A Systematic Review on the Toxicological Implications of Microplastic to Human Health

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Research Article

Keywords: Bioavailability, Human health, Ingestion, MNPs Impact, MNPs, toxicity.

Posted Date: September 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-874079/v1

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Abstract

The environmental, economic, and social impacts of micro and nano plastic (MNP) pollution have caused significant global concern, which is exacerbated by the MNPs associated chemicals and biological entities that could directly or indirectly impact human health. The systematic review of research accomplished on this issue could enhance the understanding surrounding the toxicological risks of MP and its pathways to the human system. A significant amount of research is available on microplastic; still, the research executed to define the chemical impact and risk scenarios of microplastics on human health is limited. The objective of this study was to catalogue the literature on the toxicological impacts of MNPs on humans and the resulting biological consequences. A total of 95 publications were reviewed following the Cochrane protocol and screened based on the direct and indirect health impacts of MNPs to the human systems using the RevMan 5 software. Processing of collected data resulted in a total of 19 publications (until July 2021) that fulfilled the inclusion criteria and provided evidence of the potential impacts of MNPs, particularly in relation to the average sizes of Large MPs - 5mm - 1mm; MPs - 1mm - 0.1μm; NPs - 1-1000nm. Detailed analysis of data categorized into scenarios of chemical, toxicological, and biological impacts of MNPs on human health indicated that additives and associated contaminants of MNPs would pose a significant risk to human health. This is the first review that streamlines the notion that indirect impacts of MNPs caused due to MNP-associated chemicals are more severe than the direct impacts such as ingestion of MNPs.

Introduction

Plastic has become a universal pollutant and a topic of concern for the wellbeing of the planet due to its unique and continuous accumulation in the environment and ecosystems (Thushari and Senevirathna, 2020; Prata et al., 2021). Microplastics (MPs) refer to plastic fragments that are < 5mm in size. Smaller sizes ranging from 1-1000nm are termed nano-plastics (NPs) (Jiang et al., 2020). Primary MNPs are produced for a variety of purposes such as plastic production pellets, microspheres in personal care products, plastic blast media (air blasting) for surface preparation. Most MNPs are released into the aquatic environment with a concurrent average of 300 million tons of plastic production (Mathur, Mathur and Singh, 2014). Plastics released from household and commercial drainage systems are released to the aquatic environment in the form of wastewater effluent (Mattsson, Hansson and Cedervall, 2015). MNPs are ingested by a variety of marine species, including plankton (Lusher et al., 2017), invertebrates (De Sales-Ribeiro et al., 2020), fish (Alomar et al., 2017), marine mammals and turtles (Ašmonaite et al., 2018). MNP materials affect aquatic and other species by disrupting their reproductive cycles (Carr, 2017). These plastics, upon ingestion, eventually ends up in the human system (Barboza et al., 2018) and may, directly and indirectly, affect human health by acting as physical stressors or vectors of environmental contaminants entering through the human digestive, respiratory or circulatory systems (Senathirajah et al., 2021). Some of the exposure routes are i) Ingestion through food webs that leads to human consumption (Van Cauwenberghe and Janssen, 2014), (Senathirajah, et al, 2020) ii) Inhalation due to the presence of anthropogenic fibres in the atmosphere (Mandin et al., 2017), (Prata, 2018) iii)
Technical and medical applications with concerns regarding the use of plastic equipment (Frohlich et al., 2009; Yoo et al., 2011). vi) the intake from various other sources such as consumables (Senathirajah et al., 2021) air pollutants or through medical or drug delivery (Fröhlich et al., 2009).

Published literature on MP research has been exponentially increasing since 1997 and most of the studies have been focused on marine toxicology. Only since 2010, literature has begun to focus on human health and has described human health implications through invitro and in vivo studies based on model MNPs (Horton and Barnes, 2020). An in vitro study experimentation exposed the cerebral and epithelial human cells to polyethylene (PE) and polystyrene (PS) confirmed oxidative stress is one of the mechanisms of cytotoxicity at cell level (Schirinzi et al., 2017). Literature on nano-particles, indicates interactions with proteins, lipids and carbohydrates via in vivo transport across membranes (Waring, Harris and Mitchell, 2018). Overall, MNPs can potentially impact human health by particle toxicity that causes lung issues (Barroso et al., 2002), endocrine disruption (Chen et al., 2019) and reproductive development issues (Vethaak and Leslie, 2016). Evidence also suggest that ingestion rates may be greater than excretion rates (Senathirajah et al, 2020), resulting in a critical minimum mass. Due to geographical, personal, cultural and biological differences in the global human population, this mass has not been determined which not only creates uncertainty surrounding measurable impacts of MNPs on human health but also hinders the adaptation of management strategies and development of policies in many countries. This uncertainty can be reduced by deriving the following details: (a) the actual sizes and amount of MNPs that enters the human system; (b) the common polymers that may pose a high risk to human health; (c) the potential chemical impacts of ingested MNPs on the human system. With these objectives in mind, this systematic review aims at analyzing the pathways of direct and indirect toxicological impacts of MNPs to consolidate their diverse impacts on human health.

Methods

Literature Search Strategy

To ensure a broader search with scientific quality and minimum the risk for bias, this systematic review was conducted using RevMan 5 with part of Cochrane protocol. The Cochrane protocol is a widely used method to systematically review and compare the available literature in the medical field. The literature search was performed in July 2021 using PubMed, Google Scholar, Science Direct, and Web of Science databases. To assess the correlating impact of MNPs on human health, the search items used were: ‘microplastic or ‘nano-plastic‘ with ‘impact on human health‘ combined with ‘bioavailability‘ or ‘toxicity‘. Selection of publication, it needed to meet the following criteria: (i) English as primary written language; (ii) published between 2001 and July 2021; (iii) research showing physical, chemical or toxicity, biological impacts of MNPs; (iv) different sizes and quantitative estimates of MNPs.; (v) research linking participant or concept to possible human impact e.g. in vitro analysis. The inclusion criteria were developed to determine and capture all evidence of possible impacts of MNPs to human physiological and other health indicators.
To properly assess the applicability of publications to the outlined criteria for this review, all the included publications were categorized using the characteristics table as shown in table 1. A thorough selection of articles using the RevMan method to consolidate and analyse the selected publications therefore investigating two impacts. Firstly, direct impact refers to the direct access of MNPs into the human body through consumption or inhalation. Secondly, indirect impact refers to MNPs accessing the human system through a medium causing issue through existing biological and toxicological issues.

Depending on the types of impacts on humans, the publications were categorized based on methods, participants, intervention and outcomes in a ‘characteristics of included studies’ table provided in the Supplementary Information (SI) shown at table 1. The “participants” section included humans and aquatic animals consumed by humans, as well as laboratory medium used for analysis. Items listed under the “intervention” section were mostly solution or mixtures that contain MNPs particles that underwent laboratory analysis. The “outcomes” sections categorised the impacts of MNPs into: i) physical impact to humans through ingestion that may affect gut system or skin abrasions; ii) the biological impact of MNPs to human or the bioavailability of ingested MNPs in humans or invitro experiments based on this concept; iii) the toxicity or chemical impact of MNPs that affects the human's body functions.

Synthesis of Results

The in-depth analysis was based on the characteristics of included studies’ table. The exposure routes of MNPs (figure 2) that affects the human physiological system included: i) Ingestion through food webs that leads to human consumption, and attested by evidence suggesting that ingestion rates may be greater than excretion rates (Senathirajah et al, 2020), (Van Cauwenberghe and Janssen, 2014). In the case of ingestion, it has been recently researched that common source of foods that alters the presence of MNP in humans are drinking water, salt, beer, honey, sugar and commonly seafoods (Senathirajah et al., 2021). ii) Inhalation due to the presence of anthropogenic fibers in the atmosphere (Mandin et al., 2017), (Prata, 2018) iii) Technical and medical applications with concerns regarding the use of plastic equipment (Frohlich et al, 2009; Yoo et al, 2011).

Results

Outputs from systematic literature search

In total, 19 publications fulfilled the inclusion criteria and were identified and assessed according to the different scenarios regarding the direct and indirect impacts of MNPs to the human system. Categories of different scenarios of plastic impacts from the 19 publications that met the inclusion criteria differentiated the different researches that provided evidence of the potential impacts of MNPs particularly in relation to the average sizes of: Large MPs - 5mm - 1mm; MPs - 1mm - 0.1μm; NPs - 1-1000nm.
Total of 13 articles were published between 2018 and 2021, and 6 articles were published between 2000 and 2017. A total of 19 included articles analyzed according to 'direct' and 'indirect' impacts of MNPs to human health (*table 2*) have 22 events that mentioned 40 direct impacts and 19 events that mentioned 39 indirect impacts of MNPs to the human system. The events showed in *table 2* refers to the number of times a point is made on the impact of microplastic to human in a publication. The assessment of publications and its content, considering the different impacts of MP’s can be analyzed in many different forms and it must be noted that the selection method can affect the scientific quality of the systematic review. The review is focused on the outcome of previous publications regarding impact of plastic pollution resulting in the analysis. The forest plot (*table 2*) describes the heterogeneity of the included publications particularly on the impacts to human health and categorized under direct and indirect impacts. The direct impact in this case refers to the direct access of MNPs and its contaminants to human with evidence of human health issues as an outcome. Indirect impact refers to the access of MNPs and its contaminants to human via a secondary medium such as food that has the potential to affect human health.

As shown in *table 2*, heterogeneity ($I^2$) is 40%, indicating moderate variation between trials or methods used in the different publications. The p-value for the analysis is 0.46 (thus $>0.05$) which indicates that there is no statistical difference found between direct and indirect impacts. A total of 40 events showed that ‘direct’ impact of plastic has been more commonly stated in included publications. There were 39 events describing indirect impact which is indicative of the health impact and issues caused by MNPs. The direct impacts are mainly based on laboratory research such invitro experiments and cases of inhalation impacts.

**Toxico-chemical Impacts**

A total of 6 publications (Alimba Gideon and Faggio, 2019; Van Cauwenberghe and Janssen, 2014; Ravit *et al.*, 2019; Huang *et al.*, 2021; Da Costa Araújo and Malafaia, 2021 and Smith *et al.*, 2018) indicated that MNPs can have direct and indirect impact on human health system from the chemical or toxicological aspect. From the analysis of toxicological impacts, it is imperative to streamline the review focus to additives used in plastic processing of plastic and investigate their impacts on human health. Scenarios based from 2 publications discussed an existing impact of plastic additives that disrupt the human physiological system (Alimba and Faggio, 2019; Smith *et al.*, 2018). Possible outcome included cell damage through cellular uptake of plastic including the enhancement of gut infectivity through ingested MNPs. Chemicals such as polybrominated diphenyl ethers, nonyphenol, and octylphenol are released when ingested by marine and freshwater fish and later could pose risks to human health indirectly if consumed (Smith *et al.*, 2018; Lusher, Hollman and Mandoza-Hill, 2017 and Groh, 2019; Tanaka *et al.*, 2013). The Endocrine Society with its report outlines about 144 chemicals or chemical groups that are actively used as additives are hazardous to human health (The Endocrine Society, 2020).
Exposure to BPA itself at high dosage during pregnancy can affect the development or growth of offspring and reduce the survival rate and birth weight (Koch and Calafat, 2009). BPA is also considered a hormone due to its ability to mimic reproductive hormones, ‘estrogen’ and can cause health issues such as cardiovascular disorder and diabetes (Proshad et al., 2018). A recent study showed the concerning toxicity of MNPs and NPs whereby the virgin, coronated and isolated NP have toxicological prospective on human blood cells (Gopinath, Saranya and Vijayakumar, 2019).

Chemicals described in these cases and supported with publications are BPA, Vinyl chloride (VC), Benzyl butyl phthalate (BBP), 1,3-butadiene (BD), 4,4’-methyleneedianiline (MDA) and Epichlorohydrin (Table 3). Some of health issues that arises from these chemicals are carcinogenicity skin sensitisation, reproductive toxicity, severe eye damage, and mutagenicity (The Danish Environmental Protection Agency, 2014). The common addictive chemicals that are detected in humans are phthalates and BPA (Lithner, 2011; Koch and Calafat, 2009). Evidences shows that these chemicals can cause endocrine disrupting properties, affect developmental growth and as well as irritate the respiratory systems of humans (Lithner, 2011; Colon et al, 2000). Laboratory experiments have demonstrated that phthalates increase the risk of asthma (Stilund et al., 2007). Phthalates access human through environmental contaminants and even ends up in the milk of breast-feeding mothers (Zhu et al., 2006) hence exposing newborn to phthalates. BPA is mainly used for the manufacturing of polycarbonate plastic and epoxy resins.

MP can accumulate 10^6 times chemicals and one of the initial concerns was the ability of MNPs to bind organic contaminants and metals which can be toxic once ingested by humans. Invitro analysis from an included publication, (Alimba and Faggio, 2019), indicated that MNPs and its accumulated chemicals have potential to cause neurotoxicity, embryotoxicity, trans-generational toxic and reproduction abnormalities. The cellular uptake of NPs in a nonvascular method through the membrane may allow these particles to release their pollutant loads, such as POP's into the cytoplasm. This leads to the accumulation of POP's in the cell, thus creating toxicological effects to the human body (Lehner et al., 2019). POP's such as DDT, PCB, and HCB and heavy metals such as Ni and Pb are toxic chemicals which can causes human developmental abnormalities by affecting the biological systems of juvenile humans and animals (Smith et al., 2018). DDT (Dichlorodiphenyltrichloroethane) is an effective chemical for insect control and the booming industry for such chemicals are an issue as have been observed to be associating MNPs (El-Shahawi et al., 2010). Polymers such as polypropylene are carriers of POP's which are currently transferred to marine organisms during its degradation phase (Smith et al., 2018), (El-Shahawi et al., 2010). NP’s have positive surface charge which increase its cytotoxicity and cellular uptake by binding to harmful charged particles.

**Plastic-associated Chemicals**

A variety of environmental chemicals such as metals, PAHs (Lusher, Hollman and Mandoza-Hill, 2017), phthalates (Heudorf, et al., 2007), PFAAS (Taylor et al., 2019) are known to accumulate on the surface of
plastics over decades. The associated chemicals directly or indirectly access its way through the human system contributes to human health issues such as; the induction of acute inflammation in the liver due to associated metals (Revel, Châtel and Mouneyrac, 2018a), the impact of POPs to the lymphatic system (Heinrich and Braunbeck, 2019) and the leaching POPs that enhance gut infectivity or immune-stimulatory properties of the biological agents adsorbed to their surface (Van Cauwenberghe and Janssen, 2014), and (Ravit et al., 2019). These studies exemplify that most MNP associate chemicals are toxic and the rising concern are its accumulation (through adsorption) in marine organisms when consumed which later disrupts the endocrine system, and subsequently to humans causing reproductive disorders and risk of cancers (Revel, Châtel and Mouneyrac, 2018). Heinrich and Braunbeck, 2019 states that associated organic compounds adsorbed by MNPs were basically sourced from cosmetic, industrial, pharmaceutical, and food additives. There are 3 publications (Van Cauwenberghe and Janssen, 2014; Ravit et al., 2019; Groh, 2019) that describes toxicity of MNPs from the increasing leaching of associated chemicals such as polychlorinated biphenyls (PCBs). Another finding (Hartmann et al., 2017) supports the role of MNPs as vectors of contaminants when it associates with hydrophobic organic chemicals (HOC's) and are transferred into aquatic or marine organisms and then to humans.

The assessment of data from the included publications showed 14 publications that described the resulting biological impacts of plastic debris to the human system. The indirect mode of access was described by 6 publications (Alimba Gideon and Faggio, 2019; Heinrich and Braunbeck, 2019; Van Cauwenberghe and Janssen, 2014; Smith et al., 2018; Wang et al., 2019). One of many outcome of such impact is an increase in dysregulation of gene expression required for the control of oxidative stress, which can lead to cell and tissue damage (Alimba Gideon and Faggio, 2019). This included two studies, Smith et al., 2018, and Wang et al., 2019, describing the presence of MNPs in marine organisms’ digestive tracts during carcass dissections and also the presence of MNPs (mainly PVC) of size of 1-50μg. These articles also mentioned that the associated Fluoranthene was the primary cause of such human health issues. The direct mode of access was described by 6 publications (Alimba, Gideon and Faggio, 2019; Koch et al., 2017; Turcotte et al., 2013; Colón et al., 2000; Brown et al., 2001; Huang et al., 2021). According to these publications, MNPs size such as 70μm can restrict feeding and cause reproductive complications, intestinal damage, skin abrasions and skeletal injuries. A study conducted in Canada shows cases of lung disease caused from flocked nylon and have affected workers in a plastic manufacturing industry due to direct inhalation (Turcotte et al., 2013). According to Brown et al., 2001, cases of such lung diseases that occurs from ultrafine plastic particles are also associated with exacerbation of respiratory disease and deaths from cardiovascular causes. Another instance of direct impact is described by Koch et al., 2017, relating the analysis of 24-hrs urine samples from the German Environmental Specimen Bank confirming presence of phthalate metabolites with considered factors (age, geographical locations) that facilitates its direct access or exposure to human. A recent study by Huang et al., 2021 also states that MNP impact can include oxidative damage and gut inflammation. Supporting article (Rainieri et al., 2018) described the impact of MP associating PFOS, found in fish and eventually ends up in a meal. With the above assessment, it is observed that MNPs, have a vast negative impact to the human physiological system.
Size fractions amenable for ingestion and physiological impact

Research from the past 5-10 years focused more on plastic entanglement and ingestion at a macro level mainly on marine organisms. However, with the evolution of analysis techniques, research on smaller plastics and the toxicological profiling of marine plastic pollution has increased. Size fraction of MNPs plays a vital role in all analysis that have been produced in terms of its impacts. The categories of MNP sizes from micro to nano sizes and its physiological impacts as described from the reviewed studies are provided in *Table 4*. Also included in *Table 4* is the 'Impact' on human which shows the scenarios from different publications elaborating impacts of MNPs according to their individual assessments. The column for 'MP Size' displays different ranges of MP sizes which may have impact on the human system as highlighted in the publications.

Aquatic organisms such as fish and bivalves was shown to have ingested micro sized plastics from 3800μm down to 4μm (Baalkhuyur et al., 2018; Smith, 2018; Van Cauwenberghe 2014; Alimba 2019; Browne et al.2008). Such sizes of MNPs eventually were found accessing human body through gastrointestinal tract, gut cavity and soft tissues of bivalves. The NPs from 500nm to 20nm were mentioned to have affected humans, shrimp larvae, and freshwater invertebrate (Yoo, Doshi and Mitragotri, 2011; Brown 2001; Bergami et al., 2016). Smaller sizes have higher access advantage and studies have noted the vulnerability of human body for smaller size particles either through inhalation, food ingestion or medical treatment. Such nano sizes have a remarkable ability to be translocated and biodistributed with potentially higher contaminant loads (Triebskorn et al., 2019). The usage of nano-sized material in medical applications and nanotechnology is a concern due to its physiochemical and biological properties. Particles between 20nm – 200nm were observed to be cytotoxic and were efficiently taken up by the cells inducing cellular damage by induction of apoptosis and necrosis (Fröhlich et al., 2009).

**Commonly found Polymer Types**

Several publications have identified various high-risk plastic polymers with evidence of adverse health issues (Table 4). Four common polymers links to human health issues are Polystyrene (PS), Polyvinyl chloride (PVC), Polyethylene (PE) and Polypropylene (PP). PS is a common polymer used for plastic utensils and CD casings with impacting sizes of 4-16μm and 64nm (Browne et al.2008). Similar sizes for such polymers called PM10, ultrafine particles, are usually produced in plastic industries through bulk material handling, combustion and minerals processing (Gideon and Faggio, 2019). The sizes of up to 64nm are mentioned to have risks to human health when inhaled as it may cause adverse lung issues such as proinflammatory activities (Prata et al., 2020). Likewise, an invitro study demonstrated that the exposure of PS particles (10μm) could cause the high production of oxygen reactive species in the cerebral and epithelial cells (Alimba and Faggio, 2019).

Supporting publication states that similar sizes of MNPs (10μm - 90μm) is a concern due its ability to cause cellular toxicity to human liver cells and ability to enhance the bioavailability of plastic derived
toxicants (Alimba and Faggio, 2019, Rainieri et al., 2018). Similarly, PE with the size as small as 500 µm, was found to be a carrier of POP’s and other associated chemicals that may affect the biological systems and pose specific threats to the juveniles of humans (Smith et al., 2018; El-Shahawi et al., 2010; Hati and Dimari, 2010). Vinyl chloride (VC), a monomer known to be carcinogenic (Brandt-Rauf et al., 2012) is polymerised to form Poly Vinyl Chloride (PVC). PVC is a commonly observed polymer which is used to produce material such as PVC pipes which are used to convey water and wastewater. Exposure of this chemical occurs commonly in the petrochemical and plastic industries (Wesleybrandt-rauf et al., 2012). As VC is in a gas form, most if its exposure is through inhalation where absorption is rapid in humans, leading to subsequent metabolism occurring in the liver (WHO, 2004). An existing human health impact occurs during the production of PVC due to the toxic nature of the VC monomer involved Thornton, 2002. VC exposure is also known to causes liver cancer, malignant tumor of the endothelial cells of the liver (Wesleybrandt-rauf et al., 2012). The evidence of human health impacts due to chemicals which are linked with plastic materials is of concern (Table 5). Plastic materials and packaging are diverse and are made up of multiple polymers and other chemical components such as plasticisers, lubricants, acid scavengers, antimicrobial agents, heat stabilisers (Lithner, 2011). A database of Chemical associated with chemical packaging (CPPdb), was listed by Groh (Groh et al., 2019), shows 63 chemicals ranked the highest for human health hazards from the 906 chemicals listed to be associated with plastic packaging.

As shown in table 5, polyethylene (PE), a polymer commonly found in materials such as plastic bags and bottles are a risk to human health as they are carriers of POP’s (Hati et al., 2010). Similarly, polypropylene (PP), a polymer commonly used for materials such as ropes and bottles are also carriers of POP’s at the sizes of 16-20 µm (Smith et al., 2018; Heinrich and Braunbeck, 2019).

Identified Review Outcomes

Findings obtained from the outcome of included articles regarding modes of MP accessing the human body were discussed in two common scenarios which are; physically ingestion or access and chemical ingestion. All the investigations carried out by the 15 included publications showed the biological disruptive ability of MNPs and NPs once it accesses the human body. More so, The Endocrine Society, 2020 states that about 144 addictive chemicals to plastic pose threat to human health by disrupting the hormones and causing dieses such as cancer, diabetes, and reproductive disorders. The outcomes statements regarding the physical impacts of MP shows sizes of 70µm causing intestinal damage and restricted feeding in marine vertebrates. Likewise, the analysis included studies displays that MNPs sizes <5mm commonly affects marine organisms but there were also conclusive statements which articulates similar plastic sizes that are consumed by humans. Whilst the human body’s excretory system eliminates some of the ingested MNPs and NPs via feces (Smith et al, 2018), there might be more ingested (0.1 – 5 g/week) than excreted (1.1 – 677.1 mg/week) (Senathirajah et al, 2020). The ingestion of MNPs may also cause inflammation in tissue, cellular proliferation, and may compromise immune cells (Lehner et al., 2019). The human related biological impacts are either direct or indirect. The exposure of MNPs in its smaller sizes enhance their ability to translocate through gastrointestinal membranes via
endocytosis-like mechanism, which eventually leads to the distribution of MNPs into the tissues and organs (Alimba and Faggio, 2019). The primary source of these MNPs into humans is through ingestion of food (Revel, Châtel and Mouneyrac, 2018) and the impactful aspect of these particles is its association with chemicals and causes metabolic disorder (Kannan and Vimalkumar, 2021)

Figure 3 shows a review on an experiment which describes various molecular mechanisms leading to obesogenic effects of MPs and plastic additives (Kannan and Vimalkumar, 2021). Exposure of MNPs to animal cells have possibility to triggers initial source of obesogenic effects which are activation of PPAR receptors, damage of mitochondrial membrane and dybiosis of gut microbiome. This leads to obesogenic issues such as increase adipocyte differentiation, abnormal fatty acid metabolism and disruption of metabolic activity. Additionally, entry routes of nanoparticles into the human body via the lung, the gastrointestinal (GI) tract and the skin (Lehner et al., 2019) have been suggested. The mentioned workers at a nylon production industry in Canada confirmed the impact of NPs on its workers who were diagnosed with persistent interstitial lung disease and two workers died from hypoxemic respiratory failure and secondary pulmonary hypertension (Schwartz, 2015). Studies have shown that upon high doses, ultrafine particles in the size of 64nm or PM10 (particulate matter ≥10) caused health issues such as lung inflammation, increase chemokine expression, epithelial cell hyperplasia and lung tumors (Revel, Châtel and Mouneyrac, 2018).

The adverse impacts to the lungs can be attributed to the fact that the lungs have a large alveolar surface area with extremely thin tissue barrier of less than 1μm, which clearly can allow nano sized particles to penetrate the blood system, and then distributes it throughout the body (Dris et al., 2017). The cellular uptake of nano plastic is influenced mainly by their interaction with surrounding biological components in the body such as proteins and phospholipids due to their size and chemistry charge (Prata, 2018). Recent studies comparing the interaction of NPs to human cells have caused concern particularly regarding the polystyrene (PS) polymer. PS is a commonly found MP and NP polymer and has demonstrated the ability to translocate into underlying tissues. In vitro studies have proved this through intestine cell monocultures and even complex human cell models (Lehner et al., 2019). Its observed that nanosized PS particles could permeate easily across biological cell membrane altering the lipid bilayer membrane and reducing molecular diffusion thus affecting cell functions (Lehner et al., 2019) as shown in Figure 4A and 4B. A supportive research by (Goodman et al., 2021), observes the potential toxicological effects of MPs on human cells exposed alveolar A549 cells to polystyrene revealed significant changes in the morphology of cells exposed.

The included publications as categorized in figure 5A and 5B, showed that 79% of the included publications supported the impact of nanoparticles (1-1000nm) to the human health. Sizes of MP from 1mm – 0.1μm were showed to have 68% supporting included articles and 16% supported the impact of large MP from 5mm – 1mm. Hence according to this review, majority of the related impact of microplastic to humans are contributed by sizes of NPs from 1 – 1000nm followed by MP sizes from 1mm – 0.1μm.
Conclusive Outcome of the Review, Knowledge Gaps and Recommendations

The approach taken in the assessment of publications differed in terms of their individual focus and objectives taking in consideration direct and indirect impacts to humans. The approach taken in this review is based on different types of impacts or physiological processes that takes place once MNPs and/or NPs are either ingested, inhaled or transported into the human body. Thus, looking at the approach of this study, it is note-worthy to have executed a study that based its objective from the actual size of nano-particles that can penetrate through the human body and cells and directly to the fate of the particle in the body. The systematic review of the available evidence indicated that the size, type of polymer including the additive and associated chemicals, were the main characteristics of concern that influenced suggestive conclusions to the impacts of plastics to humans (Figure 6).

**Polymer Types:** Suggestive evidence states possible impact of polymers such as PP, PE, and PS, having indirect impact to human health as these polymer particles are carriers of toxic chemicals (such as POP’s) or its potential to leach chemicals that have the capability to affects human health (Smith et al., 2018; Wesleybrandt-rauf et al., 2012; El-Shahawi et al., 2010; Heinrich and Braunbeck, 2019).

**MNPs sizes:** Most reviewed included articles have illustrated the different impact of MP sizes due to its mode of access through marine food web or direct ingestion to humans. Concerning issues in relation to sizes is its access through marine organism such as bivalves (Van Cauwenberghe, 2014) which are a source of food to humans. There is still a need of more research on the transfer and fate of plastic from food to human and its direct impacts. There is abundant evidence on the impacts of nano-sized particles through mode of inhalation and medical treatment, even if not necessarily focused on plastic materials. Through drug delivery, laboratory analysis has proven that particle size \( \leq 500 \text{nm} \) impacts the extent of cellular uptake by phagocytosis and endocytosis (Turcotte et al., 2013; Schwartz, 2015; Yoo, Doshi and Mitragotri, 2011; Bhargava et al., 2018).

**Associated chemicals:** There is suggestive evidence that showed additive and associated chemicals such as phthalates (Zhu et al., 2006; Colón et al., 2000; Stilund et al., 2007), Bisphenol A (Koch and Calafat, 2009; Gopinath, Saranya and Vijayakumar, 2019), and Vinyl Chloride (Wesleybrandt-rauf et al., 2012) causes human health issues such as asthma, development or growth of human offspring, and liver cancer.

The connections of these MP characteristics as shown in figure 7 conclusively demonstrated short-term reactions of the types of polymer, the size fractions that are presence in our environment, the type of chemicals that associate MP which eventually have long-term impacts to human health.

Conclusion
This systematic review evaluated the impacts of MNPs and NPs to human health regarding its physical, toxicological and biological consequences. The results suggest that there are confirmed impacts to the three scenarios, wherein MNPs (5mm - 0.1µm) and NPs (1-1000nm) particle sizes are critical factors in biological and toxicological process in the human body. The method of assessment in categorizing impacts of the three scenarios can limit the overall evidence of health impacts to the human system. The evidence developed from the review indicates a strong supportive conclusion of the impacts of plastic to human health. The impacts were mostly indirect to humans as demonstrated by the large number of laboratory analyses which were described in all the publications reviewed. These impacts to humans are mostly subjective to the three plastic characteristic factors which are chemicals, size fractions of plastics and the types of polymers. There is a need of more structured research to direct the exact fates of MNPs in the human body, as well as strategic action to control and mitigate all direct and indirect ingestion of MNPs in humans and aquatic organisms.

**Abbreviations**

BPA: Bisphenol A

BBP: Benzyl butyl phthalate

PBDEs: Polybrominated diphenyl ethers

GI: Gastrointestinal tract

HOC: Hydrophobic organic chemicals

MPs: Microplastic

MNPs: Micro and Nano Plastics

NP: Nonylphenol

OP: Octyl phenol

PCBs: Polychlorinated biphenyls

PE: Polyethylene

POP: Persistence Organic Pollutants

PP: Polypropylene

PS: Polystyrene

PVC: Poly Vinyl Chloride
VC: Vinyl Chloride

Declarations

Author contributions

Malelili Naulivou Rokomatu conducted the underlying research, investigations and writing. Geetika Bhagwat and Kala Senathirajah contributed on editing, graphics, and proof reading the manuscript. Thava Palanisami conceptualized the idea and supervised the work.

Compliance with ethical standards

Hereby, the authors consciously assure that for the manuscript, A Systematic Review on the Toxicological Implications of Microplastic to human health, the following is fulfilled:

1. This material is the authors' own original work, which has not been previously published elsewhere.
2. The paper is not currently being considered for publication elsewhere.
3. The paper reflects the authors' own research and analysis in a truthful and complete manner.
4. The paper properly credits the meaningful contributions of co-authors and co-researchers.
5. The results are appropriately placed in the context of prior and existing research.

We agree with the above statements and declare that this submission follows the policies of Committee on Publication Ethics (COPE) as outlined in the Guide for Authors and in the Ethical Statement.

Declaration of Competing Interest

The listed authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Acknowledgement

The authors acknowledge the support offered by the University of Newcastle through the Australian Government Research Training Program (RTP) Scholarship and the services offered by the Global Innovative Centre for Advanced Nanomaterials (GICAN), Faculty of Engineering and Built Environment. Acknowledge the contribution of UON-SPREP pacific partnership, World Wide Fund for Nature (WWF) and the Newcastle Institute of Energy and Resources (NIER).

Availability of Data and Material
All data generated or analyzed in this study are included in this published article. Request for any further data clarification can be made to the corresponding author.

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Methods
Randomized controlled trial.

Author
Bhargava 2018

Participants
Baby hamster kidney cells

Interventions
Hydrophobic polymer nano-particles (Poly (methyl methacrylate) (PMMA))

Outcome

Physical impact
The results collected indicated that the polymer nano-particles permeated the cellular membrane. Clear visualization of nanoparticle distribution inside the cell. It is understood that the process of internalization occurs through clathrinid-dependent endocytosis which led to the localization of the nanoparticles inside lysosomes and endosomes.

Bioavailability or biological impact

Toxicity or chemical impact
Pure PMMA nanoparticles showed a cell death greater than 30% at particle concentrations between 150 and 200 ppm. At lower concentrations (<150 ppm) of our polymer particles, the cell death was less than 10%. The PMMA−PTE nanoparticles showed a similar trend in toxicity as the pure PMMA particles at high concentrations; however, the toxicity of the PTE-loaded nanoparticles was 17 and 20% at concentrations of 50 and 100 ppm, respectively.

Table 1: Model characteristics of included articles formed under RevMan method.

| Studies          | Direct Human Impact | Indirect Human Impact | Weight | Odds: Ratio M-H, Fixed, 95% CI | Year |
|------------------|---------------------|-----------------------|--------|-------------------------------|------|
| Colon et al., 2000 | 1                    | 2                     | 3.2%   | 1.00(0.92, 50.40)             | 2000 |
| Brown 2001       | 1                    | 1                     | 0.8%   | 9.00(0.10, 831.78)            | 2001 |
| Zhu et al., 2006 | 2                    | 2                     | 0.5%   | 25.00(0.34, 1931.59)          | 2006 |
| Frohlich 2009    | 0                    | 2                     | 13.5%  | 0.04(0.00, 2.97)              | 2009 |
| Turcotte et al., 2013 | 2                | 1                     | 2.6%   | 2.00(0.95, 78.25)             | 2013 |
| Van Caunembergh et al., 2014 | 0              | 2                     | 19.8%  | 0.02(0.00, 1.35)              | 2014 |
| Koch et al., 2013 | 2                    | 0                     | 0.5%   | 25.00(0.34, 1931.59)          | 2017 |
| Bhargava 2018    | 2                    | 1                     | 0.8%   | 9.00(0.10, 831.78)            | 2018 |
| Smith 2018       | 0                    | 3                     | 8.1%   | 0.20(0.00, 8.82)              | 2018 |
| Revek 2018       | 1                    | 2                     | 8.1%   | 0.20(0.00, 8.82)              | 2018 |
| Waring 2018      | 1                    | 2                     | 1.6%   | 5.00(1.11, 220.62)            | 2018 |
| Almira 2019      | 0                    | 3                     | 19.8%  | 0.02(0.00, 1.35)              | 2019 |
| Henricks 2019    | 0                    | 1                     | 7.3%   | 0.11(0.00, 10.27)             | 2019 |
| Ponsa et al., 2019 | 1                | 2                     | 3.2%   | 1.00(0.92, 50.40)             | 2019 |
| Wang 2019        | 0                    | 2                     | 8.6%   | 0.25(0.01, 7.45)              | 2019 |
| Freitas et al., 2020 | 4               | 4                     | 0.3%   | 81.00(1.36, 5046.33)          | 2020 |
| Da Costa Aranjo, 2021 | 2              | 2                     | 0.5%   | 25.00(0.34, 1931.59)          | 2021 |
| Hoaze et al., 2021 | 3                | 0                     | 0.4%   | 49.00(0.74, 3256.99)          | 2021 |

Total (95% CI) 40 39 100.0% 1.29(0.66, 2.50)
Total Events 23 18
Heterogeneity: Chi² = 25.16, df = 17 (P=0.04), I² = 40%
Test for overall effect: Z = 0.74 (P=0.46)

Table 2. Summary of included publications and forest plot produced by the RevMan5 software

Table 3. Addictive chemicals and impacts to human health
| Plastic Chemicals (Monomers) | Human Health Impact | Publications |
|-------------------------------|---------------------|--------------|
| Bisphenol A                   | Skin sensitization, Reproductive toxicity, Serious eye damage | (Koch and Calafat, 2009), (Gopinath, Saranya and Vijayakumar, 2019), |
| Vinyl chloride                | Carcinogenicity      | (Wesleybrandt-rauf et al., 2012) |
| Benzyl butyl phthalate (BBP) (Note: plasticizer) | Reproductive toxicity, Aquatic chronic | (Herrero, Planelló and Morcillo, 2015) |
| 1,3-butadiene (BD)            | Carcinogenicity, Mutagenicity | (Jr, 2001) |
| 4,4'-methyleneedianiline (MDA) | Carcinogenicity, Mutagenicity, Skin sensitization | (Wellner et al., 2008) |
| Epichlorohydrin               | Carcinogenicity, Skin sensitization | (Bhatt, 2000) |
| Polyfluoroalkyl (PFAS)        | Changes in liver enzymes, decreases in infant birth weights | (Taylor et al., 2019) |
| Persistent Organic Pollutant (POPs) | Alter normal function of endocrine and reproductive systems in humans and wildlife | (El-Shahawi et al., 2010) |

Table 4. Size fractions relevant for ingestion

| MP Size | Organism / Medium | Parts                  | Impact                                                                                                               | Source |
|---------|-------------------|------------------------|-----------------------------------------------------------------------------------------------------------------------|--------|
| 3800μm  | Fish - gold banded job fish | Gastrointestinal tract | The Red Sea mesopelagic fish examined were captured at depth (700 m) and yet contained floating plastic debris. Plastic with POP’s hazardous to marine biota through their role as endocrine-disrupting chemicals | Basikivuyur et al., 2018 |
| 500μm   | Fish              | Gastrointestinal tract | Microplastics may contact the airway or gastrointestinal epithelium demonstrating several routes of uptake and translocation, such as endocytic pathways and perosorption. PCBE’s in the tissue | Smith, 2018 |
| 16 - 500μm | Bivalves            | Soft tissue            | Enhance gut infectivity or immune-stimulatory properties of the biological agents adsorbed to their surface            | Van Cauwenbergh, 2014 |
| 4 -16μm | Bivalves (mussel)  | Gut cavity and digestive tubules | It is possible that plastic particles permeated the cell membrane of the epithelial lining of the mussel gut via endocytosis-like mechanisms. | Gideon and Faggio, 2019, Browne et al. (2008) |
| 500nm   | Human             | Blood stream – through drug delivery | Particle size impacts the extent of cellular uptake by phagocytosis and endocytosis. Particles smaller than 500 nm are usually internalized by endocytosis. | Yoo, Doshi and Mitrakoti, 2011, Bhargava et al., 2018 |
| 64nm    | In-vitro analysis - Human | Inhalation system | Air pollution particles (PM10) are associated with exacerbations of respiratory disease and deaths from cardiovascular causes in epidemiological studies. | Brown 2001 |
| 40 – 50nm | Brine shrimp _Arista franciscana_ larvae | Digestive tract | Hypothesized that accumulation of PS NPs aggregates in the digestive tract may limit food intake and significantly affect growth and development of brine shrimp larvae | Bergami et al., 2016 |
| 20nm    | Freshwater invertebrate _Daphnia magna_ | Soft tissue | Uptake of nano plastic particles by algae, through transport up the food chain | Mattson 2017, Revel, 2018 |

Table 5. Studies on polymers and possible impact to humans
| Particle | Source                  | Impact                                                                 | Article                                      |
|----------|-------------------------|------------------------------------------------------------------------|----------------------------------------------|
| Size     |                         |                                                                       |                                              |
| PE       | 4-16 μm, 64-nm          | Cause intestinal damage.                                               | Brown et al., 2001                          |
|          | Plastic utensils        | Research proves ultrafine PS have that proinflammatory activity because of their large surface area | Gideon and Faggio, 2019                     |
|          |                         |                                                                       |                                              |
| PPE      | 500 μm                  | Carriers of POP's. Direct exposures to POPs and other chemicals associated with microplastics may affect biological systems and pose specific threats to juvenile humans and animals | Smith et al., 2018                          |
|          | Plastic bags, Bottles   |                                                                       | El-shahawi et al., 2010                     |
|          |                         |                                                                       | Hati et al., 2010                           |
|          |                         |                                                                       |                                              |
| PO        | 16 - 20 μm              | Carriers of POP's. POPs have been implicated in reduced immunity in infants, and developmental abnormalities, neurobehavioral impairment. | Smith et al., 2018                          |
|          | Rope, binder covers, plastic bottles |                                                                       | Heinrich and Braunbeck, 2019               |
|          |                         |                                                                       |                                              |
| Vinylde  | 20-40ppm vinyl chloride (monomer) | Human carcinogen. Strongly associated with liver cancer, malignant tumor of the endothelial cells of the liver. | Wesleybrandt-trauf et al., 2012              |
|          | Petrochemical and plastics' industries |                                                                       | Thornton, 2002                             |

## Figures
Figure 1

Process flow for literature review
Figure 2

Potential exposure routes of MNPs into the human system considering this meta-analysis. Source: (Senathirajah et al., 2021); https://thesafehealthyhome.com/should-you-worry-about-microplastics-in-your-drinking-water.
Figure 3
Mechanisms of obesogenic effects of microplastics and their additives. Reproduced from Kannan and Vimalkumar, 2021

Figure 4
A. Human lung epithelial cancer cells (A549) labeled for F- actin (purple) and the nuclei (blue) showing uptake of 200 nm amino-modified polystyrene particles labeled with FITC (yellow) after exposure for 24
Figure 5

A. The different categories of MNP sizes and the number of times its mentioned in the 19 reviewed included articles. B shows an overall percentage of the mentioned size range of MNP from the 19 reviewed articles.
Figure 6
The connections between plastic characteristics that influence impacts to humans described in a gear metaphor.

Supplementary Files
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