity	[97,145–172]
Cardiovascular system	Heart	Accumulation leads to oxidative stress, heart fibrosis and heart damage	[173–176]
Nervous system	Brain	Leads to neuroinflammation and cognitive deficits	[94,98,177–182]
Reproductive health	Testes, ovaries	DNA damage, reduced fertility rates and impaired sperm and oocyte quality	[183–191]

PS MNPs have also been shown to translocate to distant organs; Eyles et al. [137] demonstrated that such particles (0.87 μm) could move from the gastrointestinal tract to the stomach in rats, and subsequent research by Eyles et al. (2001) indicated that PS spheres (1.5 μm) could reach the liver and spleen in mice [138]. Notably, cylindrical MPs with diameters of 2.56 and 5.56 μm show higher deposition rates, whereas 1.6 μm cylindrical particles have lower deposition rates at a flow rate of 7.5 L/min. Spherical and tetrahedral MPs exhibit similar deposition rates at this flow rate. However, the overall deposition efficiency at 7.5 L/min is higher than at 30 L/min for all MNP sizes. This difference arises due to the longer residence time at lower flow rates, which affects the passage of MPs through the upper airway region. Factors such as gravitational sedimentation and Brownian diffusion are crucial, with Brownian diffusion being more significant at lower flow rates and decreasing as flow rates increase [139]. Human consumption of MPs is estimated to be 39,000–52,000 particles per year, potentially increasing to 74,000–121,000 particles per year when inhalation is included [77].

4.2.2. Pathophysiological Consequences of Microplastics Exposure

The primary focus of current research on MNPs' potential consequences includes two main areas: the intrinsic toxicity of MNPs and the risks posed by their associated co-contaminants. Pristine MNPs have been shown to cause inflammation and cytotoxic effects [140,141]. Additionally, when plastic additives or surface-adsorbed pollutants are released into the human body, they may lead to more severe health outcomes. The interactions between MNPs and other pollutants are complex, influenced by the characteristics of the MNPs themselves and the environmental conditions, which can significantly impact their combined toxicity [117]. However, there remains a lack of consensus regarding the toxic effects of plastic particles and their co-contaminants, indicating a clear need for further investigation. Similarly, a study by Deng et al. found that exposure to pristine PS MPs (5 μm and 20 μm) in mice led to disruptions in energy and lipid metabolism, oxidative stress and neurotransmission, as well as inflammation in the liver [142]. Another in vitro study on human cerebral and epithelial cells showed that exposure to PS MPs (3–16 μm)

at concentrations of 0.05–10 mg/L could lead to increased oxidative stress, a mechanism associated with cytotoxicity [140]. Additionally, positive-charged PS with a particle size of 60 nm was found to be highly toxic to macrophages as well as lung epithelial cells, inducing autophagic cell death [143]. Polyethylene (PE) MPs (10–45 µm) on the other hand did not cause cytotoxicity directly, but were found to induce genomic instability in human peripheral lymphocytes [144].

Apart from the intrinsic risks of pristine MNPs, the chemical additives incorporated during plastic production, along with environmental pollutants that can absorb these particles pose significant additional health risks. Common plastic additives include plasticizers, stabilizers, antioxidants, and flame-retardants, to name a few. Phthalate esters (PAEs), widely used as plasticizers to enhance the flexibility, durability, and stretchability of plastics, have already been detected in various organisms, suggesting potential release from MPs over time [142]. This was corroborated by the fact that mice can bioaccumulate PAEs in their gut and liver after being exposed to PAEs and MPs for 30 days [192]. The chemical effects of MPs can arise from several factors, including their composition, the leaching of unbound chemicals and residual monomers and the desorption of hydrophobic organic contaminants (HOCs). Many HOCs are priority pollutants with established human health risks. The cellular uptake of MPs could, therefore, facilitate the entry of these contaminants into cells [193].

4.2.3. Types of Cancer Linked to Microplastic Particles and Associated Chemicals

The bio-persistence of MPs may trigger various biological responses such as inflammation, genotoxicity, oxidative stress, apoptosis and necrosis [145,146]. Prolonged exposure to these conditions can result in tissue damage, fibrosis, and potentially lead to carcinogenesis (see [97] and references therein). Recent studies have highlighted the alarming link between chronic MP exposure and the development of various types of cancer [97].

- **Breast Cancer**

Breast tissues are highly sensitive to steroid hormones such as estrogens, which play a crucial role in regulating cell proliferation in the mammary glands. BPA, a common component of MNPs, can mimic estrogen and has been shown to enhance the proliferation of mammary gland cells, increasing the risk of breast cancer [147]. BPA exposure has been linked to increased ductal density in mammary glands and the activation of oncogenic pathways, such as STAT3, PI3K/AKT and MAPK, which are known to contribute to tumor development [148]. Additionally, irregularly shaped polypropylene MPs have been found to alter the expression of genes related to the cell cycle in human breast cancer cell lines and to promote the secretion of pro-inflammatory cytokines like IL-6, further fueling cancer progression [149].

- **Lung Cancer**

One of the primary routes for how MNPs can enter the human body is through inhalation, making the lungs particularly vulnerable [150]. Studies have identified various particles, including PE and PP, in human lung tissues, and these particles have been found to accumulate more frequently in the lungs of cancer patients compared to healthy individuals [4]. The inhalation of PS MPs has been shown to induce significant morphological changes and alter cell proliferation in lung epithelial cells [151]. Furthermore, BPA exposure has been implicated in the upregulation of matrix metalloproteinases (MMPs), which are enzymes that facilitate cancer cell invasion and metastasis, thereby increasing the risk of lung cancer [152].

- **Hepatocellular Carcinoma**

Liver cancer, specifically hepatocellular carcinoma (HCC), can develop from chronic liver diseases such as cirrhosis, which may be exacerbated by MNP exposure. In this respect, particularly PS particles have been shown to induce oxidative stress and alter lipid metabolism in vitro in liver cells and organoids [153,154]. Studies have reported higher

concentrations of MPs in cirrhotic liver tissues compared to healthy liver tissues, suggesting a role for MPs in liver fibrosis and cancer. Additionally, MNPs have been linked to the overexpression of hepatic enzymes like CYP2E1, which are associated with the progression of liver disease and the development of HCC [154,155].

- **Cervical Cancer**

Cervical cancer is another malignancy that has been associated with plastic particle exposure, particularly due to the influence of endocrine-disrupting chemicals like BPA [156]. MNPs can trigger oxidative stress and alter the balance of antioxidants in cervical tissues, potentially leading to carcinogenesis. In vitro studies have shown that PS MNPs can invade cervical cancer cell lines, promoting cellular stress and inflammatory responses that may contribute to tumor development [157,159].

- **Prostate Cancer**

Prostate cancer is hormonally driven, similar to breast cancer, and has been linked to environmental pollutants carried by MPs [158]. BPA and other endocrine disruptors found in MPs can interfere with androgen and estrogen receptors in the prostate, leading to abnormal cell growth and an increased risk of cancer [160,161]. Studies have shown that exposure to low doses of BPA can disrupt the normal development of prostate cells, increase the risk of neoplastic changes and contribute to the progression of prostate cancer [162–164].

- **Leukemia**

Leukemia, a cancer of the blood-forming tissues, has also been connected to MP exposure [165]. MPs, particularly those made of PE and PS, can accumulate in the circulatory system, leading to hematotoxicity and disruptions in white blood cell counts [166]. BPA exposure has been shown to exacerbate the proliferation of leukemia cells and reduce the effectiveness of chemotherapy treatments, highlighting the potential role of MPs in the development and progression of blood cancers [167,168].

- **Ovarian Cancer**

Ovarian cancer, often diagnosed at a late stage, may be influenced by exposure to MPs and their associated chemicals, such as BPA and phthalates. These chemicals can disrupt normal ovarian function, leading to altered hormone levels, irregular menstrual cycles and increased cancer risk. BPA exposure has been shown to upregulate genes involved in cell cycle progression and to activate signaling pathways that promote tumor growth in ovarian cells [169,170].

- **Colon Cancer**

Colon cancer is one of the most common types of cancer worldwide and has been linked to MNP exposure through ingestion. On the one hand, particles can disturb the gut microbiota, leading to inflammation and altered immune responses in the colon [171]. On the other hand, associated chemicals like BPA and phthalates found in MPs have been described to interfere with normal colon cell function, directly promoting carcinogenesis. Additionally, MP exposure has been associated with the downregulation of protective genes like Muc2, which is crucial for maintaining gut integrity and preventing early-onset colorectal cancer [172].

4.2.4. Microplastics and Cardiovascular Diseases

Oxidative stress and inflammation induced by MNP exposure can also impact cardiovascular health, potentially leading to an increased risk of conditions like hypertension, atherosclerosis and heart disease [173,174]. Studies have already described the detection of MNPs in cardiomyocytes, indicating a translocation route to the heart via the circulatory system [175]. Additionally, extensive apoptosis of myocardial tissue at doses of 5 and 50 mg/L of PS-MPs has been described. This was evidenced by elevated levels of myocardial creatine-kinase MB and cardiac troponin I, both critical markers of heart damage.

Moreover, the activation of the Wnt/ β -catenin signaling pathway, triggered by oxidative stress, contributed to heart fibrosis and ultimately led to cardiac dysfunction [176].

4.2.5. Microplastics and the Nervous System

The blood–brain barrier (BBB) is a protective shield that helps prevent harmful substances in the bloodstream from entering brain tissue. It is composed of endothelial cells that are tightly joined by junctions that form a selective barrier, allowing only certain molecules to pass through. However, recent research has shown that MNPs can directly breach this barrier due to their size and/or geometry or via exosomal transport, raising concerns about their impact on neurological health [94,98,177]. Once MNPs enter the brain, they can cause alterations in tissue structure, damage to the blood–brain barrier and impaired neurological function. These effects may contribute to the onset of neurodevelopmental disorders and neurodegenerative diseases. A study observed behavioral changes in *Daphnia* fish after being fed 52 nm PS particles, noting alterations in activity levels and feeding time. However, these effects were size-dependent. Fish that received 180 nm particles displayed the fastest feeding rates and the highest activity levels. Additionally, MNP particles were found in all fish that had been fed PS, while no MNPs were detected in the brains of the control group [179]. In studies on mice, PS-MPs of varying diameters were detected in the brain following oral exposure. This exposure resulted in a disruption of the BBB, increased dendritic spine density and an inflammatory response in the hippocampus. Moreover, the mice displayed cognitive and memory deficits, which were found to be dependent on the concentration of the MPs rather than their size [180]. These findings are underscored by recent research on the influence of environmentally relevant levels of micro- and nanoplastics particles and their influence on ROS-dependent degeneration of human neurons and neurodegeneration in general during amyotrophic lateral sclerosis [180–182].

4.2.6. Microplastics and Reproductive Health—Fertility Issues

When MPs enter the bloodstream, they can be transported to reproductive organs, raising concerns about their potential impact on fertility. Especially, chemicals associated with plastic particles are known to be endocrine disruptors, which can interfere with hormonal functions and potentially compromise fertility by mimicking or blocking natural hormones in the body. Infertility rates and the number of couples facing unfulfilled desires to have children are steadily increasing [183]. Primary infertility is defined as the inability of a couple, after being in a relationship without using contraceptives for more than five years, to achieve a live birth. In contrast, secondary infertility refers to couples who have not had a live birth in the same time period, following a previous successful pregnancy. A cross-sectional study highlighted the rising prevalence of primary infertility in men, showing an increase from 287.1 ± 100.0 cases per 100,000 people in 1993 to 291.9 ± 111.9 in 2017 across Central and Eastern Europe, as well as Central Asia (slope 5.4). In women, the rates rose from 348.8 ± 115.9 to 347.3 ± 125.3 in the same regions (slope 3.0). The highest increase occurred in South Asia, where female infertility rates climbed from 798.4 ± 197.4 per 100,000 in 1993 to 960.4 ± 254.5 in 2017 (slope 40.9). For secondary infertility, the most significant increase was observed in North Africa and the Middle East, where rates rose from 1031.7 ± 329.4 per 100,000 people in 1993 to 1544.2 ± 451.3 in 2017 [184]. Despite the increasing prevalence of infertility, research exploring potential links between MNPs and reproductive health remains limited. However, emerging evidence suggests that such particles and their associated chemicals could have a significant impact on both male and female fertility, making this an area of growing concern.

- Male Fertility

Studies reported that chronic as well as short-term oral exposure to MPs led to accumulation in testicular tissue causing testicular inflammation, blood–testis barrier disruption and impaired spermatogenesis. Jin et al. [185] discovered in a mouse model that the blood–testis barrier (BTB), found in the seminiferous epithelium and formed by a layer of Sertoli cells, plays a crucial role in supporting spermatogenesis. Mechanistically, MPs

disrupt the organization of F-actin and lower the levels of tight junction proteins in the BTB [185]. Another mechanism describes a decrease in the BTB-associated proteins occluding, connecin-43 and N-cadherin resulting in a decline in sperm quantity and quality. This study, therefore, provides experimental support for the direct adverse effect of PS-MPs on male reproduction [186]. Another study, performed by Hou et al. [187], administered PS in drinking water to mice for 35 days. After the exposure to MP, the ratio of live sperm in the epididymis to the total number of sperm was significantly lower compared to not-exposed mice. Furthermore, the SPZ were morphologically analyzed. The germinal epithelium within the testis revealed cell damage, a reduced number of spermatids, detached cells from the germinal epithelium, pyknosis and nucleus rupture. Analysis of expression levels revealed increased levels of genes involved in inflammatory responses such as NF κ Bp65 and p-NF- κ Bp65, Interleukin-1 β (IL-1 β), IL-6 and tumor necrosis factor (TNF α) and decreased levels of critical transcriptional factors in the antioxidant defense system and related downstream target such as Nrf2 and HO-1 protein. An increased Bax-to-Bcl2 ratio and apoptosis were observed [187].

On the other hand, spermatozoa not only carry the genomic information of a haploid nucleus into the egg cell but also play a crucial role in early embryo development and the health of the offspring through their epigenetic signature. These epigenetic modifications are highly sensitive to environmental factors, such as endocrine-disrupting chemicals often associated with plastic particles [188]. In summary, although research in mammals is still limited, early findings suggest that MPs may pose a significant risk to male fertility.

- **Female Fertility**

Several studies indicated that MNP exposure is highly correlated to reproductive problems in females. Oral PE administration (10–150 μ m, 40 mg/kg/day) over a 30-day period resulted in DNA damage, apoptosis, oxidative stress, and mitochondrial dysfunction in the oocytes of Kunming mice. These cellular injuries in germ cells were followed by reduced oocyte maturation, lower fertilization rates, and impaired embryonic development [189]. Furthermore, after 35 days of continuous exposure to PS-MPs, a reduction in the first polar body extrusion rate and a lower survival rate of superovulated oocytes were observed in the ovaries of mice. This study also led to indications of ovarian inflammation [190]. Another study showed decreased concentrations of 17 β -estradiol (E2) and testosterone in the plasma of female *Oryzias melastigma* after sixty days of PS-MP exposure [191].

5. Microplastic Particles Do Not Disappear After the End of Biological Life

After death, tissue and cell degradation processes, along with environmental interactions, influence the fate of MNPs in human and animal bodies. Bacteria, enzymes and microorganisms promote organic degradation, but synthetic polymer particles are largely resistant to biodegradation. As organic matter decays, MNPs are gradually released into the environment, with the specific pathway depending on burial or cremation practices. In burial, MNPs may be transferred into the soil, potentially contaminating groundwater or being absorbed by plants and animals, re-entering the ecosystem. Due to their persistence, MNPs can remain in the environment long after complete decomposition, perpetuating cycles of pollution. It is generally accepted that incineration at high temperatures represents a way to permanently eliminate plastic waste. Nonetheless, during incineration, where typical temperatures range between 760 and 980 $^{\circ}$ C (1400–1800 $^{\circ}$ F), there are reports that MNPs may not fully combust and unburned material still exists in the bottom ash, i.e., the solid residue from such furnaces [194]. Unlike pyrolysis, which converts plastics into smaller compounds under oxygen-free conditions, cremation of deceased people using traditional wood pyres can therefore be expected to allow MNPs to be released into the atmosphere or remain in the ashes [195,196]. Therefore, MNPs will undoubtedly continue to persistent environmental contamination. The resistance of plastic particles from biological waste material to naturally degraded has far-reaching ecological consequences, including soil and water contamination, food chain disruption and potential human health affects via bioaccumulation. This underscores the urgency of reducing plastic consumption, improv-

ing waste management, and limiting the spread of MNPs. The life cycle of plastics does not end with death; their release during decomposition or cremation sustains environmental contamination, posing long-term risks to ecosystems and future generations.

6. Conclusions

MNPs represent an inescapable threat that begins as early as fetal development and continues throughout life, culminating in a return to the environment after death. The exposure of fetuses and infants to these particles is particularly alarming, given their vulnerability during critical stages of development. The accumulation of MPs in the human body, combined with their potential to cause chronic diseases and disrupt biological processes, underscores the urgent need for comprehensive strategies to mitigate this global threat. Despite the obvious problems, there are still limitations that restrict further action to reduce the risk of MP exposure. Firstly, the different detection methods and the data obtained with them make it difficult to carry out comparative studies quickly and to the extent necessary. The number of particles and their composition as well as the structure can lead to very different pathophysiological results in this context. Plastic has nowadays permeated all aspects of our lives, and it is practically no longer possible to reduce contact with MNPs in a simple way, let alone avoid it completely. Addressing MNP pollution requires, therefore, coordinated efforts to protect human health and ensure a safer environment for future generations.

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