



Review

Micro to nano plastics and its link to human health

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Abstract

This article reviews the recent publications on the effects of micro and nano plastics being bioaccumulated, inhaled, ingested, digested, absorbed, or excreted in models and humans. Also, the retention of microplastics and nano plastics in the blood and lymphatic circulation, and their possible toxic effects on tissues at the cellular and biomolecular level is discussed.

Keywords: Circulation, microplastics, interference, nano plastics, prion, protein misfolding

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Plastic originated from the Greek word “plastikos” (easily grown or shaped and moulded), and refers to a generic family name that covers the polymerisation and condensation process of natural materials such as crude oil, cellulose, or salt to produce synthetic materials such as bakelite, polystyrene, vinyl, acrylic, nylon, polyethylene, epoxy resins, fluoropolymers, polyolefins.

The plastic family can be divided into two: thermoplastics and thermosets according to their structural changes when treated with heat. Even though hydrolysis, mechanical abrasion, thermal degradation (as heat), photodegradation (as ultraviolet (UV) radiation), and biodegradation apply great lytic activity on plastics; plastics cannot be degraded easily. Although the chemical structure tends to shrink with deterioration, it takes hundreds of years for plastics to completely breakdown [1].

Since these additives are not attached to the polymer matrix by chemical bonds, they can easily separate from the matrix and can mix with the external environment. Plasticizers, antioxidants, fire resistance enhancers, ultraviolet stabilisers, lubricants, and colouring agents are some of the additive polymers, fillers/reinforcements that are used to produce the desired properties in the final product [2]. The mostly addressed additives at this stage are phthalates, bisphenol A, nonylphenol, and flame retardants with an impact on health cumulatively worse.

The classification that is used by the US National Ocean and the Atmospheric Administration defines microplastic (MPs) as spherical particles, fibres, granules, or flakes having a diameter smaller than 5 millimetres (5000 micrometres). Thompson et al. [1] extend the term by adding a must-have optical detectability for the small-size granular or fibrous debris. Nano plastics (NPs) with a more varied range, change from 1 to 100 nm, and are comparatively more visible. Mesoplastics can be as smaller as 2.5 cm to 1 mm [3].

However, MPs can be classified as primary and secondary plastics according to their genuine sources. Primary microplastics, are moulded, manufactured, commercialised, or intended to be used in special compact sizes as they are only functional in small sizes such as microbeads for their exfoliating properties in cosmetics such as in skin care products (facial or body scrubs, cleaners, or exfoliating foam or soap products) and household cleaning essentials such as in detergents. Secondary microplastics, the micro-nano pollutants formed indirectly because of comminution, are formed due to the destruction and disintegration of carelessly disposed of plastic products in the environment due to natural biotic factors such as microorganisms or abiotic factors such as weather, wind, sun, UV rays [4]. Also, synthetic fibres of textile, or microfibers such as from sponges, foam particles from food packaging containers, or

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fragments of cutlery and lids, separated from the main plastic made from materials (e.g., polyester, nylon) while wearing and washing are attributed to the secondary sources.

The direct involvement of Plasticsphere*

One way for MPs to enter the food chain is through aquatic organisms. As MPs and NPs have a similar or smaller size to zooplankton, they are being ingested by plankton-fed aquatic organisms and biomagnified in higher organisms at different trophic levels such as dolphins and humans [5, 6]. Among the studied marine food webs and marine bioaccumulation processes, especially seafood and salt from sea or rock holds the first place. But groundwater, lakes, sediments, soil, and the atmosphere are also affected [7]. On the agricultural level, the pollutant degree is 4-23 times more likely to be higher in terrestrial environments than in aquatic environments due to the origin which is contaminated by land-based sources such as municipal solids and compost wastes, biosolids in sewage sludge, and plastic mulches [8]. Studies on MPs and NPs have shown that the physical and chemical properties of soil, microbiota (including the bacteria, algae, and fungi) of soil, and its complex network groups are selective and can modify, leading to a change in the productivity of the crops. Recently a few studies presented that NPs could accumulate and travel from the roots by straining the cell walls and a few types of NPs could accumulate in the leaves and edible parts of the plants, although no significant degrowth was observed [9, 10]. According to Dessi et al. [11] in store-bought rice, according to Conti et al. [12] in apple, carrot, and lettuce from supermarkets "cellularly translocated" NMPs can be observed. Not solely contaminants from micronanoplastics (MNPs) but also the sorption of chemical pollutants and their vector effect in living are problematic issues. During the degradation process when pH is low, the surface of MPs enhances the anionic pollutants, and when salinity increases cations compete for sorption; coating the MPs with ionic surfactants increases the capacity of adsorption 3-26 times more. This adsorption leads accumulation of contaminants such as polycyclic aromatic hydrocarbons, organochloride pesticides, polychlorinated biphenyls, perfluoro alkylated substances (PFASs), and several types of antibiotics, but also heavy metals such as chromium (Cr), zinc (Zn) or lead (P) [13] which intensifies effects on health.

Ingestion, digestion, and absorption

Mostly polypropylene (PP), polyethylene (PE), and polystyrene (PS) particles were found in edible sea salt having a range changing between 45 and 680 particles per kilogram among samples from Bulgaria, France, Germany, Italy, Senegal, Thailand, India, Indonesia, and China [14]. In the drinkable water, depending on the storage conditions mostly PP, PE, nylon, polyamide, polyethylene terephthalate (PET), and poly vinyl chloride (PVC) were detected [14, 15].

The distribution of MPs to different tissues and organs in the body varies depending on the degrading size of the MPs and

NPs at the time of ingestion. But the annual average for adult exposure to microplastics by consumption of bottled water was estimated to be higher in particle concentration (range between 0 and 10,000 particles per litre at a size of 0.1-5 mm), followed by tap water ranging between 0 and 61 particles per litre in different studies when 1.5 µm filtration was used [15]. Senathirajah et al. using the current literature estimated the global average ingestion of MPs in human were in the range of 0.1-5 g per week [7, 16].

In 2007, Enders et al. [17] studied in vitro degradation protocols for MPs. Among the corrosive candidates, are sodium or potassium hydroxide, alkaline cleaning agents, concentrated acid mixtures of nitric acid and hydrochloric acid, oxidants such as hydrogen peroxide and sodium hypochlorite, and the International Council for the Exploration of the Sea's recommended procedure of acid mixed treatment of 4:1 nitric acid to perchloric acid; the most effective treatment was of 1:1 KOH: NaClO for PA, PU, and a black tire rubber elastomer. To a lesser degree acrylonitrile butadiene styrene, polymethyl methacrylate, and polyvinylchloride were also chemically digested. The most effective medium was the acidic treatment of HClO₄ for acrylonitrile butadiene styrene (ABS) and polyethylene terephthalate (PET). In the presence of these abiotic factors, it was suggested that an acidic environment in the stomach and an alkaline environment in the intestine could also facilitate chipping off the MPs and NPs in the body as well. According to the study by Schwabl et al. [18] by using Transform Infrared Microspectroscopy, it was possible to identify unabsorbed PP, PET, PS, and PE particles larger than 50 µm in the human stool.

Once MPs enter the human body by ingestion they pass through the oesophagus to the stomach. In the in vitro studies that were carried out in acidic conditions at 37.5 °C, green fluorescent labelled microplastics were detected in tight and adherent junctions of the stomach lining after 24 hours [19]. In co-culture cells, MNPs were digested approximately 2-6 hours into the body while some larger PS particles are transported to the midgut and hindgut lasting about 18 hours [7]. The other insoluble MPs are smaller than 1.09 µm passed from the stomach to the intestinal epithelium, detected in the microvilli [20]. According to Bredeck et al. [21] absorption of the MPs from the intestine first affects the epithelial barrier and mimicking the peristaltic movement either leads to excretion in the stool or further absorption into the circulatory system; by not only deforming the lamina propria but also leading to leaky gut. Other MPs up to 130 µm in size are carried into human tissues by paracellular transport in the form of desorption [22].

In their study, Krasucka et al. [23] found that after digestion, the polymers (PS, HDPE) were less hydrophobic and had a stronger affinity to polar functional groups. This may suggest that instead of hydrophobic and π-π interactions due to the hydrophilicity of the plastic, hydrogen bonds take over, which again arises an issue involving any biomolecule with a hydrogen bond.

Microplastics in circulation, lymphatic system, and adipose tissue

In a validated study for the first-time polymers from plastics of poly methyl methacrylate (PMMA), PP, materials containing PS, PE, and polyethylene terephthalate PET were detected and quantified in human blood. To do this double shot pyrolysis - gas chromatography/ mass spectrometry method (Py-GC/MS) was used [24]. The results of this study naturally raised questions about the fate of plastics that can be absorbed into capillaries that are typically only 5-8 μm in diameter and how would the particles likely have an impact on microvascular fluid dynamics or clogging [24]. According to Yuan et al.'s [25] study PUR, PAN, PVC, Epoxy resin, and ABS particles up to <150 μm can be absorbed into lymph nodes in cell models of human intestinal systems. However, some larger MPs (>0.2 μm) may pass through the intestines via splenic filtration. It is assumed that some small NPs (<0.1 μm) remain in the bloodstream [26] and can accumulate in other organs [8, 27] reported that ingested MPs have a significant positive correlation with the severity of inflammatory bowel disease (IBD). Also, stool from IBD patients (41.8 substances/g dm) showed higher concentrations of MPs than healthy people (28.0 substances/g dm).

In other studies, rats were orally administered single doses of 125 mg/kg or fewer plastics for 24 hours to one week and subsequent in their intestinal walls, kidneys, spleen, testis, placenta, and heart NP involvements were shown especially for the negatively charged NPs whereas positively charged plastics were found to increased the permeability of the intestinal barrier [28]. The gut-brain axis at the vagus nerve, at X cranial nerve, and branches of the autonomic nervous system were also studied only to find the plastics destabilise the lipid membranes, (more specifically lipopolysaccharides) and accumulate in the microglia and neuronal stem cells, too [28, 29].

Microplastic accumulation in adipose tissue

Adipocytes, besides their capacity to store fat, are known for their ability to have a role in energy homeostasis in the body and release various effectors, including exosomes, miRNAs, lipids, inflammatory cytokines, and peptide hormones. Through the principle of dissolution, petroleum-based plastics have been studied in the adipose tissue of model animals. To test this Meng et al. [30] investigated the different sizes in 50 nm, 300 nm, 600 nm, and 4 μm PS pieces' bioaccumulation and bio toxicity in rats' adipose tissue and found the aggregation of 600 nm PS-MPs exacerbated biotoxicity the most where smaller NPs particles caused weight loss, increased death rate, histological damage of the kidneys. Also, exposure to PS-NPs and PS-MPs induced oxidative stress and the development of inflammation [31]. In another study exposure to PS beads for 3 weeks was enough to accelerate weight gain, and impair glucose homeostasis and HOMA-IR and gene expression change in perivascular adipose tissue [32].

Inhalation and plastics

Ingestion is not the only way to integrate with plastics. In studies, it has been shown that particles below 25 μm can pass through the respiratory organs and be retained in the lungs to a large extent. The annual human ingestion of plastic particles during evening meals in the form of airborne MP fibres has been estimated to range between 13,731 and 68,415 fibres per person, numbering out the seafood-related integration [33].

In the case of continuous inhalation or ingestion by humans, it has been determined that microplastics weaken the immune system and cause particle toxicity [26]. Toxic chemicals such as PUR, PAN, PVC, Epoxy resin, and ABS are classified as the most toxic polymers [34]. Releasing toxic chemicals from MNPs could have acute, subacute, or chronic toxic effects causing diseases such as certain cancers Unlike inhaled MPs against ingestion ones, accumulate in the alveolar regions of human lungs and migrate to epithelial layers through gas exchange between alveoli and capillaries [35]. It is reported that lung tissues contain higher levels of MPs than females and thus could be due to the smaller airways of females.

Possible link with obesity, cancer, and inflammation

Local effects of microplastics such as inflammation in the intestines are possible and thus may affect the immune system. Microplastics can act as vehicles or carriers for environmental pollutants through additive chemicals such as styrene, toxic metals, phthalates, bisphenol A, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons as they can be absorbed on the surface of microplastics and act as hormone-like substrates. These pollutants and additives can be transferred from ingested MPs to animal tissues and disrupt essential body functions [21]. According to Fackelmann et al. [36] metabolised MNPs cause alteration of feeding activity in low trophic levels such as marine life, but the reduction of food assimilation efficiency in higher animals shows the same stunted growth, altered gene expression, oxidative stress, and neurotoxicity effect in humans.

BPA, for example, is used as an estrogenic agent in a therapeutic context. BPA is also widely used in the production of plastics and synthetic resins causing a wide range of disruptive effects in the body, while it interferes, at very low doses, with oestrogen receptors.

Phthalates and some brominated flame retardants have been shown to have adverse effects, too [37]. These endocrine disrupting chemicals (EDCs) can alter foetal programming at an epigenetic level, can pass down through generations, and may play a role in the development of various chronic disorders later in life, such as metabolic, reproductive, and degenerative diseases, as well as some forms of cancer. MPs can also release carcinogenic monomers, such as propylene oxide and vinyl chloride [38]. Another result revealed that 500 nm polystyrene microplastics, on SMMC-7721 cells at 20 $\mu\text{g}/\text{ml}$ for 24-hour treatment, lead to morphological alteration, membrane damage [39], and increased cell apoptosis via oxidative stress and can lead to hepatic toxicity and hepatic cancer [19].

Micro-nano plastic interaction with prions and protein misfolding

After entering the cells, NPs were shown to alter the lipid bilayer of membranes (and probably the membrane of the endoplasmic reticulum (ER), too). When protein-nanoparticle interactions and 3-D structure of the proteins are studied, the possibility of NPs acting as a template to change the secondary and tertiary structure of the proteins arose. Hollóczy et al. [40] in their study have chosen two important proteins; tryptophan zippers and α -helix polypeptide of 12 alanine amino acids to show the alteration in samples treated with polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and nylon-6,6 (N66) in size of 5 nm. According to their study amino acids with non-polar side chains, such as phenylalanine and tryptophan, were prone to adsorb onto the surface of the PNPs.

In their study, Kihara et al. [41] managed to show adsorption of polystyrene to human albumin proteins creating a corona complex shielding the protein. One interesting finding was that the size of the nanoparticles was able to influence the adsorption of the corona as with larger NPs particles favouring the formation of a soft corona, due to the decreased PS–HSA attraction, meaning that albumins' capacity to carry molecules can alter, too.

Likewise, Gopinath et al. [42] found that plasma proteins such as albumins, globulins, and fibrinogens that play significant roles in, maintaining osmotic pressure, molecule transport, immune response, enzyme activity, and blood coagulation displayed strong affinity towards NPs and shield a multi-layered corona size of 13–600 nm. And according to their finding, these increased protein conformation changes caused denaturation, and higher genotoxic and cytotoxic effects in human blood cells.

Detection techniques and possible interference with routine parameters

For detecting the MPs and NPs in the tissue optical scanning methods such as basic optical microscopy, scanning electron microscopy with energy-dispersive X-ray (SEM/EDX) analysis, coupled plasma mass spectroscopy labelled by iridium, time-of-flight secondary ion mass spectrometry, photoinduced forced microscopy, Raman (or stimulated Raman (SRS)) or Fourier (attenuated total reflection-FTIR and μ FTIR) transformed infrared microscopy techniques are mostly used. Another technique to detect the NPs and MPs in living is to use co-cultures monocultures, organs on a chip, and multipotent derived cells organoids to mimic the possible movement across the lining. In silico experiments, the behaviour of PE-NP in various solvents and hydrophobic core of lipid bilayers are studied revealing that different modelling is valid in microstructured amphiphilic liquids, e.g., ionic liquids [43]. Thermal desorption mass spectrometry-based techniques to identify and quantify the mass of individual polymers in a sample is also useful tool [44], and particle counting techniques and

mass determination of polymers are too complementary approaches. However, for real-world biological matrices methods are currently still under development. Also, limited studies are done about single-use plastics; the laboratory tubes such as PE, PP and PVC whose rubber stoppers containing the plasticizer tris-(2-butoxy ethyl)-phosphate (TBEP) have been reported to displace certain drugs from plasma-protein binding sites, such as the α 1-acid glycoprotein resulting in increased drug uptake by red blood cells (RBCs), thus artificially lowering serum or plasma levels [45].

Conclusion

NP can penetrate all tissues, including the intestine, and placenta, and through the brain-blood barrier to the brain, and can be transported into cell membranes [46]. Human exposure to MPs and NPs can vary, but mainly through ingestion, inhalation, and dermal contact, and can easily lead to the accumulation in the body and thus trigger or induce the immune system which could result in local, particularly toxicity [47]. Methods and libraries to determine the amount or the possible interference with the biological molecules or even samples (that might affect the laboratory results) are required as well as guidelines to reduce and dispose of the waste.

Also, supplementation (such as Vitamin D) from aquatic nutrients including the aquatic planktons such as Krills and seafood [48] and quality assurance for livestock animals must be controlled and revised accordingly.

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