Biochimie 246 (2026) 54–75

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Nanoplastic-driven white pollution: Biochemical insights into ecosystem and human health impacts - a critical-interpretative narrative review

Matheus Naia Fioretto *, Natália Magosso, Patrick Vieira de Souza, Mirella Franco Moreira, Vanessa Aguiar Rocha, Victória Cristina Pinha, Vinicius Luís Rocha da Silva Maria, Luis Antonio Justulin, Wellerson Rodrigo Scarano

Department of Structural and Functional Biology, Institute of Biosciences, Sao Paulo State University, Botucatu, SP, Brazil

ARTICLE INFO

Article history:
Received 23 January 2026
Received in revised form
4 March 2026
Accepted 3 April 2026
Available online 6 April 2026

Keywords:
Biochemistry
Ecosystems
Environment
Metabolism
Nanoplastics
Organs and systems

ABSTRACT

Plastic production has become a global challenge, and its accelerated growth and widespread waste release justify the characterization of the current era as the "Age of Plastic". The concern is how additives or plastic degradation can impact different ecosystems and human health. Microplastics and certain plastic additives (e.g., phthalates) are already well-established in the literature as endocrine disruptors, posing a risk to human health. However, little is known about these issues regarding Nanoplastics (NPs). Therefore, this narrative review aimed to examine the potential biochemical disruptions induced by NPs across multiple organs and biological systems, while also considering their ecological, ecosystem-level, and human health risks. The NPs affect mitochondria and endoplasmic reticulum in experimental models and across various organs, affecting lipid, energy, and amino acid metabolism. In the environmental context, NPs can interfere with xylem/phloem transport, root absorptive function, and photosynthesis in both terrestrial and aquatic models. This raises concerns not only at the ecological levels, but also for production and the economy, with potential risks to human health through food. This review strengthens the understanding of environmental toxicology and the imminent risks of NPs on various ecosystems, highlighting the disruptions of these nanomolecules, whether isolated or adsorbed, to important catalytic pathways and metabolic pathways in an organ-wide manner.

Contents

* Corresponding author. Sao Paulo State University (UNESP), Institute of Biosciences of Botucatu, SP, 18618-689, Brazil.
E-mail address: matheus.fioretto@unesp.br (M.N. Fioretto).

https://doi.org/10.1016/j.biochi.2026.04.001

1. Introduction

Plastic pollution - white pollution - is an alarming and exponential problem that poses a potential immediate and long-term risk to ecosystems and human health. Global data and concern about microplastics (MPs) and nanoplastics (NPs) are growing, but proven evidence of their health consequences remains insufficient [1]. Every year, 19 to 23 million tons of plastic waste leak into aquatic ecosystems, polluting lakes, rivers, and seas. Plastic pollution can alter habitats and natural processes, reducing the ability of ecosystems to adapt to climate change, directly affecting livelihoods, food production capacity, and the social well-being of millions of people. Therefore, the environmental, social, economic, and health risks of plastics need to be assessed alongside other environmental stressors, such as climate change, ecosystem degradation, and resource use [2].

The plastics era exists; it is a reality and likely to involve multiple variables that are still unknown to the environment, human, and planetary health. Given their global abundance and environmental persistence, the exposure of humans and aquatic animals to MPs and NPs is inevitable. Current evidence indicates that MPs and NPs can be absorbed by aquatic organisms as well as mammals [3]. Micro- and nanoplastics (MNPs) are fragments derived from the physical, chemical, or biological degradation of plastics and are a major source of marine and terrestrial white pollution [4]. In a historical-industrial context, synthetic polymers emerged in the late 19th century, and after World War II, plastics were massively used, benefiting global economic growth. However, plastic currently poses a significant threat, being the main source of marine and terrestrial pollution [4–7]. This threat is compounded by secondary byproducts resulting from the fragmentation and leaching of plastic items, which have been detected in various ecosystems for over 50 years, leading researchers to call the current era "*Plasticene*" or "*The Plastic Age*" [8,9].

From a physicochemical perspective, plastic fragments are classified by size as megaplastics (>50 cm), macroplastics (5–50 cm), mesoplastics (0.5–5 cm), MPs (<0.5 mm), and NPs (<100 nm). According to the literature, the smaller the size of the waste, the greater its potential for dissemination and bioaccumulation [10]. These pollutants are mainly composed of synthetic polymers such as polystyrene (PS), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and polyvinyl chloride (PVC) [11]. From a general point of view, several studies have demonstrated the extensive mobility of MPs and NPs in external [12,13] and domestic [14,15] environments, and they have been identified in human lung samples [16,17], placenta [18], and breast milk [19]. It is essential to note, therefore, that MPs have garnered considerable attention in the scientific community; however, their smaller counterparts – NPs – still require thorough study.

As a starting point, pregnant mice exposed to MPs (5 μM - 102 ng/L, 104 ng/L, 106 ng/L) demonstrated, from the metabolomic profile, a decrease in the concentration of placental lysine and glucose, highlighting disturbances in biotin metabolism, glycolysis, and gluconeogenesis [20]. Studies like this are of paramount importance for elucidating the potential of MNPs to cross the placental barrier and lead to metabolic impacts not only on mothers, but also on the embryo/fetus and even on the postnatal life of offspring. The decrease in placental lysine and glucose will certainly impair the capacity of fetal energy metabolism, causing anabolic disorders that can impair not only development, but also increase the chances of malformations. Furthermore, this is an example of the various studies on MPs, which have been gaining a broad understanding of their impacts. However, although intuitively these MPs degrade into smaller particles (NPs) and have greater potential for bioaccumulation and bioavailability, we know little about the impacts of these nanoparticles.

In this context, MPs and NPs are capable of adsorbing various environmental chemicals, such as phthalates, classified as EDCs (Endocrine Disrupting Chemicals) [21,22], increasing their bioavailability and toxicity. In all these scenarios, it is quite plausible to consider adverse effects on key organelles involved in biochemical responses, leading to metabolic, systemic, and organ-specific disturbances. Furthermore, the literature has established the effects of phthalates and MPs on health, disease, and environmental contexts; however, few studies evaluate the direct association of NPs with these scenarios. Therefore, the objective of this narrative review was to provide a comprehensive and integrative overview of the biochemical effects of NPs across biological systems. Specifically, we synthesize *in vitro* and *in vivo* preclinical evidence to contextualize potential implications for human health, while also examining findings from terrestrial and aquatic models to address broader ecological and ecosystem-level consequences. By bridging mechanistic toxicology with environmental impact, this review aims to outline the systemic and cross-species biochemical perturbations associated with NP exposure and their broader biological derivations.

2. Review methodology

2.1. General protocol and search strategy

This critical and interpretative narrative review sought its literary basis on the PubMed platform (https://pubmed.ncbi.nlm.nih.gov), including only studies published in English.

The following search terms were applied in different combinations using the Boolean operator "AND": *Biochemistry and Nanoplastics*; *Nanoplastics and Mitochondria*; *Nanoplastics and Amino acids Metabolism*; *Nanoplastics and Carbohydrates Metabolism*; and *Nanoplastics and Lipid Metabolism* (Fig. 1).

2.2. Eligibility and study selection criteria

For our eligibility and study selection criteria, we did not apply time restrictions. All previously selected manuscripts were exported to tables in Microsoft Excel and organized according to study type. Eligible studies were considered when: (1) they traced some effect of NPs on biochemical aspects and (2) they had consequences in different cells, tissues, and organs in experimental or epidemiological models, or (3) they had consequences that stipulated ecological/environmental contexts.

The exclusion criteria included: (1) Meta-analyses, preprints, retractions, review articles, scientific integrity assessments, non-peer-reviewed reports, and comparative studies, (2) Articles that investigated only the effects of MPs without characterizing NPs, (3) Studies that did not evaluate specific impacts on metabolites and/or biochemical mechanisms/routes, (4) and manuscripts associated with methodologies not applicable in a physicochemical context. In all, we found 113 manuscripts, using 76 and excluding 37 (Fig. 1).

2.3. Data extraction and analysis

Data extraction and organization were performed by MNF and subsequently reviewed and validated by all co-authors. All information was compiled into standardized spreadsheets (Microsoft Excel) to ensure methodological consistency, transparency, and independent evaluation of each manuscript by the research team. After independent screening, eligibility decisions were collectively discussed by all authors, with final inclusion determined by consensus. Any discrepancies were resolved through structured discussion among all co-authors.

It is important to emphasize that we chose not to use the PRISMA protocol in this review because the central objective is to provide a critical-interpretive narrative, elucidating the main results in this context while also offering future perspectives, possible associated dysregulated biochemical mechanisms, and identifying important gaps that still exist in the literature when we focus on the NPs-biochemistry context. It is important to emphasize that narrative reviews allow for a more comprehensive and interpretive analysis of the literature, especially when there is insufficient methodological uniformity among studies to allow for a more quantitative analysis [23] - which centralizes our core objective - a broad context of different ecosystems and potential impacts on animal and human health. Therefore, we sought to develop a clear, critical, and logical understanding of the biochemical environmental toxicology of NPs, to build a broad and integrative view of the mechanisms already observed, rather than answering a single well-defined question, as required by PRISMA-based systematic reviews [24]. Although they present less systematic aspects, narrative reviews also rely on rigorous and transparent methods to ensure the reliability of the results [24], being a different and potentially complementary scientific way of presenting what is within the literature [25,26].

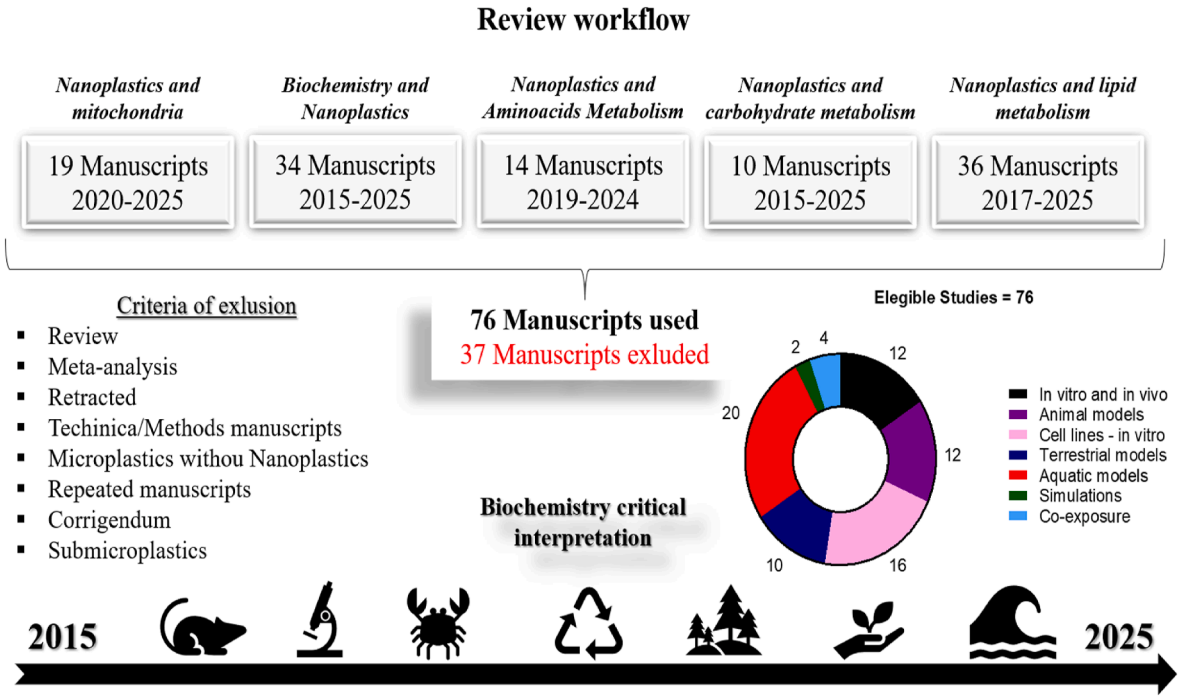

Fig. 1. Flowchart illustrating the study selection process, detailing the criteria and sequential steps used for manuscript identification, screening, eligibility assessment, and final inclusion.

3. Systemic aspects - metabolism, preclinical, and clinical insights in several organs and systems

3.1. Neuroendocrine aspects

Given the likelihood of NPs bioaccumulating in regions of the central nervous system and endocrine glands, investigating neuroendocrine aspects is essential to establish integrative links between organ-specific and systemic responses. This is particularly relevant as NPs can adsorb EDCs, thereby altering hormonal and neurotransmitter synthesis, receptor interactions, and associated signaling pathways. In an *in vitro* and *in vivo* study, differentiated dopaminergic SH-SY5Y cells and C57BL/6J mice were exposed to Polystyrene Nanoplastics (PS-NPs), leading to mitochondrial dysfunction *in vivo*, and a mitochondria accumulation, interference with complex I, mitochondrial damage, and decreased mitochondrial membrane potential and ATP *in vitro*, a scenario suggestive of cytotoxicity that led to mitophagy (dysregulation of the AMPK/ULK1, pAMPK, pULK1, LC3-II, and p62 pathways). Conversely, the authors identified melatonin as a potential mitochondrial protector, both *in vivo* and *in vitro* models [27]. This study is particularly compelling as it demonstrates the potential interactions of NP monomers with specific mitochondrial targets in a neural context. It highlights how NPs can disrupt oxidative phosphorylation, triggering cellular stress responses that may impair neurotransmitter synthesis and synaptic function.

Exposure to PS-NPs in neural progenitor cells caused G1 cell cycle arrest, decreased cyclin D expression, oxidative stress, and mitochondrial accumulation and dysfunction, indicating cellular senescence *in vitro* (increased levels of Il6, Ccl2, Ccl3, Mmp1, and Mmp3). *In vivo*, NPs impaired hippocampal neurogenesis and memory (passive avoidance task) [28]. Therefore, we can consider disruptions in anabolic and catabolic hormone signaling, along with impaired neuronal signaling, hinder macromolecule mobilization and oxidation, affecting both neurodevelopment and neuroplasticity.

In general, few studies directly assess the consequences of NPs on neuroendocrine biochemical disturbances. Although we know that NPs can adsorb EDCs, we still lack a direct understanding of hormonal biosynthesis or even the action of these hormones. However, considering what is already known about MPs, it is quite plausible that NPs also exacerbate hormonal and systemic adverse effects. Furthermore, from a neuronal perspective, whether about the Central or Peripheral Nervous System, we can consider that NPs' understanding of neuronal biochemistry still represents a scientific gap. It is necessary to investigate in depth how NPs can carry certain molecules (e.g., phthalates or bisphenol) or even act directly on enzymatic catalysis, interfering, for example, in neuronal glycolytic pathways, in the uptake of macromolecules via astrocytes, or even in the ability to metabolize ketone bodies (e.g., B-hydroxybutyrate). The general information of this topic is compiled in Table 1 and Fig. 2.

3.2. Absorption, metabolization, and bioaccumulation – intestine-liver-microbiome axis

From a dietary perspective, the digestive system represents the primary interface between the organism and the external environment, functioning not only as the gateway for energy substrates but also as a potential entry route for toxic substances and EDCs capable of bypassing or overwhelming innate immune barriers. Understanding how NPs may initially interfere with digestive processes and gut microbiota composition—and subsequently impact nutrient absorption, metabolic regulation, and hepatic function—is essential for a comprehensive assessment of their biochemical and systemic effects. Such an integrative perspective enables a more holistic evaluation of the metabolic disturbances and health risks potentially associated with NP exposure.

Considering musculature, it can be associated with any organ that contains smooth muscle cells and exhibits a direct response from the autonomic nervous system. An *in vitro* study of progressive doses of PS-NPs using an *in vitro* model of pre-differentiated C2C12 myoblasts observed an increase in the characteristics of cellular senescence, with increased β-galactosidase activity, expression of p16, p21, and cell cycle arrest. The authors also observed an increase in the expression levels of IL-6, IL-1β, TNF-α, MMP-2, and MMP-13 and a decrease in the expression levels of *Timp*-2 mRNA at a concentration of 400 μg/mL, several fragmented mitochondria, and a reduction in ATP generation, concluding that exposure to high doses of NPs leads to senescence and biochemical-mitochondrial disorders in pre-differentiated myoblasts [29]. In an integrative experimental analysis, mice subjected to a chronic colitis model and NPs exhibited exacerbation of intestinal inflammation, oxidative stress, and disorders of hepatic lipid metabolism (increased fat vacuoles - bile acids, unsaturated fatty acids, triglycerides, and oxidized cholesterol), mainly at medium and high doses [30]. These results highlight the dysregulation in the intestine-liver axis, mainly about lipid metabolism and mobilization. At environmentally relevant concentrations of NPs in Nile tilapia liver, there was severe toxicity, including hepatic steatosis, lipid metabolism disorders, inflammatory response, and disturbed liver function (decreased CYP1A, CYP3A), with impacted endoplasmic reticulum-chaperone homeostasis (*calr*, *calr3a*, *calr3b, hsp90b1, dnajb11, hspa5, pdia4, and pdia6*) [31].

A multiomics study with a transcriptomic/metabolomic approach investigated the intestinal effects in mice exposed to NPs and observed pro-inflammatory signaling (Il1b, Stat 4, Ifi47, Ptpn22, Il2rb, Cxcr6, Irf7, and Rasal3) and major histocompatibility complex (MHC) molecules. In addition, NPs reduced junction proteins (e.g., occludin, zonula occluden-1), which increases susceptibility to infections and structural and functional disorders. In another experiment, the authors observed that NPs administration increased intestinal permeability and exacerbated dextran sulfate sodium-induced colitis. Regarding metabolites, exposure to NPs

Table 1
Resumed results and references for Neuroendocrine and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Oxidative phosphorylation decreased in neural cells and in mice – mitochondrial dysfunction.	PS-NPs (50 nm).	0,5-500 μg/mL - *in vitro*. 250 mg/kg/day for 28 days - *in vivo*.	Dopaminergic differentiated SH-SY5Y cells and C57BL/6J mice.	Huang et al., 2023 *Particle and fibre toxicology* [27]
Accumulation in mitochondria – dysfunction and cellular senescence; impaired hippocampal neurogenesis and memory.	PS-NH_3^+ (50 nm); PS-NH_3^+ (2000 nm); PS-COO^- (30 nm); PS-COO^- (2000 nm).	100 mg/mL - *in vitro*. 50 or 200 mg/kg for 10 days (orally) - *in vivo*.	Neuronal progenitor cells and C57BL/6 mice (5 weeks, male).	Yang et al., 2023 *Free radical biology & medicine* [28]

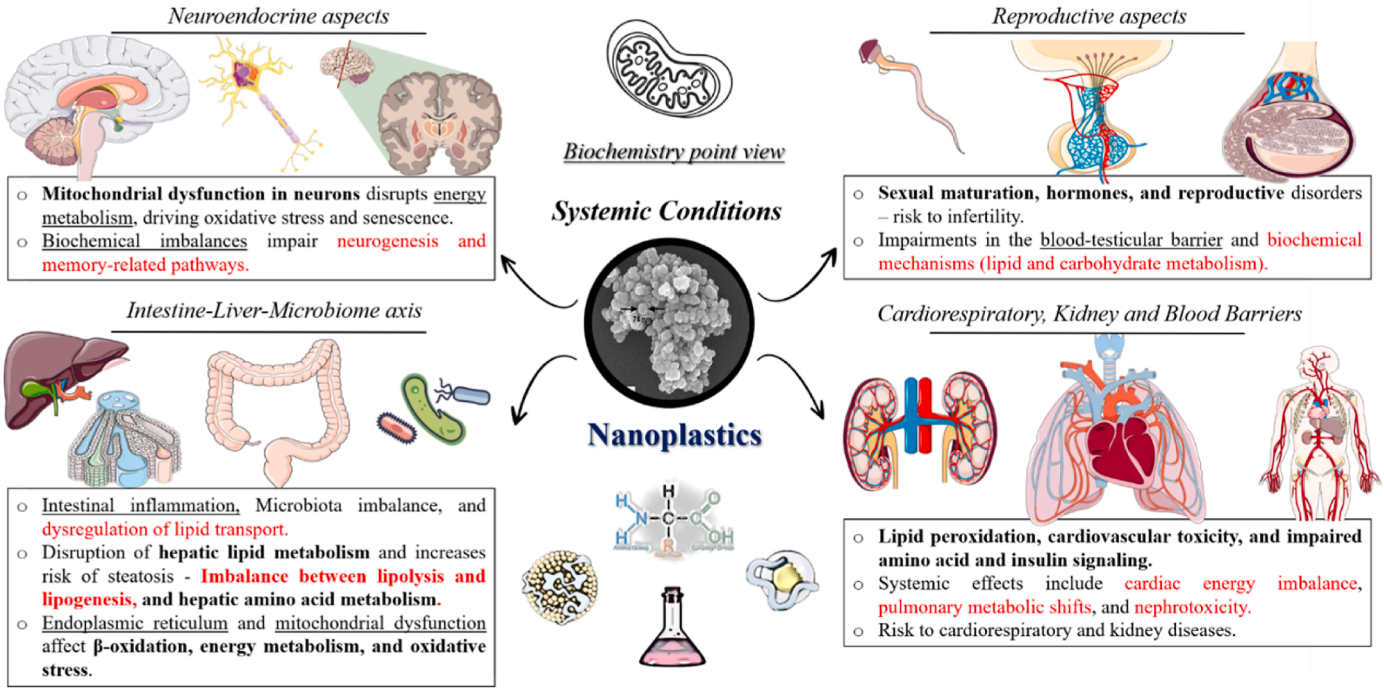

Fig. 2. Key systemic conditions and biochemical axes affected by nanoplastic exposure. The diagram illustrates, from a biochemical perspective, how NPs may disrupt neuroendocrine and reproductive systems, the gut–liver–microbiome axis, and cardiorespiratory, renal, and blood–tissue barriers. Reported effects include mitochondrial dysfunction, oxidative stress, metabolic imbalances (lipids, carbohydrates, amino acids), placental metabolic alterations, cardiovascular toxicity, infertility risk, and gut microbiota dysbiosis. The Figure was composed using some illustrations from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

depleted taurine [32], which probably leads to difficulties in fat digestion and an imbalance of the intestinal microbiota, as a starting point for systemic biochemical disorders. In contrast, Schwarzfischer et al. (2022) showed an accumulation of PS-NPs in the small intestine and liver in mice induced to chronic or acute colitis – however, without initial barrier disruption and without exacerbating acute colitis [33]. Although some findings suggest that NPs do not exacerbate colitis, this outcome appears to depend on the induction method. Notably, exposure to NPs results in extra-intestinal accumulation, which - especially in the context of environmental factors and additional stressors - may contribute to an increased risk of metabolic disorders.

Using an insect model exposed to environmentally relevant NP concentrations, Muhammad et al. (2024) demonstrated increased lipid energy reserves, alterations in gut microbiome structure, and enrichment of *Acinetobacter* and *Enterococcus* in larvae, indicating a potential exacerbation of lipid metabolism [34]. Another study evaluated the effects of environmentally relevant secondary PE-MNPs on a high-fat food model using simulated *in vitro* small intestinal epithelium, observing increased fat digestion and fat absorption after exposure. Analyzing the NP corona, the authors observed predominantly triacylglycerols with fatty acid enrichment in the small intestine, which is associated with the enrichment of triacylglycerol lipase and depletion of β-casein [35]. These interactions likely occur through the adsorption capacity and the biochemical mechanisms by which NPs interact with hydrophobic components, possibly increasing not only their bioaccumulation but also exacerbating the dysregulation of lipid metabolism pre- and post-digestion/absorption. Based on global proteomic profiling, human THP-1 cells exposed to MNPs exhibit proteins overexpressed in the serum-coated PS100 corona associated with complement and coagulation cascades (e.g., apolipoprotein A-II, vitamin D-binding protein, elongation factor 1-alpha 2, and apolipoprotein A-I) [36]. This study provides important targets for NP protein corona dysregulation of the intestine, which will certainly affect digestion and absorption mechanisms, effectively linked to lipid metabolism and lipid transport.

Teng et al. (2023) utilized a zebrafish model to investigate the NPs, observing impacts on the structure of the blood-brain barrier, goblet cells, and intestinal mitochondria, as well as intestinal viral abundance, contributing to gut-brain neurotoxicity and immunotoxicity disorders. On the other hand, the authors observed the reverse effect of Vitamin D, improving these aspects and increasing serotonin content [37]. This work reinforces the integrative impacts of NP exposure, highlighting potentially biochemical aspects of gut microbiota metabolism and its influence on the gut-brain axis. The accumulation of PS-NPs in the spleen, lung, kidney, small intestine, large intestine, testis, and brain of mice results in cell apoptosis, inflammation, and structural disorders, damage to the hematologic system, and disruption of lipid metabolism. In contrast, *in vitro* studies demonstrated the uptake of NPs by intestinal epithelial Caco-2 cells by macropinocytosis and clathrin-mediated endocytosis [38]. In rodents, NPs presented characteristics similar to Crohn's ileitis, with structural alterations, increased pro-inflammatory cytokines, and necroptosis of intestinal epithelial cells. This study also observed the accumulation of NPs in mitochondria, leading to mitochondrial stress [39]. This is another study that corroborates the biochemical effects of NPs, particularly on mitochondrial dysfunction.

From an immune system point of view, PS-NPs in *in vitro* macrophage populations impact the expression of several surface markers involved in the immune response (e.g., CD11a/b, CD18, CD86, PD-L1, and CD204). There was also a positive correlation between greater NP internalization, smaller size, and mitochondrial dysfunction, oxidative stress, and altered immune system function were observed due to surface proteins [40]. Although they

did not specifically explore biochemical pathways, this study corroborates that smaller particles have a greater potential for bioaccumulation, generating cellular stress that will certainly lead to metabolic disturbances with consequences for the immune response and systemic homeostasis. Zingaro et al. (2023), in a well-designed study from a physicochemical and experimental perspective, found that the subpopulation of human M1 macrophages exposed to labeled polypropylene and polyvinyl chloride NPs presented modifications in their macromolecular chemical composition, suggesting disturbances in the macrophage lipid response (ultrastructural appearance of shiny vesicles). The authors confirmed the accumulation of lipid droplets in macrophages - chemical maps of fatty acids and triglycerides - a characteristic of phagocytosis and oxidative stress [41].

Although the available studies are largely organ-specific—examining isolated systems rather than integrated physiology—their findings reveal interconnected biochemical patterns. The convergence of *in vitro* and *in vivo* evidence suggests that NP-induced effects are not confined to a single tissue but may reflect systemic metabolic disruption. These observations underscore the need for future investigations focused on organ-specific consequences within a coordinated physiological framework. In this context, the liver represents a primary and strategic target for further study, given its direct exposure to absorbed compounds via the hepatic portal circulation and its central role in intermediary metabolism, detoxification, and systemic metabolic regulation. *In vitro*, NPs impact the hepatic lipid metabolism, mainly through cellular dysregulation via accumulation of lipid droplets and blockage of lipophagy (via AMPK/ULK1) [42]. In both murine and *in vitro* models, PS-NPs impair β-adrenergic signaling, leading to reduced lipolysis and compromised lipid mobilization in subcutaneous white adipose tissue. This disruption contributes to metabolic disturbances - particularly in the liver and intestine - by inhibiting glycerol release following lipolytic stimulation, an effect that is exacerbated under high-fat diet conditions [43].

When a high-fat diet and NPs are associated in C57BL/6 J mice, NPs exacerbated diet-induced hepatic steatosis (Fatp2) through hepatic oxidative stress (Nrf2), structural impact on the endoplasmic reticulum and mitochondria, increased serum LDL-C, reduced ATP levels, and miR26a expression. Biochemically, the authors evidence the exacerbation of the negative consequences of diet via exposure to NPs, emphasizing the mechanisms of β-oxidation, transport, and biosynthesis of fatty acids, leading to dysregulation of the endoplasmic reticulum and mitochondria, which impacts energy metabolism [44]. This study is quite interesting because, although it does not demonstrate that NPs alone lead to non-alcoholic steatohepatitis, it highlights the potential of the effects of diet when combined with NPs, providing an important biochemistry insight into the sum of negative effects on liver and systemic health and the risk of developing pathologies. In addition, synthetic NPs accumulate in macrophages, disrupting mitochondrial function - enhancing complex I activity while suppressing complexes II and V - leading to reduced ATP, elevated reactive oxygen species (ROS), and oxidative stress markers (e.g., TNF-α, MDA). In the rodents, the PS-NPs trigger liver necroptosis and systemic effects, including liver injury marked by increased ALT, AST, LDH, and depleted antioxidant defenses (SOD, GSH) [45].

Using Nile tilapia as model, Wu et al. (2023) investigated the exposure to Polypropylene Nanoplastics (PP-NPs) on the global hepatic metabolomic profile, finding several adversities on glycerophospholipid (phosphatidylcholine) metabolism, amino acid metabolism (proline, valine, leucine, ornithine, histidine, and arginine), and aminoacyl-tRNA biosynthesis, increasing the risk of hepatitis development due to the significantly upregulated signals of arachidonic acid [46]. This study elucidates that NPs have the potential to exacerbate hepatic amino acid metabolism, likely as an adaptive response to their interference with energy metabolism and catabolic and anabolic homeostasis. In addition, using the same model, Wu et al. (2024) used NIDS-EESI-MS to reveal disruptions in amino acid metabolism - specifically in the biosynthesis of phenylalanine, tyrosine, tryptophan, and branched-chain amino acids, along with lysine degradation - likely due to NP interactions with protein functional groups in aqueous environments [47]. Brandts et al. (2021) found that exposure to polymethylmethacrylate NPs in sea bream resulted in increased mRNA levels of key genes associated with hepatic lipid metabolism (apolipoprotein A1, retinoid X receptor, and *Pparβ*), plasma cholesterol and triglycerides, clastogenic/aneugenic damage in fish erythrocytes, causing antioxidant disorders and genotoxicity [48].

NPs at different concentrations induced oxidative stress and DNA damage in hepatocyte cell lines from 3-month-old male mice (C57BL6-J). These nanomolecules also disrupted the aromatic amino acid microenvironment of SOD [49]. Another study with PS-NPs in transgenic zebrafish larvae observed aggregation of NPs and neutrophils in the abdomen of the larvae, corresponding to increased inflammation and hepatic ROS. From a biochemistry point of view, NPs increased the expression of Fabp10a in the larval livers. Metabolic profiling revealed increased catabolic processes (galactose metabolism and glycerolipid metabolism), the citrate cycle pathway (including methylmalonic acid, 3-hydroxypropanoate acid 1, citric acid, and citrulline 2), the amino acid and purine pathways, and steroid hormone biosynthesis [50]. In a specific physical study, Rajendran et al. (2022) observed that PS-NPs interact spontaneously with human serum albumin via hydrogen bonds, van der Waals forces, and hydrophobic interactions. These changes alter the environment of key aromatic residues (e.g., tryptophan-214). Spectroscopic and docking reveal secondary structure disruptions and reduced esterase activity of albumin [51]. The findings highlight the need for regulation and deeper investigation into the biological impact of NPs, mainly in the fatty acids' transporter and systemic deregulation of hydrophobic molecules mobilization.

These findings underscore the dose-dependent capacity of NPs to disrupt the gut–liver–microbiome axis, compromising gastrointestinal homeostasis. Such disruption alters digestive and absorptive functions, impairs intestinal barrier integrity, and interferes with microbial metabolism, increasing the risk of dysbiosis and microbiota metabolization homeostasis. Consequently, this starting point for NP effects can potentiate the bioaccumulation of hepatic NPs, interfere with the uptake of macromolecules and micronutrients, enhance lipid metabolism, and increase their hepatic deposition. Consequently, all of this affects central energy metabolism, potentially impacting important processes such as gluconeogenesis, glycogenolysis, glycolysis, and ketogenesis, among others, with significant biochemical impacts not only on the liver but also on liver-dependent extrahepatic organs. The general information on this topic is compiled in Table 2 and Fig. 2.

3.3. Disruption of cardiorespiratory, renal, and circulatory homeostasis

Understanding how NPs can interfere with cardiorespiratory homeostasis, transport aspects, and renal function is also of paramount importance given the possible systemic effects (e.g., oxygen uptake, CO2 elimination, regulation of blood pH, osmolarity, blood pressure, and hydroosmotic balance). In the blood context, using lipidomics, Leroux et al. (2022) evaluated mussel hemocytes exposed to NPs, revealing a decrease in highly unsaturated membrane lipids, which may be associated with excessive

Table 2
Resumed results and references for the Intestine-Liver-Microbiome axis and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Impairment in the mitochondria homeostasis, decreased ATP generation, and increased senescence – increased β-galactosidase.	PS-NPs (100 nm).	10, 25, 50, 100, 200, and 400 μg/mL for 48 h.	C2C12 murine myoblasts.	Bang et al., 2025 *Toxicology* [29]
Exacerbated chronic colitis, intestinal inflammation, and disorders in lipid metabolism.	Pristine polystyrene nanobeads (PS-NPs, 0.1 μm).	1 mg/kg, 5 mg/kg or 25 mg/kg for 28 days – Gavage.	7-week-old male C57BL/6J mice induced to chronic colitis.	Ma et al., 2023 *Particle and fibre toxicology* [30]
Disturbed liver function, raising ecotoxicological and health concerns.	NPs (three sizes).	1, 10, and 100 μg/L.	Nile tilapia (*O. niloticus*).	Wang et al., 2023 *Environmental science & technology* [31]
Exacerbated colitis *in vivo*, depletion of taurine, inflammation, and compromised gut barrier function in the mouse colon.	————————————————	0.5 mg/day – *in vitro*. 1.5 mg/day (orally) for 28 days – *in vivo*.	Mice colitis model.	Kim et al., 2024 *Environmental research* [32]
High distribution of NPs in gut and other organs – do not induce small intestine inflammation.	PS-NPs (50 nm).	0.05 mg/ml diluted in water (drinking) for six months or three months before induction of acute or chronic colitis.		Schwarzfischer et al., 2022 *NanoImpact* [33]
Impacts on the survivorship, gut metabolome, microbiome, and transcriptome, leading to dysbiosis and lipid metabolism deregulation.	PS-NPs (50 to 100 nm).	0.25, 0.5, and 1.0 μg/mL by food exposure.	Silkworm strain (Jinsong × Haoyue) - Neonate larvae.	Muhammad et al., 2024 *Journal of advanced research* [34]
Increased fat digestion and absorption in a triculture intestinal epithelium model.	PE-NPs ($PM_{0.1}$).	400 μg/mL - *in vitro*. PE-I $PM_{0.1}$ MNPs in a high fat (11.7%) food model – *in vivo*.	Intestinal epithelium; Caco-2, HT29-MTX, and Caco-2 cells transformed by Raji B feeder cells - *in vitro*.	DeLoid et al. (2022) *Environmental science & technology* [35]
Lipid droplet accumulation in hepatocytes, with autophagy inhibition and activated lipophagy.	PS-NPs (50 nm, 100 nm, and 200 nm).	3.125, 6.25, 12.5, 25, and 50 μg/mL PSNPs for 24h.	Normal human hepatic cell line.	Fan et al., 2024 *Journal of hazardous materials* [42]
NPs and a high-fat diet suppressed lipolysis, increased NPs in fat tissue and the liver, and induced inflammation in the small intestine.	PS-NPs (3.64×10^{14} particles/ml).	10^5 and 10^{10} particles/ml NPs - *in vitro*. Drinking water 0, 2.8, 223 μg/day/kg, and high-fat diet added for 8 consecutive weeks – *in vivo*.	Three-week-old male C57BL/6 J mice and 3T3-L1 murine preadipocytes.	Shiu et al., 2022 *Journal of hazardous materials* [43]
Increased risk of non-alcoholic fatty liver due to NP potential to induce oxidative stress and liver dysfunction.	PS-NPs (70 nm).	80 μg/g of NPs in high-fat diet (4398.4 kcal/kg) – food exposure.	Three-week-old female C57BL/6J mice.	Wei et al., 2024 *Journal of hazardous materials* [44]
Macrophages NPs accumulation and disrupted mitochondrial function, decreasing intracellular ATP - liver injury; systemic disorders: Increased serum ALT, AST, LDH, and MDA levels in mice.	Synthetic PSNPs (20 nm).	50 μg/mL – *in vitro*. 60 mg/kg – *in vivo*.	Wild-type BALB/c mice (male, 6–8 weeks old), bone marrow-derived macrophages, and peritoneal macrophages isolated from mice; murine macrophage cell line RAW 264.7, J774A.1, and the human hepatocarcinoma cell line (Huh7).	Fan et al., 2024 *Particle and fibre toxicology* [45]
Exacerbation of hepatic amino acid metabolism and impairment of lipid metabolism; adaptive responses suggest inflammation, oxidative stress, and potential risk of steatosis.	Polypropylene nanoplastics (PP-NPs - 100 nm).	100 mg g^{-1}, 10 mg g^{-1}, 1 mg g^{-1} in 50 L of glass aquaria filled with dechlorinated tap water.	Nile tilapia.	Wu et al., 2023 *Analytical chemistry* [46]
Impacts on the biosynthesis of phenylalanine, tyrosine, and tryptophan, the degradation of lysine, and the biosynthesis and metabolism of the valine, leucine, and isoleucine pathways.	PP-NPs (100 nm).	1 mg/g, 10 mg/g, 100 mg/g.		Wu et al., 2024 *Analytical chemistry* [47]
Increased the expression of antioxidant genes, oxidative stress, and liver injury.	Polymethylmethacrylate NPs (PMMA-NPs - 45 nm).	0.001, 0.01, 0.1, 1 and 10 mg L^{-1}.	*S. aurata* juveniles.	Brandts et al., 2021 *Journal of hazardous materials* [48]

Table 2 (*continued*)

Mainly results	Exposition	Dose	Organism	Authors
Oxidative stress and desoxyribonucleic acid damage in the liver.	PS-NPs (50 nm).	1, 5, 10, 20, and 30 [× 10−6 mol/L].	3-month-old male mice (C57BL6-J) - hepatocyte suspensions.	Zheng et al., 2019 *Journal of molecular recognition* [49]
Hepatic immune toxicity, ROS accumulation, and disorders in steroid hormone biosynthesis.	PS-NPs (100 and 50 nm).	0.1, 0.5, 2, and 10 mg L^{-1}.	Adult wild-type zebrafish and three transgenic zebrafish lines: Tg (lyz:DsRed2), Tg (mpeg1:EGFP), and Tg (fabp10a: dsRed).	Cheng et al., 2022 *Environment international* [50]
Structural deformation in human serum albumin, changes near active site tryptophan-214.	Monodispersed non-functionalized PS-NPs (0.10).	4.55 × 10^{13} particles/ml.	Human serum albumin.	Rajendran et al., 2022 *NanoImpact* [51]
Alterations in the complement factor and apolipoprotein levels in the NP protein corona – possible intestine barrier disorders with metabolic consequences.	MNPs (50 nm, 100 nm, 200 nm, 500 nm, 1000 nm).	7.8, 15.6, 31.3, 62.5, and 125 μg/ml for 24 h.	THP-1 human cells.	Brouwer et al., 2024 *Particle and fibre toxicology* [36]
Biochemistry impacts on mitochondria in the intestine; serotonin disposition and neurotoxicity in the brain.	PS-NPs (80 nm).	15 μg/L, 150 μg/L - 21 days of exposure.	Zebrafish model.	Teng et al., 2023 *Microbiome* [37]
Internalization of NPs into intestinal cells and the mice intestine, with surface modifications – potential disorder in the gut barrier.	Fluorescent unmodified (PS), carboxyl-modified (PS–COOH) and amino-modified (PS–NH2) NPs (100 nm).	30, 60, 120, 240, 480 μg/mL for 24 h, 48 h, or 96 h – *in vitro*. 10 mg/mL - 1 mg/day: by gavage 28 days – *in vivo*.	Specific pathogen-free (SPF) BALB/c mice (Male, 6 weeks) and Caco-2 cells (human intestinal epithelial cells).	Xu et al., 2021 *Journal of hazardous materials* [38]
NPs triggered the occurrence of IBD-like features in mice, caused necroptosis rather than apoptosis, and caused mitochondrial stress.	Nonfluorescent-labeled or green fluorescent-labeled PS, PS-COOH, and PS-NH2 (100 nm) (density: 25 mg/mL).	30, 60 and 120 μg/mL – *in vitro*. PS, PS-COOH and PS-NH_2 (1 mg/day) by gavage for 28 consecutive days – *in vivo*.	Male-specific pathogen-free BALB/c mice and the human intestine epithelial cell line Caco-2.	Xu et al., 2023 *Environment international* [39]
Disrupted macrophage surface, inducing mitochondrial dysfunction, mainly in smaller particles.	NPs (40-90 nm).	20 μg/ml for 24 h.	J774A.1 cell line (mouse macrophages).	Collin-Faure et al., 2023 *Frontiers in immunology* [40]
Macrophages' lipid metabolism disorders and accumulation.	Polymeric labeled and non-labeled NPs - PP and PVC NPs.	1, 5, 20, and 50 μg/ml.	Human monocytic THP-1 cells (ATCC TIB-202) - polarized into M1 macrophages by IFN-γ and LPS.	Zingaro et al., 2023 *Frontiers in immunology* [41]

oxidation of lipids with a high number of double bonds, membrane reorganization for endocytosis, and immune responses [52]. This work certainly clarifies possible systemic impacts associated with the biochemical interference of NPs on transporters within the circulatory system.

ApoE−/− mice exposed to NPs and a high-fat diet for 19 weeks exhibit NP presence in the aorta and liver, and atherosclerotic plaque formation at higher doses. Biochemically, NPs activate M1 macrophage phagocytosis, disrupting lipid metabolism and increasing long-chain acyl carnitines by inhibiting hepatic carnitine palmitoyltransferase 2 [53]. This study is very important because it provides insights into how NPs interfere with lipid metabolism in a systemic and organ-wide manner, likely impacting not only vascular but also hepatic function, with hepatoperipheral consequences. Furthermore, the combination of NP exposure with a high-fat diet offers valuable insights and invites multidisciplinary discussion, as NPs can adsorb hydrophobic molecules or acquire charge, enhancing their affinity for lipids and increasing their bioavailability. This raises important concerns regarding the compounded risk of obesity, high-fat consumption, and plastic waste exposure - highlighting potential negative synergistic effects.

From a multiomics perspective, a study of zebrafish exposed to NPs found temperature-specific cardiovascular toxicity, with downregulation of branched-chain amino acid biosynthesis (valine, leucine, and isoleucine, alanine, aspartate, glutamate, and beta-alanine metabolism) and insulin signaling pathways. Furthermore, there was an increase in the rate of oxidative phosphorylation in mitochondria, resulting in an additive effect on the mortality of zebrafish larvae. From an electrophysiological perspective, NPs caused disturbances in heart rate, in addition to pericardial edema. Interestingly, the proteins NADH dehydrogenase (NDUFA2 and NDUFA8), cytochrome *c* reductase (UQCR10), cytochrome *c* oxidase (COX6C), and ATP synthase (ATP5PD), involved in oxidative phosphorylation complexes I, III, IV, and V, were upregulated [54]. This study provides interesting insights into the disturbances caused by NPs on cardiovascular function, demonstrating oxidative and energetic overload at the expense of anabolic decrease, which potentially impairs cardiac function in the short and long term, predisposing to the development of cardiovascular diseases due to biochemical dysregulations.

A well-designed study using RNA-seq in mice exposed to PS-NPs demonstrated the presence of cardiac fibrosis after 12 weeks of exposure. In addition, serum and cardiac tissue levels of biomarkers of injury and inflammation - troponin T (cTnT), ANP, N-terminal proBNP (NT-proBNP), and LDH - were increased, leading to disruption of the balance between oxidase and antioxidant activity (MDA, CAT, SOD, and GSH-px). Subacute and subchronic

exposure reduced cardiac systolic function, impairing mitochondrial structure and the TCA cycle. Enrichment of disease-associated pathways was observed in long-term exposure, including cardiomyopathies, dilated cardiomyopathy, heart failure, and atherosclerosis [55]. This is another investigation that highlights the negative effects of NPs in the mitochondria, likely impairing energy metabolism through probable disturbances in fatty acid oxidation (β-oxidation), influencing energy uptake, and increasing susceptibility to heart disease. If these animals were evaluated long-term, they would likely exhibit the diseases suggested by the authors. Using the Polyvinyl Chloride Nanoplastics (PVC NPs), Liu et al. (2025) observed lysosomal and mitochondrial accumulation in the cardiomyocytes, impacting autophagy (impaired autophagosome-lysosome fusion and dysfunctional lysosomes) and mitochondrial energy metabolism (reduced ATP content) in an *in vitro* model. *In vivo*, the authors found lower heart rate, altered cardiac electrophysiology, and mitochondrial abnormalities [56]. These results offer new insights into the specific and organelle-specific mechanisms of NP-induced cardiotoxicity. Interestingly, we can consider significant impacts on cardiac biochemical homeostasis, possibly through dysregulated energy substrate uptake mechanisms mediated by mitochondrial disruption and alterations in vesicular transport within the endomembrane system.

In the context of personalized medicine, nanotechnology has been gaining prominence in recent years. BEAS-2B bronchial epithelial cells exposed to NPs (10 and 50 mg/ml) and a widely used metal nanoparticle (nanoZnO) exhibit low toxicity. However, this exposition led to endoplasmic reticulum stress and higher levels of amino acids (phenylalanine, tryptophan, methionine, lysine, proline, alanine, glycine, serine, and aspartic acid), carbohydrates (pyruvate and lactate), and intermediate metabolites of TCA (succinate, fumarate, and malic acid) [57]. It is plausible to consider that these results indicate disturbances in energy metabolism and the TCA, associated with glucogenic and ketogenic amino acids, and classic anaerobic metabolism of the tumor environment of proliferation and invasiveness.

Through the mechanical decomposition method, Ji et al. (2024) used NPs (bulk plastic), mimicking the characteristics within nature, and observed an increase in pulmonary toxicity, from mitochondrial dysfunction (BH3 - Bid and NCOA4) [58]. In an in vitro study, PS-NPs induced epithelial–mesenchymal transition in A549 lung cells, compromising cell viability through cytotoxic mechanisms driven by oxidative stress involving ROS and NADPH oxidase 4. These effects disrupted cellular energy metabolism by impairing mitochondrial transmembrane potential ($\Delta\psi m$), oxidative phosphorylation coupling, and mitochondrial membrane integrity, ultimately triggering endoplasmic reticulum stress. Notably, the authors confirmed previous findings that smaller, positively charged PS-NPs exerted more pronounced effects [59]. When exposed to NPs for a short period (7 days), male and female C57BL/6 mice showed morphological lesions in the lungs (predominantly lymphocytic inflammation in a bronchiolocentric pattern, substantial perivascular lymphocytic inflammation, and collagen deposition). Based on this, bronchial lung cell lines exposed to NPs were investigated, which exhibited disturbances in transcripts associated with lipid biosynthesis, lipid metabolism, and iron ion binding processes and ferroptosis (mediated by HIF-1α/HO-1) [60]. All these studies provide a solid basis for how NPs may have a biochemical (perhaps catalytic) potential to exacerbate inflammatory processes and pulmonary oxidative stress, generating reticulum and mitochondrial stress that will certainly impact energetic mechanisms and, ultimately, pulmonary physiological aspects (e.g., compliance, elasticity, resistance, and volumetric homeostasis - altering hematosis).

Aged PS-NPs cause nephrotoxicity in mice, a process mediated by ferroptosis, as confirmed through *in vitro* validations in human renal tubular epithelial cells [61]. An *in vitro* study using renal cell lines exposed to NPs observed inflammation (TNFα, IL-6, and IL-1β) and senescence (p16, p53, H2AX, H3K27me3), mediated by ROS accumulation, increased MDA, and decreased SOD, interestingly leading to decreased mitochondrial membrane potential [62]. This study not only highlights a direct impact on renal homeostasis but also a metabolic exacerbation to NPs that induces impaired mitochondrial antioxidant response, which likely impacts renal function and the systemic environment (e.g., blood pressure control).

Regarding transport and circulatory aspects, there are still few studies directly indicating the biochemical impact of NPs - for example, evaluating possible changes in hemoglobin, iron, and polypeptide chains, or even how NPs can impact ionic concentrations and hydrostatic and colloid osmotic pressures, which will have systemic impacts on various cells and specific organs. In the renal system, the same applies, particularly to understanding how NPs can interfere with the processes that regulate osmolarity, as well as how they can affect the intrinsic or extrinsic regulation of blood pressure. Finally, regarding the cardiorespiratory system, the results are promising and demonstrate, including through specific signaling pathways, how NPs can increase the risk of cardiovascular and pulmonary diseases. Certainly, more preclinical studies are needed for a more detailed and complete view of the interference of NPs in essential signaling pathways, in order to establish a panorama and subsidy for clinical studies that seek to understand these possible relationships of biochemical disorders in human health. The general information of this topic is compiled in Table 3 and Fig. 2.

3.4. Reproductive aspects

Elucidating the molecular, biochemical, and hormonal mechanisms through which NPs disrupt reproductive physiology is essential for a comprehensive understanding of their biological impact. Such insight would clarify not only the direct effects on fertility and reproductive function, but also the potential long-term implications for sex-specific cancers—conditions of high global incidence and significant public health concern. Hu et al. (2024) explored the impact of prepubertal exposure to NPs on post-maturation male reproductive function in rats. The authors found an accumulation of NPs in the testes and seminiferous tubules (by scanning electron microscopy, fluorescent imaging, and confocal microscopy) and reduced sperm quality (sperm concentration and motility) and serum reproductive hormones (FSH, LH, and testosterone), mainly in high-dose and long-term groups. On the other hand, the authors observed that exposure to NPs did not alter feeding and water intake behavior. A very important result was that NPs disrupted the blood-testis barrier by decreasing junction proteins (B-catenin, Zo-1, occludin, and N-cadherin) - mainly at postnatal day (PND)95, inducing inflammation and apoptosis (increased BAX and decreased BCL2). From transcriptomics, the authors identified enrichment of testicular tissue peptidase regulation, neutrophil activation, fatty acid transport, transmembrane glucose transport, transmembrane monosaccharide transport, adipocytokine signaling, phosphatidylinositol signaling, and TLR4 signaling [63]. The authors did little to explore the metabolic aspects evidenced in the enrichment of pathways, but it is possible to infer that NPs may impact glucose uptake and fatty acid transport by interfering with the anabolic insulin response, or even by causing problems in subsequent signaling pathways, a situation that subsequently impairs oxidative aspects that will lead to the production of electron

Table 3
Resumed results and references for Cardiorespiratory Function, Renal Physiology, Circulatory Dynamics, Blood-Tissue Barriers and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
PS-NPs may contribute to atherosclerosis by upregulating macrophage collagen receptors, with synergistic effects observed alongside endogenous LCACs, highlighting their combined impact on cardiovascular health.	PS-NPs (50 nm).	2.5–250 mg kg-1 – gavage - with a high-fat diet for 19 weeks.	ApoE−/− mice.	Wang et al., 2023 *Advanced science* [53]
Cardiovascular toxicity and enhanced cardiac contractility, leading to up-regulates oxidative phosphorylation process.		0.1 mg L-1 - 24 h after fertilization.	Entered zebrafish (*Danio rerio*) embryos.	Duan et al., 2023 *Journal of hazardous materials* [54]
Cardiac fibrosis, mitochondrial dysfunction, increased heart injury and inflammation, oxidative stress imbalance, and TCA cycle disruption - impaired systolic function; enriched pathways linked to cardiac diseases in long-term exposure.	PS-NPs (40 nm).	16 μg/day, 40 μg/day, and 100 μg/day - 1 week, 4 weeks, 12 weeks by inhalation.	Mice.	Zhang et al., 2023 *Particle and fibre toxicology* [55]
NPs accumule in the cardiomyocytes, lysosomes, and mitochondria, leading to deregulation in lysosomal autophagy and mitochondrial function.	PVC-NPs and GFP-tagged PVC-NPs.	4 μg/ml PVC-GFP for 0, 1, 2, 4, 12, or 24 h – *in vitro*. 5 mg/kg PMMA-GFP (gavage) – *in vivo*.	HL-1 cells and ten-week-old male C57BL/6 mice.	Liu et al., 2025 *Biochemical and biophysical research communications* [56]
Fatty acids and triglycerides disorders in hematocytes.	PS-NPs (50 and 500 nm).	10^6 and 10^9 particles/mL for 24 h.	Mussel hemocytes.	Leroux et al., 2022 *Environmental research* [52]
Disorders in the TCA and energetic metabolism – pyruvate-lactate conversion; impacts on amino acids and TCA cycle.	————————	10 and 50 mg/ml.	Bronchial epithelial BEAS-2B cells.	Lim et al., 2019 *Nanotoxicology* [57]
Respiratory deregulation by NPs – mediated by mitochondrial imbalances.	PS, PET, PVC, and PE NPs (100 nm).	————————————————————	Cell lines.	Ji et al., 2024 *ACS nano* [58]
Endoplasmic reticulum stress, mitochondrial disorders, and risk for pulmonary diseases such as fibrosis.	PS-NP20+ and PS-NP20 (20 nm); PS-NP50 (50 nm).	PS-NP20 +: 10, 20 and 40 μg/ml; PS-NP20: 10, 20 and 40 μg/ml; PS-NP50: 40, 80 and 160 μg/ml.	Human alveolar type II epithelial A549 cell line.	Halimu et al., 2022 *Journal of hazardous materials* [59]
Pulmonary injury; ferroptosis in lung tissues and bronchial epithelial cells.	PS-NPs (100 and 200 nm).	12.5 mg/kg, 25 mg/kg - By intratracheal instillation once per day for 7 consecutive days – *in vivo*. 100 μg/ml, 200 μg/ml, and 400 μg/ml – *in vitro*.	Eight-week-old C57BL/6 mice and Human pulmonary bronchial epithelial cell line BEAS-2B.	Wu et al., 2024 *Journal of advanced research* [60]
Lipidic peroxidation and nephrotoxicity.	Aged PS-NPs.	Orally – *in vivo*.	Mice and *in vitro* human cells.	He et al., 2024 *Small* [61]
Senescence, inflammation, oxidative stress, and mitochondrial membrane disorders.	NPs.	Ranging from 0 to 50 μg/mL.	Porcine IB-RS-2 and PK15 cells – Kidney cells.	Lu & Wei (2024) *Toxicology* [62]

transporters and ATP synthesis, necessary for biosynthetic processes - the decrease in blood-testicular barrier junction proteins may be a consequence of these biochemical disorders. Another important pathway is that of phosphatidylinositol, which is partly responsible for spermatogenesis and cell differentiation, and once again indicates that the metabolism of macromolecules, as well as mitochondrial function (through the apoptotic mechanism), are key points in the negative effects of cumulative NPs on reproductive function.

Daphnia galeata exposed to PS-NPs had their survival and reproduction rates impaired, with consequences on the embryos (mortality rate and abnormality), with accumulation of gonadal NPs and also lipid accumulation [64]. From an *in vivo* and *in vitro* perspective, investigations of polylactic acid (PLA) microplastic and derived NPs in male mice revealed NP penetration of the blood-testis barrier, reproductive toxicity (lower sperm concentration and motility), increased sperm deformity rates, and altered sex hormone levels, leading to mitochondrial damage and testicular oxidative stress. Interestingly, PLA NPs internalized into the mitochondrial sheath and disrupted sperm mitochondrial structure [65]. These studies provide an interesting basis for NPs derived from components other than polystyrene, highlighting their potential ability to internalize mitochondria and impair oxidative aspects necessary for ATP generation, which is crucial for sperm motility and reproductive success.

Bisphenol A, phthalates, and other plastic residues are well known for their influence as EDCs on the hypothalamic-pituitary-gonadal axis, causing sex-specific reproductive harm and even the risk of tumor development. NPs can potentiate these effects, but their biochemical/metabolic implications remain largely unexplored, even more so if we consider the sex-specific aspects and the consequences on female hormonal-reproductive health. The general information of this topic is compiled in Table 4 and Fig. 2.

Table 4
Resumed results and references for Reproductive aspects and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Impacts on anabolic hormones - FSH, LH, and testosterone; impairment in the metabolism of carbohydrates and fatty acids; changes in phosphatidylinositol; impairment in motility, sperm quality, and the blood-testicular barrier.	PS-NPs (80 nm).	0, 3, 6, 12 mg/kg/day from postnatal day 21 to 95 – via gavage	Rats.	Hu et al., 2024 *Particle and fibre toxicology* [63]
Disturbed spermatogenesis; male reproductive toxicity testis mitochondrial dysfunction.	PLA-MP derived nanoparticles.	————————————————————————	Mice.	Zhao et al., 2025 *ACS nano* [65]
Impacts on reproductive aspects and consequences on the mortality and abnormalities in embryos.	PS-NP 51 nm - 52 ± 5 nm.	5 mg/L – for 5 days.	*D.galeata* specimens – cultured.	Cui et al., 2017 *Scientific reports* [64]

4. Toxicological models and microbiochemical disruptions in environmental contexts

4.1. Terrestrial environments

Adopting an ecological and ecosystemic perspective on the effects of NPs is crucial - not only to grasp the full extent of biodiversity loss and environmental degradation linked to white pollution, but also to understand the direct and indirect impacts on human life, including those related to food production, industry, ecological balance, and trophic dynamics. The widespread distribution of NPs across terrestrial ecosystems poses a significant threat to the biochemical integrity of soil, fauna, and flora, thereby heightening the risks of contamination, bioaccumulation, and systemic disruption at multiple biological and environmental levels.

In a holistic manner associated with the discussion, an environmental multi-omics study evaluated earthworms exposed to PS-NPs contaminated with soil at a relatively low concentration (0.02% w:w), evidencing the accumulation of NPs in the intestine (through scanning electron microscopy and confocal), in addition to deleterious effects (oxidative and inflammatory stresses) in the gastrointestinal tract of earthworms. Furthermore, the same authors found a disturbance in the diversity of intestinal microorganisms (with a predominance of *Proteobacteria* and *Firmicutes*), increasing aldosterone-regulated sodium reabsorption, inositol phosphate and 2-hexyl-5-ethyl-furan-3-sulfonic acid metabolism, and decreasing betaine and myoinositol concentrations - decreasing the biodiversity and species richness of the intestinal microbiota, osmoregulatory metabolism, arachidonic acid metabolism, and carbohydrate metabolism [66]. This cross-sectional study indicates the evident environmental damage of NPs in the ecosystem, specifically in the soil, which will certainly indirectly impact aspects of production, “environmental homeostasis”, and human health. From a biochemical perspective, this study demonstrates that NPs affect the “gateway” of metabolism, impacting aspects of digestion and absorption, as well as altering metabolism through the microbiota, specifically by disrupting carbohydrate and arachidonic acid metabolisms.

Using the analysis of aged PS-NPs and metabolomics, Huang et al. (2024) investigated the accumulation in *spinach roots* (using scanning electron microscopy), verifying the enrichment of metabolites associated with ABC transporters, purine metabolism, and pyrimidine metabolism in intact PSNPs; and ABC transporters, aminoacyl-tRNA biosynthesis, pentose and glucuronate interconversions, valine, leucine, and isoleucine biosynthesis, cyanoamino acid metabolism, and galactose metabolism in aged PSNPs [67]. This study provides an important and integrative view of the negative effects of intact and aged PSNPs, considering a temporal and cumulative perspective on the terrestrial ecosystem, evidencing impacts on biochemical cycles important for protein biosynthesis and energy reserves, as well as the supply of energy necessary for survival. In a multiomics investigation, experimental data showed that PS-NPs accumulated in the roots and leaves of Populus, impacting chloroplast thylakoid disintegration and chlorophyll degradation, which led to decreased photosynthesis, stunted growth, and etiolation and/or wilting - with upregulation of the flavonoid biosynthetic process and xenobiotic export and downregulation of catalytic and oxidoreductase activities - in addition to observing aspects of dysregulation in flavonoids, amino acids and their derivatives, lipids, organic acids and their derivatives, and carbohydrates and their derivatives. Other classes related to plant secondary metabolism included terpenoids, phenols and their derivatives, phenolic acids, phenylpropanoids and polyketides, alkaloids and their derivatives, vitamins, and phytohormones. The authors highlight the deleterious effects of NPs on key biochemical pathways in plant responses, which will certainly lead to energetic impairment [68].

Evaluating NPs in *Caenorhabditis elegans*, Qu et al. (2023) observed transgenerational reproductive toxicity, resulting from the inhibition of mitochondrial unfolded protein responses, disturbances in membrane potential, and mitochondrial apoptosis. In the biochemical context, the authors found that amino and sulfonate modifications exacerbate the transgenerational toxicity induced by NP exposure [69]. This study highlights the role of mitochondria in the transgenerational reproductive toxicity caused by NPs in environmental organisms. A multiomics study exposed PS-NPs to *Thompson Seedless* grape seedlings (TS, *Vitis vinifera* L.) and observed accumulation in the cell walls of roots, stems, and leaves, being transported upwards via the xylem. It elucidated the impacts on plant hormone signal transduction, biosynthesis of flavonoids, flavanols, and phenylpropanoids [70]. This study provides important evidence on anabolic and species-sustaining impacts, which will certainly cause negative effects from the production/economic, and ecological points of view.

In a production-focused study, barley (*Hordeum vulgare* L.) irrigated with PS-NPs showed nanoparticle accumulation in plant cells, indicating their ability to penetrate cell walls. This exposure led to a temperature-dependent decline in Rubisco activity, ATP production, and carbon assimilation, alongside reduced expression of key

enzymes involved in sucrose breakdown, glycolysis, and starch metabolism (e.g., UGPase, PGM, G6PDH, FK, PFK, AGPase) [71]. This demonstrates a direct impact on energy metabolism, storage biosynthetic capacity, and disturbances in mitochondria and chloroplasts. Barley plants (*Hordeum vulgare* L.) were irrigated with zinc oxide nanoparticles, either co-exposed or not, which led to increased H_2O_2, abscisic acid, and disturbances in carbohydrate metabolism (e.g., sucrose synthase) in the roots. In this study, based on the global phosphoproteomic analysis, it was identified that the combination of nanomaterials impacted targets related to photosynthesis, carbon fixation, nitrogen metabolism, and arginine and proline metabolism [72]. A study evaluated the impacts of NPs on terrestrial aspects, based on exposure to wheat seedlings (*Triticum aestivum* L.), and observed structural changes, increased carbon, nitrogen and plant biomass contents, in addition to the absorption and accumulation of four micronutrients (Fe, Mn, Cu and Zn) in wheat, which were generally reduced to varying degrees, directly impacting energy metabolism and amino acid metabolism (e.g., amino acids, sugars, organic acids, alcohols, threonic acid, boric acid, butanedioic acid, glycolic acid, aconitic acid, malic acid, mannose and tagatose) [73].

In a study using onion (*Allium cepa*) root tip cells, co-exposure to PS-NPs and BPA significantly increased toxicity, oxidative stress, and lipid peroxidation [74]. Similarly, Jiang et al. (2022) demonstrated that in peanut (*Arachis hypogaea* L.) and rice (*Oryza sativa* L.), PS-NPs translocated from roots and accumulated in grains at maturation, impairing seed formation and reducing levels of essential minerals (Mg, Ca, Mn, Fe, Zn), amino acids (e.g., Glu, Met, Ile, Tyr, Phe, Lys, His, Arg), and unsaturated fatty acids - ultimately compromising nutritional quality [75]. These findings raise concern, as NP exposure may disrupt mineral and vitamin uptake, affecting coenzyme and cofactor functions essential for both biosynthetic and oxidative metabolic pathways.

Overall, these studies elucidate not only specific ecological/environmental impacts but also possible implications for production/industrial/economic aspects, as well as their consequences, including those affecting human health (via food). It is evident, across different models and terrestrial species (fauna and flora), that NPs have a degree of soil toxicity and imbalance in natural composting; metabolic disturbances in anabolic and catabolic aspects of amino acids, sugars, and lipids; photosynthetic damage mainly via disruptions of key enzymes involved in Rubisco activity, ATP and chlorophyll/chloroplast oxidation-reduction; reproductive toxicity via mitochondrial stress; and transport and signaling disorders mediated by xylem/phloem damage, hormonal signaling, and secondary metabolism. The general information of this topic is compiled in Table 5 and Fig. 3.

4.2. Aquatic environments

Aquatic exposure to NPs and their bioaccumulation plays a vital role in the ecological, ecosystem, and global context. Their biochemical adsorption capabilities and interference with key organelles of energy metabolism can certainly affect early microorganisms in the trophic cascade, impacting the ecological scale and potentially reaching humans. Thus, studies investigating the impact of NPs in aquatic environments offer a comprehensive perspective, revealing consequences not only for aquatic species, water quality, and white pollution, but also for broader environmental, industrial, and human health domains.

An experimental and ecosystem study evaluated marine rotifers (marine zooplankton) exposed to MPs/NPs using metabolomic techniques, identifying population and growth impacts, altering reproduction and fecundity in the F0–F2 generation. The authors also observed the accumulation of plastic waste and impacts on feeding patterns, leading to biochemical disturbances associated with purine-pyrimidine metabolism, the tricarboxylic acid cycle, and the protein synthesis pathway, specifically in the upregulated levels of uridine and thymine and downregulated ADP, xanthosine, adenine, uric acid, and L-malic acid. They also showed that the smaller the plastic particle size, the greater the toxicity to rotifers [76]. These results demonstrate the environmental impact of MNPs, specifically in terms of marine ecology, evolution, and ecotoxicology - demonstrating the environmental impacts in numerous directions of the trophic cascades. Biochemically, this study demonstrated how MNPs interfere with energy metabolism, in addition to having direct impacts on amino acid metabolism and oxidative interconversions of amino groups (ammonia ion) and biosynthetic aspects that corroborate the depletion of population growth. Still in the environmental context, experimental data with NPs (smaller sizes) of high-density polyethylene (HDPE) in the freshwater zooplankton *Daphnia magna* affect reproductive aspects, while the fraction with smaller sizes is toxic. This work is based more on the characterization of NPs; however, this degradation results in increasingly smaller, irregular, and oxidized NP particles, demonstrating the potential for dispersion and direct impacts on micro and possibly biochemical aspects [77].

Using neutral NPs, nPS-COOH and nPS-NH2, Liu et al. (2024) observed the inhibition of RuBisCo activity and algal photosynthesis in numerous biological cascades, leading to increased ROS levels and lipid peroxidation, impairing chlorophyll biosynthesis. These exposures also impact photosynthetic electron transport proteins within the thylakoid lumen (e.g., the D1 and D2 proteins of the P680 reaction center of photosystem II) and antenna proteins in photosynthesis (e.g., the chlorophyll *a*/b-binding proteins of light-harvesting complex II and I) [78]. The exposure to positive and negative NPs in *Daphnia magna* proved lethal at a concentration of 0.32 mg/L (positive NP). Negatively charged carboxylated NPs were also toxic at all concentrations used in our long-term study. The authors observed no impairment of reproductive function. This is an important study that provides a necessary framework for understanding the future impacts of NPs in natural aquatic environments [79]. This study corroborates the findings of other studies regarding the impacts of NPs at different doses and bioaccumulation on zooplankton, which certainly affect photosynthetic and energy capture capacity, leading to negative consequences not only for the algal population in the trophic cascade but also at subsequent ecological scales.

The literature elucidates that exposure to NPs, hypoxia, and immunological stress in solitary ascidian Ciona decreases the innate memory and adaptive response to environmental changes in the pharynx and intestine - essential organs for homeostasis of this species - with distinct expressions of molecules between organs (Tnf, Tgfb, VCBP-B, VCBP-C, Il17-2, and Tlr-2) [80]. Although this study does not detail specific biochemical mechanisms, it reveals alterations in the immune responses of both the upper and lower gastrointestinal tracts - changes that likely impair nutrient absorption and metabolism, ultimately affecting population dynamics and serving as indicators of ecosystem disruption caused by plastic exposure. Another study evaluated exposure to high environmental concentrations of NPs in *C. pyrenoidosa* (microalgae), mimicking occupational aspects of environmental toxicology. The authors found, using the metabolomics technique, that there were antioxidant disturbances, decreased metabolism of nucleotides, arachidonic acid, and tryptophan, and increased metabolism of cysteine and methionine, finally leading to a reduction in cellular non-enzymatic antioxidant capacity. On the other hand, intriguingly, the study concluded that, when exposed to NPs + Cadmium, the toxicological effects were mitigated, finding important biochemical interactions with adsorbed NPs and

Table 5
Resumed results and references for Terrestrial Environment aspects and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Oxidative and inflammatory stress in earthworms damages the intestinal epithelium, disrupting gut microbiota diversity and impairing osmoregulation, carbohydrate metabolism, and arachidonic acid pathways.	NPs (90-110 nm).	Relatively low concentration (0.02% w:w).	Contaminated soil and earthworms.	Tang et al., 2023 *Journal of hazardous materials* [66]
Absorbed by roots and transported to aboveground tissues, stress, and metabolic disorders.	Aged and prestine PSNPs.	100 mg/L for 3 weeks to the seedlings.	Spinach.	Huang et al., 2024 *Journal of hazardous materials* [67]
Toxicity in roots, thylakoid disintegration, and shifts in metabolic patterns.	PS-NP (50 nm).	200, 400, 600, and 800 mg/L in 700 mL - 10 mg/mL.	Populus × euramericana cv. '74/76' (Poplar 107).	Xu et al., 2024 *Journal of hazardous materials* [68]
Anabolic disorders.	NPs (100 nm).	15 days of exposition.	Thompson Seedless (TS, *Vitis vinifera* L.) grape.	Zhang et al., 2024 *Journal of hazardous materials* [70]
Transgenerational biochemistry disorders in the antioxidant defense, mitochondrial homeostasis, and reproductive toxicity.	Approximately 52.3 nm for PS, 50.7 nm for PS–SOOOH, and 49.7 nm for PS–NH_2.	1 mg/L from L1 stage to adult day 1.	Age-synchronized L1 *C. elegans*.	Qu et al., 2023 *Journal of hazardous materials* [69]
Aggravated photosynthetic, reactive oxygen species burst in mitochondria, and suppressed carbohydrate metabolism.	PS-NPs (65.776 nm).	Irrigated with a 2 g L-1 solution - 7 days.	Barley (*Hordeum vulgare* L.).	Wang et al., 2022 *Journal of hazardous materials* [71]
Reduction in the number of seeds, impairment of catalytic cofactors, reserve biosynthetic aspects (minerals, fatty acids, and amino acids), and nutritional quality.	PS-NPs ≈80 nm.	Soil - 50 or 250 mg kg^{-1}.	Seeds of peanut (*Arachis hypogaea* L.) and rice (*Oryza sativa* L.).	Jiang et al., 2022 *Advanced science (Weinheim, Baden-Wurttemberg, Germany* [75]
Inhibited the roots' elongation and leaf growth, increased the accumulation of ROS and ABA, and changed protein phosphorylation and carbohydrate metabolism.	Red fluorescently labeled and non-fluorescent NPs (100 nm).	Irrigated with zinc oxide nanoparticles (0.5 g L−1), NPs (1 g L−1), and the combination of these two nanomaterials for 10 days.	Barley (*Hordeum vulgare* L.) plants.	Guo et al., 2023 *Journal of hazardous materials* [72]
Growth parameters and chlorophyll content were greatly increased, reducing the shoot to root biomass ratio and micronutrients content.	Fluorescent (Nile red) and non-fluorescent nanospheres (100 nm).	0.01, 0.1, 1.0, 10 mg/L.	Wheat seeds (*Triticum aestivum*).	Lian et al., 2020 *Journal of hazardous materials* [73]
PSNPs increase BPA uptake and toxicity in *Allium cepa* roots, enhancing genotoxic effects.; EPS corona formation mitigates PSNP–BPA toxicity through antioxidant enzyme interaction.	PSNPs 200 nm.	Coexposure to Bisphenol A and PS-NPs - 100 mgL^{-1} (PSNPs) and 2.5, 5, and 10 mgL^{-1} of BPA.	Rhizosphere soil.	Giri et al., 2024 *Journal of hazardous materials* [74]

reduction of free Cd2+ [81]. Therefore, it can be understood that NPs impact the trophic cascade of products and their ecosystem aspects, interfering with intermediate protection factors associated with the biosynthesis of amino acids and polyunsaturated fatty acids, while increasing the response to stress and metabolites that indicate cellular stress. Another interesting point of view is to understand the biochemistry of NPs and generate a basis for future studies that evaluate ways to mitigate or saturate the adsorption potential of NPs.

In *Tetrahymena thermophila*, PS-NPs disrupt calcium homeostasis by inducing inositol-1,4,5-trisphosphate-dependent Ca2+ release from the endoplasmic reticulum to the cytosol, primarily affecting membrane proteins or proteins involved in metabolic processes or catalytic activity. These conditions increased mitochondrial permeability and the generation of reactive oxygen species (Ca2+, Sod1, Sod2, Gpx, Gsr, Hsp703, Hsp704, Hsp705, and Hsp90), leading to inhibition of growth and multixenobiotic resistance transporter activity [82]. Intriguingly, PS-NPs in Spirulina platensis reduced growth rate, chlorophyll, and carotenoid levels, increasing proline levels and lipid peroxidation [83]. In the context of amino acid metabolism, the overload of the non-essential amino acid proline production may indicate an adaptive stress response, due to its function as a protective osmolyte and signaling, which are essential for membrane stability, cytosolic pH, catalytic functions, and protein synthesis. In another study exploring biochemical aspects in algae, exposure to NPs increased the production of microcystin-leucine-arginine (MC-LR) by *Microcystis aeruginosa*, a common but toxic secondary metabolite. Consequently, this mechanism impaired pigment biosynthetic aspects and oxidative aspects of photosynthesis, stimulating an increase in leucine and arginine levels and oxidative stress - and impairing biological pathways associated with amino acids, linoleic acids, dicarboxylic acids, fatty acids, carbohydrates, purines, amines, steroids, eicosanoids, and isoflavonoids [84]. *Microcystis aeruginosa* exposed to amino-modified PS-NPs in conjunction with nitrate, urea, or ammonium has impaired growth rates due to disruptions in nitrogen transport pathways. Furthermore, an adaptive response occurs, leading to increased amino acid production, carbonic anhydrase synthesis, the Calvin cycle, microcystin synthesis, extracellular polymeric substances, and membrane phospholipid production [85]. These 4 manuscripts provide numerous biochemical and organelle-specific insights into NP exposure, important for highlighting disturbances not only in these organisms but also in aquatic ecosystems and freshwater

quality.

PS-NPs, amino-modified PS-NPs (nPS-NH2), and carboxylated PS-NPs (nPS-COOH) led to decreased bacterial diversity, fungal communities, and nitrification in sediments, while denitrification increased in the nPS-NH2 and nPS-COOH treatments (NAR, NIR, NOR, and NOS). Furthermore, a decrease in the richness of *Proteobacteria* and an increase in the relative abundance of *Bacteroidetes* and *Actinobacteria* were observed. On the other hand, *Firmicutes* and *Chloroflexi* were slightly inhibited in the nPS-NH2 and nPS-COOH treatments [86]. This work provides an important basis for the biochemical modifications of NPs on microbial communities and functions, and possible ecological impacts. In this context, the physicochemical properties of plastic derivatives are extremely important, as they can increase their capacity for bioaccumulation, adsorption, and even metabolic dysregulation. Microalgae exposed to high concentrations of NPs showed impaired growth, but the authors found no changes in photosynthesis [87].

A very interesting and important study of the ecological context evaluated the food chain including *Chlorella pyrenoidosa*, *Daphnia magna*, and *Micropterus salmoides* (algae-crustacean-fish) and a higher trophic level in fish after isolated or co-exposure of NPs and di (2-ethylhexyl) phthalate (DEHP), demonstrating the great adsorption and transfer capacity of NPs in conjunction with other DEs. Finally, this study verified the biochemical impacts of lipids (fasn, hsl, cpt1a, atgl, apob, fabp1, lpl, cetp) in the last trophic chain [88].

Bivalve models are widely explored in the environmental context of plastic exposure, and provide important insights into biochemical changes with consequences for survival and ecosystem homeostasis. Environmental studies using multiomic strategies (transcriptomics and proteomics) evaluated the exposure of environmentally relevant positively or negatively charged NPs on the digestive glands and gills of the mollusc *Ruditapes philippinarum* and observed impairment of mitochondrial function (e.g., ATP generation and mitochondrial respiratory chain induced ferroptosis). In contrast, the charged NPs stimulated innate immune responses and complement and coagulation cascades. *In vitro* tests in mollusc immune cells confirmed that internalized charged NPs triggered changes in mitochondrial morphology (ADP/ATP ratio), a decrease in membrane potential, and the onset of ferroptosis [89]. In addition, in an *in vitro* modeling-based study with marine bivalves *Ruditapes philippinarum* exposed to NPs, there was a growth inhibition, oxidative stress, lipid peroxidation, and DNA damage [90]. Interestingly, this study deepened the cell-specific impacts of exposure to NPs specifically on mitochondria, highlighting their deleterious potential on the energy production-oxidative stress-immune system axis. Another point that deserves to be highlighted in the discussion is the environmental impact that this can cause, harming the survival of these mollusks, predation, and leading to an accumulation of prey that leads to deregulation in ecological trophic cascades. In cell culture of hemocytes, small semigranular cells and small agranular or hyaline cells of *Mytilus galloprovincialis* exposed to PS NPs had an increased immune response, and the release of toxic radicals was observed, effectively in the imbalance between oxygen, hydrogen peroxide, reactive oxygen species, and nitric toxic radicals) [91].

Based on research on large yellow croaker *Larimichthys crocea* exposed to dietary NPs, Lai et al. (2021) observed impaired survival and growth, excessive hepatic lipid accumulation via impaired lipolysis (ATGL, PPARα, and ACO), and antioxidant imbalance, in addition to increased AST and ALP. *In vitro*, NPs also disrupted hepatocyte lipid metabolism. Furthermore, fish muscle analysis revealed lipogenesis-related genes (FAS, SREBP1, and PPARγ) and lipid catabolism-related genes (ATGL and PPARα) [92]. This study provides interesting insights into the detrimental effects of NPs on production, potentially impacting consumer health, particularly in the intake of long polyunsaturated fatty acids (e.g., Omega-3 and 6).

Regarding the aquatic ecosystem with production-associated bias, marine fish *Dicentrarchus labrax* exposed to NPs exhibited biochemical disturbances related to lipid metabolism, immune

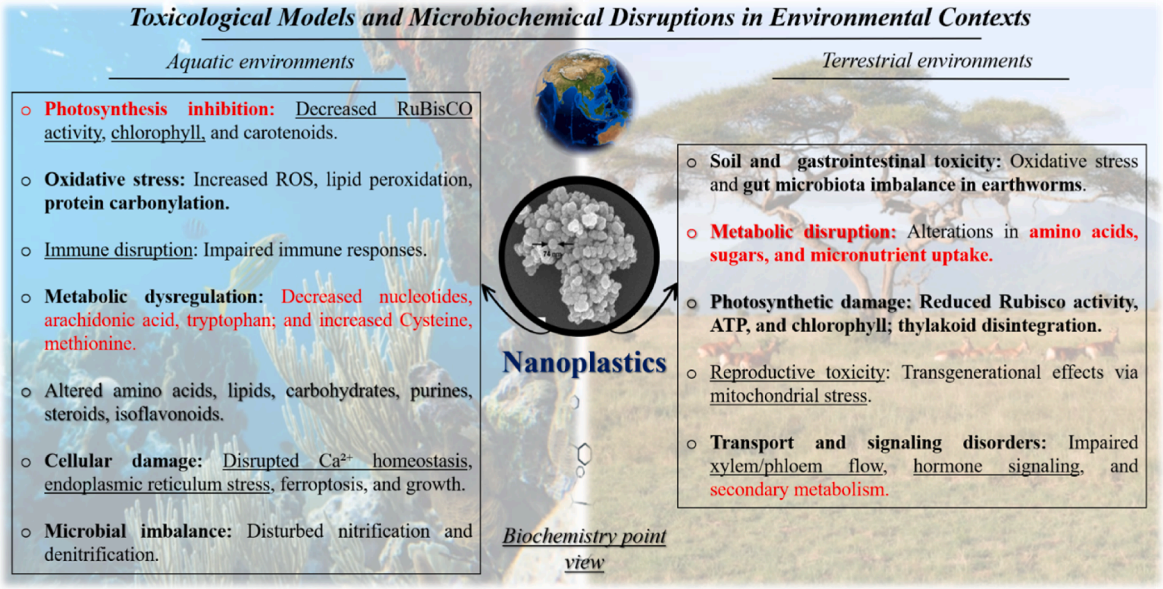

Fig. 3. Toxicological models and microbiochemical disruptions induced by nanoplastics (NPs) in aquatic and terrestrial environments. In aquatic systems, NPs impair photosynthesis, induce oxidative stress, disrupt immune and metabolic processes, alter biochemical composition, cause cellular damage, and disturb microbial balance. In terrestrial systems, NPs trigger oxidative stress and gut microbiota imbalance, alter plant metabolism and photosynthesis, cause reproductive toxicity, and disrupt transport and signaling pathways. The Figure was composed using some illustrations from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

system, and general cellular stress (pparα and pparγ), with decreased levels of esterase activity and ALP in plasma, and lower alkaline phosphatase levels were found in skin mucus [93]. Using parental pre-exposure to NPs and the response of *Hediste diversicolor* to another contaminant (arsenic), a study verified lipid peroxidation and protein carbonylation, elucidating the ability of NPs to sensitize these organisms to the negative effects of other pollutants [94]. In an important model for production and aquaculture, there was mixed pollution of NPs and lead (M07) in anglerfish during the exposure and recovery phases, observing lead accumulation in muscle tissue, increased hepatic lipid droplets and elevation of the gill epithelium - from the omics profile, the functions related to the proteasome, protein processing in the endoplasmic reticulum and endocytosis, as well as the metabolites deoxycytidine monophosphate, L-aspartic acid, L-tyrosine, methylmalonic acid, N-carbamoyl-L-aspartic acid, N-palmitoylsphingosine, 3-sulfopyruvic acid and L-aspartic acid [95].

In the aquatic environment, perhaps one of the most studied aspects of MPs and NPs, studies have demonstrated numerous disturbances from the point of view of cell-biochemical pathways. Among the numerous species-specific and route-specific disorders observed, we can interestingly highlight primary/tropic aspects from an ecological point of view and even consequences in the economic and human health sense, indirectly, such as: Inhibition of RuBisCO activity and chlorophyll biosynthesis, reduction of photosynthetic efficiency and carotenoid levels, elevation of ROS levels, lipid peroxidation and protein carbonylation, immunological dysfunction, decreased metabolism of nucleotides, arachidonic acid and tryptophan, increased metabolism of cysteine and methionine as an adaptive effect, impairment in the pathways of amino acids, linoleic acid, dicarboxylic acid, fatty acids, carbohydrates, purines, steroids and eicosanoids, interruption of the Calvin cycle and isoflavonoid biosynthesis, cellular damage correlated with the interruption of calcium homeostasis and the integrity of the endoplasmic reticulum, activation of ferroptosis, reduction of growth rates and levels of photosynthetic pigments, disturbance of the microbial process of nitrification and denitrification. The general information of this topic is compiled in Table 6 and Fig. 3.

5. Applications and co-exposure

In vivo and *in vitro* models try to mimic certain environments or microenvironments, including those exposed to EDCs and toxic substances. Furthermore, some authors investigate not only the isolated effects of toxic substances but also a combination of others, highlighting co-exposure in an attempt to approximate reality. Other studies do not effectively evaluate exposure in *in vivo* or *in vitro* models, but rather from mathematical and computational models, trying to mimic, through programmed physicochemical strategies, how NPs can interfere in biological systems - interestingly approaching the current context that increasingly requires studies - personalized medicine.

In a computational study (simulations of dissipative particle dynamics) that is quite descriptive from a physicochemical perspective, it was observed that tetrahedral NPs with high shape anisotropy and sharp edges exhibit strong absorption in lipid membranes. Two distinct dynamic states were observed: out-of-plane motion was significantly restricted by membrane confinement, leading to cage translation and subdiffusive rotation, while in-plane diffusion remained Brownian. These findings highlight how nanoparticle shape influences membrane interactions and intracellular dynamics [96]. A fascinating and innovative study explored the influence of PS-NPs on the viral transmission of vaccinia virus, observing that they accelerate the formation of migrasomes early in the infectious process. From a biochemical perspective, this study elucidated an increase in the size of lipid droplets, highlighting this condition as critical for cargo transport during viral infections [97]. PS-NPs also disrupt iron-binding protein transferrin (TF) binding, unfolding, and loosening of the polypeptide chain and TF structure, impairing protein folding and denaturation, and disrupting the surrounding aromatic amino acid microenvironment [98].

Co-exposure of NPs and ciprofloxacin in unicellular cyanobacterium *Synechocystis sp.* NPs negatively regulated the TCA cycle and glycerophospholipid metabolism [99]. Co-exposure studies are extremely important for a holistic view of the potential disorders caused by different combined adverse effects—mainly to mimic and more closely approximate what occurs in the natural environment. In another study with *Euglena gracilis*, using co-exposure to NPs and Cd2+, there was an increase in superoxide dismutase, peroxidase, and extracellular polymeric substances. Based on the metabolomic profile, both NPs and Cd2+, alone or in combination, induced disturbances in the pathways of nucleotide metabolism, carbohydrate metabolism (e.g., hydrogen phosphate due to oxidative phosphorylation of ATP), amino acid metabolism (e.g., L-cysteine and L-histidine), lipid metabolism (e.g., glycerolipid, diacylglycerol), and membrane transport [100]. Another study with co-exposure of norfloxacin and NPs in *T. tridentatus* elucidated an imbalance in the antioxidant response, developmental impairments associated with ecdysone, and a high relative abundance of *Bacteroidetes*, which certainly increases the risk of dysbiosis and cell-specific metabolic and biochemical impairments [101].

In a multivariate study with co-exposure of PS NPs with oxLDL *in vitro*, the results indicated significant lipid accumulation, oxidative stress (MDA, CAT, ROS), and inflammation (TNFα, IL-6, IL-10) in the RAW264.7 macrophage cell line – mainly at the highest doses. In addition, NPs were used *in vivo* in apolipoprotein knockout (ApoE−/−) mice, and a lesion similar to hepatic steatosis was observed, in addition to the elevation of ALS, TC, TG, LDL-C, and HDL-C in the livers (10 mg/kg) and decreased gene expression of ABCA1 and ABCG1, in addition to the appearance of atherosclerotic plaques in the aortic arch [102]. This work is very important, as it demonstrates the isolated effects of NPs - especially at high doses - on inflammation-responsive strains and their *in vivo* association with atherosclerosis, in addition to the potential disturbance in co-exposure - in the strains - or with high-fat diets in the *in vivo* model, which generated a picture of fatty liver injury.

Although the focus of this narrative review is not on co-exposure, which even more closely mimics real-world exposure, we have highlighted a few biochemical aspects that are altered by the co-exposure of NPs and other substances, primarily elucidating the adsorptive capacity and exacerbating the negative effects of NPs. This opens the door for preclinical and clinical studies that utilize this combination of molecules, their biochemical interactions, and how this affects different organisms and cell-specific biochemistry. The general information of this topic is compiled in Table 7 and Fig. 4.

6. General insights

This review is quite broad in outlining numerous effects of NPs at different biological scales, characterizing different consequences, *in vivo* and *in vitro*, on distinct organs and systems, with experimental, preclinical, ecological, and environmental implications, specifically emphasizing biochemical aspects. Despite this, this breadth highlights a difficulty in elucidating biological patterns, or even providing methodologies and technical standards as a basis for future studies. To clarify these contexts and highlight the different doses of NPs – considered environmental or

Table 6
Resumed results and references for Aquatic Environment aspects and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Deregulation in the algal chloroplast homeostasis, photosystem II P680 reaction center D2 protein, and the photosynthesis process.	Neutral, carboxylic-modified, and amino-modified PS-NPs.	Cell density of 1×10^6 cells/mL - 10 μg/mL NPs for 48 h.	Chlorella sp. (No. FACHB-9).	Liu et al., 2024 *Journal of hazardous materials* [78]
Ecological consequences and decreased survival.	Positively (aminated, 53 nm) and negatively charged (carboxylated, 26 and 62 nm) NPs.	103 days - 0.32, 0.032, 0.0032; 3.2, 0.32; 7.6, 3.2, 0.76, 0.32 mg/L.	*Daphnia magna*.	Kelpsiene et al., 2020 *Scientific reports* [79]
Impacts on the Ca homeostasis, increased mitochondrial permeability, ROS production, and growth inhibition.	PS-NPs (~20 nm).	0, 0.3, 1, 3, 10, and 30 mg/L or 0, 6×10^{13}, 2×10^{14}, 6×10^{14}, 2×10^{15}, and 6×10^{15} particles/L).	Ciliate *T. thermophila* SB210.	Wu et al., 2021 *Journal of hazardous materials* [82]
Decreases in specific physiological factors and an elevation in lipid peroxidation in Spirulina.	PS-NPs (100, 300 nm and the average size 185 nm.	0.1 mg L^{-1}, 1 mg L^{-1}, and 10 mg L^{-1}.	Microalgae Spirulina platensis.	Karimi et al., 2024. *Journal of hazardous materials* [83]
Enhancement of MC-LR synthesis due to the upregulation of Leucine and Arginine, in addition to membrane damage.	Amine (-NH_2, positive charged) and carboxyl (-COOH, negative charged) modified PS-NPs (20 nm).	10 mg/L.	*M. aeruginosa* (FACHB-905).	Huang et al., 2024 *Journal of hazardous materials* [84]
Membrane damage, affecting nitrogen transport and oxidative stress responses, and alteration in the carbon and nitrogen metabolism.	Particle-sized amino-modified polystyrene nanoplastics (PS–NH2) (50 nm).	Exposed to nitrate, urea, or ammonium/10 μg/mL PS-NH_2.		Liu et al., 2024 *ACS nano* [85]
Alterations in the diversity of bacteria and fungi significantly inhibited microbial nitrification.	nPS; nPS-NH_2 and nPS-COOH (100 nm).	60-day exposure - 100 mg/L stock suspensions of nano-PS.	Sediment and overlying water - bacteria and fungi.	Zhao et al., 2023 *Journal of hazardous materials* [86]
No direct effects on photosynthesis, however, in the growth.	Polystyrene NPS – Uncharged (0.05-6 μm) and Negatively charged (0.5 μm).	25, 250 (mg/L).	Microalgae (D. tertiolecta) *C. vulgaris* and *T. pseudonana*.	Sjollema et al., 2016 *Aquatic toxicology* [87]
Inhibition of population growth, reduced ingestion rates and volume of marine rotifers, impacts on life-history traits, and nutrient metabolism.	MPs/NPs (70 nm, 500 nm, and 2 μm).	20, 200, and 2000 μg/L.	Marine rotifers (*Brachionus plicatilis*).	Li et al., 2023 *Journal of hazardous materials* [76]
Small particles of NPs with environmental potential to deregulate and oxidize the primary cascade of ecology.	NPs (~3 nm) of high-density polyethylene (HDPE).	Polyethylene breakdown (PEBD) NPs 10 kDa and less than 1% compared to in 1st toxicity test.	Freshwater zooplankton *Daphnia magna*.	Ekvall et al., 2022 *Scientific reports* [77]
Trophic transfer of PSNPs and DEHP induces oxidative stress and disrupts lipid metabolism, revealing biochemical toxicity across the food chain.	Polystyrene nanoplastics (80 nm).	Coexposure to PSNPs and DEHP, 5 mg/L, DEHP (2 μg/L) for 24 h.	C. pyrenoidosa (FACHB-9), *D. magna*, and *M. salmoides*.	Liao et al., 2023 *Journal of hazardous materials* [88]
Impaired mitochondrial function – ATP/ADP ratio, oxidative stress, inflammation, and ferroptosis in the digestive glands and gills of the clams.	69.6 ± 12.2 nm for p-NPs (positive) and 65.3 ± 8.7 nm for n-NPs (negative).	NPs at 3.6×10^9 particles/mL.	*Ruditapes philippinarum*.	Zhou et al., 2024 *ACS nano* [89]
Lipidic peroxidation and mitochondrial deregulation.	NPs at 3.6×10^9 particles/mL.	1.6×10^9-1.6×10^{11} particles/mL (p/mL) of NPs.		Zhou et al., 2024 *ACS nano* [90]
Greatest effects on the immune system and oxidative stress generation.	PS-NPs (50 nm, 100 nm and 1 μm).	3 and 24 h at different concentrations 1 and 10 mg L^{-1}).	*Mytilus galloprovincialis* (Mollusca).	Sendra et al., 2020 *Scientific reports* [91]
Decreased survival rate and growth performance, liver lipid metabolism disorders *in vivo* and *in vitro*, and muscle composition alterations.	Green fluorescent PS NPs beads (80 nm).	Suspensions of 0, 1, 10, and 100 mg/kg in diet.	Large yellow croaker juveniles (*Larimichthys crocea* - five months old).	Lai et al., 2021 *Journal of hazardous materials* [92]
Molecular signaling pathways related to lipid metabolism were altered in the liver and had an impact on the immune response in skin mucus.	Polymethylmethacrylate (PMMA) NPs - ~45 nm	0 mg/L (control), 0.02 mg/L, 0.2 mg/L, 2 mg/L and 20 mg/L NPs – In water	Juvenile *D. labrax* specimens	Brandts et al., 2018 *Genomics* [93]
Behavior and protein oxidation alterations.	100 nm PS NPs.	Parents exposed for 28 days to 0.005 mg/L of PS NPs (PEO – parentally exposed organisms).	Six-months-old Specimens of *H. diversicolor*.	Silva et al., 2022 *Environmental research* [94]
Lipid droplets and epithelial lifting were the primary lesion types in red drum; the cell cycle, proteasome, and spliceosome contribute to detoxification in red drum.	(PS-NPs, 30 nm, 2.0 % w:v)	5 mg/L 30 nm PS-NPs and 0.7 mg/L of lead, labeled as m07. In water.	Three-month-old red drum juveniles	Sun et al., 2024 *Journal of hazardous materials* [95]
Environmental stress mounts a robust adaptation response, based on changes in the expression of several immune/stress-related genes.	0.1 μm or 0.35 μm diluted NPs.	Hypoxia. NPs (9.1×10^8 particles/mL and 7.4×10^7 particles/mL), and immunological stress.	Adults of *C. robusta*.	Marino et al., 2023 *Frontiers in immunology* [80]
Impacts on the Cd2+ content and antioxidant enzymes.	Polyvinyl chloride (PVC) NP beads (200 nm).	1 mg mL^{-1} and 1 μg mL^{-1}.	C. pyrenoidosa.	Li et al., 2024 *Environment international* [81]

Table 7
Resumed results and references for the general aspects and Nanoplastics studies.

Mainly results	Exposition	Dose	Organism	Authors
Toxicity in co-exposure or isolated – impacts on the metabolism and survival.	NPs (0.05 μm).	Co-exposure: Ciprofloxacin - 0, 20, 30, 40, 50 and 60 μg/L; NPs/MPs - 5, 50, and 100 mg/L.	*Synechocystis sp.* PCC 6803.	You et al., 2021 *Environment international* [99]
PS-NPs and Cd co-exposure enhanced microalgal toxicity through metabolic disorders and oxidative stress.	PS-NPs (100 nm).	NPs PS-NPs (0, 0.05, 0.5, and 5 mg/L; Co-exposure to 50 μg/L (1.1 × 1010 particles/L) of PS and 50 μg/L of Cd2+.	Microalgae *Euglena gracilis.*	Cao et al., 2022 *Journal of hazardous materials* [100]
Computational simulation between NPs tetrahedra and plasmic membrane – potential interactions that affect membrane homeostasis.	————————————	Hydrophobic nanotetrahedra (varying sizes).	Membrane-only simulations - simulation box constructed by placing DOPC molecules.	Yong & Du, 2023 *The journal of physical chemistry* [96]
Oxidative stress and dysbiosis in horseshoe crabs.	PS-NPs (100 nm).	0.5 μg/L of NPs and norfloxacin.	First instar *T. tridentatus* horseshoe crabs.	Huang et al., 2024 *Journal of hazardous materials* [101]
Migrasome formation, elevated PI(4,5)P2, cholesterol, and lipid droplets in host cells.	Red fluorescent PS-NPs (80 nm) and PS-NPs (150 nm).	Plasmids.	Huh7.5.1 cells in DMEM - Viruses VACV Western Reserve (WR) stain and a fluorescently labeled VACV (A4YFP).	Tang et al., 2024 *Biochemical and biophysical research communications* [97]
Co-exposure of NPs and ox-LDL induces lipid accumulation, oxidative stress, and inflammation; *In vivo*, there were atherosclerotic plaques and liver fat accumulation in PS NPs-exposed ApoE−/− mice.	PS-NPs (100 nm, red fluorescence).	Co-exposure to PS NPs (50 μg/mL) and Human ox-LDL - *in vitro*. 5 and 10 mg/kg of NPs and high-fat diet twice a week for three months, by gavage - *in vivo*.	Mouse leukemic monocyte macrophage RAW264.7 and Male ApoE$^{-/-}$ mice (C57BL/6 background) at 6–8 weeks of age.	Wen et al., 2024 *Journal of hazardous materials* [102]
Release of free Fe ions from iron-loaded TF protein; the TF-PS-NPs interaction was confirmed by *in vitro* binding experiments.	PS-NPs (100 nm).	Transferrin and PS-NPs were diluted with ultrapure water (1000 mg/L).	Dialysis, ICP-MS, multi-spectroscopic techniques, and computational simulation.	He et al., 2024 *Journal of hazardous materials* [98]

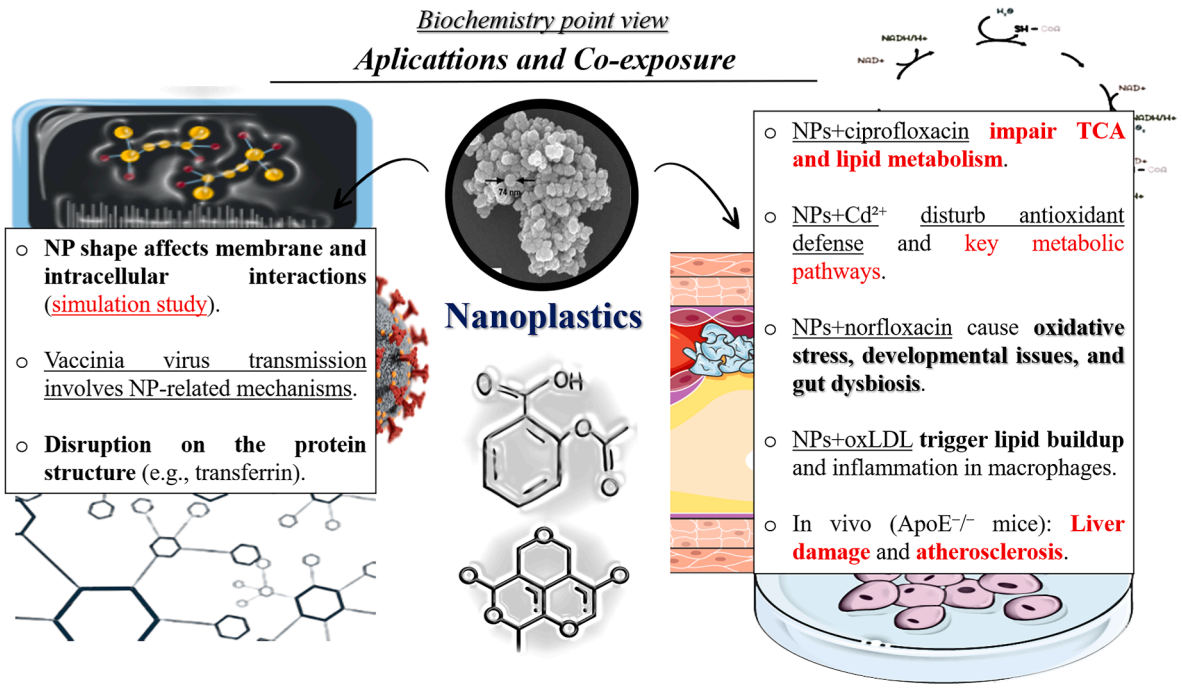

Fig. 4. Biochemical perspectives on nanoplastic (NP) applications and co-exposure effects. The left panel illustrates molecular-level findings, including the influence of NP shape on membrane and intracellular interactions (simulation study), NP-related mechanisms in vaccinia virus transmission, and NP-induced protein structural disruption (e.g., transferrin). The right panel summarizes co-exposure outcomes: NPs combined with ciprofloxacin impair the TCA cycle and lipid metabolism; with Cd^{2+}, they disturb antioxidant defense and key metabolic pathways; with norfloxacin, they induce oxidative stress, developmental impairments, and gut dysbiosis; with oxidized LDL (oxLDL), they promote lipid accumulation and macrophage inflammation. *In vivo*, exposure in ApoE$^{-/-}$ mice leads to liver damage and atherosclerosis. The Figure was composed using some illustrations from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

supradoses – in their different applications – *in vivo* or *in vitro* – Supplementary Table 1 clarifies these observed patterns.

6.1. Preclinical perspective and clinical potential

Collectively, the findings summarized in this review support the plausibility of an associative and potentially cumulative health risk arising from NP exposure, particularly given their small size and unique physicochemical properties, which facilitate cellular uptake and tissue distribution. Although the full impact of NPs on neuroendocrine, cardiovascular, digestive, and reproductive systems remains incompletely understood, both *in vitro* and *in vivo* studies provide consistent evidence that key metabolic and biochemical processes are vulnerable targets—especially those involving mitochondria and the endoplasmic reticulum.

Current data suggest that NP exposure may promote organ-wide oxidative imbalance, potentially initiated by disruptions in core oxidative metabolic pathways such as glycolysis and the tricarboxylic acid (Krebs) cycle. Perturbations in these pathways may compromise the generation of electron carriers (NADH and $FADH_2$), impair oxidative phosphorylation, and reduce ATP production. Concurrently, interference with the pentose phosphate pathway and NADPH availability may hinder glutathione-dependent antioxidant defenses, while alterations in coenzymes and essential micronutrients (e.g., vitamins and catalytic minerals) may further exacerbate redox instability.

Beyond redox disturbances, the literature also suggests broader systemic consequences resulting from tissue-specific metabolic disruptions. Notably, consistent alterations in lipid metabolism—including effects on lipolysis, lipogenesis, and β-oxidation—have been described, along with changes in amino acid metabolism, possibly reflecting increased mobilization of glucogenic and ketogenic substrates. Such shifts may impose additional metabolic burden on organs such as the liver and kidneys, thereby amplifying systemic dysfunction. Together, these mechanistic insights suggest that NP exposure may not act through isolated pathways, but rather through interconnected metabolic and redox networks, ultimately contributing to multi-organ vulnerability.

Thus, in the experimental context, progress has been made in understanding NPs' cell-organ-specific biochemical aspects. However, relevant data already exist that direct their impact on both anabolism and catabolism, including the metabolism of the three macromolecules. However, clinical studies on NPs are still scarce, even without effectively considering their biochemistry. However, reviews like this one and further experimental work will certainly provide a solid foundation for interventional, translational, and epidemiological research.

6.2. Environmental and toxicological perspectives

The results obtained from both terrestrial and aquatic studies have revealed key biochemical pathways impacted by NPs, which certainly lead to losses in survival, with consequences related to trophic cascades, production/industrial and economic aspects, and even indirect consequences for humans - taking into account the cumulative effects, bioaccumulation, and bioavailability of NPs. These various studies have provided interesting insights into the potential risk of NPs interfering with chloroplasts and pigments, transport via xylem and phloem, and bioaccumulation in different regions of these plants - providing a global view of the biochemical impacts on fauna across different climatic and territorial aspects. Interestingly, all of these changes demonstrated negative effects on plant energy metabolism, photosynthetic capacity, and key pathways such as the Calvin and TCA cycles. Biosynthetic impairments in reserves (e.g., polysaccharides and polypeptides) were also observed, as well as cellular stress mediated by disturbances in amino acid metabolism and the depletion of polyunsaturated fatty acid formation. This finding is particularly significant, as long-chain polyunsaturated fatty acids - essential for immune function and vascular responses - are obtained directly or indirectly from the human diet of these synthesizing organisms.

6.3. Cellular-physiological projections

The global and holistic view of the effects of NPs will certainly be increasingly understood in different cascades: genomic, epigenomic, transcriptomic, proteomic, metabolomic, and finally physiological and systemic effects. Regarding experimental models, the biochemical changes observed in lipid metabolism due to exposure to NPs strongly suggest a possible imbalance: In the anorexigenic and orexigenic response (satiety and hunger behavior), which may indicate an impairment in the hypothalamic response (arcuate nucleus) or even in the synthesis and interaction of these hormones (e.g., leptin, ghrelin, NPY); in addition to the anabolic (insulin, GH) and catabolic mechanisms - to the sympathetic response (noradrenaline) and the hormones glucagon, cortisol/corticosterone and adrenaline - which would be correlated with the damage to the mechanisms of lipolysis and lipogenesis - in addition to the association with exacerbated muscle and liver catabolism - a context that is also associated with the altered routes in these macromolecules. Still in the neuroendocrine sense, due to the context of bioaccumulation and interactions of NPs, it is plausible to create the hypothesis, given the disturbances in metabolites that determine hormone biosynthesis, that there is a disturbance in hormones that adjust motility, gastric emptying and enzyme release (e.g. cholecystokinin, secretin, gastrin), in addition to hormones associated with the regulatory axes of reproduction (e.g. GnRH, FSH, LH, androgens and estrogens), growth (GHRH, GH, IGF1) and basal metabolism (TRH, TSH, T3, T4 - even more so considering the ionic need for iodine and how NPs can interfere with mineral uptake). About plants, it is evident that NP disorders can be directly associated with impaired mechanisms of growth, reproduction and photosynthetic regulation, in addition to secondary factors - which can have a direct impact on auxins (growth and rooting), gibberellins (germination), cytokinins (cell division and delayed senescence), ethylene (fruit ripening - a context highly associated with economic aspects), ABA (dormancy and stomatal closure), salicylic acid (defense against pathogens), among others.

6.4. Biochemical gaps and future perspectives

Despite a considerable range of associative data related to the consequences of plastic exposure of NPs on numerous biochemical aspects, there are still some interesting gaps that can be investigated to better articulate and assess the pertinence of what we know so far. Regarding faunal aspects, certainly highlighting the enzymes and intermediates of the photosynthetic process, Calvin cycle (e.g., fructose-6-phosphate), and TCA cycle (e.g., oxaloacetate, malate, α-ketoglutarate) are necessary to have a more tangible mechanistic overview of how NPs can interfere in these processes - in addition to investigating the intermediates of biosynthetic pathways of proteins, polysaccharides (e.g., UDP-glucose, ADP-glucose), and fatty acids (acetyl-CoA, Acyl-ACP, Glycerol-3-phosphate) - finally, also evaluating the nitrogen cycle (e.g., nitrate reductase, nitrite). Reductase).

Regarding experimental studies with potential implications for the health of mammals - including humans - a key point is to evaluate how NPs can biochemically interfere with neuronal energy uptake and macromolecule oxidation (e.g., ketone bodies and

β-hydroxybutyrate). Furthermore, they also affect hormone synthesis, mediated not only by systemic evaluation, but also by biosynthetic pathways (e.g., catalysis in steroids or post-translational mechanisms in peptides). Given the large number of studies indicating deleterious effects on lipid metabolism, it is necessary to investigate which metabolites, enzymes, and co-enzymes are potentially impacted by NPs (e.g., β-oxidation, acyl-CoA transferase, carnitine shuttle, acyl-CoA carboxylase, malonyl-CoA, acetyl-CoA, etc.). Following this reasoning, it is also crucial to thoroughly evaluate whether there is an imbalance in the catabolic process (excessive catabolism), checking amino acids such as glutamine, glutamate, aspartate, and direct components of the urea cycle (e.g., carbamoyl phosphate, ornithine, citrulline, etc.), which can certainly indicate widespread problems (muscle, kidney, liver). Additionally, it is interesting to understand whether these NPs cause excessive ketogenesis or compensatory gluconeogenesis, evaluating ketogenic and glucogenic amino acids, as well as intermediates of ketogenesis (e.g., acetoacetate, β-hydroxybutyrate, etc.). Regarding carbohydrate metabolism, a relevant and necessary point of study is the pentose phosphate pathway (glucose-6-phosphate, ribose-5-phosphate), necessary for the formation of NADPH, which is essential for glutathione interconversion and antioxidant action. Future studies could also seek to evaluate substrate concentration and allosterism, observing levels of NAD, NADH, FAD, FADH2, ATP, ADP, and the activity of shuttles (e.g., malate-aspartate and glycerol-3-phosphate). Finally, as a valuable perspective, since NPs can interfere with digestive and absorptive aspects, or even enzymatic reactions, assessing the status of fat-soluble vitamins (e.g., A, E, K), water-soluble vitamins (e.g., B1, B2, B6, B12, C), and minerals would be of paramount importance to understand whether, perhaps, the interference of NPs is not directly in the action of the enzyme, but rather in its cofactors or coenzymes necessary for this (e.g., pyruvate dehydrogenase complex).

6.5. Limitations

The principal limitation of this review lies in its broad conceptual scope, encompassing diverse biochemical outcomes across multiple organs, physiological systems, ecological contexts, and experimental models. Although this integrative approach provides a comprehensive and holistic overview of the biochemical effects associated with NP exposure, it inherently limits the feasibility of quantitative synthesis. It reduces the precision with which specific biological patterns can be statistically consolidated.

This narrative review was designed to critically interpret and integrate biochemical alterations reported in the literature rather than to generate pooled quantitative estimates. Given this defined focus, certain domains remain underexplored, particularly neuroendocrine regulation and integrative physiological responses. Moreover, the limited number of studies directly examining human exposure underscores a significant translational gap and reinforces the need for expanded research in environmental toxicology and public health contexts.

Additionally, this review concentrates exclusively on reported biochemical outcomes, without comprehensively addressing non-biochemical endpoints or complex co-exposure scenarios that more closely reflect real-world environmental and human conditions. Another notable limitation in the current literature—and consequently reflected in this synthesis—is the tendency to report isolated metabolites or discrete biochemical pathways without constructing a cohesive mechanistic framework. Future investigations would benefit from integrative approaches that connect multiple biomarkers and pathways into a unified and articulated model of NP-induced biological disruption.

7. Conclusion

Therefore, although the full impact of NPs on environmental and human health remains incompletely characterized, the biochemical evidence accumulated to date warrants considerable concern regarding their short-, medium-, and long-term consequences. As an emerging and pervasive form of pollution, NPs are now ubiquitous across ecosystems, with physicochemical properties that facilitate widespread biological interaction and potential bioaccumulation.

From a biochemical standpoint, current data consistently indicate that NPs interfere with central metabolic pathways (both convergent and divergent) across plant and animal systems. Reported alterations span antioxidant defense, inflammation, energy metabolism, lipid homeostasis, carbohydrate utilization, and protein turnover, occurring at organ- and cell-specific levels. Such disturbances suggest not merely localized effects, but the potential for cascading impacts across species, food webs, and entire ecosystems.

This narrative synthesis highlights key metabolites, pathways, and molecular targets that merit further investigation. Future studies should aim to delineate the precise biochemical nodes directly or indirectly modulated by NPs, thereby establishing a more integrated and mechanistically robust NP–biochemistry–cell-specific framework. Advancing this understanding will be essential to support translational research, environmental risk assessment, and the development of preventive or interventional strategies for human health.

CRediT authorship contribution statement

Matheus Naia Fioretto: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Natália Magosso:** Writing – review & editing, Writing – original draft. **Patrick Vieira de Souza:** Writing – review & editing, Writing – original draft. **Mirella Franco Moreira:** Writing – review & editing, Writing – original draft. **Vanessa Aguiar Rocha:** Writing – review & editing, Writing – original draft. **Victória Cristina Pinha:** Writing – review & editing, Writing – original draft. **Vinicius Luís Rocha da Silva Maria:** Writing – review & editing, Writing – original draft. **Luis Antonio Justulin:** Writing – review & editing, Writing – original draft. **Wellerson Rodrigo Scarano:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of generative ai and ai-assisted technologies in the writing process

All the text of the manuscript was initially written without Generative AI. Generative AI was partially used to correct some English formulations or to improve the formulation of a few sentences.

Funding statement

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES 88887.112689/2025-00 to MNF) – Finance Code 001; The São Paulo Research Foundation (FAPESP 2024/22188-6 to MNF; 2022/12304–3 and 2025/01977-5 to WRS) and National Council for Scientific and Technological Development (CNPq, Process: 312028/2022–9 to WRS).

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biochi.2026.04.001.

References

[1] World Health Organization, Dietary and Inhalation Exposure to nano- and Microplastic Particles and Potential Implications for Human Health, World Health Organization, Geneva, 2022. ISBN 9789240054608.

[2] United Nations Environment Programme. (s.d.). plastic pollution. UNEP. Recuperado de https://www.unep.org/plastic-pollution.

[3] M. Prüst, J. Meijer, R.H.S. Westerink, The plastic brain: neurotoxicity of micro- and nanoplastics, Part. Fibre Toxicol. 17 (1) (2020) 24, https://doi.org/10.1186/s12989-020-00358-y. Published 2020 Jun 8.

[4] A.M. Volsa, E. Iacono, B. Merlo, Micro-nanoplastics pollution and mammalian fertility: a systematic review and meta-analysis, Theriogenology 238 (2025) 117369, https://doi.org/10.1016/j.theriogenology.2025.117369.

[5] Plastic waste is everywhere - and countries must be held accountable for reducing it, Nature 619 (7969) (2023) 222, https://doi.org/10.1038/d41586-023-02252-x.

[6] V. Nava, S. Chandra, J. Aherne, et al., Plastic debris in lakes and reservoirs, Nature 619 (7969) (2023) 317–322, https://doi.org/10.1038/s41586-023-06168-4.

[7] H.T. Pinheiro, C. MacDonald, R.G. Santos, et al., Plastic pollution on the world's coral reefs, Nature 619 (7969) (2023) 311–316, https://doi.org/10.1038/s41586-023-06113-5.

[8] R.C. Thompson, S.H. Swan, C.J. Moore, F.S. vom Saal, Our plastic age, Philos. Trans. R. Soc. Lond. B Biol. Sci. 364 (1526) (2009) 1973–1976, https://doi.org/10.1098/rstb.2009.0054.

[9] C. Campanale, C. Massarelli, I. Savino, V. Locaputo, V.F. Uricchio, A detailed review study on potential effects of microplastics and additives of concern on human health, Int. J. Environ. Res. Publ. Health 17 (4) (2020) 1212, https://doi.org/10.3390/ijerph17041212. Published 2020 Feb 13.

[10] O.S. Alimi, J. Farner Budarz, L.M. Hernandez, N. Tufenkji, Microplastics and nanoplastics in aquatic environments: aggregation, deposition, and enhanced contaminant transport, Environ. Sci. Technol. 52 (4) (2018) 1704–1724, https://doi.org/10.1021/acs.est.7b05559.

[11] J. Yang, J. Kamstra, J. Legler, H. Aardema, The impact of microplastics on female reproduction and early life, Anim. Reprod. 20 (2) (2023) e20230037, https://doi.org/10.1590/1984-3143-AR2023-0037. Published 2023 Jul 24.

[12] J. Brahney, M. Hallerud, E. Heim, M. Hahnenberger, S. Sukumaran, Plastic rain in protected areas of the United States, Science 368 (6496) (2020) 1257–1260, https://doi.org/10.1126/science.aaz5819.

[13] H. Dong, L. Wang, X. Wang, et al., Microplastics in a remote Lake basin of the Tibetan Plateau: impacts of atmospheric transport and glacial melting, Environ. Sci. Technol. 55 (19) (2021) 12951–12960, https://doi.org/10.1021/acs.est.1c03227.

[14] C. Dessì, E.D. Okoffo, J.W. O'Brien, et al., Plastics contamination of store-bought rice, J. Hazard Mater. 416 (2021) 125778, https://doi.org/10.1016/j.jhazmat.2021.125778.

[15] W.A. da Silva Brito, F. Mutter, K. Wende, A.L. Cecchini, A. Schmidt, S. Bekeschus, Consequences of nano and microplastic exposure in rodent models: the known and unknown, Part. Fibre Toxicol. 19 (1) (2022) 28, https://doi.org/10.1186/s12989-022-00473-y. Published 2022 Apr 21.

[16] L.F. Amato-Lourenço, R. Carvalho-Oliveira, G.R. Júnior, L. Dos Santos Galvão, R.A. Ando, T. Mauad, Presence of airborne microplastics in human lung tissue, J. Hazard Mater. 416 (2021) 126124, https://doi.org/10.1016/j.jhazmat.2021.126124.

[17] L.C. Jenner, J.M. Rotchell, R.T. Bennett, M. Cowen, V. Tentzeris, L.R. Sadofsky, Detection of microplastics in human lung tissue using μFTIR spectroscopy, Sci. Total Environ. 831 (2022) 154907, https://doi.org/10.1016/j.scitotenv.2022.154907.

[18] A. Ragusa, A. Svelato, C. Santacroce, et al., Plasticenta: first evidence of microplastics in human placenta, Environ. Int. 146 (2021) 106274, https://doi.org/10.1016/j.envint.2020.106274.

[19] A. Ragusa, V. Notarstefano, A. Svelato, et al., Raman microspectroscopy detection and characterisation of microplastics in human breastmilk, Polymers (Basel) 14 (13) (2022) 2700, https://doi.org/10.3390/polym14132700. Published 2022 Jun 30.

[20] Z. Aghaei, G.V. Mercer, C.M. Schneider, et al., Maternal exposure to polystyrene microplastics alters placental metabolism in mice, Metabolomics 19 (1) (2022) 1, https://doi.org/10.1007/s11306-022-01967-8. Published 2022 Dec 20.

[21] J.S. Fisher, Environmental anti-androgens and Male reproductive health: focus on phthalates and testicular dysgenesis syndrome, Reproduction 127 (3) (2004) 305–315, https://doi.org/10.1530/rep.1.00025.

[22] S.K. Hanna, G.A. Cooksey, S. Dong, et al., Feasibility of using a standardized *Caenorhabditis elegans* toxicity test to assess nanomaterial toxicity, Environ. Sci. Nano 3 (5) (2016), https://doi.org/10.1039/c6en00105j, 10.1039/c6en00105j.

[23] T. Greenhalgh, S. Thorne, K. Malterud, Time to challenge the spurious hierarchy of systematic over narrative reviews? Eur. J. Clin. Invest. 48 (6) (2018) e12931 https://doi.org/10.1111/eci.12931.

[24] Z. Munn, M.D.J. Peters, C. Stern, C. Tufanaru, A. McArthur, E. Aromataris, Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach, BMC Med. Res. Methodol. 18 (1) (2018) 143, https://doi.org/10.1186/s12874-018-0611-x. Published 2018 Nov 19.

[25] M. Petticrew, E. Rehfuess, J. Noyes, et al., Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute, J. Clin. Epidemiol. 66 (11) (2013) 1230–1243, https://doi.org/10.1016/j.jclinepi.2013.06.005.

[26] M. Dixon-Woods, S. Agarwal, D. Jones, B. Young, A. Sutton, Synthesising qualitative and quantitative evidence: a review of possible methods, J. Health Serv. Res. Policy 10 (1) (2005) 45–53, https://doi.org/10.1177/135581960501000110.

[27] Y. Huang, B. Liang, Z. Li, et al., Polystyrene nanoplastic exposure induces excessive mitophagy by activating AMPK/ULK1 pathway in differentiated SH-SY5Y cells and dopaminergic neurons in vivo, Part. Fibre Toxicol. 20 (1) (2023) 44, https://doi.org/10.1186/s12989-023-00556-4. Published 2023 Nov 22.

[28] S. Yang, S. Lee, Y. Lee, et al., Cationic nanoplastic causes mitochondrial dysfunction in neural progenitor cells and impairs hippocampal neurogenesis, Free Radic. Biol. Med. 208 (2023) 194–210, https://doi.org/10.1016/j.freeradbiomed.2023.08.010.

[29] E. Bang, H. Hwangbo, H. Lee, et al., Exposure to polystyrene nanoplastics promotes premature cellular senescence through mitochondrial ROS production and dysfunction in pre-differentiated skeletal myoblasts, Toxicology 510 (2025) 154002, https://doi.org/10.1016/j.tox.2024.154002.

[30] J. Ma, Y. Wan, L. Song, et al., Polystyrene nanobeads exacerbate chronic colitis in mice involving in oxidative stress and hepatic lipid metabolism, Part. Fibre Toxicol. 20 (1) (2023) 49, https://doi.org/10.1186/s12989-023-00560-8. Published 2023 Dec 18.

[31] W. Wang, X. Mao, R. Zhang, et al., Nanoplastic exposure at environmental concentrations disrupts hepatic lipid metabolism through oxidative stress induction and endoplasmic reticulum homeostasis perturbation, Environ. Sci. Technol. 57 (38) (2023) 14127–14137, https://doi.org/10.1021/acs.est.3c02769.

[32] D.H. Kim, S. Lee, J. Ahn, et al., Transcriptomic and metabolomic analysis unveils nanoplastic-induced gut barrier dysfunction via STAT1/6 and ERK pathways, Environ. Res. 249 (2024) 118437, https://doi.org/10.1016/j.envres.2024.118437.

[33] M. Schwarzfischer, A. Niechcial, S.S. Lee, et al., Ingested nano- and micro-sized polystyrene particles surpass the intestinal barrier and accumulate in the body, NanoImpact 25 (2022) 100374, https://doi.org/10.1016/j.impact.2021.100374.

[34] A. Muhammad, N. Zhang, J. He, et al., Multiomics analysis reveals the molecular basis for increased body weight in silkworms (Bombyx mori) exposed to environmental concentrations of polystyrene micro- and nanoplastics, J. Adv. Res. 57 (2024) 43–57, https://doi.org/10.1016/j.jare.2023.09.010.

[35] G.M. DeLoid, X. Cao, R. Coreas, et al., Incineration-generated polyethylene micro-nanoplastics increase triglyceride lipolysis and absorption in an *in vitro* small intestinal epithelium model, Environ. Sci. Technol. 56 (17) (2022) 12288–12297, https://doi.org/10.1021/acs.est.2c03195.

[36] H. Brouwer, M. Porbahaie, S. Boeren, M. Busch, H. Bouwmeester, The in vitro gastrointestinal digestion-associated protein corona of polystyrene nano- and microplastics increases their uptake by human THP-1-derived macrophages, Part. Fibre Toxicol. 21 (1) (2024) 4, https://doi.org/10.1186/s12989-024-00563-z. Published 2024 Feb 4.

[37] M. Teng, Y. Li, X. Zhao, et al., Vitamin D modulation of brain-gut-virome disorder caused by polystyrene nanoplastics exposure in zebrafish (Danio rerio), Microbiome 11 (1) (2023) 266, https://doi.org/10.1186/s40168-023-01680-1. Published 2023 Nov 27.

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

[39] D. Xu, Y. Ma, C. Peng, et al., Differently surface-labeled polystyrene nanoplastics at an environmentally relevant concentration induced Crohn's ileitis-like features via triggering intestinal epithelial cell necroptosis, Environ. Int. 176 (2023) 107968, https://doi.org/10.1016/j.envint.2023.107968.

[40] V. Collin-Faure, M. Vitipon, A. Torres, O. Tanyeres, B. Dalzon, T. Rabilloud, The internal dose makes the poison: higher internalization of polystyrene particles induce increased perturbation of macrophages, Front. Immunol. 14 (2023) 1092743, https://doi.org/10.3389/fimmu.2023.1092743. Published 2023 May 12.

[41] F. Zingaro, A. Gianoncelli, G. Ceccone, et al., Morphological and lipid metabolism alterations in macrophages exposed to model environmental

nanoplastics traced by high-resolution synchrotron techniques, Front. Immunol. 14 (2023) 1247747, https://doi.org/10.3389/fimmu.2023.1247747. Published 2023 Sep. 8.
[42] Z. Fan, Y. Zhang, Y. Fang, et al., Polystyrene nanoplastics induce lipophagy via the AMPK/ULK1 pathway and block lipophagic flux leading to lipid accumulation in hepatocytes, J. Hazard Mater. 476 (2024) 134878, https://doi.org/10.1016/j.jhazmat.2024.134878.
[43] H.T. Shiu, X. Pan, Q. Liu, et al., Dietary exposure to polystyrene nanoplastics impairs fasting-induced lipolysis in adipose tissue from high-fat diet fed mice, J. Hazard Mater. 440 (2022) 129698, https://doi.org/10.1016/j.jhazmat.2022.129698.
[44] J. Wei, J. Liu, H. Wang, et al., Nanoplastic propels diet-induced NAFL to NASH via ER-mitochondrial tether-controlled redox switch, J. Hazard Mater. 465 (2024) 133142, https://doi.org/10.1016/j.jhazmat.2023.133142.
[45] J. Fan, L. Liu, Y. Lu, et al., Acute exposure to polystyrene nanoparticles promotes liver injury by inducing mitochondrial ROS-dependent necroptosis and augmenting macrophage-hepatocyte crosstalk, Part. Fibre Toxicol. 21 (1) (2024) 20, https://doi.org/10.1186/s12989-024-00578-6. Published 2024 Apr 12.
[46] X. Wu, M. Li, S. Yang, et al., Liver metabolic dysregulation induced by polypropylene Nano- and microplastics in Nile Tilapia using internal extractive electrospray ionization mass spectrometry, Anal. Chem. 95 (20) (2023) 7863–7871, https://doi.org/10.1021/acs.analchem.2c05672.
[47] X. Wu, S.A. Yang, Y. Kan, et al., Revealing metabolic dysregulation induced by polypropylene Nano- and microplastics in Nile Tilapia via noninvasive probing epidermal mucus, Anal. Chem. 96 (23) (2024) 9416–9423, https://doi.org/10.1021/acs.analchem.4c00351.
[48] I. Brandts, C. Barría, M.A. Martins, et al., Waterborne exposure of gilthead seabream (Sparus aurata) to polymethylmethacrylate nanoplastics causes effects at cellular and molecular levels, J. Hazard Mater. 403 (2021) 123590, https://doi.org/10.1016/j.jhazmat.2020.123590.
[49] T. Zheng, D. Yuan, C. Liu, Molecular toxicity of nanoplastics involving in oxidative stress and desoxyribonucleic acid damage, J. Mol. Recogn. 32 (11) (2019) e2804, https://doi.org/10.1002/jmr.2804.
[50] H. Cheng, Z. Duan, Y. Wu, et al., Immunotoxicity responses to polystyrene nanoplastics and their related mechanisms in the liver of zebrafish (Danio rerio) larvae, Environ. Int. 161 (2022) 107128, https://doi.org/10.1016/j.envint.2022.107128.
[51] D. Rajendran, N. Chandrasekaran, Y. Waychal, A. Mukherjee, Nanoplastics alter the conformation and activity of human serum albumin, NanoImpact 27 (2022) 100412, https://doi.org/10.1016/j.impact.2022.100412.
[52] N. Leroux, M. Hosseinzadeh, A. Katsumiti, C. Porte, M.P. Cajaraville, Lipidomic analysis of mussel hemocytes exposed to polystyrene nanoplastics, Environ. Res. 214 (Pt 1) (2022) 113763, https://doi.org/10.1016/j.envres.2022.113763.
[53] B. Wang, B. Liang, Y. Huang, et al., Long-chain acyl carnitines aggravate polystyrene nanoplastics-induced atherosclerosis by upregulating MARCO, Adv. Sci. (Weinh.) 10 (19) (2023) e2205876, https://doi.org/10.1002/advs.202205876.
[54] Z. Duan, J. Wang, H. Zhang, et al., Elevated temperature decreases cardiovascular toxicity of nanoplastics but adds to their lethality: a case study during zebrafish (Danio rerio) development, J. Hazard Mater. 458 (2023) 131679, https://doi.org/10.1016/j.jhazmat.2023.131679.
[55] T. Zhang, S. Yang, Y. Ge, et al., Multi-dimensional evaluation of cardiotoxicity in mice following respiratory exposure to polystyrene nanoplastics, Part. Fibre Toxicol. 20 (1) (2023) 46, https://doi.org/10.1186/s12989-023-00557-3. Published 2023 Nov 29.
[56] G. Liu, Q. Bao, C. Zhang, et al., PVC nanoplastics impair cardiac function via lysosomal and mitochondrial dysfunction, Biochem. Biophys. Res. Commun. 762 (2025) 151736, https://doi.org/10.1016/j.bbrc.2025.151736.
[57] S.L. Lim, C.T. Ng, L. Zou, et al., Targeted metabolomics reveals differential biological effects of nanoplastics and nanoZnO in human lung cells, Nanotoxicology 13 (8) (2019) 1117–1132, https://doi.org/10.1080/17435390.2019.1640913.
[58] Y. Ji, L. Chen, Y. Wang, et al., Realistic nanoplastics induced pulmonary damage via the crosstalk of ferritinophagy and mitochondrial dysfunction, ACS Nano 18 (26) (2024) 16790–16807, https://doi.org/10.1021/acsnano.4c02335.
[59] G. Halimu, Q. Zhang, L. Liu, et al., Toxic effects of nanoplastics with different sizes and surface charges on epithelial-to-mesenchymal transition in A549 cells and the potential toxicological mechanism, J. Hazard Mater. 430 (2022) 128485, https://doi.org/10.1016/j.jhazmat.2022.128485.
[60] Y. Wu, J. Wang, T. Zhao, et al., Polystyrenenanoplastics lead to ferroptosis in the lungs, J. Adv. Res. 56 (2024) 31–41, https://doi.org/10.1016/j.jare.2023.03.003.
[61] S. He, J. Cai, T. Jia, et al., New sight of renal toxicity caused by UV-Aged polystyrene nanoplastics: induced ferroptosis via adsorption of transferrin, Small 20 (23) (2024) e2309369, https://doi.org/10.1002/smll.202309369.
[62] G. Lu, S. Wei, Nanoplastics trigger the aging and inflammation of porcine kidney cells, Toxicology 506 (2024) 153870, https://doi.org/10.1016/j.tox.2024.153870.
[63] Y. Hu, S. Jiang, Q. Zhang, et al., Protective effect of cordycepin on blood-testis barrier against pre-puberty polystyrene nanoplastics exposure in male rats, Part. Fibre Toxicol. 21 (1) (2024) 30, https://doi.org/10.1186/s12989-024-00590-w. Published 2024 Aug 9.
[64] R. Cui, S.W. Kim, Y.J. An, Polystyrene nanoplastics inhibit reproduction and induce abnormal embryonic development in the freshwater crustacean Daphnia galeata, Sci. Rep. 7 (1) (2017) 12095, https://doi.org/10.1038/s41598-017-12299-2. Published 2017 Sep. 21.
[65] Q. Zhao, Z. Fang, P. Wang, et al., Polylactic acid micro/nanoplastic exposure induces Male reproductive toxicity by disrupting spermatogenesis and mitochondrial dysfunction in mice, ACS Nano 19 (5) (2025) 5589–5603, https://doi.org/10.1021/acsnano.4c15112.
[66] R. Tang, D. Zhu, Y. Luo, et al., Nanoplastics induce molecular toxicity in earthworm: integrated multi-omics, morphological, and intestinal microorganism analyses, J. Hazard Mater. 442 (2023) 130034, https://doi.org/10.1016/j.jhazmat.2022.130034.
[67] D. Huang, L. Ding, S. Wang, et al., Metabolomics reveals how spinach plants reprogram metabolites to cope with intense stress responses induced by photoaged polystyrene nanoplastics (PSNPs), J. Hazard Mater. 466 (2024) 133605, https://doi.org/10.1016/j.jhazmat.2024.133605.
[68] L. Xu, C. Liu, Y. Ren, et al., Nanoplastic toxicity induces metabolic shifts in Populus × euramericana cv. '74/76' revealed by multi-omics analysis, J. Hazard Mater. 470 (2024) 134148, https://doi.org/10.1016/j.jhazmat.2024.134148.
[69] M. Qu, L. Miao, H. Chen, X. Zhang, Y. Wang, SKN-1/Nrf2-dependent regulation of mitochondrial homeostasis modulates transgenerational toxicity induced by nanoplastics with different surface charges in Caenorhabditis elegans, J. Hazard Mater. 457 (2023) 131840, https://doi.org/10.1016/j.jhazmat.2023.131840.
[70] S. Zhang, F. Zhang, L. Cai, et al., Visual observation of polystyrene nanoplastics in grape seedlings of Thompson seedless and assessing their effects via transcriptomics and metabolomics, J. Hazard Mater. 478 (2024) 135550, https://doi.org/10.1016/j.jhazmat.2024.135550.
[71] Z. Wang, S. Li, S. Jian, et al., Low temperature tolerance is impaired by polystyrene nanoplastics accumulated in cells of barley (Hordeum vulgare L.) plants, J. Hazard Mater. 426 (2022) 127826, https://doi.org/10.1016/j.jhazmat.2021.127826.
[72] J. Guo, S. Li, M. Brestic, et al., Modulations in protein phosphorylation explain the physiological responses of barley (Hordeum vulgare) to nanoplastics and ZnO nanoparticles, J. Hazard Mater. 443 (Pt A) (2023) 130196, https://doi.org/10.1016/j.jhazmat.2022.130196.
[73] J. Lian, J. Wu, H. Xiong, et al., Impact of polystyrene nanoplastics (PSNPs) on seed germination and seedling growth of wheat (Triticum aestivum L.), J. Hazard Mater. 385 (2020) 121620, https://doi.org/10.1016/j.jhazmat.2019.121620.
[74] S. Giri, A. Debroy, A. Nag, A. Mukherjee, Evaluating the role of soil EPS in modifying the toxicity potential of the mixture of polystyrene nanoplastics and xenoestrogen, bisphenol A (BPA) in Allium cepa L, J. Hazard Mater. 477 (2024) 135252, https://doi.org/10.1016/j.jhazmat.2024.135252.
[75] M. Jiang, B. Wang, R. Ye, et al., Evidence and impacts of nanoplastic accumulation on crop grains, Adv. Sci. (Weinh.) 9 (33) (2022) e2202336, https://doi.org/10.1002/advs.202202336.
[76] X. Li, L. Lu, S. Ru, et al., Nanoplastics induce more severe multigenerational life-history trait changes and metabolic responses in marine rotifer Brachionus plicatilis: Comparison with microplastics, J. Hazard Mater. 449 (2023) 131070, https://doi.org/10.1016/j.jhazmat.2023.131070.
[77] M.T. Ekvall, I. Gimskog, J. Hua, E. Kelpsiene, M. Lundqvist, T. Cedervall, Size fractionation of high-density polyethylene breakdown nanoplastics reveals different toxic response in Daphnia magna, Sci. Rep. 12 (1) (2022) 3109, https://doi.org/10.1038/s41598-022-06991-1. Published 2022 Feb 24.
[78] S. Liu, J. Han, L. Yao, et al., Integrated multilevel investigation of photosynthesis revealed the algal response distinction to differentially charged nanoplastics, J. Hazard Mater. 475 (2024) 134815, https://doi.org/10.1016/j.jhazmat.2024.134815.
[79] E. Kelpsiene, O. Torstensson, M.T. Ekvall, L.A. Hansson, T. Cedervall, Long-term exposure to nanoplastics reduces life-time in Daphnia magna, Sci. Rep. 10 (1) (2020) 5979, https://doi.org/10.1038/s41598-020-63028-1. Published 2020 Apr 6.
[80] R. Marino, D. Melillo, P. Italiani, D. Boraschi, Environmental stress and nanoplastics' effects on *Ciona robusta*: regulation of immune/stress-related genes and induction of innate memory in pharynx and gut, Front. Immunol. 14 (2023) 1176982, https://doi.org/10.3389/fimmu.2023.1176982. Published 2023 May 29.
[81] H. Li, L. Lin, H. Liu, et al., Simultaneous exposure to nanoplastics and cadmium mitigates microalgae cellular toxicity: insights from molecular simulation and metabolomics, Environ. Int. 186 (2024) 108633, https://doi.org/10.1016/j.envint.2024.108633.
[82] C. Wu, W.B. Guo, Y.Y. Liu, L. Yang, A.J. Miao, Perturbation of calcium homeostasis and multixenobiotic resistance by nanoplastics in the ciliate Tetrahymena thermophila, J. Hazard Mater. 403 (2021) 123923, https://doi.org/10.1016/j.jhazmat.2020.123923.
[83] J. Karimi, A. Asgharpour, S. Mohsenzadeh, S. Abbasi, The impact of polystyrene nanoplastics (PSNPs) on physiological and biochemical parameters of the microalgae Spirulina platensis, J. Hazard Mater. 474 (2024) 134644, https://doi.org/10.1016/j.jhazmat.2024.134644.
[84] J. Huang, P. Gu, X. Cao, H. Miao, Z. Wang, Mechanistic study on the increase of Microcystin-LR synthesis and release in microcystis aeruginosa by amino-modified nano-plastics, J. Hazard Mater. 474 (2024) 134767, https://

doi.org/10.1016/j.jhazmat.2024.134767.
[85] M.Y. Liu, X.Y. Liu, Y.Y. Guo, et al., Nitrogen forms regulate the response of *Microcystis aeruginosa* to nanoplastics at environmentally relevant nitrogen concentrations, ACS Nano 18 (18) (2024) 11828–11836, https://doi.org/10.1021/acsnano.4c00739.
[86] J. Zhao, L. Miao, Y. Yao, et al., Surface modification significantly changed the effects of nano-polystyrene on sediment microbial communities and nitrogen metabolism, J. Hazard Mater. 460 (2023) 132409, https://doi.org/10.1016/j.jhazmat.2023.132409.
[87] S.B. Sjollema, P. Redondo-Hasselerharm, H.A. Leslie, M.H.S. Kraak, A.D. Vethaak, Do plastic particles affect microalgal photosynthesis and growth? Aquat. Toxicol. 170 (2016) 259–261, https://doi.org/10.1016/j.aquatox.2015.12.002.
[88] H. Liao, D. Gao, C. Kong, et al., Trophic transfer of nanoplastics and di(2-ethylhexyl) phthalate in a freshwater food chain (Chlorella pyrenoidosa-daphnia magna-Micropterus salmoides) induced disturbance of lipid metabolism in fish, J. Hazard Mater. 459 (2023) 132294, https://doi.org/10.1016/j.jhazmat.2023.132294.
[89] Y. Zhou, W. Liu, H. Jiang, et al., Surface-charge-driven ferroptosis and mitochondrial dysfunction is involved in toxicity diversity in the marine bivalve exposed to nanoplastics, ACS Nano 18 (3) (2024) 2370–2383, https://doi.org/10.1021/acsnano.3c10536.
[90] Y. Zhou, X.X. Zhou, H. Jiang, et al., *In vitro* toxicity and modeling reveal nanoplastic effects on marine bivalves, ACS Nano 18 (26) (2024) 17228–17239, https://doi.org/10.1021/acsnano.4c04607.
[91] M. Sendra, M.I. Carrasco-Braganza, P.M. Yeste, M. Vila, J. Blasco, Immunotoxicity of polystyrene nanoplastics in different hemocyte subpopulations of Mytilus galloprovincialis, Sci. Rep. 10 (1) (2020) 8637, https://doi.org/10.1038/s41598-020-65596-8. Published 2020 May 25.
[92] W. Lai, D. Xu, J. Li, et al., Dietary polystyrene nanoplastics exposure alters liver lipid metabolism and muscle nutritional quality in carnivorous marine fish large yellow croaker (Larimichthys crocea), J. Hazard Mater. 419 (2021) 126454, https://doi.org/10.1016/j.jhazmat.2021.126454.
[93] I. Brandts, M. Teles, A. Tvarijonaviciute, et al., Effects of polymethylmethacrylate nanoplastics on dicentrarchus labrax, Genomics 110 (6) (2018) 435–441, https://doi.org/10.1016/j.ygeno.2018.10.006.
[94] M.S.S. Silva, M. Oliveira, H. Almeida, et al., Does parental exposure to nanoplastics modulate the response of Hediste diversicolor to other contaminants: a case study with arsenic, Environ. Res. 214 (Pt 2) (2022) 113764, https://doi.org/10.1016/j.envres.2022.113764.
[95] Z. Sun, L. Zhao, X. Peng, B. Kang, A comparative study on the toxic effects of lead pollution and nanoplastic-lead mixed pollution on red drum and their detoxification strategies, J. Hazard Mater. 480 (2024) 136018, https://doi.org/10.1016/j.jhazmat.2024.136018.
[96] X. Yong, K. Du, Effects of shape on interaction dynamics of tetrahedral nanoplastics and the cell membrane, J. Phys. Chem. B 127 (7) (2023) 1652–1663, https://doi.org/10.1021/acs.jpcb.2c07460.
[97] X. Tang, Y. Hou, M. Zhao, Z. Li, L. Zhang, Polystyrene nanoplastics enhance poxvirus preference for migrasome-mediated transmission, Biochem. Biophys. Res. Commun. 734 (2024) 150619, https://doi.org/10.1016/j.bbrc.2024.150619.
[98] F. He, H. Shi, S. Hu, R. Liu, Regulation mechanisms of ferric ions release from iron-loaded transferrin protein caused by nano-sized polystyrene plastics-induced conformational and structural changes, J. Hazard Mater. 465 (2024) 133495, https://doi.org/10.1016/j.jhazmat.2024.133495.
[99] X. You, X. Cao, X. Zhang, J. Guo, W. Sun, Unraveling individual and combined toxicity of nano/microplastics and ciprofloxacin to synechocystis sp. at the cellular and molecular levels, Environ. Int. 157 (2021) 106842, https://doi.org/10.1016/j.envint.2021.106842.
[100] J. Cao, Y. Liao, W. Yang, X. Jiang, M. Li, Enhanced microalgal toxicity due to polystyrene nanoplastics and cadmium co-exposure: from the perspective of physiological and metabolomic profiles, J. Hazard Mater. 427 (2022) 127937, https://doi.org/10.1016/j.jhazmat.2021.127937.
[101] M. Huang, Y. Ma, J. Qian, et al., Combined effects of norfloxacin and polystyrene nanoparticles on the oxidative stress and gut health of the juvenile horseshoe crab Tachypleus tridentatus, J. Hazard Mater. 468 (2024) 133801, https://doi.org/10.1016/j.jhazmat.2024.133801.
[102] J. Wen, H. Sun, B. Yang, E. Song, Y. Song, Long-term polystyrene nanoplastic exposure disrupt hepatic lipid metabolism and cause atherosclerosis in ApoE$^{-/-}$ mice, J. Hazard Mater. 466 (2024) 133583, https://doi.org/10.1016/j.jhazmat.2024.133583.