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Review

A review of potential human health impacts of micro- and nanoplastics exposure

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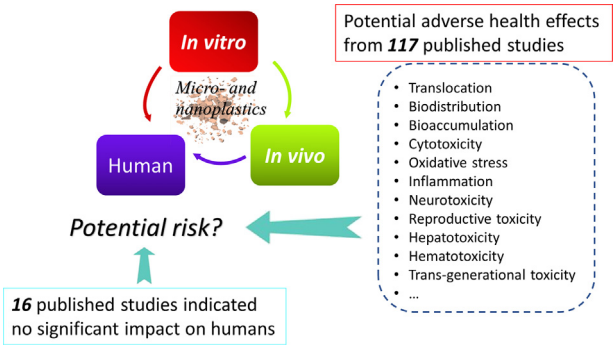
HIGHLIGHTS

- Potential human health impact of MNPs is reviewed and summarized from 133 articles.
- Most studies (105 articles) used PS spheres for research due to the availability.
- 117 articles reported different adverse health impacts of MNPs exposure.
- 16 articles showed contrasting results with insignificant impact of MNPs.
- Limitations that hinder reaching firm conclusions are highlighted.

GRAPHICAL ABSTRACT



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ABSTRACT

This systematic review aims to summarize the current knowledge on biological effects of micro- and nanoplastics (MNPs) on human health based on mammalian systems. An extensive search of the literature led to a total of 133 primary research articles on the health relevance of MNPs. Our findings revealed that although the study of MNP cytotoxicity and inflammatory response represents a major research theme, most studies (105 articles) focused on the effects of polystyrene MNPs due to their wide availability as a well characterised research material that can be manufactured with a large range of particle sizes, fluorescence labelling as well as various surface modifications. Among the 133 studies covered in this review, 117 articles reported adverse health effects after being exposed to MNPs. Mammalian *in vitro* studies identified multiple biological effects including cytotoxicity, oxidative stress, inflammatory response, genotoxicity, embryotoxicity, hepatotoxicity, neurotoxicity, renal toxicity and even carcinogenicity, while rodent *in vivo* models confirmed the bioaccumulation of MNPs in the liver, spleen, kidney, brain, lung and gut, presenting adverse effects at different levels including reproductive toxic effects and trans-generational toxicity. In contrast, the remaining 16 studies indicated an insignificant impact of MNPs on humans. A few studies attempted to investigate the mechanisms or factors driving the toxicity of MNPs and identified several determining factors including size, concentration, shape, surface charge, attached pollutants and weathering process, which, however, were not benchmarked or considered by most studies. This review demonstrates that there are still many inconsistencies in the evaluation of the potential health effects of MNPs due to the lack of comparability between studies. Current limitations hindering the attainment of reproducible conclusions as well as recommendations for future research directions are also presented.

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Contents

1. Introduction

The ubiquity of plastic particles in the global biosphere has raised growing concerns from an environmental and human health perspective. Despite no universally established definition, microplastics (MPs) usually refer to plastic particles up to 5 mm in dimensions with no defined lower size limit, while nanoplastics (NPs) represent particles in the submicron range, that is, <1 μm (Dick Vethaak and Legler, 2021). Recent evidence has made it clear that humans are constantly exposed to micro- and nanoplastics (MNPs) from food sources. For example, >690 marine species including fish and oysters, have been reported to be contaminated by MNPs, which tend to accumulate and transfer through the food chain to higher trophic levels including humans (Zhang et al., 2020). In addition to seafood, the widespread detection of MNPs in multiple food products such as honey, beer, table salt, milk and drinking water suggests that human exposure to MNPs is inevitable (Prata et al., 2020). Plastic particles unintentionally produced and released into foods from plastic food contact materials have also received increasing attention. Since 2019, scientists found that plastic bottle caps (Winkler et al., 2019), plastic teabags (Xu et al., 2021) (Hernandez et al., 2019), and infant feeding bottles (Li et al., 2020b) are capable of releasing a considerable number of MNPs. In detail, Hernandez et al. (2019) reported that steeping a single plastic teabag at brewing temperature (95 °C) released approximately 11.6 billion MPs and 3.1 billion NPs into a single cup of beverage. During the formula preparation process, Li et al. (2020b) found that 1–16 million MNPs per litre were released from the infant feeding bottle, which was significantly higher than the estimated daily MNPs consumption of about 883 particles in adults *via* food web (Mohamed Nor et al., 2021). Furthermore, many researchers (Wright et al., 2020; Dris et al., 2016) have reported the atmospheric fallout of MNPs as an emergent component of air pollution.

The pollution of MNPs has become of great concern as a potential threat to human health. Various types of MNPs have been detected in human faeces (Schwabl et al., 2019), suggesting inadvertent ingestion of MNPs from different sources. It also tells us that plastic particles can be excreted *via* the gastrointestinal tract. Apart from this, MNPs were also found in human colectomy specimens (Ibrahim et al., 2021), providing evidence that microplastics are able to travel into human colon. MNPs found in the placentas of pregnant women have also been reported (Ragusa et al., 2021; Braun et al., 2021), which has raised a serious concern. More recently, a study confirmed the presence of MNPs in human blood (Leslie et al., 2022), indicating the capability of MNPs to travel around the body and lodge in organs.

Humans could be exposed to MNPs predominantly through three main routes of entry, that is, ingestion, inhalation and dermal contact. Oral ingestion is currently the primary route of exposure as recent studies have found a large quantity of MNPs in food sources, drinking water and from the daily use of plastic food contact materials. MNPs in the submicron range and, in particular, nanoplastics below 100 nm might be capable of penetrating cell membranes and surpassing the intestinal barrier, possibly reaching the blood stream, followed by translocation to other organs. Almost all blood from the intestinal tract transfers through the liver prior to further distribution into the body, leading to the possible accumulation of MNPs that penetrate the epithelial barrier in the liver. MNPs are also likely to penetrate the blood-brain barrier, accumulate in the brain and manifest neurotoxicity. Inhalation of airborne MNPs has been reported in occupationally exposed individuals such as workers in the textile (nylon, polyester, polyolefin, and acrylic) industry and was related to a higher prevalence of respiratory irritation (Warheit et al., 2001). Respirable MNPs refer to those that can arrive and deposit in the respiratory zone of the lungs, where the alveoli are situated and gas exchange takes place. Some administered MNPs might be able to cross epithelial barriers of lungs and translocate to secondary organs. Although dermal exposure is believed to be the least relevant route of entry, there is evidence shown that nanoplastics could transverse the dermal barrier (Revel et al., 2018); however, this becomes a lesser concern as more and more countries ban microbeads in personal care products and detergents.

A growing body of evidence suggests the toxic effects of MNPs on marine species, such as growth inhibition and immune stress (Dick Vethaak and

Legler, 2021). Although these effects are significant on marine species, there is still debate on whether the contamination of MNPs poses a considerable risk to human health. Due to their complex and varied physicochemical properties (*e.g.*, polymer types, surface chemistry, size, shape), results pertaining to the toxicity of MNPs are usually hard to interpret and compare between studies. Another major issue hindering the understanding of the human health risks of MNPs is the lack of crucial data on exposure arising from analytical challenges. For example, studies on the measurement of NPs prevalence are scarce so far because it is challenging for current analytical methods to cover the entire nano-range due to the detection limit. Although research on the health risks of MNPs is still in its infancy, there is growing evidence published in very recent years implying the adverse effects of MNPs on human health. In this context, the present review aims to provide updated results on the current state of this field by summarising available evidence in the literature performed in mammalian experimental systems. We will place a special focus on the experimental design of published works and evaluate the comparability between studies. The latest results from the reviewed literature will be discussed in detail, while also underlining the limitations of current practice. Finally, we will provide recommendations for future research needs and directions.

2. Literature review search methodology

A search of online journals was performed on 18 February 2022 using Scopus (www.scopus.com) in order to collect studies on the topic of the potential health effects of MNPs. The search was performed using the searching string of TITLE-ABS-KEY ((microplastic* OR nanoplastic* OR micro-plastic* OR nano-plastic* OR "plastic particle" OR polystyrene OR microbead*) AND (health OR "human health" OR adult OR child* OR infant OR body OR cytotoxic OR "*in vitro*" OR cellular OR gut OR "*in vivo*" OR disease OR gastrointestinal OR skin OR lung)). The initial search led to 17,476 documents of potentially relevant studies. Criteria to include the studies published in the past five years (2018–2022 and studies published in English only were applied, reducing the number of eligible documents to 5698. After eliminating review articles ($n = 681$), a total of $n = 4762$ research articles were attained. Further screening was adopted based on the following exclusion criteria through the title, abstract and/or full paper reading: (1) studies that tested on nonmammalian models; (2) studies that were irrelevant to the human health research topic. A final 133 primary studies were included to map the state of the science on the health relevance of MNPs. The full list of initial $n = 4762$ research articles as well as the final included 133 publications after rigorous screening is provided in Excel file format in the Supplementary Material.

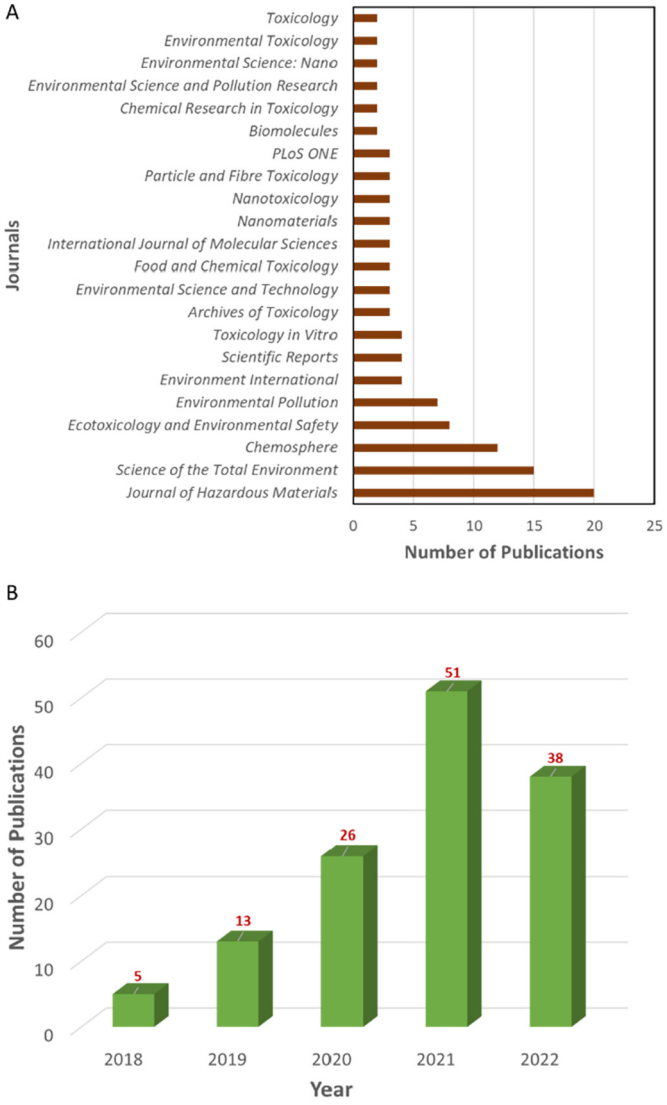

Fig. 1. Number of publications found from individual journals (A) and by year (B). Journals that have published more than one article are included in Fig. 1A. Articles published before the searching date (18 February 2022) are included to create Fig. 1B.

3. Results of literature review

3.1. Source and publications by year

The included 133 studies were published in 46 international peer-reviewed journals, of which 22 journals have published more than one article on the topic in the past five years (see Fig. 1A). In particular, journals of the *Journal of Hazardous Materials*, *Science of the Total Environment*, *Chemosphere*, *Ecotoxicology* and *Environmental Safety*, *Environmental Pollution*, have published more than five articles, showing special interest in this topic. Fig. 1B shows the distribution of the published studies by year. There is a clear increase in the number of publications on this topic per year since 2018, implying growing attention from researchers and scholars, leading to more research endeavours and engagement in recent years. It is anticipated that 2022 represents the largest number of articles since there are already 38 studies available from the first two months of a year.

3.2. Analysis of research themes

To acquire and understand the dominant research themes from the selected articles, we implemented a visualization method based on the word cloud strategy which highlights the most frequent words presented in a given body of text, by making the size of each word proportional to its frequency. In this sense, the most commonly used words appear bigger, representing the primary terms/phrases that have been considered for researching the toxicity of MNPs to humans. To do this, all words from the titles of 133 articles were first sorted in a descending order based on the frequency of use. The result was then fed to Wordclouds (www.wordclouds.com) to produce Fig. 2. The keywords including *human, cell, microplastic*, *polystyrene*, *nanoplastic*, *toxicity*, *effect*, *mice*, predominate the selected literature, suggesting that most studies utilise *in vitro* cell culture or *in vivo* mouse models to investigate the effect of MNPs on human health. The words of *microplastic*, *nanoplastic* and *polystyrene* in the wordcloud are similar in size, implying the fact that polystyrene was heavily used as a model MNP in the literature. Other frequently appearing words include *exposure*, *assessment*, *gut*, *induced*, *epithelial*, *vitro*, *particle*, showing the special emphasis on the relevance of *in vitro* gut models.

Using VOSviewer (version 1.6.18; www.vosviewer.com), the co-occurrence network visualization of content based on keywords of selected articles is presented in Fig. 3. Each circle represents a keyword and the size of the circle is proportional to the frequency of occurrence in publications; that is, the larger the size, the more frequent it appears in the selected

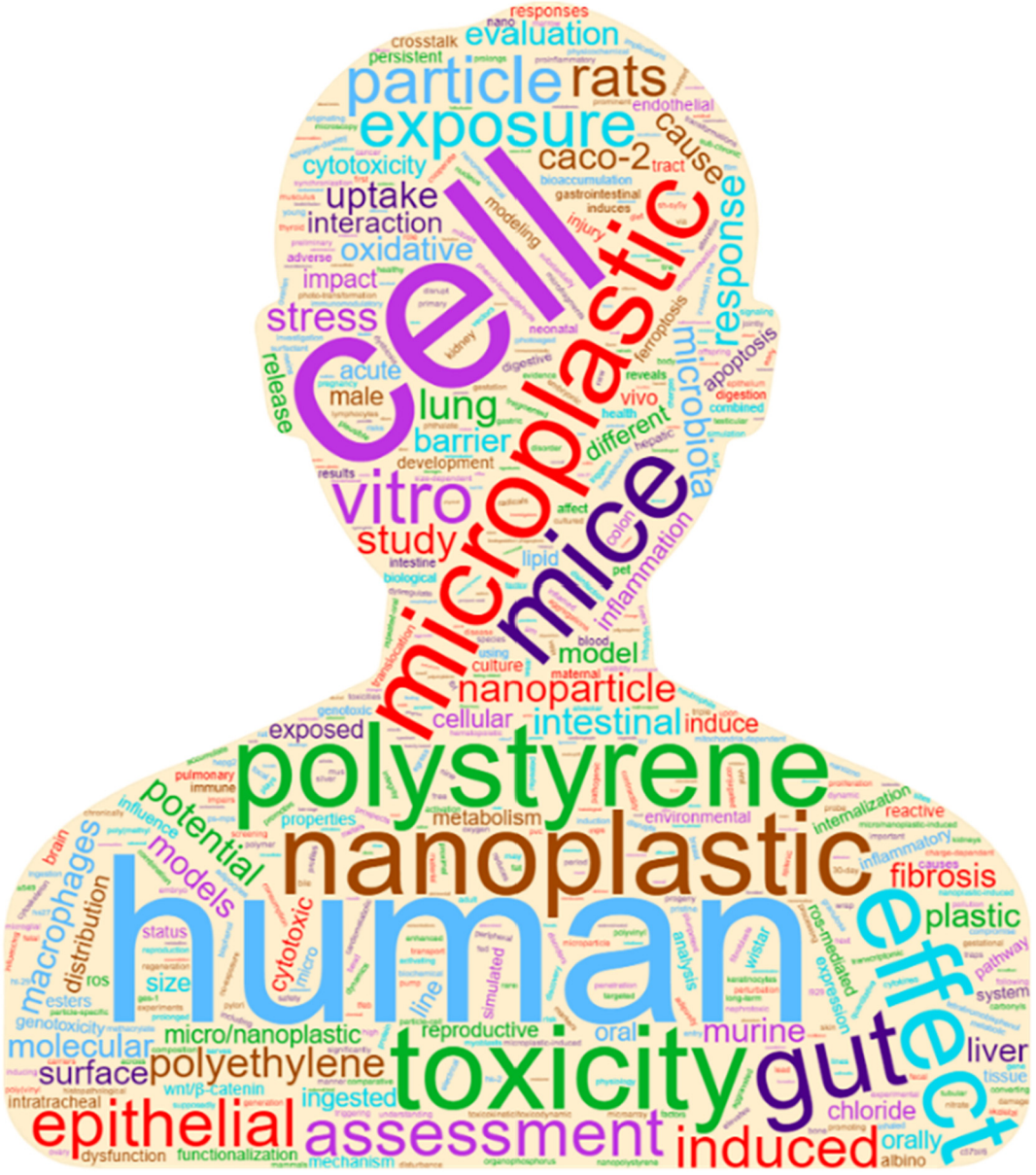

Fig. 2. Word clouds computed from the titles of the selected 133 articles in this review.

articles. Keywords that co-occur frequently are situated close to each other. It should be noticed that terms that appeared only once from all publications have been filtered out. The co-occurrence network highlights 6 main research themes which are clearly separated into clusters in Fig. 3. Cluster 1 (red) includes the keywords *polystyrene*, *nanoplastics*, *mouse embryonic fibroblasts*, *maternal exposure*, *endocytosis*, *cell viability*, *autophagy* and *apoptosis*, of which *polystyrene* and *nanoplastics* appeared the most frequently. This cluster mainly focuses on researching the impact of PS nanoplastics on the fate of human cells. It is also noted that *polystyrene* is closer to *nanoplastics* compared to *microplastics*, suggesting that more studies are using PS nanoplastics rather than PS microplastics. Cluster 2 (blue) includes the terms of *intestinal barrier*, *microplastics*, *oral uptake*, *particle size*, *rats*, *reproduction*, *toxicity* and *Wnt/β-catenin pathway*. Interestingly, both rats and mice have a shorter distance to *microplastics* than to *nanoplastics*, indicating that *in vivo* rodent models have been less likely to implement nanosized plastic particles. *Cytotoxicity* (cluster 3 in purple) and *inflammatory responses* (cluster 4 in cyan) also appear frequently in articles, indicating these are also hot topics for current research.

3.3. Characterization of the used MNPs

MNPs are complex in nature and can appear in different sizes, shapes (*e.g.*, spheres, fragments, fibers), surface charge, and chemical composition, representing a major challenge in interpreting the toxicity. Therefore, before we discuss the current evidence regarding the health effects of MNPs, it is important to gain the necessary knowledge about the MNP samples that were used in these articles. Fig. 4 displays the distribution of individual polymer types studied within the included articles. Among the selected 133 articles, 105 of them used polystyrene (PS), making it the most commonly used material for research. This is because PS MNPs are easy to be purchased from different manufacturers and readily available as research material manufactured with a range of particle sizes, fluorescence labelling as well as various surface modifications. However, PS is less than other polymers such as polyethylene (PE) and polypropylene (PP) based on the production amount and abundance as a pollutant, as estimated by Stock et al. (2022a), therefore, it is less relevant than other polymers for the purpose of researching potential adverse health effects

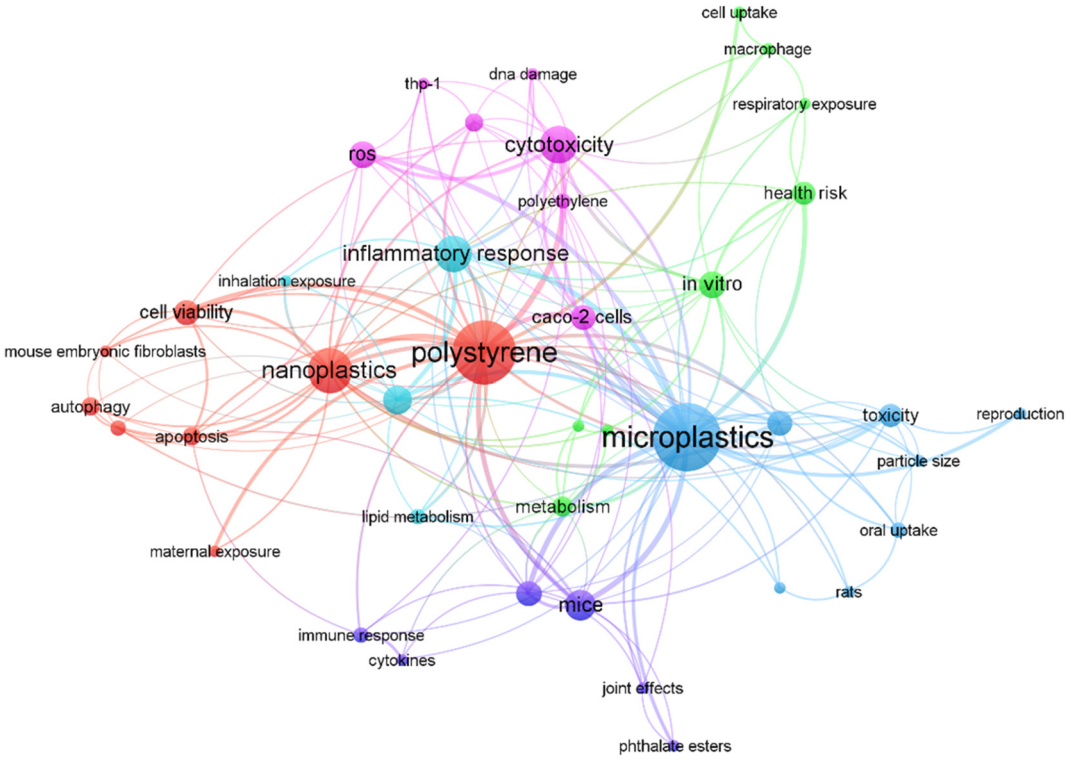

Fig. 3. Co-occurrence of keywords network visualization.

caused by MNPs. Meanwhile, the most commercially available PS particles are micro- or nanospheres, which could not present the various shapes of MNP fragments in the real world. The toxicity of fluorescence labels is also needed to be considered. PE was the next most commonly used material in investigating health effects of MNPs, appearing in 27 articles, followed by PP, polyethylene terephthalate (PET), polyvinyl chloride (PVC). Two publications (Lehner et al., 2020; Liu et al., 2022a) explored the potential health effects caused by tire wear particles (TWP) using

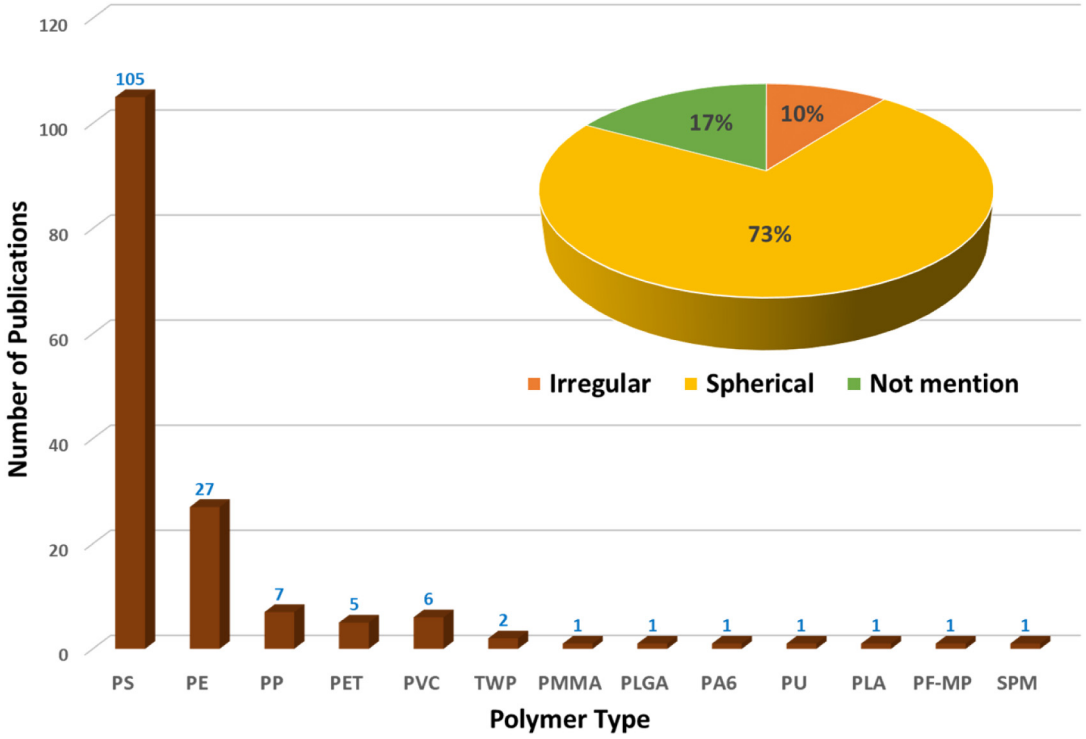

Fig. 4. The number of publications employing individual polymer types. The inset pie chart displays the proportion of morphology of particles used in the selected 133 articles. PS: polystyrene; PE: polyethylene; PP: polypropylene; PET: polyethylene terephthalate; PVC: polyvinyl chloride; TWP: tire wear particles; PMMA: poly (methyl methacrylate); PLGA: poly(lactic-*co*-glycolic) acid; PA6: polyamide 6; PU: polyurethane; PLA: polylactic acid; PF-MP: phenol-formaldehyde resin microplastic; SPM: synthetic polymer microspheres.

in vitro cell culture models. Other polymers including poly (methyl methacrylate) (PMMA) (Mahadevan and Valiyaveettil, 2021), poly(lactic-*co*-glycolic) acid (PLGA) (Tan et al., 2020), polyamide 6 (PA6) (Lehner et al., 2020), polyurethane (PU) (Lehner et al., 2020), polylactic acid (PLA) (Liao and Yang, 2020), phenol-formaldehyde resin microplastic (PF-MP) (Zhu et al., 2020), synthetic polymer microspheres (SPM) (Lu et al., 2021), were investigated in only one paper from the selected articles. It should be noted that the sum of all polymers is higher than 133 since some articles researched more than one type of MNP.

The shape of MNPs particles is one key characteristic that also deserves attention. We found that 73 % of articles (n = 97) chose spherical shapes mostly because spherical microspheres can be easily purchased from manufacturers. In addition to particles directly purchased from manufacturers, in one experiment investigating the pulmonary toxic potential of NMPs, PS particles ranging in size from 1.67 to 2.17 μm were synthesized from styrene utilizing poly(N-vinylpyrrolidone) as a stabilizer and 2, 2-azobis (2-methylpropionitrile) as the initiator (Dong et al., 2020). We also noticed that 17 % of studies (n = 23) neglected the importance of the shape of MNPs without mentioning it in the context. The rest articles (n = 13) prepared irregular MNPs particles from ball milling, grounding using homogenizer or cryogenic milling methods, followed by sieving to obtain size fractionation (Choi et al., 2020; Lehner et al., 2020; Kim et al., 2021). In this way, the acquired particles can better represent random-shaped MNPs that are degraded and formed from bulk plastics. A more recent article published in July 2022 (therefore not included in the selected literature) proposed a new method to prepare degraded MNPs representative of the environmental degradation of plastic wastes (Fuentes-cebrian et al., 2022). Briefly, pieces of PET water bottles was sanded to produce debris that were subsequently sieved and heated at different concentrations of trifluoroacetic acid. The obtained dispersion was centrifuged and sonicated to produce the final MNP samples. They demonstrated that the use of diamond burrs can avoid the metal contamination resulting from methods using metal blades/burrs for milling, trituration, or sanding.

Numerous researchers have pointed out that particle size also plays an important role in determining the toxicity of MNPs (Banerjee et al., 2021; Wu et al., 2019; Choi et al., 2020). For example, Banerjee et al. (2021) reported that the uptake of 50 nm particles in human gastric cells was significantly higher than 1000 nm particles. Therefore, it is of importance and interest to identify the size of experimented MNPs in reported studies. Our findings showed that the most frequently researched size is in the range of 1–50 μm and 50–150 μm. At the nanoscale, most researchers tended to use commercially available NPs with sizes of 50, 100, 200, 500 and 1000 nm. The lack of study on random size/shape of NPs leads to the uncertainty in human health assessment of nanosized plastics exposure.

3.4. Analysis of biological models

Using mammalian model systems, 74 out of 133 studies implemented an *in vitro* testing method, as seen from Fig. 5. *In vitro* models are frequently utilized due to cost-effective, practical, and ethical reasons. Among the different cell lines employed, as representative of the human small intestine, differentiated Caco-2 cells were used in 21 studies, being the most popular model system. This cell line, although derived from a colon, resembles the enterocytes lining the small intestine when the cells become differentiated. For some studies (Stock et al., 2019; Lehner et al., 2020; Domenech et al., 2020), researchers managed to establish an *in vitro* physiological/structural model of the intestinal barrier by co-culturing Caco-2 representing enterocytes along with HT-29 cells representing mucus secreting goblet cells and microfold or M-cells (Caco-2 cells transformed by Raji B feeder cells). Such a biological model is well suited to the investigation of cell uptake/internalization as well as translocation through the intestinal barrier. In addition to Caco-2 and HT-29 cells, other cell lines including HepG2, A549, THP-1 and Raw264.7 are also widely used. HepG2 cell line, derived from the liver tissue, is mostly used for hepatotoxicity studies, therefore, it is employed to detect the possible impact of MNPs on the liver (Stock et al., 2021; He et al., 2020). As a representative of human lung epithelial cells,

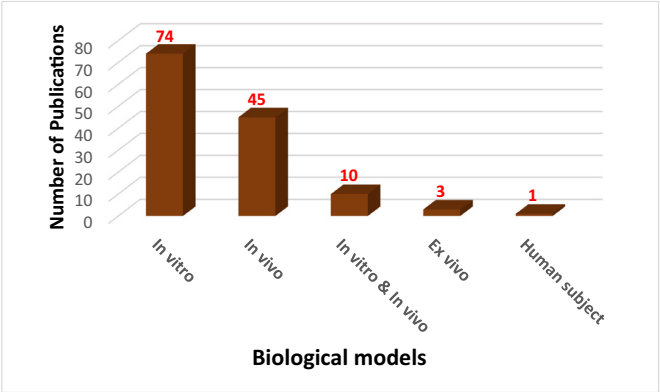

Fig. 5. The number of individual biological models used in 133 studies.

A549 cell line is commonly used to assess the impact of MNPs on the human respiratory system (Xu et al., 2019; Shi et al., 2021). There are 45 *in vivo* studies using either mice or rats. Additionally, 10 studies were endeavouring to evaluate the health risk of MNPs using combined mammalian *in vitro* and *in vivo* models. Meanwhile, three studies applied *ex vivo* models. In detail, Döge et al. (2018) implemented full-thickness human skin samples for penetration studies of fluorescently tagged MNPs, while Ballesteros et al. (2020) exposed whole blood samples from different donors to different concentrations of PS MNPs to assess genotoxic and immunomodulatory effects in human white blood cells. In the same year, Bartucci et al. (2020) used tissue slices from mice as 3D *ex vivo* models to study the uptake of PS MNPs in liver, lung, and kidney slices. A more recent study (Yan et al., 2022), for the first time, attempted to evaluate the correlation between MNPs exposure and inflammatory bowel disease (IBD) status based on human participants. They analyzed and compared the characteristics of MNPs in the faeces of patients with IBD and healthy people.

4. Summary of biological effects

4.1. Biological effects of MNPs from in vitro studies

4.1.1. Caco-2 cells

Research on the impact of MNPs on the digestive system has intensified over the past few years, which is unsurprising since ingestion is recognized as the main exposure pathway; as such, Caco-2 cells representing the human small intestine are widely used. Table 1 summarises 21 studies using *in vitro* Caco-2 cell models for evaluating the effects of MNPs. Wu et al. (2020) reported that PS MNPs (5 μm) decreased the cell viability of Caco-2 cells in a dose-dependent manner. Chronic exposure to MNPs (*i.e.* a concentration from 12.5 to 50 μg/mL) tended to induce the cytotoxicity linked to epithelial cell injury and changes in intestinal barrier function, oxidative stress, deintoxication and the transcription level of genes involved in the gut, as well as many critical metabolic pathways. In contrast, another study performed by Cortés et al. (2020) observed only slight toxic/genotoxic effects of PS MNPs (conventional PS MNPs with a size range 0.05–0.1 μm and fluorescent PS with a size range 0.04–0.09 μm) when exposed to concentrations up to 200 μg/mL. Interestingly, this result was confirmed by another two studies carried out by Domenech et al. (2020) and Domenech et al. (2021a) who used the PS particles from the same manufacturer and the same size range. The earlier work (Domenech et al., 2020) demonstrated that PS MNPs (concentration up to 200 μg/mL) exhibited neither significant cytotoxic effects nor genotoxic or oxidative DNA damage induction, although MNPs were uptaken by both barrier systems (*i.e.*, differentiated Caco-2/HT29 intestinal cells and Caco-2/HT29 + Raji-B cells) and translocated across the membrane. The more recent work (Domenech et al., 2021a) repeated that PS MNPs showed no significant cytotoxicity on Caco-2 cells up to the concentration of 200 μg/mL.

Table 1
Summary of *in vitro* studies using Caco-2 cell line.

Biological models	MNPs source	Polymer type	Shape	Particle size	Exposure concentration	Results	References
The intestinal barrier (differentiated Caco-2 monoculture and mucus- and M-cell co-culture) and hepatocytes (differentiated HepaRG cells)	Fluorescent, non-fluorescent, carboxyl-modified and amino-modified were purchased from *Thermo Fisher Scientific, Merck KGaA, Phosphorex, Polysciences, Europe GmbH and Kisker Biotech GmbH & Co. KG*.	PS	Spherical	20, 40, 100, 1000, 10,000 nm	5×10^9–2.5×10^{12} μm^2 particles surface/mL	The used dispersants could cause a more pronounced cytotoxic effect than the particles themselves. Surface modification and particle size showed a clear influence on the uptake and cytotoxicity of MNPs.	(Stock et al., 2022a)
Caco-2 cells	Purchased from *McLean Reagent Co., Ltd*.	PS	Spherical	1.0–1.9 μm	0, 50, 500 and 1000 μg/mL	PS MNPs showed concentration- dependent cytotoxicity to Caco-2 cells. Photo-transformation enhanced the cytotoxicity of PS-MPs.	(Yu et al., 2022)
*S*mall intestinal epithelium including cells representing enterocytes (Caco-2), goblet cells (HT29-MTX), and microfold or M-cells (Caco-2 cells transformed by Raji B feeder cells)	Unmodified and carboxyl modified PS MNPs were purchased from *Phosphorex Inc*, and *Thermo Inc*.	PS	Spherical	25, 100, and 1000 nm	400 and 1000 μg/mL	Uptake of carboxyl PS materials was size dependent, with significantly greater uptake at 25 nm. Carboxylated MNPs significantly reduced cell viability and increased permeability to 3 kD dextran.	(DeLoid et al., 2021)
A triple culture transwell model of the healthy and inflamed intestine (Caco-2/HT29-MTX-E12/THP-1)	Purchased from *Cospheric LLC*.	PE	Spherical	200–9900 nm	10 and 50 $\mu g/cm^2$	PE particles induced cytotoxicity and proinflammatory effects.	(Busch et al., 2021b)
In vitro Caco-2 cells and *in vivo* mice model	Green fluorescent MNPs were obtained from *Tianjin Baseline ChromTech Research Centre*.	PS	Spherical	100 nm	*In vitro*: 30, 60, 120, 240, 480 μg/mL *In vivo*: 10 mg/mL for 28 days	*In vitro*: MNPs induced disruption of tight junction between Caco-2 cells. More PS-NH2 and PS-COOH were absorbed and caused stronger toxicity compared to unmodified PS. *In vivo*: Observed accumulation of MNPs in mice spleen, lung, kidney, small intestine, large intestine, testis, and brain and induced cell apoptosis, inflammation, and structure disorder in these tissues; MNPs could bring hematological system injury and lipid metabolism disorder.	(Xu et al., 2021)
Caco-2 cells; HepG2 cells; THP-1 macrophages	Plastics were purchased from *Lotte chemical Co*. and pulverized by cryogenic high-speed milling.	PP and PS	Irregular	100 μm	625 to 20,000 particles/mL	Treatment of all types of PP and PS did not show any toxic effects to the Caco-2 cells and HepG2 cells, but showed significant toxicity towards THP-1 macrophages.	(Jeon et al., 2021)
Caco-2 cells and human gut microbiota	Powder form purchased from *Aladdin Industrial*.	PE	Spherical	30–140 μm	0, 100, 1000 mg/L	The interaction of MNPs with gut microbiota led to the increased proportion of *Clostridium*, *Bacteroides*, and *Escherichia*.	(Huang et al., 2021)
Caco-2 cells	Pristine and fluorescent yellow PSNPs were obtained from *Spherotech*.	PS	Spherical	0.05–0.1 μm; 0.04–0.09 μm	0, 10, and 100 μg/mL	Silver sorption on PS MNPs modulated the cell's uptake of silver and slightly modified some harmful cellular effects of silver, such as the ability to induce genotoxic and oxidative DNA damage.	(Domenech et al., 2021a)
Caco-2 cells	Plastic films purchased from *Goodfellow Cambridge* underwent laser ablation to create MNPs.	PET	Irregular	10–80 nm	30 μg/mL	MNPs interacted with aqueous pollutants forming nanoclusters which affected the cells metabolism, suggesting long-term risks.	(Magrì et al., 2021)
Triple culture model (Caco-2/HT29-MTX-E12/THP-1)	Amine-modified PS MNPs were ordered from *Sigma-Aldrich*; PS MNPs were purchased from *Polysciences, Inc*; PVC powder were purchased from *Werth-Metall*.	PVC and PS	Spherical	PS: 59 nm; PVC: 279 nm	0, 1, 5, 10 or 50 $\mu g/cm^2$	Pristine PS MNPs did not lead to any effects regarding cytotoxicity, DNA damage, barrier integrity or cytokine release. Exposure to PS particles did not change the mucus distribution on the epithelial cell layer of the triple culture model in stable or	(Busch et al., 2021a)

(continued on next page)

Table 1 (*continued*)

Biological models	MNPs source	Polymer type	Shape	Particle size	Exposure concentration	Results	References
						inflamed state. PVC did not exhibit any cytotoxic properties, DNA damage in epithelial cells and showed no effects on barrier integrity, LDH activity or mucus distribution.	
Caco-2, HepG2 and HepaRG cells	PE particles were purchased from *Cospheric LLC*. Polydisperse PE powders and PP granules were purchased from *Sigma-Aldrich* and polydisperse PET were from *Goodfellow GmbH*.	PE, PP, PVC, PET	Not mentioned	PE: 2.2, 16.5 and 90.1 μm; PP: 67.1 μm; PET: 60 μm; PVC: 136.5 μm;	0–100 mg/mL	Significant decrease of cell viability only occurred at high concentration of PVC particles (> 75 mg/mL) in all three cell lines.	(Stock et al., 2021)
Caco-2 cells	MNPs were obtained from the *Tianjin Base Line Chrom Tech Research Centre*.	PS	Spherical	100 nm and 5 μm	1 and 20 μg/mL	The 100 nm PS MNPs showed higher intestinal toxicity than 5 μm ones. The digestive process relieved cytotoxicity and transport function disorder of the Caco-2 monolayer, but increased proinflammatory effects.	(Liu et al., 2020)
Caco-2 cells	Fluorescent MNPs were purchased from *Shanghai Fenghui Biotechnology Co., Ltd*. PS MNPs were also obtained from polymerization using styrene.	PS	Spherical	300 nm, 500 nm, 1 μm, 3 μm, 6 μm	20, 50, 70, 90, 120 μg/mL	MNPs of 300 nm, 500 nm and 6 μm showed high toxicity to Caco-2 cell compared with 1 and 3 μm MNPs; Increasing particle size led to the decreased oxidative stress in cells; Nanometer-scale MNPs caused a significant increase in the toxicity to cells after adsorption of bisphenol A.	(Wang et al., 2020)
Caco-2 cells	Not mentioned	PS	Spherical	5 μm	12.5 μg/mL or 50.0 μg/mL	MNPs exhibited time- and concentration-dependent anti-proliferative influences on Caco-2 cells. Chronic exposure to MNPs induced epithelial cells injury and alterations to intestinal barrier function, oxidative stress, deintoxication, transcriptional level, transcription level of genes involved in the gut, as well as many critical metabolic pathways and life processes.	(Wu et al., 2020)
Caco-2 cells	Normal and fluorescent PS MNPs were purchased from *Spherotech*	PS	Spherical	0.05–0.1 μm; 0.04–0.09 μm	0, 25, 50, 100, 125, 150, 175 and 200 μg/mL	Although MNPs were easily uptaken by Caco-2 cells, the observed toxic/genotoxic effects were classified as slight.	(Cortés et al., 2020)
Caco-2 cells	MNPs were synthesized from styrene.	PS	Spherical	50 nm and 0.5 μm	0.1 to 100 μg/mL	MNPs were not acutely toxic and identified as weakly embryotoxic and non-genotoxic. There was a cellular uptake and intracellular accumulation but no transport across the intestinal and placental barrier.	(Hesler et al., 2019)
Caco-2 cells	Obtained from the *Tianjin Base Line Chrom Tech Research Centre*.	PS	Spherical	0.1 and 5 μm	1, 10, 40, 80, 200 μg/mL	MNPs exhibited low toxicity on cell viability, oxidative stress, and membrane integrity and fluidity. 5 μm MNPs induced higher mitochondrial depolarization than 0.1 μm MNPs. 0.1 μm MNPs induced higher inhibition of ATP-binding cassette transporter than 5 μm MNPs.	(Wu et al., 2019)
Intestinal model consisting of Caco-2 and HT29-MTX-E12, human blood monocyte-derived macrophages and dendritic cells	MNPs were prepared by cryo-milling.	Tire wear, PP, PA6, PU	Irregular	50–500 μm	823.5–1380.0 μg/cm^2	All MNPs and the healing earth particles did not cause any significant cytotoxicity or release of (pro-)inflammatory cytokines and did not change the barrier integrity of the	(Lehner et al., 2020)

Table 1 (*continued*)

Biological models	MNPs source	Polymer type	Shape	Particle size	Exposure concentration	Results	References
						co-culture at any of the time points investigated.	
Two different coculture models (differentiated Caco-2/HT29 intestinal cells and Caco-2/HT29 + Raji-B cells)	Pristine and fluorescent nanoparticles were purchased from *Spherotech*.	PS	Spherical	0.05–0.1 μm	0, 25, 50, 100, 125, 150, 175, and 200 μg/mL	No significant cytotoxic effects were observed; MNPs were highly uptaken by both of the barrier model systems, and that translocation across the membrane occurred. No genotoxic or oxidative DNA damage induction was detected.	(Domenech et al., 2020)
Caco-2 cells	Pristine and fluorescent nanoparticles were purchased from *Spherotech*.	PS	Spherical	50 nm	0, 6.5, 13, 26, and 39 μg/cm^2	MNPs accumulated in the cells through time, yet they induced minor changes in the different evaluated genotoxicity-related biomarkers, suggesting that no DNA damage or oxidative stress is observed after long-term exposure.	(Domenech et al., 2021b)

In addition to minor effects on cytotoxicity, Hesler et al. (2019) further demonstrated that PS MNPs (50 nm and 0.5 μm) as weakly embryotoxic and non-genotoxic for Caco-2 cells in the concentration range of 0.1 to 100 μg/mL.

An interesting study performed by Liu et al. (2020) investigated the influence of the digestive process on the intestinal toxicity of PS MNPs using the Caco-2 model. It was reported that the digestive process exerted no alterations on the chemical properties of MNPs, although the formation of a corona was observed on the surface of MNPs, leading to a reduced cytotoxicity and transport function disorder of the Caco-2 monolayer induced by the original PS MNPs. On the other side, the observed corona might result in increased proinflammatory effects due to the change in size, Zeta potential, and adsorbed compounds on MNPs.

In addition, Stock et al. (2021) carried out an experiment to investigate the cellular effect and uptake of PE (sizes of 2.2, 16.5 and 90.1 μm), PP (67.1 μm), PET (60 μm) and PVC (136.5 μm) MNPs. They found that a significant decrease in cell viability was only evident at high concentrations of PVC particles (> 75 mg/mL) in all three cell lines studied (*i.e.*, Caco-2, HepG2 and HepaRG). Concerning cell uptake, they found that only the smallest MNPs, *i.e.* PE MNPs with a size of 2.2 μm were able to be transported through a simulated intestinal barrier with higher efficacy than PS particles of the same shape and size. Their results demonstrated that intestinal exposure to plastic MNPs depended on both the material type and size. The authors further stated that only excessively high concentrations, far beyond realistic dietary exposure of consumers, induced cytotoxic effects. Busch et al. (2021a) reported similar findings using an *in vitro* triple culture model (Caco-2/HT29-MTX-E12/THP-1) to mimic the healthy and inflamed human intestine and thus investigate the acute effects of MNP toxicity. They reported that pristine PS (59 nm, spherical shape, concentrations of 0, 1, 5, 10 or 50 μg/cm^2) and PVC MNPs (279 nm, spherical shape, concentrations of 0, 1, 5, 10 or 50 μg/cm^2) led to no measurable cytotoxicity effects, DNA damage, barrier integrity or cytokine release. Exposure did not change the mucus distribution on the epithelial cell layer of the triple culture model in a stable or inflamed state.

4.1.2. HepG2 cells

Researchers have also raised concerns about the toxicity of MNPs on the liver which is one of the most important detoxifying organs; evidence has shown that MNPs can accumulate and cause cytotoxicity in the liver of marine animals such as oysters (Tallec et al., 2018). As an *in vitro* model of the human liver, the human hepatocellular carcinoma (HepG2) cell line was used in 5 recent MNP related studies. In one, the cytotoxicity of spherical PS MNPs (50 nm) with distinct surface functionalization (pristine, PS-COOH and PS-NH_2) were evaluated using HepG2 cells at an exposure dosage of 10, 50 and 100 μg/mL (He et al., 2020). This work demonstrated that more PS-COOH and PS-NH_2 than pristine PS accumulated in the cells and resulted in greater inhibition of cell viability than pristine PS. In addition, a recent study revealed that the exposure of cells to spherical PE MNPs (concentrations up to 100 μg/mL) induced severe cell membrane damage in a dose related manner (Wang et al., 2022). Interestingly, Stock et al. (2020) devised a practical *in vitro* inverse cell culture model for investigating the cellular effects of floating plastic particles (*i.e.*, Polydisperse PE MNPs, irregular shape, mean diameter of 90.1 μm, concentrations of 25, 50 and 100 mg/mL). It was found that PE MNPs incubated in overhead culture showed significant cytotoxicity to HepG2 cells, while a non-inverted cell culture system demonstrated no cytotoxicity, suggesting the importance of adapting cell culture conditions based on physicochemical properties of polymers.

4.1.3. A549 cells

Inhaled MNPs encountering the respiratory epithelium tend to cause multiple consequences, implying a potential risk to the human respiratory system. The A549 cell line, representative of human lung epithelial cells, was used in 6 studies, with 2 of them focusing on studying the factors affecting the toxicity of MNPs (as will be further discussed in Section 5). Xu et al. (2019) investigated PS MNPs of two sizes (25 and 70 nm); both significantly reduced cell viability in a dose-dependent manner, caused cell cycle S phase arrest, activated inflammatory gene transcription, and altered the expression of proteins linked to the cell cycle and pro-apoptosis. Another study (Goodman et al., 2021) exposed human alveolar A549 cells to PS MNPs (1 and 10 μm diameter). Both sizes induced a significant decrease in cell proliferation but showed little cytotoxicity even at the highest concentration of 100 μg/mL. More importantly, major changes in the morphology of cells and the uptake of MNPs were observed. Observed disturbances at the proliferative and cytoskeletal levels of human cells have evidenced that airborne PS MNPs have significant toxicologic consequences. For example, Meindl et al. (2021) investigated the toxicity of PS MNPs (20 and 200 nm) on monocultures of Calu-3 and A549 cells and co-cultures of A549 and THP-1 macrophages at the concentration of 2 μg/cm^2. After exposure to MNPs for 28 days, they evaluated particle accumulation, transepithelial electrical resistance, dextran (3–70 kDa) uptake and proinflammatory cytokine secretion. Results demonstrated that healthy respiratory cells can adapt to low levels of repeated MNPs exposure.

4.1.4. Other cell lines

Macrophages are the primary phagocytic cells in the intestinal tract, lung and liver, acting as a first-line defense against harmful foreign substances that, upon activation, can stimulate the action of other immune system cells. As a consequence of their clear importance, several studies (Florance et al., 2021; Rudolph et al., 2021) have been carried out to assess the toxicity of MNPs on macrophages. When exposed to PS MNPs (size of 0.2 μm) at 50 μg/mL, macrophages were found to undergo differentiation

into lipid laden foam cells (Florance et al., 2021). Increasing the concentration to 100 and 200 μg/mL led to increased reactive oxygen species (ROS) and impaired lysosomes in macrophages (Florance et al., 2021). Another study (Rudolph et al., 2021) explored the interaction of murine macrophages (J774A.1, ImKC) with PS MNPs of varying sizes (0.2–6.0 μm). They reported that these two cell lines ingested a large volume of MNPs, but cytotoxic effects were only noticeable for one of them (ImKC) and only at concentrations above 250 μg/mL.

Çobanoğlu et al. (2021) explored the genotoxicity and cytotoxicity of PE microbeads (size range 10–45 μm) to human blood cells, *i.e.*, human blood lypmhocytes, at various concentrations of 25, 50, 100, 250, 500 μg/mL. Results showed no decrease in cell proliferation, suggesting a lack of cytotoxic potential, yet increased genomic instabilities were observed even at lower concentrations. Another study (Roshanzadeh et al., 2021) was performed to investigate the effect of PS MNPs (50 nm) exposure on the neonatal heart using neonatal rat ventricular myocytes (NRVMs). Their findings revealed that neonatal cardiomyocytes could be more susceptible to MNPs because their functional and structural mechanisms are incomplete compared to adult cardiomyocytes. The impact of PS MNPs (50 nm) exposure to the human nervous system was also studied using neural cells, *i.e.*, human neuroblastoma cells SH-SY5Y (Ban et al., 2021). Results showed that PS exposure induced: cytotoxicity in the cells, differentiation into neuronal phenotype; and other cell changes including shrinkage of neurite outgrowth, spillage of intracellular components; morphology alteration and swelling of the nuclei. Meanwhile, the impact of PS MNPs (43.67 nm) on cell mitosis and early mammalian embryo development was also investigated using bovine oviductal epithelial cells and embryos (Barbato et al., 2020). They found the PS MNPs uptake and transport across the cellular membrane did not induce chromosome instability but influenced the normal course of cellular division. Another interesting work evaluated the effects of MNPs, parabens, and their mixture on the viability and proliferation of two human breast cancer cell lines (*i.e.*, MDA-MB 231 and MCF-7) (Roje et al., 2019). They reported that PS MNPs (60 nm) presented synergistic effects of parabens that increased the proliferation of oestrogen-sensitive breast cancer cells.

In addition, Ding et al. (2021) carried out an experiment to elucidate the entry and transport mechanisms of PS MNPs using human gastric epithelial (GES-1) cells. Their results showed that cell internalization rates of MNPs decreased after the inhibition of clathrin-mediated endocytosis and caveolin-mediated endocytosis, as well as megacytosis. Meanwhile, the inhibition of one endocytosis or macropinocytosis pathway alone could not completely block the cellular internalization of MNPs, indicating that PS MNPs entered host cells through multiple endocytosis or macropinocytosis pathways.

Evidence from the remaining *in vitro* articles has shown that MNPs exposure affects various functions of different human cells, *e.g.*, human skin fibroblast (Akhatova et al., 2022), human umbilical vein endothelial cells (Lee et al., 2021), and Madin-Darby canine kidney (MDCK) epithelial cell line (Palaniappan et al., 2021), presenting a series of toxicological effects such as embryotoxicity, hepatotoxicity, neurotoxicity, renal toxicity. Nevertheless, it is worth pointing out that there are a few studies indicating no association between MNPs exposure and toxicological effects.

4.2. Biological effects of MNPs from in vivo studies

The *in vivo* studies selected in this review mainly focused on the entry of MNPs into different organs and systems, leading to biodistribution and bioaccumulation, eventually altering normal function.

With respect to the gastrointestinal system, the effects of ingested MNPs on gut microbiota have attracted much attention. Evidence has shown that MNP particles serve as a habitat for environmental microorganisms, facilitating the formation of microbial populations and biofilms on their surfaces due to hydrophobic property and strong floating capability (Lu et al., 2019). From our selected literature, 8 articles have explored the effects of MNPs on the gut microbiota using different biological models, as summarized in Table 2. Tamargo et al. (2022) investigated the impact of PET MNPs on human microbiota and their possible biotransformation in the gastrointestinal tract. In their study, PET MNPs (irregular, with the mean size of 160 μm) were subjected to digestion simulation by combining a harmonized static model and the dynamic gastrointestinal simgi model,

Table 2
Summary of studies investigating the impact of MNPs on gut microbiota.

Biological models	MNPs source	Polymer type	Shape	Particle size	Exposure concentration	Results	Reference
In vitro digestion simulation	Pure PET pellets (purchased from *Ramapet N80*) were blade milled to obtain MNPs.	PET	Irregular	160 ± 110 μm	0.166 g/intake	Ingested MNPs modified human microbial colonic community composition.	(Tamargo et al., 2022)
In vitro	Powder form purchased from *Aladdin Industrial*.	PE	Spherical	30–140 μm	0, 100, 1000 mg/L for 48 h.	Interaction of MNPs with gut microbiota led to the increased proportion of *Clostridium*, *Bacteroides*, and *Escherichia*.	(Huang et al., 2021)
In vivo mice model	Purchased from *Polysciences*.	PS	Spherical	50 nm	0, 0.2, 1, or 10 mg/kg PS MNPs for 30 days	Oral exposure to PS MNPs accounted for the alteration of community composition of intestinal microbiota.	(Xiao et al., 2022)
In vivo mice model	Yellow-green PS MNPs purchased from *Polysciences*.	PS	Spherical	1 μm	80 μg/kg/day for 4 weeks	Did not result in significant changes of the gut microbiome.	(Rawle et al., 2022)
In vivo mice model	Pristine carboxyl-modified and amino- modified were purchased from *BaseLine ChromTech Research Centre*.	PS	Spherical	70 nm, 5 μm	0, 2, 0.2, mg/kg for 28 days	Oral administration of these MNPs resulted in marked gut microbiota dysbiosis.	(Qiao et al., 2021)
In vivo mice model	Clear PE microplastics were purchased from the *Cospheric Company*.	PE	Not mentioned	10–150 μm	6, 60, and 600 mg/day for 5 weeks.	MNPs affected the composition and diversity of gut microbiota.	(Li et al., 2020a)
In vivo mice model	Pristine and fluorescent polystyrene were purchased from *Microspheres-Nanospheres*.	PS	Not mentioned	5 μm	1.456×10^6 particles/L, 1.456×10^7 particles/L for six weeks.	The diversity of gut microbiota was altered after polystyrene MNP exposure. MNPs accumulated in the gut of mice and induced intestinal barrier dysfunction, gut microbiota dysbiosis, bile acids metabolism disorder in mice.	(Jin et al., 2019)
In vivo mice model	Purchased from *Microspheres-Nanospheres*.	PS	Not mentioned	0.5 μm and 50 μm	1000 μg/L	MNPs induced gut microbiota; decreased the secretion of mucin in gut; induced hepatic lipid metabolism disorder in mice.	(Lu et al., 2018)

enabling the recreation of different regions of the digestive tract in physiological conditions. It was found that the ingested MNPs modified the human microbial colonic community composition, possibly due to the attachment of some colonic microbiota to MNP surfaces, allowing for the formation of biofilms. In addition, in an *in vitro* simulation experiment, Huang et al. (2021) cultured gut microbiota obtained from fecal samples, finding that they also exhibited a dramatic change of community composition after interacting with PE MNPs (diameter 30 to 140 μm) with an increased proportion of *Clostridium*, *Bacteroides*. Meanwhile, a *in vivo* study (Xiao et al., 2022) reported a similar result, in that oral exposure of mice to PS MNPs accounted for the alteration of community composition of intestinal microbiota. Mice were subjected to oral administration of 0, 0.2, 1, or 10 mg/kg PS MNPs (~ 50 nm) for 30 days (Xiao et al., 2022). Meanwhile, another recent study (Rawle et al., 2022) demonstrated that mice consuming ≈80 μg/kg/day of yellow-green PS MNPs (~ 1 μm) *via* their drinking water for 4 weeks did not show significant changes in the gut microbiome. It is interesting to note that these two *in vivo* studies obtained the investigated PS MNPs from the same manufacturer, yet the concentration for oral exposure and the size of particles is very different. This suggests that the influence of MNPs on the gut microbiome is probably concentration and size dependent, as also found in the *in vitro* studies.

In addition to the impact on gut microbiota, it has been found that consumed MNPs have the tendency to surpass the intestinal barrier and accumulate in the body. In one study (Schwarzfischer et al., 2021), mice were supplemented with spherical PS MNPs (~ 50 nm) with daily consumption of approx. 0.2 mg MNPs per mouse. Results showed that MNPs accumulated in the small intestine and organs including the spleen and liver, distant from the gastrointestinal tract. However, the authors (Schwarzfischer et al., 2021) reported that the biodistribution and bioaccumulation did not affect intestinal health nor did they promote colitis severity. The effects of MNPs on hepatotoxicity in mice was investigated by Mu et al. (2022), who treated mice with 5.0 μm PP MNPs at 0.1, 0.5 and 1 mg/mL for 4 weeks. They demonstrated that MNPs exposure could damage liver structure and function, induce oxidative damage and lipid peroxidation in the liver, suggesting that pyroptosis and ferroptosis occurred in MNPs-induced liver injury, accompanied by intense oxidative stress and inflammation. With regard to the kidney, researchers (Meng et al., 2022) found that PS MNPs (size of 50 nm, 300 nm, 600 nm, 4 μm) bioaccumulated in the kidneys when treated with 5 mg/day MNPs solution for 4 weeks, and the aggregation of 600 nm MNPs exacerbated their biotoxicity. Additionally, mice weight loss, increased death rate, and significantly alternated several biomarkers were also observed, while MNPs could induce oxidative stress and the development of inflammation, exerting more adverse effects. On the contrary, Xiao et al. (2022) concluded that oral exposure to PS MNPs (sizes distributed around 50 nm) for 30 days at doses of 0.2, 1, or 10 mg/kg did not cause behavioral impairments in young mice. No significant changes in inflammatory or oxidative stress-related indicators were discovered in the liver, lung, intestine, cortex or serum of MNPs-treated animals. Furthermore, the treatment did not cause pathological changes in the liver, lung, or cortex tissues. The bioaccumulation of MNPs in the brain was recently evidenced by Zaheer et al. (2022) who identified that PE transited into the brain after PE MNPs (size of 10–20 μm) feeding with 100 ppm/100 μL of PE orally administered to mice daily. They further demonstrated a link between MNPs exposure during the prenatal and early postnatal periods and the development of autism spectrum disorder.

At the respiratory level, the presence of MNPs in the air may damage the human respiratory system following inhalation. Recent *in vivo* work (Li et al., 2022) demonstrated that inhalation of PS MNPs (diameter of 5 μm) induced pulmonary fibrosis in a dose-dependent manner in mice, *via* activation of intense oxidative stress in the lungs. Meanwhile, another study (Lu et al., 2021) exhibited that airborne MNPs had detrimental effects on the respiratory system in both healthy and asthmatic mice. In their experiment, mice were treated with 300 μg of MNPs every three days. The nasal exposure of MNPs through inhalation caused pulmonary inflammatory cell infiltration, bronchoalveolar macrophage aggregation, increased TNF-α level in bronchoalveolar lavage fluid, and increased plasma IgG1 production in normal mice. For asthmatic mice, asthma symptoms were largely altered by raising mucus production and inflammatory cell infiltration with noticeable macrophage aggregation. Moreover, the exposure also led to changes in gene clusters associated with the immune response, cellular stress response, and programmed cell death.

With regard to the impact on the hematopoietic system, Jing et al. (2022) exposed mice to PS MNPs (10 μm, 5 μm and 80 nm) at 60 μg doses for 42 days by intragastric administration. Hematopoietic toxicity was evidenced by the disorder of bone marrow cell arrangement, the decrease in colony-forming, self-renewal and differentiation capacity, and increased proportion of lymphocytes. Hematotoxicity was also seen when mice were treated with two doses (0.1 and 0.5 mg) of 5 μm PS MNPs (Sun et al., 2021), where it was shown that MNPs exposure had an impact on gene expression, and disturbed related molecular and biological pathways in mouse bone marrow cells. Another study (Li et al., 2020c) identified the impact of MNPs on the cardiovascular system. After exposing rats to 0.5 μm PS MNPs at 0.5, 5 and 50 mg/L for 90 days, they found increased Troponin I and creatine kinase-MB (CK-MB) levels in serum, leading to structural damage and apoptosis of myocardium, causing collagen proliferation of heart. Oxidative stress was also induced, activating the fibrosis-related Wnt/b-catenin signaling pathway. The collective results suggested cardiovascular toxicity induced by MNPs.

Reproductive toxic effects of MNPs in mammals are also increasingly explored. In one study (Liu et al., 2022b), female mice were exposed to PS MNPs (0.79 μm in diameter) for 35 days. Bioaccumulation was identified in multiple organs including the heart, liver, spleen, lung, kidney, brain, large intestine, small intestine, uterus, ovary and blood. These results also illustrated that MNPs exposure induced the inflammation of ovaries and reduced the quality of oocytes, generating reproductive toxicity in mice. Moreover, Hu et al. (2021) found PS MNPs (size of 10 μm) exposure to mice at the dose of 250 μg have the potential to cause adverse effects on pregnancy outcomes *via* immune disturbance, while Hou et al. (2021) showed that PS MNPs (size of 5 μm) treatment (various doses from 0.6 to 70 μg/day) increased the rate of sperm deformity.

Evidence has also been provided that MNPs could maternally transfer to offspring (Park et al., 2020; Han et al., 2021); therefore, studies to investigate the trans-generational toxicity were found from our selected articles. For example, mice were exposed gestationally and lactationally to PS MNPs (size 100 nm) at different doses (0.1, 1 and 10 mg/L) (Huang et al., 2022). A decline in birth and postnatal body weight in offspring mice was observed. High-dose exposure decreased liver weight, triggered oxidative stress, caused inflammatory cell infiltration, up-regulated proinflammatory cytokine expression, and disturbed glycometabolism in the liver, diminished testis weight, disrupted seminiferous epithelium and decreased sperm count in mouse offspring, suggesting hepatic and testicular toxicity. A similar experiment was performed to evaluate the impact of maternal exposure to MNPs on the offspring (Luo et al., 2019). They exposed pregnant mice to 100 and 1000 μg/L PS MNPs (sizes of 0.5 and 5 μm) and found an increased risk of metabolic disorder in their offspring, while larger effects were observed in 5 μm MNPs-treated groups.

In contrast, some researchers found an insignificant impact of MNPs exposure to *in vivo* mammal models. For example, Stock et al. (2019) showed the absence of histologically detectable lesions and inflammatory responses in mice after being treated three times per week by oral gavage with a mixture of 1 μm (4.55 × 107 particles), 4 μm (4.55 × 107 particles) and 10 μm (1.49 × 106 particles) spherical PS MNPs at a volume of 10 mL/kg/bw. This 28-days *in vivo* feeding study found MNPs did not interfere with the differentiation and activation of the human macrophage model. Kim et al. (2021) used an *in vivo* rat model to identify the potential toxicity of weathered PP MNPs (size of 85.2 μm), obtained by sieving particles after fragmentation and accelerated weathering processes. Their results demonstrated no adverse effects and mutagenicity even at the highest dose of 25 mg/kg/day. Additionally, the exposure did not indicate any skin or eye irritation potentials in the 3-dimensional reconstructed human skin or corneal culture model. Another study (Rafiee et al., 2018) revealed that no statistically significant neurobehavioral effects were observed in rats at

four test dosages (1, 3, 6, and 10 mg PS MNPs/kg/bw), administrated orally for five weeks. In addition, Han et al. (2021) evaluated whether PE MNPs (10–45 μm) exposed through the inhalation route could be delivered to fetal mice and exhibit systemic toxicity. Three different doses (6, 60 μg/day) were applied to pregnant mice dams (per group) from gestational day 9 to postnatal day 7 through intratracheal instillation. This study indicated that MNPs instilled intratracheally could be delivered to neonates from dams, yet adverse effects from MNPs exposure during the pregnant and lactational period were not prominent in both dam and neonate.

4.3. Biological effects of MNPs from ex vivo studies

Three *ex vivo* studies were identified investigating the impact of MNPs on the skin, internal organs and blood. A study performed by Döge et al. (2018) implemented 2-photon microscopy for penetration studies of fluorescently tagged PS MNPs (20 and 200 nm) in excised human skin. It was observed that MNPs preferentially accumulated in the stratum corneum and in the upper part of vellus hair follicles. Another study (Bartucci et al., 2020) exposed tissue slices (liver, lung and kidney) from the different organs of mice to silica, carboxylated (40 and 200 nm) and amino-modified PS MNPs (50 nm). Results showed the uptake of MNPs in all slices with a minimal level of uptake in the kidney. Applying whole blood samples from different donors, Ballesteros et al. (2020) exposed *ex vivo* blood to PS MNPs. The uptake of MNPs varied from different cell lineages with the maximum shown in monocytes and minimum in lymphocytes. They also found a significant increase in the levels of DNA damage for monocytes and polymorphonuclear cells. Furthermore, MNPs exposure induced alterations in the whole blood secretome.

4.4. Biological effects of MNPs on human subjects

Although papers on the biological effects of MNPs on human subjects are rare, we found one study (Yan et al., 2022) aiming at identifying the correlation between the abundance of fecal MNPs and inflammatory bowel disease (IBD) status based on human participants. Participants including healthy participants and IBD patients were recruited, followed by a questionnaire survey to gather information regarding their lifestyle. Fecal samples were collected from individual participants to identify and detect MNPs. A higher fecal MNP concentration was found in IBD patients compared to healthy participants. More importantly, a positive correlation was evidenced between the concentration of fecal MNPs and the severity of IBD, implying that MNP exposure may be linked to the disease process or that IBD exacerbated the retention of MPs.

5. Understanding factors directing the toxicity of MNPs

A number of investigations of MNPs toxicity were identified from our selected studies. The chemical and physical properties of MNPs, such as polymer molecular structure, size, wettability and roughness, combined with the potential of leaching of plastic additives and adhesion of contaminants are just some of the many factors which may influence toxicity. Below we review the current knowledge of the role of these factors.

5.1. Size and concentration

A plethora of studies have made it clear that the toxicity of MPNs acts in a concentration-dependent manner, with higher concentration leading to greater toxicological effects. Size also plays an important part as evidenced by several studies (Stock et al., 2022b; Banerjee et al., 2021; Wu et al., 2019). For example, a study (Wang et al., 2020) demonstrated that exposing PS MNPs with different sizes of 300 nm, 500 nm, 1 μm, 3 μm, 6 μm to Caco-2 cells for 24 h led to uptake rates of 78 %, 71 %, 48 %, 41 %, and 28 %, respectively, suggesting that larger particles are less likely to enter cells. Their results also indicated a decreased oxidative stress in cells for larger particles. Meanwhile, they found that the cytotoxicity of MNPs depends mainly on the size and concentration, that is, MNPs of 300 nm, 500 nm and 6 μm at the concentration of 120 μg/mL caused a significantly decreased cell viability compared to MNPs of 1 μm and 3 μm.

5.2. Shape

Shape is also identified as potentially influential in MNPs toxicity. It has been demonstrated that randomly-shaped PS micro-fragments with relatively rough and sharp morphologies compared to spherical MNPs cause more harmful physical effects that prompt cell toxicity (Choi et al., 2020); irregular PS MNPs were derived from the ball milling process and the associated toxicity was assessed by multiple cytotoxicity assays using different types of cell culture models (*i.e.*, peripheral blood mononuclear cells, KATO III cells, HeLa cells and human dermal fibroblasts). The results revealed that irregularly shaped MNPs increased the acute inflammation of immune cells 20 times more than the control. Randomly-shaped MNPs with high roughness and sharpness induced physical damage on the cellular membrane, leading to hemolysis and LDH release in the cytosol. Through quantitatively estimation of MNP roughness, the authors obtained a strong positive correlation between the physical damage of cells and the roughness of particles.

5.3. Surface charge

Surface charge is believed to be an important parameter that influences the interaction between MNPs particles and cells. For example, it was reported that PS-NH_2 particles significantly reduced cell viability and increased cytotoxicity in three cell lines (*i.e.*, Caco-2, HT29-MTX-E12, THP-1) (Busch et al., 2021a), ascribed to membrane destabilization and rupture, generation of ROS and lysosomal rupture after cellular uptake. They also noticed a small, statistically significant increase in DNA damage in Caco-2 and HT29-MTX-E12 cells after exposure to PS-NH_2 particles for 4 h at a concentration of 50 μg/cm^2. A similar study (Jeon et al., 2018) was performed to evaluate the role of surface charge in the cellular uptake of PP and PS MNPs. Based on phagocytic differentiated THP-1 cells or non-phagocytic A549 cells, a positive correlation was observed between the amount of internalized particles and zeta potential. The authors (Jeon et al., 2018), therefore, claimed that surface charge is the major property determining cellular uptake efficiency, although other parameters such as size, shape, protein corona formation, and compositional elements also have some contributions partly or indirectly.

5.4. Sorption of other pollutants

MNPs can act as vectors to transfer exogenous hazardous pollutants present in or on the particles into the body, causing chemical toxicity. It has been shown that MNPs (size of 0.05 to 0.1 μm; 0.04 to 0.09 μm) were able to bind metals such as silver (Domenech et al., 2021a) and that the formed complexes could modulate the uptake of silver nanoparticles in Caco-2 cells and slightly modify some toxic effects of silver compounds, such as the ability to induce genotoxic and oxidative DNA damage. Wang et al. (2020) reported that PS MNPs (300 nm, 500 nm, 1 μm, 3 μm, 6 μm) have a synergistic effect on Caco-2 cells after adsorption of bisphenol A which is recognized as an endocrine disrupting compound. Meanwhile, Shi et al. (2021) found combined toxicity of PS MNPs (~100 nm) and different phthalate esters (PAEs) on A549 cells, explaining that oxidative stress and inflammatory reactions were mechanisms for combined cytotoxicity.

5.5. Weathering process

All plastics are known to contain small concentrations of reactive oxygen species (ROS) due to the polymerization and processing history (Jeon et al., 2021). During the weathering process, the interaction with light can increase the concentration of free radicals. Using *in vitro* human lung epithelial adenocarcinoma cells (A549), Zhu et al. (2020) reported enhanced cytotoxicity of photo-aged phenol-formaldehyde resin microplastics undergoing simulated sunlight irradiation. The photoaged MNPs showed

some changes in physicochemical properties, as indicated by the enhanced levels of the conjugated carbonyls, environmentally persistent free radicals and ROS, contributing to the increase of the oxidative potential, leading to higher cytotoxicity compared to non-photo-aged MNPs. Another study (Jeon et al., 2021), in which the cytotoxicity of unmodified MNPs and aged MNPs (PS and PP, prepared by sieving after pulverization and accelerated weathering using ultraviolet and heat) showed that weathering process significantly reduced ROS generation potential, due to a higher affinity to bind serum protein, thus decreasing the toxicity compared to pristine MNPs.

6. Discussion on limitations and challenges

This review identifies some major limitations in designing and performing experiments to reach a consensus on the adverse health effects of MNPs in humans. The lack of crucial information on human exposure concentrations represents a major issue in human risk assessment. Incomparable levels of exposure concentration were detected in the reported 133 studies, which is an important constraint. For example, while many *in vitro* studies focused on a concentration range lower than 200 μg/mL, some studies involved relatively higher concentrations such as 100 mg/mL in Stock et al. (2021). It was also observed that researchers used different units, making comparison difficult to establish. For *in vitro* studies, μg/mL (or mg/L) was the most popular unit, while others include μg/cm^2 and particles/mL. Regarding *in vivo* studies, mg/kg body weight was widely used, followed by mg/day, particles/L, μg/L, g/intake, ppm/100 μL, mg per mouse. Since higher concentrations and longer exposure time are more likely to induce adverse effects, it is of great importance to use a comparable exposure level and time.

Most reported studies used purchased MNPs without considering that different manufacturers differ highly in the physico-chemical properties and surface modifications leading to prominent differences in cytotoxicity. Fluorescence labelled MNPs are advantageous in terms of measuring cellular uptake/translocation/internalization. Nevertheless, Stock et al. (2022a) found that commercial fluorescent-labelled PS MNPs could leach their fluorophore, therefore distorting results when they were used to localize the particles inside cells or animals. Besides the leakage of fluorescent stains, purchased PS MNPs are usually dispersed in solvents, yet the information about the dispersants used is not always detailed by manufacturers. In fact, ready-to-use polystyrene suspensions are often provided in media containing stabilizers or antimicrobial agents such as azide, themselves having the potential to decrease cell viability. A recent study (Stock et al., 2022a) reported that some dispersants were able to cause a more pronounced cytotoxic effect than the PS MNPs themselves. To overcome this limitation, (Stock et al., 2022a) studied PS MNPs purchased from a range of manufacturers, followed by the separation of PS particles and solvents that were used for the dispersion of MNPs. Using *in vitro* models for the intestinal barrier and hepatocytes, results showed that commercial PS suspensions contained relevant amounts of toxic dispersants that were responsible for the observed cytotoxicity. Clearly, as the authors pointed out, there is a pressing need for proper controls in similar experiments, avoiding false interpretation of results that overestimate the toxicity of MNPs.

Among 133 studies, 105 articles used PS as the target material for investigation, although this polymer type accounts for only about 7 % of total plastic production (Brachner et al., 2020). Recently, Yan et al. (2022) found 15 types of MNPs in faeces, with PET (22.3–34.0 %) and PA (8.9–12.4 %) being the dominant types. It remains rather questionable whether biological effects induced by PS MNPs can be extrapolated to MNPs of other polymer types. For example, Fuentes-cebrian et al. (2022) produced representative PET MNP samples (with a uniform size of 100 nm) and they showed no oxidative damage on the DNA bases, yet many studies using PS MNPs of the same size demonstrated negative genotoxic effects. The preparation of environmentally representative MNP samples represents a major challenge, especially in the nano range. At the same time, the contamination during the preparation of aged MNP samples should also receive some attention. As the authors (Fuentes-cebrian et al., 2022) pointed out, the use of metallic blades, which is a conventional way to prepare MNPs, has the potential to contaminate the resultant MNP samples with metals. Current literature is also biased towards microspheres, and thus less relevant to MNPs samples found in the real environment (*i.e.*, less complex morphologies and chemistries). Research has shown that the primary shapes of MNPs collected from human faeces were sheets and fibers (Yan et al., 2022), again proving that the use of the spherical shape of purchased MNPs is unideal and unrepresentative. However, with 98 out of 133 articles assessing the toxicity of spherical microbeads rather than randomly shaped MNP particles means that current research is not providing a good representation for researching the human health effects.

7. Suggestions for future research

Based on the analysis of available articles, herein we propose some possible strategies to improve current practices as follows:

(1) MNPs have various chemical compositions and physical properties. To allow the comparison between different studies, it is essential to present all relevant characteristics of MNPs particles including manufacturer, size, shape, surface charge, surface chemistry, and exposure concentration prior to drawing any conclusions. A comprehensive characterization of complex MNPs is the key to understanding the toxicity mechanism.
(2) Instead of using purchased microbeads for experimenting, there is an urgent need to perform more studies using realistic environmental MNPs samples which are more complex and relevant. Future studies of MNP health effect assessment should be carried out by creating a scenario that is imitating a real-life exposure route.
(3) Exposure of MNPs should be repeated with several concentration levels ranging from low, middle and high concentrations, while multiple exposure times should be considered lasting from a few hours to many days, or even longer if technically applicable, allowing for the inter-study comparability.
(4) Future research should endeavor to elucidate whether the observed biological effects are coming from MNPs particles or other compounds such as additives. It is of great importance to understand whether the chemicals leached from the particles, or the particles themselves, or a combination of both are the driving factors for the observed toxicity, in order to avoid overestimating the impact of MNPs. A possible solution here is to expose chemicals extracted from the investigated MNPs particles to mammalian *in vivo* or *in vitro* systems. The achieved biological outcome should be compared to the results generated from the untreated MNPs.
(5) Dosimetry should also be considered in future studies as the dispersion behavior of particles is dependent on several factors including medium viscosity, sizes and densities of particles (Stock et al., 2020). Since the size and densities of MNPs have a major influence on their diffusion and sedimentation behavior, it leads to an inhomogeneous distribution of MNPs in *in vitro* systems. Therefore, the delivered dose which reaches the cells to trigger biological effects is often not equal to the administered dose (Böhmert et al., 2018).
(6) Adverse outcome pathways should be prioritized when investigating the effects of these MNP particles, therefore more mechanistic studies should be performed in the future. Currently, the specific mechanisms and pathways by which MNPs cause adverse effects are not yet well understood. There is a need for further elucidation of mechanisms linking molecular and human adverse effects (Hampton et al., 2022).

8. Conclusion

Since adequate and standardized analytical tools to sample, detect, quantify, and characterize MNP particles, especially nanosized particles, have not yet been fully developed, crucial data on human exposure through the supposedly major uptake routes of ingestion and inhalation are still to be determined. Following exposure, *via* diet and/or inhalation, uptake is

inevitable, as evidenced by the detection of various MNPs in human faeces, placentas and blood. Among 133 studies considered herein, 16 (8 *in vitro*, 5 *in vivo*, 1 applied both *in vitro* and *in vivo*, 2 *ex vivo*) stated that the impact of MNPs on human health is not of concern, while the remaining 117 studies confirmed the adverse health consequences. All these contrasting results, possibly due to the differences in the MNP particles used. The exposure concentration, size, shape and functionalized status, demand many more new studies applying realistic human-like models and measuring multiple relevant endpoints, to evaluate the threats of MNPs on human health. One interesting study identified a positive correlation between the abundance of fecal MNPs and inflammatory bowel disease status based on human participants. While studies in humans are a priority, there is a pressing need to address some challenges to move this field forward, such as the estimation of daily exposure in human populations, high throughput and robust analysis for characterising MNPs exposed to humans. Overcoming these challenges are key to furthering research in this field.

CRediT authorship contribution statement

Jun-Li Xu: Funding acquisition, Conceptualization, Data curation, Formal analysis, Methodology, Software, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Xiaohui Lin:** Methodology, Investigation, Validation, Writing – original draft, Writing – review & editing. **Jing Jing Wang:** Validation, Writing – review & editing. **Aoife A. Gowen:** Funding acquisition, Project administration, Validation, Writing – review & editing.

Data availability

Data is shared in Supplementary material.

Declaration of competing interest

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

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Supplementary data

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References

Akhatova, F., Ishmukhametov, I., Fakhrullina, G., Fakhrullin, R., 2022. Nanomechanical Atomic Force Microscopy to Probe Cellular Microplastics Uptake and Distribution. https://doi.org/10.3390/ijms23020806.

Ballesteros, S., Domenech, J., Barguilla, I., Cortés, C., Marcos, R., Hernández, A., 2020. Genotoxic and immunomodulatory effects in human white blood cells after: ex vivo exposure to polystyrene nanoplastics. Environ. Sci. Nano 7, 3431–3446. https://doi.org/10.1039/d0en00748j.

Ban, M., Shimoda, R., Chen, J., 2021. Investigation of nanoplastic cytotoxicity using SH-SY5Y human neuroblastoma cells and polystyrene nanoparticles. Toxicol. in Vitro 76, 105225. https://doi.org/10.1016/j.tiv.2021.105225.

Banerjee, A., Billey, L.O., Shelver, W.L., 2021. Uptake and toxicity of polystyrene micro/nanoplastics in gastric cells: effects of particle size and surface functionalization. PLoS One 16. https://doi.org/10.1371/journal.pone.0260803.

Barbato, V., Talevi, R., Gualtieri, R., Pallotta, M.M., Di Nardo, M., Costanzo, V., Catapano, G., Capriglione, T., 2020. Polystyrene nanoparticles may affect cell mitosis and compromise early embryo development in mammals. Theriogenology 145, 18–23. https://doi.org/10.1016/j.theriogenology.2020.01.007.

Bartucci, R., Paramanandana, A., Boersma, Y.L., Olinga, P., Salvati, A., 2020. Comparative study of nanoparticle uptake and impact in murine lung, liver and kidney tissue slices. Nanotoxicology 14, 847–865. https://doi.org/10.1080/17435390.2020.1771785.

Böhmert, L., König, L., Sieg, H., Lichtenstein, D., Paul, N., Braeuning, A., Voigt, A., Lampen, A., 2018. In vitro nanoparticle dosimetry for adherent growing cell monolayers covering bottom and lateral walls. Part. Fibre Toxicol. 15, 1–20. https://doi.org/10.1186/s12989-018-0278-9.

Brachner, A., Fragouli, D., Duarte, I.F., Farias, P.M.A., Dembski, S., Ghosh, M., Barisic, I., Zdzieblo, D., Vanoirbeek, J., Schwabl, P., Neuhaus, W., 2020. Assessment of human health risks posed by nano-and microplastics is currently not feasible. Int. J. Environ. Res. Public Health 17, 1–10. https://doi.org/10.3390/ijerph17238832.

Braun, T., Ehrlich, L., Henrich, W., Koeppel, S., Lomako, I., Schwabl, P., Liebmann, B., 2021. Detection of microplastic in human placenta and meconium in a clinical setting. Pharmaceutics 13, 921.

Busch, M., Bredeck, G., Kämpfer, A.A.M., Schins, R.P.F., 2021a. Investigations of acute effects of polystyrene and polyvinyl chloride micro- and nanoplastics in an advanced in vitro triple culture model of the healthy and inflamed intestine. Environ. Res. 193. https://doi.org/10.1016/j.envres.2020.110536.

Busch, M., Kämpfer, A.A.M., Schins, R.P.F., 2021b. An inverted in vitro triple culture model of the healthy and inflamed intestine: adverse effects of polyethylene particles. Chemosphere 284. https://doi.org/10.1016/j.chemosphere.2021.131345.

Choi, D., Bang, J., Kim, T., Oh, Y., Hwang, Y., Hong, J., 2020. In vitro chemical and physical toxicities of polystyrene microfragments in human-derived cells. J. Hazard. Mater. 400, 123308. https://doi.org/10.1016/j.jhazmat.2020.123308.

Çobanoğlu, H., Belivermiş, M., Sıkdokur, E., Kılıç, Ö., Çayır, A., 2021. Genotoxic and cytotoxic effects of polyethylene microplastics on human peripheral blood lymphocytes. Chemosphe1. Chen, Y.-C. al. nephrotoxic potential Polystyr. microplastics Realis. Environ. Conc. J. Hazard. Mater. 427 (2022), 272. https://doi.org/10.1016/j.chemosphere.2021.129805 re.

Cortés, C., Domenech, J., Salazar, M., Pastor, S., Marcos, R., Hernández, A., 2020. Nanoplastics as a potential environmental health factor: effects of polystyrene nanoparticles on human intestinal epithelial Caco-2 cells. Environ. Sci. Nano 7, 272–285. https://doi.org/10.1039/c9en00523d.

DeLoid, G.M., Cao, X., Bitounis, D., Singh, D., Llopis, P.M., Buckley, B., Demokritou, P., 2021. Toxicity, uptake, and nuclear translocation of ingested micro-nanoplastics in an in vitro model of the small intestinal epithelium. Food Chem. Toxicol. 158. https://doi.org/10.1016/j.fct.2021.112609.

Dick Vethaak, A., Legler, J., 2021. Microplastics and human health: knowledge gaps should be addressed to ascertain the health risks of microplastics. Science (80-.) 371, 672–674. https://doi.org/10.1126/science.abe5041.

Ding, Y., Zhang, R., Li, B., Du, Y., Li, J., Tong, X., Wu, Y., Ji, X., Zhang, Y., 2021. Tissue distribution of polystyrene nanoplastics in mice and their entry, transport, and cytotoxicity to GES-1 cells. Environ. Pollut. 280, 116974. https://doi.org/10.1016/j.envpol.2021.116974.

Döge, N., Hadam, S., Volz, P., Wolf, A., Schönborn, K.H., Blume-Peytavi, U., Alexiev, U., Vogt, A., 2018. Identification of polystyrene nanoparticle penetration across intact skin barrier as rare event at sites of focal particle aggregations. J. Biophotonics 11, 1–10. https://doi.org/10.1002/jbio.201700169.

Domenech, J., Hernández, A., Rubio, L., Marcos, R., Cortés, C., 2020. Interactions of polystyrene nanoplastics with in vitro models of the human intestinal barrier. Arch. Toxicol. 94, 2997–3012. https://doi.org/10.1007/s00204-020-02805-3.

Domenech, J., Cortés, C., Vela, L., Marcos, R., Hernández, A., 2021a. Polystyrene nanoplastics as carriers of metals. Interactions of polystyrene nanoparticles with silver nanoparticles and silver nitrate, and their effects on human intestinal caco-2 cells. Biomolecules https://doi.org/10.3390/biom11060859.

Domenech, J., de Britto, M., Velázquez, A., Pastor, S., Hernández, A., Marcos, R., Cortés, C., 2021b. Long-term effects of polystyrene nanoplastics in human intestinal Caco-2 cells. Biomolecules 11. https://doi.org/10.3390/biom11101442.

Dong, C.Di, Chen, C.W., Chen, Y.C., Chen, H.H., Lee, J.S., Lin, C.H., 2020. Polystyrene microplastic particles: in vitro pulmonary toxicity assessment. J. Hazard. Mater. 385, 121575. https://doi.org/10.1016/j.jhazmat.2019.121575.

Dris, R., Gasperi, J., Saad, M., Mirande, C., Tassin, B., 2016. Synthetic fibers in atmospheric fallout: a source of microplastics in the environment? Mar. Pollut. Bull. 104, 290–293.

Florance, I., Ramasubbu, S., Mukherjee, A., Chandrasekaran, N., 2021. Polystyrene nanoplastics dysregulate lipid metabolism in murine macrophages in vitro. Toxicology 458, 152850. https://doi.org/10.1016/j.tox.2021.152850.

Fuentes-cebrian, V., Moriones, O.H., Marcos, R., Hern, A., 2022. A new source of representative secondary PET nanoplastics. Obtention , Characterization , and Hazard Evaluation, p. 439 https://doi.org/10.1016/j.jhazmat.2022.129593.

Goodman, K.E., Hare, J.T., Khamis, Z.I., Hua, T., Sang, Q.X.A., 2021. Exposure of human lung cells to polystyrene microplastics significantly retards cell proliferation and triggers morphological changes. Chem. Res. Toxicol. 34, 1069–1081. https://doi.org/10.1021/acs.chemrestox.0c00486.

Hampton, T., Hampton, L.M.T., Bouwmeester, H., Brander, S.M., Coffin, S., Cole, M., Hermabessiere, L., Mehinto, A.C., Miller, E., Rochman, C.M., Weisberg, S.B., 2022. Research recommendations to better understand the potential health impacts of microplastics to humans and aquatic ecosystems. Microplast. Nanoplast. https://doi.org/10.1186/s43591-022-00038-y.

Han, Y.H., Song, Y.M., Kim, G.W., Ha, C.S., Lee, J.S., Kim, M.H., Son, H.Y., Lee, G.Y., Gautam, R., Heo, Y., 2021. No prominent toxicity of polyethylene microplastics observed in neonatal mice following intratracheal instillation to dams during gestational and neonatal period. Toxicol. Res. 37, 443–450. https://doi.org/10.1007/s43188-020-00086-7.

He, Y., Li, J., Chen, J., Miao, X., Li, G., He, Q., Xu, H., Li, H., Wei, Y., 2020. Cytotoxic effects of polystyrene nanoplastics with different surface functionalization on human HepG2 cells. Sci. Total Environ. 723, 138180. https://doi.org/10.1016/j.scitotenv.2020.138180.

Hernandez, L.M., Xu, E.G., Larsson, H.C.E., Tahara, R., Maisuria, V.B., Tufenkji, N., 2019. Plastic teabags release billions of microparticles and nanoparticles into tea. Environ. Sci. Technol. 53, 12300–12310. https://doi.org/10.1021/acs.est.9b02540.

Hesler, M., Aengenheister, L., Ellinger, B., Drexel, R., Straskraba, S., Jost, C., Wagner, S., Meier, F., von Briesen, H., Büchel, C., Wick, P., Buerki-Thurnherr, T., Kohl, Y., 2019. Multi-endpoint toxicological assessment of polystyrene nano- and microparticles in different biological models in vitro. Toxicol. in Vitro 61, 104610. https://doi.org/10.1016/j.tiv.2019.104610.

Hou, B., Wang, F., Liu, T., Wang, Z., 2021. Reproductive toxicity of polystyrene microplastics: in vivo experimental study on testicular toxicity in mice. J. Hazard. Mater. 405, 124028. https://doi.org/10.1016/j.jhazmat.2020.124028.

Hu, J., Qin, X., Zhang, J., Zhu, Y., Zeng, W., Lin, Y., Liu, X., 2021. Polystyrene microplastics disturb maternal-fetal immune balance and cause reproductive toxicity in pregnant mice. Reprod. Toxicol. 106, 42–50. https://doi.org/10.1016/j.reprotox.2021.10.002.

Huang, W., Yin, H., Yang, Y., Jin, L., Lu, G., Dang, Z., 2021. Influence of the co-exposure of microplastics and tetrabromobisphenol a on human gut: simulation in vitro with human cell Caco-2 and gut microbiota. Sci. Total Environ. 778, 146264. https://doi.org/10.1016/j.scitotenv.2021.146264.

Huang, T., Zhang, W., Lin, T., Liu, S., Sun, Z., Liu, F., Yuan, Y., Xiang, X., Kuang, H., Yang, B., Yang, B., Zhang, D., 2022. Maternal exposure to polystyrene nanoplastics during gestation and lactation induces hepatic and testicular toxicity in male mouse offspring. Food Chem. Toxicol. 160. https://doi.org/10.1016/j.fct.2021.112803.

Ibrahim, Y.S., Tuan Anuar, S., Azmi, A.A., Wan Mohd Khalik, W.M.A., Lehata, S., Hamzah, S.R., Ismail, D., Ma, Z.F., Dzulkarnaen, A., Zakaria, Z., 2021. Detection of microplastics in human colectomy specimens. JGH Open 5, 116–121.

Jeon, S., Clavadetscher, J., Lee, D.K., Chankeshwara, S.V., Bradley, M., Cho, W.S., 2018. Surface charge-dependent cellular uptake of polystyrene nanoparticles. Nanomaterials 8, 1–11. https://doi.org/10.3390/NANO8121028.

Jeon, S., Lee, D.K., Jeong, J., Yang, S.I., Kim, J.S., Kim, J., Cho, W.S., 2021. The reactive oxygen species as pathogenic factors of fragmented microplastics to macrophages. Environ. Pollut. 281, 117006. https://doi.org/10.1016/j.envpol.2021.117006.

Jin, Y., Lu, L., Tu, W., Luo, T., Fu, Z., 2019. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Sci. Total Environ. 649, 308–317. https://doi.org/10.1016/j.scitotenv.2018.08.353.

Jing, J., Zhang, L., Han, L., Wang, J., Zhang, W., Liu, Z., Gao, A., 2022. Polystyrene micro-/nanoplastics induced hematopoietic damages via the crosstalk of gut microbiota, metabolites, and cytokines. Environ. Int. 161, 107131. https://doi.org/10.1016/j.envint.2022.107131.

Kim, J., Maruthupandy, M., An, K.S., Lee, K.H., Jeon, S., Kim, J.-S., Cho, W.-S., 2021. Acute and subacute repeated oral toxicity study of fragmented microplastics in Sprague-dawley rats. Ecotoxicol. Environ. Saf. 228. https://doi.org/10.1016/j.ecoenv.2021.112964.

Lee, H.S., Amarakoon, D., Wei, C.I., Choi, K.Y., Smolensky, D., Lee, S.H., 2021. Adverse effect of polystyrene microplastics (PS-MPs) on tube formation and viability of human umbilical vein endothelial cells. Food Chem. Toxicol. 154, 112356. https://doi.org/10.1016/j.fct.2021.112356.

Lehner, R., Wohlleben, W., Septiadi, D., Landsiedel, R., Petri-Fink, A., Rothen-Rutishauser, B., 2020. A novel 3D intestine barrier model to study the immune response upon exposure to microplastics. Arch. Toxicol. 94, 2463–2479. https://doi.org/10.1007/s00204-020-02750-1.

Leslie, H.A., van Velzen, M.J.M., Brandsma, S.H., Vethaak, D., Garcia-Vallejo, J.J., Lamoree, M.H., 2022. Discovery and quantification of plastic particle pollution in human blood. Environ. Int. 163, 107199.

Li, B., Ding, Y., Cheng, X., Sheng, D., Xu, Z., Rong, Q., Wu, Y., Zhao, H., Ji, X., Zhang, Y., 2020a. Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. Chemosphere 244, 125492. https://doi.org/10.1016/j.chemosphere.2019.125492.

Li, D., Shi, Y., Yang, L., Xiao, L., Kehoe, D.K., Gun'ko, Y.K., Boland, J.J., Wang, J.J., 2020b. Microplastic release from the degradation of polypropylene feeding bottles during infant formula preparation. Nat. Food 1, 746–754. https://doi.org/10.1038/s43016-020-00171-y.

Li, Z., Zhu, S., Liu, Q., Wei, J., Jin, Y., Wang, X., Zhang, L., 2020c. Polystyrene microplastics cause cardiac fibrosis by activating Wnt/β-catenin signaling pathway and promoting cardiomyocyte apoptosis in rats. Environ. Pollut. 265, 115025. https://doi.org/10.1016/j.envpol.2020.115025.

Li, X., Zhang, T., Lv, W., Wang, H., Chen, H., Xu, Q., Cai, H., Dai, J., 2022. Intratracheal administration of polystyrene microplastics induces pulmonary fibrosis by activating oxidative stress and Wnt/β-catenin signaling pathway in mice. Ecotoxicol. Environ. Saf. 232, 113238. https://doi.org/10.1016/j.ecoenv.2022.113238.

Liao, Y.Liang, Yang, J.Yan, 2020. Microplastic serves as a potential vector for Cr in an in-vitro human digestive model. Sci. Total Environ. 703, 134805. https://doi.org/10.1016/j.scitotenv.2019.134805.

Liu, S., Wu, X., Gu, W., Yu, J., Wu, B., 2020. Influence of the digestive process on intestinal toxicity of polystyrene microplastics as determined by in vitro Caco-2 models. Chemosphere 256, 127204. https://doi.org/10.1016/j.chemosphere.2020.127204.

Liu, Ze, Sun, Y., Wang, J., Li, J., Jia, H., 2022. In vitro assessment reveals the effects of environmentally persistent free radicals on the toxicity of photoaged Tire Wear particles. Environ. Sci. Technol. 56, 1664–1674. https://doi.org/10.1021/acs.est.1c05092.

Liu, Zhiqiang, Zhuan, Q., Zhang, L., Meng, L., Fu, X., Hou, Y., 2022. Polystyrene microplastics induced female reproductive toxicity in mice. J. Hazard. Mater. 424, 127629. https://doi.org/10.1016/j.jhazmat.2021.127629.

Lu, L., Wan, Z., Luo, T., Fu, Z., Jin, Y., 2018. Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. Sci. Total Environ. 631–632, 449–458. https://doi.org/10.1016/j.scitotenv.2018.03.051.

Lu, L., Luo, T., Zhao, Y., Cai, C., Fu, Z., Jin, Y., 2019. Interaction between microplastics and microorganism as well as gut microbiota: a consideration on environmental animal and human health. Sci. Total Environ. 667, 94–100. https://doi.org/10.1016/j.scitotenv.2019.02.380.

Lu, K., Lai, K.P., Stoeger, T., Ji, S., Lin, Z., Lin, X., Chan, T.F., Fang, J.K.H., Lo, M., Gao, L., Qiu, C., Chen, S., Chen, G., Li, L., Wang, L., 2021. Detrimental effects of microplastic exposure on normal and asthmatic pulmonary physiology. J. Hazard. Mater. 416, 126069. https://doi.org/10.1016/j.jhazmat.2021.126069.

Luo, T., Zhang, Y., Wang, C., Wang, X., Zhou, J., Shen, M., Zhao, Y., Fu, Z., Jin, Y., 2019. Maternal exposure to different sizes of polystyrene microplastics during gestation causes metabolic disorders in their offspring. Environ. Pollut. 255, 113122. https://doi.org/10.1016/j.envpol.2019.113122.

Magrì, D., Veronesi, M., Sánchez-Moreno, P., Tolardo, V., Bandiera, T., Pompa, P.P., Athanassiou, A., Fragouli, D., 2021. PET nanoplastics interactions with water contaminants and their impact on human cells. Environ. Pollut. 271. https://doi.org/10.1016/j.envpol.2020.116262.

Mahadevan, G., Valiyaveettil, S., 2021. Understanding the interactions of poly(methyl methacrylate) and poly(vinyl chloride) nanoparticles with BHK-21 cell line. Sci. Rep. 11, 1–15. https://doi.org/10.1038/s41598-020-80708-0.

Meindl, C., Öhlinger, K., Zrim, V., Steinkogler, T., Fröhlich, E., 2021. Screening for effects of inhaled nanoparticles in cell culture models for prolonged exposure. Nanomaterials 11, 1–21. https://doi.org/10.3390/nano11030606.

Meng, X., Zhang, J., Wang, W., Gonzalez-Gil, G., Vrouwenvelder, J.S., Li, Z., 2022. Effects of nano- and microplastics on kidney: physicochemical properties, bioaccumulation, oxidative stress and immunoreaction. Chemosphere 288. https://doi.org/10.1016/j.chemosphere.2021.132631.

Mohamed Nor, N.H., Kooi, M., Diepens, N.J., Koelmans, A.A., 2021. Lifetime accumulation of microplastic in children and adults. Environ. Sci. Technol. 55, 5084–5096.

Mu, Y., Sun, J., Li, Z., Zhang, W., Liu, Z., Li, C., Peng, C., Cui, G., Shao, H., Du, Z., 2022. Activation of pyroptosis and ferroptosis is involved in the hepatotoxicity induced by polystyrene microplastics in mice. Chemosphere 291. https://doi.org/10.1016/j.chemosphere.2021.132944.

Palaniappan, S., Sadacharan, C.M., Rostama, B., 2021. Polystyrene and polyethylene microplastics decrease cell viability and dysregulate inflammatory and oxidative stress markers of MDCK and L929 cells in vitro. Expo. Heal. https://doi.org/10.1007/s12403-021-00419-3.

Park, Eun Jung, Han, J.S., Park, Eun Jun, Seong, E., Lee, G.H., Kim, D.W., Son, H.Y., Han, H.Y., Lee, B.S., 2020. Repeated-oral dose toxicity of polyethylene microplastics and the possible implications on reproduction and development of the next generation. Toxicol. Lett. 324, 75–85. https://doi.org/10.1016/j.toxlet.2020.01.008.

Prata, J.C., da Costa, J.P., Lopes, I., Duarte, A.C., Rocha-Santos, T., 2020. Environmental exposure to microplastics: an overview on possible human health effects. Sci. Total Environ. 702, 134455. https://doi.org/10.1016/j.scitotenv.2019.134455.

Qiao, J., Chen, R., Wang, M., Bai, R., Cui, X., Liu, Y., Wu, C., Chen, C., 2021. Perturbation of gut microbiota plays an important role in micro/nanoplastics-induced gut barrier dysfunction. Nanoscale 13, 8806–8816. https://doi.org/10.1039/d1nr00038a.

Rafiee, M., Dargahi, L., Eslami, A., Beirami, E., Jahangiri-rad, M., Sabour, S., Amereh, F., 2018. Neurobehavioral assessment of rats exposed to pristine polystyrene nanoplastics upon oral exposure. Chemosphere 193, 745–753. https://doi.org/10.1016/j.chemosphere.2017.11.076.

Ragusa, A., Svelato, A., Santacroce, C., Catalano, P., Notarstefano, V., Carnevali, O., Papa, F., Rongioletti, M.C.A., Baiocco, F., Draghi, S., 2021. Plasticenta: first evidence of microplastics in human placenta. Environ. Int. 146, 106274.

Rawle, D.J., Dumenil, T., Tang, B., Bishop, C.R., Yan, K., Le, T.T., Suhrbier, A., 2022. Microplastic consumption induces inflammatory signatures in the colon and prolongs a viral arthritis. Sci. Total Environ. 809, 152212. https://doi.org/10.1016/j.scitotenv.2021.152212.

Revel, M., Châtel, A., Mouneyrac, C., 2018. Micro (nano) plastics: a threat to human health? Curr. Opin. Environ. Sci. Heal. 1, 17–23.

Roje, Ž., Ilić, K., Galić, E., Pavičić, I., Turčić, P., Stanec, Z., Vrček, I.V., 2019. Synergistic effects of parabens and plastic nanoparticles on proliferation of human breast cancer cells. Arh. Hig. Rada Toksikol. 70, 310–314. https://doi.org/10.2478/aiht-2019-70-3372.

Roshanzadeh, A., Oyunbaatar, N.E., Ganjbakhsh, S.E., Park, S., Kim, D.S., Kanade, P.P., Lee, S., Lee, D.W., Kim, E.S., 2021. Exposure to nanoplastics impairs collective contractility of neonatal cardiomyocytes under electrical synchronization. Biomaterials 278, 121175. https://doi.org/10.1016/j.biomaterials.2021.121175.

Rudolph, J., Völkl, M., Jérôme, V., Scheibel, T., Freitag, R., 2021. Noxic effects of polystyrene microparticles on murine macrophages and epithelial cells. Sci. Rep. 11. https://doi.org/10.1038/s41598-021-95073-9.

Schwabl, P., Köppel, S., Königshofer, P., Bucsics, T., Trauner, M., Reiberger, T., Liebmann, B., 2019. Detection of various microplastics in human stool: a prospective case series. Ann. Intern. Med. 171, 453–457.

Schwarzfischer, M., Niechcial, A., Lee, S.S., Sinnet, B., Wawrzyniak, M., Laimbacher, A., Atrott, K., Manzini, R., Morsy, Y., Häfliger, J., Lang, S., Rogler, G., Kaegi, R., Scharl, M., Spalinger, M.R., 2021. Ingested nano- and microsized polystyrene particles surpass the intestinal barrier and accumulate in the body. NanoImpact 25, 100374. https://doi.org/10.1016/j.impact.2021.100374.

Shi, Q., Tang, J., Wang, L., Liu, R., Giesy, J.P., 2021. Combined cytotoxicity of polystyrene nanoplastics and phthalate esters on human lung epithelial A549 cells and its mechanism. Ecotoxicol. Environ. Saf. 213, 112041. https://doi.org/10.1016/j.ecoenv.2021.112041.

Stock, V., Böhmert, L., Lisicki, E., Block, R., Cara-Carmona, J., Pack, L.K., Selb, R., Lichtenstein, D., Voss, L., Henderson, C.J., Zabinsky, E., Sieg, H., Braeuning, A., Lampen, A., 2019. Uptake and effects of orally ingested polystyrene microplastic particles in vitro and in vivo. Arch. Toxicol. 93, 1817–1833. https://doi.org/10.1007/s00204-019-02478-7.

Stock, V., Böhmert, L., Dönmez, M.H., Lampen, A., Sieg, H., 2020. An inverse cell culture model for floating plastic particles. Anal. Biochem. 591, 113545. https://doi.org/10.1016/j.ab.2019.113545.

Stock, V., Laurisch, C., Franke, J., Dönmez, M.H., Voss, L., Böhmert, L., Braeuning, A., Sieg, H., 2021. Uptake and cellular effects of PE, PP, PET and PVC microplastic particles. Toxicol. in Vitro 70, 105021. https://doi.org/10.1016/j.tiv.2020.105021.

Stock, V., Böhmert, L., Coban, G., Tyra, G., Vollbrecht, M.-L., Voss, L., Paul, M.B., Braeuning, A., Sieg, H., 2022. Microplastics and nanoplastics: size, surface and dispersant – what causes the effect? Toxicol. in Vitro 80. https://doi.org/10.1016/j.tiv.2022.105314.

Stock, Valerie, Böhmert, L., Coban, G., Tyra, G., Vollbrecht, M.L., Voss, L., Paul, M.B., Braeuning, A., Sieg, H., 2022. Microplastics and nanoplastics: size, surface and dispersant – what causes the effect? Toxicol. in Vitro 80. https://doi.org/10.1016/j.tiv.2022.105314.

Sun, R., Xu, K., Yu, L., Pu, Yunqiu, Xiong, F., He, Y., Huang, Q., Tang, M., Chen, M., Yin, L., Zhang, J., Pu, Yuepu, 2021. Preliminary study on impacts of polystyrene microplastics on the hematological system and gene expression in bone marrow cells of mice. Ecotoxicol. Environ. Saf. 218, 112296. https://doi.org/10.1016/j.ecoenv.2021.112296.

Tallec, K., Huvet, A., Di Poi, C., González-Fernández, C., Lambert, C., Petton, B., Le Goïc, N., Berchel, M., Soudant, P., Paul-Pont, I., 2018. Nanoplastics impaired oyster free living stages, gametes and embryos. Environ. Pollut. 242, 1226–1235. https://doi.org/10.1016/J.ENVPOL.2018.08.020.

Tamargo, A., Molinero, N., Reinosa, J.J., Alcolea-Rodriguez, V., Portela, R., Bañares, M.A., Fernández, J.F., Moreno-Arribas, M.V., 2022. PET microplastics affect human gut microbiota communities during simulated gastrointestinal digestion, first evidence of plausible polymer biodegradation during human digestion. Sci. Rep. 12, 1–15. https://doi.org/10.1038/s41598-021-04489-w.

Tan, H., Yue, T., Xu, Y., Zhao, J., Xing, B., 2020. Microplastics reduce lipid digestion in simulated human gastrointestinal system. Environ. Sci. Technol. 54, 12285–12294. https://doi.org/10.1021/acs.est.0c02608.

Wang, Q., Bai, J., Ning, B., Fan, L., Sun, T., Fang, Y., Wu, J., Li, S., Duan, C., Zhang, Y., Liang, J., Gao, Z., 2020. Effects of bisphenol a and nanoscale and microscale polystyrene plastic exposure on particle uptake and toxicity in human Caco-2 cells. Chemosphere 254, 126788. https://doi.org/10.1016/j.chemosphere.2020.126788.

Wang, W., Zhang, J., Qiu, Z., Cui, Z., Li, N., Li, X., Wang, Y., Zhang, H., Zhao, C., 2022. Effects of polyethylene microplastics on cell membranes: a combined study of experiments and molecular dynamics simulations. J. Hazard. Mater. 429, 128323. https://doi.org/10.1016/j.jhazmat.2022.128323.

Warheit, D.B., Hart, G.A., Hesterberg, T.W., Collins, J.J., Dyer, W.M., Swaen, G.M.H., Castranova, V., Soiefer, A.I., Kennedy, G.L., 2001. Potential pulmonary effects of man-made organic fiber (MMOF) dusts. Crit. Rev. Toxicol. 31, 697–736.

Winkler, A., Santo, N., Ortenzi, M.A., Bolzoni, E., Bacchetta, R., Tremolada, P., 2019. Does mechanical stress cause microplastic release from plastic water bottles? Water Res. 166, 115082. https://doi.org/10.1016/j.watres.2019.115082.

Wright, S.L., Ulke, J., Font, A., Chan, K.L.A., Kelly, F.J., 2020. Atmospheric microplastic deposition in an urban environment and an evaluation of transport. Environ. Int. 136, 105411.

Wu, B., Wu, X., Liu, S., Wang, Z., Chen, L., 2019. Size-dependent effects of polystyrene microplastics on cytotoxicity and efflux pump inhibition in human Caco-2 cells. Chemosphere https://doi.org/10.1016/j.chemosphere.2019.01.056.

Wu, S., Wu, M., Tian, D., Qiu, L., Li, T., 2020. Effects of polystyrene microbeads on cytotoxicity and transcriptomic profiles in human Caco-2 cells. Environ. Toxicol. 35, 495–506. https://doi.org/10.1002/tox.22885.

Xiao, J., Jiang, X., Zhou, Y., Sumayyah, G., Zhou, L., Tu, B., Qin, Q., Qiu, J., Qin, X., Zou, Z., Zou, Z., Chen, C., 2022. Results of a 30-day safety assessment in young mice orally exposed to polystyrene nanoparticles. Environ. Pollut. 292. https://doi.org/10.1016/j.envpol.2021.118184.

Xu, M., Halimu, G., Zhang, Q., Song, Y., Fu, X., Li, Yongqiang, Li, Yansheng, Zhang, H., 2019. Internalization and toxicity: a preliminary study of effects of nanoplastic particles on human lung epithelial cell. Sci. Total Environ. 694, 133794. https://doi.org/10.1016/j.scitotenv.2019.133794.

Xu, J.L., Lin, X., Hugelier, S., Herrero-Langreo, A., Gowen, A.A., 2021. Spectral imaging for characterization and detection of plastic substances in branded teabags. J. Hazard. Mater. 418, 126328. https://doi.org/10.1016/j.jhazmat.2021.126328.

Yan, Z., Liu, Y., Zhang, T., Zhang, F., Ren, H., Zhang, Y., 2022. Analysis of microplastics in human feces reveals a correlation between fecal microplastics and inflammatory bowel disease status. Environ. Sci. Technol. 56, 414–421. https://doi.org/10.1021/acs.est.1c03924.

Yu, X., Lang, M., Huang, D., Yang, C., Ouyang, Z., Guo, X., 2022. Photo-transformation of microplastics and its toxicity to Caco-2 cells. Sci. Total Environ. 806, 150954. https://doi.org/10.1016/j.scitotenv.2021.150954.

Zaheer, J., Kim, H., Ko, I.O., Jo, E.-K., Choi, E.-J., Lee, H.-J., Shim, I., Woo, H.-J., Choi, J., Kim, G.-H., Kim, G.-H., Kim, J.S., 2022. Pre/post-natal exposure to microplastic as a potential risk factor for autism spectrum disorder. Environ. Int. 161. https://doi.org/10.1016/j.envint.2022.107121.

Zhang, Q., Xu, E.G., Li, J., Chen, Q., Ma, L., Zeng, E.Y., Shi, H., 2020. A review of microplastics in table salt, drinking water, and air: direct human exposure. Environ. Sci. Technol. 54, 3740–3751. https://doi.org/10.1021/acs.est.9b04535.

Zhu, K., Jia, H., Sun, Y., Dai, Y., Zhang, C., Guo, X., Wang, T., Zhu, L., 2020. Enhanced cytotoxicity of photoaged phenol-formaldehyde resins microplastics: combined effects of environmentally persistent free radicals, reactive oxygen species, and conjugated carbonyls. Environ. Int. 145, 106137. https://doi.org/10.1016/j.envint.2020.106137.