



Review

Biomarkers of oxidative stress, inflammation, and genotoxicity to assess exposure to micro- and nanoplastics. A literature review

Marco Panizzolo^{a,1}, Vitor Hugo Martins^{a,1}, Federica Ghelli^a, Giulia Squillacioti^a, Valeria Bellisario^a, Giacomo Garzaro^a, Davide Bosio^c, Nicoletta Colombi^b, Roberto Bono^{a,*}, Enrico Bergamaschi^a

^a Department of Public Health and Pediatrics, University of Turin, 10126 Turin, Italy

^b Federated Library of Medicine "F. Rossi", University of Turin, 10126 Turin, Italy

^c Unit of Occupational Medicine, A.O.U Città della Salute e della Scienza di Torino, Turin, Italy



ARTICLE INFO

Editor: Professor Bing Yan

Keywords:

Microplastics
Nanoplastics
Biomarkers
Oxidative stress
Inflammation
Cytokines
Genotoxicity

ABSTRACT

The increased awareness about possible health effects arising from micro- and nanoplastics (MNPs) pollution is driving a huge amount of studies. Many international efforts are in place to better understand and characterize the hazard of MNPs present in the environment. The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology in two different databases (PubMed and Embase). The selection of articles was carried out blind, screening titles and abstracts according to inclusion and exclusion criteria. In general, these studies rely on the methodology already in use for assessing hazard from nanomaterials and particles of concern. However, only a limited number of studies have so far directly measured human exposure to MNPs and examined the relationship between such exposure and its impact on human health. This review aims to provide an overview of the current state of research on biomarkers of oxidative stress, inflammation, and genotoxicity that have been explored in relation to MNPs exposure, using

Abbreviations: A-, aged; PS, Polystyrene; AAT, alpha-1 antitrypsin; AChE, acetylcholinesterase; ACN, Acrylonitrile; AHR, aryl hydrocarbon receptor; ALT/AST, alanine aminotransferase, aspartate aminotransferase; CAS, chromosomal aberrations; CAT, catalase; CBA, multiplexing Cytometric Beads Array; CBMN, cytokinesis-block micronucleus; CBPI, cytokinesis-block proliferation index; MCP-1, monocyte chemoattractant protein-1; COL1A1, collagen type 1 alpha 2 gene; CYP1A, cytochrome P450 Family 1 Subfamily A protein; DCFDA or DCFH-DA assay, 2',7'-dichlorodihydrofluorescein diacetate; DMF, Dimethylformamide; EIA, Enzyme Immuno Assay; ELISA, Enzyme-linked immunosorbent assay; ENAs, extractable nuclear antigens; F, fluorescent; FP, foam particles; G6DPH, glucose-6-phosphate dehydrogenase; GC, Gas chromatography; GOT/AST, aspartate aminotransferase; GPx, glutathione peroxidase; GR1, gamma response 1 protein; GSH-Px, plasma glutathione peroxidase; GST, glutathione S-transferase; HCA, high content analysis; HDL, high-density lipoprotein; HDPE, high density polyethylene; IL-, Interleukin -; INF- γ , interferon gamma; KIEs, key initiating events; L-, leached; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LDPE, low density polystyrene; LPO, lactoperoxidase; LPS, lipopolysaccharides; MC2R-gene, Melanocortin 2 Receptor; MDA, malondialdehyde; MI, mitotic index; MMP, plasma matrix metalloproteinases; MN, micronuclei; MNPs, micro- and nanoplastics; MOA, mechanism of action; MPO, myeloperoxidase; MPs, generic microplastics polymers; MS, mass spectrometry; MTS, assay (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium); MTT, assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide); Muc-, muc genes; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; NH2-PS, amino functionalized polystyrene; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NPB/NBUD, nucleoplasmic bridge/ nuclear bud; NPs, nanoplastics generic polymers; P-, pristine-; PA, polyamides; PCU, polycarbonate polyurethane; PE, polyethylene; PE-BaP, polyethylene-benzo-a-pyrene; PES, polyester; PET, Polyethylene terephthalate; PI, polyisoprene; PLGA/PVA, polylactide-co-glycolide; PMA, poly methyl acrylate; PMMA, Polymethyl methacrylate; POx, peroxidase; PP, polypropylene; PPAR- α , peroxisome proliferator-activated receptor alpha; PPAR- γ , peroxisome proliferator-activated receptor gamma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PS-COOH, carboxy functionalized polystyrene; PS-COOH-, carboxy functionalized polystyrene.; PS-MP, polystyrene-microplastics; PUR, polyurethane; PVC, polyvinylchloride; qPCR, quantitative Polymerase Chain Reaction; ROS, reactive oxygen species; SCE, sister chromatids exchange; SOD, superoxide dismutase; STAT-3, signal transducer and activator of transcription 3; SULT1A1, sulfotransferase family 1 A member 1 gene; TBARS, Thiobarbituric acid reactive substances; TC, total cholesterol; TEAC, Trolox equivalent antioxidant capacity; TG, triglycerides; TGF- β 1, transforming growth factor-beta-1; TLR-4, toll-like receptor-4; TNF- α , tumor necrosis factor alpha; TTC assay, triphenyl tetrazolium chloride; U-MDX, metabolites of 4,4'-diphenylmethane di-isocyanate; U-TDX, 2,4- and 2,6-toluene diisocyanate; WST, 1 assay (4-[3-(4-Iodophenyl)-2-(4-nitro-phenyl)-2H-5-tetrazolio]-1,3-benzene sulfonate); ZO-, tight junction protein; α -SMA, alpha-smooth muscle actin.

* Corresponding author.

E-mail address: roberto.bono@unito.it (R. Bono).

¹ These authors equally contributed.

<https://doi.org/10.1016/j.ecoenv.2023.115645>

Received 30 June 2023; Received in revised form 24 October 2023; Accepted 27 October 2023

Available online 1 November 2023

0147-6513/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

human, cellular, animal, and plant models. Both in-vitro and in-vivo models suggest an increased level of oxidative stress and inflammation as the main mechanism of action (MOA) leading to adverse effects such as chronic inflammation, immunotoxicity and genotoxicity. With the identification of such biological endpoints, representing critical key initiating events (KIEs) towards adaptive or adverse outcomes, it is possible to identify a panel of surrogate biomarkers to be applied and validated especially in occupational settings, where higher levels of exposure may occur.

1. Introduction

Synthetic or semi-synthetic materials typically made from polymers derived from petroleum-based are commonly called “plastics”. Despite this oversimplification, plastics are a huge and heterogeneous class of compounds with many industrial and bio-medical applications. There are many types of polymers, but some of the most common types include polyethylene (PE), polystyrene (PS), polypropylene (PP), or polyvinyl chloride (PVC). The formers being the most widely used in the world (Cantor and Watts, 2011). Owing to their properties, these polymers find extensive applications in industrial sectors, such as automotive, in aerospace and electronics. Furthermore, the food industry relies on these polymers for packaging and wrapping purposes (Ncube et al., 2021a; Ncube et al., 2021b).

Plastics can be generated from primary sources including industrial processes, like the production of waterborne paints, medical devices, electronics, coatings, and adhesives. They can also be indirectly produced as secondary materials when larger plastic debris fractures and breakdown through various processes, both natural and non-natural.

Despite the significant increase in plastic production over years, societies have become over-reliant on plastic due to its durability, low cost, and versatility. The consequences of this heightened production include the accumulation of vast amounts of plastic waste that pollutes both terrestrial and aquatic ecosystems. Indeed, as shown in the literature LDPE (low density polyethylene), HDPE (high density polyethylene) and cellulose acetate are the types of plastics most commonly identified in landfills (Afrin et al., 2020). On the other hand, PE, PET (polyethylene terephthalate), PP, PVC, PI (polyisoprene) and PS were identified in sewage, industrial effluents and from the ocean spray (Di Bella et al., 2022; Caracci et al., 2023). The same plastics have also been identified in the atmosphere around urbanised and industrial areas, due to their small size, particles are easily transported by the wind (Pandey et al., 2022). Furthermore, it has been shown in studies by O'Brien and Syversen et al., that the plastics used in the textile and fishing industry are PA (polyamides), PP PE and PES (polyester) (O'Brien et al., 2020; Syversen et al., 2022). Nonetheless, plastic production is expected to still increase in the coming decades (Network; Walker and Fequet, 2023) and it will be a growing need to find alternative eco-friendly materials or solutions to limit their spread in the environment by better educating people (Dube, Grace, 2023). Plastic materials can broadly be classified into five categories based on their sizes which includes; megaplastics (>1 m); macroplastics (<1 m), mesoplastics (<2.5 cm), microplastics (<5 mm); and nanoplastics (<1 µm) (Barnes et al., 2009; Wang et al., 2018a).

Once disposed of, plastic waste is exposed to environmental factors that has the potential to break down into substantial quantities of microplastics (MPs) and nanoplastics (NPs). The breakdown of plastic into smaller particles raises global concerns regarding its possible impacts on the environment and human health (Wagner and Reemtsma, 2019). While MPs have been extensively studied for their environmental impact, our understanding of the quantities, types, and toxicity of NPs and their impacts on human health is limited. It is noteworthy that a single MP particle can further breakdown into billions of NP particles, indicating the widespread of NPs pollution (Zhang et al., 2023); (Hale et al., 2022). NPs may pose a greater risk than MPs due to their ability to penetrate biological membranes, but whether NPs exposure can affect human health is still debated (Gigault et al., 2016; Hernandez et al.,

2017; Ter Halle et al., 2017). The increase in plastic waste represents a health trait to human health as MNPs have been found in many food products, owing to their widespread distribution in aquatic and terrestrial areas (Kolandhasamy et al., 2018; Wagner and Reemtsma, 2019; Wang et al., 2020). MNPs can enter the human body through three primary pathways: inhalation, ingestion, and skin contact (Prata et al., 2020; Rahman et al., 2021). Airborne MPs have been detected in urban dust as a result of synthetic textiles and rubber tire degradation; these particles are typically sub-micronic in size and can be inhaled (Prata, 2018). Ingestion is considered the major route of exposure for the general population, as they are found in the food chain and water sources. Studies have shown that these tiny plastic particles enter the human food chain through various media, including consumption by animals (Santillo et al., 2017), contamination during food production (Karami et al., 2017), and leaching from plastic packaging (Mason et al., 2018). MNPs have been found in a range of food products, including honey, beer, salt, sugar, fish, shrimp, and bivalves, as well as in tap, bottled, and spring water. In fact, a high percentage of tap water sources around the world have been found to contain MPs particles (Kosuth et al., 2018; Mamun et al., 2023).

Although the number of studies about the potential effects of MNPs on living organisms steadily increases (Chang et al., 2020), research on human exposure and toxicity in this context is relatively new. A recent review summarized the current knowledge on the exposure routes of MNPs to humans, and possible pathways for translocation into body compartments (Ramsperger et al., 2023).

Prata et al., 2020 highlighted that following exposure and uptake, the potential toxicity of MNPs may result from oxidative stress and inflammation, which consequently could affect the immune and nervous systems (Prata et al., 2020). Both in-vitro and in-vivo models suggest that increased level of oxidative stress and inflammation are the primarily MOA leading to adverse effects, mainly chronic inflammation, immunotoxicity, and genotoxicity (Poma et al., 2019; Demir, 2021; González-Acedo et al., 2021). While these simplified models are useful for hazard identification, they do not fully reflect the complexity of interactions occurring within human body. However, researchers are still encountering difficulties in assessing the impact of MNPs on human health, owing to the variability of exposure scenarios, the changeable pattern of MNPs along with their constituents and contaminants and the lack of standardized protocols including biomarkers for assessing relevant biological and health endpoints. As a result, until now very few studies have measured human exposure to MNPs and assessed the relationship between MNPs exposure and its effects on human health.

This paper aims to provide a comprehensive review of the current the state of the art of biomarkers investigated following exposure to MNPs in humans, as well as cellular, animal and plant models. Biomarkers are chemicals, metabolites, or products of an interaction between a chemical and some target molecule that is measured in the human body compartments (World Health Organization, 2006). An exposure biomarkers is the concentration of a parent compound or its metabolites in biological matrices (Nieuwenhuijsen et al., 2006), whereas an effect biomarker is a measurable biochemical, physiological, and behavioral effects or other alterations within an organism that, depending on the magnitude, can be associated with an established or possible health impairment or disease (Zare Jeddi et al., 2021). Biomarkers can reveal changes in biological systems resulting from complex pathways of exposure. With the identification of such biological endpoints,

representing the KIEs towards adaptive or adverse outcomes, it should be feasible envisaged a panel of surrogate biomarkers to be applied and validated, especially in occupational settings, where exposure may occur and can be easier characterized.

2. Materials and methods

The search strategy consisted of filtering the publications with a combination of keywords specifying the following mesh terms with synonyms: “Oxidative stress”, “Inflammation”, “Genotoxic”, “Biomarkers” (full list of all biomarkers), “Microplastics”, “Nanoplastics” (full list of MNPs). The complete string is provided in the appendix A. We transferred the results from databases to Microsoft Excel spreadsheet where inclusion and exclusion criteria were recorded. Two reviewers evaluated the publications independently and a third reviewer resolved cases of disagreement.

Following PRISMA 2020 Statement (Page et al., 2021), the papers were first screened for title and next for abstract. In both steps, according to the exclusion criteria, we excluded studies (1) without biomarkers of oxidative stress, inflammation, or genotoxicity, (2) investigating micro- nanoplastic’s additives, (3) performed on bacteria, (4) all review papers, (5) full texts with unpublished data, (6) correspondences, (7) conferences abstracts without full text and (8) clinical studies (e.g. bone integration of plastic prosthesis).

Studies focused on or analyzing the possible adverse effects of MNPs as result of human mainly occupational, cell, animal, and plant models

were considered eligible.

The Fig. 1 summarizes the main steps of the searching strategy.

We reported the following information according to the study types identified: humans, in-vitro and in-vivo: animals and plants. For in-vitro studies, the information reported were the following: author’s name, publication time, title, cell type, plastic-type (also size), assessed biomarkers, exposure time, experimental methods, concentration, main results, references, and notes. For in-vivo studies were extracted: author’s name, publication time, title, organism type, number of animals or plants, plastic type (also size), matrix (only for animals), assessed biomarkers, exposure time, experimental methods, concentration, main results, references, and notes.

For studies on humans, we reported: author’s name, publication time, title, number of subjects, worker’s exposure, age, smoking habits, plastic-type (also size), matrix, analytical methods, assessed biomarkers, exposure time, experimental methods, concentration, main results, references, and notes. Data reported by graphs in original studies were extracted by the Web Plot Digitizer software (Rohatgi 2022), version 4.6, Pacifica, California, USA, <https://automeris.io/WebPlotDigitizer/> accessed on February 2023).

Among the 5818 studies identified, 757 were duplicates removed by EndNote. The remaining 5061 were screened as title and abstract. Of these, 4849 were excluded and 202 were screened as full text. Finally, 65 articles were included in this state of art review. The exclusion criteria lead to the removal of 137 studies because of the absence of biomarkers of oxidative stress (OS), inflammation, or genotoxicity (n = 79). MNPs

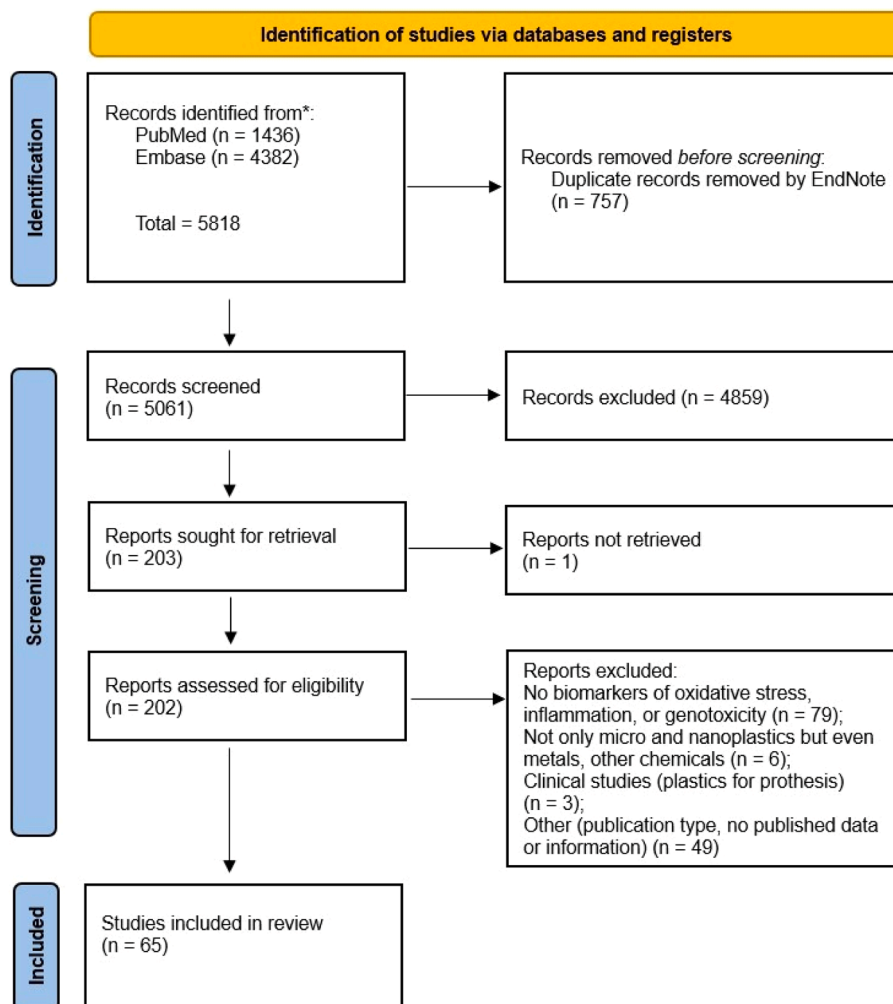


Fig. 1. Flowchart of the identification for eligible studies from a search among original articles.

were not considered as polymers but for their additives or chemicals (n = 6), no data or information published or publication type (n = 49) or were clinical studies (e.g. plastics used for dental or orthopedic prosthesis) (n = 3). Data from the 65 included articles were extracted using different templates and organized into spreadsheets according to the type of study. 28 for in-vitro models, 30 for in-vivo studies on animals, 4 for in-vivo studies on plants, and only 3 for studies on humans.

3. Results

Table 1 summarizes the number of eligible articles, according to study type, that investigated the different MNPs. PS is the most widely investigated MNPs in the studies in-vitro and in-vivo. Indeed, among the studies included in this review, 43 articles (>50%), explored the possible adverse effects of PS in-vivo, 53.4% on animals, 9.3% on plant models and 37.3% on cell lines. The second most analyzed polymer is PE being reported in 17 articles. 70.5% investigated the possible effects in animal models, and only 29.5% on in-vitro studies. It is worth mentioning that these two MNPs were not studied in humans. 8 articles explored PVC, 62.5% in cell lines, 25% in animal studies, and only 12.5% in humans, in occupational scenarios. The other MNPs investigated are: not specified polymers (n = 5), PP (n = 4), polymethyl methacrylate (PMMA) (n = 3), polyethylene terephthalate (PET) (n = 2), polyurethane (PUR) (n = 1), and polylactide-co-glycolide (PLGA/PVA) (n = 1).

Table 2 reports the size range of plastics investigated. In in-vitro studies, the plastics size range varies from 0.029 to 150 µm, while in in-vivo the plastics analyzed had a much wider range (from 0.2 µm to 5 mm which mirrors environmental exposure). In occupational studies, since the workers are exposed to mixtures and not to a single particle with defined chemical identity the size range was not provided.

3.1. Biomarkers of oxidative stress, inflammation, and genotoxicity

In the following tables are listed all the biomarkers investigated and the results reported by the included articles.

3.1.1. Oxidative stress

Oxidative stress is a central mechanism of action for both pulmonary and extra-pulmonary health effects of particulate matter (Mills et al., 2009). ROS (reactive oxygen species) are formed as a normal attribute of aerobic life as a by-product of metabolic reactions. Their excessive presence can lead to molecular and tissue damage defined as a result of oxidative stress, i.e. a perturbation of the physiological redox balance

Table 1

Number of eligible articles, according to study type, that investigated the different MNPs.

Type of MNPs	Type of study n (%)				Total
	In-vitro	In-vivo		Occupational	
		animals	plants		
PS	16 (37.3)	23 (53.4)	4 (9.3)	/	43
PE	5 (29.5)	12 (70.5)	/	/	17
PVC	5 (62.5)	2 (25.0)	/	1 (12.5)	8
MPs	2 (50.0)	2 (40.0)	/	1 (20.0)	5
PP	2 (50.0)	2 (50.0)	/	/	4
PMMA	3 (100)	/	/	/	3
PET	/	2 (100)	/	/	2
PUR	/	/	/	1 (100)	1
PLGA/PVA	1 (100)	/	/	/	1
Total	34	43	4	3	84

*Some studies investigated more than one plastic type

PS (polystyrene), PE (polyethylene), PVC (polyvinylchloride), MPs (microplastics), PP (polypropylene), PMMA (Polymethyl methacrylate), PET (Polyethylene terephthalate), PUR (polyurethane), PLGA/PVA (polylactide-co-glycolide)

Table 2

Plastics size range analyzed according to the different study types.

Type of MNPs	Plastic size range (µm)		
	In-vitro	In-vivo	
		animals	plants
PS	0.029–2.0	0.2–5000.0	0.1–20.0
PE	0.21–80.0	1.2–5000.0	/
PVC	0.12–150.0	< 0.3	/
MPs	0.1–50.0	38–355.0	/
PP	0.08–0.25	1.2–1000.0	/
PMMA	0.05–10.0	/	/
PET	0.2–0.6	10–250.0	/
PUR	/	/	/
PLGA/PVA	0.2–0.3	/	/

PS (polystyrene), PVC (poly vinyl chloride), PE (polyethylene), PP (polypropylene), PET (polyethylene terephthalate), PLGA/PVA (polylactide-co-glycolide), PMMA (polymethyl acrylate), PUR (polyurethane), MPs (generic microplastics polymers).

that is not balanced by the body's appropriate adaptive responses (Sies, 2015).

Thus, investigating biomarkers of oxidative stress, such as reactive oxygen species (ROS) and their adducts, as well as the enzyme pathways involved in the maintenance of an adequate physiological balance, superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA), in biological media, can provide direct evidence of perturbation induced in biological systems (Marrocco et al., 2017; Halappanavar et al., 2021).

Wang et al. studied the adverse effects, following exposure to PS (0.025–0.8 µg/ml) of renal tubule cells by quantifying the release of ROS (Wang et al., 2021). Similarly, Schirinzi et al. who analysed the ROS production following PE (10 ng/ml) and PS (10 µg/ml) exposure using brain and epithelial cell models, found significant increases in ROS levels as compared to untreated controls (Schirinzi et al., 2017).

20 out of 65 studies included in this review reported a possible effect following MNPs exposure. 12 out of 20 showed a statistically significant increase in ROS following MNPs exposure as compared to the untreated control groups, 5 did not show a significant increase, 2 showed no change and only one reported a statistically significant decrease in ROS generation.

Living are endowed with effective defence systems to scavenge and thus counter balance excessive ROS production (Kotha et al., 2022). Enzymes such as SOD and CAT are involved in catalysing the conversion of superoxide anion to oxygen and hydrogen peroxide (Wang et al., 2018b; Sies and Jones, 2020), making the superoxide radical less reactive, by transforming it into molecular oxygen and hydrogen peroxide (H₂O₂). SOD and glutathione peroxidase (GPx) activities are commonly measured as biomarkers of oxidative stress (Lubos et al., 2011). 12 studies included in this review investigated these enzymatic pathways counterbalancing ROS production. Moreover, lactate dehydrogenase (LDH) and GPx have been used as biomarkers in in-vitro and in-vivo (animal) studies, whereas H₂O₂ production has only been studied in-vivo (both animal and plant models). Other biomarkers of oxidative stress consistently used in animal models are glutathione S-transferase (GST) (n = 10) and glutathione (GSH) (n = 11).

Vecchiotti et al. and Chen et al., carried out in-vitro studies where human cell lines were exposed to varying concentrations of PS (from 25 to 1200.0 µg/ml) for 4 h to a maximum of 48 h, showing an early downward trend in SOD enzyme activity, with small increase after 48 h (Vecchiotti et al., 2021; Cheng et al., 2022).

From **Table 4** and **Table 5**, it is argued that similar decreasing trends in SOD enzyme activity are expected in other animal and plant model studies (Xiao et al., 2021; Li et al., 2022; Rodrigues et al., 2022; Ni et al., 2023). Conversely, studies by Cocci et al., found an increasing trend in SOD activity following exposure to PS (Lu et al., 2016; Cocci et al., 2022).

Various articles reported a significant increase in ROS levels by using

Table 3
Biomarkers of MNPs exposure analysed in in-vitro studies.

Cell type	Plastic type, size	Concentration	Exposure time	Experimental methods	Biomarkers (Oxidative stress; Inflammation; Genotoxicity and others)	Autors, Year
Onion root cells	PS, 100 nm	25, 50, 100 µg/ml	3 d	TTC and Evans Blue staining; TBARS; qPCR	ROS: ↑dose/dependent; MDA: *↑ vs ctrls; Cell viability: ↑; Comet test: *↑; MI: ↓ vs ctrls	(Maity et al., 2023)
Human intestinal (CCD-18Co) cells	PS, 0.5 and 2 µm	5 or 20 µg/ml	48 h, 28 d and 6 w	DCFDA and flow cytometry	ROS: *↑ vs ctrls; NPs internalization *↑ vs MPs	(Bonanomi et al., 2022)
Human bronchial epithelial cells	PS and NH ₂ -PS, 100 nm	25, 50, 100, 200, 400 µg/ml	24 h	WST-1 and MTT; DCFH-DA; qPCR	ROS: NH ₂ -PS *↑ vs PS; IL-1β *↑ expression NH ₂ -PS vs PS; cytotoxic effects: NH ₂ -PS *↑ vs PS	(Jeon et al., 2023)
Peripheral blood mononuclear cells	PS, 29, 44 and 72 nm	0.0001–100 µg/ml	24 h	Comet assay; ELISA	8-oxodG: *↑ 0,1 µg /ml- 100 µg /ml vs ctrls; Comet tail: 100 µg /ml: ↑ 23.1%, 29 nm ↑ 13,88%, 44 nm; ↑ 6.9% 72 nm	(Malinowska et al., 2022)
Human lung (A549) cells	wMP, < 50 µm	0.1, 1, 10, 100 µg/ml	24, 48 h	ELISA; DCFDA	ROS: no*↑ vs ctrls; IL-8*↑ vs ctrls; IL-6 ↑ vs ctrls	(Bengalli et al., 2022)
HepG2 cells, Caco-2 cells	PP, 80–250 nm PET, 200–600 nm	PP: 0–175 ng/ml, PET: 0–63 ng/ml and 0.6–7.1 µg/ml	3, 24 h	LDH; WST-1; Comet assay; DCFDA	concentration/dependent; ROS: 3 h no*; DNA damage: ↑; Metabolic activity: no* effects	(Roursgaard et al., 2022)
Human gingival fibroblasts (hGFs)	MP, 100 and 600 nm	Different concentrations	48 h	MTS; qPCR	NFKB *↑ vs ctrls; NLRP3 expression ↓ vs ctrls; Cell viability: ↓ vs ctrls	(Caputi et al., 2022)
Murine fibroblasts and canine kidney epithelial cell lines	PS, 9.5–11.5 µm PE, 1.0–4.0 µm	1, 10, 20 µg/ml	6–24 h	Hemacytometer; MTT; qPCR	SOD: ↓ PS and PE vs ctrls; IL1β, TNF-α ↑ PS exposure vs ctrls; IL-1β, TNF-α ↓ PE exposure vs ctrls; Cell viability: ↓ vs ctrls; Metabolic rates: ↑ vs ctrls	(Palaniappan et al., 2022)
Human embryonic stem cell line H1	PS, 1 µm	25 µg/ml	48 h	Commercial kits; P450-Glo assay kit; ELISA	GST activity, GSH, SOD: ↓ vs ctrls; MDA: ↑ vs ctrls; LDH: ↓ vs ctrls; ROS: ↑ vs ctrls; IL-6, COL1A1: ↑regulated dose-dependent; SULT1A1, PPARα, PPARγ: ↓ regulated and ↑ regulated dose-dependent; AST and ALT: *↑ PS-MP exposure; CYP1A: ↓regulated	(Cheng et al., 2022)
Human monocytes and dendritic cells	PS, PMMA, PVC, 50–310 nm	30–300 particles/cell	18, 20 h	ELISA	IL-6, TNF-α and IL-10: ↑ vs ctrls	(Weber et al., 2022)
A549 cells with surface modification	PS, NH ₂ -PS, PS-COOH, 2 µm and 80 nm	2.5, 5, 10, 25, 50, 100, 200, 400 µg/ml	6, 9, 24 h	MTT; fluorescence microscope; DCFH-DA	ROS: *↑ vs ctrls; MN: ↑, *↑ at ≠ concentrations; Cell viability: ↓ vs ctrls	(Shi et al., 2022)
Human embryonic kidney cells	PS, 3 and 54 µm	3–300 ng/ml	24 h	Phase-contrast microscope; DCFH-DA; Quantibody® Human Inflammation Array 3 Kit	ROS *↑ vs ctrls; HO-1 expression: no*; NF-κB: No* vs ctrls; NLRP3 expression: *↓ vs ctrls; ZO-2, AAT: ↑ vs ctrls; ↑↓ regulation 33 different cytokines dose-dependent; Cell viability*↓ vs ctrls;	(Chen et al., 2022a)
Caco-2/HT29-MTX-E12/THP-1 cell lines	PS and NH ₂ -PS, 50 nm; PVC, < 50 µm	1, 5, 10 or 50 µg/cm ² in 100 µl of medium	24 h	ELISA	IL-1β, IL-6, IL-8 and TNF-α (PS, NH ₂ -PS): No* vs ctrls; IL-1β (PVC): *↑ vs ctrls; IL-8: ↓; TNF-α and IL-6: No*; Cell viability: *↓ vs ctrls;	(Busch et al., 2021)
Human lung cell lines	PMMA, 120 nm PVC, 140 nm	25, 50, 100, 150, 200 µg/ml	24, 48, 72 h	DCFDA; LDH-Glo cytotoxicity assay	ROS*↑ vs ctrls; LDH*↑ vs ctrls; Cell apoptosis: ↑ vs ctrls	(Mahadevan and Valiyaveetil, 2021)
Colorectal Adenocarcinoma cells (HCT 116)	PS, 100 nm	100, 200, 400, 800, 1200 µg/ml	15, 30, 45 min, 1, 4, 24, 48 h	MTS; Total ROS; Western blot by OECD guidelines	ROS: depending on concentration *↑ vs ctrls; SOD1: ↓, SOD2: ↑, CAT: ↑; GPx1: ↑ depending on concentration vs ctrls; MN: ↑ vs ctrls; Cell viability: ↓ vs ctrls	(Vecchiotti et al., 2021)
Human kidney proximal tubular epithelial cells	PS, 2 µm	0.025, 0.05, 0.1, 0.2, 0.4, 0.8 µg/ml, 0.8 mg/ml	5, 10, 30, 60, 120 min, 3 days	Sulphorhodamine B; MitoSOX Red	ROS: *↑ vs ctrls; Cell viability: *↓ vs ctrls	(Wang et al., 2021)
Human peripheral blood lymphocytes	PE, 10–45 µm	25, 50, 100, 250, 500 µg/ml	48 h	CBMN assay with minor modifications	MN: *↑ vs ctrls; NBP and NBUD *↑, CIN: *↑ vs ctrls; CBPI: % index No* vs ctrls	(Çobanoğlu et al., 2021)
Human lung epithelial cells	PS, 1.72 µm	1–1000 µg/cm ²	24, 48 h	Trypan blue; DCFH-DA; ELISA	ROS: *↑ vs ctrls; IL-6*↑, IL-8 ↑ vs ctrls; ZO-1, AAT: ↑	(Dong et al., 2020)

(continued on next page)

Table 3 (continued)

Cell type	Plastic type, size	Concentration	Exposure time	Experimental methods	Biomarkers (Oxidative stress; Inflammation; Genotoxicity and others)	Autors, Year
Human hematopoietic cells	P-PS, 0.05–0.1 µm F-PS, 0.04–0.09 µm	0–50–100–150–200 µg/ml	24–48 h	Trypan Blue; DCFH-DA; Comet assay	expression; Cell viability: *↓ vs ctrls ROS: *↑ vs ctrls in 3 cell lines; Genotoxic damage: *↑ vs ctrls; Cell viability: 3 cell lines ↓ vs ctrls	(Rubio et al., 2020)
Human fibroblast (Hs27) cell line	PS, 100 nm	5, 25, 75 µg/ml	4, 24, 48 h	MTS; Total ROS; CBMN by OECD guidelines	ROS: *↑ vs ctrls; MN: *↑ dose-dependent vs ctrls; CBMN: No* vs ctrls; Cell viability: ↓ vs ctrls	(Poma et al., 2019)
Kidney leucocytes	PVC, 40–150 µm PE, 40–150 µm	1 mg/ml, 10 mg/ml, 100 mg/ml	1 h, 24 h	MTT; flow cytometry; chemiluminescence; colorimetric assay	POx: No* vs ctrls; Cell viability: ↓ vs ctrls; Phagocytic capacity: No* vs ctrls; Burst activity: *↑ vs ctrls;	(Espinosa et al., 2018)
Human cerebral and epithelial cell lines	PE, 3–16 µm PS, 10 µm	10 ng/ml to 10 µg/ml	24, 48 h	HCA	ROS: *↑, ↑ respectively PE, PS vs ctrls; Cell viability: no*↓ vs ctrls	(Schirinzi et al., 2017)
Hamster fibroblast (CHL/IU)	PS, NA	19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate	24 h, 48 h	Test di Ames	Test Ames: No* vs ctrls; CA: no* all concentrations vs ctrls; Cell growth: ↑ vs ctrls	(Nakai et al., 2014)
A549 cell line	PLGA/PVA ~ 234 nm, PLGA/CS ~ 233 nm, PLGA/PF68 ~ 229 nm, TiO2 ~ 421 nm, PS ~ 250 nm	0.005–3.5 mg/ml and 0.01–2 mg/ml	48 h	MTT; Non-radioactive Cytotoxicity Assay; multiplexing CBA	LDH: No* effects vs ctrls; IL-6, IL-8 and MCP-1: ↑ vs LPS-treated; IL-1β, TNF-α, IL-10 data were under LOD; Cell viability: ↑ vs ctrls	(Grabowski et al., 2013)
Monocyte cell line TH1 in culture	PE, PE-HM, 2, 3 µm; PCU, 1, 7 µm	Ratio 1:1, 100:1, 500:1 particles/cell	18, 24, 72 h	MTS; TiterZyme EIA assay	IL-1β, TNF-α: ↑ vs ctrls, dose-dependent; Cell viability: No* vs ctrls	(Smith and Hallab, 2010)
Pulmonary cell cultures	PVC, 0.2–2.0 µm, 50 µm	0156 mg/ml	4, 16, 24 and 48 h	ELISA	general cytokines release: ↑; IL-6, and IL-8: *↑	(Xu et al., 2003)
Three human monocytic cell lines (monomac-1, U937 and THP-1)	PE, 0.21, 0.49, 4.3, 7.2, and 88 µm	Cell number ratios: 100:1, 10:1, 1:1 and 0.1:1.	24 h	MTT; ELISA	U937 cells: IL-1β: 0.49 µm *↑ vs 0.21 µm; IL-6: 0.49, 4.3, 7.2 µm* ↑ vs ctrls; TNF-α: (0.21, 0.49, 4.3 µm) *↑ vs ctrl; THP-1 cells: IL-1β: 0.49 µm ↑ vs ctrls, 0.21 and 0.49 µm *↑ vs ctrls; IL-6: *↑ 0.21, 0.49 µm vs ctrls; TNF-α: 0.21, 0.49, 4.3 µm, 0.49 µm *↑ vs ctrls; Cell viability: no* vs ctrls;	(Matthews et al., 2001)
Human monocyte/macrophages, and fibroblast	PMMA, 1–10 µm	LOW: < 0.05% PMMA, HIGH: > 0.05%	72 h	ELISA	IL6: no co-culture ↑ vs ctrls; IL1β: ↑ co-culture + PMMA vs alone; TNF-α: co-culture + PMMA	(Lind et al., 1998)

PE (polyethylene), PVC (polyvinylchloride), PP (polypropylene), PMMA (Polymethyl methacrylate), PET (Polyethylene terephthalate), PLGA/PVA (poly(lactide-co-glycolide), P(pristine), F (fluorescent), PS (polystyrene), NH2-PS(amino functionalized polystyrene), PS-COOH (carboxy functionalized polystyrene), PCU (polycarbonate polyurethane), NPs (nanoplastics), MPs (microplastics), MI (mitotic index), MN (micronuclei), ROS (reactive oxygen species), SOD (superoxide dismutase), CAT (catalase), MDA (malondialdehyde), POX (peroxidase), GST (glutathione S-transferase), LDH (lactate dehydrogenase), COL1A1 (collagen type I alpha 2 gene), SULT1A1 (sulfotransferase family 1A member 1 gene), PPAR-α (peroxisome proliferator-activated receptor alpha), PPAR-γ (peroxisome proliferator-activated receptor gamma), ALT/AST (alanine aminotransferase, aspartate aminotransferase), CYP1A (cytochrome P450 Family 1 Subfamily A Member), TNF-α (tumor necrosis factor alpha), IL- (Interleukin -), GPx (glutathione peroxidase), CBMN (cytokinesis-block micronucleus), MCP-1 (monocyte chemoattractant protein-1), LPS (lipopolysaccharides), ZO- (tight junction protein), AAT (alpha-1 antitrypsin), CBPI (cytokinesis-block proliferation index), NPB/NBUD (nucleoplasmic bridge/ nuclear bud), TTC assay (triphenyl tetrazolium chloride), TBARS (Thiobarbituric acid reactive substances), qPCR (quantitative Polymerase Chain Reaction), DCFDA or DCFH-DA assay (2',7'-dichlorodihydrofluorescein diacetate), WST-1 assay (4-[3-(4-iodophenyl)-2-(4-nitro-phenyl)-2H-5-tetrazolio]-1,3-benzene sulfonate), MTS assay (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), ELISA (Enzyme-linked immunosorbent assay), EIA (Enzyme Immuno Assay), HCA (high content analysis), CBA (multiplexing Cytometric Beads Array), * (significantly), ↓(decreased/inhibited), ↑(increased).

onion root cells (Maity et al., 2023), intestinal (CCD-18Co) cells (Bonanomi et al., 2022), human bronchial epithelial cells (Jeon et al., 2023), and human lung cells (Dong et al., 2020) treated with PS particles (0.5–0.08 µm). *In-vivo* studies in fish (Cocci et al., 2022), broilers (Lu et al., 2023), mice (Wang et al., 2021), and sea worms (Missawi et al., 2020; Lombardo et al., 2022) also showed significant increases in ROS, SOD, and CAT levels compared to controls following exposure to PS and PE (5 mm-1 µm). However, studies in plant organisms (Maity et al., 2020; Liu et al., 2022a; Ni et al., 2023), did show increasing, albeit not significant, trends in CAT compared to controls following treatment with PS (0.01–1 µm).

Among oxidative stress endpoints, MDA has been the most widely investigated (Toto et al., 2022). MDA is a metabolite resulting from the peroxidation of fatty acids. This molecule can interact with nucleic acids and can create DNA adducts generating mutations that might evolve into cancer (Del Rio et al., 2005). Increases in MDA levels were found in 10 out of 14 studies. *In-vitro* studies conducted by Maity et al. and Cheng et al. found higher MDA levels as compared to controls after exposure to 0,01 and 0,1 µm PS, respectively (Cheng et al., 2022; Maity et al., 2023). *In-vivo* animal studies on broilers (Lu et al., 2023) and sea worms (Missawi et al., 2020) showed a significant increase of MDA levels compared to controls after exposure to PS, PE, and PP.

Table 4
Biomarkers of MNPs exposure analysed in animal studies.

Animal model, n°	Plastic type, size	Concentration	Exposure time	Experimental methods	Matrix	Biomarkers (Oxidative stress; Inflammation; Genotoxicity and others)	Autors, Year
Mullus barbatus, Merluccius merluccius, 32	PE, 5–1 mm, 1–05 mm PS, 0.5–0.1 mm	1–20 or 2–15 items/ individual	NA	qPCR	Gut tissues	SOD, CAT expression: ↑ in gut tissue vs ctrls; IL1β, IL-8, and INF-γ expression: ↑ in both species; IL-10: ↑ regulated in gut tissue	(Cocci et al., 2022)
Aeromonas hydrophila, 90	PE, 75–100 μm	0.1, 1, and 10 mg/L	35 days	Commercial kits	Intestinal and muscle tissues	SOD and CAT: * ↓ vs ctrls; GSH, GSH-Px, and GST: initially ↑ trend, then ↓ trend	(Ding et al., 2022)
Charadrius javanicus, 15	PET, 100–250 μm, HDPE, PS, 2 μm, and NH2-PS, 100 nm	(8.1 × 104 fibres/L), 0.01 mg/L (w/v), 0.01 mg/L, 0.1 mg/L (w/v), 1 mg/L (w/v)	24 h	Photometric analysis	Tissues	GST: (PET) ↑ vs ctrls; CAT activity: (PET) ↑ vs ctrls; GST: *inhibition yellow-HDPE MP; CAT: red-HDPE MP ↓ vs ctrls, blue-HDPE MP, No* , * ↓ vs ctrls	(Esterhuizen et al., 2022)
Gallus gallus domesticus, 120	PS, 5 μm	1 mg/L, 10 mg/L, 100 mg/L	6 weeks	Electron microscopy commercial kits	Lung tissue and serum	CAT, and GSH: ↓ vs ctrls; MDA: * ↑ in all groups; Pathological changes in lung tissue: ↑ damage vs ctrls	(Lu et al., 2023)
Carassius auratus, 32	PS, 44 nm	0–100 μg/L	30 days	Automated laser flow blood cell analyser; optical microscope; EIA	Liver, gut and muscle tissues	ENAs: * ↑ vs ctrls	(Brandts et al., 2022)
Oryzias melastigma, NA	PS, 6.0 μm	1.1 μg/L, 1.1 × 10 ³ μg/L, 1.1 × 10 ⁵ μg/L	14 days	qPCR	Tissues	SOD at T7: * ↑ vs ctrls; CAT, Gpx, AHR and CYP1A1 at any T: No* vs ctrls; CAT, Gpx, AHR and CYP1A1 at any T: = vs ctrls; IL-1β at T3: * ↑ vs ctrls; IL-6, TNF-α, JAK, NF-κB, and STAT-3 at T7: * ↑ vs ctrls; muc7-like at T7: * ↑ vs ctrls; NF-κB at T14: * ↓ vs ctrls; STAT-3 at T7: * ↑ vs ctrls; IL-6, IL-1β, NF-κB at T14: * ↓ vs ctrls; IL-8: ↑ vs ctrls; TNF-α: * ↑ vs ctrls; muc13-like at T3: * ↑ vs ctrls; Heg1 and muc5AC-like at T14: * ↓ vs ctrls; muc2 and muc13 at T3: * ↓ vs ctrls	(Chen et al., 2022a)
Cyprinus carpio, 8	PE, NA	1000 ng/L	21 days	Protein determination kit; ELISA	Gill tissues	SOD, AOC, CAT, NO, GSH-Px: * ↓ vs ctrls; MDA: * ↑ vs ctrls; NF-κB/NLRP3 signal: * ↑; NLRP3, IL-1β: * ↑ vs ctrls; IFN-γ, TNF-α, IL-2 and IL-10: * ↑ vs ctrls; IL-4, IL6 and IL-8: ↑ vs ctrls	(Cao et al., 2023)
Eisenia andrei, 20	PS, < 500 μm Cartyre abrasion, 600 μm	Car tyre, 1–1000 mg/kg, PS, 0.1–100 mg/kg	2, 7, 14, 28 days	Fluorescence-based measurements with microplate reader	Tissues	AChE: ↓ * Inhibited; ROS, GSH, and GPx: * ↓ vs ctrls; CAT: ↓ vs ctrls	(Lackmann et al., 2022)
Fundulus heteroclitus, Experiment A: 40 Experiment B: 45	Crum rubber, 38–355 μm	Experiment A: 0, 0.059, 0.585, 1371, 2.548 g/L Experiment B: 0, 0.01, 0.032, 0.10, and 0.25 g/L	Experiment A: 8/51 exposure days; Experiment B: 9/42 days of 24 h exposure	DNA Damage assay; colorimetric detection kit; Glutathione fluorescent detection Kit	Liver, intestinal tissues, and blood/plasma	Experiment B: 8-OHdG: ↑ dose-dependent (p + 0.27 *); MDA ↓ dose-dependent (p – 0.21 *); GSH: ↑ dose-dependent (p 0.15 *); Experiment A: CYP1A protein: ↑ vs ctrls SOD: ↓ vs ctrls; GSH: ↑ vs ctrls; Pulmonary fibrosis: a-SMA and collagen I * ↑ vs ctrls (dose-dependent)	(LaPlaca et al., 2022)
Mus musculus, 44	PS, 5 μm	Intracheal-PS: 1.25 and 6.25 mg/kg, in protective group: 6.25–50 mg/kg	48 h exposure 3x/week for 21 days	Immuno-fluorescence; detection kits; western blot	Lung tissues	SOD: ↓ vs ctrls; GSH: ↑ vs ctrls; Pulmonary fibrosis: a-SMA and collagen I * ↑ vs ctrls (dose-dependent)	(Li et al., 2022b)

(continued on next page)

Table 4 (continued)

Animal model, n°	Plastic type, size	Concentration	Exposure time	Experimental methods	Matrix	Biomarkers (Oxidative stress; Inflammation; Genotoxicity and others)	Autors, Year
Holothuria tubulosa, 30	LDPE 17%, PP 27%, PS 16%, HDPE, PVC 13%, PL 8%, PET 3%, PA 1%	3 different polluted areas	NA	Spectrophotometer; colorimetric assay kit	Gut tissues	CAT, SOD, GST, GSH: * ↑ vs ctrls; AChE, MDA: No* ↑ in all areas vs ctrls	(Lombardo et al., 2022)
Mus musculus, 19 Dicentrarchus labrax, 162	PS and NH2-PS, 100 nm Virgin PVC and incubated PVC, < 0.3 mm	50 µg/ml x mouse 4 times week MP environmental concentration 1% w/w	2 weeks 90 days	WST-1 and MTT; Duoset ELISA iQ5 optical System Software v. 2.0	Serum Blood and liver tissue	IL-1β: ↑ NH2-PS vs PS-MP LPO: both groups 30 days ↓ vs ctrls; 60, 90 days ↑ vs ctrls; CAT: 60 days ↑ incubated vs ctrls; 90 days ↓ virgin and Incubated vs ctrls; TNF-α receptor: (30, 60, 90 days) ↓ vs ctrls; PPAR-receptor-α/γ: (30, 60 days) ↑ vs ctrls, (90 days) ↓ vs ctrls	(Jeon et al., 2023) (Pedà et al., 2022)
Scrobicularia plana, 420	LDPE 4–6 µm, 20–25 µm ± Benzo A pyrene (BaP)	1 mg/L	Time 0, 7 days, and 14 days	Colorimetric assay	Gills, and digestive glands	SOD: day 14, all groups ↓ vs ctrls; day 7 PE+BaP * ↑, * ↓ (at ≠ concentration and n° exposure days); SOD activity: ↓ digestive glands vs gills; CAT activity: day 7 PE+BaP gills * ↓ vs ctrls, day 14 PE+BaP digestive glands ↓ vs ctrls; GST activity: day 7 PE+BaP, ↑ vs ctrls; AChE: day 14 PE+BaP * ↑ vs ctrls; LPO levels: day 14 PE+BaP ↑ levels vs PE	(Rodrigues et al., 2022)
Coturnix japonica, 10	PS, 3293.4 µm	11 MPs particles/quail/day, 22 MP particles/quail/day, once a day	9 days	ELISA; colorimetric assay	Crop, proventriculus, gizzard, small intestine, muscle (pectoral), brain and liver tissues	H ₂ O ₂ : No* vs ctrls; ROS: ↑ vs ctrls; NO: ↓ vs ctrls; MDA: ↑ vs ctrls; SOD activity: ↓ vs ctrls; CAT: No* in ≠ tissues; CAT: ↑ vs ctrls; AChE: No* between groups, trend ↑ in both tissues; Body mass: 9 days (PS-MPs) ↓ vs ctrls	(De Souza et al., 2022)
Rattus norvegicus, 70	PS, < 5 mm	1%, 5% and 10% PS-pellets; 1, 5, 10% FP	90 days	UV/Vis spectrophotometer	Blood (plasma)	TC, TG, HDL: No* vs ctrls; LDL: (1% PS, and 5% PS, and 5%FP) * ↑ vs ctrls; GSH, GPx, GST, SOD, CAT, and MDA: (1% PS, 5%PS, 10% FP) No* vs ctrls	(Nnoruka et al., 2022)
Macrobrachium nipponense, 300	PS-NP, 500 nm	0.04 mg/L, 0.4 mg/L, 4 mg/L, 40 mg/L	28 days	Commercial kits	Gill, liver, gut, and muscle tissues	H ₂ O ₂ : * ↑ vs ctrls; GSH-Px, GSH: * ↑, No* , * ↓ (at ≠ concentrations) vs ctrls; GST: * ↑ vs ctrls; SOD: * ↑, ↓ activity (≠ concentration); CAT ↓, ↑ (≠ concentration)	(Fan et al., 2022)
Sparus aurata, 45	MPs	according to the sea water	120 days	Commercial colorimetric kit	Blood, Plasma, and liver tissues	Liver: SOD, MPO No* vs ctrls; CAT: * ↑ vs ctrls; GPx: * ↑ t60 vs t120; MDA: ↑ vs ctrls; ROS * ↑ vs ctrls; GST: * ↑ vs ctrls Plasma: SOD No* vs ctrls; CAT, MPO: * ↑ vs ctrls; MDA: * ↓ Blood cells: CAT, MPO No* ; SOD: * ↓; MDA, ROS: * ↑ vs ctrls	(Capó et al., 2022)

(continued on next page)

Table 4 (continued)

Animal model, n°	Plastic type, size	Concentration	Exposure time	Experimental methods	Matrix	Biomarkers (Oxidative stress; Inflammation; Genotoxicity and others)	Autors, Year
Ctenopharyngodon idella, 300	PS, 32–40 µm	100 µg/L, 1000 µg/L	21 days	ELISA	Liver tissues	SOD: * ↓ vs ctrls; CAT: PS-1000 µg/L * ↓ vs PS-100 µg/L; CYP1A: ↑ (liver) dose-dependent	(Chen et al., 2022b)
Goniopora columna, 198	PE-MP, 40–48 µm	5, 10, 50, 100 and 300 mg/L	7 days	Commercial kits	Tissues	MDA, GST, CAT, GSH, SOD: * ↑ vs ctrls; GPx: * ↑, * ↓ (≠ exposure time and ≠ concentration); GSH and GST: No* vs groups	(Liu et al., 2022b)
Caenorhabditis elegans, NA	PS, 1 µm	0.1, 1.0, 10, and 100 mg/L	48 h	Fuorescence microscope; qPCR	Tissues	ROS: * ↑ vs ctrls; Clk-1, ctl-1, SOD-3, SOD-4, and SOD-5 in F0: * ↑ vs ctrls; SOD-3: * ↑ vs ctrls in the F3 and F4 generations; Metabolic activity: * ↓ vs ctrls;	(Chen et al., 2021)
Caenorhabditis elegans, 400	PS, 20–100 nm	0.1–100 µg/L	6,5 days	DCFDA	Tissues	ROS: ↑ vs ctrls; Locomotion behaviour, brood size: No* changes vs ctrls;	(Liu et al., 2021)
Dicentrarchus labrax, NA	PSNP + HA (humic acid), 30–70 nm	0.02 mg/L and 20 mg/L PSNPs ± 1 mg/L of HA	96 h	qPCR; commercial kits; spectrophotometric method; TEAC	Skin mucus, Blood, and Head kidney tissues	TNF-α, IL-10: * ↑ vs ctrls; IL-1β, IL-6, IL-8 (TNF-α): No* vs ctrls (≠ concentration); TGFβ: all exposure conditions * ↑ vs ctrls; TG, TC, TAC: No* vs ctrls; MC2R gene: * ↑ vs ctrls; GR1: * ↑ vs ctrls;	(Brandts et al., 2021)
Mus musculus, 24	PS, 5 µm	0.1 mg/day	90 days	Optical microscope; qPCR	Liver tissues	ROS: ↓ vs ctrls; MMP: ↓ vs ctrls; Liver lesions: hepatic tissue rupture vs ctrls	(Pan et al., 2021)
Mus musculus, NA	PS, 2 µm	0.2 and 0.4 g/day twice a week	4–8 weeks	Shandon HistoCentre 3; western blot	Kidney tissues	ROS: ↑; kidneys lesions: ↑	(Wang et al., 2021)
Acropora sp., NA	PET, PE, 10–40 µm	250 mg/100 ml	24 h, 96 h	Commercial kits	Tissues	LDH: 24 h ↓, 96 h values * ↓ vs ctrls; TAC: 24 h * ↑, 48 h, 72 h ↓ vs ctrls; T-SOD: 24 h ↑, 96 h ↓ vs ctrls; GSH: 24 h ↑ vs ctrls, 96 h ↓ vs ctrls; NO: 96 h * ↑ vs ctrls; G6DPH: 24 h * ↓ vs ctrls	(Xiao et al., 2021)
Mus musculus, 24	PS-MPs 1, 4, 10 µm	10, 50 and 100 µg/ml/day	14 days	Protein assay kit; western blot	Mid colon tissues	NLRP3, NF-κB, TNF-α, IL-6, IL-1 β, IL-10, and TGF-β1: * ↑ vs ctrls	(Choi et al., 2021)
mytillus spp., Exposure 1: 8 Exposure 2: 8	PS, 20 µm and 50 nm, PMA, 10 × 30 µm	PS, 500 ng/L PMA, 500 ng/L,	24 h, 7 days	Commercial kits; comet assay	Digestive glands and gills tissues	SOD: * ↑ vs ctrls; TBARS: * ↓ vs ctrls; MN: No* vs ctrls; Comet assay: No* vs ctrls	(Cole et al., 2020)
Poecilia reticulata, 60	PS, 32–40 µm	100 µg/L, 1000 µg/L	28 days	Different methods according to different studies	Gut tissues	TNF-α, IFN-γ, TLR4, and IL-6: * ↑ vs ctrls; TNF-α: no* between two MP-treated groups; TLR4: * ↑ vs ctrls (higher conc. Vs lower); Histopathological changes: in gut MPs exposed changed vs ctrls,	(Huang et al., 2020)
Hediste diversicolor, NA	PE, PP, HDPE, LDPE, PAPEVA, 1 mm to 1.2 mm	Areas with different plastic pollution	NA	Different methods according to different studies	Tissues	CAT, GST, AChE, MDA: ↑ vs ctrls	(Missawi et al., 2020)
Corbicula fluminea, NA	PS, 80 nm	0.1, 1 and 5 mg/L	96 h	ELISA	Visceral mass, gills, and mantles tissues	MDA, SOD, CAT, GSH-Px, GST, GSH: * ↑ vs ctrls; AchE and GPT: * ↓ vs ctrls; GOT: No* vs ctrls;	(Li et al., 2020)
Danio rerio, 180	PS, 5, 20 µm and 70 nm	20 mg/L	4 h, 12 h, 1, 2, 7 days (every 48 h new PS solution)	Commercial kits	Liver tissues	SOD and CAT: * ↑ dose-dependent	(Lu et al., 2016)

PE (polyethylene), HDPE (high density polyethylene), LDPE (low density polystyrene), PVC (polyvinylchloride), PP (polypropylene), PET (Polyethylene terephthalate), PMA (polymethyl acrylate), PS (polystyrene), NH₂-PS(amino functionalized polystyrene), PS-COOH (carboxy functionalized polystyrene), PS-MP (polystyrene-microplastics), NPs (nanoplastics), MPs (microplastics), ROS (reactive oxygen species), SOD (superoxide dismutase), CAT (catalase), TBARS (Thiobarbituric acid reactive substances), POX (peroxidase), GST (glutathione S-transferase), GSH (glutathione), GSH-Px (plasma glutathione peroxidase), PPAR- α (peroxisome proliferator-activated receptor alpha), PPAR- γ (peroxisome proliferator-activated receptor gamma), CYP1A (cytochrome P450 Family 1 Subfamily A protein), TNF- α (tumor necrosis factor alfa), IL- (Interleukin -), MDA (malondialdehyde), ENAs (extractable nuclear antigens), GPx (glutathione peroxidase), MCP-1 (monocyte chemoattractant protein-1), LPS (lipopolysaccharides), INF- γ (interferon gamma), AHR (aryl hydrocarbon receptor), muc- (muc genes), NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), STAT-3 (signal transducer and activator of transcription 3), TAP/TAC (total antioxidant capacity), NO (nitric oxide), NLRP3 (NOD-like receptor family pyrin domain containing 3), AChE (acetylcholinesterase), α -SMA (alpha-smooth muscle actin), PE-BaP (polyethylene-benzo-a-pyrene), LPO (lactoperoxidase), H₂O₂ (hydrogen peroxide), TC (total cholesterol), TG (triglycerides), HDL (high-density lipoprotein), LDL (low-density lipoprotein), MC2R-gene (Melanocortin 2 Receptor), GR1 (gamma response 1 protein), G6DPH (glucose-6-phosphate dehydrogenase), TGF- β 1 (transforming growth factor-beta1), TLR-4 (tool-like receptor-4), GOT/AST (aspartate aminotransferase), MPO (myeloperoxidase), FP (foam particles), MMP (plasma matrix metalloproteinases), qPCR (quantitative Polymerase Chain Reaction), DCFDA or DCFH-DA assay (2',7'-dichlorodihydrofluorescein diacetate), WST-1 assay (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolol]-1,3-benzene sulfonate), MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), ELISA (Enzyme-linked immunosorbent assay), EIA (Enzyme Immuno Assay), TEAC (Trolox equivalent antioxidant capacity) *(significantly), \downarrow (decreased/inhibited), \uparrow (increased).

Table 5

Biomarkers of MNPs exposure analysed in plants studies.

Plant model, n°	Plastic type, size	Concentration	Exposure time	Experimental methods	Biomarkers (Oxidative stress and others)	Autors, Year
Skeletonema costatum, NA	P-PS, A-PS, L-PS, 0.1–1 μ m	0, 5, 10 and 50 mg/L	0, 24, 48, 72, 96 h	Commercial kits	SOD: (P-PS) \downarrow dose-dependent; CAT: (1 μ m) \uparrow vs (0.1 μ m P-PS); MDA: \uparrow dose-dependent; Growth: all three groups * \downarrow vs ctrls;	(Ni et al., 2023)
Apostichopus japonicus, 360	PS, 20 μ m-100 nm	100 mg/kg	60 days	Different methods according to different studies	ROS, MDA: (PS 20 μ m) * \uparrow vs (PS 100 nm) and vs ctrls; SOD, CAT: 10 days (PS 20 μ m) \uparrow vs ctrls; Growth rate: < (PS, 100 nm) vs > (PS 20 μ m)	(Liu et al., 2022a)
Lemna minor L., NA	PS, 230 and 260 nm	100 and 200 mg/L	NA	Different methods according to different studies	SOD, CAT, and POX activity: \uparrow vs ctrls; low PS, H ₂ O ₂ scavenging by regulating the redox state and enzyme/non-enzyme; Growth: 100 mg/L No* toxicity effects on growth	(Arikan et al., 2022)
Allium cepa, NA	PS, 100 nm	25, 50, 100, 200 and 400 mg/L	24, 48, 72 h	Different methods according to different studies	SOD: 72 h \uparrow dose-dependent vs ctrls; MDA: 72 h No* vs ctrls; Lipidic peroxidation: 72 h * \downarrow vs ctrls; CAs index: 72 h * \uparrow vs ctrls; Root growth: \downarrow vs ctrls	(Maity et al., 2020)

P-(pristine), A-(aged), L-(leached), PS (Polystyrene), SOD (superoxide dismutase), CAT (catalase), MDA (malondialdehyde), POX (peroxidase), ROS (reactive oxygen species), H₂O₂ (hydrogen peroxide), CAs (chromosomal aberrations), * (significantly), \downarrow (decreased/inhibited), \uparrow (increased).

Table 5 summarizes the biomarkers of effect of MNPs reported in plant studies analysed. Studies in *A. japonicus* (Liu et al., 2022a) and *S. Costatum* (Ni et al., 2023) following PS exposure point to a similar trend of MDA levels as in-vivo animal studies.

Similarly to MDA, total antioxidant capacity (TAC) or total antioxidant power (TAP) has been used to assess the cumulative effects of the antioxidants (Suresh et al., 2009). In animal models, Xiao et al. observed a notable rise in TAC levels within 24 h of exposure to PET and PE (Xiao et al., 2021). Conversely, a separate study conducted by Brandts et al. on fish exhibited no alteration in micronuclei (MN) of liver and muscle tissues after PS (0,04 μ m) exposure (Brandts et al., 2021).

3.1.2. Inflammation

Inflammation is a physiological condition carried out by living organisms in response to external stimuli, such as pathogens, inorganic or organic particles, such as plastic (Pahwa et al., 2023). Based on the time course of the inflammatory response, we can distinguish acute and chronic inflammation. The mediators used in both types of responses are cytokines that play a pleiotropic function in mediating and regulating the immune response: on one side, they stimulate the cytokine production and thus increase inflammation levels; on the other side they reduce the production in order to limit the inflammatory response (Ghelli et al., 2022).

Table 3 and Table 4 summarize the studies that have investigated cytokines, such as IL (interleukin)-1 β , IL-6, IL-8, and IL-10 as biomarkers of inflammation in cell lines and animal studies.

The modulation of immune response has been investigated by the evaluation of transcription factors, e.g. the nuclear transcription factor

NF-kb, endowed with a central role in the inflammatory response, and NLRP3, one of the proteins involved in inflammation, which is expressed on the membrane of macrophages to initiate the inflammatory response.

Moreover, 7 articles analyzed the NLRP3 multi-protein complex and the MY88D protein responsible for the activation of the innate immune response (Table 3).

NFkB was investigated in 4 studies. For instance, Caputi et al. showed a significant increase in Nf-kb levels and an increase in NLRP3 protein expression in cell cultures of human gingival fibroblasts exposed to MP (0.1–0.6 μ m) (Caputi et al., 2022). Similarly, Chen et al., showed an increase in Nf-kb levels in human embryonic kidney cells exposed to PS (3.54 μ m) but at the same time, a significant decrease in NLRP3 protein expression following a 24-hour exposure (Chen et al., 2022a).

In-vivo studies in fishes exposed to PE for 21 days (Cao et al., 2023) and in mice following 14 days of PS exposure (Choi et al., 2021), showed inflammasome activation with significant increases in NFkB and NLRP3 levels compared to untreated controls.

The papers included in this review have analysed different cytokines, like the pro-inflammatory IL-1 β (n = 12), IL-6 (n = 14), TNF- α (tumor necrosis factor alfa) (n = 14) and INF- γ (interferon gamma) (n = 3) (Zhang and An, 2007). Of 10 articles dealing with IL-1 β levels, five of them showed significant increases in IL-1 β after exposure to PE or PS in in-vitro models.

Exposure to MNPs consisting of PS, PMMA, and PVC (ranging from 50 to 310 nm) led to elevated levels of IL-6, as indicated by 11 studies, which demonstrated slight changes compared to untreated controls. Additionally, 9 studies reported increased levels of TNF- α , while 3 studies showed elevated INF- γ levels.

IL-8 and IL-10 have a dual function, in stimulating the production of other cytokines and limiting their production. Increased levels have been shown in all investigated papers. This suggests that MPs can affect the regulation of pro-inflammatory cytokine production through negative feedback (Zhang and An, 2007).

In-vitro studies report the inflammatory biomarkers as the main indicators of the perturbation occurring in biological systems and cell cultures challenged with different types of MNPs. Weber et al., analysed the exposure of human monocytic dendritic cells to PMMA and PVC (0,05–0310 μm), highlighting an increasing trend of IL-10 and decreasing trend for IL-6 and TNF- α compared to controls (Weber et al., 2022). Conversely, Bengalli et al. showed a statistically significant increasing trend of IL-6 and IL-8 in human lung cells exposed to MP (<50 μm) compared to controls (Bengalli et al., 2022). Cheng et al., showed a dose-dependent increase of IL-6 in cell medium of human embryonic cell lines after exposure to PS (1 μm) (Cheng et al., 2022). Palaniappan et al. tested L929 cells after exposure to PE (1–4 μm), PS (9, 5–11,5 μm) showing dose-dependent trend of IL-1 β and TNF- α (Palaniappan et al., 2022). On the contrary, Busch et al., didn't show any changes in levels of both pro-inflammatory cytokines in Caco2 cells exposed to PS micro particles, though IL-1 β levels were significantly higher after exposure to PVC (50 nm) as compared to controls (Table 3) (Busch et al., 2021).

In animal models, exposure to particulate matter (PM) has been shown to induce increased levels of IL-1 β , IL-8, IL-10 in various tissues, such as gut, mucous membranes, blood and kidney cells, compared to controls. Cocci et al., reported progressively increasing levels of IL-1 β , IL-8, IL-10, TNF- α , and INF- γ following exposure to PE and PS with respective sizes of 5–1 mm, 1–0.5 mm, and 0.5–0.1 mm (Table 4) (Cocci et al., 2022). In the gills of carp exposed to PE for 21 days, the levels of IL-2, IL-10, INF- γ , and TNF- α were significantly higher than in controls, while IL-4, IL-6, and IL-8 showed a non-significant increase compared to non-exposed individuals (Cao et al., 2023). In the renal tissues of sea bass following exposure to PS (30–70 nm), no statistical differences were observed in the levels of IL-1 β , IL-6, and IL-8 compared to controls. Conversely, significantly higher levels of TNF- α were detected in exposed fish compared to non-exposed individuals (Brandts et al., 2021). In mice exposed to PS (1, 4, 10 μm) at a concentration of 50–100 mg/cm², the levels of IL-1 β , IL-6, IL-10, TNF- α , and Nf-kB significantly increased compared to controls. Similarly, Huang et al. showed in intestinal tissues of fish exposed to PS (32–40 μm) at 100–1000 mg/ml an increasing trend of TNF- α , IL-6 and INF- γ compared to controls (Huang et al., 2020). Regarding the studies included in this work, carried out in humans and plants, no cytokines were analysed.

3.1.3. Genotoxicity

The DNA damaging potential of MNPs is known or suspected, and has been investigated, both *in-vitro* and *in-vivo*. Oxidative stress and inflammation can lead to oxidative damage to nucleic acids.

In the present paper we found evidence of genotoxicity from MNPs following exposure to known polymers. DNA strand breaks and MN were the main biomarkers used to assess this endpoint. MNs and chromosomal aberrations (CA) were investigated both *in-vitro* and *in-vivo* (animal models) as well as in few human studies (blood nucleated cells). MNs derive from whole chromosomes or acentric fragments that do not migrate to the poles during anaphase and are not incorporated into the main nucleus, giving rise to smaller accessory nuclei (Heddle et al., 1991). In this review, 5 articles (4 on cell cultures and 1 on experimental animal models) investigated the presence of MN reporting an increase compared to controls following prolonged exposure to MNPs. In addition, CA (n = 3) and sister chromatid exchanges (SCE) (n = 1) were investigated.

Maity et al., and Malinowska et al., tested the genotoxicity of 0.1 μm , 0.029 μm , 0.044 μm , 0.072 μm PS particles in exposed cells by Comet test showing an increasing dose-dependent trend in DNA damage as compared to non-exposed (Maity et al., 2020; Malinowska et al., 2022).

MNs were investigated in lung carcinoma epithelial cells by Shi et al., highlighting an increasing trend of MN formation after exposure to 0.08–2.0 μm PS compared to controls (Shi et al., 2022). Conversely, Cole et al. who conducted a study on mussels exposed to PS (0.05–20.0 μm), and PMA (10.0 \times 30.0 μm) did not show statistical differences for MN formation between exposed and not exposed mussels (Cole et al., 2020).

Roursgaard et al., analysed PP (0,08–0,25 μm) and PET (0,2–0,6 μm) exposure toxicity, on hepatocellular carcinoma and colorectal adenocarcinoma epithelial cell lines, assessing an increasing DNA damages in a dose-dependent manner after exposure to PET compared to controls (Table 3) (Roursgaard et al., 2022). In a study carried out on fish by Laplaca et al., DNA damages (8-oxo-dG) increased in a dose-dependent manner after exposure to crumb-rubber (38–355.0 μm) compared to controls underlining a positive correlation (Rho=0,27 *) (Table 4) (LaPlaca et al., 2022).

One study carried out in workers exposed to MP analysed CA and SCE on blood cells and it was demonstrated trend towards an increase of CA in those exposed to Acrylonitrile (ACN), and a similar number of SCE compared to controls (Major et al., 1998) (Table 6). Maity et al., found significant increases of CA in plants after exposure to PS (0,1 μm) at different concentrations (Table 5) (Maity et al., 2020).

Whereas mechanistic studies in plant species seem irrelevant for human exposure, many *in-vivo* studies in rodents suggest at least three endpoints relevant for human beings, although the dose levels are, in many cases, far behind the likelihood of exposure for humans. Inflammation in gut tissues, gill, mid colon, liver, and muscle tissues may lead to alterations of lipid metabolism, and reduction of antioxidant defence system that can be defined as either oxidative stress, inflammation or general toxicity biomarkers summarized in Tables 3–6.

4. Discussion

MP are ubiquitous in the environment and have been detected in different environmental media, raising concerns about human exposure through different pathways. While there is limited evidence suggesting MPs, excluding their chemical constituents or contaminants, might have adverse effects on human health, there is a growing consensus among stakeholders and heightened public awareness to reduce exposure to MNPs.

Numerous *in-vivo* and *in-vitro* studies indicate that exposure to MNPs can lead to inflammation, ROS production, genomic instability and immune system dysfunction. These findings are consistent across living species, suggesting common pathways of disease and MOA shared with other foreign particulates, resulting in biochemical changes and subtle dysfunctions. Key biomarkers assessed in these studies often reflect imbalances in antioxidant defence system, including markers like lipid peroxidation, membrane damage, ROS, SOD, CAT, MDA, GST, GSH, GPx, and TAP.

Inflammation is one of the probable outcomes investigated following MNPs exposure; in particular, IL-1 β , IL-6, IL-8, IL-10, TNF- α , NF-kB were the cytokines most frequently investigated as an index of an inflammatory condition in clinical, environmental, and occupational studies are the same as those investigated in the papers included in this review. For genotoxicity, biomarkers such as MNs, cytokinesis-block proliferation index, Comet test index, CA, and SCE have been frequently studied as indicators of DNA damage, which is crucial for human health (Çobanoğlu et al., 2021). Recent critical reviews have provided insight into the possible mechanisms that can lead to initiation and progression of cancer pathogenesis in the body (Alimba et al., 2021; Domenech et al., 2023). The potential mechanisms underlying the development of cancer caused by MNPs revolve around the individual and/or interactive effects of ROS, the induction of oxidative stress, genome instability, and chronic inflammation. However, it is yet to be explored whether these mechanisms hold relevance for human health through dedicated studies on human subjects.

There are concerns about the potential of MNPs impact the entire

Table 6

Biomarkers of MNPs exposure analysed in human studies.

Subjects, n ^a	Plastic type	Concentration	Exposure time	Experimental methods	Matrix	Biomarkers (Inflammation, genotoxicity, and others)	Autors, Year
exposed workers, 889	PVC	1000 ppm x year	1 year	Sonography and enzymatic assays	Blood test, liver imaging	liver lesions 39,5% (BMI<27)	(Mastrangelo et al., 2004)
14 exp symptomatic, 15 exp asymptomatic, 9 non-exposed	PUR	NA	24 h	GC-MS	Urine, plasma, nasal lavage fluid	Ctrl: U-MDX [0,28[nq-2,3]], U-2,4-TDX [0,32[nq-0,6]], U-2,6-TDX [0,27[nq-0,6]]; exposed: U-MDX[0,35 [nq-0,6]],U-2,4-TDX [nq [nq-1.0]],U-2,6-TDX [0,27 [0,35 [nq-0,7]]]	(Littorin et al., 2002)
26 exposed, 26 non-exposed	MPS, ACN, DMF	NA	20 months	GC	Urine and Blood	ACN* ↑ vs ctrls; CA ↑ vs ctrls; SCE= (No*) vs ctrls	(Major et al., 1998)

ACN: Acrylonitrile, DMF (Dimethylformamide), PVC (polyvinyl chloride), PUR (polyurethane), MPs (generic microplastics polymers), SCE (sister chromatids exchange), U-MDX (metabolites of 4,4'-diphenylmethane di-isocyanate), U-TDX (2,4- and 2,6-toluene diisocyanate), GC (Gas chromatography), MS (mass spectrometry), *(significantly), ↓(decreased/inhibited), ↑(increased).

ecosystem (Mateos-Cárdenas et al., 2019), as they are found in both indoor and outdoor environments, spread by atmospheric events like rain and wind, and even transferred between marine species in aquatic ecosystems. (Zhang et al., 2020). For this reason, numerous studies have focused on aquatic ecosystems by investigating their presence and possible trophic transfer from aquatic plants to animal organisms. (Welden et al., 2018) and (Nelms et al., 2018) in their work noted a transfer of MNPs between prey-predator marine species (Welden et al., 2018); Nelms et al., 2018). While transfer to humans via plants has been suggested (Schwabl et al., 2019), it remains poorly understood, and the route of intake, whether through the food chain or other exposures including occupational, is unclear due to the lack of standardized methods and procedures for identifying and interpreting results. (Toussaint et al., 2019). Research on the effects of MNPs has primarily been conducted in controlled settings, indicating growth reductions at the cellular and apical level, lower biomass yields, and increased levels of OS and inflammation in exposed animals (Pan et al., 2021; Cocco et al., 2022), but the extent of trophic transfer has mostly been studied in laboratory models (He et al., 2021). Limited studies have explored the impact of MNPs exposure in occupational settings, potentially leading to increased intake and effects primarily observed in in-vitro or in-vivo models with animals or plants.

Inflammatory biomarkers play a crucial role in biomonitoring the effects of MNPs exposure. This review summarizes the types of MNPs studied, their sizes and the biomarkers used in in-vitro, in-vivo, and occupational studies. To assess the risks to human health, more studies considering various exposure scenarios and the size distribution of airborne plastic particles, including those reaching the alveolar region of the lungs, are necessary. Workplace studies can offer insights into dose-response relationships and overcome the limitations of in-vitro tests. The identification of reliable biomarkers should support field studies and epidemiological investigations, aiding in understanding the potential risks of MNPs and the development of mitigation strategies (Mastrangelo et al., 2004).

Therefore, the biomarkers summarised in this review may be a good starting point for investigating effects in the occupational setting to provide a complete scenario and the necessary knowledge on the adverse effects that MNPs may have on humans. Therefore, the biomarkers summarised in this review may be a good starting point for investigating effects in the occupational setting to provide a complete scenario and the necessary knowledge on the adverse effects that MNPs may have on humans. These findings suggest a minimum set of biomarkers to be assessed in biological matrices of volunteers and workers with potential exposure to MNPs should help clarifying its relationship with health outcomes. This can be further complemented with recently validated biomarkers reflecting long-term endpoints, such as chronic inflammation and fibrosis, as well as cardiovascular endpoints, considering possible interference in lipid metabolism. This consideration is

based on what we know from field investigations of nanomaterials, in which the successful implementation of a harmonized protocol allowed to demonstrate the feasibility of similar research projects in the future, facilitating further studies in target populations, and inform stakeholders of regulatory aspects targeting occupational exposure to MNPs (Bergamaschi et al., 2015; Guseva Canu et al., 2023).

Human studies on MNPs exposure remain limited. Although some recent investigations have found MNPs in stool (Schwabl et al., 2019) and in induced sputum samples (Huang et al., 2022) further research is needed to clarify the implications of MNPs presence in human biological samples. Challenges include aggregating data from various studies using different analytical methods and considering factors like plastic shape, which can significantly influence the harm caused by MNPs. As pointed out in the work of Suman et al., smaller plastics in the μm range are more bioavailable in both in-vitro and in-vivo models by increasing levels of OS, inflammation, and possible genotoxicity (Suman et al., 2021). Moreover, different studies showed that plastics with an irregular shape were the ones most ingested by organisms; this combined with the small particle size makes them more harmful (Desforgues et al., 2015; Steer et al., 2017; Sun et al., 2017; Schwabl et al., 2019). Considering these aspects, it seems reasonable to take advantage of what we already know about particles toxicology, working under the assumption that different nanoparticles may lead to the same pathway for disease, or share common mechanisms (e.g. inflammation).

5. Conclusions

Data on biomarkers of effect after inhalation or dietary exposure for characterizing the hazard of MNPs remain relatively scarce, primarily restricted to studies with model particles, such as polystyrene beads. These model particles typically fall within the regulatory size range (e.g., < 10 μm) as defined by the World Health Organization (WHO). These investigations underscore the need of more comprehensive data on the impacts of MNPs, considering factors beyond mere size, including aspects like shape, polymer composition and other attributes representative of environmentally relevant MNPs.

Despite the limited characterization of MNPs' hazards, especially concerning human health, existing literature findings suggest that MNPs may yield adverse effects akin to those observed with other extensively studied solid and insoluble particles, presumably through comparable modes of action. Nevertheless, the available data fall short of providing a definitive link between MNP exposure and specific illnesses, both directly and indirectly. Quality control concerns in published studies, as highlighted by the WHO in 2006, have not been adequately addressed. Biomarkers of effect are valuable tools in the early detection of sub-clinical changes before the onset of disease, aiding in the anticipation of potential adverse effects associated with engineered nanomaterials and the elucidating of dose-effect relationships. However, their practical

utility in environmental and occupational exposure monitoring and health surveillance remains limited.

Author contributions statement

Marco Panizzolo: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Vitor Hugo Martins:** Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Federica Ghelli:** Visualization, Methodology, Data curation, Writing – review & editing. **Giulia Squillaciotti:** Visualization, Methodology, Writing – review & editing. **Valeria Bellisario:** Visualization, Validation, Writing – review & editing. **Giacomo Garzaro:** Visualization, Writing – review & editing. **Davide Bosio:** Visualization, Writing – review & editing. **Nicoletta Colombi:** Conceptualization, Investigation, Validation, Methodology. **Roberto Bono:** Supervision, Conceptualization, Resources, Writing – review & editing. **Enrico Bergamaschi:** Funding acquisition, Conceptualization, Project administration, Writing – review & editing.

Funding

This work received funding from the European Union's Horizon 2020 Research and Innovation programme, under the Grant Agreement number 965367 (PlasticsFatE).

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

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2023.115645](https://doi.org/10.1016/j.ecoenv.2023.115645).

References

- Afrin, Sadia, Uddin, Md. Khabir, Rahman, Md. Mostafizur, 2020. Microplastics Contamination in the Soil from Urban Landfill Site, Dhaka, Bangladesh, 2020/11/01/ Heliyon no. 11, e05572. <https://doi.org/10.1016/j.heliyon.2020.e05572>, 2020/11/01/. (<https://www.sciencedirect.com/science/article/pii/S2405844020324154>).
- Alimba, Chibuisi G., Faggio, Caterina, Sivanesan, Saravanadevi, Ogunkanmi, Adebayo L., Krishnamurthi, Kannan, 2021. Micro(Nano)-plastics in the environment and risk of carcinogenesis: insight into possible mechanisms, 2021/08/15/ J. Hazard. Mater. 416, 126143. <https://doi.org/10.1016/j.jhazmat.2021.126143>, 2021/08/15/. (<https://www.sciencedirect.com/science/article/pii/S0304389421011079>).
- Arikan, B., Alp, F.N., Ozfidan-Konakci, C., Yildiztugay, E., Turan, M., Cavusoglu, H., 2022. The impacts of nanoplastic toxicity on the accumulation, hormonal regulation and tolerance mechanisms in a potential hyperaccumulator - Lemna minor L. [In eng]. Oct 15 J. Hazard Mater. 440, 129692. <https://doi.org/10.1016/j.jhazmat.2022.129692>.
- Barnes, D.K., Galgani, F., Thompson, R.C., Barlaz, M., 2009. Accumulation and fragmentation of plastic debris in global environments. Jul 27 Philos. Trans. R. Soc. Lond. B Biol. Sci. 364 (1526), 1985–1998. <https://doi.org/10.1098/rstb.2008.0205>.
- Bengalli, R., Zerboni, A., Bonfanti, P., Saibene, M., Mehn, D., Cella, C., Ponti, J., La Spina, R., Mantecchia, P., 2022. Characterization of microparticles derived from waste plastics and their bio-interaction with Human Lung A549 Cells [In eng] (Dec). J. Appl. Toxicol. 42 no. 12, 2030–2044. <https://doi.org/10.1002/jat.4372>.
- Bergamaschi, Enrico, Craig Poland, Irina Guseva Canu, Prina-Mello, Adriele, 2015. The role of biological monitoring in nano-safety. Nano Today 10 (3), 274–277. <https://doi.org/10.1016/j.nantod.2015.02.001> <https://dx.doi.org/10.1016/j.nantod.2015.02.001>.
- Bonanomi, M., Salmistraro, N., Porro, D., Pinsino, A., Colangelo, A.M., Gaglio, D., 2022. Polystyrene micro and nano-particles induce metabolic rewiring in normal human colon cells: a risk factor for human health. Chemosphere 303 (Pt 1), 134947. <https://doi.org/10.1016/j.chemosphere.2022.134947>.
- Brandts, I., Balasch, J.C., Gonçalves, A.P., Martins, M.A., Pereira, M.L., Tvarijonavičiute, A., Teles, M., Oliveira, M., 2021. Immuno-modulatory effects of nanoplastics and humic acids in the European Seabass (*Dicentrarchus labrax*) [In eng]. Jul 15 J. Hazard Mater. 414, 125562. <https://doi.org/10.1016/j.jhazmat.2021.125562>.
- Brandts, I., Cánovas, M., Tvarijonavičiute, A., Llorca, M., Vega, A., Farré, M., Pastor, J., Róher, N., Teles, M., 2022. Nanoplastics are bioaccumulated in fish liver and muscle and cause DNA damage after a chronic exposure [In eng] (Sep). Environ. Res. 212 (Pt A), 113433. <https://doi.org/10.1016/j.envres.2022.113433>.
- Busch, M., Bredeck, G., Kämpfer, A.A.M., Schins, R.P.F., 2021. Investigations of acute effects of polystyrene and polyvinyl chloride micro- and nanoplastics in an advanced in vitro triple culture model of the healthy and inflamed intestine [In eng] (Feb). Environ. Res 193, 110536. <https://doi.org/10.1016/j.envres.2020.110536>.
- Cantor, Kirk M., Watts, Patrick, 2011. 1 - Plastics Materials. In *Applied Plastics Engineering Handbook*. Myer Kutz, 3-5. William Andrew Publishing., Oxford.
- Cao, J., Xu, R., Wang, F., Geng, Y., Xu, T., Zhu, M., Lv, H., Xu, S., Guo, M.Y., 2023. Polyethylene microplastics trigger cell apoptosis and inflammation via inducing oxidative stress and activation of the Nlrp3 inflammasome in carp gills [In eng]. Fish. Shellfish Immunol. 132, 108470. <https://doi.org/10.1016/j.fsi.2022.108470>.
- Capó, X., Alomar, C., Compa, M., Sole, M., Sanahuja, I., Soliz Rojas, D.L., González, G.P., Garcinuño Martínez, R.M., Deudero, S., 2022. Quantification of differential tissue biomarker responses to microplastic ingestion and plasticizer bioaccumulation in aquaculture reared sea Bream *Sparus aurata* (Aug). Environ. Res. 211, 113063. <https://doi.org/10.1016/j.envres.2022.113063>.
- Caputi, S., Diomedea, F., Lanuti, P., Marconi, G.D., Di Carlo, P., Sinjari, B., Trubiani, O., 2022. Microplastics affect the inflammation pathway in Human Gingival Fibroblasts: a study in the Adriatic Sea [In eng]. Jun 24 Int J. Environ. Res Public Health 19 (13). <https://doi.org/10.3390/ijerph19137782>.
- Caracci, Elisa, Vega-Herrera, Albert, Dachs, Jordi, Berrojalbiz, Naiara, Buonanno, Giorgio, Abad, Esteban, Llorca, Marta, Moreno, Teresa, Farré, Marinella, 2023. Micro(Nano)Plastics in the atmosphere of the Atlantic Ocean, 2023/05/15/ J. Hazard. Mater. 450, 131036. <https://doi.org/10.1016/j.jhazmat.2023.131036>, 2023/05/15/. (<https://www.sciencedirect.com/science/article/pii/S0304389423003187>).
- Chang, X., Xue, Y., Li, J., Zou, L., Tang, M., 2020. Potential health impact of environmental micro- and nanoplastics pollution [In eng] (Jan). J. Appl. Toxicol. 40 (1), 4–15. <https://doi.org/10.1002/jat.3915>.
- Chen, H., Hua, X., Li, H., Wang, C., Dang, Y., Ding, P., Yu, Y., 2021. Transgenerational neurotoxicity of polystyrene microplastics induced by oxidative stress in *Caenorhabditis elegans*. Chemosphere 272, 129642. <https://doi.org/10.1016/j.chemosphere.2021.129642>.
- Chen, Y.C., Chen, K.F., Lin, K.A., Chen, J.K., Jiang, X.Y., Lin, C.H., 2022a. The nephrotoxic potential of polystyrene microplastics at realistic environmental concentrations [In eng]. Apr 5 J. Hazard Mater. 427, 127871. <https://doi.org/10.1016/j.jhazmat.2021.127871>.
- Chen, Y.T., Ding, D.S., Lim, Y.C., Singhanía, R.R., Hsieh, S., Chen, C.W., Hsieh, S.L., Dong, C.D., 2022b. Impact of polyethylene microplastics on coral gonopora column causing oxidative stress and histopathology damages [In eng]. Jul 1 Sci. Total Environ. 828, 154234. <https://doi.org/10.1016/j.scitotenv.2022.154234>.
- Cheng, W., Li, X., Zhou, Y., Yu, H., Xie, Y., Guo, H., Wang, H., et al., 2022. Polystyrene microplastics induce hepatotoxicity and disrupt lipid metabolism in the liver organoids. Feb 1 Sci. Total Environ. 806 (Pt 1), 150328. <https://doi.org/10.1016/j.scitotenv.2021.150328>.
- Choi, Y.J., Kim, J.E., Lee, S.J., Gong, J.E., Jin, Y.J., Seo, S., Lee, J.H., Hwang, D.Y., 2021. Inflammatory response in the Mid Colon of Icr mice treated with polystyrene microplastics for two weeks. Nov 22 Lab Anim. Res. 37 (1), 31. <https://doi.org/10.1186/s42826-021-00109-w>.
- Çobanoğlu, Hayal, Belivermiş, Murat, Sıkdokur, Ercan, Kılıç, Önder, Çayır, Akın, 2021. Genotoxic and cytotoxic effects of polyethylene microplastics on human peripheral blood lymphocytes, 2021/06/01/ Chemosphere 272, 129805. <https://doi.org/10.1016/j.chemosphere.2021.129805>, 2021/06/01/. (<https://www.sciencedirect.com/science/article/pii/S0045653521002745>).
- Cocci, P., Gabrielli, S., Pastore, G., Minicucci, M., Mosconi, G., Palermo, F.A., 2022. Microplastics accumulation in gastrointestinal tracts of mullus barbatus and merluccius merluccius is associated with increased cytokine production and signaling (Nov). Chemosphere 307 (Pt 3), 135813. <https://doi.org/10.1016/j.chemosphere.2022.135813>.
- Cole, M., Liddle, C., Consolandi, G., Drago, C., Hird, C., Lindeque, P.K., Galloway, T.S., 2020. Microplastics, microfibrils and nanoplastics cause variable sub-lethal responses in Mussels (*Mytilus* Spp.) [In eng] (Nov). Mar. Pollut. Bull. 160, 111552. <https://doi.org/10.1016/j.marpolbul.2020.111552>.
- De Souza, S.S., Freitas Í, N., Gonçalves, S.O., Luz, T.M.D., Araújo, Apdc, Rajagopal, R., Balasubramani, G., Rahman, M.M., Malafaia, G., 2022. Toxicity induced via ingestion of naturally-aged polystyrene microplastics by a small-sized terrestrial bird and its potential role as vectors for the dispersion of these pollutants [In eng]. Jul 15 J. Hazard Mater. 434, 128814. <https://doi.org/10.1016/j.jhazmat.2022.128814>.
- Del Rio, D., Stewart, A.J., Pellegrini, N., 2005. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress (Aug). Nutr. Metab. Cardiovasc Dis. 15 (4), 316–328. <https://doi.org/10.1016/j.numecd.2005.05.003>.
- Demir, E., 2021. Adverse biological effects of ingested polystyrene microplastics using *Drosophila melanogaster* as a model in vivo organism [In eng]. Aug 18 J. Toxicol. Environ. Health A 84 (16), 649–660. <https://doi.org/10.1080/15287394.2021.1913684>.

- Desforges, J.P., Galbraith, M., Ross, P.S., 2015. Ingestion of microplastics by Zooplankton in the Northeast Pacific Ocean (Oct). *Arch. Environ. Contam. Toxicol.* 69 (3), 320–330. <https://doi.org/10.1007/s00244-015-0172-5>.
- Di Bella, Gaetano, Santo, F.Corsino, De Marinis, Federica, Lopresti, Francesco, Carrubba, Vincenzo La, Torregrossa, Michele, Viviani, Gaspare, 2022. Occurrence of microplastics in waste sludge of wastewater treatment plants: comparison between membrane bioreactor (mbr) and conventional activated sludge (Cas) technologies. *Membranes* 12 (4). <https://doi.org/10.3390/membranes12040371>.
- Ding, N., Jiang, L., Wang, X., Wang, C., Geng, Y., Zhang, J., Sun, Y., et al., 2022. Polyethylene microplastic exposure and concurrent effect with aeromonas hydrophila infection on Zebrafish (Sep). *Environ. Sci. Pollut. Res. Int.* 29 (42), 63964–63972. <https://doi.org/10.1007/s11356-022-20308-9>.
- Domenech, J., Annangi, B., Marcos, R., Hernández, A., Catalán, J., 2023. Insights into the potential carcinogenicity of micro- and nano-plastics (Jan-Jun). *Mutat. Res. Rev. Mutat.* 791, 108453. <https://doi.org/10.1016/j.mrrev.2023.108453>.
- Dong, C.D., Chen, C.W., Chen, Y.C., Chen, H.H., Lee, J.S., Lin, C.H., 2020. Polystyrene microplastic particles: in vitro pulmonary toxicity assessment [In eng]. *Mar 5 J. Hazard Mater.* 385, 121575. <https://doi.org/10.1016/j.jhazmat.2019.121575>.
- Dube, Edith, Grace, E.Okuthe, 2023. Plastics and Micro/Nano-Plastics (Mnps) in the environment: occurrence, impact, and toxicity. *Int. J. Environ. Res. Public Health* 20 (17). <https://doi.org/10.3390/ijerph20176667>.
- Espinosa, C., García Beltrán, J.M., Esteban, M.A., Cuesta, A., 2018. In vitro effects of virgin microplastics on fish head-kidney leucocyte activities [In eng] (Apr). *Environ. Pollut.* 235, 30–38. <https://doi.org/10.1016/j.envpol.2017.12.054>.
- Esterhuizen, M., Buchenhorst, L., Kim, Y.J., Pflugmacher, S., 2022. In vivo oxidative stress responses of the freshwater basket clam *Corbicula javanicus* to microplastic fibres and particles (Jun). *Chemosphere* 296, 134037. <https://doi.org/10.1016/j.chemosphere.2022.134037>.
- Fan, W., Yang, P., Qiao, Y., Su, M., Zhang, G., 2022. Polystyrene nanoplastics decrease molting and induce oxidative stress in adult macrobrachium nipponense [In eng] (Mar). *Fish. Shellfish Immunol.* 122, 419–425. <https://doi.org/10.1016/j.fsi.2022.02.028>.
- Ghelli, F., Panizzolo, M., Garzaro, G., Squillacioti, G., Bellisario, V., Colombi, N., Bergamaschi, E., Guseva Canu, I., Bono, R., 2022. Inflammatory biomarkers in exhaled breath condensate: a systematic review [In eng]. *Aug 29 Int J. Mol. Sci.* 23 (17). <https://doi.org/10.3390/ijms23179820>.
- Gigault, Julien, Pedrono, Boris, Maxit, Benoît, Ter Halle, Alexandra, 2016. Marine plastic litter: the unanalyzed nano-fraction. *Environ. Sci.: Nano* 3 (2), 346–350. <https://doi.org/10.1039/c6en00008h>.
- González-Acedo, Anabel, García-Recio, Enrique, Illescas-Montes, Rebeca, Ramos-Torrecillas, Javier, Melguizo-Rodríguez, Lucía, Costela-Ruiz, Víctor Javier, 2021. Evidence from in vitro and in vivo studies on the potential health repercussions of micro- and nanoplastics, 2021/10/01/ *Chemosphere* 280, 130826. <https://doi.org/10.1016/j.chemosphere.2021.130826>, 2021/10/01/. (<https://www.sciencedirect.com/science/article/pii/S0045653521012972>).
- Grabowski, N., Hillaireau, H., Vergnaud, J., Santiago, L.A., Kerdine-Romer, S., Pallardy, M., Tsapis, N., Fattal, E., 2013. Toxicity of surface-modified plga nanoparticles toward lung alveolar epithelial cells. *Oct 1 Int. J. Pharm.* 454 (2), 686–694. <https://doi.org/10.1016/j.jipharm.2013.05.025>.
- Guseva Canu, I., Plys, E., Velarde Crézéc, C., Fito, C., Hopf, N.B., Progiou, A., Riganti, C., et al., 2023. A harmonized protocol for an international multicenter prospective study of nanotechnology workers: the nanoexplore cohort (Feb). *Nanotoxicology* 17 (1), 1–19. <https://doi.org/10.1080/17435390.2023.2180220>.
- Halappanavar, Sabina, Mallach, Gary, 2021. Adverse outcome pathways and in vitro toxicology strategies for microplastics hazard testing, 2021/12/01/ *Curr. Opin. Toxicol.* 28, 52–61. <https://doi.org/10.1016/j.cotox.2021.09.002>, 2021/12/01/. (<https://www.sciencedirect.com/science/article/pii/S2468202021000450>).
- Hale, Robert C., Meredith, E.Seeley, King, Ashley E., Yu, Lehuan H., 2022. Analytical Chemistry of Plastic Debris: Sampling, Methods, and Instrumentation. In *Microplastic in the Environment: Pattern and Process*. In: Michael, S. (Ed.), Bank, 17–67. Springer International Publishing, Cham.
- He, Defu, Zhang, Yalin, Gao, Wei, 2021. Micro(Nano)plastic contaminations from soils to plants: human food risks, 2021/10/01/ *Curr. Opin. Food Sci.* 41, 116–121. <https://doi.org/10.1016/j.cofs.2021.04.001>, 2021/10/01/. (<https://www.sciencedirect.com/science/article/pii/S2214799321000679>).
- Heddle, J.A., Cimino, M.C., Hayashi, M., Romagna, F., Shelby, M.D., Tucker, J.D., Vanparys, P., MacGregor, J.T., 1991. Micronuclei as an index of cytogenetic damage: past, present, and future. *Environ. Mol. Mutagen* 18 (4), 277–291. <https://doi.org/10.1002/em.2850180414>.
- Hernandez, Laura M., Yousefi, Nariman, Tufenkji, Nathalie, 2017. Are there nanoplastics in your personal care products? *Environ. Sci. Technol. Lett.* 4 (7), 280–285. <https://doi.org/10.1021/acs.estlett.7b00187>.
- Huang, J.N., Wen, B., Zhu, J.G., Zhang, Y.S., Gao, J.Z., Chen, Z.Z., 2020. Exposure to microplastics impairs digestive performance, stimulates immune response and induces microbiota dysbiosis in the gut of juvenile guppy (*Poecilia reticulata*) [In eng]. *Sep 1 Sci. Total Environ.* 733, 138929. <https://doi.org/10.1016/j.scitotenv.2020.138929>.
- Huang, S., Huang, X., Bi, R., Guo, Q., Yu, X., Zeng, Q., Huang, Z., et al., 2022. Detection and analysis of microplastics in human sputum. *Feb 15 Environ. Sci. Technol.* 56 (4), 2476–2486. <https://doi.org/10.1021/acs.est.1c03859>, Feb 15. (<https://www.ncbi.nlm.nih.gov/pubmed/35073488>).
- Jeon, M.S., Kim, J.W., Han, Y.B., Jeong, M.H., Kim, H.R., Sik Kim, H., Park, Y.J., Chung, K.H., 2023. Polystyrene microplastic particles induce autophagic cell death in Beas-2b human bronchial epithelial cells [In eng] (Feb). *Environ. Toxicol. no. 2*, 359–367. <https://doi.org/10.1002/tox.23705>.
- Karami, A., Golieskardi, A., Keong Choo, C., Larat, V., Galloway, T.S., Salamatinia, B., 2017. The presence of microplastics in commercial salts from different countries. *Apr 6 Sci. Rep.* 7, 46173. <https://doi.org/10.1038/srep46173>.
- Kolandhasamy, P., Su, L., Li, J., Qu, X., Jabeen, K., Shi, H., 2018. Adherence of microplastics to soft tissue of mussels: a novel way to uptake microplastics beyond ingestion [In eng], 610–611 *Sci. Total Environ.* 635–640. <https://doi.org/10.1016/j.scitotenv.2017.08.053>.
- Kosuth, M., Mason, S.A., Wattenberg, E.V., 2018. Anthropogenic contamination of tap water, beer, and sea salt. *PLoS One* 13 (4), e0194970. <https://doi.org/10.1371/journal.pone.0194970>.
- Kotha, R.R., Tareq, F.S., Yildiz, E., Luthria, D.L., 2022. Oxidative stress and antioxidants—a critical review on in vitro antioxidant assays. *Dec 1 Antioxidants* 11 (12). <https://doi.org/10.3390/antiox11122388>.
- Lackmann, C., Velki, M., Šimić, A., Müller, A., Braun, U., Ećimović, S., Hollert, H., 2022. Two types of microplastics (Polystyrene-Hbcd and Car Tire Abrasion) affect oxidative stress-related biomarkers in earthworm Eisenia Andrei in a time-dependent manner (May). *Environ. Int.* 163, 107190. <https://doi.org/10.1016/j.envint.2022.107190>.
- LaPlaca, S.B., Rice, C.D., van den Hurk, P., 2022. Chronic toxicity of tire crumb rubber particles to mummichog (*Fundulus heteroclitus*) in episodic exposures. *Sci. Total Environ.* 846 (Nov 10), 157447. <https://doi.org/10.1016/j.scitotenv.2022.157447>.
- Li, X., Zhang, T., Lv, W., Wang, H., Chen, H., Xu, Q., Cai, H., Dai, J., 2022. Intratracheal administration of polystyrene microplastics induces pulmonary fibrosis by activating oxidative stress and wnt/beta-catenin signaling pathway in mice. *Mar 1 Ecotoxicol. Environ. Saf.* 232, 113238. <https://doi.org/10.1016/j.ecoenv.2022.113238>, Mar 1. (<https://www.ncbi.nlm.nih.gov/pubmed/35121255>).
- Li, Z., Feng, C., Wu, Y., Guo, X., 2020. Impacts of nanoplastics on bivalve: fluorescence tracing of organ accumulation, oxidative stress and damage [In eng]. *Jun 15 J. Hazard Mater.* 392, 122418. <https://doi.org/10.1016/j.jhazmat.2020.122418>.
- Lind, M., Trindade, M.C., Yaszay, B., Goodman, S.B., Smith, R.L., 1998. Effects of particulate debris on macrophage-dependent fibroblast stimulation in coculture [In eng] (Sep). *J. Bone Jt. Surg. Br.* 80 (5), 924–930. <https://doi.org/10.1302/0301-620x.80b5.8710>.
- Littorin, M., Welinder, H., Skarping, G., Dalene, M., Skerfving, S., 2002. Exposure and nasal inflammation in workers heating polyurethane (Sep). *Int. Arch. Occup. Environ. Health* 75 (7), 468–474. <https://doi.org/10.1007/s00420-002-0337-1>.
- Liu, H., Tian, L., Wang, S., Wang, D., 2021. Size-dependent transgenerational toxicity induced by nanoplastics in nematode *Caenorhabditis elegans* [In eng]. *Oct 10 Sci. Total Environ.* 790, 148217. <https://doi.org/10.1016/j.scitotenv.2021.148217>.
- Liu, J., Xu, D., Chen, Y., Zhao, C., Liu, L., Gu, Y., Ren, Y., Xia, B., 2022a. Adverse effects of dietary virgin (Nano)microplastics on growth performance, immune response, and resistance to ammonia stress and pathogen challenge in Juvenile Sea Cucumber *Apostichopus japonicus* (Selenka) [In eng]. *Feb 5 J. Hazard Mater.* 423 (Pt A), 127038. <https://doi.org/10.1016/j.jhazmat.2021.127038>.
- Liu, Y., Jia, X., Zhu, H., Zhang, Q., He, Y., Shen, Y., Xu, X., Li, J., 2022b. The effects of exposure to microplastics on grass carp (*Ctenopharyngodon idella*) at the physiological, biochemical, and transcriptomic levels [In eng] (Jan). *Chemosphere* 286 (Pt 3), 131831. <https://doi.org/10.1016/j.chemosphere.2021.131831>.
- Lombardo, J., Solomando, A., Cohen-Sánchez, A., Pinya, S., Tejada, S., Ferriol, P., Mateu-Vicens, G., et al., 2022. Effects of human activity on markers of oxidative stress in the intestine of holothuria tubulosa, with special reference to the presence of microplastics. *Aug 12 Int. J. Mol. Sci.* 23 (16). <https://doi.org/10.3390/ijms23169018>.
- Lu, H., Yin, K., Su, H., Wang, D., Zhang, Y., Hou, L., Li, J.B., Wang, Y., Xing, M., 2023. Polystyrene microplastics induce autophagy and apoptosis in birds lungs via Pten/Pi3k/Akt/mTOR [In eng] (Jan). *Environ. Toxicol.* 38 (1), 78–89. <https://doi.org/10.1002/tox.23663>.
- Lu, Y., Zhang, Y., Deng, Y., Jiang, W., Zhao, Y., Geng, J., Ding, L., Ren, H., 2016. Uptake and accumulation of polystyrene microplastics in Zebrafish (*Danio rerio*) and toxic effects in liver. *Apr 5 Environ. Sci. Technol.* 50 (7), 4054–4060. <https://doi.org/10.1021/acs.est.6b00183>.
- Lubos, E., Loscalzo, J., Handy, D.E., 2011. Glutathione Peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. *Oct 1 Antioxid. Redox Signal* 15 (7), 1957–1997. <https://doi.org/10.1089/ars.2010.3586>.
- Mahadevan, Gomathi, Valiyaveetil, Suresh, 2021. Comparison of genotoxicity and cytotoxicity of polyvinyl chloride and poly(Methyl Methacrylate) nanoparticles on normal human lung cell lines, 2021/06/21 *Chem. Res. Toxicol.* 34 (6), 1468–1480. <https://doi.org/10.1021/acs.chemrestox.0c00391>. <https://doi.org/10.1021/acs.chemrestox.0c00391>.
- Maity, S., Chatterjee, A., Guchhait, R., De, S., Pramanick, K., 2020. Cytogenotoxic potential of a hazardous material, polystyrene microparticles on allium cepa L. *Mar 5 J. Hazard Mater.* 385, 121560. <https://doi.org/10.1016/j.jhazmat.2019.121560>.
- Maity, S., Guchhait, R., De, S., Pramanick, K., 2023. High doses of nano-polystyrene aggravate the oxidative stress, DNA damage, and the cell death in onions. *Jan 1 Environ. Pollut.* 316 (Pt 2), 120611. <https://doi.org/10.1016/j.envpol.2022.120611>.
- Major, J., Hudk, Aranka, Kiss, Gabriella, Jakab, M.G., Szaniszló, Judith, Nray, M., Nagy, I., Tompa, Anna, 1998. Follow-up biological and genotoxicological monitoring of acrylonitrile- and dimethylformamide-exposed viscose rayon plant workers. *Environ. Mol. Mutagen.* 31 (4), 301–310. [https://doi.org/10.1002/\(sici\)1098-2280\(1998\)31:4<301::Aid-em1>3.0.Co;2-l](https://doi.org/10.1002/(sici)1098-2280(1998)31:4<301::Aid-em1>3.0.Co;2-l).
- Malinowska, K., Bukowska, B., Piwoński, I., Foksiński, M., Kisielska, A., Zarakowska, E., Gackowski, D., Sicińska, P., 2022. Polystyrene Nanoparticles: the mechanism of their genotoxicity in human peripheral blood mononuclear cells (Aug-Oct). *Nanotoxicology* 16 (6–8), 791–811. <https://doi.org/10.1080/17435390.2022.2149360>.

- Mamun, A.A., Prasetya, T.A.E., Dewi, I.R., Ahmad, M., 2023. Microplastics in human food chains: food becoming a threat to health safety. *Feb 1 Sci. Total Environ.* 858 (Pt 1), 159834. <https://doi.org/10.1016/j.scitotenv.2022.159834>.
- Marrocco, I., Altieri, F., Peluso, I., 2017. Measurement and clinical significance of biomarkers of oxidative stress in humans. *Oxid. Med. Cell Longev.* 2017, 6501046. <https://doi.org/10.1155/2017/6501046>.
- Mason, S.A., Welch, V.G., Neratko, J., 2018. Synthetic polymer contamination in bottled water. *Front. Chem.* 6, 407. <https://doi.org/10.3389/fchem.2018.00407>.
- Mastrangelo, Giuseppe, Valentini, Federica, Agnesi, Roberto, Magarotto, G., Marchi, Teresio, Fedeli, Ugo, Marin, G., et al., 2004. Experimentation of a surveillance model for workers with previous exposure to vinyl chloride monomer and polymer, 01/01 G. *Ital. di Med. Del. Lav. Ed. Ergon.* 26, 293–294.
- Mateos-Cárdenas, Alicia, Scott, David T., Seitmaganbetova, Zulzara, van Pelt Frank, N.A. M., John, O.'Halloran, Jansen Marcel, A.K., 2019. Polyethylene Microplastics Adhere to Lemna minor (L.), yet have no effects on plant growth or feeding by *Gammarus duebeni* (Lillj.). 2019/11/01/ *Sci. Total Environ.* 689, 413–421. <https://doi.org/10.1016/j.scitotenv.2019.06.359>, 2019/11/01/. (<https://www.sciencedirect.com/science/article/pii/S0048969719329328>).
- Matthews, J.B., Green, T.R., Stone, M.H., Wroblewski, B.M., Fisher, J., Ingham, E., 2001. Comparison of the response of three human Monocytic cell lines to challenge with polyethylene particles of known size and dose [In eng] (*Mar*). *J. Mater. Sci. Mater. Med.* 12 (3), 249–258. <https://doi.org/10.1023/a:1008967200706>.
- Mills, N.L., Donaldson, K., Hadoke, P.W., Boon, N.A., MacNee, W., Cassee, F.R., Sandström, T., Blomberg, A., Newby, D.E., 2009. Adverse cardiovascular effects of air pollution [In eng] (*Jan*). *Nat. Clin. Pr. Cardiovasc Med.* 6 (1), 36–44. <https://doi.org/10.1038/npcardio1399>.
- Missawi, O., Bousserhine, N., Belbekhouche, S., Zitouni, N., Alphonse, V., Boughattas, I., Banni, M., 2020. Abundance and distribution of small microplastics ($\leq 3\ \mu\text{m}$) in sediments and seaworms from the southern mediterranean coasts and characterisation of their potential harmful effects (*Aug*). *Environ. Pollut.* 263 (Pt A), 114634. <https://doi.org/10.1016/j.envpol.2020.114634> (<https://www.ncbi.nlm.nih.gov/pubmed/33618468>).
- Nakai, M., Tsubokura, M., Suzuki, M., Fujishima, S., Watanabe, Y., Hasegawa, Y., Oyama, K., Ogura, S., 2014. Genotoxicity of styrene oligomers extracted from polystyrene intended for use in contact with food [In eng]. *Toxicol. Rep.* 1, 1175–1180. <https://doi.org/10.1016/j.toxrep.2014.11.007>.
- Ncube, Lindani K., Albert, U.Ude, Ogunmuyiwa, Enoch N., Zulkifli, Rozli, Beas, Isaac N., 2021a. An overview of plastic waste generation and management in food packaging industries. *Recycling* 6 (1). <https://doi.org/10.3390/recycling6010012>.
- Ncube, Lindani Koketso, Ude, Albert Uchenna, Ogunmuyiwa, Enoch Nifise, Zulkifli, Rozli, Beas, Isaac Nongwe, 2021b. An overview of plastic waste generation and management in food packaging industries. *Recycling* 6 (1). <https://doi.org/10.3390/recycling6010012>.
- Nelms, Sarah E., Galloway, Tamara S., Godley, Brendan J., Jarvis, Dan S., Lindeque, Penelope K., 2018. Investigating microplastic trophic transfer in marine top predators, 2018/07/01/ *Environ. Pollut.* 238, 999–1007. <https://doi.org/10.1016/j.envpol.2018.02.016>, 2018/07/01/. (<https://www.sciencedirect.com/science/article/pii/S0269749117343294>).
- Ni, Z., Tan, L., Wang, J., Chen, Y., Zhang, N., Meng, F., Wang, J., 2023. Toxic effects of pristine and aged polystyrene and their leachate on marine microalgae *Skeletonema costatum*. *Jan 20 Sci. Total Environ.* 857 (Pt 3), 159614. <https://doi.org/10.1016/j.scitotenv.2022.159614>.
- Nieuwenhuijsen, Mark, Paustenbach, Dennis, Duarte-Davidson, Raquel, 2006. New developments in exposure assessment: the impact on the practice of health risk assessment and epidemiological studies, 2006/12/01/ *Environ. Int.* 32 (8), 996–1009. <https://doi.org/10.1016/j.envint.2006.06.015>.
- Nnoruka, U.C., Okonkwo, C.J., Ilechukwu, I., Okonkwo, C.J., Belonwu, D.C., 2022. Impact of polystyrene microplastic exposure on lipid profile and oxidative stress status of male and female wistar rats (Sep). *Environ. Anal. Health Toxicol.* 37 (3). <https://doi.org/10.5620/eaht.20220224>.
- O'Brien, Stacey, Elvis, D.Okoffo, O'Brien, Jake W., Ribeiro, Francisca, Wang, Xianyu, Wright, Stephanie L., Samanipour, Saer, et al., 2020. Airborne emissions of microplastic fibres from domestic laundry dryers, 2020/12/10/ *Sci. Total Environ.* 747, 141175. <https://doi.org/10.1016/j.scitotenv.2020.141175>.
- Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., et al., 2021. The Prisma 2020 statement: an updated guideline for reporting systematic reviews. *Mar 29 Bmj* 372, n71. <https://doi.org/10.1136/bmj.n71>.
- Pahwa R., Goyal A., Jialal I. *Chronic Inflammation.* 2023 Aug 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. PMID: 29630225.
- Palaniappan, S., Sadacharan, C.M., Rostama, B., 2022. Polystyrene and polyethylene microplastics decrease cell viability and dysregulate inflammatory and oxidative stress markers of MdcK and L929 cells in vitro. *Expo. Health* 14 (1), 75–85. <https://doi.org/10.1007/s12403-021-00419-3>.
- Pan, Lingai, Yu, Dongke, Zhang, Yuan, Zhu, Changyu, Yin, Qinan, Hu, Yu, Zhang, Xiaoqin, Yue, Ruiming, Xiong, Xuan, 2021. Polystyrene microplastics-triggered mitophagy and oxidative burst via activation of perk pathway, 2021/08/10/ *Sci. Total Environ.* 781, 146753. <https://doi.org/10.1016/j.scitotenv.2021.146753>.
- Pandey, D., Banerjee, T., Badola, N., Chauhan, J.S., 2022. Evidences of microplastics in aerosols and street dust: a case study of Varanasi City, India (Nov). *Environ. Sci. Pollut. Res. Int.* 29 (54), 82006–82013. <https://doi.org/10.1007/s11356-022-21514-1>.
- Pedà, C., Romeo, T., Panti, C., Caliani, I., Casini, S., Marsili, L., Campani, T., et al., 2022. Integrated biomarker responses in European Seabass *Dicentrarchus labrax* (Linnaeus, 1758) chronically exposed to Pvc Microplastics. *Sep 15 J. Hazard Mater.* 438, 129488. <https://doi.org/10.1016/j.jhazmat.2022.129488>.
- Poma, A., Vecchiotti, G., Colafarina, S., Zarivi, O., Aloisi, M., Arrizza, L., Chichiriccò, G., Di Carlo, P., 2019. In vitro genotoxicity of polystyrene nanoparticles on the human fibroblast Hs27 cell line.. *Sep 11 Nanomaterials* 9 (9). <https://doi.org/10.3390/nano9091299>.
- Prata, J.C., 2018. Airborne microplastics: consequences to human health (*Mar*). *Environ. Pollut.* 234, 115–126. <https://doi.org/10.1016/j.envpol.2017.11.043>.
- Prata, J.C., da Costa, J.P., Lopes, I., Duarte, A.C., Rocha-Santos, T., 2020. Environmental exposure to microplastics: an overview on possible human health effects. *Feb 1 Sci. Total Environ.* 702, 134455. <https://doi.org/10.1016/j.scitotenv.2019.134455>.
- Rahman, A., Sarkar, A., Yadav, O.P., Achari, G., Slobodnik, J., 2021. Potential human health risks due to environmental exposure to nano- and microplastics and knowledge gaps: a scoping review. *Feb 25 Sci. Total Environ.* 757, 143872. <https://doi.org/10.1016/j.scitotenv.2020.143872>.
- Ramsperger, Anja F.R.M., Bergamaschi, Enrico, Panizzolo, Marco, Fenoglio, Ivana, Barbero, Francesco, Peters, Ruud, Undas, Anna, et al., 2023. Nano- and microplastics: a comprehensive review on their exposure routes, translocation, and fate in humans, 2023/01/01/ *Nanolimpact* 29, 100441. <https://doi.org/10.1016/j.impact.2022.100441>.
- Rodrigues, A.R., Mestre, N.C.C., Fonseca, T.G.D., Pedro, P.Z., Carteny, C.C., Cormier, B., Keiter, S., Bebianno, M.J., 2022. Influence of particle size on ecotoxicity of low-density polyethylene microplastics, with and without adsorbed Benzo-a-Pyrene, in *Clam Scrobicularia plana*. *Jan 5 Biomolecules* 12 (1). <https://doi.org/10.3390/biom12010078>.
- Roursgaard, M., Hezarah Rothmann, M., Schulte, J., Karadimou, I., Marinelli, E., Møller, P., 2022. Genotoxicity of particles from grinded plastic items in Caco-2 and Hepp2 Cells. *Front. Public Health* 10, 906430. <https://doi.org/10.3389/fpubh.2022.906430>.
- Rubio, L., Bargailla, I., Domenech, J., Marcos, R., Hernández, A., 2020. Biological effects, including oxidative stress and genotoxic damage, of polystyrene nanoparticles in different human hematopoietic cell lines. *Nov 5 J. Hazard Mater.* 398, 122900. <https://doi.org/10.1016/j.jhazmat.2020.122900>.
- Santillo, D., Miller, K., Johnston, P., 2017. Microplastics as contaminants in commercially important seafood species (*May*). *Integr. Environ. Assess. Manag* 13 (3), 516–521. <https://doi.org/10.1002/ieam.1909>.
- Schirizzi, G.F., Pérez-Pomeda, I., Sanchís, J., Rossini, C., Farré, M., Barceló, D., 2017. Cytotoxic effects of commonly used nanomaterials and microplastics on cerebral and Epithelial Human Cells (*Nov*). *Environ. Res* 159, 579–587. <https://doi.org/10.1016/j.envres.2017.08.043>.
- Schwabl, P., Köppel, S., Königshofer, P., Bucsics, T., Trauner, M., Reiberger, T., Liebmann, B., 2019. Detection of various microplastics in human stool: a prospective case series. *Oct 1 Ann. Intern. Med.* 171 (7), 453–457. <https://doi.org/10.7326/m19-0618>.
- Shi, X., Wang, X., Huang, R., Tang, C., Hu, C., Ning, P., Wang, F., 2022. Cytotoxicity and genotoxicity of polystyrene micro- and nanoplastics with different size and surface modification in A549 cells. *Int. J. Nanomed.* 17, 4509–4523. <https://doi.org/10.2147/ijn.S381776>.
- Sies, H., 2015. Oxidative stress: a concept in redox biology and medicine. *Redox Biol.* 4, 180–183. <https://doi.org/10.1016/j.redox.2015.01.002>.
- Sies, H., Jones, D.P., 2020. Reactive oxygen species (Ros) as pleiotropic physiological signalling agents (*Jul*). *Nat. Rev. Mol. Cell Biol.* 21 (7), 363–383. <https://doi.org/10.1038/s41580-020-0230-3>.
- Smith, R.A., Hallab, N.J., 2010. In vitro macrophage response to polyethylene and polycarbonate-urethane particles [In eng] (*Apr*). *J. Biomed. Mater. Res. A* 93 (1), 347–355. <https://doi.org/10.1002/jbm.a.32529>.
- Steer, M., Cole, M., Thompson, R.C., Lindeque, P.K., 2017. Microplastic ingestion in fish larvae in the Western English Channel (*Jul*). *Environ. Pollut.* 226, 250–259. <https://doi.org/10.1016/j.envpol.2017.03.062>.
- Suman, K.H., Haque, M.N., Uddin, M.J., Begum, M.S., Sikder, M.H., 2021. Toxicity and biomarkers of micro-plastic in aquatic environment: a review (*Feb*). *Biomarkers* 26 (1), 13–25. <https://doi.org/10.1080/1354750x.2020.1863470>.
- Sun, Ying, Wang, Shanyong, Li, Jun, Zhao, Dingtao, Fan, Jin, 2017. Understanding consumers' intention to use plastic bags: using an extended theory of planned behaviour model, 2017/12/01 *Nat. Hazards* 89 (3), 1327–1342. <https://doi.org/10.1007/s11069-017-3022-0>.
- Suresh, D.R., Annam, V., Pratibha, K., Prasad, B.V., 2009. Total antioxidant capacity-a novel early bio-chemical marker of oxidative stress in hiv infected individuals. *Jul 7 J. Biomed. Sci.* 16 (1), 61. <https://doi.org/10.1186/1423-0127-16-61>.
- Syversen, Tore, Lilleng, Grethe, Vollstad, J.ørgen, Hanssen, B.ård Johan, Sønvisen, Signe A., 2022. Oceanic plastic pollution caused by danish seine fishing in Norway, 2022/06/01/ *Mar. Pollut. Bull.* 179, 113711. <https://doi.org/10.1016/j.marpolbul.2022.113711>.
- Ter Halle, A., Jeanneau, L., Martignac, M., Jarde, E., Pedrono, B., Brach, L., Gigault, J., 2017. Nanoplastic in the North Atlantic Subtropical Gyre. *Dec 5 Environ. Sci. Technol.* 51 (23), 13689–13697. <https://doi.org/10.1021/acs.est.7b03667>. *Dec 5.* (<https://www.ncbi.nlm.nih.gov/pubmed/29161030>).
- Toto, A., Wild, P., Graille, M., Turcu, V., Crézé, C., Hemmendinger, M., Sauvain, J.J., et al., 2022. Urinary Malondialdehyde (Mda) concentrations in the general population-a systematic literature review and meta-analysis. *Mar 29 Toxics* 10 (4). <https://doi.org/10.3390/toxics10040160>.
- Toussaint, B., Raffael, B., Angers-Loustau, A., Gilliland, D., Kestens, V., Petrillo, M., Rio-Echevarria, I.M., Van den Eede, G., 2019. Review of micro- and nanoplastic contamination in the food chain (*May*). *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* 36 (5), 639–673. <https://doi.org/10.1080/19440049.2019.1583381>.

- Vecchiotti, G., Colafarina, S., Aloisi, M., Zarivi, O., Di Carlo, P., Poma, A., 2021. Genotoxicity and oxidative stress induction by polystyrene nanoparticles in the colorectal cancer cell line Hct116. *PLoS One* 16 (7), e0255120. <https://doi.org/10.1371/journal.pone.0255120>.
- Wagner, S., Reemtsma, T., 2019. Things we know and don't know about nanoplastic in the environment [In eng]. *Nat. Nanotechnol.* 14 (4), 300–301. <https://doi.org/10.1038/s41565-019-0424-z>.
- Walker, Tony R., Fequet, Lexi, 2023. Current trends of unsustainable plastic production and micro(nano)plastic pollution, 2023/03/01/ TrAC Trends Anal. Chem. 160, 116984. <https://doi.org/10.1016/j.trac.2023.116984>.
- Wang, J., Zheng, L., Li, J., 2018a. A critical review on the sources and instruments of marine microplastics and prospects on the relevant management in China (Oct). *Waste Manag. Res.* 36 (10), 898–911. <https://doi.org/10.1177/0734242x18793504>.
- Wang, Y., Branicky, R., Noë, A., Hekimi, S., 2018b. Superoxide dismutases: dual roles in controlling ros damage and regulating ros signaling. *Jun 4 J. Cell Biol.* 217 (6), 1915–1928. <https://doi.org/10.1083/jcb.201708007>.
- Wang, Y.L., Lee, Y.H., Chiu, I.J., Lin, Y.F., Chiu, H.W., 2020. Potent impact of plastic nanomaterials and micromaterials on the food chain and human health. *Mar 3 Int J. Mol. Sci.* 21 (5). <https://doi.org/10.3390/ijms21051727>.
- Wang, Y.L., Lee, Y.H., Hsu, Y.H., Chiu, I.J., Huang, C.C., Huang, C.C., Chia, Z.C., et al., 2021. The kidney-related effects of polystyrene microplastics on human kidney proximal tubular epithelial cells Hk-2 and male C57bl/6 mice (May). *Environ. Health Perspect.* 129 (5), 57003. <https://doi.org/10.1289/ehp7612>.
- Weber, A., Schwiebs, A., Solhaug, H., Stenvik, J., Nilsen, A.M., Wagner, M., Relja, B., Radeke, H.H., 2022. Nanoplastics affect the inflammatory cytokine release by primary human monocytes and dendritic cells (May). *Environ. Int.* 163, 107173. <https://doi.org/10.1016/j.envint.2022.107173>.
- Welden, N.A., Abylkhani, B., Howarth, L.M., 2018. The effects of trophic transfer and environmental factors on microplastic uptake by plaice, pleuronectes plastessa, and spider crab, maja squinado (Aug). *Environ. Pollut.* 239, 351–358. <https://doi.org/10.1016/j.envpol.2018.03.110>.
- (WHO) World Health Organization, 2006. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals, 2006. In: Environmental health criteria, 237. World Health Organization., Geneva, 2006. (<https://apps.who.int/iris/handle/10665/43604>).
- Xiao, B., Li, D., Liao, B., Zheng, H., Yang, X., Xie, Y., Xie, Z., Li, C., 2021. Effects of Microplastics Exposure on the Acropora Sp. antioxidant, immunization and energy metabolism enzyme activities [In eng]. *Front. Microbiol.* 12, 666100 <https://doi.org/10.3389/fmicb.2021.666100>.
- Xu, H., Dinsdale, D., Nemery, B., Hoet, P.H., 2003. Role of residual additives in the cytotoxicity and cytokine release caused by polyvinyl chloride particles in pulmonary cell cultures (Mar). *Toxicol. Sci.* 72 (1), 92–102. <https://doi.org/10.1093/toxsci/kfg003>.
- Zare Jeddi, M., Hopf, N.B., Viegas, S., Price, A.B., Paini, A., van Thriel, C., Benfenati, E., et al., 2021. Towards a systematic use of effect biomarkers in population and occupational biomonitoring (Jan). *Environ. Int.* 146, 106257. <https://doi.org/10.1016/j.envint.2020.106257>.
- Zhang, J.M., An, J., 2007. Cytokines inflammation and pain (Spring). *Int. Anesth. Clin.* 45 (2), 27–37. <https://doi.org/10.1097/AIA.0b013e318034194e>.
- Zhang, W., Sik Ok, Y., Bank, M.S., Sonne, C., 2023. Macro- and microplastics as complex threats to coral reef ecosystems (Apr). *Environ. Int.* 174, 107914. <https://doi.org/10.1016/j.envint.2023.107914>.
- Zhang, Yulan, Shichang Kang, Steve Allen, Deonie Allen, Tanguang Gao, Sillanpää, Mika, 2020. Atmospheric microplastics: a review on current status and perspectives, 2020/04/01/ *Earth-Sci. Rev.* 203, 103118. <https://doi.org/10.1016/j.earscirev.2020.103118>.