Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 4, 2023, 381
https://doi.org/10.33263/BRIAC134.381

A Systematic Review on the Impact of Micro-Nanoplastics Exposure on Human Health and Diseases

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Scopus Author ID 15845677300
Received: 12.08.2022; Accepted: 20.09.2022; Published: 31.10.2022

Abstract: Plastic production is continuously increasing worldwide for daily use. Micro-plastics and nano-plastics remain major emerging pollutants and threaten the environment, ecosystem, human health, and well-being. Micro-nanoplastics (MNPs) are also exposed to humans through cosmetics, inhalation, ingestion, drinking water, dietary sources, and drug formulations. Oral uptake is the major among the different exposure routes of MNPs to humans. After entry, it gets absorbed due to its nano size (<100 nm) and easily distributed to all parts of the body through blood, affecting multiple organs, especially vital organs of the human body leading to severe diseases. It causes cancer, heart, liver, and kidney diseases, crosses the blood-brain barrier, and affects the brain. Its adsorption with protein leads to multi-layered corona formation in human blood plasma. MNPs interact with immune cells and induce pro-inflammatory mediators, inflammatory reactions, reactive oxygen species (ROS) production, and associated cytotoxicity. MNPs suppress T lymphocyte activity which results in a lack of immune regulation leading to autoimmune diseases. Hence, it is necessary to understand the impact of MNPs exposure on humans. Strict control measures for the production and use of plastics and developing appropriate strategies for safe disposal would prevent MNPs-mediated toxicity in humans.

Keywords: microplastics; nanoplastics; micro-nanoplastics; environmental pollution; ecotoxicity; inflammation; human health.

1. Introduction

Plastics are the most dangerous, long-lasting pollutants and remain a major threat to human health and well-being. Global plastic production for multiple uses reached nearly 368 million tons in 2019 [1]. Plastics possess high toughness, flexibility, transparency, and durability, and their use by common people has increased manifold in the last decade [2]. Because of its cost-effectiveness, it is extensively used by different people worldwide in a day to day life. Slow degradation, lack of effective recycling mechanisms, and improper disposal methods lead to severe environmental pollution affecting the ecosystem and human health. Micron-sized plastic fragments -microplastics (MPs) and sub-micron-sized fragments - nanoplastics (NPS) are widely distributed in the environment, soil, and water and thereby enter the food chain [3]. Plastics are exposed to humans in multiple ways, including inhalation, drinking water, food [4], and medicines (tablets, capsules, and various medical devices manufactured using plastics). An average daily exposure of 382 ± 205, 594 ± 269, and 1036 ± 493 MPs per person were reported through drinking water, inhalation of atmospheric air, and consumption of food, respectively [5]. It was reported that an average daily exposure of 2012

± 598 microplastic particles per person. The plastic intake was calculated to be 122.25 ± 177.38 to 202.80 ± 294.25 mg per person per day [5]. The exposed micro-nanoplastics (MNPs) are responsible for causing several health problems in humans. More often leads to the onset of severe untreatable human diseases. MNPs effects on humans include cellular cytotoxicity, neurotoxicity, mortality, reproductive failure, genotoxicity, alteration of metabolic enzymes, physicochemical and behavioral changes [6]. It also causes reactive oxygen species (ROS) mediated oxidative stress and injury to various cells, including lung, gastrointestinal, liver, heart, and kidney cells [7]. MNPs interact with proteins and form protein corona [8], it also causes DNA damage, and the resultant gene mutation affects the cell cycle, cell proliferation, and repair mechanisms [9]. Workers from different industries, including textile, flocking, and VC/PVC (vinyl chloride/polyvinyl chloride), plastic is more susceptible to the development of occupational diseases due to MNPs exposure [10]. The toxicity of MNPs is due to their size, shape, zeta potential, and bio-persistence time in the exposed cells, tissues, and organs [10].

2. MNPs in Air

Airborne MNPs pose a new challenge to human health. Humans are susceptible to both outdoor and indoor MNPs [11]. Airborne particulate MNPs, including fibers, fragments, and films, have been widely distributed in various environments. Many reports suggest the occurrence of more and more MPs in urbanized areas. There are few studies on airborne MNPs on human health [6]. It was reported that increased fiber (synthetic and plastic) concentrations in the indoor air compared to outdoor air [12]. These fibers undergo photo-oxidative degradation followed by wind shear-mediated fiber fragmentation. Eventually, these MNPs were widely distributed over terrestrial, coastal, and marine environments [13]. MNPs, due to their size and density, can easily spread to wider locations and become inexhaustible pollutants.

3. MNPs in Soil

Plastics dumped in land fillings and disposed of without proper treatment are considered a major source of soil contamination and are converted to MNPs in the long run. Earthworms digest normal plastics and form fragments of microplastics [14]. Exposure to road dust, accumulated garbage, stagnated industrial plastics, continuous soil sedimentation, and prolonged atmospheric deposition also contribute to microplastic pollution [14]. Plastic mulching, plastic-containing compost, untreated wastewater, sewage, and river water passing through plastic-polluted sites are major sources of MNPs in agricultural soil [15]. The distribution of different-sized MNPs on different layers of the agricultural soil also varied. Letting unprocessed sewage containing MNPs to water bodies also results in soil contamination [16]. Polyester (PE), polypropylenes (PP), plasticized polyvinyl chloride (PVC), polyethylene terephthalate (PET), polyolefin (PO), and polysulfone (PSU) were some of the commonly occurring MNPs in the polluted soil [17].

4. MNPs in Drinking Water

The presence of varying concentrations of MNPs in both tap water and bottled water has been reported [18, 19]. The possible source of MNPs in drinking water is PVC pipes for distribution. These pipes get degraded/ eroded under prolonged use and are found to be a source for MNPs [20]. The use of pet plastic bottles and caps for packing drinking water and the occurrence of possible degradation processes during manufacture, distribution, storage,

marketing, and repeated use of bottles are the major source for MNPs in drinking water [21]. Prolonged use of water bottle and opening and closing of water bottle repeatedly also leads to the discharge of plastics from water bottle also contribute to MNPS [21].

5. Exposure of MNPs to Humans

MNPs are exposed to humans through multiple routes. The different routes of exposure of MNPs to humans, their impact on toxicity, and associated health issues in humans are depicted in Figure 1.

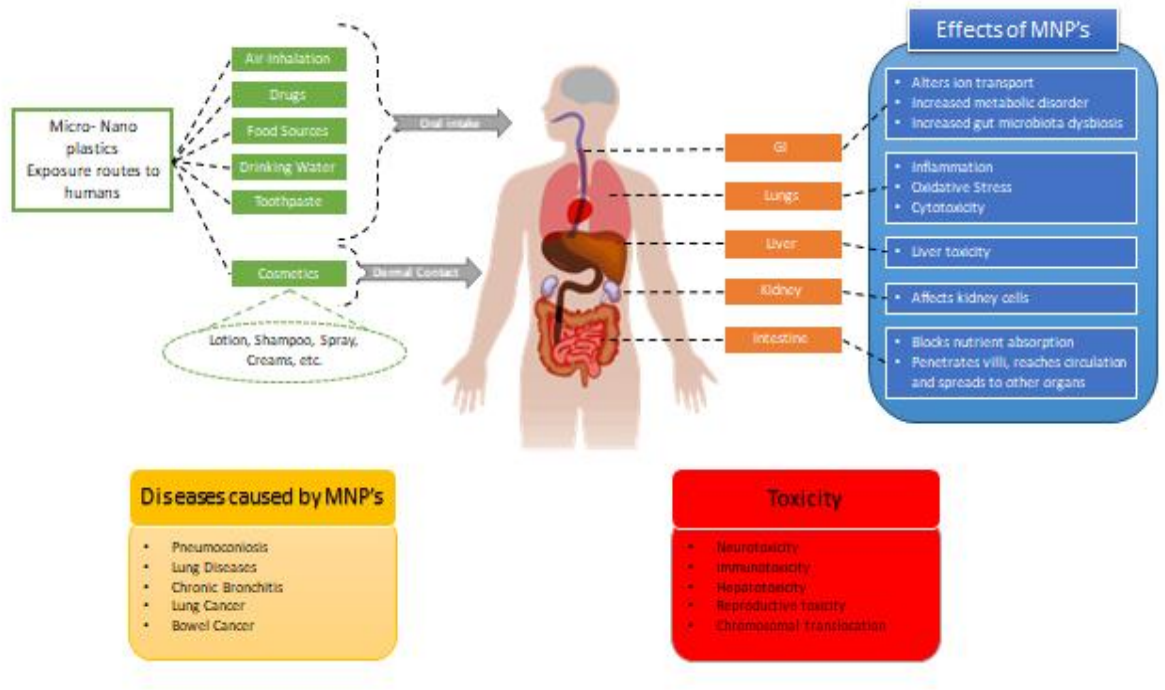

Figure 1. Exposure routes of MNPs, their effect on different organs, associated toxicity, and human diseases.

5.1. Inhalation of MNPs.

Inhalation is one of the important routes of MNPs exposure in humans. In a polluted site during normal breathing (6 L min^{-1}), humans might inhale 26–130 airborne MNPs of varying sizes per day [22]. It measured the exposure of 272 MNPs to humans in indoor air itself [11]. Inhalation exposure of MNPs from indoor and outdoor dust has also been recently reported [4]. Previously settled particles from carpets and doors are detached during common human activities such as walking, crawling, and cleaning from surfaces can contribute to indoor MNPs [23, 24]. Inhalation exposes humans to more than 48,000 MNPs per day [11]. Children are more susceptible to indoor MNPs due to crawling and other activities. The use of medical devices made up of plastics, such as an inhaler, nebulizers, and other respiratory aides and therapeutic agents, can also contribute to MNPs' release to the lungs [8].

5.2. Ingestion.

Ingestion is considered one of the major routes of MNPs exposure in humans [25]. MNPs are reported in various food sources, including vegetables, fish, other seafood, table salt, sugar, honey, milk, and beer [4, 10, 26], and other dietary sources consumed daily. The other route of MNPs exposure is consuming food packed using plastic materials [27]. Hot beverages, soups, and other food items served in plastic cups are considered the major source of MNPs.

Hot tea or coffee served in plastic cups can release millions of MNPs [28]. Food items stored in plastic jars, cups, and boxes for a prolonged period also served as a source for MNPs. MNPs in the atmosphere get deposited onto the surface of food materials when consumed, which contributes to a significant quantity of MNPs exposure to humans through diet [5]. Some of the major MNPs, including polyethylene terephthalate, polystyrene, polynorbornene, nylon, polychloroprene, and copolymer polyacrylamide, are reported to be present in different food samples [5].

Liquid and solid pharmaceutical products are packed in plastic containers and supplied to consumers. Not many reports are available on the release of MNPs into the drug. After packing, storage, and transportation, pharmaceutical ingredients are adsorbed to the plastic polymers—their sorption results in the leaching of MNPs from the plastic container to the drug [3]. The quantity of MNPS mixed with the drugs also serves as a source of MNPs to the consumers. These MNPs not only affect the efficacy of the drug and also affect the patients who consume the drug.

Some additives added to the plastic containers, such as antistatic agents, antioxidants, and hindered amine light stabilizers in pharmaceutical formulations, also increase the release of MNPs from plastic containers into the drug [29]. In addition, prolonged storing and aging of plastic containers due to physical and chemical changes is also detrimental to the packed drugs. This aging also increases the release of MNPs from the plastic container, and adverse chemical reactions between the drug and the plastic container substantially increase the release of MNPs [3].

5.3. Dermal exposure.

It is implicated that MNPs are exposed to humans through the dermal route due to their extensive distribution, abundant atmospheric availability, etc. MNPs in cosmetics, personal care products, toothpaste, exfoliation, and cleansing agents have already been reported [30]. Nnanoplastics (<100 nm) (i.e.) can directly enter through the skin [31]. Transdermal entry of microplastics through hair follicles, sweat glands, or open skin injuries are some of the possible sources of the entry of plastics into humans [32]. Inflammation and oxidative stress-induced skin damage are other root causes of exposure to MNPs in humans [33].

5.4. Lung.

MNPs penetrate the lower respiratory tract [22] and are taken up by endothelial cells [34]. Plastic fibers also can enter the deep human lung and cause inflammation [35]. The exposed MNPs can accumulate in the trachea, bronchi, and alveoli, which are cleared by mucociliary escalator or by pulmonary macrophages. But the MNPs escaping from the clearance mechanism are forming bimolecular aggregates mimicking protein or drug-protein aggregates. The accumulation of MNPs can cause extensive airway inflammation, leading to bronchial lesions, alveolitis and fibrosis of the lower airway, thereby severely impacting lung functions [22]. Prolonged friction between MNPs and lung tissue leads to the onset of respiratory diseases. MNPs accumulation can also cause Ground glass nodules (GGNs). The presence of more MPs in human tumors than in normal tissue was reported, and prolonged exposure to MPs might be responsible for the carcinogenesis process [36].

5.5. Gastrointestinal tract.

MNPs enter the gastrointestinal tract via inhalation and ingestion through drinking water, food, other dietary sources, vegetables, and medicines. Larger plastics (MPs) are trapped by villi in the intestine and block nutrient absorption. Smaller plastics (NPs) penetrate the villi, enter the circulation, and reach other tissues and organs. MNPs deposits on the surface of food during preparation and consumption are also found to be another source for MNPs in the GI tract [37]. Microplastics are generally excreted from the gastrointestinal tract [38]. Internalization of MNPs into the surrounding tissues by paracellular and transcellular mechanisms followed by its uptake by M-cells of Peyer's patches was also reported [39].

6. MNPs Distribution

MNPs entered into tissues are taken care of by tissue macrophages [40]. MNPs also interact with immune cells leading to transport to the lymphatic system [41] and also to different organs [42]. From the lymphatic system, MNPs can enter the bloodstream [43] and also from primarily exposed organs into the bloodstream [44]. Once MNPs reach the bloodstream via blood, they distribute to the whole body. MNPs have been found in various organs, including the liver [45], spleen [43], kidneys and urine [45], bone marrow [41], brain and cerebrospinal fluid [44], and the placenta [46]. MNPs-associated inflammatory responses decrease the integrity of epithelial barriers and activate macrophages leading to increased internalization of MNPs [47]. Irreversible accumulation of MNPs in human tissues for a prolonged period of time contributes to severe health issues [48].

6.1. Liver.

MNPs can cause hepatotoxicity and also affect lipid metabolism in the liver. MNPs can induce DNA damage and release in the nucleus and mitochondria. Potential risks of MNPs on the onset of liver steatosis, fibrosis, and cancer were also reported. MNPs are permeable to liver cells and accumulate in the liver [49].

6.2. Heart.

MPs exposure has been reported to increase troponin I and creatine kinase-MB (CK-MB) levels in serum, leading to structural damage to the myocardium and apoptosis, also associated with collagen proliferation in the heart. Exposure to MPs can cause cardiac fibrosis by activating the Wnt/β-catenin pathway. It was also reported that MPs-induced oxidative stress mediates cardiovascular toxicity [50].

7. Effect of MNPs on Immune function

MNPs, once entered into the human body, interact with immune cells to produce an inflammatory response, it depends on the size of the plastic particles, and it was reported to be more with microplastics than nanoplastics [51]. Increased production of IL-6 and IL-8 by macrophages on exposure to polystyrene nanoplastics results in a profound increase in the inflammatory response. TNFα and IL-1 mediated inflammatory response on exposure to polyethylene MNPs has been reported [52]. Prolonged exposure-mediated increased inflammation and associated ROS production are responsible for hemolysis [51]. Increased ROS production is also associated with the onset of autoimmune diseases. MNPs-mediated

production of anti-inflammatory mediators and suppression of T-cells was also reported [53]. MNPs exposure also induces cytokine production associated with inflammation, immune stimulation, stress response, and proliferation of human white blood cells [54]. It was reported that increased pro-inflammatory mediator secretion due to MNPs exposure is associated with cytotoxicity [55]. The involvement of toll-like receptors in mediating inflammatory reaction cascade in response to MNPs exposure has also been reported [56]. Disruption in microbiome composition due to exposure to MNPs has been reported to be responsible for changes in immune response [57].

8. Strategies to Control the Exposure of MNPS to Humans and Associated Health Effects

Controlling the amount of MNPs reaching the environment and effective cleanup or recycling of already accumulated plastics is the primary task to protect the environment and the ecosystem. Large-scale production and lack of effective disposal and recycling methods pave the way for large-scale accumulation in the environment, leading to uncontrolled distribution in soil and drinking water, thereby entering the food chain and affecting the consumers. Many pharmaceutical drugs stored in plastics and medical devices made up of plastics are widely used to save the individual's life during in-patient and outpatient treatment procedures in hospitals and serve as a source for MNPs. Extensive studies are needed to understand the transport, accumulation, and impact of MNPs on human lungs, the gastrointestinal system, blood (blood-brain barrier), and skin. Multiple routes of exposure of MNPs to humans, their distribution in different organs, and their interaction with various cells are associated with multicellular toxicity leading to the onset of severe diseases.

To control the impact of plastics on humans, a considerable reduction in the use of plastics in daily life and the development of novel methods for proper disposal of plastics must be strictly followed and implemented.

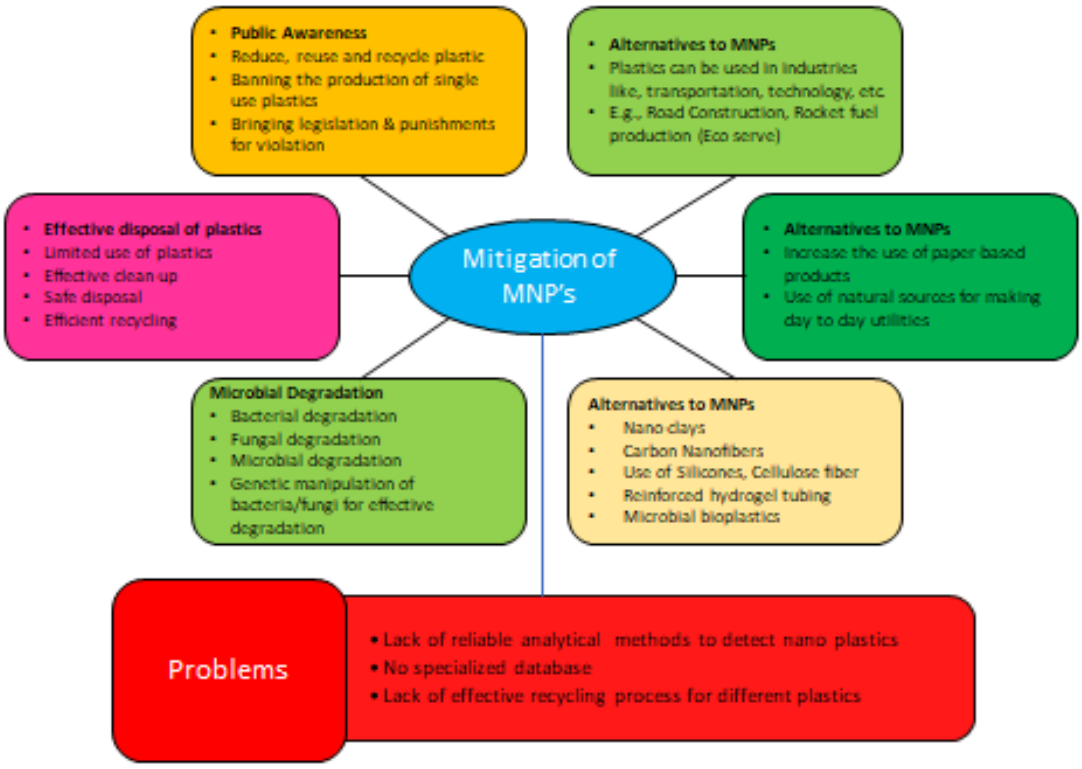

Figure 2. Strategies for mitigating the effects of plastics.

The threat associated with MNPS exposure could be effectively controlled and managed by multiple approaches, as suggested in Figure 2. Among the strategies, microbial bioremediation is the more prominent method for MNPs pollution using a single bacteria or fungal strain or consortium of bacterial or fungal strains or co-culturing of bacterial and fungal strains for effective degradation of plastics. The bacterial strain *Ideonella sakaiensis* [58] and marine fungal strain *Zalerion maritimum* are reported to be very effective in degrading plastics [59]. Many *Aspergillus* fungal species, including *A. nidulans, A. flavus, A. glaucus, A. oryzae, A. nomius, Penicillium griseofulvum, Bjerkandera adusta, Phanerochaete chrysosporium* and *Cladosporium cladosporioides* have been reported to degrade plastics effectively [60].

Microbial extracellular enzymes such as carboxyl esterases, lipases [61], laccases [62], and peroxidases (class II peroxidases such as manganese peroxidase, lignin peroxidase, and versatile peroxidase) [63] are used for degradation of plastics. These enzymes increase the hydrophilicity and convert the plastics into carbonyl and alcohol functional groups, which facilitate the attachment of microbes with plastics [64]. Hydrolases (lipases, esterase, and poly (3-hydroxybutyrate)), depolymerases, and cutinases degrade complex polymers into small molecules [65]. Proteases hydrolysis complex proteins to polypeptides and degradation of polylactic acid by serine protease have already been reported [66]. Alternatively, biosimulation, bioaugmentation, use of genetically engineered organisms, and biosurfactants approach are suggested for the effective degradation of plastics [67].

MNPs exposure is associated with several disease conditions. It was reported that prolonged exposure to MNPs increases human carcinogenic risk [68]. Currently, we have very limited knowledge of the effect of MNPs on the human system. The long-term effects of MNPs and mode(s) of action on various cells, tissues, and organs of the human body need to be explored in depth. Systematic risk assessment and risk management protocols should be followed to secure human health and safety. It is impossible to avoid plastics use completely, and hence a suitable replacement for plastics for daily use would be ideal for overcoming the impact of plastics on the environment and human health. One possible alternative to synthetic plastic polymer is the use of bioplastics produced by microbes, but the production cost of bioplastics remains very high. In order to reduce the cost, the use of cheap sources such as chitin, starch, lignin, and alginate are tried and found to be successful. Still, these plastics do suffer from thermal instability and durability issues. An attempt was made to overcome this issue by using nano clays, carbon nanotubes, and silicones in bioplastics production [69]. 1% cellulose fiber reinforced biodegradable hydrogel tubing was produced to increase the durability of bioplastics [70]. But all these approaches have to go a long way to implement it in the commercial scale production of bioplastics and to replace synthetic polymer-based plastics. Several challenges remain that need to be assessed for exposure risk toxicity and associated health issues in humans [71].

9. Conclusions

Plastics remain to be the major emerging pollutant worldwide, including in developed and underdeveloped countries. The lack of sufficient quantitative data to assess the toxic impact of MNPS remains to be a major challenge. The research on MNPs' impact on humans is still in its infancy; more and more studies are needed to understand better the pathophysiology and toxicity associated with its exposure. Though animal model *in vitro* and *in vivo* studies are useful for understanding the effect of MNPs on humans, very few studies are still conducted, but they do suffer from a few problems, which include effective extraction and detection of

MNPs in human samples. Hence, developing sensitive and cost-effective diagnostic methods to detect and quantify the MNPs in human samples needs to be prioritized on a war footing. Due to its slow degradation, the long-term exposure effect on humans through multiple routes and its fate in the human body need to be explored further.

Creating awareness among people, minimizing its use, completely banning of manufacturing of single-use plastics, bringing very stringent rules and imposing severe punishments for violators, proper disposal, and effective recycling are some of the effective measures to be followed to overcome the toxic effects of MNPs. Other approaches include converting the waste into useful products, exploring better biodegrading methods and making viable alternatives to synthetic plastics, and developing sensitive analytical methods to detect and quantify the MNPs are some of the strategies to be explored by the scientific community to protect the environment, living creatures and to save the globe from plastic toxicity.

Funding

This review received no external funding.

Acknowledgments

The author would like to thank the Management of Vellore Institute of Technology for providing the necessary facilities and encouragement to write this review.

Conflicts of Interest

The authors declare no conflict of interest.

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