



Review

Potential lifetime effects caused by cellular uptake of nanoplastics: A review

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ABSTRACT

Plastics have been used for about 100 years, and daily-use products composed of plastics are now prevalent. As a result, humans are very easily exposed to the plastic particles generated from the daily-use plastics. However, studies on cellular uptake of nanoplastics in “human cells” have only recently begun to attract attention. In previous studies, definitions of nanoplastics and microplastics were vague, but recently, they have been considered to be different and are being studied separately. However, nanoplastics, unlike plastic particles of other sizes such as macro- and microplastics, can be absorbed by human cells, and thus can cause various risks such as cytotoxicity, inflammation, oxidative stress, and even diseases such as cancer^{82, 83} and diabetes (Fan et al., 2022; Wang et al., 2023). Thus, in this review, we defined microplastics and nanoplastics to be different and described the potential risks of nanoplastics to human caused by cellular uptake according to their diverse factors. In addition, during and following plastic product usage a substantial number of fragments of different sizes can be generated, including nanoplastics. Fragmentation of microplastics into nanoplastics may also occur during ingestion and inhalation, which can potentially cause long-term hazards to human health. However, there are still few *in vivo* studies conducted on the health effect of nanoplastics ingestion and inhalation.

1. Introduction

Since plastics are light in weight, convenient, low-priced, and can be easily formed into various sizes and shapes by different processes as occasion demands, they became the most widely used materials in the world. At present, plastics can be easily found everywhere within reach, including the home, the office, and even outdoors. Synthetic plastics were first invented by Leo H. Baekland (Crespy et al., 2008) for electric and mechanical use, and, since then, numerous synthetic plastics have been invented for various process needs. Indeed, such plastics have become increasingly essential to the daily life of humans. According to Euromap, in 2015, the United States and China produced the largest amounts of plastics in the world, at 36.004 kt and 63.771 kt, respectively (Hossain et al., 2021). According to a report by the United Nations (UN), consumer and institutional products and packaging accounted for total 56.6% of all plastics produced between 2002 and 2014 (Tsakana and Rucevska, 2020). This represents a very large amount of plastic in total, considering that more than 380 million tonnes of plastics are produced every year (Rafey and Siddiqui, 2021; Sahajwalla and Gaikwad, 2018; Alabi et al., 2019).

However, the increased use of plastics in daily life such as plastic containers for the delivery of foods, along with the use of personal protective equipment such as masks and gloves during COVID-19, has raised great concerns about the disposal and use of plastics. Since annual production of biodegradable plastics is less than 1% of the total plastic production (Folino et al., 2020), most of the plastics do not decompose like natural materials, they will remain for extended periods of 450 to 1000 years once they are discarded into the natural environment (Gazal and Gheewala, 2020). The production of plastics has increased to an all-time high, and plastic wastes are still being accumulated (Rafey and Siddiqui, 2021). Such synthetic plastic wastes can be broken down into very small pieces of plastic particles when exposed to the environment, and may even include granules, beads, fragments, and fibers that are intentionally designed to be very small. Primary plastic particles are defined as those that are intentionally fabricated to the desired size, while secondary plastic particles arise from the fragmentation and degradation of plastic particles during material use, or by being exposed to natural weathering processes such as UV light, wind, and waves after being discharged into the environment (Zeng, 2018; Talvitie et al., 2017; C  zar et al., 2014).

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Table 1
Various plastic particles existing in daily-use products.

Daily-use products	Plastic particle concentration	Factors examined	References
Bottles and Packaging	Baby bottles	16,200,000 particles/L	Li et al.(2020) Zuccarello et al.(2019)
	Bottles	Adults: 1,531,524 particles/kg/day; Children: 3,350,208 particles/kg/day	
	Bottled water	5 - 500 particles/L	Koelmans et al.(2019)
	Paper cups for use with hot water	250,000 particles/L	Ranjan et al.(2021)
Food and drinks	Packaging	3 - 9 items/container	Zhang et al.(2021a)
	Salt	50 - 280 particles/kg	
	Teabags	14,900,000,000 MPa particles/cup	Iniguez et al.(2017) Hernandez et al.(2019)
	Milk	6.5 ± 2.3 particles/L	Kuttralam-Muniasamy et al. (2020)
Personal care and cosmetic products (PCCPs)	Beer	5 - 85 particles/L	Liebezeit and Liebezeit(2014) Lei et al.(2017)
	Facial cleansers	25.04 ± 10.69 mg/g	
	Shower gels	17.80 ± 7.50 mg/g	Lee et al.(2021) Carr et al.(2016)
	Eye-glasses	1380 - 62,539 g/L	
Other daily necessities	Toothpaste	18.5 mg/g	Po et al.(2020)
	Drinking straws	75 particles/g	

Many plastic particles have been found in daily-use products and indoor durable goods. As mentioned above, primary plastic particles can be generated during the manufacturing process of daily-use products and indoor durable goods. Meanwhile, secondary plastic particles may also occur by human behavior such as discarding and using. Thus, humans are easily exposed to the plastic particles in daily life regardless of primary or secondary plastic particles. Numerous plastic particles have been detected in baby products such as baby bottles, pacifiers, and baby lotions, and the estimated exposure for the baby is approximately 1.6 million particles/year (Li et al., 2020). As humans grow up, a variety of plastic products are used in daily life. Children generally drink milk (Kuttralam-Muniasamy et al., 2020) every day for their growth, and often use plastic straws; children play with plastic toys, and sometimes even put them in their mouths. During adolescence, females begin menstruating and typically use sanitary pads for approximately half of their lifespan. Nevertheless, it is concerning to note that these pads contain plastic materials (Mishra and Das, 2021). Many people also smoke, drink alcohols such as beers, and use cosmetics such as mascara, lipstick, and face and body scrubs that require direct contact with the skin which also contain plastic particles (Belzagui et al., 2021; Shen et al., 2021; Liebezeit and Liebezeit, 2014; Gouin et al., 2011; Chang, 2015; Napper et al., 2015; Kalčíková et al., 2017). In addition, plastic food packaging containers for delivery (Kedzierski et al., 2020; Du et al., 2020; Sobhani et al., 2020), paper cups (Ranjan et al., 2021) for coffee, hot water (Koelmans et al., 2019), or tea (Hernandez et al., 2019), and water bottles (Zuccarello et al., 2019) in the office are frequently used on a day-to-day basis in the office and outdoors. So it is no exaggeration to say that humans live with plastic particles throughout their lifetimes. To add to this existing problem, the masks that have traditionally been used for respiratory syndromes or protection from fine dust have more recently entered daily, worldwide use against SARS-COV-2. These also contain fibers, which can be degraded into micro- or nano-sized plastic particles during use (Ma et al., 2021; Aragaw, 2020; Wang et al., 2021). The diversity of polymer sizes, shapes, and typed that have been found in daily-use products are summarized in Table 1. These plastic particles can be micro- or nano-sized. Airborne plastic particles can be introduced into the human body by inhalation into the human respiratory systems (Prata, 2018; Chen et al., 2020). Alternatively, they can be ingested during food/drink consumption.

Although microplastics generated by the daily-use products above have attracted much research attention, and have intrigued many researchers, there are three remaining problems with such studies. First, the term microplastic is currently ambiguous in definition, as regardless

of the actual size or characteristics of these plastic particles, micro-sized plastic particles and nano-sized plastic particles which are smaller than 5 mm are generally all referred to as *microplastics* (Mitrano et al., 2021b). Several articles had demonstrated that the definition of plastic particles should be based not only on sizes, but also on additional characteristics such as shape (Gigault et al., 2021; Mitrano et al., 2021b). Hence, in this review, we define the plastic particles which may cause human health risks due to cellular uptake by their nano-sizes as *nanoplastics* (<1 µm) (Ma et al., 2021). Recently, Julien et al. demonstrated the major differences between *nanoplastics* and *microplastics* (Gigault et al., 2021), including distinct uptake, transportation, accumulation pathways, and distinct properties. Moreover, the *nanoplastics* have more affinity towards environmental pollutants and microbial pathogens as they have enhanced surface interactions due to larger surface area per mass ratio compared to *microplastics*. Therefore, compared to the *microplastics*, the modification of surface chemistry on the *nanoplastics* can be more readily facilitated by harmful absorbants. In particular, *microplastics* can be accumulated in the human body such as lung (Jenner et al., 2022), liver (Horvatits et al., 2022) and kidney (Deng et al., 2017) by ingestion, inhalation and skin contact, but are not easily taken up at the cellular level, whereas the nano-sized plastic particles are readily absorbed by the cells for their higher affinity to the lipid bilayers (Zhang et al., 2021c; Singh et al., 2022; Zhang et al., 2022b).

Secondly, in spite of exposure of human beings to plastic particles, the existing research has been mainly focused on the environment. Even the majority of *in vivo* and *in vitro* studies on plastic particles have focused on the risks to marine systems (Lu et al., 2019; Yan et al., 2021; Fueser et al., 2020; Sun et al., 2017; Galloway et al., 2017), while relatively few such studies have been related to the human body. However, it should be borne in mind that *nanoplastics* can also be generated by the digestive fragmentation of micro-, meso- and macro-sized plastic particles (Dawson et al., 2018). Hence, *microplastics* can be broken down by specific processes or chemicals reactions in the intestinal or pulmonary tract to generate *nanoplastics* that can then undergo cellular uptake. In turn, cellular uptake causes serious problems such as cytotoxicity (He et al., 2020; Ding et al., 2021), inflammation (Hu and Palic, 2020), oxidative stress (Thubagere and Reinhard, 2010; Prietl et al., 2014; Florance et al., 2021), and DNA damage (Paget et al., 2015). Therefore, the impact of *nanoplastics* on human health should be given as much attention as their impact on the environment.

Finally, bulk plastic particles and *microplastics* can be easily and rapidly fragmented by diverse stressors such as digestion and

environmental conditions and generate unstable sizes and shapes of smaller nanoplastics (Gigault et al., 2021). Therefore, the plastic particles produced from daily-use products shown in Table 1 can be deformed and fragmented into nanoplastics, which indicates that nanoplastics can be generated by the fragmentation or deformation of microplastics from the environment and also in the human body. However, according to our knowledge, there are still few studies related to fragmentation microplastics in the human body.

As described above, the cellular uptake of nanoplastic has been studied mainly concerning marine systems, and is widely known to depend upon the size, shape, surface charge, concentration, polymer type, and cell type. Nevertheless, studies on the morphological and physicochemical properties of nanoparticles have not been sufficient to date. Cells are the basic structural and functional units of living organisms; hence, when the cells are damaged, the whole organism can be affected. Hence, the extent to which the nanoplastic properties affect human cells should be studied and reviewed. The present review mainly describes the cellular uptake of nanoplastics and the diverse factors of nanoplastics that can affect the cellular uptake level.

2. Health risks of nanoplastics due to cellular uptake

Human exposure to plastic particles can occur mainly by ingestion, inhalation, or skin contact. According to recent studies, however, ingestion is the primary cause of exposure to, and the toxicity of nanoplastics. As we drink and eat, the daily use of products such as packaging (Shopova et al., 2020), water bottles, teabags, paper cups, toothbrushes, toothpaste (Carr et al., 2016), tap water (Kosuth et al., 2018), and indoor dust (Zhang et al., 2022a) allow the human to uptake nanoplastics by ingestion. Due to the wide variety of such daily-use products, the gastrointestinal tract is exposed to more microplastics and nanoplastics than any other organ. Meanwhile, the second most significant pathway of nanoplastics exposure is inhalation. Airborne (Briain et al., 2020) nanoplastics are mainly generated by textiles such as towels and clothes, and, as noted in the Introduction, both microplastics and nanoplastics are present in the masks that have recently become a normal feature of daily life worldwide due to the influence of SARS-COV-2. Consequently, inhalation has also become a high-risk exposure pathway. Thus, microplastics and nanoplastics can be drawn by inhalation into the lungs, where the fine tissue barriers less than 1 μm are significantly thin to allow small plastic particles to penetrate the capillaries (Lehner et al., 2019b). Thus, microplastics and nanoplastics can be circulated throughout the whole body via the blood vessels (Lehner et al., 2019a).

The third-ranked exposure route is that of skin contact, and nanoplastics have also been found in personal care and cosmetic products (PCCPs) (Xiong et al., 2020; Hernandez et al., 2017). Since microplastics and nanoplastics are typically hydrophobic (Yu et al., 2019; Liu et al., 2015; Zhang and Goss, 2021), they may be expected to enter the body through sweat glands, skin wounds, or hair follicles, and especially through the skin injury (Schneider et al., 2009). Then, it is highly probable that the primary permeation pathway via the skin contact is the intercellular pathway, where the nanoparticles diffuse through the lipid matrix between the corneocytes (Bouwstra et al., 2000). However, R. Alvarez-Román et al. (2004) reported that the exposure of pig skin tissue to fluorescent polystyrene (PS) particles of 20 nm and 200 nm in size for 0.5–2 h resulted in a large accumulation at the entrance of the pig hair follicle, with both sizes being unable to infiltrate the keratin layer and penetrate deep into the skin tissue. Even so, there is currently very little evidence as to whether nanoplastics can penetrate the human skin (Huang et al., 2022) as there is only one article which has studied the skin penetration of nanoplastics so far according to our knowledge (Alvarez-Román et al., 2004). Nevertheless, nanoplastics smaller than 100 nm may be capable of human skin penetration (Revel et al., 2018), and direct contact with the genitals can occur due to the daily use of products such as sanitary pads, which could potentially affect the uterus and ovaries. Indeed, PS microplastics and nanoplastics have been shown

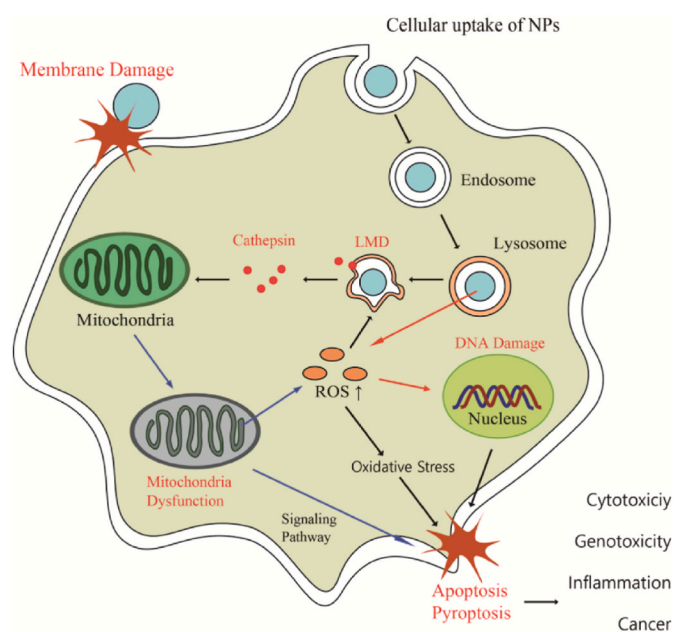


Fig. 1. The cellular uptake mechanism of nanoplastics inducing cellular damage.

to cause apoptosis, pyroptosis, fibrosis, and even reproductive disorders in the granulosa cells of the ovaries due to oxidative stress (An et al., 2021; Hou et al., 2021; Wang et al., 2019). Hence, risks such as oxidative stress and cell death may occur due to cellular uptake.

When the human body uptakes the nanoplastics, macromolecules such as proteins, lipids, phospholipids, and carbohydrates can form biological protein coronas around the nanoplastics (Mahmoudi et al., 2011). The formation of coronated nanoplastics causes higher cellular uptake level (Nasser and Lynch, 2016) by immunoglobulin (IgG) (Smith et al., 1995). When the nanoplastics come into contact with the cell membrane, about 50% of the nanoplastics can be absorbed, and can trigger uptake via endocytosis (Lesniak et al., 2013; Kolandhasamy et al., 2018).

As shown in Fig. 1, the effects due to this endocytosis mechanism are various. First, the nanoplastics enter the cytoplasm through the early endosomes, which then mature into late endosomes and subsequently bind to the lysosomes (Mosquera et al., 2018). The nanoplastics then primarily accumulate in the lysosomes (Liu et al., 2021), where they generate reactive oxygen species (ROS) that can lead to lysosomal membrane damage (LMD) (Avio et al., 2015). When lysosomal cathepsin is released into the cytoplasm in response to LMD (Guicciardi et al., 2004), it causes a DNA mutation in the mitochondria, thus resulting in mitochondrial dysfunction and further ROS release (Yuan et al., 2019; Auten and Davis, 2009). These increased levels of ROS lead to oxidative stress (Xie et al., 2020) and, through these processes, a specific signaling pathway is generated that results in apoptosis, necrosis, and pyroptosis of cells (Hou et al., 2021; Guo et al., 2013). Effects such as cytotoxicity (Hwang et al., 2019; Hwang et al., 2020), genotoxicity (Poma et al., 2019; Cole et al., 2020), and inflammation may occur via this mechanism. Cancer is also known potential risk caused by the cellular uptake of nanoplastics because the presence of ROS promotes the growth and proliferation of cancer cells (Poillet-Perez et al., 2015; Roje et al., 2019). Inorganic nanoparticles such as silver nanoparticles are known to generate ROS, which can pose a risk to human health (Böhmer et al., 2014). However, nanoparticles are typically considered to be relatively safe because they can be readily cleared from the human body as their characteristics are associated with optimal clearance (Longmire et al., 2008). In contrast, nanoplastics that accumulate in human body can pose a higher potential risk, as they cannot be easily removed and can

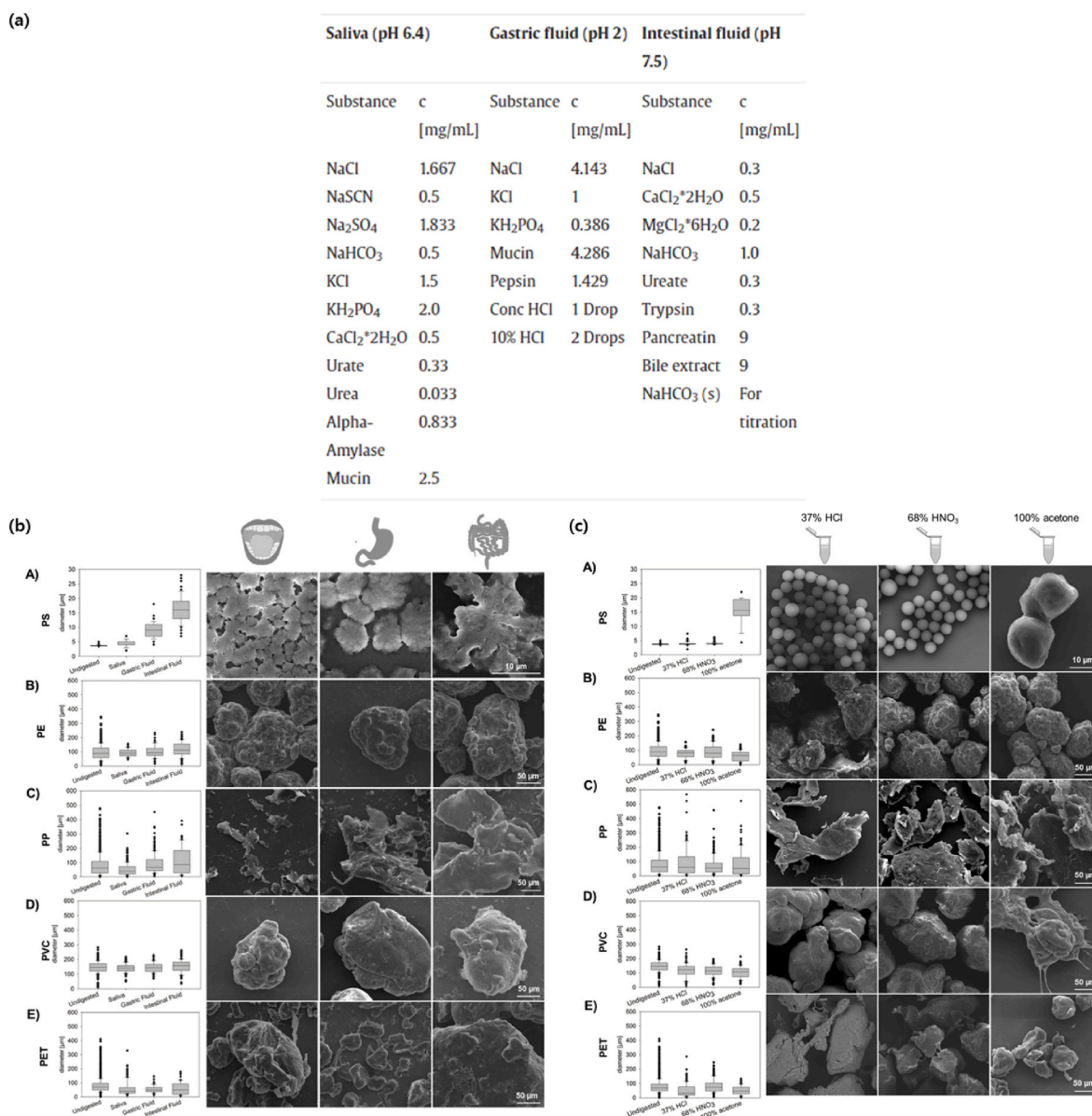


Fig. 2. The morphological modification of plastic particles during *in vitro* digestion. (Reproduced with permission from ref (Stock et al., 2020), Copyright 2020, Elsevier). (a) The compositions of the artificial digestion media. (b) The size distributions of polystyrene (PS), polyethylene (PE), polypropylene (PP), poly(vinyl chloride) (PVC), and polyethylene terephthalate (PET) microplastics after digestion in artificial saliva (left), gastric fluid (middle) and intestinal fluid (right). (c) The changes in the characteristics of undigested particles after treatment 37% HCl, 68% HNO₃ and 100% acetone.

persistently exist in the intra-lysosomal membranes (Hornung et al., 2008). Additionally, both nanoparticles and nanoplastics can induce vascular endothelial leakiness at the micro-scale level (Peng et al., 2019; Wei et al., 2022), potentially contributing to adverse effects, especially in cancer patients, where cancer invasion and metastasis can be accelerated. Hence, the unremoved nanoplastics continue to circulate in the body and can constantly present health risks (Van Cauwenberghe and Janssen, 2014).

Two forms of cell death due to nanoplastics, namely apoptosis and pyroptosis, have been studied to date. Apoptosis is a type of programmed cell death, in which two signaling pathways exist, namely: the death-inducing signaling complex (DISC), and intrinsic signaling through mitochondria (Xu and Shi, 2007). These signaling pathways can lead to the formation of apoptosomes that activate the protein degradation enzymes, initiator caspases (initiator caspase-2, initiator caspase-8, initiator caspase-9, and initiator caspase-10), and common effector caspases (common effector caspase-3, common effector

caspase-6, and common effector caspase-7). These, in turn, decompose the cytoplasm and specific proteins in the nucleus to induce apoptosis (Fink and Cookson, 2005). In particular, PS nanoplastics activate the Wnt/ β -catenin signaling pathway and induce apoptosis of the cardiomyocyte and granulosa cells in mice. Meanwhile, pyroptosis is a form of cell death associated with proinflammatory signals and inflammation, and relies on caspase-1 activation (Bergsbaken and Cookson, 2007). Caspase-1 activates the inflammatory cytokines IL-1 β and IL-18, and induces physical rupture of cells in the immune, central nervous, and cardiovascular systems (Man et al., 2017). Plasma membrane pores that respond to caspase-1 extinguish the cellular ionic gradients and cause increased osmotic pressure, water influx, cell swelling, and, ultimately, osmotic lysis, thereby releasing the intracellular contents (Yang et al., 2015). The rupture of the plasma membrane, and the release of proinflammatory intracellular contents, lead to increased cell size and chromosomal DNA division, thus inducing pyroptosis and inflammation. Accordingly, nanoplastics may cause various and serious risks to the

human body through cellular uptake.

As described above, the level of cellular uptake varies according to the form of endocytosis and, hence, the cell type. Currently, the most commonly studied cells concerning the cellular uptake of nanoplastics are caco-2 cells and macrophages. By contrast, studies on other types of cells are rare, so a more diverse range of cells must be studied.

Moreover, the modification of nanoplastics properties such as their size, surface chemistry or structure can also be triggered by the internal environment conditions such as pH and temperature of the human body, thereby leading to variations in the level of cellular uptake. For example, as shown in Fig. 2, changes in the shapes and sizes of microplastics were observed by Stock et al. (2020) via artificial *in vitro* digestion in accordance with DIN ISO 19738. The authors also emphasized that irregular surfaces could be created, thereby resulting in morphological modification to the microplastics and also their fragmentation into the nanoplastics inside the human body. In addition, the changes in the characteristics of particles that remained undigested by the various artificial digestion media were examined after treatment with positive control media (37% HCl, 68% HNO₃, and 100% acetone) in order to investigate the resistance of the various plastic particles. The study results suggest that the level of cellular uptake could be affected by the *in vivo* modification of micro- and nanoplastics, thereby resulting in more serious risks, just as in the case of microplastics fragmentation and nanoplastics modification by the external environment.

3. Factors affecting the cellular uptake of nanoplastics

After plastic was commercialized and became widely used in daily-use products, research on the uptake of plastics particles into tissues using Peyer's patches became of interest between the 1980s and 2000s. In recent years, active studies have been widely performed on the toxicity and inflammatory reactions of cells due to plastic particles. As outlined in Section 2, these harmful effects can be caused by cellular uptake.

However, to date, studies on nanoplastics and their cellular uptake have mainly focused on non-human cells such as plants (Yin et al., 2021; Bhargava et al., 2018; Chen et al., 2022; Weert et al., 2019), microorganisms (Bergami et al., 2017; Venâncio et al., 2019; Eliso et al., 2020; Besseling et al., 2014; Yang et al., 2020; Larue et al., 2021) and zebrafish (Sendra et al., 2021a; Barfá et al., 2020; Lin et al., 2016; Skjolding et al., 2017; Van Pomerén et al., 2017; Pitt et al., 2018), while studies on human cells have only recently begun to gain interest. Therefore, most of the reviews on nanoplastics and cells that have been written to date include studies on both human and non-human cells (Sharma and Chatterjee, 2017; De-la-Torre, 2020; Ali et al., 2021). However, human cells and non-human cells have distinct structures, properties and specialized functions. Thus, human cells and the cells of non-human cells should be reviewed separately.

From the perspective of drug delivery systems, it has been demonstrated that the size, shape, and surface properties of nanoparticles have various effects on cellular uptake (Verma and Stellacci, 2009). Hence, the therapeutic effect can be greatly assisted via optimization of these cellular uptake factors. The biomedical properties of nanoparticles provide a broader biomedical knowledge for present-day research on nanoplastics (Mitrano et al., 2021a).

Moreover, factors that increase the cellular uptake of nanoplastics can lead to fatal toxicity. The main factors that influence the cellular uptake of nanoplastics include concentration (Domenech et al., 2020; Shi et al., 2021a; Hesler et al., 2019), size (Xu et al., 2019; DeLoid et al., 2021; Shi et al., 2021b; Forte et al., 2016; Fröhlich et al., 2012; Wang et al., 2020), shape (Dasgupta et al., 2014; Choi et al., 2020; Rubio et al., 2020; Tanaka et al., 2021; Choi et al., 2021), surface properties (Loos et al., 2014; Anguissola et al., 2014; Li et al., 2022; Roshanzadeh et al., 2020; Lunov et al., 2011; Qiao et al., 2021; Han et al., 2021), etc. The mechanisms of these factors are therefore described, and the associated risks to human cells are reviewed, in the following subsections.

3.1. Concentration

As indicated in Table 1, various concentrations of nanoplastics have been generated from daily-use products. According to the probabilistic lifetime exposure model prediction, children are exposed to approximately 184 ng/day of plastic particles, while adults are exposed to 583 ng/day, which also can be irreversibly accumulated during the lifetime (Nor et al., 2021). Moreover, since plastic particles in the meso- and micro-size ranges can be broken down in the human body to form nanoplastics, there should be more nanoplastics present than the detected amount. For example, an analysis using masks has shown that the amount of nanoplastics present in one N95 mask is about 1.6 µg, which was 10⁸ times the amount of microplastics in the same masks (Ma et al., 2021). However, since nanoplastics are very difficult to separate and identify due to their small size compared to microplastics, accurate concentration measurement of nanoplastics still remains a challenge, especially in the complex environmental media (Zhang et al., 2022a; Blanco et al., 2021).

Domenech et al. added PS nanoplastics to human colorectal adenocarcinoma-derived Caco-2 and HT29 cells, as well as to the lymphoblast-like Raji-B cells, at concentrations ranging from 0 µg/mL to 200 µg/mL¹¹³, to confirm that uptake into each of the three cell types increased with increasing concentration. Further, while no significant genotoxicity occurred, cellular uptake was found to assist the nanoplastics in crossing the epithelial barrier of the digestive system. Likewise, Shi et al. observed the internalization of 100 nm PS nanoplastics in human lung epithelial A549 cells at various concentrations, and found that the cytotoxicity was occurred only at a very high concentration of 200 µg/mL¹¹⁴.

While the above results indicate that cytotoxicity and genotoxicity are not the main risks, there are other cellular effects that can be influenced by nanoplastics concentration. For example, Hesler et al. (2019) found that the uptake of PS nanoplastics at concentrations above 5 µg/mL caused a significant increase in the metabolic activity of intestinal cells and placental cells. Moreover, a sharp increase in the uptake of 50–100 nm PS beads into Caco-2 cells was observed at a concentration of 25 µg/mL. As the level of uptake increases with increasing concentration and also influences mitochondrial metabolism, these results can be attributed to changes in the mitochondrial membrane potential, which lead to a high osmotic pressure of the inner mitochondrial membrane and hence, to mitochondrial swelling (Vander Heiden et al., 1997). Through this mechanism, rupture of the outer mitochondrial membrane eventually occurs, and apoptosis-inducing factors are thereby released. Even though cells that do not experience immediate cytotoxicity upon exposure to small concentrations of nanoplastics, changes in the membrane-bound proteins lead to a decrease in membrane fluidity (Schirizzi et al., 2017), thus allowing the intracellular accumulation (Bano and Prehn, 2018) of apoptosis-inducing factors.

These results suggest that concentration can be an important factor of cellular uptake. While nanoplastics may not directly cause immediate cytotoxicity or genotoxicity, they do adversely influence mitochondrial metabolism and allow for the continuous intracellular accumulation of apoptosis-inducing factors, posing persistent risk to cells as they cannot be easily removed from the human body (Hornung et al., 2008). Therefore, in order to confirm the effects of various concentrations, it is necessary to focus on continuous exposure of nanoplastics, and also concentrate upon the mitochondrial disease rather than the cell viability in future studies.

3.2. Size

The human body is exposed to the wide size distribution of plastic particles during daily life and, as noted above, microplastics can be transformed into nanoplastics of various sizes. Unlike microplastics, nanoplastics can be internalized by cells due to their small size and can

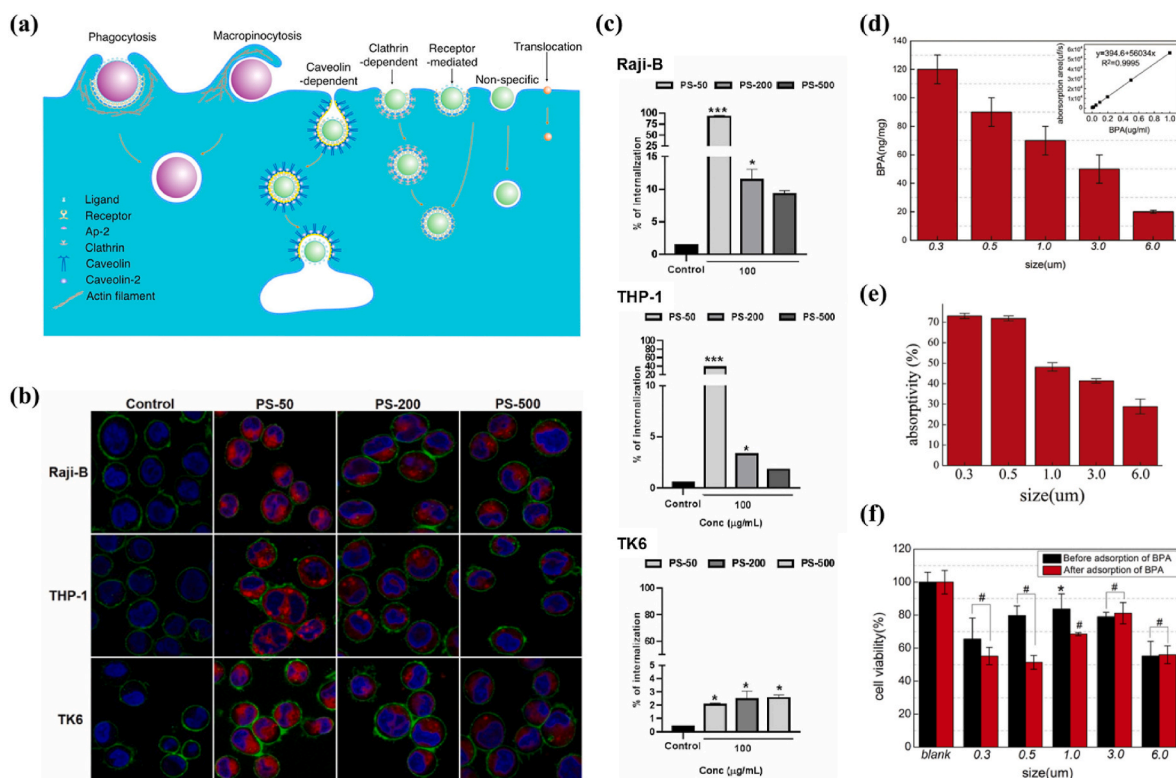


Fig. 3. Size-dependent cellular uptake. (a) A schematic diagram showing the various size-dependent endocytosis mechanisms (reproduced with permission from ref (Zhang et al., 2015), Copyright 2015, Elsevier). (b) Confocal image of PS nanoplastics cellular uptake in blood cells and (c) the percentage of cellular uptake in Raji-B, THP-1, and TK6 cells (reproduced with permission from ref (Tavakolpournegari et al., 2023), Copyright 2023, Elsevier). (d) The amount of BPA adsorbed by various sizes of PS nanoplastics. (e) The uptake rate of various sizes of PS nanoplastics by Caco-2 cells. (f) *In vitro* Caco-2 cells after exposure to various sizes of PS nanoplastics (reproduced with permission from ref (Wang et al., 2020), Copyright 2020, Elsevier).

damage the cellular structure. Therefore, the size of nanoplastics is a major and the most studied factor.

In this respect, the size of nanoparticles that are used in drug delivery is the most widely considered factor. All cellular uptake pathways for nanoparticles are known to vary in a size-dependent manner. Size-dependent endocytosis in drug delivery helps to provide an enhanced therapeutic effect. Similarly, the cellular uptake mechanism of nanoplastics is known to be size-dependent and, in contrast to the case of drug delivery, this size-dependent mechanism is the basis for incurring severe risks. As shown in Fig. 3a¹¹⁹, size-dependent endocytosis can be classified into phagocytosis, pinocytosis, non-specific endocytosis, and translocation.

Phagocytosis is mainly responsible for the uptake of relatively large particles (≥ 500 nm) (Uribe-Querol et al., 2020), and can even allow the uptake of particles that cannot be absorbed via other endocytosis pathways. In phagocytosis, foreign ligands bind to various receptors on the cell surface and induce a rearrangement of the actin cytoskeleton, thereby triggering diverse signals (Gagnon et al., 2002). Consequently, the cell membrane closes, and phagosomes are formed to internalize the particles. Thereafter, early phagosomes undergo sequential fusion and fission with endocytic vesicles to form late phagosomes and, finally, the late phagosomes are converted into phagolysosomes via various levels of maturation (Flannagan et al., 2009).

Pinocytosis is classified into macropinocytosis and micropinocytosis according to actin-dependence (Kruth et al., 2005). Macropinocytosis is an actin-dependent pathway that can rapidly and non-specifically encapsulate particles in the size range of 200–500 nm (Zhao and Stenzel, 2018). Macropinocytosis can help polymers materials such as nanoplastics enter the cytoplasm by creating non-specific entry pathways (Lim and Gleeson, 2011). With the help of growth factors on the outer cell membrane, macropinosomes are formed to internalize

nanoplastics via the activation of actin and microfilaments connected to the plasma membrane (Mercer and Helenius, 2009).

By contrast, micropinocytosis is an actin-independent pathway that encapsulates particles smaller than 200 nm, and forms small vesicles that can uptake smaller amounts of nanoplastics than do the macropinosomes via membrane invagination and scission (Anzinger et al., 2010). The micropinocytosis pathway is further sub-divided into clathrin-dependent and caveolin-dependent endocytosis, each of which can uptake very small nano-sized particles (Foroozandeh and Aziz, 2018). In the caveolin-dependent endocytosis pathway, bulb-shaped caveolae are generated by peripheral membrane proteins (cavins) and integral membrane proteins (caveolins). Particles are then uptaken by the caveolae, which can be then fuse to form early endosomes (Rennick et al., 2021). In clathrin-dependent endocytosis, vesicles for the uptake of particles are formed by clathrins with adapter proteins such as adapter protein 2 (AP2) and accessory proteins such as AP180 and epsin (McMahon and Boucrot, 2011). After internalization, the vesicle, receptors, and ligands used during clathrin-dependent and caveolin-dependent endocytosis are returned to the plasma membrane for recycling.

Once the nanoplastics have been internalized by one or other of the above processes, the lysosome should become activated in order to eliminate the particles by digestion (Safitig and Klumperman, 2009). However, the nanoplastics cause lysosome dysfunction that enables the particles to accumulate intracellularly and present health risks (Hu and Palic, 2020).

Thus, when Xu et al. (2019) exposed the A549 cell line to 25 nm and 75 nm of PS nanoplastics, the 25 nm particles were more abundantly and easily internalized than the 70 nm particles. After cellular uptake, the 70 nm nanoplastics did not affect cell viability at concentrations of 100 μg/mL or lower, whereas the 25 nm nanoplastics showed significant

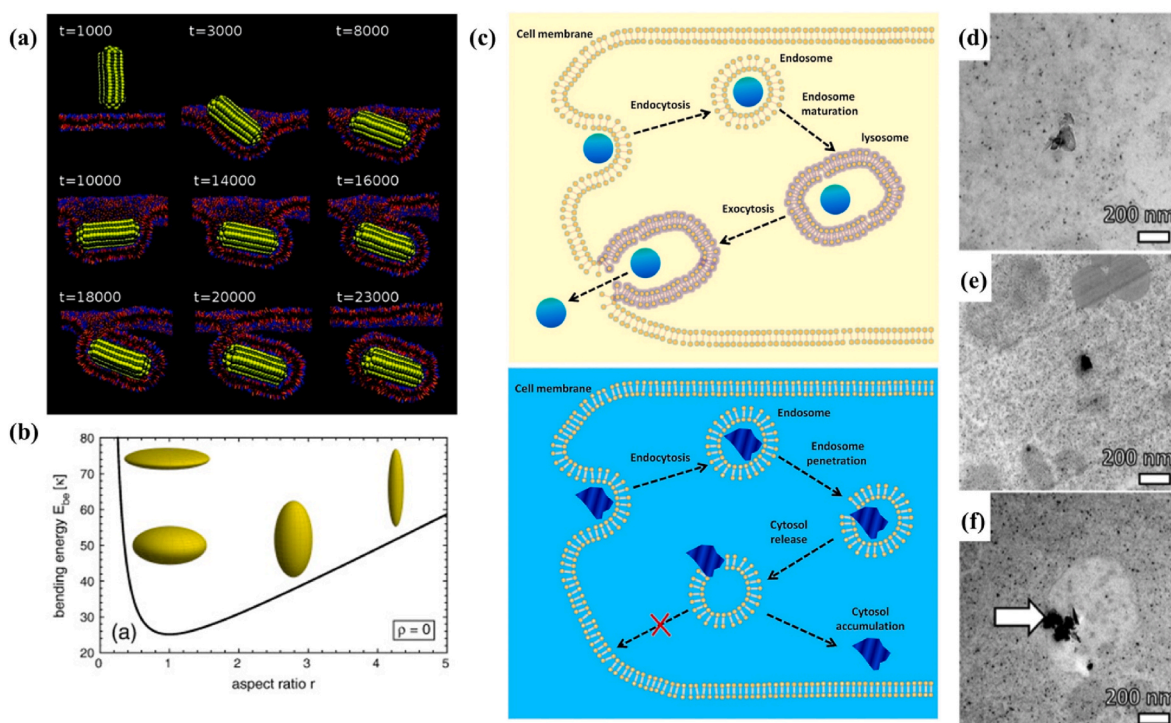


Fig. 4. The shape-dependent cellular uptake. (a) The cellular uptake mechanism of non-spherical nanoplastics (reproduced with permission from ref (Vácha et al., 2011), Copyright 2011, American Chemical Society). (b) The dependency of the cell membrane bending energy upon the nanoplastics aspect ratio (reproduced with permission from ref (Bahrami et al., 2014), Copyright 2014, American Chemical Society). (c) The effect of nanoplastics sharpness upon cellular uptake. (d and e) TEM images of sharp nanoparticles in the cytoplasm. (f) A TEM image of sharp-shaped nanoparticles rupturing the cell membrane of the vesicle (reproduced with permission from ref (Bahrami et al., 2014), Copyright 2014, Nature Portfolio).

toxicity at concentrations as low as 25 $\mu\text{g/mL}$. Further, the amount of 25 nm PS nanoplastics that were uptaken continued to increase after 1 h of exposure, whereas the amount of 75 nm PS nanoplastics decreased over the same time. Similarly, DeLoird et al. (2021) exposed epithelial cells to 25 nm, 100 nm and 1000 nm of PS nanoplastics to find that only the 25 nm of PS nanoplastics were uptaken intracellularly, while the larger PS nanoplastics were restricted to the apical surface of the cell, thus confirming that both uptake and translocation are size-dependent. Similarly, as the size of the nanoplastics decreased, the cellular uptake level by the A549 cells increased (Shi et al., 2021b), thus resulting in higher cytotoxicity, oxidative stress, membrane damage, mitochondrial dysfunction, and intracellular accumulation. In addition to the above-mentioned and commonly known risks of nanoplastics, Forte et al. (2016) demonstrated that AGS gastric adenocarcinoma cells exhibit significant changes in cell morphology and dramatically altered gene expression upon exposure to nanoplastics. In addition, Wu et al. (2023) investigated the toxic effects of nanoplastics on the respiratory system and found that PS nanoplastics exposure induced pulmonary injury in the lung tissues through ferroptosis. Moreover, 100 nm PS nanoplastics have greater toxicity on human placental cells than 200 nm.

The above results demonstrate that all risks posed by nanoplastics are highly size-dependent.

Nevertheless, there are limitations to size-dependent endocytosis. For instance, Fröhlich et al. (2012) exposed the human umbilical vein EAhy926 cell line to various sizes of carboxyl PS nanoplastics to find that while uptake with co-localization generally increased as the size decreased, the cellular uptake of 20 nm PS nanoplastics was usually less than that of 40 nm PS nanoplastics and more than that of 100 nm PS nanoplastics. Recently, Tavakolpournegari et al. (2023) conducted a study using 50 nm, 200 nm, and 500 nm of PS nanoplastics to investigate the cellular uptake level in blood cells such as B-lymphocyte (Raji-B), macrophage (THP-1) and lymphoblastoid (TK6) model, as shown in

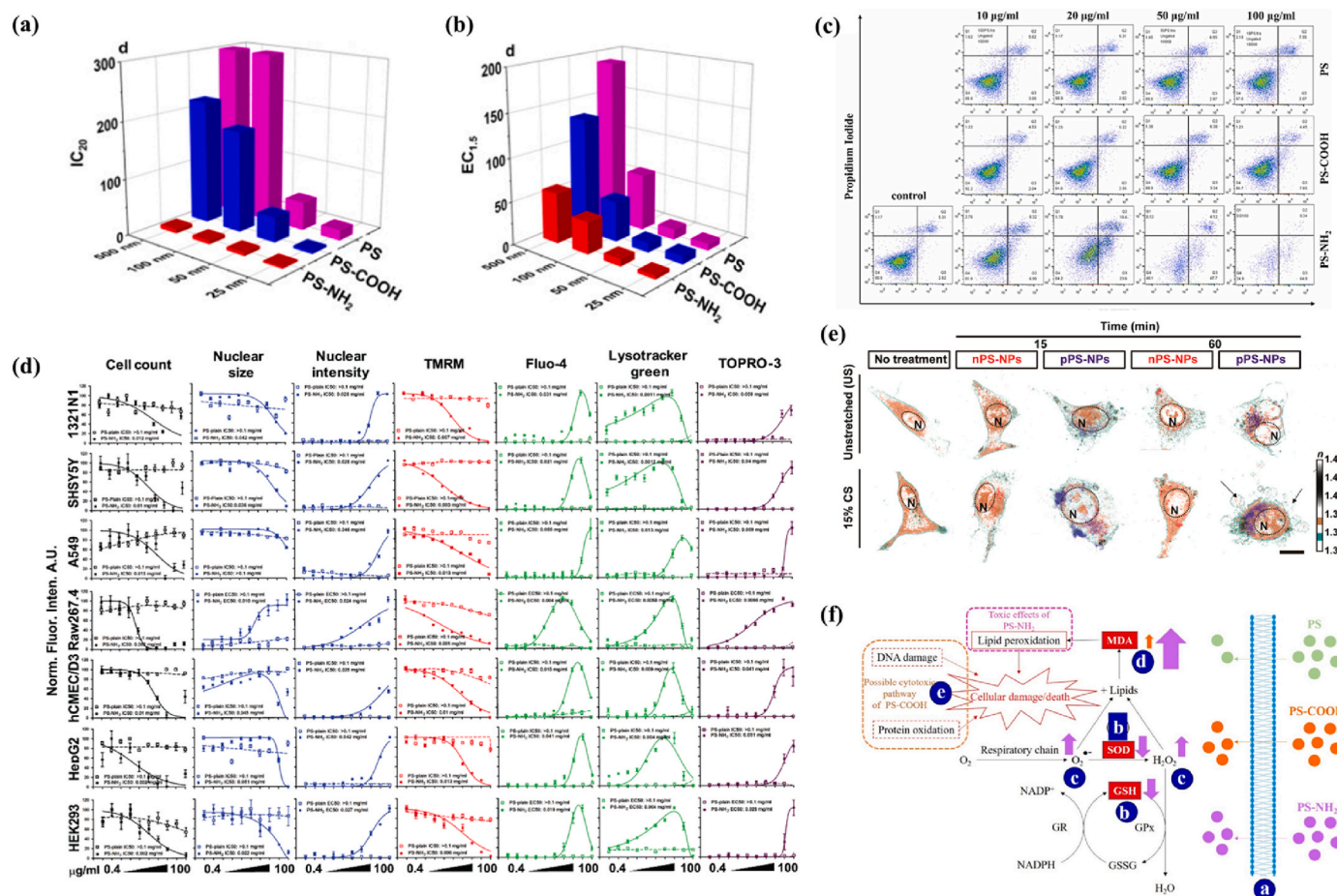
Fig. 3b and c. The results showed that the 50 nm nanoplastics were uptaken more than the larger nanoplastics in Raji-B and THP-1 cells, and induced mitochondrial membrane potential loss. However, there was no significant effect of sizes in TK6 cells, which demonstrates that cell type can also be an important factor for endocytosis mechanism.

As well as increasing level of cellular uptake, the smaller nanoplastics also increased the adsorption of hazardous chemicals such as some additives due to their large surface to mass ratio. For example, as shown in Fig. 3d and e, Wang et al. (2020) exposed cells to various nano- and micro sized of PS nanoplastics for 24 h at a fixed concentration of 20 $\mu\text{g/mL}$ to find that both the adsorption of additives and the cellular uptake level increased in a size-dependent matter. In particular, the adsorption of bisphenol A (BPA) was 6 times higher at 300 nm than at 6 μm due to the large specific surface area. Without additives, large-sized nanoplastics did not show any noticeable cytotoxicity, whereas particles of less than 1 μm exhibited greater cellular uptake levels and cytotoxicity (Fig. 3f). Meanwhile, the internalized nanoplastics with BPA are released intracellularly and generally pose greater health risks (Shen et al., 2019).

In clathrin- or caveolin-dependent endocytosis, the smaller particles require fewer receptors for membrane bending. Furthermore, the amount of energy needed for the cell membrane to internalize the nanoplastics is reduced with a decrease in particle size thermodynamically (Liu et al., 2021). When the nanoplastics are sufficiently small, cellular uptake can occur via phagocytosis, micropinocytosis, and clathrin-mediated endocytosis simultaneously so that nanoplastics can be internalized readily in large amounts (Ding et al., 2021).

3.3. Shape

The types of plastic particle shapes known to exist in daily-use products (Baldwin et al., 2016) and daily life include polymer fibers (Ghosh and Mandal, 2018), polymer films (Liu et al., 2016), spherical



adhesion may occur preferentially between the tip of the vertically oriented particle and the cell membrane, thereby inhibiting the wrapping process. Instead, nanoplastics with high degrees of sharpness and roughness cause cell membrane disruption, thus damaging the cell structure and causing cytotoxicity (Choi et al., 2020). Therefore, depending on the shapes of their tips, nanoplastics can either be taken up by cells or cause damage to the cell membrane, leading to the cellular damage through various mechanisms. In addition, the crystallinity of the nanoplastics varies according to the particle shape, which directly affects the density and permeability (Rubio et al., 2020) and, consequently varies the cellular uptake level.

Due to their simple and uniform shapes, spherical nanoplastics have been utilized in most studies for convenience (Tanaka et al., 2021). Unfortunately, despite the existence of other shapes, no studies on the uptake of such nanoplastics into human cells *in vitro* or *in vivo* have been performed. Choi et al. (2021) compared the effects of smoothly-curved microbeads versus rough microfragments upon various cell types to demonstrate that, while the microbeads had no significant effect, the microfragments caused apoptosis of peripheral blood mononuclear cells (PBMCs), cytokine and histamine release of human mast cell line 1 (HMC-1), and hemolysis of red blood cells (RBCs). This is due to cell membrane disruption induced by the high sharpness and curvature of the irregularly shaped particles. In addition, Yong et al. (Yong and Du, 2023) used dissipative particle dynamics simulations to model the interactions between a cell membrane and hydrophobic nanotetrahedra plastic particles with high shape anisotropy and large surface curvature, in order to simulate environmental nanoplastics. The results showed that the nanoplastics with tetrahedra form were readily adsorbed by the lipid membrane due to their sharp vertices and edges, as cell membrane prefers flat tips for absorption. This indicates that non-spherical nanoplastics may have higher uptake rate than spherical nanoplastics. Sharp nanomaterials are known to disrupt vesicles (Fig. 4f) after cellular uptake and remain inside the cytoplasm (Fig. 4d and e), promoting the accumulation of nanomaterials on the lysosome (Chu et al., 2014). Hence, sharp nanoplastics may also cause disruption of vesicles and accumulate in the lysosome, which may cause severe risks such as cytotoxicity (Fig. 4c). Therefore, non-spherical nanoplastics can be more easily uptaken by cells, rupture the vesicles and accumulated on the lysosome, which can cause dramatically higher risk than spherical form which have been widely studied. Accordingly, the shape is expected to have a significant effect on the cellular uptake level of nanoplastics. Thus, it is essential to study the cellular uptake levels of differently shaped nanoplastics in the future.

3.4. Surface functionalization (surface charge)

Recently, nanoplastics with sizes of less than 100 nm have become a major issue (Gigault et al., 2018), and the effects of both their size and surface characteristics upon their cellular uptake level have received significant attention (Tallec et al., 2019). Surface functionalization of the nanomaterials can occur *in vivo* via the surface adsorption of macromolecules such as polysaccharides, organic matter, or proteins (Lowry et al., 2012), and *ex vivo* by condensation onto the surfaces of airborne nanoplastics by organic matter in the atmosphere and the nanoplastics in the aquatic environment (Kihara et al., 2019; Cao et al., 2022). In particular, the surface adsorption of macromolecules leads to the formation of a protein corona, that can allow the surface of the nanoplastics to be modified with negatively- or positively-charged amino acids (Kihara et al., 2019). Positively-charged nanoplastics can be internalized mainly through phagocytosis (He et al., 2010) and macropinocytosis, while negatively-charged nanoplastics are uptaken via clathrin-mediated endocytosis (Dausend et al., 2008). Thus, functionalized nanoplastics differ in their interactions with the cell surface and, hence, in their cellular uptake levels and cellular damage pathways (Schultz et al., 2021).

For example, Loos et al. (2014) confirmed that positively-charged,

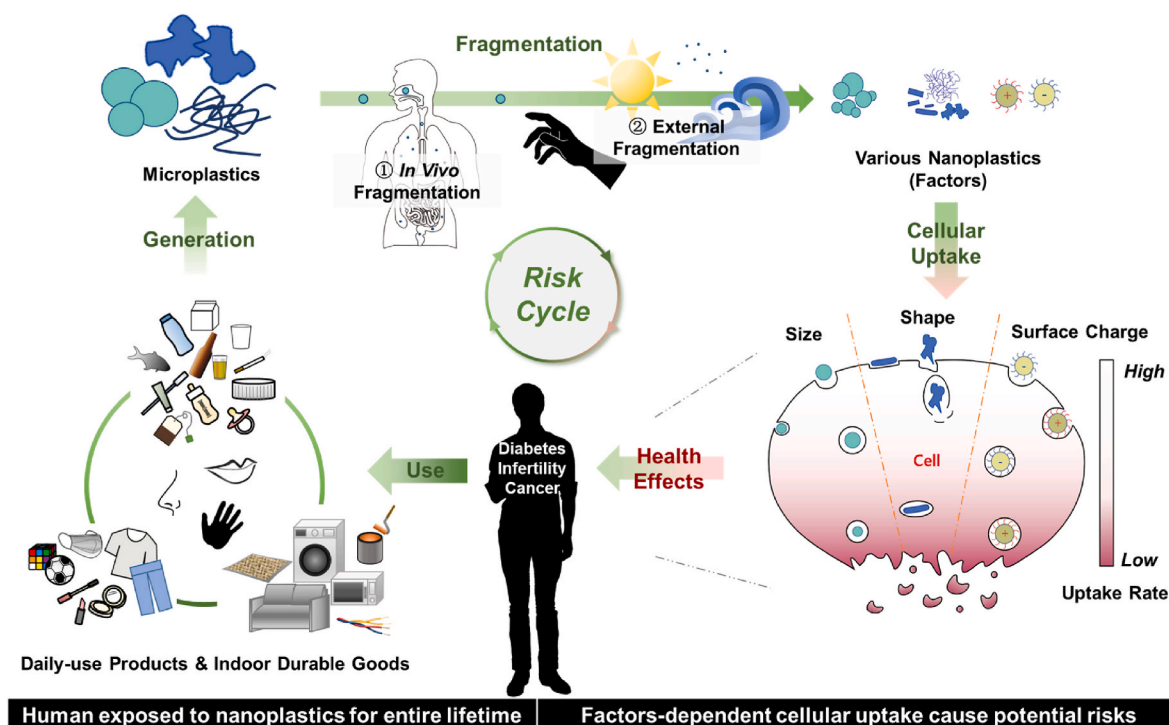
amino-functionalized PS (PS-NH₂), and negatively-charged, carboxylic-functionalized PS (PS-COOH) were taken up by THP-1 cells. As a result, the PS-COOH showed no toxicity, while the PS-NH₂ stopped cell division and caused apoptosis. Similarly, Anguissola et al. (2014) compared the cellular uptake of PS-NH₂, PS-COOH, and unfunctionalized PS, to find that PS-NH₂ caused cell death due to mitochondrial membrane damage and permeabilization of the lysosomes in various organ cell types, including lung, liver, kidney and macrophages, thereby indicating that PS-NH₂ was lethal compared to the other two nanoplastics (Fig. 5d). In addition, Li et al. (2022) found that PS-NH₂ sharply decreased the intracellular calcium levels and mitochondrial membrane potential, and increased the decrement in myocardial contractility, the inhibition of CD8⁺ T cell differentiation, and the suppression of helper T cell cytokine expression compared to PS-COOH and unfunctionalized PS. Shen et al. (2022) used human placental choriocarcinoma (JEG-3) cells to investigate the effect of surface charge on nanoplastics. The study showed that PS-NH₂ resulted in lysosome damage and mitochondria destruction, which further induced apoptosis and cytotoxicity (Fig. 5a). Conversely, the effect of negatively charged and unfunctionalized PS was minimal. Furthermore, positively charged nanoplastics caused significant increased intracellular ROS levels (Fig. 5b) due to cellular uptake in JEG-3 cells. As PS-NH₂ nanoplastics were also found to aggregate in lysosomes with the highest uptake efficiency among unfunctionalized and negatively charged nanoplastics, they caused cell membrane damage and upregulated genes expressions related to the mitochondrial apoptosis pathway, leading to apoptosis in RAW264.7 cells. These findings indicate that functionalized nanoplastics may have negative impacts on the RAW264.7 cells (Fig. 5c).

Positively charged nanoplastics have greater electrostatic interactions and more easily binds to anionic head groups and negatively-charged membrane protein molecules in the cell membrane, resulting in a significantly higher increase in intracellular ROS levels compared to negatively charged nanoplastics (Roshanzadeh et al., 2020). Consequently, while PS-COOH has no significant effect on cell morphology, ROS-induced membrane permeabilization promotes the uptake of PS-NH₂ via endocytosis (Fig. 5fⓐ) (He et al., 2020). After cellular uptake, the morphology of cell may change, leading to acute uptake and risks associated with PS-NH₂ (Fig. 5e) while PS-COOH did not. After cellular uptake, the PS-NH₂ significantly decreased the superoxide dismutase (SOD) activity, the glutathione (GSH) content (Fig. 5fⓑ) and the malondialdehyde (MDA) level due to greater accumulation of O₂⁻ and H₂O₂ than observed in the presence of PS-COOH (Fig. 5fⓒ). So, in most of the studies on the surface functionalization of nanoplastics, NH₂ functionalized nanoplastics shows more obvious risks than COOH functionalized nanoplastics (Lunov et al., 2011; Qiao et al., 2021; Han et al., 2021).

3.5. Other factors

As well as the main factors described above, there are also other factors that may affect the cellular uptake level and subsequent risks of nanoplastics, which are still insufficiently studied.

Most significantly, the endocytosis pathway varies depending upon the cell type. For example, Ding et al. (2021) confirmed that gastric epithelial (GES-1) cells uptake PS nanoplastics mainly via micropinocytosis, along with clathrin-mediated endocytosis and caveolin-dependent endocytosis, whereas macrophages absorb nanoplastics via micropinocytosis, phagocytosis, and clathrin-mediated endocytosis, and A549 uptaken nanoplastics via caveolin-dependent endocytosis and clathrin-mediated endocytosis (Kuhn et al., 2014). Meanwhile, PS nanoplastics are uptaken into SH-SY5Y cells, via caveolin-dependent endocytosis (Nie et al., 2021). However, for the red blood cells, phagocytosis cannot take place since there are no phagocytic receptors on the surface of the red blood cells (Shi et al., 2021c). Instead, red blood cells uptake nanoplastics via diffusion, so that PS nanoplastics with diameters of less than 200 nm can be absorbed, while those larger



Scheme 1. Fragmentation of daily-use plastic products to nanoplastics may pose diverse risks by factor-dependent cellular uptake.

than 1000 nm are not uptaken because neither phagocytosis nor pinocytosis may occur (Rothen-Rutishauser et al., 2006).

In general, environmental exposure and human use of plastics can gradually cause aging to the generated microplastics and nanoplastics by biodegradation, physical abrasion and chemical oxidation (Zha et al., 2022). Different types of risks can arise depending on the nanoplastics aged time. As aged nanoplastics are more hydrophilic and less electro-negative, cytotoxicity can be increased due to particle aggregation and surface adsorption of bioactive compounds (Prüst et al., 2020). Increased sorption of proteins has been shown to enhance the cellular uptake of aged PS nanoplastics by lung macrophages J774A.1 through phagocytosis and clathrin-mediated endocytosis (Du et al., 2023). Shi et al. (2021d) used transcriptomic analysis and demonstrated that the aged nanoplastics exhibited aggravated interference in gene expression of A549 cells and resulted in the stronger oxidative stress and intensive mitochondrial dysfunction. They also found that the toxicity of nanoplastics significantly increased according to the aging time. According to Zhang et al. (2021b), 6 weeks aged plastics simulating 34 months exposure of indoor sunlight storage generated a large number of nanoplastics and microplastics. Therefore, plastics that are used as daily-use products for a long time may have a significant adverse effect on human health in the future, due to the increasing use of plastic and the difficulty in elimination after being discarded into the environment.

Most plastics contain additives, and related research has been a great issue for several years (Shi et al., 2021d). Additives (Buekens and Yang, 2014) include bisphenol A, phthalates, brominated flame retardants, and zeolites, which have been widely used as plasticizers, light and heat stabilizers, and acid scavengers (Hahladakis et al., 2018). In particular, nanoplastics can adsorb environmental contaminants with great affinity, which can cause further serious risks to human cells and tissues (EFSA, 2016). Additives have different release profiles depending on aging time, surface roughness, polymer types, etc. (Shen et al., 2019), and can further pose severe risk to the human body such as cancer, obesity, and reproductive disorders (Sendra et al., 2021b).

Finally, the type of nanoplastics is a very important factor for cellular uptake. Physical and chemical properties such as density and thermal stability are different depending on the type of nanoplastics, which can

affect the fragmentation or deformation degree of the plastic particles (Stock et al., 2021). Accordingly, the cellular uptake level can vary depending on the type of plastic particles. Unfortunately, most of the current nanoplastic research mainly focuses on PS particles. Stock et al. (Shi et al., 2021d) studied the cellular effects of polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and Polyvinyl chloride (PVC) microplastics, and found that they had different *in vitro* cytotoxicity levels depending on the material types. However, the size of plastic particles they used for cellular studies was over 5 μm , which is a size that is difficult to be absorbed by cells. In fact, since the most frequently used plastic types are PP, PET, PE, and PVC, we can predict that the most abundant nanoplastics are these types of polymers. Therefore, it is necessary to simulate the real condition and compare the cellular uptake level of nano-sized various polymer types with various human cell types.

4. Conclusions

Plastics are the most common industrial materials and have been highly produced and are utilized extensively by humans in household and personal products, resulting in potential for exposure to them, their fragments and chemicals that may be released from them in the human life. Nanoplastics can be generated through various pathways in human life, and recently raised more concern than microplastics for their hazards.

In summary, the nanoplastics have specific cellular uptake mechanisms depending on their concentration, size, shape, surface functionalization, target cell type, aging time, and physical & chemical properties. Increase in concentration, decrease in size, aspect ratio, sharpness, roughness, and surface functionalization will each pose a higher risk. In addition, since the specific endocytosis pathway also varies according to the cell type, the requisite size, aspect ratio, or tip sharpness for cellular uptake may be very depending on the cell type. However, studies on cellular uptake using human cells are still insufficient and unsubstantial. *In vitro* studies often use extremely high concentrations in short time, and long-term studies are still missing. Moreover, most of the plastic particles used for cellular uptake studies

are PS, and there are still only few studies on other polymer types. Also, PS used for the assessment of cellular uptake are usually commercially available PS, but not from the real environment or daily-use products. In addition, various sizes, shapes, surface charges and polymer types of plastics often exist together conventionally. Therefore, in the future nanoplastic studies, it is necessary to use various types of plastics with different factors generated by daily-use products to stimulate the real environment of daily life by each plastic types or by the mixture of the different types of plastics.

The cellular uptake of nanoplastics generated from daily-use products has received extensive attention especially following the emergence of COVID-19 and the widespread use of masks. According to recent studies, the cellular uptake of nanoplastics is related to numerous potential diseases such as reduced contractility of cardiomyocytes in the neonatal heart (Roshanzadeh et al., 2021), diabetes (Fan et al., 2022; Wang et al., 2023), infertility (Bojic et al., 2020), and cancer. In addition, since nanoplastics can cross the placental barrier, they trigger hazards in fetal development (Nie et al., 2021). However, for the difficulty of visualization and chemical identification of nanoplastics due to their small sizes, studies on the characterization of nanoplastics such as physicochemical properties, environmental exposure concentration, and toxicity of nanoplastics are still insufficient (Zhang et al., 2022a). Therefore, more research on this emerging contaminant is needed, and additional studies should be conducted consistently in the future (see Scheme 1).

Credit author statement

Yoojin Lee: Conceptualization and writing-Original draft preparation. **Seongeun Cho:** Investigation. **Kyungtae Park:** Supervision and Editing. **Taihyun Kim:** Investigation. **Jiyu Kim:** Validation. **Du-Yeol Ryu:** Editing. **Jinke Hong:** Writing- Reviewing and Editing.

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.

Data availability

The authors do not have permission to share data.

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