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Human exposure to micro- and nanoplastic: biological effects and health consequences

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Abstract Microplastics and nanoplastics are significant contributors to pollution as a consequence of increased plastic manufacturing and consumption, which has resulted in a worldwide environmental crisis. These small plastic particles (microplastics and nanoplastics with diameters less than 5 mm respectively 100 nm) originate from a wide range of sources, including packings, synthetic textiles, personal care products, and medical and laboratory consumables. The environmental effects and potential health hazards linked with microplastics and nanoplastics exposure are addressed in this review. Research has demonstrated a link between these plastic particles and human digestive, reproductive, respiratory, endocrine and cardiovascular pathologies. Microplastics and nanoplastics have the potential to be chronically detrimental given that they accumulate in human tissues and organs and are small enough to slip through cell membranes. In hopes of fully comprehending the mechanisms of toxicity and long-term consequences of exposure to microplastics and nanoplastics on human health, further research is urgently required. Policies that reduce the production and consumption of plastics and improve waste management practices are essential to combating plastic pollution.

Keywords: microplastic; nanoplastic; human health; toxicity; environmental pollution

Introduction

Nowadays, one of the most significant source of pollution in oceans, seas, and all other bodies of water is plastic, a synthetic substance made up of various polymers. The plastic fragments can have many sizes, forms, and structures and macroscopic or microscopic dimensions. The latter are represented by microplastics and nanoplastics, having dimensions from few micrometers to few nanometers, respectively.

The first mention of plastic was in 1862, at the International Exhibition in London, when Alexander Parkes, a metallurgist who was trying to make a synthetic material that could change its shape in the presence of heat, presented "Parkesine". After World War II and between the 1960s and 1970s, when this material was able to replace conventional ones because of its affordability, adaptability and simplicity of production, plastic started to be employed on a worldwide scale (www.plasticsindustry.org).

Plastic use has quadrupled in the past 30 years, but recycling technology is still in its infancy; in 2022, only 9% of plastic worldwide was recycled, while 22% was improperly handled, 19% was incinerated, and 49% was dumped in landfills. As more and more plastic enters the oceans each year—1.15-2.41 million tons—the issue is growing more and more concerning. This resulted in the formation of 5 primary locations where all the waste that arrives here collects, with the Great Pacific Garbage Patch which lies between Hawaii and California being the most significant of them (theoceancleanup.com).

Plastics are frequently employed in many different sectors, including textiles, medical equipment and devices, packaging, and other areas of daily life. Due to their durability, plastics are utilized in the medical industry for manufacturing tools like syringes, intravenous infusion bags, and catheters (Rivera et al., 2005). Plastics in the food packaging industry offer a cheap, flexible and lightweight alternative for transporting and preserving products (Weber Macena et al., 2021). Moreover, synthetic polymers are becoming more and more common in the textile sector because they have a number of advantages, including durability and moisture and chemical resistance, which make them perfect for sportswear and outdoor garments (Patti and Acierno 2022).

Microplastics (MPs) are generated as a result of wastewater treatment, tire wear, paint failure, washing of textiles, and at-sea losses, among other operations. Micro- and nanoplastics (NPs) assemble in aggregates

and sink in surface waters where they are consumed by organisms and spread out by currents. The proportion of species able to consume MPs rises as their quantity increases simultaneously with the decrease of fragments' size (de Sá et al., 2018).

Plastics disperse toxins in environment, release additives such as bisphenol A (BPA) or phthalates (PHTs) and act as a substrate for biofilms containing pathogenic organisms, such as bacteria or viruses. Human viruses have a significant capacity to establish a link with the plastisphere given the increased prevalence of enteric and respiratory viruses in society and environment (Kannan and Vimalkumar 2021). Viral adherence to biofilms on polymer substrates may increase the viability and ecological spread of the virus. Particles that can penetrate cells and are less than 20 μm in diameter may raise risks. Storms, natural disasters or the movement of rivers and the atmosphere all contribute to the enhancement of releases. In oceans, plastic trash includes the debris of fishing gear and litter such as lost or abandoned fishing nets and buoys, discarded lines and traps or netting from shrimp trawls and gillnets, plastic buckets or crates cut open by seabirds to release their catch. Plastic trash is one of the most pervasive forms of pollution in the oceans of the world (Hale et al., 2020).

Plastic fibers and particles enter the water column via rivers, winds, waves and other natural processes. They are consumed by a wide range of marine life, including plankton, fish and seabirds. Plastic particles ingested by wildlife accumulate in their intestines, where they either pass into the body fluids or remain in the gut, causing blockages. According to Greenpeace, a global network of non-governmental organizations (NGOs) preoccupied by a greener future, a single human can consume up to 50,000 pieces of plastic per year. Plastic waste has a particularly negative impact on cetaceans, causing entanglement, undernourishment and death (Carrington 2019).

Polystyrene-MPs (PS-MPs) of 5 μm and 20 μm diameter accumulated in the liver, kidneys or gut of mice, altering the biochemical biomarkers, metabolomic profiles, and generating oxidative stress (OS), as well as modifications in lipid and energy metabolism (Deng et al., 2018). Most studies focused on aquatic organisms, such as: mussels (Browne et al., 2008), crabs (Watts et al., 2014) or fish (Lu et al., 2016) while research on mammals is scanty.

Furthermore, freshwater hasn't gotten enough priority in studies on plastic contamination despite being essential for human survival. MPs and NPs have a significant impact on global freshwater systems due to their entry into the human food chain, leading to systemic dysregulations (Badea et al., 2023).

Inhalation, ingestion and dermal contact are the three main ways MPs and NPs enter the human body, with the first two being the most significant. But the last type of exposure should not be neglected. For example, polyethylene (PE) beads can be utilized as emulsion stabilizers or viscosity regulators in cosmetics, increasing the amount of contact that these substances have with the user (Leslie 2014; Lei et al., 2017). Furthermore, some items contain glitter, which is frequently created using polyethylene terephthalate (PET) (Yurtsever 2019).

The main purpose of this review is presentation of the effects of environmental plastic pollution on humans. Due to the ever-increasing exposure of people to these particles, in various forms, it becomes a necessity to know the current state of knowledge in this domain.

How humans are exposed to microplastics and nanoplastics

Human beings become into contact with MP particles through inhaling dust indoors, breathing through face masks, inhaling contaminated air in much polluted areas or by ingesting dust, contaminated food or contaminated water due to plastic packaging.

Inhalation

Synthetic fabrics, the erosion of materials and the resuspension of MPs in different surfaces are just a few of the factors that contribute to the release of MPs into the atmosphere. It has been approximated that each person inhales 26 - 130 airborne MPs per day (Prata 2018). The size and density of the particles will affect how they accumulate on the respiratory system, with less densely packed and finer particles entering the lungs further. Particle translocation may occur following accumulation, macrophage clearance or migration to the circulatory or lymphatic systems. The vast surface of microscopic particles inside the respiratory system, however, may trigger an acute flow of chemotactic agents that inhibit macrophage motility and enhance permeability, resulting in persistent inflammation, also referred to as dust overload (Donaldson et al., 2000).

Due to the proven strong oxidizing potential brought on by the vast surface area, PS nanospheres (64 nm) trigger neutrophil inflow, inflammation in respiratory pathways of mammals and the transcription of proinflammatory genes in epithelial cells (Brown et al., 2001).

Employees in the synthetic textile, flock and polyvinyl chloride (PVC) industries who are exposed to airborne MP particles at work have respiratory issues linked to the progression of airway and interstitial pulmonary disease (Porter et al., 1999; Xu et al., 2004; Atis et al., 2005). Fibers of 250 μm have also been observed in human pulmonary biopsies, as well as in cancer biopsies (Pauly et al., 1998). Probably inhaled plastic particles could potentially harm the respiratory system in circumstances where there is an increase in the concentration or a significant individual vulnerability.

The usage of plastic face masks became necessary due to the recent Coronavirus disease 2019 (COVID-19) outbreak, which raised the question of how much MP particles are inhaled as a result. Like many previous studies, one was carried out in China in 2020 and attempted to provide an explanation. Face masks of

various kinds have been evaluated. Utilizing various disinfection techniques, such as sunlight exposure, washing, using ultraviolet light (UV light) or alcohol, or just blowing air, as well as just reusing them increases the danger of inhaling MPs (Chua et al., 2020; Song et al., 2020). Face masks became less effective when their fiber structures were damaged because they provided less protection. The recommended time frame, during which there was a reduced risk of breathing MPs, was 4 hours. The N95 face masks had the lowest risk of MP inhalation, and UV disinfection was the best technique for reusing face masks (Li et al., 2021).

Ingestion

Because our food and environment are polluted with MPs, human contact by ingestion is highly probable (Prata et al., 2020).

The major sources of MP exposure are indoor air, as well as drinking bottled water or eating food from plastic packaging (Kannan and Vimalkumar 2021). It is estimated that a person consumes daily $39x10^3$ – $52x10^3$ particles of MP (Cox et al., 2019). These may access the gastrointestinal tract (GIT) through contaminated products or by mucociliary clearance following inhalation, potentially causing an inflammatory reaction, higher permeability and modifications in intestinal microbiota population and body metabolism (Salim et al., 2014). MPs have been detected in foods including mussels (Li et al., 2016), market fish (Neves et al., 2015), table salt (Karami et al., 2017), sugar (Liebezeit and Liebezeit 2013), but also in bottled water (Oßmann et al., 2018).

The gut may adsorb nanoparticles following ingestion by specialized M-cells overlaying gastrointestinal lymphoid tissues - Peyer's patches - based on their adherence to GIT mucous secretions, which in turn enhances particle clearance ratios (Ensign et al., 2012). Due to the adsorption of a "corona" formed by the components of intestinal contents (Powell et al., 2007), non-soluble particles may pass through the intestinal mucus.

Evidence from a research on 14 nm and 415 nm PS (latex particles) in rat intestinal segments proved that their size is a major determinant in how easily they transit through the digestive tract (Szentkuti 1997).

Another route of particle internalization that has been proposed involves paracellular transport of particles across the intestinal epithelium's single membrane (Volkheimer 1977). MPs may be prone to the same processes, since their migration to the circulatory system upon orally administered has been proven *in vivo*. Nevertheless, the harm of consuming MPs is unknown because little study has been undertaken to determine the total people exposure to them as well as its consequences.

Dermal contact

Since a paper in 2018 noted, the idea that MPs can transverse the dermal barrier has arisen (Revel et al., 2018). This pathway is far more frequently linked to contact with plastic monomers and additives, for instance the endocrine disruptors BPA and PHTs, from regular usage of everyday items.

Plastic materials have been proven to cause fibrous encapsulation, an external body response, and mild inflammatory processes. Although inflammation and responses to foreign bodies may also be brought by MPs and NPs exposure, variations in interface characteristics may also have various impacts. Contact with these particles could lead to OS in human epithelial cells as well (Schirinzi et al. 2017).

Therefore, the need for more studies in this field is supported by the possible negative consequences of NPs and the ubiquitous cutaneous exposure to plastic particles (from dust, synthetic fibers, and microbeads in cosmetics) (Hirt and Body-Malapel 2020). These cosmetic microbeads are applied to the skin and dentition (Strand 2014). It was observed that a high percentage of them are fabricated out of PE (Lei et al., 2017). And these microbeads have a role as emulsions stabilizers, viscosity regulators and skin conditioners. Therefore, while emulsions are the basis of the vast majority of cosmetic products, it can be estimated the wide range of possible contact while doing makeup, washing ourselves or during skin care (Leslie 2014). Likewise, some makeup or washing products contain glitters, which typically are made from PET polymers (Yurtsever 2019). Another concern is the mechanical processing of these MPs during their use, generating potentially harmful NPs. Their prevalence in items for personal care containing PE microbeads has also been proven previously (Hernandez et al., 2017).

Microplastics and their obesogenic effect in humans

In addition to microbiome dysbiosis caused by MPs and their additives, peroxisome proliferator-activated receptors (PPAR) α, β and γ activation, OS and membrane damage are also caused by exposure to MPs. These processes lead to altered adipogenesis and obesity.

These plastics can be of different types: polypropylene (PP), PS, polycarbonate (PC), PET, PHTs, PE like High and Low Density polyethylene (HDPE and LDPE), polybrominated diphenyl ethers (PBDEs), PVC, benzothiazole and organotins (Kannan and Vimalkumar 2021). Exposure these plastics that contain traces of co-polymers sucha as BPA also activates other nuclear receptors, such as the retinoid X receptor (RXR), which results in cytotoxicity, altered energy production, immunotoxicity, and disturbance of thyroid hormones (Kannan and Vimalkumar 2021).

Nuclear receptor activation increases adipocyte differentiation while also expanding the white fat accumulation.

The dysbiosis of gut microbiome induces a metabolic disruption which provokes a rise in fat storage, an effect to which it also contributes to altered energy metabolism,

a consequence of damaged mitochondrial membranes. This cellular damage, along with a peculiar lipid, fatty and bile acid metabolism are listed in Figure 1.

According to the size of the MPs particles, various obesogenic effects have been found in numerous studies. So, PS particles of 5-20 μm accumulate in kidneys, gut and liver, leading to reduced adenosine triphosphate (ATP) synthesis, modified lipid metabolism and, also, hepatic steatosis in mice (Deng et al., 2017; Yang et al., 2019). Also in mouse gut, PS particles of 5 μm diluted in certain dosage (100 μg/L and 1000 μg/L) in their drinking water accumulated and caused dysbiosis in microbiota and bile acids malabsorption (Jin et al., 2019). In addition, this dysbiosis was caused by PS particles between 10 μm and 150 μm (Li et al., 2020).

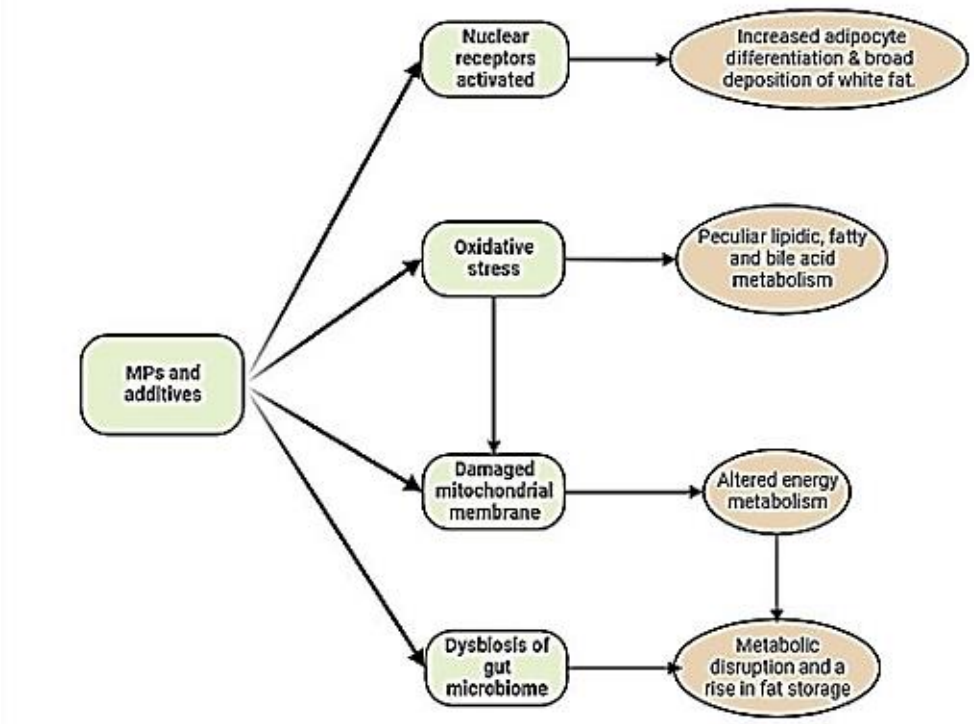

Fig. 1. Obesogenic effect and the mechanisms of MPs and additives. Generated with BioRender.com

Various metabolic pathologies appeared in mice after exposure to PS particles with sizes between 0.5-50 μm, especially due to the changes in lipid metabolism. In addition to this recurrence, alterations have been observed, such as: a lower body and liver weight (Lu et al., 2018), accumulation in gut and liver, alongside PE beads (Deng et al., 2018), pathologic levels of serum liver markers, modified glycolipid metabolism and due to exposure of the maternal parent, metabolic changes in first filial generation (F1), respectively F1 and second filial generation (F2) descendants have been noticed (Luo et al., 2019).

Human respiratory system

The behavior, dispersion, and retention period of MPs in the atmosphere may be dependent on particle size and density as well as meteorological and environmental variables such as rainfall totals, wind direction and velocity, temperature, and urban topography (Prata, 2018). Previously, it was found that the sewage of wastewater treatment plants (WWTPs) contains fibers, particles and microbeads that might play a role in the air contamination (Li et al., 2018; Mahon et al., 2017). There is also a significant amount of MPs collected in urban soil and vehicle dust. Low density polymeric materials can become rapidly airborne by wind and traffic circulation (Abbasi et al., 2018).

In addition to microbial biofilms developing on MPs, exposure to various climatic conditions can also cause these MPs to absorb different contaminants (Foulon et al., 2016; Besseling et al., 2017). MPs are not only forced to change their physical characteristics, including their size and density, when biofilms develop (McCormick et al., 2014), but they can also carry infectious agents, such as *Vibrio crassostreae*, for example (Foulon et al., 2016). As far, no studies to date have been done in order to measure the proportion of MPs within airborne particulate matter.

The discovery of plastic fibers in pulmonary tissue in the framework of a human biomonitoring investigation (Pauly et al., 1998) raised the possibility that airborne MPs can deposit or accumulate in the lungs. It has been reported that lungs accumulate fibrous particles that are a few tens of μm in size (Gasperi et al., 2018). Despite the fact that alveolar macrophages ”eat” MPs, harmful

particles to these cells are measuring 15-20 μm in size. Numerous different research findings have revealed that MPs can end up causing lung tissue to respond with inflammation, cytotoxicity, and genotoxicity (Donaldson et al., 2000); such an interaction between airborne MPs with workers in synthetics manufacturing facilities is linked to lung diseases and therefore this exposure for a large period of time causes lung conditions such as asthma and pneumoconiosis (Turcotte et al., 2013; Prata, 2018).

An additional effort to standardize the methodological approaches is required as a preliminary move in this regard, since there is currently no consistent method for quantifying MP amounts in air and dust. In the light of these findings, it is clear that polymeric fibers can reach deep compartments of the lungs, and therefore further studies are necessary (Amato-Lourenço et al., 2020).

Atis et al. (2005) investigated the pulmonary consequences of occupational PP flock inhalation. In comparison with the control group, the incidence of breathing issues elevated to 3.6 fold in workers. Lung samples collected from employees who had been subjected to various airborne man-made fibers (acrylic, polyester (terylene), nylon) exhibited various levels of inflammation, granulomas and interstitial fibrosis (Pimentel et al., 1975).

There is some evidence that MPs contamination may contribute to interstitial lung disease. However, the original cause of the disease remains largely unknown.

The toxicology of MPs and NPs exposure on cultures of human epithelial lung cells has not been much studied. Xu et al. (2019) examined the impact of PS nanoparticles of 25 nm and 70 nm on the human alveolar epithelial A549 tumor cell line. The results showed an altered cell viability, stimulated inflammatory genes transcription and changes in the expression of proteins linked with cell cycle and mechanisms that encourage apoptosis. Similar effects were also discovered in human lung epithelial BEAS-2B cells by generating reactive oxygen species (ROS) (Dong et al., 2020). So far, no *in vitro* investigations of pulmonary toxicity based on ecologically relevant circumstances or primary lung cell cultures have been published.

Given the rising percentage of enteric and respiratory viruses in the community and environment, human viruses have a great capability to develop a connection with the plastisphere. This term refers to the microbial films found at the junction between the polymer surface and environment. At this level, different species of infectious agents can be found, such as *Enterobacteriaceae* (Rodrigues et al., 2019), *Campylobacter* (Zettler et al., 2013) and *Vibrio* (Kirstein et al., 2016). Because enteric and respiratory viruses are so common, there are numerous opportunities for them to engage with plastic areas in the environment, such as through transport in wastewater systems, fecal contamination of environmental plastic passive vectors and respiratory virus accumulation on polymer substrates (Moresco et al., 2021).

The processes whereby virions get in contact with and adhere to biofilms on plastic interfaces in the environment are poorly studied, as evidenced by the scarcity of information on potential associations between viruses like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which possesses an envelope, and biofouled plastic substrates (Moresco et al., 2021).

Effects of microplastics on human digestive system

According to previous studies, the ubiquity of MPs in water and food, especially in the case of fish and seafood was proved. Even so, it is difficult to prove a direct correlation between these and human intestinal health, due to insufficient data and studies. The majority of research focused on animal experiments, so it cannot be said for sure that the effects observed already are applicable for humans. Nevertheless, among the repercussions of MPs and NPs ingestion, there are known: the dysbiosis of intestinal microbiota, altered intestinal homeostasis or gut permeability, and gut inflammation which can lead to immunological consequences (Hirt and Body-Malapel 2020). These outcomes can precede the occurrence of chronic disorders of immune nature. It is also vital to consider the fact that MPs are not only pieces of plastic, but also contain additives and other contaminants. These can also be bacteria or viruses delivery systems. Needless to say, these can trigger adverse effects.

Also according to animal experiments, it was shown that plastic particles with diameters more than 150 μm are not able to cross the intestinal mucus barrier; they remain in this layer, while the apical area of enterocytes is directly exposed to them. MPs, with a lower diameter than the previously mentioned limit, have the capacity to cross the barrier (Alexander et al., 2016). Powell et al. (2010) presented various mechanisms for the crossing of these particles, among which are: endocytosis by intestinal epithelial cells, transcytosis through M-cells, persorption or paracellular uptake. It is also a possibility of accumulation of MPs in some organs, like stomach, liver, kidneys or lungs, as it was identified in mice. If the size of the plastic particles are small enough, they can travel through the blood-brain barrier and accumulate in the brain (Grodzicki et al., 2021).

It is worth considering the connection between the brain and the digestive system, namely the gut-brain axis (GB axis). The central key of this axis is the 10th cranial nerve, the vagus nerve, along with the corresponding connection with the autonomic nervous system (ANS). Knowing that the GIT is the most vulnerable due to the fact that ingestion is the major pathway for MPs to pervade in the organism, it is obvious that it is getting the most of the amount of MPs to which the human body is

exposed to (Cox et al., 2019; Carbery et al., 2018). In a previous study, the researchers spotted the accumulation of NPs, namely combustion-derived NPs, in the vagus nerve in humans. This can have devastating effects on the nervous system, which can lead to neurodegenerative diseases, such as Parkinson's or Alzheimer's disease (Calderón-Garcidueñas et al., 2017).

Another study tried to provide both *in vivo* and *in vitro* details about the effect, absorption or possible accumulation of PS-MPs in the human intestinal wall. The researchers used an *in vitro* human system, with Caco-2 cell line of human intestinal epithelium cells in co-culture to resemble the M and goblet cells, while the *in vivo* experiments were performed on mice. It was observed that the highest cytotoxicity was registered for the smallest particles, while those with a bigger diameter had no toxic effect (Stock et al., 2019). This can be explained by the high ratio between surface and volume of the smaller particles (Sharifi et al., 2012).

Medium sized particles, of 4 μm in diameter, were identified as having entered the cells due to different size-dependent import pathways. Regarding the *in vivo* experiments, too few particles were found to be considered relevant in the first two thirds of the small intestine, while in other organs no evidence of the presence of these particles was found (Stock et al., 2019). However, it is possible that these results are not found in the case of people suffering from diseases that affect the permeability of the intestinal barrier, such as celiac disease or irritable bowel disease. From a toxicological point of view, PS-MPs did not show effects in *in vivo* studies, unlike those on fishes or other aquatic animals (Della Torre et al., 2014; Lu et al., 2016), and as a result, the relevance of these studies for mammals is still uncertain. Also, other variables such as the size, shape and type of MPs, but also the interaction between different types of MPs must be taken into account, which can determine various, even potentially harmful effects.

Regarding human exposure, it was found that MPs can be excreted through feces (Zhang et al., 2021) and can be present in colectomy samples (Ibrahim et al., 2020), but also, more concerning is the fact that PP-MPs were found in the human placenta (Ragusa et al., 2021), along with nanobeads of PS (Wick et al., 2010).

Due to the scarcity of human experiments in this respect, researchers are trying to offer hypotheses regarding the effects of MPs in the intestine based on the effects observed in studies on mice. Therefore, recently it was observed that an exposure of 5 weeks to PS-MPs determined the appearance of some worrying effects, such as loose glands, swollen lamina propria, inflammation and infiltration of immune cells, along with elevated amounts of proteins with immune implications, such as Toll-like receptor 4 (TLR4), interferon regulatory factor 5 (IRF5) and activator protein 1 (AP-1) in human duodenum and colon (Li et al., 2020). Also, the secretion of mucus decreased, along with expression of genes related to it (Jin et al., 2019), especially the main one, mucin 1, cell surface associated (Muc1) (Lu et al., 2018) and the level of serum bile acids was lessened (Jin et al., 2019).

Effects of microplastics on the human cardiovascular system

A very recent research regarding the ability of plastic particles to be absorbed through membranes observed the presence of these particles in human blood. The prevalence was higher for PET, PE, various types of PS and polymethyl methacrylate (PMMA) particles, but traces of PP were also discovered. Besides, this study measured for the first time the plastic concentration in human blood, which was found to be 1.6 μg/ml, an average value obtained from investigating samples of 22 healthy people (Leslie et al., 2022). Obviously, there is a lack of information on human contact as well as toxicology regarding the potential health risks, which makes the long term effects difficult to understand.

Due to preclinical experiment regarding delivery of different drugs, researchers know about „accelerated blood clearance" (Dams et al., 2000), a phenomenon which can, probably, also happen to these plastic particles found in human blood. Moreover, MPs can be studied in the near future along with their mechanisms of transport in the bloodstream, including whether they float in plasma or are carried by white cells, as well as the consequences for the immune system.

Due to the fact that plastic particles can travel through cellular membranes, they can get to tissues and organs (Yong et al., 2020), such as brain (Prüst et al., 2020) or placenta (Gruber et al., 2020), which can induce OS and inflammation, that could lead to various illnesses, such as cardiovascular diseases (Kelly and Fussell 2020).

The cardiovascular system can be influenced by hypercoagulability (Lippi et al., 2008) besides the inflammation, mechanisms that could be affected by particulate matter (Bai et al., 2007; Apte et al., 2015; Yuan et al., 2019), in addition to what was previously mentioned (Hayes et al., 2020).

Regarding the red blood cells (RBC), it was found that plastic particles can attach to their surface (Avsievich et al., 2019), altering their ability to aggregate and adhere (Barshtein et al., 2016). In a recent study, the effects of PS-NPs on human RBCs and, the increased rate of thrombosis in rats in an *in vivo* experiment have been observed. Among these, it was taken in account an increase in the rate of hemolysis and thrombin formation, externalization of phosphatidylserine, ability to adhere to human umbilical vein endothelial cells (HUVECs) and microvesicles (MVs) generation. Not only this, but modifications in ATP, reduced glutathione (GSH) and calcium levels were present, which activated the scramblase, a protein with a role in phospholipid translocation in cells (Kim et al., 2022).

All these consequences lead to damaged RBCs, cardiovascular toxicity (Kim et al., 2020) and venous

thrombosis, raising the procoagulant activity (Gillespe and Doctor, 2021). The MVs also carry procoagulant proteins, which intensify the process of coagulation (Van Der Meijden et al., 2012), joining to the pathological causes for thrombotic diseases (Litvinov and Weisel 2017). On account of the features and characteristics of plastic particles, it is intricate to assume the degree of connection between these particles and thrombosis. The dysregulated levels of calcium and ATP are adding to the procoagulant characteristic of RBCs (Shin et al., 2007), and are further related to other vascular pathologies, such as thalassemia (Shalev et al., 1984) and drepanocytic anemia (Bookchin and Lew 1980).

It is well-known that functional groups, which are connected to the particle surface, influence their toxicity (Qian et al., 2021). Kim et al. (2022) observed that the amine-modified PS-MPs had the highest procoagulant effects – compared to plain or carboxyl-modified PS-MPs. Additional research supported this conclusion, and other effects, such as the ability to cause apoptosis or the loss of potential in the mitochondrial membrane in the lungs, kidneys, and liver, have been reported (Anguissola et al., 2014).

Effects of microplastics on the human reproductive system

Besides other human systems, the reproductive system is also affected by plastic exposure. The damage produced by it is different in the female and male systems. So, for PHTs an anti-progestogenic activity (Morgenstern et al, 2017) and anti-estrogenic/-androgenic one (Lauretta et al., 2019) have been noticed. Research on these compounds found that the anogenital distance in male infants was altered (Suzuki et al., 2012), and an effect in the case of BPA (Miao et al., 2011) was also observed. BPA is a notorious competitive estrogen inhibitor and has the ability to damage nervous, immune or reproductive tissues (Sinha and Wilson, 2021). It binds to the receptor of estrogens (ERα/β), altering the expression of genes controlled by these transcription factors (Wetherill et al., 2007). The interaction with PHTs in humans may impair fertility, emphasizing the significance of restricting access to these endocrine-disrupting chemicals (EDCs). Despite the fact that exposure concerns are not fully defined, PHTs have the ability to cause an endocrine disruption to the human reproductive system.

Female reproductive system

Given that there have been very few studies on the female reproductive system and the effects of EDCs on it, the issue is not well understood. PHTs and BPA have been associated with an increased risk of developing endometriosis (Upson et al., 2013) and polycystic ovarian syndrome (PCOS) (Vagi et al., 2014). Furthermore, di-(2-ethylhexyl) phthalate (DEHP), a substance used to increase the flexibility of plastics, may also play a role in this increased risk (Cobellis et al., 2003). Due to its activity on the ovules or changes in the hypothalamic-pituitary-ovary axis, PHTs exposure was found to have a directly related link with primary ovarian insufficiency (POI), precocious puberty (Mesquita et al., 2021), and menopause (Grindler et al., 2015)

Regarding pregnancy, PTH exposure determined a higher risk of preterm pregnancy, but this mechanism and the altogether effect on pregnancy is still not fully understood (Kamai et al., 2019; Mesquita et al., 2021). In the case of *in vitro* fertilization, the risk of failure is higher due to this exposure, mainly because of the decline in number and degree of maturation and fertilization of oocytes. Also, a higher chance of low-quality embryos generation occurred (Mesquita et al., 2021).

Male reproductive system

Regarding the masculine reproductive system, a modification in erectile, arousal and orgasmic functions due to the exposure to BPA (Li et al., 2010) was noticed. Moreover, a variation in sperm concentration, mobility of spermatozoids and damage of deoxyribonucleic acid (DNA) due to BPA and PHTs toxicity was reported (Li et al., 2011; Lassen et al., 2014; Pant et al., 2014).

The exposure to PHTs caused a variety of effects, depending on the subtype of PHTs and the biological sample analyzed. The main features followed were: the volume of ejaculated semen, its spermatozoa concentration, motility and morphology, but also their DNA damage. In the case of the last mentioned biomarker, a clear increase was recorded, despite the sample analyzed, due to the effect of DEHP (Wang et al., 2016; Huang et al., 2011) and mono-n-butyl phthalate (MnBP) (Jurewicz et al., 2013). Regarding to the correlation between spermatozoa motility and DEHP exposure, no changes were registered in semen probes in some studies (Zhang et al., 2006; Thurston et al., 2016), while others found a decline of this feature in the semen exposed to this EDC (Pant et al., 2008; Huang et al., 2011). About the relationship between spermatozoa motility and exposure to dibutyl phthalate (DBP), no modifications were observed in semen (Zhang et al., 2006; Thurston et al., 2016), whereas other studies found a decrease of this parameter (Hauser et al., 2006; Pant et al., 2008). The only increase in motility was noticed in the samples exposed to mono-(2-ethylhexyl) phthalate (MEHP) (Bloom et al., 2015) and mono-isobutyl phthalate (MiBP) (Thurston et al., 2016).

Considering the correlation between spermatozoa concentration and exposure of semen to DBP, no alteration was seen in some studies (Zhang et al., 2006; Thurston et al., 2016), while others observed a decrease of it (Hauser et al., 2006; Pant et al., 2008; Wang et al., 2015). The contact of these types of samples with DEHP showed either no change (Zhang et al., 2006; Thurston et al., 2016), either a lower concentration of spermatozoa (Wirth et al., 2008; Pant et al., 2008; Wang et al., 2015, Mínguez-Alarcón et al., 2018). Also, the morphology of

spermatozoa exposed to DBP was not affected by PHT exposure (Zhang et al., 2006), whereas this was affected by DEHP presence (Pant et al., 2008).

After of PE-MPs administration, levels of testosterone, luteinizing hormone (LH), and foliculo-stimulating hormone (FSH), which are essential for sperm production, were significantly decreased. While LH is responsible for stimulating Leydig cells (LCs) to synthesize testosterone, FSH maintains the proliferation of juvenile Sertoli cells (SCs) and spermatogonia (Ramaswamy and Weinbauer, 2014). PE-MPs intake decreased levels of testosterone and gonadotropins LH and FSH, potentially as a result of disrupting the hypothalamus-pituitary-gonadal axis (HPGA) (Ijaz et al., 2022).

Conclusions

To summarize, MPs and NPs are highly varied, originating from a wide range of sources and impacting the whole environment. Although there are alternatives to reduce the amount of plastics, such as: the decrease of their usage in everyday life, recycling or use of bacteria and worms that can digest plastic, their effectiveness is limited because some plastics are not biodegradable. The consequences of these particles exposure vary depending on their size, shape, concentration, and source, and they can disrupt any human biological system, such as the pulmonary, digestive or cardiovascular system. Increased risk of asthma, granulomas, interstitial fibrosis, pneumoconiosis, dysbiosis of gut microbiota, altered gut permeability and inflammation, altered bile secretion, immunological implications, increased risk of thrombosis can all be induced by these particles. Taking in consideration that MPs have been found in the human placenta, the effects can be exerted on the fetus. Despite countless animal studies, many questions about the severity of the condition remain unresolved, particularly in the case of humans, due to the bioethical aspects. Further research on the consequences on various organisms, as well as novel methods for combating these polymers and the particles derived from them, are required.

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