Cambridge Prisms: Plastics

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Mitochondria as a target of micro- and nanoplastic toxicity

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Review

Cite this article: Dal Yöntem F and Aydoğan Ahbab M (2024). Mitochondria as a target of micro- and nanoplastic toxicity. *Cambridge Prisms: Plastics*, **2**, e6, 1–11
https://doi.org/10.1017/plc.2024.6

Received: 07 June 2023
Revised: 28 February 2024
Accepted: 09 March 2024

Keywords:
microplastics; nanoplastics; mitochondria; mitophagy; mitochondrial membrane dynamics

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Abstract

Mitochondria are unique organelles to perform critical functions such as energy production, lipid oxidation, calcium homeostasis, and steroid hormone synthesis in eukaryotic cells. The proper functioning of mitochondria is crucial for cellular survival, homeostasis, and bioenergetics. Mitochondrial structure and function are maintained by the mitochondrial quality control system, which consists of the processes of mitochondrial biogenesis, mitochondrial dynamics (fusion/fission), mitophagy, and mitochondrial unfolded protein response UPR^{MT}. Mitochondrial dysfunction and/or damage is associated with the initiation and progression of several human diseases, including neurodegenerative, cardiovascular, age-related diseases, diabetes, and cancer. Environmental stress and contaminants may exacerbate the sensitivity of mitochondria to damage which causes mitochondrial dysfunction. There is growing evidence about the impact of nanoplastics (NPs) and microplastics (MPs) on mitochondrial health and function. MPs/NPs were reported to trigger oxidative stress and reactive oxygen species production, which eventually change mitochondrial membrane potential. MPs/NPs can cross through the biological barriers in the human body and be internalized by the cells, potentially altering mitochondrial dynamics, bioenergetics, and signaling pathways, thus impacting cellular metabolism and function. This review states the effects of MPs/NPs on mitochondrial homeostasis and function as well as on mitochondrial membrane dynamics, mitophagy, and mitochondrial apoptosis are discussed.

Impact statement

Given the critical role of mitochondria in cellular and organismal health, MPs/NPs pose a significant threat to mitochondrial health and function. The current evidence underscores the urgency of addressing the pervasive problem of MP/NP pollution, not only for the protection of the environment but also for human health. The information provided here should inspire and guide further research in several directions. The specific molecular mechanisms by which MPs/NPs affect mitochondrial health need to be elucidated. A deeper understanding of these processes could inform the development of strategies to mitigate these effects or be used as biomarkers of exposure or toxicity. In addition, this information should motivate regulators to reassess the environmental and health risks associated with MP/NP pollution, incorporating new knowledge on mitochondrial effects into these assessments. This could help to shape more comprehensive and effective strategies for dealing with plastic pollution, ranging from policies to reduce plastic waste and promote more sustainable materials, to remediation of existing pollution.

Introduction

Background on microplastics (MPs) and nanoplastics (NPs)

During the past 70 years, the use of plastics has increased more than many other products, but the waste of plastics has spread throughout the environment as well (Kayan and Küçük, 2020). This has given rise to the term 'plastic debris', which is defined as "human-generated solid polymeric material waste that is intentionally or accidentally released into the environment." The production of plastic products reached approximately 390.7 million tons in 2021, and the negative impacts of persistent plastic waste on aquatic and terrestrial environmental health are of serious concern (Thompson et al., 2009; European Commission, 2019; Plastics Europe, 2022). Polyethylene (PE), polypropylene, polystyrene (PS), polyvinyl chloride (PVC), polyethylene terephthalate (PET), and polyurethane used in the production of plastics are attracting more attention because they are produced in large quantities and are widespread in the environment (Vert et al., 2012; Revel et al., 2018; European Commission, 2019; Science Advice for Policy by

European, 2019; Pinto Da Costa et al., 2020; Plastics Europe, 2021). Although studies to determine the potential effects of plastic debris on human health have increased exponentially over the past decade, current knowledge is still insufficient to determine the risk. Of all the plastic produced, ~33% is not suitable for recycling and is thrown into the environment within 1 year of production (Koelmans et al., 2014). During the incineration process, which is one of the ways of dealing with plastic waste, toxic chemicals (such as furan and dioxin) that are harmful to human health and the environment are released. Furthermore, many countries have yet to introduce legislation to regulate the recycling of plastic waste, often opting instead for the cheaper and easier route of landfilling (Crawford and Quinn, 2017).

Plastic waste accumulates in large quantities in terrestrial, marine, and freshwater ecosystems. Today, plastic debris and the pollution it causes are recognized as one of the most important global environmental threats (Ryan et al., 2009; Villarrubia-Gómez et al., 2018; European Commission, 2019; Science Advice for Policy by European, 2019; Hale et al., 2020; Plastics Europe, 2021). It is estimated that ~10% of all plastics produced to date end up as litter in the oceans (Laglbauer et al., 2014). It has been reported that 61–87% of litter ≥5 mm in size and 98–99% of litter <5 mm in size is plastic (plastic film, plastic fibers, polystyrene, plastic pellets) (Tekman et al., 2021). Recently, in addition to the visible macro form of plastic waste, microplastic (MP) and nanoplastic (NP) particles have also raised ecotoxicological concerns (Mattsson et al., 2018). MPs and NPs can be found as primary and secondary plastic particles, depending on the way they are formed. Primary particles are produced in a fixed size for the purpose, usually in the form of beads, while secondary particles are formed by the degradation of larger plastic materials (McDevitt et al., 2017). Secondary MPs/NPs are much more abundant in the environment than primary ones (Hale et al., 2020). Anthropogenic impacts, environmental factors such as solar radiation (UV photooxidation reactions), wind and waves, and abrasion from car tires are effective in the formation of secondary MP/NP pollution (Andrady, 2015; Wagner et al., 2018). Although the rate and amount of nanofragmentation in nature is unknown, it is predicted that the fragmentation of MP particles with a size >100 nm-5 mm into NP particles with a size of 100 nm would lead to an NP particle concentration > 10^{14} times higher than the current MP particle concentration (Besseling et al., 2019). Ter Halle et al. (2017) detected PVC, PET, PS, and PE polymers with a size of 1–999 nm in ocean surface samples for the first time. Although MP/NP pollution is considered a global problem, their potential risks to human health are far from known with the available data (Thompson et al., 2004; 2005). Field studies have shown the presence of MP in a large proportion of living organisms in the food chain (Lusher et al., 2013; 2017; Hermsen et al., 2018). MPs have also been detected in bottled water and tap water (Mintenig et al., 2017; Kosuth et al., 2018; Mason et al., 2018; Mintenig et al., 2019). Studies have started to reveal that MPs/NPs can trigger physical and chemical toxicity in organisms (Bergmann et al., 2015; Klages et al., 2015; Wagner and Lambert, 2018). In aquatic organisms, MPs have been shown to cause oxidative stress, genotoxicity, neurotoxicity, developmental delay, reduced reproductive success, and death (De Sá et al., 2018). In addition, in vivo studies have shown that primary MPs/NPs accumulate in tissues after oral or respiratory exposure (Deng et al., 2021; Xu et al., 2021; Fan et al., 2022; Meng et al., 2022; Yang et al., 2022; Jeong et al., 2022a).

Exposure and toxicity of MPs/NPs

In humans, to determine whether exposure to plastic particles poses a public health risk, it is first necessary to understand the exposure to these substances and the hazards associated with exposure. Humans are exposed to MPs/NPs primarily through oral and dermal routes, inhalation, and during medical procedures (Prata et al., 2020). The fact that MPs have been detected in human feces and tissues (placenta, lung, and whole blood) in clinical studies and are beginning to be associated with disease suggests that the potential effects of MP/NP exposure should be taken seriously (Schwabl et al., 2019; Amato-Lourenço et al., 2021; Ragusa et al., 2021; Jenner et al., 2022; Leslie et al., 2022; Yan et al., 2022). While the detection of human MP exposure is still very new, the extent of NP exposure is unfortunately not yet known due to the lack of methods to detect particles of this size (European Commission, 2019; Science Advice for Policy by European, 2019).

Plastic particles smaller than 150 μm can enter the system by crossing the intestinal epithelium; NPs smaller than 100 nm can easily be taken into the cell and pose a threat to humans (EFSA, 2016; Celebi Sözener et al., 2020). in vitro studies have shown that primary PS MPs/NPs are taken into cells, reduce cell viability, trigger apoptosis, alter reactive oxygen species (ROS) production, mitochondrial membrane potential (MMP), and function (Prietl et al., 2014; Forte et al., 2016; Wu et al., 2019; Xu et al., 2019a; Li et al., 2022; Wang et al., 2022a; Sun et al., 2023b).

When considering the routes of human exposure to NPs and MPs, the respiratory and digestive systems are the first areas of concern. However, it clearly demonstrates that MPs/NPs, which are small in size, can overcome biological barriers in humans and circulate through the blood system to access other tissues (Leslie et al., 2022). It has also been reported that NPs can cross the air-blood barrier in the lung and enter the bloodstream (Prata et al., 2020), while primary exposure to PS NPs can cause lung damage (Wu et al., 2023). In addition, primary PS NPs have been shown to accumulate in the brain by crossing the blood–brain barrier after intravascular injection (Yang et al., 2004). Mice exposed to primary PS NPs had a significant increase in blood glucose, glucose intolerance, and insulin resistance. PS NPs exacerbated STZ-induced type 2 diabetes (Wang et al., 2023). PS NPs induced Parkinson's disease-like neurodegeneration in mice, so NP exposure should be carefully considered as a neurological health risk (Liang et al., 2022). Mitochondrial dysfunction, endoplasmic reticulum (ER) stress, oxidative stress, and lysosomal membrane damage are observed in diseases such as neurodegenerative diseases, inflammation, metabolic stress, oxidative stress, diabetes, cardiovascular diseases, gastrointestinal diseases, kidney and lung diseases, skin diseases, aging, and cancer (Calì et al., 2011; Herst et al., 2017; Ryter et al., 2018; Burgos-Morón et al., 2019; Shacham et al., 2019; Xu et al., 2019b; Rana, 2020; Lee et al., 2022). The organelles mitochondria, endoplasmic reticulum, and lysosome, which play an important role in the pathophysiology of these diseases, are also targets of MP/NP toxicity (Lim et al., 2019; Wang et al., 2021; Halimu et al., 2022). In this review, we will discuss studies revealing the effects of MPs/NPs on mitochondria.

Mitochondrial toxicity of MPs/NPs

Impact of MPs/NPs on mitochondrial structure and function

Due to their size and surface properties, MPs/NPs can physically interact with cellular structures, including mitochondria. Often

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

referred to as the 'powerhouses of the cell', mitochondria are key organelles responsible for ATP production through oxidative phosphorylation. In addition to energy production, they regulate several cellular processes, including calcium homeostasis, apoptosis, and the generation of reactive oxygen species (ROS). Exposure to these pollutants can induce mitochondrial damage and dysfunction, disrupting normal cellular operations and potentially leading to cell death. There is evidence that these particles can penetrate cell membranes and accumulate inside cells, possibly targeting mitochondria (Lee et al., 2022). This penetration appears to be facilitated by NP small size, allowing them to cross biological barriers more easily than larger particles (Yang et al., 2021). Once inside the cell, MPs/NPs can disrupt mitochondrial structure. Studies in mice have shown that exposure to PS MPs can cause significant morphological changes in mitochondria, such as swelling and loss of cristae (Lin et al., 2022a). Building on the structural disruption mentioned above, these physical interactions may also induce functional abnormalities in mitochondria, further contributing to their toxicity. As the powerhouse of the cell, mitochondria play a critical role in maintaining cellular energy homeostasis (Lee et al., 2015). Recent evidence suggests that PS NPs can impair mitochondrial energy production capacity by disrupting the electron transport chain, leading to reduced ATP synthesis (Trevisan et al., 2019; Lin et al., 2022b; 2023a). The impairments observed in mitochondrial function are not limited to energy production but also extend to other vital processes such as signaling, mitochondrial dynamics, mitophagy, calcium homeostasis, and apoptosis. In in vitro (Table 1) and in vivo (Table 2) studies, decreased mitochondrial membrane potential ($\Delta\Psi m$) was observed after PS, PVC and PET MPs/NPs (Wu et al., 2019; Wang et al., 2020; Chen et al., 2022; Florance et al., 2022; Halimu et al., 2022; Li et al., 2022; Liu et al., 2022; Salimi et al., 2022; Zhang et al., 2022a; Chen et al., 2023; Koner et al., 2023; Zhang et al., 2023). In a study by Sun et al., exposure to PS NPs (size 20 nm) resulted in collapse of $\Delta\Psi m$, an event associated with the activation of cellular apoptosis, at TM3 mouse Leydig cells (Sun et al., 2023b). This finding was reinforced by studies showing increased expression of apoptosis-related proteins in cells exposed to MPs/NPs, providing further evidence that these particles may interfere with the role of mitochondria in the regulation of apoptosis (Li et al., 2021; Wang et al., 2022b; Li et al., 2023b). In addition, the interaction of MPs/NPs with mitochondria could also affect cellular calcium homeostasis, as calcium is critical for several mitochondrial functions, including ATP production, this disruption could have significant consequences for cellular health. Research has shown that PS nanoparticles with a size of 20 nm can increase intracellular calcium levels, possibly by disrupting mitochondrial calcium handling at SHSY-5Y human neuroblastoma cells and protozoan *Tetrahymena thermophila* which has a strong ability to ingest particles (Meindl et al., 2015; Wu et al., 2021). The impact of MPs/NPs on mitochondrial structure and function potentially links to various pathologies, highlighting the importance of elucidating the mechanistic pathways of these interactions for understanding systemic and long-term health effects.

Induction of mitochondrial ROS by MPs/NPs

One of the critical consequences of the interaction of MPs/NPs with mitochondria is the induction of ROS. ROS are chemically reactive molecules that can be a by-product of normal metabolic processes, but when produced in excess they can lead to oxidative stress, causing damage to DNA, proteins, and lipids in cells (Thannickal and Fanburg, 2000). MPs/NPs have been reported to trigger the overproduction of ROS in mitochondria. A study by Li et al. showed that exposure to PS NPs with a diameter of 21.5 nm increased mitochondrial ROS levels in human hepatocellular carcinoma cells in a dose-dependent manner (Li et al., 2023a). Similar findings were observed in fish gills exposed to 1–5 μm sized MPs, where elevated levels of mitochondrial ROS were associated with a significant increase in lipid peroxidation, a marker of oxidative damage (Santos et al., 2022). Furthermore, this ROS-induced oxidative stress may exacerbate mitochondrial dysfunction by damaging mitochondrial proteins and disrupting $\Delta\Psi m$, thereby amplifying the detrimental effects of MPs/NPs on mitochondrial function (Wang et al., 2021; Li et al., 2023a). Adding to this complexity, shape also appears to play a role in the interaction of these pollutants with cellular systems. Spherical and fiber/fragment-shaped PS MPs and NPs reduced intracellular H_2O_2 levels attributable to mitochondrial stress responses such as increased mitochondrial DNA content, footprint, and morphology in Caco-2 cells (Saenen et al., 2023).

Effects of MPs/NPs on mitochondrial dynamics

MPs/NPs can also affect mitochondrial dynamics, a process that is critical for maintaining mitochondrial function and overall cellular health. Mitochondrial dynamics involves the balanced processes of mitochondrial fission and fusion, which are necessary for cell survival, adaptation to metabolic changes, and removal of damaged mitochondria (Youle and van der Bliek, 2012). In general, Fis1, Mff, MiD49, MiD51, and dynamin-associated protein 1 (Drp1) are involved in mitochondrial fission (Bleazard et al., 1999; Mozdy et al., 2000; Tieu and Nunnari, 2000). In mammals, Drp1 is usually distributed in the cytosol and some of it is found in the form of a dot on the outer membrane of mitochondria (Smirnova et al., 2001). During fission, dynamin homologs are transported to the Drp1 outer membrane knuckle region by intermediary proteins (Fis1, Mff, MiD49, and MiD51), where they form large homomultimetric structures that spirally envelop the mitochondria (Atkins et al., 2016). Mitochondrial fission also plays an active role in the even distribution of mitochondria to daughter cells during cell division, as well as in the transport of the organelle to energy-demanding sites in the cell, such as neuronal axons and lamellipods. Recent studies revealed that MPs/NPs may disrupt this balance and cause abnormal mitochondrial dynamics. A study in human liver cells showed that exposure to PS NPs led to increased mitochondrial fission, as evidenced by a significant increase in the expression of the fission protein Drp1 and p-Drp1 (Li et al., 2023a). Excessive fission is often associated with mitochondrial fragmentation and cell death, suggesting a potential pathway for NP-induced toxicity. Conversely, NPs may also interfere with mitochondrial fusion, a process necessary for the sharing of mitochondrial DNA and other essential components. Mitochondrial fusion is a complex process in which two neighboring organelles are connected to each other and two independent membranes (inner and outer membranes of mitochondria) are fused in harmony without any significant loss of mitochondrial proteins (e.g. cytochrome *c*) that could lead to cell death. In mammals, Mfn1 and Mfn2 proteins called mitofusins are involved in outer membrane fusion, while OPA1 protein is involved in inner membrane fusion. Fu et al. found that exposure to amino-functionalized PS NPs increased the mRNA expression level of MFN2 (mitochondrial fusion-related gene) in Human Umbilical Vein Endothelial Cells (HUVECs) (Fu et al., 2022). Another study conducted on human bone marrow-derived mesenchymal stem cells (hBM-MSCs) also revealed that surfactant-free amine-functionalized PS NPs and PS NPs with decreased cross-linking density

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Table 1. Summary of in vitro studies assessing the effects of MP/NP exposure on mitochondrial function

Author (year)	Cell type	MP/NP type (size)	Concentrations (exposure time)	Outcomes
Im et al. (2022)	hBM–MSCs human bone marrow mesenchymal stem cells	PS NP and amine–functionalized PS NP (400 nm)	0.6, 1.2, and 2.4 mg/mL (24 h)	Decreased cytotoxicity and ROS scavenging effects and promoted mitochondrial fusion and inhibited mitochondrial fission after PS NP and amine–functionalized PS NP exposure in hBM–MSCs.
Fu et al. (2022)	HUVEC human umbilical vein endothelial cell line	PS NP and NH2–PS NP (50 nm)	10 and 20 μg/mL (24 or 48 h)	Enhanced ROS generation; decreased ΔΨm triggered by NH2–PS NP
Saenen et al. (2023)	Caco–2 human epithelial colorectal adenocarcinoma cells	PS MP/NP Spherical (200 nm and 2 μm) and fiber−/fragment–shaped (8.9–10.1 μm by 1.14–0.97 μm)	10 and 100 μg/mL (24 h)	Decreased intracellular H_2O_2 levels linked to mitochondrial stress responses; increased mitochondrial DNA content, footprint, and morphology observed; the most profound effects at 200 nm PS NP
Halimu et al. (2022)	A549 human alveolar type II epithelial cell line	unmodified PS NP (20 and 50 nm), amino functionalized PS NP (20 nm)	10, 20, and 40 μg/mL for 20 nm; 40, 80, and 160 μg/mL for 50 nm (24 h)	Increased intracellular ROS production and NADPH oxidase 4 (NOX4); bidirectional effect on Δψm (increased Δψm at low concentration indicating transient mitochondrial hyperpolarization; decreased Δψm at intermediate and high concentrations); elevated OCRs at low concentration, enhancing spare respiratory capacity, promoting proton leak, and increasing ATP production; decreased spare respiratory capacities and ATP levels at intermediate and high concentrations of PS NPs.
Lin et al. (2022b)	L02 human hepatic cell line BEAS–2B human lung epithelial cell line	Nonfluorescent fluorescent PS NP (80 nm)	0.006, 0.0125, 0.03125, 0.0625, 0.125, and 0.25 mg/mL (48 h)	Mitochondrial damage evidenced by overproduction of mitochondrial ROS and alterations in ΔΨm; decreased ATP production and suppression of mitochondrial respiration
Wang et al. (2021)	HK–2 human kidney proximal tubular epithelial cell line	PS MP (2 μm)	0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 μg/mL (6 h)	Higher mitochondrial ROS levels at 0.2, 0.4, or 0,8 mg/mL PS MP; increased the expression of Bad after 0.8 mg/mL PS MP exposure for 5–60 min; decreased expression of Bcl2 after PS MP exposure for 20–60 min
Chen et al. (2022)	HEK293 human embryonic kidney cells	PS MP (3.39 ± 0.30 μm)	300 ng/mL (24 h)	Increased ROS and oxidative stress; decreased ΔΨm
Li et al. (2022)	Murine splenic lymphocytes	unmodified PS NP (20 and 50 nm), PS NP–FITC (20 and 50 nm), surface–charged PS SO3H–NPs (20 nm) and PS NH2–NPs (20 nm)	40 μg/mL for 20 nm, 200 μg/mL for 50 nm (6 h)	Increased ROS after PS SO3H–NP (20 nm), PS NP (20 and 50 nm); decreased ΔΨm after PS NH2–NPs (20 nm) after 6 h of exposure; decreased ΔΨm after PS SO3H–NP (20 nm), PS NP (20 and 50 nm) exposure with ROS accumulation; affected the basic respiratory capacity and ATP production capacity of splenocytes accompanying with the damage of mitochondrial membrane by all four PS NPs
Xu et al. (2023)	Caco–2 human intestine epithelial cell line	unmodified and fluorescent–labeled PS NP, PS NP–COOH, and PS NP–NH2 (~100 nm)	30, 60, and 120 μg/mL (24 h)	Increased mitochondrial ROS; fractured, fuzzy cristae, ruptured membrane, blocked mitophagic flux, and vacuols in mitochondria; accumulation of PS NPs in the mitochondria and the subsequent induction of mitochondrial stress, which led to PINK1/Parkin–mediated mitophagy.
Zhang et al. (2022a)	A549 human lung carcinoma cells	PET NP (122–221 nm)	4.92 μg/mL and 49.20 μg/mL (24 h)	Increased ROS, decrease tendency of ΔΨm induced by PET NP exposure
Sun et al. (2023b)	TM3 mouse Leydig cells	PS–NPs (20 nm)	50, 100, and 150 μg/mL (24 h)	Increased ROS generation and initiated cellular oxidative stress and apoptosis; affected the mitochondrial DNA copy number and collapsed ΔΨm after PS NPs exposure accompanied by a disrupted energy metabolism
Chen et al. (2023)	RAW264.7 macrophage cells	Green fluorescence–labeled and unlabeled PS NP, PS NP–COOH, and PS NP–NH2 (100 nm)	10, 20, 50, and 100 μg/mL (24 h)	Increased intracellular ROS, depolarized ΔΨm after PS NP exposure; the most pronounced mitochondrial damage effect exhibited by PS NP–NH2

(*Continued*)

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Table 1. (*Continued*)

Author (year)	Cell type	MP/NP type (size)	Concentrations (exposure time)	Outcomes
Florance et al. (2022)	HaCaT human keratinocytes, A549 human lung cancer cell line, RAW 264.7 murine macrophages THP–1 human monocytes Chang Liver cells	Yellow–green fluorescently labeled PS NP and sulfate modified PS NP (0.20 μm)	50 and 100 μg/mL (24 h)	Increased mitochondrial ROS and decreased ΔΨm in RAW 264.7 and THP–1 cells
Liu et al. (2022)	GC–2 mouse spermatocyte line	PS MP (5 μm)	50, 100, 200, 400, and 800 μg/mL (24 h)	Increased ROS and MDA, decreased ATP content, reduced ΔΨm; damaged the integrity of the mitochondrial genome; imbalance of homoeostasis between mitochondrial division and fusion
Koner et al. (2023)	THP–1 macrophage cells	PS NP (≤ 450 nm)	50, 100, 150, 200, and 500 μg/mL (4/ 24/48/72 h)	Increased ROS at 50 μg/mL after 24 h exposure. Mitochondrial membrane damage after PS NP exposure for 4 and 24 h
Li et al. (2023a)	HepG2 human hepatocellular carcinoma cell line	PS NP (21.5 ± 2.7 nm)	6.25, 12.5, 25, and 50 μg/mL (24 h)	Induced morphological changes of mitochondria; decreased ATP production and the loss of ΔΨm; increased ROS and mitochondrial fission by increased DRP1 and decreased OPA1 protein levels
Wu et al. (2019)	Caco–2 human colon adenocarcinoma	PS NP/MP (0.1 and 5 μm)	1, 10, 40, 80, and 200 μg/mL (12/24 h)	Low toxicity on cell viability, oxidative stress, and membrane integrity and fluidity; disrupted ΔΨm by both sizes of PS NP/MP; higher effects induced by 5 μm PS MP than 0.1 μm PS NPs

(DPS-NPs) led to upregulation of MFN2 expression and downregulation of FIS1 (mitochondrial fission related gene) expression (Im et al., 2022). Interestingly there were opposite results regarding OPA1 levels in mouse and chicken experiments when exposed to PS MP's. It was found that after GC-2 mouse cells were exposed to PS MP's for 24 h, both mRNA and protein expression levels of OPA1 were increased along with Drp1 (Liu et al., 2022). However, in another study conducted on chickens, it was shown that after 42 days of exposure to PS MP's, mRNA and protein expression levels of OPA1 were decreased along with Mfn1 and Mfn2 suggesting a decrease at mitochondrial fusion. Conversely, Drp1 mRNA and protein expression levels were increased suggesting an increase in mitochondrial fission (Zhang et al., 2022b). These conflicting findings underscore the complexity of MP interactions within biological systems and highlight the species-specific responses to PS MP exposure, which may affect mitochondrial dynamics in diverse ways.

Induction of mitochondrial unfolded protein response (UPR^{mt}) by MPs/NPs

MPs/NPs may also exert their toxic effects by disrupting the mitochondrial unfolded protein response (UPR^{mt}), a protective cellular mechanism that is activated in response to the accumulation of misfolded proteins in mitochondria (Xu et al., 2022). The UPR^{mt} plays a critical role in maintaining mitochondrial proteostasis, thereby contributing to overall mitochondrial health and functionality. Due to their ability to induce oxidative stress and disrupt mitochondrial function, MPs/NPs may lead to protein misfolding within mitochondria. A study by Liu and Wang showed that exposure to PS NP particles with a size of 100 nm significantly increased the expression of HSP6, a marker of the UPR^{mt}, in *Caenorhabditis elegans* (Liu and Wang, 2021). This suggests that NPs may lead to protein misfolding and subsequent activation of the UPR^{mt}. However, chronic activation of the UPR^{mt}, as may occur with continuous or repeated exposure to NPs, may become maladaptive. Prolonged activation of the UPR^{mt} has been associated with mitochondrial dysfunction (Lin et al., 2016). Therefore, MPs/NP-induced activation of the UPR^{mt} may represent another mechanism of their cellular toxicity. In addition, disruption of the UPR^{mt} may have further implications for mitochondrial dynamics, as protein homeostasis is crucial for maintaining balanced fission and fusion processes. Thus, the interaction of MPs/NPs with the UPR^{mt} could add another layer of complexity to their impact on mitochondrial health.

Effects of MPs/NPs on mitophagy

Another important aspect to consider in the interaction between MPs/NPs and mitochondria is the process of mitophagy, the selective degradation of damaged mitochondria by autophagy. This mechanism plays an important role in maintaining cellular homeostasis by removing dysfunctional mitochondria and recycling their components (Onishi et al., 2021). In the context of MP/NP-induced mitochondrial damage, the PINK1/Parkin pathway plays a pivotal role. Upon mitochondrial depolarization or damage, PINK1, a kinase, stabilizes on the outer mitochondrial membrane. This stabilization signals the recruitment of Parkin, an E3 ubiquitin ligase and once Parkin is recruited, it ubiquitinates various mitochondrial proteins (Mfn1, Mfn2, Drp1, and TOM20) marking the damaged mitochondria for degradation (Gegg and Schapira, 2011; Wang et al., 2011; Yoshii et al., 2011). This selective autophagy process, crucial for cellular health, ensures the removal of dysfunctional mitochondria, thereby preventing potential cellular damage induced by MPs/NPs. A study by Xu et al. found that PS NPs with the size of 100 nm accumulated in mitochondria and induced

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Table 2. Summary of in vivo studies assessing the effects of MP/NP exposure on mitochondrial function

Author (year)	Organism	MP/NP type (size)	Concentrations (exposure time)	Outcomes
Wu et al. (2021)	*Tetrahymena thermophila*	PS NP (20 nm)	0.3, 1, 3, 10, and 30 mg/L (24 h)	Ca accumulation in mitochondria, which increased mitochondrial permeability and the generation of ROS
Jeong et al. (2022b)	*Daphnia magna*	PS MP/6 μm (Nonfunctionalized)	0, 2.5, 5, 10, 20, and 30 mg/L (24 /48 h)	Increased oxidative stress; inhibiting the adverse effects of chromium by increasing mitochondrial biogenesis
Zhang et al. (2023)	*Danio rerio*	Freen fluorescent PS NP (100 nm)	1 mg/L (30 days)	Increased ROS; damaged the mitochondrial membrane and mtDNA in brain tissue
Trevisan et al. (2019)	*D. rerio* wild–type zebrafish, transgenic lines Tg (Flk1:EGFP) and Tg(MLS–EGFP)	PS NP (44 nm)	0.1, 1, or 10 ppm (24 or 96 h)	Decreased the mitochondrial coupling efficiency and increased NADH production, suggesting and impairment on ATP production
Zhang et al. (2022b)	One–day–old chicks	PS MP (5 μm)	1, 10, and 100 mg/L (42 days)	Increased ROS; induced mitochondrial damage (TFAM, OPA1, MFN1 and MFN2 down–expression, DRP1 and Fis1 overexpression) and energy metabolism disorders (HK2, PKM2, PDHX and LDH up–regulation) by inhibiting AMPK–PGC–1α pathway in cardiomyocytes.
Xu et al. (2023)	Male–specific pathogen–free BALB/c mice (6 weeks old)	unmodified and fluorescent–labeled PS NP, PS NP–COOH, and PS NP–NH2 (~100 nm)	1 mg/day, gavage (28 days)	Increased PINK1 and Parkin expression and mitophagy in ileum tissues
Lin et al. (2022a)	Male C57BL/6 mice (8 weeks old)	PS NP (94.09 ± 8.07 nm)	5 μg/g body weight, intraperitoneally (once every other day for 2 weeks)	Increased ROS, MDA; decreased T–SOD, GSH and CAT; observed swollen and vacuolized mitochondria in myocardial cells

PINK1/Parkin-mediated mitophagy in mice, likely as an effort to eliminate mitochondria damaged by oxidative stress and mitochondrial dysfunction (Xu et al., 2023). This observation is consistent with the known role of mitophagy as a response to stressful conditions, such as ROS overproduction (Onishi et al., 2021). However, continuous or high-level activation of mitophagy could be detrimental. Prolonged stimulation of mitophagy, especially in the absence of effective biogenesis to replace degraded mitochondria, could lead to overall loss of mitochondrial mass and function, contributing to further cellular stress and even cell death (Kubli and Gustafsson, 2012). Furthermore, the involvement of mitophagy highlights the interconnectedness of the different mitochondrial responses to MP/NP exposure. These findings also emphasize the complex and potentially detrimental effects of MP/NP pollution on mitochondrial health and cellular function, including disruptions in energy production, increased oxidative stress, and induction of apoptotic pathways. The urgent need for targeted research to fully understand the extent of MP/NP toxicity, the implementation of stricter pollution controls to reduce exposure, and the development of innovative solutions to remove existing pollutants from the environment is underscored by these negative outcomes. This will help protect public health and biodiversity. Mitochondrial biogenesis, the formation of new mitochondria within the cell, is another critical cellular process that could be disrupted by exposure to MPs/NPs. Mitochondrial biogenesis is essential for replacing damaged mitochondria and adjusting the mitochondrial population within a cell to meet changing metabolic demands (Kubli and Gustafsson, 2012). Disruption of this process can have a significant impact on cellular health, potentially leading to energy depletion, increased oxidative stress, and increased susceptibility to cell death. Exposure to environmental stressors, such as MPs/NPs, could potentially trigger such disruptions. However, a latest study by Jeong et al. revealed that mitochondrial biogenesis was increased at PS MPs and chromium exposed freshwater flea, *Daphnia magna*, compared to chromium only treated group suggesting that MPs expel chromium from cells (Jeong et al., 2022b). The group exposed to chromium-only showed a decrease in PGC-1a gene expression and an increase in Drp1 gene expression, indicating that chromium may cause mitochondrial dysfunction. However, exposure to both MPs and chromium resulted in increased PGC-1a expression and decreased Drp1 expression, suggesting a potential mitigating effect on mitochondrial dysfunction compared to chromium exposure alone. While the available study provides initial insights into the potential impacts of MPs/NPs on mitochondrial biogenesis in freshwater fleas, including their intriguing role in mitigating the effects of heavy metals, it should be emphasized that this research does not extend to human data. Consequently, a comprehensive understanding and broader conclusions regarding such effects in humans necessitate further in-depth studies.

Conclusion

The toxicity of MPs/NPs is a serious environmental and public health problem that is not yet fully understood. The unique physicochemical properties of these particles, including their small size and large surface area, enable them to penetrate biological membranes and accumulate in various organs where they can induce a

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range of adverse effects. This review has highlighted one particular area of concern - the effects of exposure to MPs/NPs on mitochondria, a critical cellular organelle responsible for energy production and several other vital functions.

Evidence suggests that MPs/NPs can induce mitochondrial dysfunction, primarily through the generation of oxidative stress, which damages mitochondrial components and impairs mitochondrial function. This can result in reduced ATP production, which can disrupt cellular processes and lead to cell death. MPs/NPs have also been found to physically interact with mitochondria, causing structural damage and contributing to functional impairment. These effects can in turn trigger a cascade of cellular responses, from inflammation to apoptosis, contributing to the overall toxicity of MPs/NPs. In addition, exposure to MPs/NPs may disrupt the dynamic processes that maintain mitochondrial health, including mitochondrial dynamics and the UPR^{mt}. Also, emerging research suggests that MPs/NPs could disrupt mitochondrial biogenesis, potentially leading to a decrease in mitochondrial mass and further impairing cellular health and function. Such a chain of detrimental effects highlights the importance of understanding the impact of MP/NP exposure on mitochondria, not only in terms of cellular health but also considering potential systemic effects and long-term effects on organismic health.

Knowledge gaps and future perspectives

Mitochondrial damage and dysfunction are related to numerous health conditions, suggesting that exposure to MPs/NPs could have far-reaching effects on human health. Therefore, it is crucial to investigate the potential impact of MPs and NPs on human cells to raise awareness of this issue and take necessary precautions. The analytical methods used are inadequate to measure the concentration of NPs in the environment and organisms and therefore little is known about the importance of NPs for human health (Science Advice for Policy by European, 2019). Therefore, it is important to first develop analytical methods that can analyze not only MPs but also NPs, which will enable a full understanding of human exposure.

The type of PS NPs that have been shown to cause adverse effects in human and animal cells in in vitro and in vivo studies are primary ones. Primary MPs/NPs have a smooth surface and uniform shape (uniform; nanobeads). Secondary MPs/NPs, on the other hand, are formed in a wide variety of shapes compared to those of primary origin (Koelmans et al., 2015; Lei et al., 2018). At the same time, when primary PS NPs are released into the environment, their structures deteriorate and their properties change after a certain period of time like secondary particles (Im et al., 2022). The shapes of secondary MP/NP particles are amorphous and it has been shown that the negative effects of particles without smooth surfaces on the cell are more than those with smooth surfaces (Qin et al., 2022; Völkl et al., 2022). Therefore, the effects of secondary MPs/NPs, which are more abundant in the environment, need to be investigated and studies need to be designed to realistically assess human exposure.

In addition, the studies in the literature were conducted with commercially available PS-type MPs/NPs. However, MPs/NPs in the environment also consist of other types of plastic polymers other than PS. Therefore, the effects of MPs/NPs composed of these types of plastic polymers on the mitochondria should be investigated as well.

Furthermore, given the wide range of plastic types, sizes, shapes, and chemical compositions present in the environment, research should also focus on investigating whether and how these different factors modulate the effects of MPs/NPs on mitochondria and other cellular components.

The field of MPs/NPs research, particularly in relation to their effects on mitochondria, is still evolving. Existing studies have primarily used in vitro models, and more in vivo and human epidemiological research is needed to validate these findings and gain a more nuanced understanding of these interactions and their implications for organismal health. Such studies will provide a more realistic understanding of exposure levels, uptake mechanisms, and physiological consequences of MP and NP exposure. Moreover, further work is needed to clarify the molecular mechanisms underlying the effects of MPs/NPs on mitochondria and to determine the extent to which these effects contribute to the overall toxicity of these pollutants. Research in this area could help to inform risk assessments and guide the development of strategies to mitigate the effects of NP and MP pollution.

In the production of plastics, some additives (UV stabilizers, antioxidants, plasticizers (such as phthalate diester), colorants, fillers, etc.) are added to the products along with the polymer (Murphy, 2001; Ventrice et al., 2013; ECHA, 2018). There are many studies revealing the effects of these chemicals added to plastics on animals and humans (Gray Jr et al., 2000; Frederiksen et al., 2007; Lyche et al., 2009; Svensson et al., 2011; Ding et al., 2021). NP/MP act as vectors for toxic chemical contaminants and pathogenic microbes by sorbing to their surfaces and cavities (Rai et al., 2022). MPs/NPs have certain properties that facilitate their ability to adsorb various environmental pollutants. In this way, they increase exposure to these chemicals along with themselves (Sun et al., 2023a). The combined effects of these chemicals need to be taken into account when elucidating the effects of MPs/NPs on mitochondria and other cell components.

This extensive body of information emphasizes the importance of increasing awareness among individuals, communities, industries, and policymakers about the potential health risks associated with MP and NP pollution. These risks include respiratory problems, endocrine disruption, and other long-term health effects. There is an urgent need for comprehensive research to better understand the impacts of plastic pollution. Effective waste management practices should be implemented to reduce pollution at the source. Policies aimed at minimizing the production and use of plastic products are necessary to protect human health and the environment. This awareness should be channeled into individual action and policy development aimed at reducing plastic waste and promoting sustainable alternatives. In addition, further research is crucial to fill gaps in our understanding of the impacts of MPs/NPs on human health, particularly the long-term effects. More comprehensive studies are needed to better characterize human MPs/NPs exposure to elucidate their mechanisms of action in our bodies, and to identify potential strategies to mitigate their impacts. The public should also be aware that these findings are based on experimental models and while they indicate potential risks, the actual human health outcomes from real-world exposure scenarios might differ, which further underscores the need for ongoing research in this field. These potential risks underscore the urgency to better understand the precise mechanisms of MP and NP toxicity and to develop effective strategies to mitigate their presence in our environment. The collective effort towards these goals will necessitate cross-disciplinary collaboration encompassing environmental science, toxicology, public health, policymaking, and more.

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Open peer review. To view the open peer review materials for this article, please visit http://doi.org/10.1017/plc.2024.6.

Author contribution. F.D.Y. and M.A.A. contributed equally to the conception, design, and writing of the review article. They conducted the literature search, analyzed the selected articles, and synthesized the information in the review. Both authors participated in drafting and revising the manuscript. They read and approved the final version of the manuscript.

Financial support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interest. The authors declare no conflicts of interest.

References

Amato-Lourenço LF, Carvalho-Oliveira R, Júnior GR, Dos Santos Galvão L, Ando RA and Mauad T (2021) Presence of airborne microplastics in human lung tissue. *Journal of Hazardous Materials* **416**, 126124. https://doi.org/10.1016/j.jhazmat.2021.126124.

Andrady AL (2015) Persistence of plastic litter in the oceans. In Bergmann M, Gutow L and Klages M (eds), *Marine Anthropogenic Litter*. Cham: Springer International Publishing, pp. 57–72.

Atkins K, Dasgupta A, Chen KH, Mewburn J and Archer SL (2016) The role of Drp1 adaptor proteins MiD49 and MiD51 in mitochondrial fission: Implications for human disease. *Clinical Science (London, England)* **130**(21), 1861–1874. https://doi.org/10.1042/CS20160030.

Bergmann M, Gutow L, and Klages M (2015) *Marine Anthropogenic Litter*. Cham: Springer. SpringerLink (Online service).

Besseling E, Redondo-Hasselerharm P, Foekema EM and Koelmans AA (2019) Quantifying ecological risks of aquatic micro- and nanoplastic. *Critical Reviews in Environmental Science and Technology* **49**(1), 32–80. https://doi.org/10.1080/10643389.2018.1531688.

Bleazard W, McCaffery JM, King EJ, Bale S, Mozdy A, Tieu Q, Nunnari J and Shaw JM (1999) The dynamin-related GTPase Dnm1 regulates mitochondrial fission in yeast. *Nature Cell Biology* **1**(5), 298–304. https://doi.org/10.1038/13014.

Burgos-Morón E, Abad-Jiménez Z, Martínez de Marañón A, Iannantuoni F, Escribano-López I, López-Domènech S, Salom C, Jover A, Mora V, Roldan I, Solá E, Rocha M and Víctor VM (2019) Relationship between oxidative stress, ER stress, and inflammation in type 2 diabetes: The Battle continues. *Journal of Clinical Medicine* **8**(9), 1385.

Calì T, Ottolini D and Brini M (2011) Mitochondria, calcium, and endoplasmic reticulum stress in Parkinson's disease. *BioFactors* **37**(3), 228–240. https://doi.org/10.1002/biof.159.

Celebi Sözener Z, Cevhertas L, Nadeau K, Akdis M and Akdis CA (2020) Environmental factors in epithelial barrier dysfunction. *Journal of Allergy and Clinical Immunology* **145**(6), 1517–1528. https://doi.org/10.1016/j.jaci.2020.04.024.

Chen J, Xu Z, Liu Y, Mei A, Wang X and Shi Q (2023) Cellular absorption of polystyrene nanoplastics with different surface functionalization and the toxicity to RAW264.7 macrophage cells. *Ecotoxicology and Environmental Safety* **252**, 114574. https://doi.org/10.1016/j.ecoenv.2023.114574.

Chen YC, Chen KF, Lin KA, Chen JK, Jiang XY and Lin CH (2022) The nephrotoxic potential of polystyrene microplastics at realistic environmental concentrations. *Journal of Hazardous Materials* **427**, 127871. https://doi.org/10.1016/j.jhazmat.2021.127871.

Crawford CB and Quinn B (2017) *Microplastic Pollutants*. Amsterdam: Elsevier.

De Sá LC, Oliveira M, Ribeiro F, Rocha TL and Futter MN (2018) Studies of the effects of microplastics on aquatic organisms: What do we know and where should we focus our efforts in the future? *Science of the Total Environment* **645**, 1029–1039.

Deng Y, Yan Z, Shen R, Huang Y, Ren H and Zhang Y (2021) Enhanced reproductive toxicities induced by phthalates contaminated microplastics in male mice (Mus musculus). *Journal of Hazardous Materials* **406**, 124644. https://doi.org/10.1016/j.jhazmat.2020.124644.

Ding Y, Xu T, Mao G, Chen Y, Qiu X, Yang L, Zhao T, Xu X, Feng W and Wu X (2021) Di-(2-ethylhexyl) phthalate-induced hepatotoxicity exacerbated type 2 diabetes mellitus (T2DM) in female pubertal T2DM mice. *Food and Chemical Toxicology* **149**, 112003. https://doi.org/10.1016/j.fct.2021.112003.

ECHA (2018) EC (European Commission). Commission Regulation (EU) 2018/2005 of 17 December 2018 Amending Annex XVII to REGULATION (EC) No 1907/2006 of the European Parliament and of the Council Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as Regards Bis(2-ethylhexyl) Phthalate (DEHP), Dibutyl Phthalate (DBP), Benzyl Butyl Phthalate (BBP) and Diisobutyl Phthalate (DIBP).

EFSA (2016) EFSA Panel on Contaminants in the Food Chain: Presence of microplastics and nanoplastics in food, with particular focus on seafood. 1831–4732.

European Commission, Directorate-General for Research and Innovation (2019) *Environmental and health risks of microplastic pollution.* Publications Office of the European Union.

Fan X, Wei X, Hu H, Zhang B, Yang D, Du H, Zhu R, Sun X, Oh Y and Gu N (2022) Effects of oral administration of polystyrene nanoplastics on plasma glucose metabolism in mice. *Chemosphere* **288**(Pt 3), 132607. https://doi.org/10.1016/j.chemosphere.2021.132607.

Florance I, Chandrasekaran N, Gopinath PM and Mukherjee A (2022) Exposure to polystyrene nanoplastics impairs lipid metabolism in human and murine macrophages in vitro. *Ecotoxicology and Environmental Safety* **238**, 113612. https://doi.org/10.1016/j.ecoenv.2022.113612.

Forte M, Iachetta G, Tussellino M, Carotenuto R, Prisco M, De Falco M, Laforgia V and Valiante S (2016) Polystyrene nanoparticles internalization in human gastric adenocarcinoma cells. *Toxicology In Vitro* **31**, 126–136. https://doi.org/10.1016/j.tiv.2015.11.006.

Frederiksen H, Skakkebaek NE and Andersson AM (2007) Metabolism of phthalates in humans. *Molecular Nutrition & Food Research* **51**(7), 899–911. https://doi.org/10.1002/mnfr.200600243.

Fu Y, Fan M, Xu L, Wang H, Hu Q and Jin Y (2022) Amino-functionalized polystyrene nano-plastics induce mitochondria damage in human umbilical vein endothelial cells. *Toxics* **10**(5), 215. https://doi.org/10.3390/toxics10050215.

Gegg ME and Schapira AH (2011) PINK1-parkin-dependent mitophagy involves ubiquitination of mitofusins 1 and 2: Implications for Parkinson disease pathogenesis. *Autophagy* **7**(2), 243–245. https://doi.org/10.4161/auto.7.2.14332.

Gray Jr LE, Ostby J, Furr J, Price M, Veeramachaneni DNR and Parks L (2000) Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicological Sciences* **58**(2), 350–365. https://doi.org/10.1093/toxsci/58.2.350.

Hale RC, Seeley ME, La Guardia MJ, Mai L and Zeng EY (2020) A global perspective on microplastics. *Journal of Geophysical Research: Oceans* **125**(1), e2018JC014719. https://doi.org/10.1029/2018JC014719.

Halimu G, Zhang Q, Liu L, Zhang Z, Wang X, Gu W, Zhang B, Dai Y, Zhang H, Zhang C and Xu M (2022) Toxic effects of nanoplastics with different sizes and surface charges on epithelial-to-mesenchymal transition in A549 cells and the potential toxicological mechanism. *Journal of Hazardous Materials* **430**, 128485. https://doi.org/10.1016/j.jhazmat.2022.128485.

Hermsen E, Mintenig SM, Besseling E and Koelmans AA (2018) Quality criteria for the analysis of microplastic in biota samples: A critical review. *Environmental Science & Technology* **52**(18), 10230–10240.

Herst PM, Rowe MR, Carson GM and Berridge MV (2017) Functional mitochondria in health and disease. *Frontiers in Endocrinology* **8**, 296–296. https://doi.org/10.3389/fendo.2017.00296.

Im GB, Kim YG, Jo IS, Yoo TY, Kim SW, Park HS, Hyeon T, Yi GR and Bhang SH (2022) Effect of polystyrene nanoplastics and their degraded forms on stem cell fate. *Journal of Hazardous Materials* **430**, 128411. https://doi.org/10.1016/j.jhazmat.2022.128411.

Jenner LC, Rotchell JM, Bennett RT, Cowen M, Tentzeris V and Sadofsky LR (2022) Detection of microplastics in human lung tissue using μFTIR spectroscopy. *Science of the Total Environment* **831**, 154907. https://doi.org/10.1016/j.scitotenv.2022.154907.

Jeong B, Baek JY, Koo J, Park S, Ryu Y-K, Kim K-S, Zhang S, Chung C, Dogan R, Choi H-S, Um D, Kim T-K, Lee WS, Jeong J, Shin W-H, Lee J-R, Kim N-S

and Lee DY (2022a) Maternal exposure to polystyrene nanoplastics causes brain abnormalities in progeny. *Journal of Hazardous Materials* **426**, 127815. https://doi.org/10.1016/j.jhazmat.2021.127815.

Jeong H, **Lee YH**, **Sayed AEH**, **Jeong CB**, **Zhou B**, **Lee JS and Byeon E** (2022b) Short- and long-term single and combined effects of microplastics and chromium on the freshwater water flea Daphnia magna. *Aquatic Toxicology* **253**, 106348. https://doi.org/10.1016/j.aquatox.2022.106348.

Kayan A and Küçük A (2020) Plastik Kirliliğin Çevresel Zararları ve Çözüm Önerileri. *Ankara Hacı Bayram Veli Üniversitesi İktisadi ve İdari Bilimler Fakültesi Dergisi* **22**(2), 25.

Klages M, **Gutow L and Bergmann M** (2015) *Marine Anthropogenic Litter*. Cham, Switzerland: Springer.

Koelmans AA, **Besseling E and Shim WJ** (2015) Nanoplastics in the aquatic environment. Critical review. In Bergmann M, Gutow L and Klages M (eds), *Marine Anthropogenic Litter*. Cham: Springer International Publishing, pp. 325–340.

Koelmans AA, **Gouin T**, **Thompson R**, **Wallace N and Arthur C** (2014) Plastics in the marine environment. *Environmental Toxicology and Chemistry* **33**(1), 5–10. https://doi.org/10.1002/etc.2426.

Koner S, **Florance I**, **Mukherjee A and Chandrasekaran N** (2023) Cellular response of THP-1 macrophages to polystyrene microplastics exposure. *Toxicology* **483**, 153385. https://doi.org/10.1016/j.tox.2022.153385.

Kosuth M, **Mason SA and Wattenberg EV** (2018) Anthropogenic contamination of tap water, beer, and sea salt. *PLoS One* **13**(4), e0194970.

Kubli DA and Gustafsson AB (2012) Mitochondria and mitophagy: The yin and yang of cell death control. *Circulation Research* **111**(9), 1208–1221. https://doi.org/10.1161/CIRCRESAHA.112.265819.

Laglbauer BJL, **Franco-Santos RM**, **Andreu-Cazenave M**, **Brunelli L**, **Papadatou M**, **Palatinus A**, **Grego M and Deprez T** (2014) Macrodebris and microplastics from beaches in Slovenia. *Marine Pollution Bulletin* **89**(1–2), 356–366. https://doi.org/10.1016/j.marpolbul.2014.09.036.

Lee C, **Zeng J**, **Drew BG**, **Sallam T**, **Martin-Montalvo A**, **Wan J**, **Kim SJ**, **Mehta H**, **Hevener AL**, **de Cabo R and Cohen P** (2015) The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metabolism* **21**(3), 443–454. https://doi.org/10.1016/j.cmet.2015.02.009.

Lee SE, **Yi Y**, **Moon S**, **Yoon H and Park YS** (2022) Impact of micro- and nanoplastics on mitochondria. *Metabolites* **12**(10), 897. https://doi.org/10.3390/metabo12100897.

Lei L, **Liu M**, **Song Y**, **Lu S**, **Hu J**, **Cao C**, **Xie B**, **Shi H and He D** (2018) Polystyrene (nano)microplastics cause size-dependent neurotoxicity, oxidative damage and other adverse effects in Caenorhabditis elegans. *Environmental Science: Nano* **5**(8), 2009–2020. https://doi.org/10.1039/C8EN00412A.

Leslie HA, **van Velzen MJM**, **Brandsma SH**, **Vethaak AD**, **Garcia-Vallejo JJ and Lamoree MH** (2022) Discovery and quantification of plastic particle pollution in human blood. *Environment International* **163**, 107199. https://doi.org/10.1016/j.envint.2022.107199.

Li S, **Ma Y**, **Ye S**, **Tang S**, **Liang N**, **Liang Y and Xiao F** (2021) Polystyrene microplastics trigger hepatocyte apoptosis and abnormal glycolytic flux via ROS-driven calcium overload. *Journal of Hazardous Materials* **417**, 126025. https://doi.org/10.1016/j.jhazmat.2021.126025.

Li Y, **Guo M**, **Niu S**, **Shang M**, **Chang X**, **Sun Z**, **Zhang R**, **Shen X and Xue Y** (2023a) ROS and DRP1 interactions accelerate the mitochondrial injury induced by polystyrene nanoplastics in human liver HepG2 cells. *Chemico-Biological Interactions* **379**, 110502. https://doi.org/10.1016/j.cbi.2023.110502.

Li Y, **Xu M**, **Zhang Z**, **Halimu G**, **Li Y**, **Li Y**, **Gu W**, **Zhang B and Wang X** (2022) In vitro study on the toxicity of nanoplastics with different charges to murine splenic lymphocytes. *Journal of Hazardous Materials* **424**(Pt B), 127508. https://doi.org/10.1016/j.jhazmat.2021.127508.

Li Z, **Xu T**, **Peng L**, **Tang X**, **Chi Q**, **Li M and Li S** (2023b) Polystyrene nanoplastics aggravates lipopolysaccharide-induced apoptosis in mouse kidney cells by regulating IRE1/XBP1 endoplasmic reticulum stress pathway via oxidative stress. *Journal of Cellular Physiology* **238**(1), 151–164. https://doi.org/10.1002/jcp.30913.

Liang B, **Huang Y**, **Zhong Y**, **Li Z**, **Ye R**, **Wang B**, **Zhang B**, **Meng H**, **Lin X**, **Du J**, **Hu M**, **Wu Q**, **Sui H**, **Yang X and Huang Z** (2022) Brain single-nucleus transcriptomics highlights that polystyrene nanoplastics potentially induce Parkinson's disease-like neurodegeneration by causing energy metabolism disorders in mice. *Journal of Hazardous Materials* **430**, 128459. https://doi.org/10.1016/j.jhazmat.2022.128459.

Lim SL, **Ng CT**, **Zou L**, **Lu Y**, **Chen J**, **Bay BH**, **Shen HM and Ong CN** (2019) Targeted metabolomics reveals differential biological effects of nanoplastics and nanoZnO in human lung cells. *Nanotoxicology* **13**(8), 1117–1132. https://doi.org/10.1080/17435390.2019.1640913.

Lin P, **Tong X**, **Xue F**, **Qianru C**, **Xinyu T**, **Zhe L**, **Zhikun B and Shu L** (2022a) Polystyrene nanoplastics exacerbate lipopolysaccharide-induced myocardial fibrosis and autophagy in mice via ROS/TGF-beta1/Smad. *Toxicology* **480**, 153338. https://doi.org/10.1016/j.tox.2022.153338.

Lin S, **Zhang H**, **Wang C**, **Su X-L**, **Song Y**, **Wu P**, **Yang Z**, **Wong M-H**, **Cai Z and Zheng C** (2022b) Metabolomics reveal nanoplastic-induced mitochondrial damage in human liver and lung cells. *Environmental Science & Technology* **56**(17), 12483–12493. https://doi.org/10.1021/acs.est.2c03980.

Lin YF, **Schulz AM**, **Pellegrino MW**, **Lu Y**, **Shaham S and Haynes CM** (2016) Maintenance and propagation of a deleterious mitochondrial genome by the mitochondrial unfolded protein response. *Nature* **533**(7603), 416–419. https://doi.org/10.1038/nature17989.

Liu H and Wang D (2021) Intestinal mitochondrial unfolded protein response induced by nanoplastic particles in Caenorhabditis elegans. *Chemosphere* **267**, 128917. https://doi.org/10.1016/j.chemosphere.2020.128917.

Liu T, **Hou B**, **Wang Z and Yang Y** (2022) Polystyrene microplastics induce mitochondrial damage in mouse GC-2 cells. *Ecotoxicology and Environmental Safety* **237**, 113520. https://doi.org/10.1016/j.ecoenv.2022.113520.

Lusher A, **Hollman P and Mendoza-Hill J** (2017) *Microplastics in Fisheries and Aquaculture: Status of Knowledge on their Occurrence and Implications for Aquatic Organisms and Food Safety*. FAO Fisheries and Aquaculture Technical Paper (615), I, III, IV, V, X, XI, XV, XVI, XVII, 1-7, 9-35, 37-53, 55-65, 67-69, 71-73, 75-83, 85-123, 125, 126.

Lusher AL, **Mchugh M and Thompson RC** (2013) Occurrence of microplastics in the gastrointestinal tract of pelagic and demersal fish from the English Channel. *Marine Pollution Bulletin* **67**(1–2), 94–99.

Lyche JL, **Gutleb AC**, **Bergman A**, **Eriksen GS**, **Murk AJ**, **Ropstad E**, **Saunders M and Skaare JU** (2009) Reproductive and developmental toxicity of phthalates. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* **12**(4), 225–249. https://doi.org/10.1080/10937400903094091.

Mason SA, **Welch VG and Neratko J** (2018) Synthetic polymer contamination in bottled water. *Frontiers in Chemistry* **6**, 407.

Mattsson K, **Jocic S**, **Doverbratt I and Hansson L-A** (2018) Chapter 13 - Nanoplastics in the aquatic environment. In Zeng EY (ed), *Microplastic Contamination in Aquatic Environments*. Elsevier, pp. 379–399. https://doi.org/10.1016/B978-0-12-813747-5.00013-8.

McDevitt JP, **Criddle CS**, **Morse M**, **Hale RC**, **Bott CB and Rochman CM** (2017) Addressing the issue of microplastics in the wake of the microbead-free waters act-a new standard can facilitate improved policy. *Environmental Science & Technology* **51**(12), 6611–6617. https://doi.org/10.1021/acs.est.6b05812.

Meindl C, **Kueznik T**, **Bosch M**, **Roblegg E and Frohlich E** (2015) Intracellular calcium levels as screening tool for nanoparticle toxicity. *Journal of Applied Toxicology* **35**(10), 1150–1159. https://doi.org/10.1002/jat.3160.

Meng X, **Zhang J**, **Wang W**, **Gonzalez-Gil G**, **Vrouwenvelder JS and Li Z** (2022) Effects of nano- and microplastics on kidney: Physicochemical properties, bioaccumulation, oxidative stress and immunoreaction. *Chemosphere* **288**(Pt 3), 132631. https://doi.org/10.1016/j.chemosphere.2021.132631.

Mintenig S, **Löder M**, **Primpke S and Gerdts G** (2019) Low numbers of microplastics detected in drinking water from ground water sources. *Science of the Total Environment* **648**, 631–635.

Mintenig SM, **Int-Veen I**, **Löder MG**, **Primpke S and Gerdts G** (2017) Identification of microplastic in effluents of waste water treatment plants using focal plane array-based micro-Fourier-transform infrared imaging. *Water Research* **108**, 365–372.

Mozdy AD, **McCaffery JM and Shaw JM** (2000) Dnm1p GTPase-mediated mitochondrial fission is a multi-step process requiring the novel integral membrane component Fis1p. *Journal of Cell Biology* **151**(2), 367–380. https://doi.org/10.1083/jcb.151.2.367.

Murphy J (2001) *Additives for Plastics Handbook*. Oxford, UK: Elsevier. https://doi.org/10.1016/B978-1-85617-370-4.50035-X.

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Onishi M, **Yamano K**, **Sato M**, **Matsuda N and Okamoto K** (2021) Molecular mechanisms and physiological functions of mitophagy. *EMBO Journal* **40**(3), e104705. https://doi.org/10.15252/embj.2020104705.

Pinto Da Costa J, **Rocha-Santos T and Duarte AC** (2020) The environmental impacts of plastics and micro-plastics use, waste and pollution: EU and national measures. © European Union.

PlasticsEurope (2021) What are plastics? Available at https://www.plasticseurope.org/en/about-plastics/what-are-plastics (accessed).

PlasticsEurope (2022) Plastics–The Facts 2022. Available at https://plasticseurope.org/wp-content/uploads/2022/10/PE-PLASTICS-THE-FACTS_V7-Tue_19-10-1.pdf (accessed).

Prata JC, **da Costa JP**, **Lopes I**, **Duarte AC and Rocha-Santos T** (2020) Environmental exposure to microplastics: An overview on possible human health effects. *Science of the Total Environment* **702**, 134455. https://doi.org/10.1016/j.scitotenv.2019.134455.

Prietl B, **Meindl C**, **Roblegg E**, **Pieber TR**, **Lanzer G and Fröhlich E** (2014) Nano-sized and micro-sized polystyrene particles affect phagocyte function. *Cell Biology and Toxicology* **30**(1), 1–16. https://doi.org/10.1007/s10565-013-9265-y.

Qin J, **Xia P-F**, **Yuan X-Z and Wang S-G** (2022) Chlorine disinfection elevates the toxicity of polystyrene microplastics to human cells by inducing mitochondria-dependent apoptosis. *Journal of Hazardous Materials* **425**, 127842. https://doi.org/10.1016/j.jhazmat.2021.127842.

Ragusa A, **Svelato A**, **Santacroce C**, **Catalano P**, **Notarstefano V**, **Carnevali O**, **Papa F**, **Rongioletti MCA**, **Baiocco F**, **Draghi S**, **D'Amore E**, **Rinaldo D**, **Matta M and Giorgini E** (2021) Plasticenta: First evidence of microplastics in human placenta. *Environment International* **146**, 106274. https://doi.org/10.1016/j.envint.2020.106274.

Rai PK, **Sonne C**, **Brown RJC**, **Younis SA and Kim KH** (2022) Adsorption of environmental contaminants on micro- and nano-scale plastic polymers and the influence of weathering processes on their adsorptive attributes. *Journal of Hazardous Materials* **427**, 127903. https://doi.org/10.1016/j.jhazmat.2021.127903.

Rana SVS (2020) Endoplasmic reticulum stress induced by toxic elements—A review of recent developments. *Biological Trace Element Research* **196**(1), 10–19. https://doi.org/10.1007/s12011-019-01903-3.

Revel M, **Châtel A and Mouneyrac C** (2018) Micro(nano)plastics: A threat to human health? *Current Opinion in Environmental Science & Health* **1**, 17–23. https://doi.org/10.1016/j.coesh.2017.10.003.

Ryan PG, **Moore CJ**, **Franeker JAv and Moloney CL** (2009) Monitoring the abundance of plastic debris in the marine environment. *Philosophical Transactions of the Royal Society B: Biological Sciences* **364**(1526), 1999–2012. https://doi.org/10.1098/rstb.2008.0207.

Ryter SW, **Rosas IO**, **Owen CA**, **Martinez FJ**, **Choi ME**, **Lee CG**, **Elias JA and Choi AMK** (2018) Mitochondrial dysfunction as a pathogenic mediator of chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Annals of the American Thoracic Society* **15**(Suppl 4), S266–S272. https://doi.org/10.1513/AnnalsATS.201808-585MG.

Saenen ND, **Witters MS**, **Hantoro I**, **Tejeda I**, **Ethirajan A**, **Van Belleghem F and Smeets K** (2023) Polystyrene microplastics of varying sizes and shapes induce distinct redox and mitochondrial stress responses in a Caco-2 monolayer. *Antioxidants* **12**(3), 739.

Salimi A, **Alavehzadeh A**, **Ramezani M and Pourahmad J** (2022) Differences in sensitivity of human lymphocytes and fish lymphocytes to polyvinyl chloride microplastic toxicity. *Toxicology and Industrial Health* **38**(2), 100–111. https://doi.org/10.1177/07482337211065832.

Santos D, **Luzio A**, **Felix L**, **Bellas J and Monteiro SM** (2022) Oxidative stress, apoptosis and serotonergic system changes in zebrafish (Danio rerio) gills after long-term exposure to microplastics and copper. *Comparative Biochemistry and Physiology Part C Toxicol Pharmacol* **258**, 109363. https://doi.org/10.1016/j.cbpc.2022.109363.

Schwabl P, **Köppel S**, **Königshofer P**, **Bucsics T**, **Trauner M**, **Reiberger T and Liebmann B** (2019) Detection of various microplastics in human stool: A prospective case series. *Annals of Internal Medicine* **171**(7), 453–457. https://doi.org/10.7326/m19-0618.

Science Advice for Policy by European A (2019) *A Scientific Perspective on Microplastics in Nature and Society*. Berlin: Science Advice for Policy by European Academies.

Shacham T, **Sharma N and Lederkremer GZ** (2019) Protein misfolding and ER stress in Huntington's disease. *Frontiers in Molecular Biosciences* **6**, 20. https://doi.org/10.3389/fmolb.2019.00020.

Smirnova E, **Griparic L**, **Shurland DL and van der Bliek AM** (2001) Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. *Molecular Biology of the Cell* **12**(8), 2245–2256. https://doi.org/10.1091/mbc.12.8.2245.

Sun N, **Shi H**, **Li X**, **Gao C and Liu R** (2023a) Combined toxicity of micro/nanoplastics loaded with environmental pollutants to organisms and cells: Role, effects, and mechanism. *Environment International* **171**, 107711. https://doi.org/10.1016/j.envint.2022.107711.

Sun Z, **Wen Y**, **Zhang F**, **Fu Z**, **Yuan Y**, **Kuang H**, **Kuang X**, **Huang J**, **Zheng L and Zhang D** (2023b) Exposure to nanoplastics induces mitochondrial impairment and cytomembrane destruction in Leydig cells. *Ecotoxicology and Environmental Safety* **255**, 114796. https://doi.org/10.1016/j.ecoenv.2023.114796.

Svensson K, **Hernández-Ramírez RU**, **Burguete-García A**, **Cebrián ME**, **Calafat AM**, **Needham LL**, **Claudio L and López-Carrillo L** (2011) Phthalate exposure associated with self-reported diabetes among Mexican women. *Environmental Research* **111**(6), 792–796. https://doi.org/10.1016/j.envres.2011.05.015.

Tekman MB, **Gutow L**, **Macario A**, **Haas A**, **Walter A and Bergmann M** (2021) Litterbase. Available at https://litterbase.awi.de/ (accessed).

Ter Halle A, **Jeanneau L**, **Martignac M**, **Jardé E**, **Pedrono B**, **Brach L and Gigault J** (2017) Nanoplastic in the North Atlantic subtropical gyre. *Environmental Science & Technology* **51**(23), 13689–13697. https://doi.org/10.1021/acs.est.7b03667.

Thannickal VJ and Fanburg BL (2000) Reactive oxygen species in cell signaling. *American Journal of Physiology. Lung Cellular and Molecular Physiology* **279**(6), L1005–1028. https://doi.org/10.1152/ajplung.2000.279.6.L1005.

Thompson R, **Moore C**, **Andrady A**, **Gregory M**, **Takada H and Weisberg S** (2005) New directions in plastic debris. *Science* **310**(5751), 1117. https://doi.org/10.1126/science.310.5751.1117b.

Thompson RC, **Olsen Y**, **Mitchell RP**, **Davis A**, **Rowland SJ**, **John AWG**, **McGonigle D and Russell AE** (2004) Lost at sea: Where is all the plastic? *Science* **304**(5672), 838–838. https://doi.org/10.1126/science.1094559.

Thompson RC, **Swan SH**, **Moore CJ and vom Saal FS** (2009) Our plastic age. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **364**(1526), 1973–1976. https://doi.org/10.1098/rstb.2009.0054.

Tieu Q and Nunnari J (2000) Mdv1p is a WD repeat protein that interacts with the dynamin-related GTPase, Dnm1p, to trigger mitochondrial division. *Journal of Cell Biology* **151**(2), 353–366. https://doi.org/10.1083/jcb.151.2.353.

Trevisan R, **Voy C**, **Chen S and Di Giulio RT** (2019) Nanoplastics decrease the toxicity of a complex PAH mixture but impair mitochondrial energy production in developing zebrafish. *Environmental Science & Technology* **53**(14), 8405–8415. https://doi.org/10.1021/acs.est.9b02003.

Ventrice P, **Ventrice D**, **Russo E and De Sarro G** (2013) Phthalates: European regulation, chemistry, pharmacokinetic and related toxicity. *Environmental Toxicology and Pharmacology* **36**(1), 88–96. https://doi.org/10.1016/j.etap.2013.03.014.

Vert M, **Doi Y**, **Hellwich K-H**, **Hess M**, **Hodge P**, **Kubisa P**, **Rinaudo M and Schué F** (2012) Terminology for biorelated polymers and applications (IUPAC recommendations 2012). *Pure and Applied Chemistry* **84**(2), 377–410. https://doi.org/10.1351/PAC-REC-10-12-04.

Villarrubia-Gómez P, **Cornell SE and Fabres J** (2018) Marine plastic pollution as a planetary boundary threat – The drifting piece in the sustainability puzzle. *Marine Policy* **96**, 213–220. https://doi.org/10.1016/j.marpol.2017.11.035.

Völkl M, **Jérôme V**, **Weig A**, **Jasinski J**, **Meides N**, **Strohriegl P**, **Scheibel T and Freitag R** (2022) Pristine and artificially-aged polystyrene microplastic particles differ in regard to cellular response. *Journal of Hazardous Materials* **435**, 128955. https://doi.org/10.1016/j.jhazmat.2022.128955.

Wagner M and Lambert S (2018) *Freshwater Microplastics: Emerging Environmental Contaminants?* Cham: Springer Nature.

Wagner S, **Hüffer T**, **Klöckner P**, **Wehrhahn M**, **Hofmann T and Reemtsma T** (2018) Tire wear particles in the aquatic environment-A review on generation, analysis, occurrence, fate and effects. *Water Research* **139**, 83–100.

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press

Wang H, **Shi X**, **Gao Y**, **Zhang X**, **Zhao H**, **Wang L**, **Zhang X and Chen R** (2022a) Polystyrene nanoplastics induce profound metabolic shift in human cells as revealed by integrated proteomic and metabolomic analysis. *Environment International* **166**, 107349. https://doi.org/10.1016/j.envint.2022.107349.

Wang H, **Song P**, **Du L**, **Tian W**, **Yue W**, **Liu M**, **Li D**, **Wang B**, **Zhu Y**, **Cao C**, **Zhou J and Chen Q** (2011) Parkin ubiquitinates Drp1 for proteasome-dependent degradation: Implication of dysregulated mitochondrial dynamics in Parkinson disease. *Journal of Biological Chemistry* **286**(13), 11649–11658. https://doi.org/10.1074/jbc.M110.144238.

Wang Q, **Bai J**, **Ning B**, **Fan L**, **Sun T**, **Fang Y**, **Wu J**, **Li S**, **Duan C**, **Zhang Y**, **Liang J and 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 X, **Zhang X**, **Sun K**, **Wang S and Gong D** (2022b) Polystyrene microplastics induce apoptosis and necroptosis in swine testis cells via ROS/MAPK/HIF1alpha pathway. *Environmental Toxicology* **37**(10), 2483–2492. https://doi.org/10.1002/tox.23611.

Wang Y, **Wei Z**, **Xu K**, **Wang X**, **Gao X**, **Han Q**, **Wang S and Chen M** (2023) The effect and a mechanistic evaluation of polystyrene nanoplastics on a mouse model of type 2 diabetes. *Food and Chemical Toxicology* **173**, 113642. https://doi.org/10.1016/j.fct.2023.113642.

Wang Y-L, **Lee Y-H**, **Hsu Y-H**, **Chiu I-J**, **Huang CC-Y**, **Huang C-C**, **Chia Z-C**, **Lee C-P**, **Lin Y-F and Chiu H-W** (2021) The kidney-related effects of polystyrene microplastics on human kidney proximal tubular epithelial cells HK-2 and male C57BL/6 mice. *Environmental Health Perspectives* **129**(5), 057003. https://doi.org/10.1289/EHP7612.

Wu B, **Wu X**, **Liu S**, **Wang Z and Chen L** (2019) Size-dependent effects of polystyrene microplastics on cytotoxicity and efflux pump inhibition in human Caco-2 cells. *Chemosphere* **221**, 333–341. https://doi.org/10.1016/j.chemosphere.2019.01.056.

Wu C, **Guo W-B**, **Liu Y-Y**, **Yang L and Miao A-J** (2021) Perturbation of calcium homeostasis and multixenobiotic resistance by nanoplastics in the ciliate Tetrahymena thermophila. *Journal of Hazardous Materials* **403**, 123923. https://doi.org/10.1016/j.jhazmat.2020.123923.

Wu Y, **Wang J**, **Zhao T**, **Sun M**, **Xu M**, **Che S**, **Pan Z**, **Wu C and Shen L** (2023) Polystyrenenanoplastics lead to ferroptosis in the lungs. *Journal of Advanced Research* **56**, 31. https://doi.org/10.1016/j.jare.2023.03.003.

Xu D, **Ma Y**, **Han X and Chen Y** (2021) Systematic toxicity evaluation of polystyrene nanoplastics on mice and molecular mechanism investigation about their internalization into Caco-2 cells. *Journal of Hazardous Materials* **417**, 126092. https://doi.org/10.1016/j.jhazmat.2021.126092.

Xu D, **Ma Y**, **Peng C**, **Gan Y**, **Wang Y**, **Chen Z**, **Han X and Chen Y** (2023) Differently surface-labeled polystyrene nanoplastics at an environmentally relevant concentration induced Crohn's ileitis-like features via triggering intestinal epithelial cell necroptosis. *Environment International* **176**, 107968. https://doi.org/10.1016/j.envint.2023.107968.

Xu M, **Halimu G**, **Zhang Q**, **Song Y**, **Fu X**, **Li Y**, **Li Y and Zhang H** (2019a) Internalization and toxicity: A preliminary study of effects of nanoplastic particles on human lung epithelial cell. *Science of the Total Environment* **694**, 133794. https://doi.org/10.1016/j.scitotenv.2019.133794.

Xu R, **Hua X**, **Rui Q and Wang D** (2022) Polystyrene nanoparticles cause dynamic alteration in mitochondrial unfolded protein response from parents to the offspring in C. Elegans. *Chemosphere* **308**(Pt 1), 136154. https://doi.org/10.1016/j.chemosphere.2022.136154.

Xu S, **Di Z**, **He Y**, **Wang R**, **Ma Y**, **Sun R**, **Li J**, **Wang T**, **Shen Y**, **Fang S**, **Feng L and Shen Y** (2019b) Mesencephalic astrocyte-derived neurotrophic factor (MANF) protects against Aβ toxicity via attenuating Aβ-induced endoplasmic reticulum stress. *Journal of Neuroinflammation* **16**(1), 35. https://doi.org/10.1186/s12974-019-1429-0.

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

Yang CS, **Chang CH**, **Tsai PJ**, **Chen WY**, **Tseng FG and Lo LW** (2004) Nanoparticle-based in vivo investigation on blood-brain barrier permeability following ischemia and reperfusion. *Analytical Chemistry* **76**(15), 4465–4471. https://doi.org/10.1021/ac035491v.

Yang D, **Zhu J**, **Zhou X**, **Pan D**, **Nan S**, **Yin R**, **Lei Q**, **Ma N**, **Zhu H**, **Chen J**, **Han L**, **Ding M and Ding Y** (2022) Polystyrene micro- and nano-particle coexposure injures fetal thalamus by inducing ROS-mediated cell apoptosis. *Environment International* **166**, 107362. https://doi.org/10.1016/j.envint.2022.107362.

Yang S, **Cheng Y**, **Chen Z**, **Liu T**, **Yin L**, **Pu Y and Liang G** (2021) In vitro evaluation of nanoplastics using human lung epithelial cells, microarray analysis and co-culture model. *Ecotoxicology and Environmental Safety* **226**, 112837. https://doi.org/10.1016/j.ecoenv.2021.112837.

Yoshii SR, **Kishi C**, **Ishihara N and Mizushima N** (2011) Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane. *Journal of Biological Chemistry* **286**(22), 19630–19640. https://doi.org/10.1074/jbc.M110.209338.

Youle RJ and van der Bliek AM (2012) Mitochondrial fission, fusion, and stress. *Science* **337**(6098), 1062–1065. https://doi.org/10.1126/science.1219855.

Zhang C, **Li Y**, **Yu H**, **Ye L**, **Li T**, **Zhang X**, **Wang C**, **Li P**, **Ji H**, **Gao Q and Dong S** (2023) Nanoplastics promote arsenic-induced ROS accumulation, mitochondrial damage and disturbances in neurotransmitter metabolism of zebrafish (Danio rerio). *Science of the Total Environment* **863**, 161005. https://doi.org/10.1016/j.scitotenv.2022.161005.

Zhang H, **Zhang S**, **Duan Z and Wang L** (2022a) Pulmonary toxicology assessment of polyethylene terephthalate nanoplastic particles in vitro. *Environment International* **162**, 107177. https://doi.org/10.1016/j.envint.2022.107177.

Zhang Y, **Yin K**, **Wang D**, **Wang Y**, **Lu H**, **Zhao H and Xing M** (2022b) Polystyrene microplastics-induced cardiotoxicity in chickens via the ROS-driven NF-κB-NLRP3-GSDMD and AMPK-PGC-1α axes. *Science of the Total Environment* **840**, 156727. https://doi.org/10.1016/j.scitotenv.2022.156727.

https://doi.org/10.1017/plc.2024.6 Published online by Cambridge University Press