Tracing the malignant trajectory of microplastics and nanoplastics: Biological pathways potentially implicated in carcinogenesis (Review)

MARY A. VASILOPOULOU[1], MARIA ADAMAKI[1,2], PANAGIOTIS ZOUMPOURLIS[1], DEMETRIOS A. SPANDIDOS[3], DIMOSTHENIS SARIGIANNIS[4-8] and VASSILIS ZOUMPOURLIS[1,4]

[1]Institute of Chemical Biology, National Hellenic Research Foundation, 11635 Athens, Greece; [2]Department of Biomedical Sciences, New York College, 10558 Athens, Greece; [3]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion, Greece; [4]Center of Excellence for Cancer Theranostics, National Hellenic Research Foundation, 11635 Athens, Greece; [5]HERACLES Research Center on Health and The Exposome, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, 57001 Thessaloniki, Greece; [6]Department of Urology, School of Medicine, Johns Hopkins University, Baltimore, MD 21287, USA; [7]School of Public Health, Yale University, New Haven, CT 06510, USA; [8]University School for Advanced Studies IUSS, I-27100 Pavia, Italy

Received June 9, 2026; Accepted November 3, 2026

DOI: 10.3892/ijmm.2026.6047

Abstract. Microplastics and nanoplastics have emerged as significant environmental challenges, exerting a considerable impact on ecosystems. Simultaneously, a growing body of evidence indicates their accumulation within human tissues and organs, including tumor samples from patients with cancer, thereby raising concerns about their potential implications for human health. In recent years, extensive research has demonstrated that exposure to plastic particles induces toxicity, with the overproduction of reactive oxygen species (ROS) being one of the most prominent effects. ROS subsequently trigger oxidative stress, DNA damage, genotoxicity and chronic inflammation, while dysbiosis and endocrine disruption have also been associated with plastic exposure, among other effects. Apart from observations from *in vitro* and *in vivo* experiments suggesting that exposure to plastics can modulate critical signaling pathways, a number of which are linked to carcinogenesis, a critical question arises regarding the potential role of exposure to plastics in the development of cancer. To address this issue, the present review aimed to integrate mechanistic evidence concerning the potential implications of plastics in carcinogenesis. Particular attention was paid to biological pathways that may contribute to tumor initiation and progression, rather than seeking to establish a definitive causal association.

Correspondence to: Dr Vassilis Zoumpourlis, Institute of Chemical Biology, National Hellenic Research Foundation, 48 Vassileos Constantinou Ave., 11635 Athens, Greece
E-mail: vzub@eie.gr

Abbreviations: MPLs, microplastics; NPLs, nanoplastics; MNPLs, microplastics and nanoplastics; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; CAT, catalase; GSH, L-γ-glutamyl-L-cysteinyl glycine; GST, glutathione S-transferase; MDA, malondialdehyde; ERKs, extracellular regulated kinases; JNKs, c-Jun N-terminal kinases; γ-H2AX, phosphorylated histone H2AX; 8-oxodG, 8-hydroxy-2'-deoxyguanosine; IL, interleukin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B-cells; NLRP3, NOD-like receptor protein 3

Key words: microplastics, nanoplastics, carcinogenesis, oxidative stress, genotoxicity, inflammation, dysbiosis

Contents

1. Introduction
2. Classification of plastics
3. Routes of entry of MNPLs into the human body
4. Potential mechanisms linking MNPL exposure to carcinogenesis
5. Conclusions and future perspectives

1. Introduction

Plastics are versatile materials used worldwide in packaging, healthcare, automotive and construction (1,2). The earliest evidence of plastics originates from the Mesoamericans, who used latex from *Castilla elastica* and processed it into rubber items, such as balls and figurines (3). Later, numerous scientists and researchers achieved significant breakthroughs until 1907, when the chemist, Leo Baekeland, invented Bakelite, the first true synthetic plastic, marking the start of the thriving plastic industry (1). Despite significant progress and the benefits

plastics provide in daily life, no one has foreseen the adverse effects of this discovery. Recent data indicate that global plastic production reached ~430 million tons in 2024 (4). By 2060, global plastic consumption is expected to reach 1,231 million tons, while improper management leads to plastic pollution in the air, water and soil (5-8).

Plastic-based products are almost non-biodegradable in nature; however, they break down into smaller particles known as microplastics (MPLs) and nanoplastics (NPLs) through biological, physical and chemical processes (9). Due to their inability to degrade and their small size, MPLs and NPLs are found even in the most unusual places. For instance, MPLs have been identified in Arctic sea ice (10), in deep-sea sediments and surface water in Antarctica (11), and even in snow and stream water at Mt. Everest (12). Jamieson *et al* (13) also detected MPLs within the digestive systems of marine amphipods in six Pacific Ocean trenches, thereby confirming that plastic pollution impacts the marine ecosystem and that marine organisms can readily absorb these particles, leading to bioaccumulation and biomagnification that concentrate them higher up the food chain (9). Moreover, NPLs can penetrate biological barriers and gain entry into the bloodstream, rendering them particularly hazardous (9,14). As humans occupy the apex of the trophic hierarchy, they are the final recipients of these pollutants within the chain. It is estimated that humans ingest an amount of MPLs equivalent to a credit card each week (15). MPLs have been detected in various biological fluids and human tissues, including amniotic fluid, placenta, breast milk, liver, lungs, colon, feces and the brain, among others (4,15-20).

2. Classification of plastics

The classification of plastic debris remains challenging, as current size-based definitions are primarily practical rather than scientifically rigorous, potentially neglecting significant properties and influencing research priorities and risk assessments (6). Therefore, Hartmann *et al* (6) proposed a definition and classification system based on the following criteria: Chemical composition, solid state, solubility, size, shape and structure, color and origin. For the purposes of the present review, the focus is limited to size, origin and chemical composition.

According to Hartmann *et al* (6), plastic materials are classified into four main groups based on their size: Macroplastics (plastic pieces or objects >1 cm in size), mesoplastics (particles measuring between 1 and 10 mm), MPLs (particles ranging from 1 to 1,000 μm) and NPLs (particles <1,000 nm in size) (6). Nevertheless, the research articles cited in the present review do not include the term 'mesoplastics', nor was it mentioned elsewhere in the present review.

Macroplastics represent the predominant proportion of plastics in the environment and serve as the primary source of MPLs and NPLs (hereafter referred to as MNPLs), which are insoluble in water (9). These materials disintegrate into smaller particles over time. MNPLs come in various shapes (fragments, spheres, fibers, spheroids, granules, pellets, foam and beads) and originate either from their initial form (primary microplastics) or from the degradation of larger plastic debris (secondary microplastics) (4,7,14). Primary MNPLs, produced in specific sizes, are used in products, such as cosmetics, detergents, industrial items and medical applications (7,9,21). Conversely, secondary MNPLs result from the physical, chemical and biological breakdown of larger plastics caused by use or environmental factors, such as ultraviolet radiation, mechanical stress, pH, or salinity changes (7,9,21).

The most frequently detected plastics in the environment are polyethylene, polypropylene, polystyrene, polyethylene terephthalate (PET), polyvinyl chloride (PVC), polyurethane and various polyamides, such as nylon. All these types of plastics are under the umbrella of two main categories: Thermoplastics and thermosets (1,6,9,22). Thermoplastics are very stable at high temperatures and soften upon heating, facilitating their processing, reprocessing, or recycling. Upon cooling, they harden and retain their shape (1,22,23). The majority of global plastic production comprises thermoplastics, including polyethylene, polypropylene, PVC, polystyrene and PET. Polyethylene, a thermoplastic polymer derived from ethylene monomers, is widely used in packaging due to its stability and flexibility, as seen in the manufacture of plastic bags, bottles and films. Its advantageous properties and cost-effective production render it the most produced plastic polymer worldwide, followed by polypropylene and PVC (9,22,23). Polypropylene is produced through the polymerization of propylene and is used in automotive parts, luggage, syringes, appliances, toys, carpets and rugs, among other applications (9,22). PVC results from the polymerization of vinyl chloride and is favored for its transparency, flame resistance and electrical properties. However, its high chlorine content complicates processing and increases susceptibility to degradation, requiring the use of stabilizers to ensure proper performance. PVC is mainly used in construction, packaging, credit cards and other applications (22,24). Another example is polystyrene, produced via the addition polymerization of styrene. Its ease of processing, rigidity, clarity and affordability render it suitable for a wide range of applications, including toys, food packaging, consumer electronics, such as audio and video devices, and medical items such as labware and tissue culture flasks (9,22). PET is manufactured through the condensation polymerization of terephthalic acid (or dimethyl terephthalate) with ethylene glycol and is commonly used in beverage bottles, textile fibers and packaging films (22,23). Conversely, thermosets are incapable of being melted or reshaped due to their inability to withstand high temperatures (1,6,9,22). Polyurethane, composed of polyols and isocyanates, serves as an example of this category and is used in products such as skateboards and shoe soles (22).

In industrial applications, plastics are rarely used as pure polymers, but rather as complex formulations that incorporate a variety of additives designed to enhance processing, functionality and long-term stability. Common additives include plasticizers (to improve flexibility and durability), stabilizers (to prevent thermal or chemical degradation), antioxidants (to delay oxidative degradation), acid scavengers, flame retardants, pigments, lubricants and antistatic agents (6,25). However, the breakdown of plastics releases these additives into the environment, where some are persistent, bioaccumulative, and ultimately, harmful to humans and other organisms (25). Studies have shown that a myriad

Table I. Comparison of major plastic polymers according to their monomers, common applications, physicochemical characteristics, and environmental persistence and toxicity-related properties.

Plastic type	Monomer	Examples of common applications and sources	Key physicochemical characteristics	Environmental persistence and potential toxicity-related characteristics	(Refs.)
Polyethylene	Ethylene	Packaging films, plastic bags, bottles, etc.	Low density; hydrophobic; insoluble; high molecular weight; absence of functional groups	High resistance to degradation; accumulation in shallow waters; reported phytotoxic effects	(9,22,23)
Polypropylene	Propylene	Automotive parts, luggage, syringes, toys, carpets, rugs, etc.	Low density; hydrophobic; absence of functional groups	Slow degradation; high environmental persistence	(9,22)
Polyvinyl chloride (PVC)	Vinyl chloride	Construction materials, clothing, packaging, credit cards, etc.	High density; hydrophobic; insoluble; high molecular weight; rich in additives (e.g., phthalate)	Resistance to degradation; accumulation in sediments; degradation may release chlorinated compounds and plasticizers	(22,24)
Polystyrene	Styrene	Food packaging, toys, electronics, medical and laboratory materials (labware, tissue culture flasks), etc.	Hydrophobic; high molecular weight; absence of functional groups	High resistance to degradation; toxicity may be influenced by residual monomers and additives	(9,22)
Polyethylene terephthalate (PET)	Terephthalic acid (or dimethyl terephthalate) + ethylene glycol	Beverage bottles, food packaging films, textile fibers, etc.	Hydrophobic; relatively rigid polymer chain; high melting point	High resistance to degradation; potential migration of antimony compounds and leaching of additives	(22,23)

of chemicals associated with plastics are hazardous or even carcinogenic to living organisms in marine and terrestrial ecosystems, as well as to human health, including phthalates (26), di-(2-ethylhexyl) phthalate (DEHP) (27), bisphenol A (BPA) (28) and brominated flame retardants (BFRs) (9,25). The physical and chemical properties of various types of plastics discussed later in the present review, along with examples of sources and key factors that may affect their toxicity in both the environment and living organisms, are summarized in Table I. These hazardous additive profiles precisely align with the objectives of the safe and sustainable by design (SSbD) framework by the European Union, which aims to address chemical hazards during the early stages of material design and development, rather than relying primarily on downstream risk management. The SSbD framework promotes material design that incorporates hazard and sustainability considerations from the outset (29). Experience with BPA has demonstrated that structural analog substitution, such as bisphenol S and bisphenol F, can replicate or even exacerbate the original hazard profile (30,31). Consequently, a hazard-led substitution strategy, integrated with mechanistic data from new approach methodologies (NAMs), is essential to prevent regrettable substitutions within the plastics value chain (29,30,32).

3. Routes of entry of MNPLs into the human body

Understanding human exposure to MNPLs is vital for evaluating their possible health effects. Considering all the factors mentioned above, a key question arises regarding the mechanisms through which MNPLs penetrate the human body. Current evidence delineates three main routes of exposure: Ingestion, inhalation and dermal absorption, as summarized in Fig. 1.

Oral intake. The primary route of human exposure to MNPLs occurs through the gastrointestinal system, via the ingestion of contaminated food and beverages. Upon consumption, MNPLs can penetrate the intestinal epithelium and enter the circulatory system, allowing them to distribute to various tissues and organs (4,33-35). These MNPLs have been identified in a plethora of everyday consumables, including beer, honey, sugar, salt, seafood, rice, fruits and vegetables, beverages, as well as both tap and bottled water (4,21,33).

Seafood has been recognized as a main source of human exposure to MNPL particles (20,33,36). Therefore, in countries where seafood consumption is high due to dietary customs and cultural practices, such as China and Japan, exposure to MPLs tends to be greater (37). It is noteworthy that limited

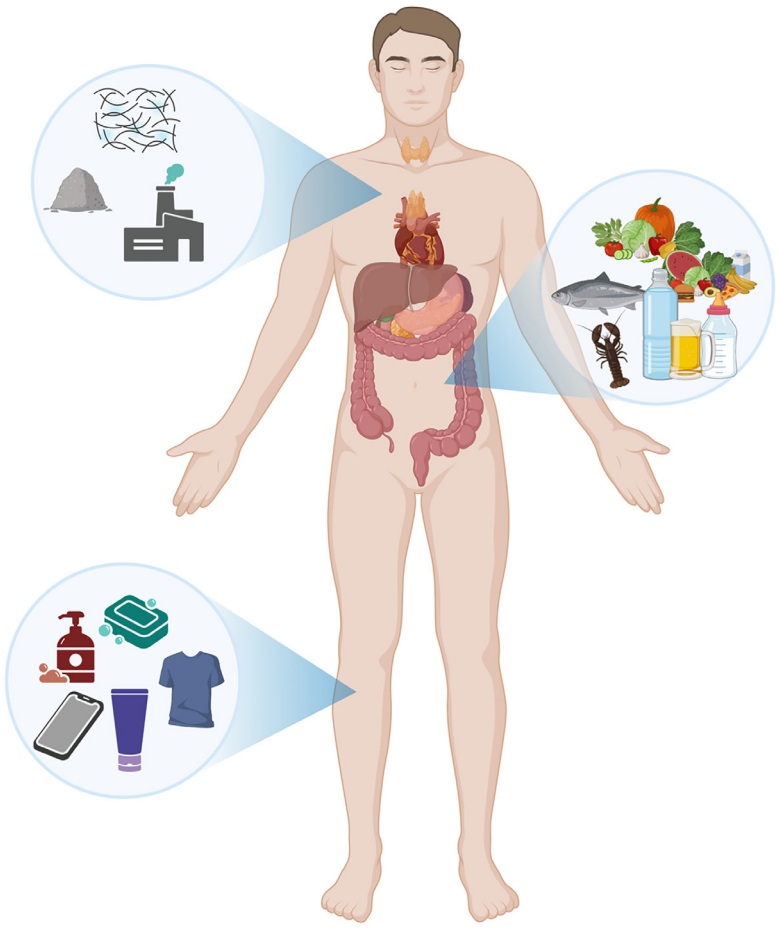


Figure 1. Routes of entry of MNPLs into the human body. MNPLs enter the human organism through inhalation (including fabrics, fibers, dust, industrial emissions, and manufacturing processes), ingestion (via food, water, and beverages), and dermal contact (such as clothing, cosmetics, soap, phone cases, and toothpaste). Among these pathways, ingestion is regarded as the most common route of exposure. MNPLs, microplastics and nanoplastics. The figure was created using BioRender (https://BioRender.com/s7w3ql4).

information exists regarding the ingestion of MNPLs through alternative protein sources (e.g., poultry or beef), which may alter the understanding of overall human exposure (37). Of particular concern is the detection of MPLs in various fruits and vegetables (7,33,36,38), with apples identified as among the most heavily contaminated (7,38).

The consumption of bottled water markedly elevates exposure to MPLs, with individuals who exclusively consume bottled water ingesting up to 90,000 particles annually, compared to ~4,000 particles for those who consume tap water (37). Furthermore, research conducted by two separate groups revealed MPL leakage from silicone-rubber infant teats caused by elevated temperatures during sterilization (39,40), leading to ~660,000 MPL particles entering the body of an infant within 1 year of regular bottle feeding (16). Moreover, food packaging represents another source of human exposure to MPLs, as plastics are extensively used, and their degradation can lead to food contamination (16,36,41). For instance, steeping a plastic teabag at 95˚C releases ~11.6 billion MPLs and 3.1 billion NPLs into a single cup (42).

Human stool studies have consistently demonstrated the presence of MNPLs, providing direct evidence of their ingestion and subsequent gastrointestinal excretion (4,9,35,43). Significant discrepancies in documented concentrations arise from variations in analytical techniques used (4). Notably, polypropylene is frequently identified as the predominant polymer (44-46), while higher PET concentrations have been observed in infants compared to adults (47). Additionally, MPLs have been detected in human urine samples (43), indicating another pathway of excretion.

Inhalation. Numerous studies have indicated that inhalation constitutes an additional route through which humans are exposed to MNPLs. Major sources include synthetic fabrics, tire wear, household dust and industrial emissions (16,18,33,36,41). The study conducted by Geng *et al* (48) revealed that among 30 individuals from Shanghai, China, the majority of MPLs inhaled indoors (mainly small fragments and fibers) were retained within the lungs and airways, with only a minor proportion being exhaled (48). Moreover, Vianello *et al* (49) demonstrated that an average male would inhale up to 272 MPLs daily during light physical activity. A study involving surgical patients revealed that 87% of lung tissue samples contained plastic or cellulose fibers, demonstrating that these microfibers are capable of penetrating lung tissue (50). When considering both ingestion and inhalation pathways, overall human exposure is significantly increased (37). Notably, workers in plastic manufacturing, recycling facilities, or MPL-related environments are at a higher risk of experiencing respiratory irritation (7).

Dermal absorption. While the primary routes of human exposure to MPLs are ingestion and inhalation, dermal absorption also constitutes a significant pathway (16,21,34). MPLs are present in various products, including cosmetics and personalized items. Although a number of countries have recently banned the use of microbeads in the aforementioned products (51,52), these small, sphere-shaped plastics are still found in scrubs, facial cleansers, shampoos, and toothpastes (36,41). Studies have demonstrated that MPLs can cross the skin barrier, primarily penetrating via hair follicles and glands (21,34,36). Another noteworthy example of skin contact with plastics was demonstrated in the study by Li *et al* (53). They demonstrated that 3 months of using plastic mobile phone cases resulted in the release of MPLs, with a large amount of MPLs detected on both the phone case and the user's palms (53). Furthermore, textiles are another route of human exposure to MPLs. Fabrics composed of fibers such as polyester, nylon, and acrylic release MPLs during wear and laundering, which can directly contact the skin and become airborne, thereby increasing exposure risks (36). Additionally, workers in the plastic and textile sectors may experience higher exposure levels through contact with materials and dust (34,36).

Although dermal contact with MNPLs may occur through cosmetics, personal care products, textiles and other plastic-containing materials, current evidence indicates that the contribution of this route to overall human exposure is relatively limited. Specifically, experimental studies have demonstrated that the penetration of plastic particles through intact skin is minimal, with the majority of particles remaining confined to the outer layers of the stratum corneum; deeper penetration appears to depend on factors, such as particle size and skin integrity. Nevertheless, data regarding the dermal absorption of MNPLs in human skin remains scarce and warrants further investigation (4).

Characterizing external exposure through these three routes is essential, yet insufficient for a comprehensive risk assessment. Translating ingested, inhaled, or dermally absorbed particle burdens into doses for target tissues requires physiologically based kinetic/pharmacokinetic modeling adapted to particulates, combined with the quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) of mechanistic endpoints. Such biokinetic-mechanistic coupling provides the quantitative link between the exposome and the key events discussed below. Moreover, this approach is increasingly feasible for MNPLs as parameters concerning size, shape and surface charge-resolved uptake become available (54). Framing MNPLs as a discrete class of environmental contaminants, however, underestimates their biological complexity. Within the life-course exposome paradigm, MNPLs should be regarded as multicomponent stressors that jointly deliver the polymer matrix, residual monomers, processing additives and a sorbed mixture of co-contaminants acquired during environmental aging. Their inclusion in human biomonitoring and mixtures-risk infrastructures, most notably the human biomonitoring for Europe (HBM4EU) and its successor, the European partnership for the assessment of risks from chemicals (PARC), represents not merely an analytical expansion, but also a conceptual reframing: MNPLs function concurrently as carriers, sources, and exposure matrices (55-57).

4. Potential mechanisms linking MNPL exposure to carcinogenesis

Cellular uptake constitutes a crucial step bridging external exposure and the intracellular effects of MNPLs (4). Upon entry into the human body through ingestion, inhalation, or dermal absorption, MNPLs interact with cells through mechanisms that depend primarily on particle size and cell type (58-60). Specifically, *in vitro* and *in vivo* studies have demonstrated that larger MPLs (>0.5 μm) are predominantly internalized by gastrointestinal (35,58) and immune cells (60), such as macrophages, neutrophils and dendritic cells, mainly via phagocytosis. Conversely, smaller particles (<0.5 μm) are internalized through endocytosis, including clathrin-mediated and caveolin-mediated endocytosis, and micropinocytosis. It is noteworthy that very small NPLs (<50 nm) have the ability to penetrate cellular membranes via passive diffusion, facilitated by hydrophobic interactions and van der Waals forces (21,60,61).

Once internalized, MNPLs are primarily sequestered in lysosomes, where they tend to accumulate. In the acidic environment of the lysosome, MNPLs can remain intact, exhibiting no evidence of degradation. Moreover, their removal via exocytosis appears to be limited (21,35,60,61). Significantly, during mitosis, internalized MNPLs can be transferred to daughter cells, thereby ensuring their persistent intracellular presence (62). This long-term retention is regarded as a crucial factor underlying their biological effects, as it facilitates sustained disruption of cellular homeostasis. Accumulating evidence suggests that MNPLs may interfere with various cellular processes, including the induction of oxidative stress (63), DNA damage, genotoxic effects (64), inflammatory responses (65), dysbiosis (65) and the disruption of essential cellular signaling pathways (66); these are all related to carcinogenesis. Indeed, MNPLs appear to influence cellular viability through multiple mechanisms rather via a single pathway (8,36).

In recent years, extensive research has sought to elucidate the potential association between MNPL exposure and cancer development. Although direct causal evidence in humans remains limited, both experimental and observational studies have provided evidence supporting their involvement in oncogenic processes (17). For instance, Zhao *et al* (66) reported the presence of MPLs in tumor tissues obtained from 61 patients with cancer. These MPLs were detected in lung (with the highest detection rate), cervical, gastric, colorectal and pancreatic tumors, whereas no MPLs were detected in esophageal cancer samples. Among the polymers identified, polystyrene, polyethylene and PVC were the most common across various tumor types. Specifically, these three polymers were detected in lung cancer tissues, with polystyrene being predominant; in pancreatic cancers, polystyrene and PVC were most prevalent; in colorectal cancers, polystyrene was the primary polymer; in gastric tumors, PVC was mainly observed; and in cervical cancer, limited quantities of polystyrene or polyethylene were identified (66). More recently, Alaraby *et al* (20) reported that polyethylene and polypropylene were the most frequently reported polymers identified in human cancer tissues across the studies included in this review, followed by PVC, polyamide and polystyrene. Additional studies further

support the presence of elevated MNPL levels in human tumor tissues, including colorectal (67,68), gastric (69), prostate (70), breast (71) and cervical cancers (72), when compared with adjacent normal tissues. In certain cases, the MNPL burden has been associated with tumor progression and metastasis; however, it remains unclear whether these particles actively contribute to carcinogenesis or merely accumulate within malignant tissues (73).

Recent reviews have underscored the growing concern regarding the potential involvement of MNPLs in various types of cancer, including ovarian, gastric, hematological, neurological, colorectal, pulmonary, hepatic, breast and cervical cancers, while emphasizing the necessity for further mechanistic and human studies to elucidate their role in cancer development (17,20,74,75). Notably, Bailey and Hofseth (76) highlighted that the increase in plastic production and environmental exposure to MNPLs over recent decades has coincided with an increase in the incidence of early-onset cancers. This observation has led to the hypothesis that chronic MNPL exposure beginning at early life stages and subsequent bioaccumulation may promote oncogenesis in individuals <50 years of age (76). Although current evidence remains insufficient to establish a definitive causal association, it underscores the importance of elucidating the molecular and cellular mechanisms through which MNPLs may contribute to carcinogenesis (75,76).

While numerous reviews have examined the toxicological and potential carcinogenic effects of MNPLs, a comprehensive understanding of the molecular and cellular mechanisms that may underlie their involvement in cancer-related processes has yet to emerge. The present review adopted a strictly mechanism-oriented perspective, focusing on studies that elucidated the molecular and cellular events through which MNPL exposure may contribute to carcinogenesis, rather than solely reporting phenotypic or toxicological observations. Accordingly, the available evidence was organized around the principal biological processes involved in cancer development, including oxidative stress, DNA damage and genotoxicity, inflammation, dysbiosis, endocrine disruption, as well as the 'Trojan horse' effect, which may further modulate carcinogenic risk through the transport of sorbed chemical and biological contaminants. Notably, these mechanisms are not regarded as isolated phenomena, but as interconnected biological events that may collectively contribute to tumor initiation and progression. By integrating mechanistic evidence from cellular, animal, and human studies into a cohesive carcinogenesis-focused framework, the present review aimed to provide a comprehensive overview of the pathways through which MNPLs may influence cancer-associated processes. Furthermore, emerging concepts, such as adverse outcome pathways (AOPs), NAMs and exposome-based approaches are briefly discussed as promising tools for translating mechanistic evidence into future cancer risk assessments.

The mechanisms outlined below may be regarded as parallel branches of a single adverse outcome network (AON) that converges on cancer. The cellular internalization and lysosomal persistence of MNPLs constitute the molecular initiating event. Downstream key events (KEs) include the overproduction of reactive oxygen species (ROS) and the depletion of antioxidants, oxidative and clastogenic DNA damage, persistent pro-inflammatory responses and inflammasome activation, microbiome dysbiosis accompanied by altered immune and metabolic outputs, and perturbations of endocrine receptors (discussed in the sections below); these are all further amplified or temporally displaced by the 'Trojan horse' transport of sorbed carcinogens and metals (discussed below). These KEs map onto established cancer hallmarks, namely genome instability, tumor-promoting inflammation, and deregulated proliferative signaling (77). Their quantitative parameterization within a quantitative AOP would convert the current descriptive evidence base into a risk-assessable framework (77-79).

Oxidative stress. Among the proposed mechanisms, oxidative stress has emerged as one of the most extensively studied and consistently reported effects of MNPL exposure. While low levels of ROS are vital for normal cellular function, elevated ROS levels are detrimental, leading to DNA and RNA damage, lipid peroxidation and protein oxidation. The disruption of the balance between oxidant production and the antioxidant defense system within cells leads to oxidative stress (80), a condition widely recognized as a critical molecular mechanism in carcinogenesis (81). Specifically, oxidative stress can induce mutations in essential genes, compromise genome integrity, and modulate signaling pathways crucial for cell survival, proliferation and apoptosis, such as the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), and Kelch-like ECH-associated protein 1 (Keap-1)/nuclear factor erythroid 2-related factor 2 (Nrf2) pathways (81).

Oxidative stress is recognized as a pivotal mechanism underlying the toxicity of MNPLs (63), and its magnitude appears to depend on particle size, concentration and duration of exposure (63,82-84). Notably, smaller plastic particles tend to induce greater oxidative modifications in cells, likely due to enhanced cellular uptake. Additionally, ROS generation generally escalates with increased concentrations and prolonged exposure periods. These effects have been evidenced in various *in vitro* models, including HCT-116 colorectal cancer cells (85), the HepG2 hepatocellular carcinoma cells (86), CT26-WT colon carcinoma cells (87) and A549 lung adenocarcinoma cells (88), among others (89).

MNPLs can affect and neutralize both enzymatic and non-enzymatic cellular antioxidants. Enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidases (GPxs), as well as non-enzymatic antioxidants, such as L-γ-glutamyl-L-cysteinyl glycine [glutathione (GSH)], are frequently disrupted following exposure to MNPLs. For example, in *Carassius auratus*, exposure to 50-500 μm polystyrene MPLs was shown to result in a concentration-dependent decrease in the activities of CAT, glutathione S-transferase (GST), and SOD enzymes (90), indicating that the antioxidant defense system was unable to counteract excessive ROS production. By contrast, shorter exposures in zebrafish (*Danio rerio*) have been shown to be associated with increased SOD and CAT activities (82,91), likely reflecting an early compensatory response to oxidative stress. Similarly, a 14-day exposure to 50 nm polystyrene NPLs increased ROS levels and elevated SOD, CAT and GST activities in *Oryzias melastigma*, with more pronounced effects observed in the liver compared to the

gut of the animals (92). Conversely, 45 μm MPLs administered over the same duration induced a gut dysbiosis-related response in the same model (92), pinpointing the distinct effects induced by MPLs and NPLs *in vivo*. The exposure of BV2 microglial cells and *Aurelia coerulea* polyps to 50 nm polystyrene NPLs for 12 and 48 h, respectively, led to reduced CAT levels and increased malondialdehyde (MDA) levels, an indicator of lipid peroxidation, suggesting heightened oxidative stress, while brain tissue and serum samples from ICR mice also confirmed these results (93). Importantly, transcriptomic analyses of BV2 cells and *Aurelia coerulea* revealed that polystyrene NPLs triggered activation of the MAPK signaling pathways in both models; however, distinct genes were expressed in each case (93).

The primary MAPK sub-families include the extracellular regulated kinases (ERKs), the c-Jun N-terminal kinases (JNKs) and the p38 MAPKs. These kinases play a crucial role in regulating transcription factors involved in cellular processes such as growth, survival, and apoptosis (94,95). The persistent activation of MAPK signaling pathways has been shown to be associated with uncontrolled cellular proliferation, the evasion of apoptosis and metastasis. Furthermore, the dysregulation of these signaling cascades has been reported in a plethora of cancers (96). The detrimental effects associated with MNPLs have been linked to the activation of the MAPK signaling cascade, a process that can be triggered or facilitated by ROS (63,81). Supporting this, the ingestion of 0.05 μm polystyrene microbeads by *Paracyclopina nana* was shown to result in oxidative stress, which subsequently activated phospho-ERK, phospho-p38 and Nrf2, thereby affecting the growth rate and fecundity of the animals. Of note, the co-administration of a ROS scavenger decreased ROS production and reduced phosphorylation levels of ERK and p38 (97). Similar findings were reported in *Brachionus koreanus*, where elevated ROS levels were associated with the increased phosphorylation of JNK and p38, along with the reduced growth rate, fecundity and lifespan of the animals (98). Furthermore, Amado *et al* (99) reported that polystyrene NPLs increased ROS production in *Daphnia pulex*, resulting in a concentration-dependent increase in *ERK* gene and protein expression levels. They also demonstrated that the expression of *JNK*, *p38* and *VEGFA* was significantly upregulated, whereas higher concentrations caused a decline. At the protein level, the expression of JNK, AKT, hypoxia inducible factor 1 subunit α (HIF1α), and nuclear factor κ-light-chain-enhancer of activated B-cells (NF-κB) p65 increased in a concentration-dependent manner, while the activities of CAT and SOD enzymes decreased (99). In another study, healthy Balb/c mice subjected to micro-polystyrene exposure for 6 weeks exhibited increased levels of oxidative stress, marked by elevated ROS and MDA levels. The exposure also triggered the phosphorylation of p38 and JNK in a concentration-dependent manner (100). Furthermore, as demonstrated in another study, in C57BL/6J mice, inhalation exposure to micro- (0.25 μm) and nano- (20 nm) polystyrene particles for 6 and 12 weeks elicited a sustained activation of the MAPK signaling cascade in the lungs, accompanied by an enrichment of pathways associated with carcinogenesis and an increased expression of genes involved in the epidermal growth factor receptor (EGFR)/MAPK signaling pathway. Notably, the upregulation of amphiregulin, an EGFR ligand, and mitogen-activated protein kinase kinase kinase 13, a kinase involved in the activation of the MAPK pathway was observed. Additionally, elevated phosphorylation levels of EGFR and JNK further substantiated the activation of the EGFR/MAPK signaling axis (101).

In addition to the MAPK signaling pathways, MNPL-induced oxidative stress has been suggested to contribute to the activation of the Wnt/β-catenin pathway. The Wnt/β-catenin pathway is a critical pathway implicated in development, tissue homeostasis, proliferation, apoptosis and migration, and its aberrant activation has been associated with gastrointestinal cancers, leukemia, melanoma and breast cancer, among others (102,103). In a recent study, young primary cells (dermal fibroblasts and epidermal keratinocytes) isolated from healthy SKH1-hr hairless immunocompetent mice were exposed to polystyrene microspheres of various sizes, either once or repeatedly (104). During acute exposure, MNPLs stimulated ROS production, which led to Nrf2 activation and elevated mRNA levels of oxidative stress-related genes, such as heme oxygenase-1, NAD(P)H:quinone oxidoreductase 1 (*NQO1*), *SOD1*, *CAT*, *GPX2*, *GSR* and *GSTA1*, reflecting the effort of the cell to manage oxidative stress (Fig. 2). Moreover, the expression of *p53*, *BAX* and *p21* was increased as a response to DNA damage, as evidenced by accumulated phosphorylated histone H2AX (γ-H2AX). Concurrently, the expression of *CTNNB1* and *CDH1* was augmented, accompanied by higher levels of lymphoid enhancer-binding factor 1 (*LEF1*) mRNA, indicating the activation of the Wnt/β-catenin pathway (104). Under chronic exposure, while ROS generation persisted, Nrf2 remained activated, accompanied by the downregulation of *NQO1*, *CAT*, *GPX2* and *GSR*, indicating the cell's inability to neutralize ROS and counteract MNPL-induced oxidative stress. In addition, the decrease in B-cell lymphoma 2 (Bcl-2) expression suggested increased resistance to apoptosis induced by DNA damage. The activation of the Wnt/β-catenin signaling pathway was further evidenced by β-catenin translocating to the nucleus and an increase in the mRNA levels of *Wnt1*, *Wnt7a*, *LEF1*, *c-JUN* and matrix metalloproteinase 7. Simultaneously, cytoskeletal changes occurred, including disruption of actin filaments, modifications in keratin expression (the upregulation of keratin 1 and the downregulation of keratin 14), alterations in proteins of adhesive integrin complexes (the increased levels of focal adhesion kinase and vinculin, and the upregulation of integrin *ITGB1*), and markers indicative of fibroblast-to-myofibroblast transition (the upregulation of α smooth muscle actin and collagen *COL1A*) (104).

In study using healthy rats, exposure to polystyrene MPLs for 90 days led to their accumulation in all tissues except the heart, with the highest concentrations detected in gastric tissues and the spleen (105). Notably, there was damage to cellular membranes, abnormal nuclear shapes, mitochondrial impairment, elevated MDA levels, decreased levels of CAT, SOD and GSH-Px, and increased levels of DNA damage markers [8-hydroxy-2'-deoxyguanosine (8-oxodG) and γ-H2AX] in gastric epithelial cells of rats. These findings were also observed in human gastric epithelial GES-1 cells (105), where polystyrene MPLs caused excessive ROS production, leading to the dissociation of the nucleoredoxin/dishevelled 1 complex, a redox-sensitive inhibitor of the Wnt/β-catenin signaling pathway. Such a dissociation resulted in the

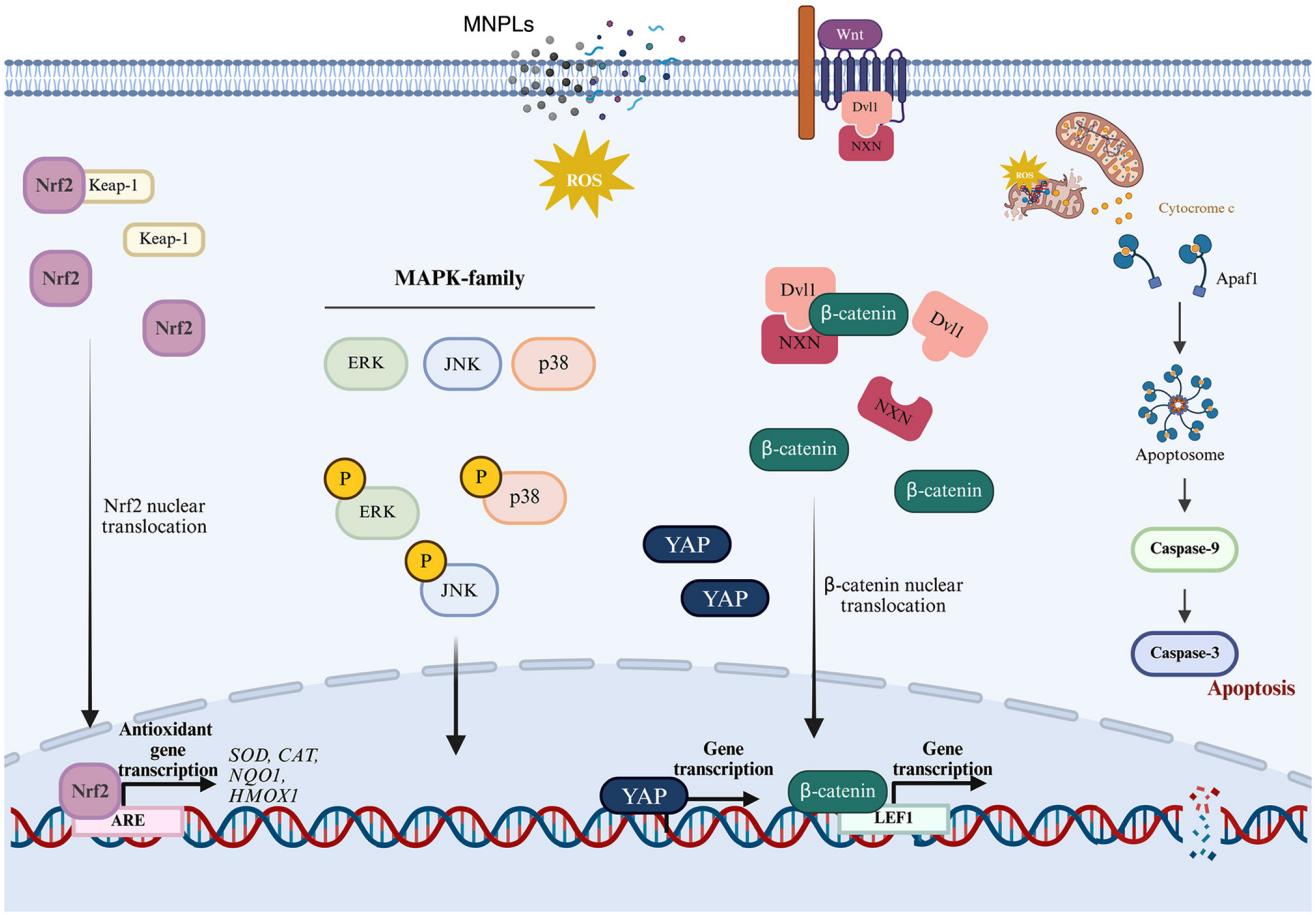


Figure 2. Oxidative stress and signaling dysregulation induced by MNPLs. Exposure to MNPLs results in increased intracellular production of ROS and/or the suppression of antioxidant enzyme activity. Elevated ROS levels cause damage to DNA and mitochondria, thus compromising cell viability. These effects activate Nrf2 following its release from Keap-1, resulting in its subsequent translocation to the nucleus, where it promotes the transcription of antioxidant genes through binding to AREs in their promoter regions. ROS also stimulate MAPK signaling pathways (ERK, JNK and p38), thereby activating transcription factors involved in cell survival and apoptosis. Excessive ROS generated by MNPL exposure facilitates the dissociation of the NXN/Dvl1 complex, a redox-sensitive regulator of Wnt signaling that restrains β-catenin in the cytoplasm. This dissociation leads to β-catenin stabilization and its subsequent translocation into the nucleus, where it binds to LEF1 to activate the Wnt/β-catenin signaling pathway. Crosstalk between the Wnt/β-catenin and Hippo pathways, mediated through YAP activation, further enhances β-catenin transcriptional activity. Furthermore, extensive mitochondrial damage caused by oxidative stress triggers apoptosis through cytochrome *c* release and the subsequent activation of caspase-9 and caspase-3. MNPLs, microplastics and nanoplastics; ROS, reactive oxygen species; AREs, antioxidant response elements; Nrf2, nuclear factor erythroid 2-related factor 2; Keap-1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated kinase; JNK, c-Jun N-terminal kinase; NXN, nucleoredoxin; Dvl1, dishevelled 1; LEF1, lymphoid enhancer-binding factor 1; YAP, yes-associated protein; SOD, superoxide dismutase; CAT, catalase; NQO1, NAD(P)H: quinone oxidoreductase 1; HMOX1, heme oxygenase-1; Apaf1, apoptotic protease activating factor 1. Phoshorylation is depicted using the letter 'P' within a yellow circle. The figure was created using BioRender (https://BioRender.com/tp2pkvk).

increased expression of β-catenin, indicating the activation of the Wnt/β-catenin signaling pathway. At the same time, the increased expression of yes-associated protein (YAP) was observed (Fig. 2) (105). YAP protein is a transcriptional activator in the Hippo pathway, playing a significant role in cellular proliferation, survival, and differentiation, and has been linked to cancer (106,107). In addition, crosstalk between the Wnt/β-catenin and Hippo pathways has been described in cancer development (102,108).

Finally, oxidative stress induced by MNPLs is closely associated with mitochondrial dysfunction, as illustrated in Fig. 2. Mitochondria are considered significant targets of MNPL toxicity, since exposure has been shown to diminish mitochondrial membrane potential and impair ATP production *in vitro*. Such modifications may activate the intrinsic apoptotic pathway, ultimately leading to apoptosis and increasing MNPL-induced cytotoxicity (19). In zebrafish larvae, exposure to aged polystyrene MPLs induced oxidative stress and mitochondrial impairment, thereby leading to developmental toxicity (109). These MPLs increased ROS, lipid peroxidation and DNA damage, thereby disrupting mitochondrial function through the reduction of ATP synthesis, compromising mitochondrial membrane potential and promoting the release of cytochrome *c*. Consequently, the activities of caspase-3 and caspase-9 increased, accompanied by upregulation of apoptosis-related genes, such as *bax*, *caspase-3*, *caspase-9* and apoptotic protease activating factor 1 (*apaf-1*), while *bcl-2* was downregulated. These findings collectively indicate the activation of a mitochondrial-mediated apoptotic pathway (109).

Overall, oxidative stress, driven by excessive ROS production, represents a key mechanism underlying MNPL toxicity and has been consistently documented in both *in vitro* and *in vivo* experimental models. Nonetheless, its potential contribution to human carcinogenesis remains to be fully elucidated.

Key indicators, including Nrf2 and MAPK activation, DNA and mitochondrial damage and the depletion of antioxidants, may serve as quantitative KE descriptors within regulatory-relevant AOP frameworks. The harmonization of these biomarkers across various experimental models could enhance cross-study integration and facilitate the derivation of point of departure values for MNPL mixtures (32,78). An overview of the principal pathways involved in MNPL-induced oxidative stress and the associated downstream signaling pathways is summarized in Fig. 2.

DNA damage and genotoxicity. Maintaining genome integrity is fundamental for cell survival; however, DNA damage and genomic instability can facilitate carcinogenesis (110). Research indicates that exposure to MNPLs is associated with DNA damage and genotoxic effects (8,19,36,59,75,111), with the extent of impact seemingly influenced by particle size, concentration, and cell type. Exposure to MNPL has been shown to be associated with numerous DNA alterations, including single-strand breaks (SSBs), double-strand breaks (DSBs) and oxidative modifications of purines and pyrimidines (64,89). Malinowska *et al* (112) demonstrated that polystyrene NPLs of varying sizes induced genotoxic effects in human peripheral blood mononuclear cells (PBMCs), as evidenced by the formation of SSBs and DSBs, increased levels of 8-oxodG, and oxidation of purines and pyrimidines. Notably, although all tested NPLs caused DNA damage, the smallest particles (29 nm) exhibited the most significant effect, underscoring a size-dependent phenomenon. Furthermore, in the same study, while DNA damage induced by NPLs of 44 and 72 nm in size was repaired within 2 h, that caused by NPLs of 29 nm in size remained incomplete (112), indicating the detrimental impact of smaller particles. Similarly, in another study, the exposure of human intestinal organoids to 1 μm and 100 nm polystyrene particles resulted in significant γ-H2AX accumulation, accompanied by mitochondrial dysfunction and ROS generation, with NPLs eliciting a stronger genotoxic response than MPLs (113). Additionally, the induction of micronuclei and nuclear buds was observed in human foreskin fibroblasts (Hs27) following treatment with polystyrene NPLs of 100 nm in size, with more pronounced effects at the concentration of 75 μg/ml, where frequencies of micronuclei and nuclear buds reached 52 and 50%, respectively. Of note, although NPLs also increased ROS production, co-treatment with the antioxidant extract of *Crocus sativus L*. reduced ROS generation (114). However, the researchers did not evaluate DNA damage markers after administering the extract, thus limiting mechanistic insights. Furthermore, in A549 human cells exposed to plastic particles from a subway station or a nearby heavily trafficked urban street, concentration-dependent DNA damage was observed, as evidenced by comet assay results and elevated levels of 8-oxodG. The most concerning finding was that the most significant genotoxic effects were associated with subway particles (115). Additional evidence from *in vitro* studies further supports the notion that MNPLs induce genomic instability. Cytotoxicity and genotoxicity have been documented in human lymphocytes exposed to polystyrene NPLs of 50 nm in size (116) and polyethylene MPLs of 10-45 μm in size, which resulted in increased frequencies of micronuclei formation and nuclear abnormalities, such as nucleoplasm bridges and nuclear buds (117). Cellular responses appeared highly cell-type-specific. The study by Rubio *et al* (111) demonstrated differential responses among three cell lines exposed to spherical polystyrene NPLs of 50 nm in size. Specifically, THP-1 monocytes did not exhibit genotoxic lesions despite the highest particle internalization among the studied cell lines. TK6 lymphoblasts exhibited increased ROS production leading to oxidative DNA damage, while DNA breaks were observed in Raji-B-cells (B-lymphocytes), indicating distinct mechanisms of action (111).

In vivo models provide additional, albeit heterogeneous, evidence. The exposure of *Scrobicularia plana* to polystyrene MPLs of 20 μm in size resulted in their accumulation within the gills and digestive glands, subsequently inducing oxidative stress. The MPLs elevated levels of antioxidant enzymes such as CAT, SOD, GPx, and GST, and also induced genotoxicity and neurotoxicity, with the severity of these effects dependent on exposure duration (118). A meta-analysis revealed that aquatic organisms exposed to MNPLs exhibited genotoxic damage compared to control groups, as evidenced by multiple genotoxic indicators (119). The significance of these effects was linked to the size of the plastics (smaller particles causing greater effects), the environmental conditions in which the organisms live and the species tested, with freshwater organisms demonstrating greater susceptibility than marine species (119). In another study, exposure to MPLs for 15 days also increased the activities of SOD, CAT, total peroxides and MDA in *Oreochromis niloticus*, accompanied by lipid peroxidation and DNA fragmentation. Following a 15-day recovery period, all the previously mentioned indicators returned to normal levels (120). In another study, the administration of virgin and aged (post-120 days of ultraviolet exposure) low-density polyethylene MPLs (average size, 500 μm) reduced the proportion of normal cells in *Perca fluviatilis* by increasing the number of binucleated cells, cells containing a micronucleus and cells with a micronucleus connected to the main nucleus (121). Notably, virgin polyethylene MPLs had more harmful effects compared to the aged ones. DNA damage was also observed in the liver and muscle tissues of *Perca fluviatilis* in both MPL groups, with the liver showing the most significant damage. Although the link between ROS generation and DNA damage was not experimentally tested, the authors of that study attributed the DNA damage observed to excessive ROS production induced by MPL treatment (121). A separate study highlighted the differences between acute and chronic exposure to spherical and fibrous MPLs in *Mytilus galloprovincialis* (122). Both particle types caused morphological disorders in the gills and digestive glands, with effects varying according to exposure duration and particle dose; fibrous particles were more toxic. These effects were accompanied by increased DNA fragmentation and apoptosis, as evidenced by the upregulation of *caspase 3/7*. In fact, MPL exposure activated both extrinsic (upregulation of Fas-associated death domain) and intrinsic (downregulation of *Bcl-1* and *Bcl-2*, and upregulation of *Bax*) apoptotic pathways. Additionally, transcript levels of *Gadd45α*, *Gadd45γ*, and *p53*, genes involved in growth arrest and DNA damage response, were elevated, while the PI3K/AKT and ERK pathways, essential for cell survival, were inhibited (122), indicative of genotoxic stress.

Despite the above, it is important to note that not all studies report genotoxic effects. For instance, intestinal and placental

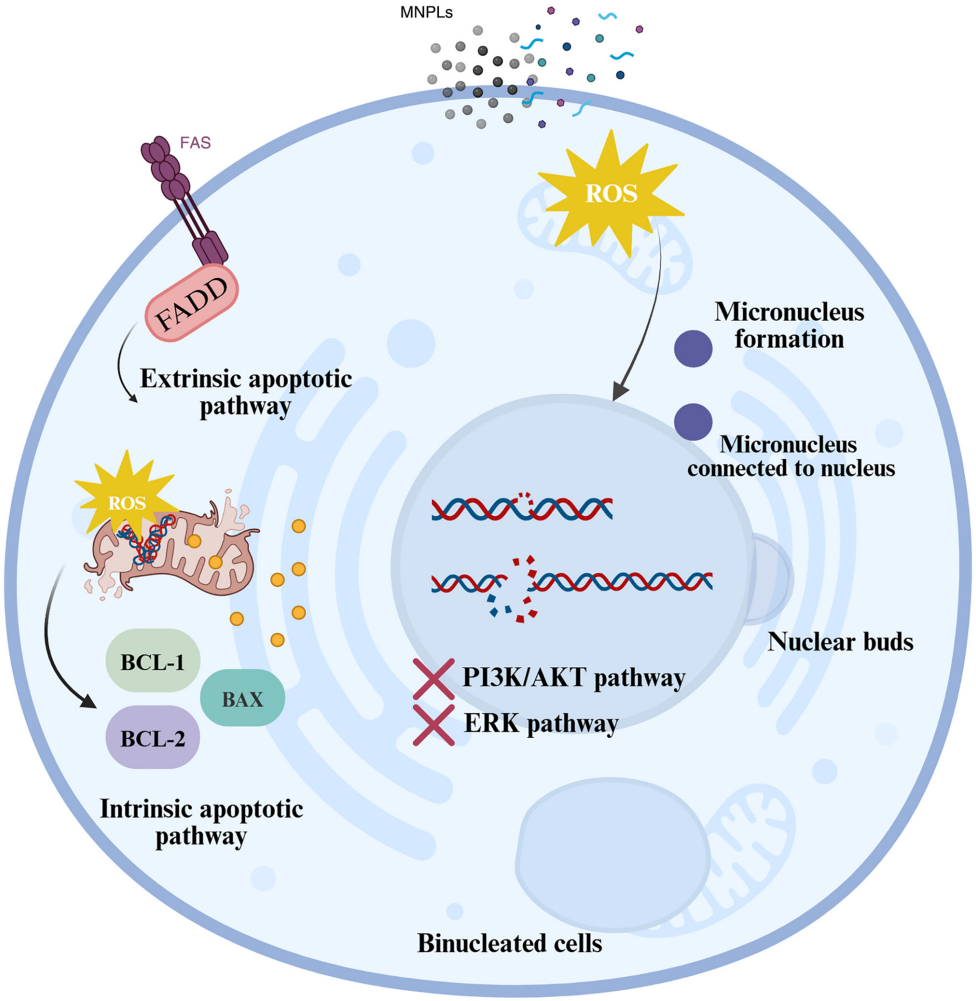


Figure 3. DNA damage and genotoxicity induced by MNPLs. ROS generation resulting from MNPLs leads to oxidative DNA damage, including single- and double-strand breaks, micronuclei formation (represented by a blue sphere), micronuclei connected to the main nucleus, and nuclear buds. This DNA damage triggers the initiation of apoptosis, with the extrinsic pathway activated through FADD, while mitochondrial dysfunction in the intrinsic pathway promotes cytochrome *c* release, along with the upregulation of BAX and suppression of BCL-1 and BCL-2. Additionally, the PI3K/AKT and ERK signaling pathways are inhibited. MNPLs, microplastics and nanoplastics; ROS, reactive oxygen species; FADD, Fas-associated death domain; BAX, Bcl-2-associated X-protein; BCL-1, B-cell lymphoma 1; BCL-2, B-cell lymphoma 2; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; ERK, extracellular regulated kinase. The figure was created using BioRender (https://BioRender.com/9pgdyx0).

co-cultures exposed to various concentrations of polystyrene MNPLs did not exhibit genotoxicity, as assessed by p53 expression levels and micronuclei formation (123). In line with these findings, in a previous study, negatively charged carboxylated polystyrene (COOH-PS) and positively charged amino-modified (NH2) polystyrene NPLs were administered to cancerous HeLa cells and normal NIH 3T3 fibroblasts. Both cell lines internalized NPLs, which remained in the cytoplasm. It is noteworthy that these particles were distributed across all phases of mitosis without causing chromosomal abnormalities or disruption of mitotic spindle formation, although G0/G1 cell cycle arrest was observed, particularly in response to NH2 polystyrene NPLs (124). Additionally, NPLs are divided equally between daughter cells (124), which aligns with the study conducted by Brynzak-Schreiber *et al* (62). Of note, both types of NPLs were more toxic to normal cells than to cancerous cells (124). These discrepancies likely reflect differences in particle properties, exposure conditions and model systems, highlighting the necessity for standardized experimental approaches.

These findings collectively suggest that DNA damage and genotoxicity may serve as crucial molecular mechanisms linking MNPL exposure to carcinogenesis. Although the exact mechanisms of DNA damage caused by MNPLs are not yet fully understood, an overview of the current understanding of the genotoxic mechanisms induced by MNPLs and the corresponding cellular responses is presented in Fig. 3.

Pro-inflammatory responses and inflammation. MNPLs are recognized by the immune system as foreign entities, thereby activating both innate and adaptive immune responses (65,125). Within the innate immune system, MNPLs stimulate neutrophils, macrophages and dendritic cells, leading to the increased production of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ). Concurrently, MNPLs can modulate adaptive immunity by affecting T-cell differentiation and facilitating immune evasion through anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). As a result, their presence triggers an immune response, increasing the levels

of neutrophils, macrophages (M1 and M2), T-cells [T helper 2 (Th2), Th17, regulatory T-cells (Tregs)], B lymphocytes and phagocytes at the 'injury site' (65,125). In the event that MNPLs are not combated by the immune system, this persistent immune activation may lead to chronic inflammation (65), which is known to promote DNA damage, cytokine and chemokine release, and the activation of signaling pathways (e.g., NF-κB) that may contribute to tumor growth, metastasis and progression (19,126-129).

Experimental studies support the pro-inflammatory potential of MNPLs, although the responses appear to be dependent on factors, such as particle size, duration of exposure and the specific model system used. For instance, in the study by Hwang *et al* (130), smaller propylene MPLs (20 μm in size) elicited more potent inflammatory responses compared with larger particles (25-200 μm), as evidenced by the increased secretion of IL-6 and TNF-α in PBMCs and RAW 264.7 murine macrophages, along with elevated histamine release from the human mast cell line 1 (HMC-1). Notably, the anti-inflammatory cytokines, IL-2 and IL-10, exhibited no significant alterations (130), suggesting that the cell-mediated immune response was not activated. Similarly, the exposure of primary dermal fibroblasts and epidermal keratinocytes, isolated from SKH1-hr mice, to polystyrene microspheres increased the mRNA expression of TNF-α, IL-1β and IL-6. When comparing acute and chronic exposure, the latter was found to be more detrimental (104). In another study, polystyrene NPLs of 50 nm in size also induced an inflammatory response in BV2 microglial cells by elevating ROS levels, upregulating the *CD32* and *CD11b* genes, both associated with promoting an M1 polarization shift, and increasing mRNA levels of IL-1β and TNF-α. Following 12 h of exposure, the apoptotic rate was higher compared to the control-treated cells (93). Furthermore, the type of polymer appears to influence immune responses. Han *et al* (131) demonstrated that treating PBMCs with 25-75 μm acrylonitrile butadiene styrene (ABS), a thermoplastic polymer, increased IL-6 production, whereas treatment with similarly sized PVC increased TNF-α secretion, while both ABS and PVC inhibited histamine release (131). However, they did not reveal the exact mechanism of action.

Similar findings have been reported in animal models. In zebrafish, polystyrene MPLs (0.5 μm in size) significantly increased the mRNA and protein levels of IL-1α, IL-1β and IFN following 14 days of exposure (132), while in *Poecilia reticulata*, larger particles (32-40 μm in size) elevated TNF-α, IFN-γ, Toll-like receptor 4 (TLR4) and IL-6 levels in a dose-dependent manner (133), implicating TLR4 signaling in MNPL-induced inflammation. TLR4 is a receptor for pathogens that triggers downstream signaling pathways associated with the inflammatory response (126,129). In C57BL/6J mice, a 3-week exposure to 0.1 and 2 μm polystyrene MPLs also increased the mRNA expression of TNF-α and calgranulins S100a8 and S100a9, which are involved in mediating inflammatory responses (134), further supporting activation of inflammatory pathways.

However, not all studies report consistent immune activation. For example, THP-1 monocytes internalized polystyrene particles of various sizes (1, 4 and 10 μm), without significant changes in M1/M2 polarization markers [signal transducer and activator of transcription (STAT)-1 and STAT-6], chemokine expression (CXCL10, CCL22), or surface receptors (CD209, CD206)], indicating that particle uptake alone may not be sufficient to trigger inflammatory responses under these certain experimental conditions (135).

MNPLs may also interfere with adaptive immune function. Li *et al* (136) demonstrated that polystyrene NPLs suppressed T-cell activation and differentiation in murine splenic lymphocytes by diminishing the expression of $CD3^+CD69^+$ and $CD3^+CD25^+$, as well as impairing $CD8^+$ T-cell differentiation. This was accompanied by decreased IL-2 and INF-γ production (136). At the molecular level, the authors of that study found that polystyrene NPLs significantly reduced the expression of phospho-protein kinase Cθ (PKCθ), p65, phospho-inhibitor of κBα, phospho-inhibitory kappa B kinase β and phospho-STAT-5 in T-cells; these essential proteins are involved in the PKCθ/NF-κB and IL-2 receptor/STAT-5 pathways that regulate T-cell activation and function (136) (Fig. 4), indicating a potential immunosuppressive effect that may compromise anti-tumor immunity.

Mechanistically, MNPL-induced inflammation has been closely linked to oxidative stress, DNA damage and innate immune pathways (8,36,65,125). In both HL-7702 human liver cells and C57L/5 mice, polystyrene MPLs (0.1 and 1 μm in size) caused DNA damage in the nucleus and mitochondria, leading to the presence of DNA fragments in the cell cytoplasm. This leakage triggered the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) signaling pathway by stimulating cGAS, a double-strand DNA sensor, which in turn activated STING (Fig. 4). As a result, NF-κB translocated to the nucleus, where phospho-NF-κB induced the mRNA expression of IL-1β, IL-6 and TNF-α, ultimately contributing to liver fibrosis in mice (137). Consistent with the involvement of NF-κB signaling in MNPL-induced toxicity, a recent study conducted by Ye *et al* (138) reported that in clear cell renal cell carcinoma cells, exposure to polystyrene MPLs promoted cellular proliferation, migration, and invasion, while concurrently inhibiting apoptosis through activation of the NF-κB and TGF-β signaling pathways. Notably, the pharmacological inhibition of these pathways mitigated the pro-tumorigenic effects in both cellular and preclinical models, thereby supporting their potential involvement in cancer progression (138). In addition, the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome has emerged as a key pathway involved in MNPLs-induced inflammation (129). In normal human epithelial cells (HaCat), 1 μm polyethylene MPLs inhibited proliferation in a concentration- and time-dependent manner by impairing cell cycle progression (139). This effect was caused by an inflammatory response (elevated levels of TNF-α, IL-6 and IL-1β), which activated the NLRP3 inflammasome, ultimately leading to cell pyroptosis, a form of programmed cell necrosis (139). Conversely, in cancer cells (SCL-1 and A431), polyethylene MPLs induced ROS accumulation, mitochondrial membrane potential changes and mitochondrial DNA damage. The damaged mitochondrial DNA entered the cytoplasm through the mitochondrial permeability transition pore, which triggered the NLRP3 inflammasome, resulting in increased TNF-α, IL-6 and IL-1β levels, as well as enhanced cell proliferation (139). Consistently, the activation of the NLRP3/caspase-1

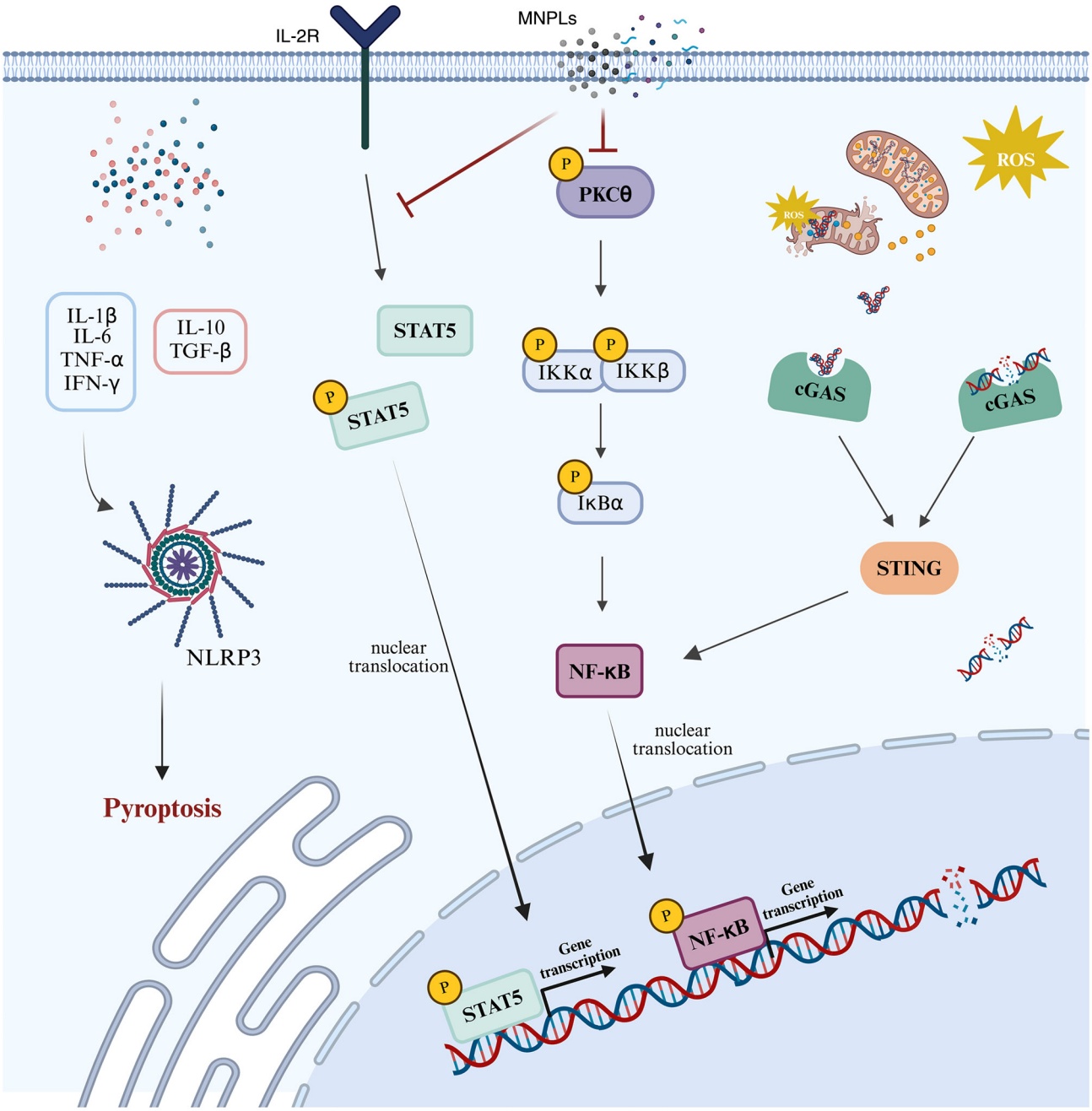


Figure 4. Pro-inflammatory and inflammatory responses induced by MNPLs. MNPLs provoke either acute or chronic inflammation through the secretion of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) and anti-inflammatory cytokines (IL-10, TGF-β). This inflammatory response activates the NLRP3 inflammasome, leading to pyroptosis. The activation of NLPR3 may also result from mitochondrial DNA damage caused by elevated ROS production following MNPL exposure. Damage to nuclear and mitochondrial DNA stimulates the cGAS sensor detecting double-stranded DNA, which subsequently activates STING. This process induces phosphorylation and nuclear translocation of NF-κB, thereby promoting cytokine expression. Moreover, MNPLs suppress the PKCθ/NF-κB and IL-2R/STAT-5 signaling pathways by reducing the levels of phosphorylated PKCθ, IκBα, IKKβ, and STAT-5; critical regulators of T-cell differentiation. MNPLs, microplastics and nanoplastics; IL, interleukin; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; TGF-β, transforming growth factor-β; NLRP3, NOD-like receptor protein 3; ROS, reactive oxygen species; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; PKCθ, protein kinase Cθ; NF-κB, nuclear factor κ-light-chain-enhancer of activated B-cells; IL-2R, interleukin-2 receptor; STAT-5, signal transducer and activator of transcription-5; IKKα, inhibitory κB kinase α; IKKβ, inhibitory κB kinase β; IκBα, inhibitor of κBα. Phosphorylation is depicted using the letter 'P' within a yellow circle. The figure was created using BioRender (https://BioRender.com/ki4bx1j).

signaling pathway and the induction of pyroptosis following exposure to polystyrene MPLs have also been observed in *in vivo* models (140-142).

Taken together, these findings highlight the complex role of MNPL-induced inflammation, which varies according to particle characteristics and exposure conditions by modulating inflammatory responses and exerting both pro-tumorigenic and immunomodulatory effects. As inflammation predisposes individuals to cancer development and facilitates all stages of tumorigenesis (128), the precise mechanisms through which MNPLs could initiate tumor proliferation remain limited. An overview of the primary pathways involved in MNPL-induced inflammation and signaling dysregulation is summarized in Fig. 4.

Dysbiosis. Recent evidence highlights the crucial role of the microbiome in the initiation and progression of cancer (143-145). The gut microbiota, a complex and dynamic consortium of microorganisms including bacteria, viruses, fungi and archaea, plays a vital role in maintaining host homeostasis through the regulation of immune responses and support of metabolic equilibrium. The disruption of this bidirectional communication between the microbiome and the host results in dysbiosis. Such dysbiosis has been associated with carcinogenesis through multiple mechanisms, including the activation of oncogenic signaling pathways (e.g., Wnt/β-catenin), the induction of DNA damage and genomic instability, the modulation of immune signaling pathways (e.g., NF-κB, JAK/STAT and the inflammasome), epigenetic modifications and the induction of aberrant metabolic processes. Additionally, specific microbes and their metabolites may exert protective and anti-tumor effects. Beyond tumor initiation, the microbiome is increasingly recognized as a fundamental regulator of the tumor microenvironment, influencing cancer progression, metastasis, and response to therapies, such as chemotherapy, radiotherapy and immunotherapy (143-145). Notably, environmental factors, including exposure to MPLs, have also been shown to disrupt microbial composition, potentially contributing to inflammation, metabolic imbalance, and impaired intestinal immunity (65).

Experimental evidence indicates that alterations in the microbiome induced by MNPLs are affected by particle type, size, and the model system used. Lei *et al* (146) demonstrated that various types of MPLs (polyamides, polyethylene, polypropylene, polystyrene and PVC) caused intestinal damage in zebrafish, characterized by villi cracking and enterocyte splitting, whereas in *Caenorhabditis elegans*, they induced lethality and developmental toxicity. Notably, the authors of that study established that the observed toxicity is dependent on particle size rather than chemical composition (146).

Consistent with these observations, several studies using aquatic models have reported significant shifts in gut microbiota composition following exposure to MNPLs. In zebrafish, exposure to 0.5 and 50 μm polystyrene MPLs for 14 days resulted in decreased relative abundance of *Proteobacteria* and *Bacteroidetes*, and increased levels of *Fusobacteria* and *Firmicutes*, along with changes in 29 bacterial genera. These microbiome modifications were accompanied by elevated mRNA and protein levels of IL-1α, IL-1β and IFN (132), indicative of an inflammatory response. Comparable outcomes were observed following exposure to 5 μm polystyrene MPLs in the same model for 21 days, which also altered the intestinal metabolomic profile and induced oxidative stress (82). In crustaceans, such as *Eriocheir sinensis*, exposure to 5 μm polystyrene MPLs decreased the relative abundance of *Firmicutes* and *Bacteroidetes*, whereas *Fusobacteria* and *Proteobacteria* increased. Additionally, MPL exposure altered the levels of enzymes that play key roles in crustaceans' immune response (147). It is noteworthy that in a recent study, the *Firmicutes*/*Bacteroidetes* ratio was found to be significantly decreased in patients with breast cancer compared to healthy individuals, while the risk of developing breast cancer was associated with this ratio (148). However, such associations require further evaluation.

Evidence from mammalian models further supports the link between MNPL exposure and microbiome dysbiosis. In ICR mice, exposure to 0.5 and 50 μm polystyrene MPLs reduced the relative abundance of *Firmicutes* and α-*Proteobacteria* in both cecal contents and feces; a reduction in *Actinobacteria* was observed only in cecal contents exposed to 50 μm MPLs (149). Additionally, there were changes in the number of gut microbes in the cecal content and colon at the genus level, while genes related to glucose and lipid metabolism were also affected (149). Similarly, exposure to 5 μm polystyrene MPLs caused modifications in fifteen bacterial species within the same animal model, accompanied by metabolic disorders (150). Moreover, in C57BL/6 mice, polyethylene particles increased bacterial abundance and enhanced the diversity of the intestinal microbiota, as evidenced by increases in the *Staphylococcus* genus (*Firmicutes*) and decreases in the *Parabacteroides* genus, among others (151). These microbiota modifications were associated with modulation of immune responses, including elevated levels of IL-1α and IL-9 and altered T-cell populations characterized by reduced proportions of Th17 and Treg cells. Furthermore, inflammation was observed in the colon and duodenum, concomitant with activation of the TLR4 signaling pathway, as demonstrated by elevated expression levels of TLR4, AP-1 transcription factor subunit and interferon regulatory factor 5 in the intestine (151).

Recent metagenomic analyses in patients with colorectal cancer further indicate that MPL exposure may be associated not only with alterations in gut microbial composition, but also with modifications in the functional profiles of the tumor-associated microbiome. Specifically, exposure to polystyrene was found to be associated with pathways involved in inflammation, immune regulation and cancer-related signaling, including HIF-1, Wnt, JAK/STAT, IL-17 and NOD-like receptor signaling pathways. This underscores a potential role of MNPL-associated dysbiosis in tumor progression (152).

Collectively, existing evidence indicates that MNPL-induced dysbiosis may indirectly contribute to carcinogenesis through its influence on inflammation, immune modulation and metabolic disruption. Nevertheless, the majority of these findings are derived from experimental models, and definitive causal associations in humans have yet to be established.

Endocrine disruption. MNPLs, together with the chemical additives incorporated to enhance their properties, such as BPA and phthalates, may influence hormonal signaling pathways, potentially leading to endocrine disruption. These compounds, known as endocrine-disrupting chemicals (EDCs), can mimic or inhibit hormones and affect hormonally sensitive organs, including the breast, ovaries, prostate, and thyroid, thereby potentially increasing the risk of carcinogenesis (8,36,75,153).

Among these, BPA is one of the most extensively studied EDCs. It functions as an endocrine disruptor and has been linked to carcinogenesis through its involvement in cancer cell survival, proliferation, migration, and invasion, among other processes (28,154). Mechanistically, BPA can modulate cancer-related cellular signaling pathways by binding to or activating various receptors, including estrogen receptor α/β, androgen receptor, G protein-coupled estrogen receptor, insulin-like growth factor-1 receptor, and estrogen receptor γ (28,154). Current evidence suggests that BPA affects mammary gland development and alters gene methylation patterns, thereby elevating the risk of developing cancer

following early-life exposure even at low doses in rodents (28). Although BPA is considered a potential risk factor for breast cancer development (28), its involvement in other malignancies remains less clearly defined and warrants further research. This topic has been extensively reviewed elsewhere (28,154).

Moreover, a significant yet insufficiently discussed aspect is the landscape of substitution. The progressive regulatory restrictions on BPA have resulted in its replacement by structurally related bisphenols, such as bisphenol S, bisphenol F and bisphenol AF, several of which exhibit comparable or enhanced estrogenic, androgenic and metabolic-disrupting activities. In matrices abundant in MNPLs, where polymer aging continuously releases residual additives, this substitution pattern may therefore sustain rather than mitigate endocrine-disrupting exposures. Integrating mechanistic data from NAMs into SSbD substitution decisions is imperative to disrupt this cycle (29-31).

Another well-characterized EDC is DEHP, which is recognized for its potential role in both cancer initiation and progression. DEHP exerts its effects by interacting with estrogen, progesterone, and androgen receptors, among others and functions as an endocrine disruptor by activating pathways associated with cancer development, including PI3K/AKT, TGF-β, MAPK and Wnt/β-catenin (27). The involvement of DEHP in carcinogenesis has been thoroughly examined in the review by Zhou *et al* (27).

The 'Trojan horse' effect. MNPLs have a wide range of mechanisms capable of potentially contributing to carcinogenesis, as previously described. Nonetheless, owing to their intrinsic properties, they may absorb or even facilitate the transport of other compounds, including established carcinogens, toxic chemicals (e.g., heavy metals), and pathogenic microorganisms (155). Lee *et al* (156) demonstrated that polystyrene, polyethylene and polypropylene exhibit high sorption capacities for hydrophobic organic chemicals, such as polycyclic aromatic hydrocarbons (PAHs), hexachlorocyclohexanes and chlorinated benzenes that may be present in aquatic environments. As a result, MPLs may serve as vectors or 'sponges' for toxic compounds within the marine ecosystem, thereby influencing their bioavailability (156). Notably, under realistic conditions where contaminants exist as mixtures, sorption behavior may vary. Bakir *et al* (157) observed that in mixed-contaminated environments, compounds such as dichlorodiphenyltrichloroethane can competitively inhibit the sorption of other pollutants such as phenanthrene onto polyethylene and PVC, indicating that interactions among contaminants can modify their affinity for plastics. These findings suggest that MNPLs may function as 'Trojan horses' and may serve as dynamic carriers, with their toxicological impacts depending on the chemical context in which they are present. Accordingly, the toxicological consequences of MNPLs may be substantially modified by co-exposure to sorbed contaminants, with outcomes varying from changes in bioavailability to additive or synergistic toxicity, depending on the characteristics of both the particles and the associated contaminants (155-157). Various studies support the notion that MNPL-associated contaminants can enhance toxicological outcomes. Sharma *et al* (5) demonstrated that smaller MPLs (<0.1 μm) can absorb and concentrate PAHs at levels significantly higher than those found in water, thereby potentially increasing the estimated lifetime cancer risk associated with ingestion through drinking water, salt and seafood. In another study, *in vitro* experiments further revealed that polyethylene and polystyrene MPLs can absorb pyrene, a PAH, in a dose- and time-dependent manner (158). When pyrene-treated polyethylene and polystyrene MPLs were administered to *Mytilus galloprovincialis*, pyrene-contaminated MPLs were detected and bioaccumulated in the hemolymph, gills, and digestive glands at higher levels compared to virgin MPLs. Although nuclear abnormalities were observed in all treatments, pyrene-contaminated MPLs induced greater frequencies of micronuclei formation, along with alterations in processes related to DNA repair, antioxidative functions, lysosomal metabolism, immune responses and apoptosis (158). Conversely, when a combination of polyethylene microspheres (1-5 μm) and pyrene was administered to *Pomatoschistus microps*, pyrene-induced death was delayed (159), indicating that sorption to MPLs may, in certain cases, temporarily reduce bioavailability and alter the timing of toxic effects.

Similarly, co-exposure to MNPLs and mixtures of environmental contaminants has been shown to be associated with enhanced toxicity. In zebrafish, polyethylene MPLs (125-250 μm) combined with a mixture of chemical pollutants present in the aquatic environments, including polychlorinated biphenyls, BFRs, perfluorinated chemicals and methylmercury, resulted in increased liver damage and overexpression of genes related to oxidative stress and detoxification processes, compared to exposure to MPLs or chemicals alone (160). In *Tegillarca granosa*, polystyrene MPLs combined with hydrophobic persistent organic pollutants (POPs), particularly 17β-estradiol (E2) and benzo[a]pyrene (B[a]P), induced immunotoxicity in a dose- and size-dependent manner; smaller particles (500 nm) amplified POP toxicity, likely by enhancing bioavailability and facilitating internalization, whereas larger particles (30 μm) mitigated toxicity, possibly due to limited internalization and more rapid elimination from the organism. Both pollutants, when combined with MPLs, produced effects proportional to the increases in B[a]P or E2 concentrations (161). Supporting these findings, in *C. elegans,* co-exposure to B[a]P and 80 nm polystyrene NPLs accelerated aging and shortened nematodes' lifespan by elevating ROS levels. This process compromised mitochondrial integrity and function, triggered the mitochondrial unfolded protein response, and induced ferroptosis (162). In a recent study, researchers examined the long-term effects of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and PET MPLs on *Daphnia magna*, assessing both individual and combined exposures. All chemicals tested adversely affected development, reproduction, growth, and sexual maturation, with PFOS showing higher toxicity than PFOA. The combined chemical effects were predominantly additive (59%), with a significant proportion (41%) exhibiting synergistic interactions (163). Of particular concern is that responses to these chemicals varied according to genotype; *Daphnia magna* populations previously exposed to chemical stressors exhibited diminished tolerance compared to populations with no history of chemical exposure, underscoring the importance of genetic background in modulating sensitivity to chemical stressors (163).

Evidence from human cellular models further supports synergistic effects. Exposing human lymphocytes to 1 μm polystyrene MPLs and BPA increased the frequency of micronuclei and nuclear bud formation compared to treatment with each compound independently (164), thereby highlighting a synergistic genotoxic effect. Moreover, the combination of 70 nm polystyrene NPLs or 1 μm polystyrene MPLs with triphenyl phosphate (TPHP) increased intracellular ROS levels, impaired mitochondrial function, and ultimately induced apoptosis in HepG2 cells more effectively than TPHP alone. Significantly, the effects observed with TPHP in conjunction with NPLs were more pronounced than with MPLs, potentially due to the enhanced absorption and better cell membrane penetration capabilities of NPLs (165), further strengthening the notion that smaller particles induce more significant biological effects.

The synergistic effects of plastics were also assessed in conjunction with metals. In zebrafish, combined exposure to polypropylene or PVC and cadmium induced inflammation (elevated IL-1β) and oxidative stress (increased SOD and MDA), along with alterations in microbiota abundance by increasing *Proteobacteria* and *Vibrio* and decreasing *Gemmobacter*; the combination of polypropylene and cadmium resulted in more pronounced effects than PVC (166). These results were also replicated in mice. The administration of polystyrene MPLs and cadmium affected the livers of the animals and activated the Keap-1/Nrf2 antioxidant signaling pathway, as well as the endogenous apoptosis signaling pathway p53/Bcl-2/Bax (167). The study by Feng *et al* (168) is particularly noteworthy as it provides a mechanistic explanation of the mechanisms through which co-exposure to polystyrene MPLs and lead exacerbates ovarian toxicity in C57BL/6 mice. This combination affected ovarian tissue by disrupting sex hormone levels and inducing oxidative damage through excessive ROS production. Moreover, this co-exposure stimulated endoplasmic reticulum (ER) stress and activated the protein kinase RNA-like endoplasmic reticulum kinase/eukaryotic initiation factor 2α/C/EBP homologous protein signaling pathway, ultimately leading to apoptosis through the downregulation of Bcl-2 and the upregulation of caspase-3 and caspase-12. The administration of salubrinal, an ER-stress inhibitor, and N-acetylcysteine, an antioxidant, mitigated the observed toxicity (168), further confirming the initial findings.

Finally, MNPLs may also interact with biological agents. In a previous study, co-exposure to polyethylene MPLs and *Salmonella enterica* serovar *Typhimurium* in chicken ceca resulted in more pronounced microbiome disruption compared to either stressor alone (169). More specifically, while treatment with polyethylene fibers exerted a greater impact on the cecal microbiome, resulting in a lower mean relative abundance of *Firmicutes* and a higher abundance of *Bacteroidetes*, the addition of *Salmonella* induced an even more significant disruption. This included a reduction in the *Firmicutes*/*Bacteroidetes* ratio, an increase in *Lactobacillus*, and alterations in biotin- and arginine-related metabolites (169).

Overall, current evidence indicates that MNPLs can influence the toxicity of co-existing environmental contaminants. However, the magnitude of these effects is highly dependent on experimental conditions, and while several studies suggest increased toxicity (158,160,163-166,169), others demonstrate decreased bioavailability (159,161). Therefore, although MNPLs may indirectly contribute to carcinogenesis by acting as carriers of hazardous substances, further research is necessary to elucidate their impact under realistic exposure conditions.

From an exposome perspective, this 'Trojan' phenomenon exemplifies a quintessential mixture problem: The particulate functions as both a vector and a concentrator, thus rendering internal dose prediction from the free-phase concentration of co-contaminants. The implications are particularly critical during vulnerable life-course windows (prenatal development, infancy, and puberty), when biotransformation capacity is limited and developmental plasticity is at its peak. During these stages, even minor additive or synergistic shifts in internal dose can lead to long-lasting phenotypic effects. Quantitative mixture frameworks established through HBM4EU and PARC, along with PBPK-coupled AOPs, provide the methodological basis for translating findings from *in vitro* and animal studies into human risk estimates (54,55,57).

The primary mechanisms by which MNPL exposure may influence carcinogenic processes are summarized in Table II. The table integrates the main experimental models, molecular and cellular events, representative mechanistic findings, and their possible relevance to carcinogenesis, providing an overview of the interconnected biological responses discussed throughout the present review.

5. Conclusions and future perspectives

Plastics are widely regarded as a significant scientific breakthrough of recent centuries, and their discovery has revolutionized the materials utilized in daily life. Nonetheless, their excessive utilization and improper management have resulted in substantial environmental pollution, ultimately endangering human health. Consequently, the scope of the exposome has recently expanded to encompass plastic particles, as MNPLs have emerged as a significant environmental factor influencing individuals from the prenatal period onwards.

Research on the health implications of plastics initially focused on their toxicity and effects in aquatic organisms, which are among the first to be exposed in their natural habitats. Although experimental studies have identified multiple biological responses to MNPL exposure, the field remains in its preliminary stages, and substantial uncertainty persists regarding the molecular mechanisms underlying these effects, particularly in humans. Further research is therefore required to prioritize environmentally relevant exposures, systematically considering polymer type, particle size and morphology, physicochemical properties, dosage and exposure duration to address existing knowledge gaps and enable a more comprehensive assessment of the potential health impacts of MNPLs.

An essential element to be integrated into the equalization process is the recognition that both animals and humans encounter a wide array of chemicals throughout their lifetimes as part of the exposome. The ability of plastics to absorb various chemicals and microorganisms, acting as vectors and thereby facilitating their entry into organisms, has attracted increasing attention in recent years. Consequently, concerns are rising about the potential of these polymers to adsorb environmental pollutants, as well as the synergistic effects that such combinations may yield.

Table II. Summary of the principal mechanisms potentially linking MNPL exposure to carcinogenesis.

Mechanism	Experimental models	Key molecular and cellular events	Representative experimental evidence	Potential relevance to carcinogenesis	(Refs.)
Oxidative stress	*In vitro*: Murine cell lines (BV2, fibroblasts, keratinocytes), human GES-1 cells *In vivo*: *Brachionus koreanus*, *Paracyclopina nana*, *Daphnia pulex*, *Aurelia coerulea*, *Danio rerio*, *Carassius auratus*, rodents (Balb/c, C57BL/6J, ICR)	Excessive ROS production Lipid peroxidation Depletion of antioxidant enzymes (CAT, SOD and GSH) DNA damage (↑ γ-H2AX) Mitochondrial membrane potential loss, reduced ATP production and cytochrome *c* release Pathways: MAPK, Nrf2, Wnt/β-catenin, YAP, mitochondrial-mediated apoptotic pathway	Induction of ROS accumulation accompanied by activation of signaling pathways (e.g., MAPK, Nrf2, HIF1α, Wnt/β-catenin), and DNA and mitochondrial damage	Persistent oxidative stress may promote DNA damage and protein/lipid oxidation and sustained activation of signaling cascades, potentially creating conditions conducive to tumor initiation and progression	(93,97-101,104, 105,109)
DNA damage and genotoxicity	*In vitro*: Human cell lines (PBMCs, Hs27, A549), human intestinal organoids *In vivo*: *Scrobicularia plana, Mytilus galloprovincialis*, *Oreochromis niloticus*, *Perca fluviatilis*	Single- and double-strand breaks Micronuclei Nucleoplasmic bridges Nuclear buds Binucleated cells Oxidative modifications of purines and pyrimidines ↑ γ-H2AX, 8-oxodG Pathways: p53 activation, apoptosis, PI3K/AKT inhibition, ERK inhibition	DNA fragmentation and oxidative DNA modifications, accompanied by alterations in apoptosis- and survival-related signaling	Genomic instability and accumulation of DNA lesions may increase the likelihood of persistent genetic alterations relevant to carcinogenesis	(112-115,117, 118,120-122)
Inflammation	*In vitro*: Murine cell lines (BV2, lymphocytes, fibroblasts, keratinocytes, RAW 264.7), human cell lines (PBMCs, HL-7702, HACAT, SCL-1, A431) *In vivo*: *Danio rerio*, *Poecilia reticulata*, rodents (C57BL/J, C57L/5)	Increase of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) Increase of anti-inflammatory cytokines (IL-10 and TGF-β) ROS production Mitochondrial impairment Pathways: TLR4, PKCθ/NF-κB, IL-2R/STAT-5, cGAS/STING, NF-κB, NLRP3 inflammasome signaling, apoptosis/pyroptosis	Persistent immune activation and induction of inflammatory response, accompanied by cytokine alterations and activation of related signaling pathways	Chronic inflammation may promote cytokine-mediated responses and activation of signaling pathways (e.g., NF-κB, NLRP3) that could support tumor development and progression	(93,104,130, 132-134, 136,137,139)

Table II. Continued.

Mechanism	Experimental models	Key molecular and cellular events	Representative experimental evidence	Potential relevance to carcinogenesis	(Refs.)
Dysbiosis	*In vivo*: *Danio rerio*, *Caenorhabditis elegans*, *Eriocheir sinensis*, rodents (ICR, C57BL/6), colorectal cancer patients	Alteration in gut microbial composition (*Firmicutes*, *Bacteroidetes*, *Fusobacteria*, *Proteobacteria*) Pathways: TLR4, inflammatory response	Changes in microbial diversity and bacterial genera accompanied by activation of immune responses	Disruption of microbial composition may contribute to inflammation, immune dysregulation, and altered microbial metabolite signaling, potentially influencing cancer-related processes	(132,146,147, 149,151,152)
Endocrine disruption	Various *in vitro* and *in vivo* models	Interaction with endocrine receptors (estrogen, progesterone, androgen) Pathways: PI3K/AKT, TGF-β,MAPK, Wnt/β-catenin	Exhibiting endocrine-disrupting activity and altering hormone signaling	Endocrine perturbation may affect hormonally sensitive organs (breast, ovaries, prostate, thyroid), potentially contributing to cancer-related processes	(27,28,154)
'Trojan horse' effect	*In vitro*: Human cell lines (lymphocytes, HepG2) *In vivo*: *Caenorhabditis elegans*, *Daphnia magna*, *Mytilus galloprovincialis*, *Tegillarca granosa*, *Danio rerio*, *Pomatoschistus microps*, rodents (C57BL/6), chicken	Sorption and transport of co-pollutants (carcinogens, toxic chemicals, microorganisms, etc.) Altered bioavailability of substances Pathways: Keap-1/ Nrf2, p53/Bcl-2/Bax, PERK/eIF2α/CHOP, apoptosis	Carriers for other substances associated with oxidative stress, ER stress, mitochondrial impairment, genotoxic effects, inflammation, and alterations in microbiota	Enhancement of intracellular delivery of co-transported substances, potentially enhancing their biological effects and contributing to cancer-related processes	(158-165,168, 169)

MNPLs, microplastics and nanoplastics; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Keap-1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; CAT, catalase; GSH, L-γ-glutamyl-L-cysteinyl glycine; ERKs, extracellular regulated kinases; JNKs, c-Jun N-terminal kinases; HIF1α, hypoxia inducible factor 1 subunit α; BAX, Bcl-2-associated X-protein; Bcl-2, B-cell lymphoma 2; γ-H2AX, phosphorylated histone H2AX; 8-oxodG, 8-hydroxy-2'-deoxyguanosine; YAP, yes-associated protein; PBMCs, peripheral blood mononuclear cells; IL, interleukin; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; TGF-β, transforming growth factor-β; NF-κB, nuclear factor κ-light-chain-enhancer of activated B-cells; TLR4, Toll-like receptor 4; STAT-5, signal transducer and activator of transcription-5; PKCθ, protein kinase Cθ; IL-2R, interleukin-2 receptor; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; NLRP3, NOD-like receptor protein 3; PERK, protein kinase RNA-like endoplasmic reticulum kinase; eIF2α, eukaryotic initiation factor 2α; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum.

Among the adverse effects associated with MNPLs are oxidative stress, DNA damage, inflammation, endocrine disruption and dysbiosis. These processes are interconnected, resulting in a broad spectrum of cellular responses. Moreover, MNPLs have been shown to influence critical pathways, including MAPK, Wnt/β-catenin and NF-κB, which are involved in the initiation and progression of cancer. Therefore, considerable concern has been raised regarding their potential to induce carcinogenesis. By integrating evidence from these mechanistic pathways, the present review emphasizes the multifactorial nature of the biological processes through which MNPLs may initiate or promote malignancy and highlights key knowledge gaps that need to be addressed. Given that evidence is derived from studies conducted using cell cultures and animal models, the actual impact of MNPLs on the complex human organism requires comprehensive and long-term research. Therefore, this issue warrants urgent and thorough investigation.

Finally, the term 'microplastome' has recently been proposed to describe the entire spectrum of plastic particles <5 mm in size, including all associated elements, such as absorbed chemicals, additives and microorganisms, as well as their environmental and toxicological impacts. This terminology provides a comprehensive perspective on their environmental behavior and biological effects, thereby aiming to advance our understanding of their impact on ecosystems (170).

Advancing in this discipline necessitates the pursuit of five interconnected strategies: i) Formalizing mechanistic evidence into a quantitative AON with cancer as the apical outcome; ii) parameterizing PBPK-QIVIVE pipelines for MNPL particulates to facilitate the translation of external-dose metrics into target tissue concentrations; iii) deploying NAM-based mixture testing that encompasses both the polymer matrix and the sorbed chemical and microbial cargo; iv) embedding hazard-informed SSbD principles into the plastics value chain to prevent regrettable substitutions; and v) evaluating MNPL exposure through a One Health, life-course perspective that recognizes the continuum between planetary, ecosystem and human health endpoints. The integration of germline susceptibility within this exposome framework, an 'exposogenomic' interpretation of cancer risk, presents a notably promising avenue for translational oncology (29,55,79,171).

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MAV and VZ conceptualized the study. MAV was involved in the literature search, the interpretation of data from the literature and visualization. MAV was also involved in the writing and preparation of the original draft of the manuscript. MAV, MA, PZ, DAS, DS and VZ were involved in the writing, reviewing and editing of the manuscript. VZ supervised the study. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief of the journal, but had no personal involvement in the review process, nor any influence in adjudicating the final decision for this article. The other authors declare that they have no competing interests.

References

1. Ramaswamy S, Kaveri V, Sutha V, Selvakumar D, Geethalakshmi N and Mohan SP: The Science Behind Plastics: Understanding Their Traits and Uses. Materials Science, Environmental Science, 2024.
2. Andrady AL and Neal MA: Applications and societal benefits of plastics. Philos Trans R Soc Lond B Biol Sci 364: 1977-1984, 2009.
3. Hosler D, Burkett SL and Tarkanian MJ: Prehistoric polymers: Rubber processing in ancient mesoamerica. Science 284: 1988-1991, 1999.
4. Pan Y, Janjua TI, Thomas KV, Shepherd CE and Rauert C: A critical review of micro- and nanoplastic permeation in the human body. Micropl.&Nanopl 6: 21, 2026.
5. Sharma MD, Elanjickal AI, Mankar JS and Krupadam RJ: Assessment of cancer risk of microplastics enriched with polycyclic aromatic hydrocarbons. J Hazard Mater 398: 122994, 2020.
6. Hartmann NB, Hüffer T, Thompson RC, Hassellöv M, Verschoor A, Daugaard AE, Rist S, Karlsson T, Brennholt N, Cole M, *et al*: Are we speaking the same language? Recommendations for a definition and categorization framework for plastic debris. Environ Sci Technol 53: 1039-1047, 2019.
7. Blackburn K and Green D: The potential effects of microplastics on human health: What is known and what is unknown. Ambio 51: 518-530, 2022.
8. Giri S, Lamichhane G, Pandey J and Khadka D: Micro(Nano) plastics in human carcinogenesis: Emerging evidence and mechanistic insights. Microplastics 4: 48, 2025.
9. Baj J, Dring JC, Czeczelewski M, Kozyra P, Forma A, Flieger J, Kowalska B, Buszewicz G and Teresiński G: Derivatives of plastics as potential carcinogenic factors: The current state of knowledge. Cancers (Basel) 14: 4637, 2022.
10. Peeken I, Primpke S, Beyer B, Gütermann J, Katlein C, Krumpen T, Bergmann M, Hehemann L and Gerdts G: Arctic sea ice is an important temporal sink and means of transport for microplastic. Nat Commun 9: 1505, 2018.
11. Waller CL, Griffiths HJ, Waluda CM, Thorpe SE, Loaiza I, Moreno B, Pacherres CO and Hughes KA: Microplastics in the Antarctic marine system: An emerging area of research. Sci Total Environ 598: 220-227, 2017.
12. Napper IE, Davies BFR, Clifford H, Elvin E, Koldewey HJ, Mayewski PA, Miner KR, Potocki M, Elmore AC, Gajurel AP, *et al*: Reaching New Heights in Plastic Pollution-Preliminary Findings of Microplastics on Mount Everest. One Earth 3: 621-630, 2020.
13. Jamieson AJ, Brooks LSR, Reid WDK, Piertney SB, Narayanaswamy BE and Linley TD: Microplastics and synthetic particles ingested by deep-sea amphipods in six of the deepest marine ecosystems on Earth. R Soc Open Sci 6: 180667, 2019.
14. Vethaak AD and Legler J: Microplastics and human health: Knowledge gaps should be addressed to ascertain the health risks of microplastics. Science (New York, N.Y.) 371: 672-674, 2021.
15. Chartres N, Cooper CB, Bland G, Pelch KE, Gandhi SA, BakenRa A and Woodruff TJ: Effects of microplastic exposure on human digestive, reproductive, and respiratory health: A rapid systematic review. Environ Sci Technol 58: 22843-22864, 2024.
16. Li Y, Tao L, Wang Q, Wang F, Li G and Song M: Potential health impact of microplastics: A review of environmental distribution, human exposure, and toxic effects. Environ Health (Wash) 1: 249-257, 2023.
17. Nivedita J, Megha P, Daisy PS, Sivachandran R, Ramprasath A, Rajkumar M and Anitha TS: Microplastics and cancer: A comprehensive review of their impact on tumor progression and mechanisms of carcinogenesis. J Environ Pathol Toxicol Oncol 44: 31-46, 2025.
18. Widjaja JT and Hanisia RH: Breathing plastics: Influence of airborne microplastics on the respiratory microbiome and health of human lungs (Review). World Acad Sci J 8: 1-10, 2026.
19. He Z, Shen Z, Zhang H, Na C and Bai C: From exposure to oncogenesis: A review on the multifaceted roles of microplastics in tumor initiation and progression. J Transl Med 24: 73, 2025.
20. Alaraby M, Abass D, Marcos R and Hernández A: Emerging evidence on micro- and nanoplastics carcinogenicity: Mechanisms, models, and signaling networks. Mol Cancer 25: 93, 2026.

21. Yee MS, Hii LW, Looi CK, Lim WM, Wong SF, Kok YY, Tan BK, Wong CY and Leong CO: Impact of microplastics and nanoplastics on human health. Nanomaterials (Basel) 11: 496, 2021.
22. Peters EN: 9 Thermoplastics, Thermosets, and Elastomers-Descriptions and Properties. In: Mechanical Engineers' Handbook. John Wiley & Sons, Inc., 2015.
23. Lewanska M and Barczynska R: Microplastics from food packaging: Polymer degradation pathways, environmental distribution, and effects on the human gastrointestinal tract. Polymers (Basel) 17: 2923, 2025.
24. Kudzin MH, Piwowarska D, Festinger N and Chruściel JJ: Risks associated with the presence of polyvinyl chloride in the environment and methods for its disposal and utilization. Materials (Basel) 17: 173, 2023.
25. Hahladakis JN, Velis CA, Weber R, Iacovidou E and Purnell P: An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling. J Hazard Mater 344: 179-199, 2018.
26. Mughees M, Chugh H and Wajid S: Mechanism of phthalate esters in the progression and development of breast cancer. Drug Chem Toxicol 45: 1021-1025, 2022.
27. Zhou X, Ye W, Xu J, Luo Q, Huang Y, Li J, Zhu Q and Liu G: The role of di-(2-ethylhexyl) phthalate in cancer initiation and progression: Mechanisms and health implications. Sci Total Environ 959: 178285, 2025.
28. Seachrist DD, Bonk KW, Ho SM, Prins GS, Soto AM and Keri RA: A review of the carcinogenic potential of bisphenol A. Reprod Toxicol 59: 167-182, 2016.
29. Caldeira C, Farcal R, Garmendia Aguirre I, Mancini L, Tosches D, Amelio A, Rasmussen K, Rauscher H, Riego Sintes J and Sala S: Safe and sustainable by design chemicals and materials-Framework for the definition of criteria and evaluation procedure for chemicals and materials. Office of the European Union, Luxembourg, 2022.
30. Rochester JR and Bolden AL: Bisphenol S and F: A systematic review and comparison of the hormonal activity of bisphenol a substitutes. Environ Health Perspect 123: 643-650, 2015.
31. Pant J, Agarwal R and Mohan L: Bisphenol S: A potential toxicant in daily use (Review). World Acad Sci J 5: 17, 2023.
32. Schmeisser S, Miccoli A, von Bergen M, Berggren E, Braeuning A, Busch W, Desaintes C, Gourmelon A, Grafström R, Harrill J, *et al*: New approach methodologies in human regulatory toxicology-Not if, but how and when! Environ Int 178: 108082, 2023.
33. Dzierżyński E, Gawlik PJ, Puźniak D, Flieger W, Jóźwik K, Teresiński G, Forma A, Wdowiak P, Baj J and Flieger J: Microplastics in the human body: Exposure, detection, and risk of carcinogenesis: A state-of-the-art review. Cancers (Basel) 16: 3703, 2024.
34. Kumar N, Lamba M, Pachar AK, Yadav S and Acharya A: Microplastics-A growing concern as carcinogens in cancer etiology: Emphasis on biochemical and molecular mechanisms. Cell Biochem Biophys 82: 3109-3121, 2024.
35. Zhou L, Ran L, He Y and Huang Y: Mechanisms of microplastics on gastrointestinal injury and liver metabolism disorder (Review). Mol Med Rep 31: 98, 2025.
36. Joseph MM, Nair JB and Joseph AM: Microscopic menace: Exploring the link between microplastics and cancer pathogenesis. Environ Sci Process Impacts 27: 1768-1795, 2025.
37. Cox KD, Covernton GA, Davies HL, Dower JF, Juanes F and Dudas SE: Human consumption of microplastics. Environ Sci Technol 53: 7068-7074, 2019.
38. Oliveri Conti G, Ferrante M, Banni M, Favara C, Nicolosi I, Cristaldi A, Fiore M and Zuccarello P: Micro- and nano-plastics in edible fruit and vegetables. The first diet risks assessment for the general population. Environ Res 187: 109677, 2020.
39. Su Y, Hu X, Tang H, Lu K, Li H, Liu S, Xing B and Ji R: Steam disinfection releases micro(nano)plastics from silicone-rubber baby teats as examined by optical photothermal infrared microspectroscopy. Nat Nanotechnol 17: 76-85, 2022.
40. Li D, Shi Y, Yang L, Xiao L, Kehoe DK, Gun'ko YK, Boland JJ and Wang JJ: Microplastic release from the degradation of polypropylene feeding bottles during infant formula preparation. Nat Food 1: 746-754, 2020.
41. Xu JL, Lin X, Wang JJ and Gowen AA: A review of potential human health impacts of micro- and nanoplastics exposure. Sci Total Environ 851 (Pt 1): 158111, 2022.
42. Hernandez LM, Xu EG, Larsson HCE, Tahara R, Maisuria VB and Tufenkji N: Plastic Teabags release billions of microparticles and nanoparticles into tea. Environ Sci Technol 53: 12300-12310, 2019.
43. Roslan NS, Lee YY, Ibrahim YS, Anuar ST, Yusof KMKK, Lai LA and Brentnall T: Detection of microplastics in human tissues and organs: A scoping review. J Glob Health 14: 04179, 2024.
44. Schwabl P, Koppel S, Konigshofer P, Bucsics T, Trauner M, Reiberger T and Liebmann B: Detection of various microplastics in human stool: A prospective case series. Ann Intern Med 171: 453-457, 2019.
45. Zhang N, Li Y Bin, He HR, Zhang JF and Ma GS: You are what you eat: Microplastics in the feces of young men living in Beijing. Sci Total Environ 767: 144345, 2021.
46. Wibowo AT, Nugrahapraja H, Wahyuono RA, Islami I, Haekal MH, Fardiansyah Y, Sugiyo PWW, Putro YK, Fauzia FN, Santoso H, *et al*: Microplastic contamination in the human gastrointestinal tract and daily consumables associated with an indonesian farming community. Sustainability 13: 12840, 2021.
47. Zhang J, Wang L, Trasande L and Kannan K: Occurrence of polyethylene terephthalate and polycarbonate microplastics in infant and adult feces. Environ Sci Technol Lett 8: 989-994, 2021.
48. Geng Y, Zhang Z, Zhou W, Shao X, Li Z and Zhou Y: Individual exposure to microplastics through the inhalation route: Comparison of microplastics in inhaled indoor aerosol and exhaled breath air. Environ Sci Technol Lett 10: 464-470, 2023.
49. Vianello A, Jensen RL, Liu L and Vollertsen J: Simulating human exposure to indoor airborne microplastics using a breathing thermal manikin. Sci Rep 9: 8670, 2019.
50. Pauly JL, Stegmeier SJ, Allaart HA, Cheney RT, Zhang PJ, Mayer AG and Streck RJ: Inhaled cellulosic and plastic fibers found in human lung tissue. Cancer Epidemiol Biomarkers Prev 7: 419-428, 1998.
51. Kentin E and Kaarto H: An EU ban on microplastics in cosmetic products and the right to regulate. RECIEL 27: 254-266, 2018.
52. Giustra M, Sinesi G, Spena F, De Santes B, Morelli L, Barbieri L, Garbujo S, Galli P, Prosperi D and Colombo M: Microplastics in cosmetics: Open questions and sustainable opportunities. ChemSusChem 17: e202401065, 2024.
53. Li Q, Yuan M, Chen Y, Jin X, Shangguan J, Cui J, Chang S, Guo M and Wang Y: The neglected potential source of microplastics from daily necessities: A study on protective mobile phone cases. J Hazard Mater 441: 129911, 2023.
54. Sarigiannis DA, Karakitsios S, Dominguez-Romero E, Papadaki K, Brochot C, Kumar V, Schuhmacher M, Sy M, Mielke H, Greiner M, *et al*: Physiology-based toxicokinetic modelling in the frame of the European human biomonitoring initiative. Environ Res 172: 216-230, 2019.
55. Wild CP: Complementing the genome with an 'exposome': The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 14: 1847-1850, 2005.
56. Ganzleben C, Antignac JP, Barouki R, Castaño A, Fiddicke U, Klánová J, Lebret E, Olea N, Sarigiannis D, Schoeters GR, *et al*: Human biomonitoring as a tool to support chemicals regulation in the European Union. Int J Hyg Environ Health 220 (2 Pt A): 94-97, 2017.
57. Marx-Stoelting P, Rivière G, Luijten M, Aiello-Holden K, Bandow N, Baken K, Cañas A, Castano A, Denys S, Fillol C, *et al*: A walk in the PARC: developing and implementing 21st century chemical risk assessment in Europe. Arch Toxicol 97: 893-908, 2023.
58. Banerjee A and Shelver WL: Micro- and nanoplastic induced cellular toxicity in mammals: A review. Sci Total Environ 755 (Pt 2): 142518, 2021.
59. Alimba CG, Faggio C, Sivanesan S, Ogunkanmi AL and Krishnamurthi K: Micro(nano)-plastics in the environment and risk of carcinogenesis: Insight into possible mechanisms. J Hazard Mater 416: 126143, 2021.
60. Mishra SK, Sanyal T, Kundu P, Kumar R, Ghosh D, Chakrabarti G, Sikdar N, Bhattacharya S, Paul S and Das A: Microplastics as emerging carcinogens: From environmental pollutants to oncogenic drivers. Mol Cancer 24: 248, 2025.
61. Liu L, Xu K, Zhang B, Ye Y, Zhang Q and Jiang W: Cellular internalization and release of polystyrene microplastics and nanoplastics. Sci Total Environ 779: 146523, 2021.
62. Brynzak-Schreiber E, Schögl E, Bapp C, Cseh K, Kopatz V, Jakupec MA, Weber A, Lange T, Toca-Herrera JL, Del Favero G, *et al*: Microplastics role in cell migration and distribution during cancer cell division. Chemosphere 353: 141463, 2024.
63. Kadac-Czapska K, Ośko J, Knez E and Grembecka M: Microplastics and oxidative stress-current problems and prospects. Antioxidants (Basel) 13: 579, 2024.

64. Tang KHD: Genotoxicity of microplastics on living organisms: Effects on chromosomes, DNA and gene expression. Environments 12: 10, 2025.
65. Cheng Y, Yang Y, Bai L and Cui J: Microplastics: An often-overlooked issue in the transition from chronic inflammation to cancer. J Transl Med 22: 959, 2024.
66. Zhao J, Zhang H, Shi L, Jia Y and Sheng H: Detection and quantification of microplastics in various types of human tumor tissues. Ecotoxicol Environ Saf 283: 116818, 2024.
67. Pan W, Hao J, Zhang M, Liu H, Tian F, Zhang X, Jiang Z, Chen C, Gao M and Zhang H: Identification and analysis of microplastics in peritumoral and tumor tissues of colorectal cancer. Sci Rep 15: 16130, 2025.
68. Cetin M, Demirkaya Miloglu F, Kilic Baygutalp N, Ceylan O, Yildirim S, Eser G and Gul Hİ: Higher number of microplastics in tumoral colon tissues from patients with colorectal adenocarcinoma. Environ Chem Lett 21: 639-646, 2023.
69. Chen L, Li J, Wu Y, Bao H, Yang X, Lv G, Ji K, Zhang J, Wu X, Zhou K, *et al*: Characterization of microplastics in human gastric cancer and control tissues and analysis of associated genetic features. Adv Healthc Mater 15: e04291, 2025.
70. Deng C, Zhu J, Fang Z, Yang Y, Zhao Q, Zhang Z, Jin Z and Jiang H: Identification and analysis of microplastics in para-tumor and tumor of human prostate. EBioMedicine 108: 105360, 2024.
71. Sun B, Liu J, Wen X, Hu D, Gao Z, Qiu M, Wang S, Jiang Z, Zhang M, Chen C, *et al*: Differential distribution of microplastics in breast cancer and peritumoral tissues and relationship with clinical characteristics. Apoptosis 31: 166, 2026.
72. Xu H, Dong C, Xiang T, Shentu X, Yu Z, Xu J, Yu J, Ma D and Xie Y: Microplastic changes during the development of cervical cancer and its effects on the metabolomic profiles of cancer tissues. J Hazard Mater 483, 2025.
73. Thube HR, Deokar RB and Parekh U: Analytical trends and pathogenesis of microplastics in human cancer tissues: A toxicology mini-review. Journal of Indian Academy of Forensic Medicine 48: 211-214, 2025.
74. Verma SK, Mishra S, Simnani FZ, Sinha A, Kaushik A, Ghosh A and Mishra YK: Insights to cellular and molecular impacts of micro/nanoplastics and their additives for carcinogenic risks. Results Chem 26: 2211-7156, 2026.
75. Casella C, Dondi D and Vadivel D: Do microplastics (MPs) and nanoplastics (NPs) directly contribute to human carcinogenesis? Environ Pollut 388: 127343, 2026.
76. Bailey AM and Hofseth LJ: Microplastics in early onset carcinogenesis. Carcinogenesis 47: bgaf093, 2026.
77. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
78. Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, *et al*: Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29: 730-741, 2010.
79. Spinu N, Cronin MTD, Enoch SJ, Madden JC and Worth AP: Quantitative adverse outcome pathway (qAOP) models for toxicity prediction. Arch Toxicol 94: 1497-1510, 2020.
80. Zhang Y, Du Y, Le W, Wang K, Kieffer N and Zhang J: Redox control of the survival of healthy and diseased cells. Antioxid Redox Signal 15: 2867-2902, 2011.
81. Iqbal MJ, Kabeer A, Abbas Z, Siddiqui HA, Calina D, Sharifi-Rad J and Cho WC: Interplay of oxidative stress, cellular communication and signaling pathways in cancer. Cell Commun Signal 22: 7, 2024.
82. Qiao R, Sheng C, Lu Y, Zhang Y, Ren H and Lemos B: Microplastics induce intestinal inflammation, oxidative stress, and disorders of metabolome and microbiome in zebrafish. Sci Total Environ 662: 246-253, 2019.
83. Zou H, Qu H, Bian Y, Sun J, Wang T, Ma Y, Yuan Y, Gu J, Bian J and Liu Z: Polystyrene microplastics induce oxidative stress in mouse hepatocytes in relation to their size. Int J Mol Sci 24: 7382, 2023.
84. Lei L, Liu M, Song Y, Lu S, Hu J, Cao C, Xie B, Shi H and He D: Polystyrene (nano)microplastics cause size-dependent neurotoxicity, oxidative damage and other adverse effects in Caenorhabditis elegans. Environ Sci Nano 5: 2009-2020, 2018.
85. Vecchiotti G, Colafarina S, Aloisi M, Zarivi O, Di Carlo P and Poma A: Genotoxicity and oxidative stress induction by polystyrene nanoparticles in the colorectal cancer cell line HCT116. PLoS One 16: e0255120, 2021.
86. He Y, Li J, Chen J, Miao X, Li G, He Q, Xu H, Li H and Wei Y: Cytotoxic effects of polystyrene nanoplastics with different surface functionalization on human HepG2 cells. Sci Total Environ 723: 138180, 2020.
87. Wang X, Ren X, Hu H, Zhang P, Zhao F, Zhang L, He H, Huang B and Pan X: Micro- and Nano-Polystyrene Plastic Particles Induce Apoptosis Through the Production of Intracellular ROS on CT26.WT Cells. SSRN Electronic Journal, 2022.
88. Shi X, Wang X, Huang R, Tang C, Hu C, Ning P and Wang F: Cytotoxicity and genotoxicity of polystyrene micro- and nanoplastics with different size and surface modification in A549 cells. Int J Nanomedicine 17: 4509-4523, 2022.
89. Płuciennik K, Sicińska P, Misztal W and Bukowska B: Important factors affecting induction of cell death, oxidative stress and DNA damage by nano- and microplastic particles in vitro. Cells 13: 768, 2024.
90. Li X, Huang Y, Li W, Deng C, Cao W and Yao Y: Effects of polystyrene microplastic exposure on liver cell damage, oxidative stress, and gene expression in juvenile crucian carp (Carassius auratus). Toxics 13: 53, 2025.
91. Lu Y, Zhang Y, Deng Y, Jiang W, Zhao Y, Geng J, Ding L and Ren H: Uptake and accumulation of polystyrene microplastics in zebrafish (Danio rerio) and toxic effects in liver. Environ Sci Technol 50: 4054-4060, 2016.
92. Kang HM, Byeon E, Jeong H, Kim MS, Chen Q and Lee JS: Different effects of nano- and microplastics on oxidative status and gut microbiota in the marine medaka Oryzias melastigma. J Hazard Mater 405: 124207, 2021.
93. Song M, Wei Z, Wang J, Li L, Li X, Ma X, Pozzolini M, Liu X, Xiao L and Zhong P: Polystyrene nanoplastics induce oxidative stress in Aurelia coerulea polyps, microglia, and mice. Front Immunol 16: 1609208, 2025.
94. McCubrey JA, LaHair MM and Franklin RA: Reactive oxygen species-induced activation of the MAP kinase signaling pathways. Antioxid Redox Signal 8: 1775-1789, 2006.
95. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG and Pae HO: Mitogen-activated protein kinases and reactive oxygen species: How can ROS activate MAPK pathways? J Signal Transduct 2011: 792639, 2011.
96. Kadasah SF: Targeting the MAPK pathway in cancer. Int J Mol Sci 27: 214, 2025.
97. Jeong CB, Kang HM, Lee MC, Kim DH, Han J, Hwang DS, Souissi S, Lee SJ, Shin KH, Park HG and Lee JS: Adverse effects of microplastics and oxidative stress-induced MAPK/Nrf2 pathway-mediated defense mechanisms in the marine copepod Paracyclopina nana. Sci Rep 7: 41323, 2017.
98. Jeong CB, Won EJ, Kang HM, Lee MC, Hwang DS, Hwang UK, Zhou B, Souissi S, Lee SJ and Lee JS: Microplastic size-dependent toxicity, oxidative stress induction, and p-JNK and p-p38 activation in the monogonont rotifer (Brachionus koreanus). Environ Sci Technol 50: 8849-8857, 2016.
99. Liu Z, Huang Y, Jiao Y, Chen Q, Wu D, Yu P, Li Y, Cai M and Zhao Y: Polystyrene nanoplastic induces ROS production and affects the MAPK-HIF-1/NFkB-mediated antioxidant system in Daphnia pulex. Aquat Toxicol 220: 105420, 2020.
100. Xie X, Deng T, Duan J, Xie J, Yuan J and Chen M: Exposure to polystyrene microplastics causes reproductive toxicity through oxidative stress and activation of the p38 MAPK signaling pathway. Ecotoxicol Environ Saf 190: 110133, 2020.
101. Shanmugiah J, Kim S, Jeong H, Kong J, Lee SS, Kang DK and Kim JS: Size-dependent pulmonary toxicity of inhaled micro- and nano-polystyrene and initial identification of microplastics in human lung cancer tissue. J Hazard Mater 508: 141897, 2026.
102. Zhan T, Rindtorff N and Boutros M: Wnt signaling in cancer. Oncogene 36: 1461-1473, 2016.
103. Liang J, Pan Y, Yang J, Zeng D and Li J: WNT signaling in cancer: Molecular mechanisms and potential therapies. Mol Biomed 6: 83, 2025.
104. Schmidt A, da Silva Brito WA, Singer D, Mühl M, Berner J, Saadati F, Wolff C, Miebach L, Wende K and Bekeschus S: Short- and long-term polystyrene nano- and microplastic exposure promotes oxidative stress and divergently affects skin cell architecture and Wnt/beta-catenin signaling. Part Fibre Toxicol 20: 3, 2023.
105. Ding R, Chen Y, Shi X, Li Y, Yu Y, Sun Z and Duan J: Size-dependent toxicity of polystyrene microplastics on the gastrointestinal tract: Oxidative stress related-DNA damage and potential carcinogenicity. Sci Total Environ 912: 169514, 2024.

106. Calses PC, Crawford JJ, Lill JR and Dey A: Hippo pathway in cancer: Aberrant regulation and therapeutic opportunities. Trends Cancer 5: 297-307, 2019.
107. Harvey KF, Zhang X and Thomas DM: The Hippo pathway and human cancer. Nat Rev Cancer 13: 246-257, 2013.
108. Kim M and Jho EH: Cross-talk between Wnt/β-catenin and Hippo signaling pathways: A brief review. BMB Rep 47: 540-545, 2014.
109. Ding P, Xiang C, Yao Q, Li X, Zhang J, Yin R, Zhang L, Li AJ and Hu G: Aged polystyrene microplastics exposure affects apoptosis via inducing mitochondrial dysfunction and oxidative stress in early life of zebrafish. J Environ Manage 367: 121995, 2024.
110. Moon J, Kitty I, Renata K, Qin S, Zhao F and Kim W: DNA damage and its role in cancer therapeutics. Int J Mol Sci 24: 4741, 2023.
111. Rubio L, Barguilla I, Domenech J, Marcos R and Hernández A: Biological effects, including oxidative stress and genotoxic damage, of polystyrene nanoparticles in different human hematopoietic cell lines. J Hazard Mater 398: 122900, 2020.
112. Malinowska K, Bukowska B, Piwoński I, Foksiński M, Kisielewska A, Zarakowska E, Gackowski D and Sicińska P: Polystyrene nanoparticles: The mechanism of their genotoxicity in human peripheral blood mononuclear cells. Nanotoxicology 16: 791-811, 2022.
113. Xue Z, Cheng S, Liu X, Zhang Y, Huang Y, Du S, Chen X, Zhang Z, Yang X, Xu M and Huang J: Evaluation of intestinal toxicity of polystyrene micro/nanoplastics using intestinal organoids. Chem Biol Interact 432: 112060, 2026.
114. Poma A, Vecchiotti G, Colafarina S, Zarivi O, Aloisi M, Arrizza L, Chichiriccò G and Di Carlo P: In vitro genotoxicity of polystyrene nanoparticles on the human fibroblast Hs27 cell line. Nanomaterials (Basel) 9: 1299, 2019.
115. Karlsson HL, Nilsson L and Möller L: Subway particles are more genotoxic than street particles and induce oxidative stress in cultured human lung cells. Chem Res Toxicol 18: 19-23, 2005.
116. Berber AA, Akinci Kenanoğlu N, Nur Demi`r R Ş and Aksoy H: Genotoxic and cytotoxic effects of polystyrene nanoplastics on human lymphocytes: A comprehensive analysis. Mutat Res Genet Toxicol Environ Mutagen 902: 503850, 2025.
117. Çobanoğlu H, Belivermiş M, Sıkdokur E, Kılıç Ö and Çayır A: Genotoxic and cytotoxic effects of polyethylene microplastics on human peripheral blood lymphocytes. Chemosphere 272: 129805, 2021.
118. Ribeiro F, Garcia AR, Pereira BP, Fonseca M, Mestre NC, Fonseca TG, Ilharco LM and Bebianno MJ: Microplastics effects in Scrobicularia plana. Mar Pollut Bull 122: 379-391, 2017.
119. Sun T, Zhan J, Li F, Ji C and Wu H: Evidence-based meta-analysis of the genotoxicity induced by microplastics in aquatic organisms at environmentally relevant concentrations. Sci Total Environ 783: 147076, 2021.
120. Hamed M, Soliman HAM, Osman AGM and Sayed AEH: Antioxidants and molecular damage in Nile Tilapia (Oreochromis niloticus) after exposure to microplastics. Environ Sci Pollut Res Int 27: 14581-14588, 2020.
121. Sampsonidis I, Michailidou K, Spritinoudi K, Dimitriadi A, Ainali NM, Bobori DC, Lambropoulou DA, Kyzas GZ, Bikiaris DN and Kalogiannis S: Genotoxicity and metabolic changes induced via ingestion of virgin and UV-aged polyethylene microplastics by the freshwater fish Perca fluviatilis. Chemosphere 362: 142619, 2024.
122. Mai NTQ, Batjargal U, Kim WS, Kim JH, Park JW, Kwak IS and Moon BS: Microplastic induces mitochondrial pathway mediated cellular apoptosis in mussel (Mytilus galloprovincialis) via inhibition of the AKT and ERK signaling pathway. Cell Death Discov 9: 442, 2023.
123. Hesler M, Aengenheister L, Ellinger B, Drexel R, Straskraba S, Jost C, Wagner S, Meier F, von Briesen H, Büchel C, *et al*: Multi-endpoint toxicological assessment of polystyrene nano- and microparticles in different biological models in vitro. Toxicol In Vitro 61: 104610, 2019.
124. Liu Y, Li W, Lao F, Liu Y, Wang L, Bai R, Zhao Y and Chen C: Intracellular dynamics of cationic and anionic polystyrene nanoparticles without direct interaction with mitotic spindle and chromosomes. Biomaterials 32: 8291-8303, 2011.
125. Yang W, Jannatun N, Zeng Y, Liu T, Zhang G, Chen C and Li Y: Impacts of microplastics on immunity. Front Toxicol 4: 956885, 2022.
126. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y and Li Y: Inflammation and tumor progression: Signaling pathways and targeted intervention. Signal Transduct Target Ther 6: 263, 2021.
127. Nishida A and Andoh A: The role of inflammation in cancer: Mechanisms of tumor initiation, progression, and metastasis. Cells 14: 488, 2025.
128. Greten FR and Grivennikov SI: Inflammation and cancer: Triggers, mechanisms and consequences. Immunity 51: 27-41, 2019.
129. Chen Y, Zhang Z, Ji K, Zhang Q, Qian L and Yang C: Role of microplastics in the tumor microenvironment (Review). Oncol Lett 29: 193, 2025.
130. Hwang J, Choi D, Han S, Choi J and Hong J: An assessment of the toxicity of polypropylene microplastics in human derived cells. Sci Total Environ 684: 657-669, 2019.
131. Han S, Bang J, Choi D, Hwang J, Kim T, Oh Y, Hwang Y, Choi J and Hong J: Surface pattern analysis of microplastics and their impact on human-derived cells. ACS Appl Polym Mater 2: 4541-4550, 2020.
132. Jin Y, Xia J, Pan Z, Yang J, Wang W and Fu Z: Polystyrene microplastics induce microbiota dysbiosis and inflammation in the gut of adult zebrafish. Environ Pollut 235: 322-329, 2018.
133. Huang JN, Wen B, Zhu JG, Zhang YS, Gao JZ and Chen ZZ: Exposure to microplastics impairs digestive performance, stimulates immune response and induces microbiota dysbiosis in the gut of juvenile guppy (Poecilia reticulata). Sci Total Environ 733: 138929, 2020.
134. Gaspar L, Bartman S, Coppotelli G and Ross JM: Acute exposure to microplastics induced changes in behavior and inflammation in young and old mice. Int J Mol Sci 24: 12308, 2023.
135. Stock V, Böhmert L, Lisicki E, Block R, Cara-Carmona J, Pack LK, Selb R, Lichtenstein D, Voss L, Henderson CJ, *et al*: Uptake and effects of orally ingested polystyrene microplastic particles in vitro and in vivo. Arch Toxicol 93: 1817-1833, 2019.
136. Li Y, Xu M, Zhang Z, Halimu G, Li Y, Li Y, Gu W, Zhang B and Wang X: In vitro study on the toxicity of nanoplastics with different charges to murine splenic lymphocytes. J Hazard Mater 424 (Pt B): 127508, 2022.
137. Shen R, Yang K, Cheng X, Guo C, Xing X, Sun H, Liu D, Liu X and Wang D: Accumulation of polystyrene microplastics induces liver fibrosis by activating cGAS/STING pathway. Environ Pollut 300: 118986, 2022.
138. Ye S, Xiang J, Zhou S, Ge Q, Anwaier A, Chang K, Wei G, Lu J, Tian X, Zhu S, *et al*: Polystyrene microplastics exposure aggravates clear cell renal cell carcinoma progression via the NF-κB and TGF-β signaling pathways. Adv Sci (Weinh) 13: e18500, 2026.
139. Wang Y, Xu X and Jiang G: Microplastics exposure promotes the proliferation of skin cancer cells but inhibits the growth of normal skin cells by regulating the inflammatory process. Ecotoxicol Environ Saf 267: 115636, 2023.
140. Hou J, Lei Z, Cui L, Hou Y, Yang L, An R, Wang Q, Li S, Zhang H and Zhang L: Polystyrene microplastics lead to pyroptosis and apoptosis of ovarian granulosa cells via NLRP3/Caspase-1 signaling pathway in rats. Ecotoxicol Environ Saf 212: 112012, 2021.
141. Wei J, Wang X, Liu Q, Zhou N, Zhu S, Li Z, Li X, Yao J and Zhang L: The impact of polystyrene microplastics on cardiomyocytes pyroptosis through NLRP3/Caspase-1 signaling pathway and oxidative stress in Wistar rats. Environ Toxicol 36: 935-944, 2021.
142. Mu Y, Sun J, Li Z, Zhang W, Liu Z, Li C, Peng C, Cui G, Shao H and Du Z: Activation of pyroptosis and ferroptosis is involved in the hepatotoxicity induced by polystyrene microplastics in mice. Chemosphere 291 (Pt 2): 132944, 2022.
143. Cullin N, Azevedo Antunes C, Straussman R, Stein-Thoeringer CK and Elinav E: Microbiome and cancer. Cancer Cell 39: 1317-1341, 2021.
144. Whisner CM and Athena Aktipis C: The role of the microbiome in cancer initiation and progression: How microbes and cancer cells utilize excess energy and promote one another's growth. Curr Nutr Rep 8: 42-51, 2019.
145. Yao Y, Zhu Y, Chen K, Chen J, Li Y, Li D and Wei P: Microbiota in cancer: Current understandings and future perspectives. Signal Transduct Target Ther 11: 39, 2026.
146. Lei L, Wu S, Lu S, Liu M, Song Y, Fu Z, Shi H, Raley-Susman KM and He D: Microplastic particles cause intestinal damage and other adverse effects in zebrafish Danio rerio and nematode Caenorhabditis elegans. Sci Total Environ 619-620: 1-8, 2018.

147. Liu Z, Yu P, Cai M, Wu D, Zhang M, Chen M and Zhao Y: Effects of microplastics on the innate immunity and intestinal microflora of juvenile Eriocheir sinensis. Sci Total Environ 685: 836-846, 2019.
148. An J, Kwon H and Kim YJ: The firmicutes/bacteroidetes ratio as a risk factor of breast cancer. J Clin Med 12: 2216, 2023.
149. Lu L, Wan Z, Luo T, Fu Z and Jin Y: Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. Sci Total Environ 631-632: 449-458, 2018.
150. Jin Y, Lu L, Tu W, Luo T and Fu Z: Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Sci Total Environ 649: 308-317, 2019.
151. Li B, Ding Y, Cheng X, Sheng D, Xu Z, Rong Q, Wu Y, Zhao H, Ji X and Zhang Y: Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. Chemosphere 244: 125492, 2020.
152. Peng D, Liu X, Wang L, Pan Y, Kang B, Liu X, Xu R and Cheng Y: A multi-omics signature of microplastic exposure and its clinical, metabolic, and microbial correlates in colorectal cancer. Environ Pollut 405: 128426, 2026.
153. Deng X, Gui Y and Zhao L: The micro(nano)plastics perspective: Exploring cancer development and therapy. Mol Cancer 24: 30, 2025.
154. Murata M and Kang JH: Bisphenol A (BPA) and cell signaling pathways. Biotechnol Adv 36: 311-327, 2018.
155. P SP and Tanushree P: Synergistic human health risks of microplastics and co-contaminants: A quantitative risk assessment in water. J Hazard Mater 491: 137809, 2025.
156. Lee H, Shim WJ and Kwon JH: Sorption capacity of plastic debris for hydrophobic organic chemicals. Sci Total Environ 470-471: 1545-1552, 2014.
157. Bakir A, Rowland SJ and Thompson RC: Competitive sorption of persistent organic pollutants onto microplastics in the marine environment. Mar Pollut Bull 64: 2782-2789, 2012.
158. Avio CG, Gorbi S, Milan M, Benedetti M, Fattorini D, d'Errico G, Pauletto M, Bargelloni L and Regoli F: Pollutants bioavailability and toxicological risk from microplastics to marine mussels. Environ Pollut 198: 211-222, 2015.
159. Oliveira M, Ribeiro A, Hylland K and Guilhermino L: Single and combined effects of microplastics and pyrene on juveniles (0+ group) of the common goby Pomatoschistus microps (Teleostei, Gobiidae). Ecol Indic 34: 641-647, 2013.
160. Rainieri S, Conlledo N, Larsen BK, Granby K and Barranco A: Combined effects of microplastics and chemical contaminants on the organ toxicity of zebrafish (Danio rerio). Environ Res 162: 135-143, 2018.
161. Tang Y, Rong J, Guan X, Zha S, Shi W, Han Y, Du X, Wu F, Huang W and Liu G: Immunotoxicity of microplastics and two persistent organic pollutants alone or in combination to a bivalve species. Environ Pollut 258: 113845, 2020.
162. Ren H, Yin K, Lu X, Liu J, Li D, Liu Z, Zhou H, Xu S and Li H: Synergy between nanoplastics and benzo[a]pyrene promotes senescence by aggravating ferroptosis and impairing mitochondria integrity in Caenorhabditis elegans. Sci Total Environ 946: 174418, 2024.
163. Soltanighias T, Umar A, Abdullahi M, Abdallah MA and Orsini L: Combined toxicity of perfluoroalkyl substances and microplastics on the sentinel species Daphnia magna: Implications for freshwater ecosystems. Environ Pollut 363 (Pt 1): 125133, 2024.
164. Santovito A, Lambertini M and Nota A: In vitro and in vivo genotoxicity of polystyrene microplastics: evaluation of a possible synergistic action with bisphenol A. J Xenobiot 14: 1415-1431, 2024.
165. Huang W, Yang Y, Tang S, Yin H, Yu X, Yu Y and Wei K: The combined toxicity of polystyrene nano/micro-plastics and triphenyl phosphate (TPHP) on HepG2 cells. Ecotoxicol Environ Saf 279: 116489, 2024.
166. Li H, Yang Z, Liu Y, Sun P, Wu B and Chen L: Combined effects of polyvinyl chloride or polypropylene microplastics with cadmium on the intestine of zebrafish at environmentally relevant concentrations. Sci Total Environ 954: 176289, 2024.
167. Sheng S, Han N, Wei Y, Wang J, Han W, Xing B, Xing M and Zhang W: Liver injury induced by exposure to polystyrene microplastics alone or in combination with cadmium in mice is mediated by oxidative stress and apoptosis. Biol Trace Elem Res 202: 2170-2183, 2024.
168. Feng Y, Yuan H, Wang W, Xu Y, Zhang J, Xu H and Fu F: Co-exposure to polystyrene microplastics and lead aggravated ovarian toxicity in female mice via the PERK/eIF2alpha signaling pathway. Ecotoxicol Environ Saf 243: 113966, 2022.
169. Chatman CC, Olson EG, Freedman AJ, Dittoe DK, Ricke SC and Majumder EL-W: Co-exposure to polyethylene fiber and Salmonella enterica serovar Typhimurium alters microbiome and metabolome of in vitro chicken cecal mesocosms. Appl Environ Microbiol 90: e0091524, 2024.
170. Li C, Li X, Bank MS, Dong T, Fang JK, Leusch FDL, Rillig MC, Wang J, Wang L, Xia Y, *et al*: The 'Microplastome'-A holistic perspective to capture the real-world ecology of microplastics. Environ Sci Technol 58: 4060-4069, 2024.
171. Duarte SAC, Pinto-Leite R and Queiroga FL: A one health perspective on cancer: A narrative review. Med Sci (Basel) 14: 221, 2026.

Copyright © 2026 Vasilopoulou et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.