

REVIEW ARTICLE

Microplastics and nanoplastics with co-contaminants: A comprehensive review of neurotoxic effects

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Abstract

The widespread accumulation of microplastics (MPs) and nanoplastics (NPs) in the environment, along with their capacity to adsorb and transport co-contaminants, raises increasing concern regarding potential neurotoxic effects. This review synthesizes recent evidence on the combined neurotoxicity of MPs/NPs with environmental co-contaminants, including heavy metals, phthalates, pharmaceuticals, and flame retardants. These contaminants interact with MPs/NPs to enhance bioavailability, facilitate translocation to neural tissues, and trigger adverse biological responses. Mechanistic pathways—including oxidative stress, disruption of neurotransmitter systems, neuroinflammation, and increased blood–brain barrier permeability—have been examined in various *in vivo* models, particularly fish and rodents. Notably, recent reports indicate that humans may ingest thousands of MP and NP particles annually, with some studies detecting up to 2,000 particles per gram in biological tissues, including the brain. These findings underscore the urgent need for a comprehensive assessment of the potential neurological risks associated with combined exposure to MPs, NPs, and co-contaminants. The synergistic and additive effects of combined exposures underscore the potential for impairments in cognitive, behavioral, and neurochemical functions. This review integrates cross-species evidence to identify key research gaps, including undefined dose thresholds for combined exposures, limited understanding of particle–contaminant interaction kinetics, and insufficient mapping of brain-region–specific vulnerabilities. This review underscores the need for integrated toxicological assessments and strengthened regulatory strategies to address these environmental threats, with particular attention to pharmacologically relevant neurotoxic mechanisms.

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1. Introduction

Microplastics (MPs; <5 mm) and nanoplastics (NPs; <100 nm) have emerged as significant environmental contaminants with the potential to interact with co-contaminants, leading to adverse effects on living organisms, including humans.¹ These small plastic particles, resulting from the degradation of larger plastic items or intentional production at microscopic scales, are ubiquitous in various environmental compartments, such as water bodies, soils, and air.² Consequently, concerns regarding their impact on ecosystem

health and human well-being have escalated, particularly their interactions with co-contaminants, such as heavy metals, organic pollutants, and other toxic substances, which may result in synergistic or additive neurotoxic effects³ (Figure 1).

Neurotoxicity, defined as the ability of substances to damage the nervous system, is a critical aspect of environmental health research due to the central role of the nervous system in regulating physiological functions and behavior.^{4,5} Understanding the neurotoxic effects of MPs, NPs, and co-contaminants is essential for assessing risks to neurological health and developing effective mitigation strategies. Previous studies have demonstrated that MPs and NPs can act as carriers for co-contaminants, facilitating their transport and accumulation in neural tissues.⁶

Additional investigations further support this carrier-mediated transport mechanism. For example, recent work has shown that polystyrene (PS) MPs enhance the

uptake and neurotoxicity of co-exposed contaminants in *Danio rerio* (zebrafish) larvae and *Mus musculus* (mouse) brain tissues.⁷ Similarly, PS NPs have been demonstrated to induce oxidative stress, mitochondrial dysfunction, synaptic alterations, and behavioral impairments in both fish and rodent models, further supporting cross-species neurotoxic effects.⁸

The mechanisms underlying the neurotoxic effects of interactions between MPs/NPs and co-contaminants are multifaceted and may involve oxidative stress, inflammation, and disruption of blood–brain barrier (BBB) integrity.⁹ These processes can impair neurotransmission, induce neuroinflammation, and ultimately contribute to cognitive impairments and behavioral abnormalities.¹⁰

Chronic exposure to neurotoxic substances carried by MPs/NPs may result in long-term neurological dysfunction, potentially increasing the risk of neurodegenerative disorders and other neurological conditions.¹¹ Accordingly,

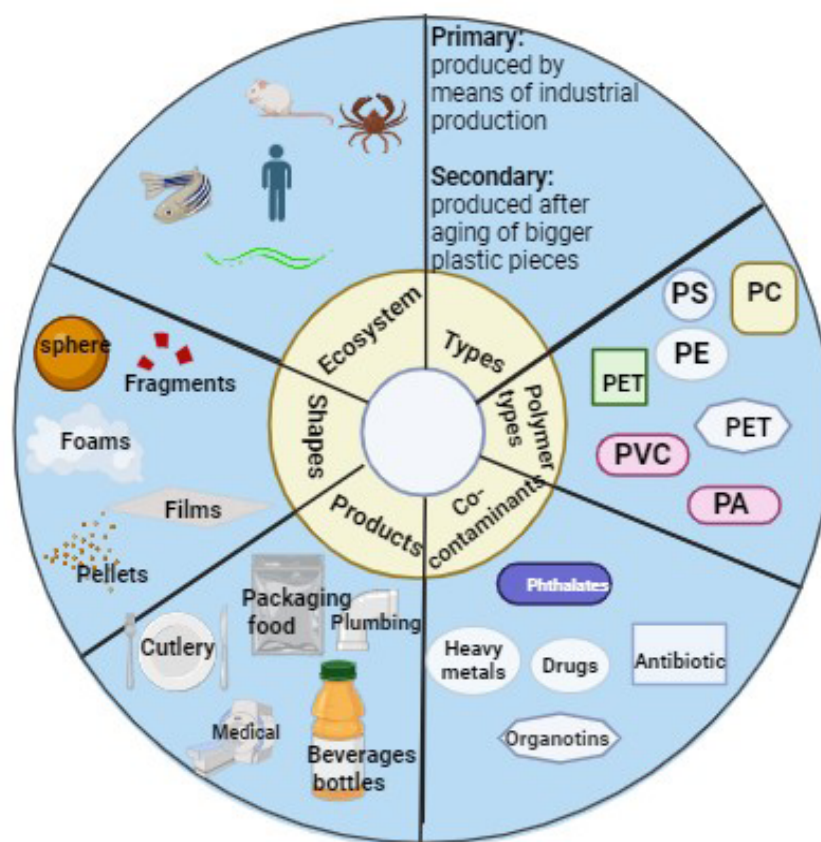


Figure 1. Characteristics of microplastics, including types, shapes, major polymer compositions, associated products, and the organisms and ecosystems they affect, along with common co-contaminants.

Abbreviations: PA: Polyamides; PC: Polycarbonate; PS: Polystyrene; PE: Polyethylene; PET: Polyethylene terephthalate; PVC: Polyvinyl chloride. Created with BioRender. Sharma, K (2026). <https://BioRender.com>.

this review synthesizes existing evidence on the combined neurotoxic effects of MPs/NPs and co-contaminants to clarify the potential risks these interactions pose to neurological health.

2. Methodology

A comprehensive literature search was conducted to identify experimental studies evaluating the neurotoxic effects of MPs and NPs, alone or in combination with environmental co-contaminants. Searches were performed in PubMed, ScienceDirect, Elsevier, Google Scholar, ResearchGate, and relevant peer-reviewed journals for articles published up to January 2024. The search strategy employed Boolean operators and truncation symbols using predefined search strings, including “microplastic* AND neurotoxicity,” “nanoplastic* AND neurotoxicity,” “microplastic* AND co-contaminant*,” “nanoplastic* AND heavy metal*,” “plastic particle* AND phthalate*,” and “microplastic* OR nanoplastic* AND oxidative stress AND brain.” Additional keywords such as “blood–brain barrier,” “endocrine disruptors,” and “neuroinflammation” were included to capture mechanistic studies relevant to nervous system toxicity. Keywords were selected to encompass particle size (micro and nano scales), co-exposure scenarios, exposure pathways, and mechanistic neurotoxicity endpoints.

Studies were included if they met the following criteria:

- (i) Original research articles.
- (ii) *In vivo* or *in vitro* experimental studies.
- (iii) Exposure to MPs and/or NPs alone or in combination with co-contaminants (e.g., heavy metals, phthalates, flame retardants, and pharmaceuticals).
- (iv) Clear reporting of exposure parameters (e.g., particle size, polymer type, dose, route, and duration).
- (v) Use of biological models relevant to neurotoxicity (e.g., fish, rodents, marine bivalves, and neuronal cell lines).
- (vi) Assessment of at least one neurotoxicity-related endpoint, including oxidative stress markers, neurotransmitter alterations, behavioral changes, neuroinflammation, or BBB integrity.

Studies were excluded if they were review articles, non-experimental reports, lacked neurotoxic endpoints, did not define exposure parameters, were non-English, or focused solely on environmental distribution without biological assessment.

The initial search yielded 412 records. After removing duplicates and screening titles and abstracts, 52 articles were selected for full-text review. Ultimately, 20 studies met all inclusion criteria, with four additional studies identified through citation tracking. Across all included

studies, two primary organism groups were identified: fish and rodents. Specifically, two studies examined marine bivalves, 10 focused on fish species, and six investigated rodent models. Three studies utilized *in vivo* bivalve exposures, and one study employed an *in vitro* mouse neuronal cell culture system to characterize mechanistic neurotoxicity. Eight studies evaluated co-exposure to PS particles and heavy metals, nine investigated polyethylene (PE) particles combined with phthalates, and four assessed MPs/NPs with other co-contaminants (Table 1).

The quality of included studies was evaluated based on clarity and completeness of exposure characterization, inclusion of appropriate control groups, statistical robustness, reproducibility of experimental design, and the range of neurotoxicity-related endpoints assessed. Overall, most studies adequately described particle size, polymer type, and exposure route; however, reporting of surface chemistry, aggregation state, and particle aging or weathering was often inconsistent. A major potential bias stems from the frequent use of experimental doses exceeding environmentally relevant concentrations, which may overestimate neurotoxic risk and limit extrapolation to ecological or human health contexts.

Additional biases include heterogeneity in exposure durations, variability in behavioral and biochemical endpoints, and limited standardization of neurotoxicity assays. Publication bias toward positive or synergistic outcomes cannot be excluded, as studies reporting null or antagonistic effects are comparatively underrepresented. Furthermore, few studies employed blinding or randomization, and sex-specific neurotoxic responses were rarely evaluated, further constraining interpretability.

3. Combined toxicity of microplastics and nanoplastics with heavy metals

Plastic pollution and heavy-metal contamination pose significant threats to living organisms worldwide. The widespread use and inappropriate disposal of plastics, coupled with industrial activities, have led to the accumulation of MPs and heavy metals in the environment.¹¹ These persistent pollutants have profound effects on living organisms, including humans.¹² Understanding the combined neurotoxicity of MPs/NPs and heavy metals is critical due to their omnipresence in the environment. Here, we review recent studies highlighting the intricate interplay between these environmental stressors and their combined neurotoxic effects.

Few recent studies have explored the mechanisms underlying the transport, accumulation, and effects of MPs and heavy metals in various models. Recent research

Table 1. Study selection criteria, including study design, organisms, and inclusion/exclusion parameters

Criteria	Inclusion criteria	Exclusion criteria
Study design	Original research articles investigating the neurotoxic potential of MPs/NPs in combination with co-contaminants	Studies without neurotoxic endpoints, or those lacking experimental designs involving neurotoxicity
Organism studied	Studies involving fish, mice, bivalves, or <i>in vivo</i> cell cultures with mouse cells	Studies focusing on organisms other than fish, mice, bivalves, or <i>in vitro</i> cell cultures with mouse cells
Types of contaminants	Studies investigating co-exposure of MPs/NPs with heavy metals, phthalates, or other co-contaminants	Studies examining individual compounds were excluded
Source of publication	Articles published in peer-reviewed scientific journals, including PubMed, Google Scholar, Elsevier, Research Gate, and Science Direct	Non-peer-reviewed sources or publications lacking credibility and scientific accuracy
Time period	Articles published up to January 1, 2024	Studies published before 2011 were excluded from the review
Search method	Articles identified through comprehensive literature searches using specific combinations of search words (e.g., neurotoxicity, phthalates, co-exposure, and MPs/NPs).	Papers not discovered through the specified search strategy or obtained from non-standard sources were excluded from the review
Selection	Appropriate selection criteria to ensure the reliability and validity of the findings	Studies with biased sample selection, or insufficient methodological details that may compromise the study's quality

Abbreviations: MP: Microplastic; NP: Nanoplastic.

investigated the comparative effects of PE terephthalate (PET) MPs in granular (p-PET) and fibrous (f-PET) forms on zebrafish embryo development, both individually and in combination with cadmium (Cd) exposure. The unique effects of p-PET and f-PET on blood flow velocity, heart rate, and hatching of zebrafish embryos were identified, attributed to their distinct effects on embryonic chorion channels and mechanical strength. Notably, p-PET enhances Cd accumulation in the chorion through adsorption, while f-PET, with increased dissociation in the culture medium, results in lower Cd content in the chorion. This co-exposure demonstrates a substantial reduction in Cd accumulation in eggs, showcasing a mitigation of Cd toxicity due to reduced bioavailability. Additionally, f-PET exhibits a more pronounced detoxification effect at 72 h post-fertilization compared to p-PET. These findings underscore the form-related dynamics of MP-induced toxicity, providing valuable insight into the potential interplay between different MP structures and Cd in ecosystems.¹³

To further explore these interactions, a chronic 30-day study in zebrafish exposed to MPs (2 mg/L) and copper (25 µg/L), individually and in combination, demonstrated alterations in the brain antioxidant system, cholinergic activity, neurogenesis-related genes, and associated behavioral changes.¹⁴ Moreover, a study investigated the short-term (96 h) toxic effects of MPs and mercury at concentrations of 0.26 mg/L and 0.69 mg/L, individually and in combination, in European seabass (marine fish). MPs and mercury, when given individually, induced neurotoxicity, oxidative stress, and changes in energy-related enzyme activities in the fish. Binary mixtures of the two substances also exhibited significant neurotoxic and oxidative effects, with varying outcomes based on the composition of the mixture. Mercury bioaccumulated in the fish's brain and muscle, and its decay in water increased with MP concentration.¹⁵

Another study investigated the influence of MPs on the accumulation and chronic toxic effects of Cd in zebrafish. The study found that co-exposure to MPs and

Cd led to increased Cd accumulation in zebrafish tissues, with the highest levels observed in the gills, followed by the gut and liver. This combined exposure also resulted in oxidative damage and inflammation in zebrafish tissues, highlighting the enhanced toxicity of Cd in the presence of MPs. Additionally, the study demonstrated the neurotoxic effects of the combined exposure, suggesting potential cognitive impairment and dopaminergic dysfunction in adult zebrafish. These findings underscore the importance of considering the interactions between MPs and heavy metals in assessing the environmental risks to aquatic organisms, particularly in terms of neurotoxic effects and cognitive impairment.¹⁶

A study examined the combined toxicity of PS MPs and lead on zebrafish, specifically examining their effects on the gut–liver and gut–brain axes. The study reveals that exposure to various sizes of PS MPs and lead disrupts the gut microbiota, resulting in alterations in gut barrier integrity and hepatic inflammation. Notably, the combined exposure to 0.1 µm and 250 µm PS MPs induces significant neurotoxic effects, impacting neurotransmitter pathways within the gut–brain axis. Histological analysis further reveals brain vacuoles and changes in the expression of key genes associated with brain function. These findings underscore the intricate interplay between MPs, heavy metals, and neurotoxicity in aquatic organisms, underscoring the importance of further research into the potential risks posed by environmental contaminants on neurological health through the gut–liver and gut–brain axes.¹⁷

The combined neurotoxicity of MPs/NPs and heavy metals has gained substantial attention due to its potential implications for aquatic ecosystems and human health. One study investigated *Pomatochistus microps* juveniles (fish) exposed to Cd (3–13 mg/L), MPs (1–5 µm; 0.14 mg/L), and MP–Cd mixtures. Cd alone exhibited LC₁₀ and LC₅₀ values of 2 mg/L and 8 mg/L, respectively. Exposure to MPs (0.14 mg/L) altered acetylcholinesterase (AChE) activity in juveniles, and plastic-exposed periphytic biofilm further modulated AChE responses in L-est juveniles. Intriguingly, co-exposure to MPs (0.14 mg/L) and Cd (3–13 mg/L) resulted in an antagonistic interaction and neurotoxicity.¹⁸

Furthermore, a 30-day exposure study in zebrafish evaluated PS NPs, arsenic (As), and their combination. The presence of NPs enhanced As accumulation in the brain, leading to increased reactive oxygen species (ROS) production, oxidative stress, mitochondrial dysfunction, neuronal impairment, structural alterations, and disrupted neuromodulation. Combined exposure produced more pronounced neurotoxic effects than single-contaminant

treatments.¹⁹

These studies highlight the complex and concerning consequences of the combined toxicity of MPs/NPs and heavy metals on living organisms (Table 2). The interactions between these pollutants can lead to enhanced tissue accumulation of heavy metals, oxidative stress, inflammation, and neurotoxicity. The size and surface characteristics of NPs are critical determinants of cellular toxicity, with specific NP types amplifying heavy metal-induced toxic effects. Moreover, combined exposure has been associated with gut microbiota dysbiosis, impaired gut barrier integrity, hepatic inflammation, and pronounced neurotoxicity, underscoring the involvement of the gut–brain axis. Furthermore, the facilitation of heavy metal bioaccumulation by MPs/NPs promotes excessive ROS generation, oxidative stress, mitochondrial dysfunction, neuronal impairment, structural modifications, and disrupted neuromodulation. Collectively, these findings emphasize the need for further investigations and the development of effective mitigation strategies.

4. Combined neurotoxicity of microplastics and nanoplastics with phthalates

Phthalates, also known as phthalic acid diesters, are widely used synthetic chemicals found in numerous industrial and consumer products.²⁰ They are primarily used as plasticizers in polyvinyl chloride plastics and are also incorporated into pharmaceuticals and cosmetic formulations as additives.²¹ One of their notable characteristics is their ability to leach out from plastic-containing products, posing environmental concerns as they are metabolized into monoesters and excreted in urine.²² These compounds are known endocrine disruptors that may affect human health through ingestion, inhalation, and dermal exposure. Prenatal exposure is also possible, underscoring the complex pathways through which phthalates impact both human health and the environment.²³

Understanding the combined neurotoxicity of MPs/NPs and phthalates is particularly critical because these chemicals frequently co-occur in air, water, food, and biological tissues. This section distinguishes phthalates from other classes of co-contaminants (e.g., organophosphorus flame retardants [OPFRs], bisphenol A [BPA], and pollutant mixtures) and evaluates their individual and combined neurotoxic mechanisms, exposure relevance, and biological endpoints.

Organophosphorus flame retardants (e.g., Tris[2-chloroethyl] phosphate [TCEP], Tris[1,3-dichloro-2-propyl] phosphate [TDCPP]) combined with PE MPs induced marked oxidative stress and cholinergic alterations in mice following a 90-day chronic exposure.²⁴

Table 2. Summary of studies investigating the combined neurotoxicity of microplastics and nanoplastics with heavy metals

Model	Size of MPs/NPs	Type of MPs/NPs with concentrations	Duration of exposure	Route of administration	Type of interactions	Co-contaminant	Effect	References
Zebrafish embryos	p-PET: 150 µm; f-PET: 3–5 mm length, 20 µm diameter	p-PET and f-PET	72 h	Waterborne	NA	Cd	Accelerated blood flow and heart rate, inhibited hatching, and reduced Cd bioavailability	13
Zebrafish (<i>Danio rerio</i>)	Virgin MPs (proprietary polymer)	Polystyrene microplastics, 2 mg/L	30 days (chronic)	Waterborne exposure	Combined exposure showed additive/interactive neurotoxicity	Copper (Cu), 25 µg/L	Oxidative stress, cholinergic alteration, gene dysregulation, apoptosis, and behavioral alterations	14
European seabass (<i>Dicentrarchus labrax</i>)	1–5 mm	MPs	96 h	Water exposure	Additive	Hg	Lethargic and erratic swimming behavior, signs of rapid fatigue, loss of swimming control, swimming upside down, and erratic jumping	15
Zebrafish (<i>Danio rerio</i>)	5 µm diameter	20 µg/L and 200 µg/L PS MPs	3 weeks	Water exposure	Synergistic	Cd	Increased Cd accumulation in liver, gut, and gills, oxidative damage and inflammation in tissues, and cognitive impairment	16
Zebrafish	PS MPs: 0.1, 10, and 250 µm	20 µg/L and 200 µg/L PS MPs	21 days	Water exposure	Synergistic, additive	50 µg/L Pb	Gut microbiota changes, brain toxicity, and liver inflammation	17
<i>Pomatochistus microps</i> juveniles (fish)	1–5 µm	0.14 mg/L MPs	96 h	Waterborne	Antagonistic	Cd LC10 = 2mg/L; LC50 = 8mg/L	Neurotoxic effects by inhibiting acetylcholinesterase activity, leading to potential impairments in behavior and survival	18
Zebrafish (<i>Danio rerio</i>)	100 nm	1 mg/L NPs	30 days	Waterborne	Synergistic	200 µg/L As	Increased reactive oxygen species production, mitochondrial damage, and neurotransmitter metabolism disturbance	19

Abbreviations: As: Arsenic; Cd: Cadmium; f-PET: Fibrous polyethylene terephthalate; Hg: Mercury; NA: Not available; NP: Nanoplastic; MP: Microplastic; Pb: Lead; p-PET: Granular polyethylene terephthalate; PS: Polystyrene.

OPFRs are commonly used as flame retardants and have been associated with neurotoxicity in previous studies.²⁴ In one study, TCEP and TDCPP were selected as target compounds. The results showed that the combination of TDCPP and PE MPs at a concentration of 10 µg/L led to a 21% increase in superoxide dismutase (SOD) and a 26% increase in catalase (CAT) activity. Additionally, lactate dehydrogenase levels in the TDCPP + MP groups were 18–30% higher compared to TDCPP alone. Interestingly, AChE levels were 18–30% higher in the TCEP + PE groups than in TCEP alone, while AChE levels were 10–19% lower in TCEP + PE groups than in TCEP alone. Metabolomics analysis identified significant alterations in metabolites related to amino acids and energy metabolism.²⁴

In another study, co-exposure to BPA and PS NPs significantly increased BPA accumulation in the brain and viscera of zebrafish, demonstrating carrier-mediated uptake. BPA is a known endocrine disruptor commonly found in plastics, with potential adverse effects on brain development. NPs, specifically PS particles, were selected due to their global production volume and observed neurotoxic effects in zebrafish. This enhanced uptake led to neurotoxic effects, as indicated by the upregulation of neurotoxic biomarkers in the central nervous system and dopaminergic systems. Notably, the activity of AChE, a common neurotoxicity biomarker, was no longer inhibited in the combination group, suggesting a different mode of action in the presence of both contaminants. Overall, these findings highlight that NPs can act as carriers for BPA uptake in zebrafish, enhancing bioaccumulation and neurotoxic effects and underscoring the importance of considering the impact of plastic particles on the bioavailability and toxicity of other pollutants in aquatic environments.²⁵

Another study investigated the immunotoxicity and neurotoxicity of BPA and MPs in *Tegillarca granulosa* (blood clam). Two-week exposure to BPA and MPs at environmentally relevant concentrations induced immunotoxic effects, including altered hematic indices and suppressed immune-related gene expression. Additionally, neurotoxicity was evident, with increased neurotransmitter levels but reduced expression of genes related to neurotransmitter modulation. Intriguingly, co-exposure to BPA and MPs enhanced the toxic effects, suggesting complex interactions. These findings emphasize the need to consider the combined effects of BPA and MPs on immune and neural responses in marine invertebrates, highlighting potential ecological risks.²⁶

A recent study demonstrated that chronic exposure to Di(2-ethylhexyl) phthalate (DEHP) combined with MPs induces significant neurotoxicity in both *in vivo* (mice)

and *in vitro* (NS20Y neuronal cells) models. DEHP, a widely used plasticizer, is found in various consumer products, while MPs are small plastic particles increasingly recognized as environmental pollutants. Mice were exposed to 200 mg/kg DEHP and 10 mg/L MPs (representing environmentally relevant high-end concentrations), while NS20Y cells were treated with 25 µM DEHP and 775 mg/L MPs. Both DEHP and MPs disrupted mitochondrial function, altered GSK-3β and phosphatidylinositol 3-kinase/protein kinase B signaling, and triggered neuronal apoptosis. Co-exposure produced synergistic neurotoxicity, with greater impairments in mitochondrial membrane potential, ATP levels, and apoptotic markers compared with single exposures. The inhibition of phosphatidylinositol 3-kinase/protein kinase B activates GSK-3β-driven apoptosis, explaining neuronal loss and potential cognitive decline. Moreover, simultaneous exposure to DEHP and MPs exacerbated neurotoxic effects in the mouse cerebrum. These findings highlight the importance of understanding the neurotoxicity of DEHP and MPs, especially in combination.²⁷

Another mammalian study reported that co-exposure to DEHP and polypropylene (PP) MPs exacerbated neurotoxicity across behavioral, molecular, and histological endpoints. Both pollutants individually impaired cognitive performance, reduced AChE activity, induced oxidative stress, and damaged hippocampal neurons, whereas combined exposure produced more severe cognitive deficits and hippocampal degeneration. Transcriptomics revealed activation of the unfolded protein response, endoplasmic reticulum (ER) stress, and suppression of heat-shock responses, suggesting chronic proteostatic imbalance. Exposure concentrations corresponded to upper-range environmental scenarios, supporting ecological plausibility. Long-term ER stress suggests potential irreversible neuronal injury.²⁸

Polystyrene and DEHP are prevalent in the environment, yet their distribution within organisms remains uncertain. A study employed PS particles of three sizes (50 nm, 500 nm, and 5 µm) and DEHP to investigate the distribution, accumulation, and potential toxicity of these substances in mice and nerve cell models (HT22 and BV2 cells). The findings demonstrated PS entry into the bloodstream of mice, with distinct tissue distribution patterns based on particle size. Following combined exposure to PS and DEHP, PS served as a carrier for DEHP, leading to a significant increase in DEHP and its metabolite, mono(2-ethylhexyl) phthalate (MEHP), particularly in the brain. Decreasing PS particle size correlated with increased PS, DEHP, and MEHP contents in the body. Elevated levels of inflammatory factors in the serum of the PS and/

or DEHP groups indicated the induction of systemic inflammation. Particularly, PS particles of 50 nm were identified as carriers for MEHP in nerve cells, suggesting a potential neurotoxic pathway. This study reveals, for the first time, that combined exposure to PS and DEHP can induce systemic inflammation, with the brain identified as a critical target organ. These findings provide valuable reference points for future assessments of neurotoxicity induced by combined exposure to PS and DEHP.²⁹

Another study investigated the neurotoxic effects of pollutants (e.g., aromatic hydrocarbons, food and paint additives, plastic, and industrial antioxidants) and MPs on fish brains, focusing on oxidative stress biomarkers and monoaminergic neurotransmitters in gilthead seabream. Juveniles were exposed to three dietary treatments for 90 days. The juveniles were divided into three treatment groups: control (standard feed), virgin (feed with 10% MPs), and exposed (feed with 10% MPs enriched with pollutants from seawater). Results showed increased oxidative stress biomarkers (e.g., CAT and glutathione S-transferase activity) and alterations in dopaminergic and serotonergic system activity in seabream brains after exposure. However, a 30-day detoxification period post-exposure indicated a tendency toward recovery in enzymatic and neurotransmitter levels. These findings highlight the potential neurofunctional effects associated with MPs and pollutant ingestion in marine organisms.³⁰

These studies demonstrate that simultaneous exposure to phthalates and plastic particles can exacerbate neurotoxicity compared to exposure to either pollutant alone (Table 3).

Collectively, available studies demonstrate consistent synergistic or additive neurotoxic effects from co-exposure to phthalates, OPFRs, BPA, and pollutant mixtures with MPs/NPs. Mechanistic patterns across taxa include oxidative stress (increased SOD, CAT, and GST), cholinergic dysfunction (reduced AChE or bidirectional dysregulation), mitochondrial dysfunction, unfolded protein response/ER stress and apoptosis, neurotransmitter imbalance (e.g., dopamine, serotonin), inflammation, and altered proteostasis.

Behavioral outcomes (in mice, fish, or invertebrates) consistently include cognitive deficits, increased anxiety-like behavior, and motor impairments. However, major gaps remain: (i) few mammalian chronic exposure studies; (ii) lack of low-dose, environmentally realistic time-frames; (iii) incomplete mechanistic mapping of phthalate-MP interactions; and (iv) limited data on reversibility and recovery at neural and behavioral levels. The demonstrated ability of MPs/NPs to act as carriers for phthalates and other contaminants, their accumulation in the brain, and

mechanistic convergence on oxidative, mitochondrial, and cholinergic pathways directly support human neurological risk concerns and inform regulatory needs.

5. Combined neurotoxicity of microplastics and nanoplastics with other co-contaminants

The concurrent neurotoxicity from interactions between MPs/NPs and co-contaminants arises through complex sorption-mediated mechanisms, including hydrophobic partitioning, electrostatic attractions, and π - π interactions, which enhance contaminant bioaccumulation and potentiate toxic effects in neural tissues.³¹ These plastic-contaminant complexes act as vectors that amplify bioavailability through controlled desorption in organismal guts and tissues, disrupting neurotransmitter systems, inducing oxidative stress, and altering neurodevelopmental pathways across aquatic and terrestrial models.³¹

Triphenyltin (TPT), an organotin compound from antifouling paints, sorbs strongly to PS MPs via hydrophobic interactions, with polymer crystallinity and surface oxidation influencing binding affinity. In 42-day common carp exposures (0.5 mg/L MPs + 1 μ g/L TPT; environmentally realistic concentrations), TPT alone induced lipid metabolism disorders, while MPs caused immunosuppression; combined exposure produced synergistic immunotoxicity via enhanced TPT bioavailability from MP-mediated desorption, with AChE inhibition and neurobehavioral deficits.³²

Avobenzene, an ultraviolet (UV) filter, exhibits synergistic accumulation with PS NPs in zebrafish larvae through hydrophobic sorption onto NP surfaces, persisting even after 72 h recovery and resisting elimination. Gene expression analysis revealed avobenzene targets nervous system development genes, while NPs affected retinal genes; combined exposure inhibited locomotor activity, AChE, and antioxidant enzymes (although SOD remained elevated post-recovery).³³

Ciprofloxacin sorption onto PS MPs/NPs in sediments followed the Freundlich isotherms, reducing free dissolved ciprofloxacin and showing antagonistic effects in *Corbicula fluminea* digestive glands but synergistic siphoning inhibition. Methodologically, clams were exposed to environmentally relevant concentrations, showing concentration-dependent AChE inhibition, oxidative damage, and filtration rate declines.³⁴

Polystyrene MPs enhanced roxithromycin bioaccumulation in red tilapia via carrier effects but mitigated roxithromycin-induced neurotoxicity and oxidative damage, demonstrating plastic-dependent

Table 3. Summary of studies investigating the combined neurotoxicity of microplastics and nanoplastics with phthalates

Model	Size of MPs/NPs	Type of MPs/ NP with concentrations	Duration of exposure	Route of administration	Type of interactions	Co-contaminant	Effect	References
Mice (<i>Mus musculus</i> , CD-1)	0.5–1.0 μm	2 mg/L of PE and PS	90 days	Oral ingestion	Antagonistic	TCEP: 10 $\mu\text{g/L}$ and 100 $\mu\text{g/L}$; TDCPP: 10 $\mu\text{g/L}$ and 100 $\mu\text{g/L}$	Increased SOD (21%) and CAT (26%) in 10 $\mu\text{g/L}$ TDCPP + PE group; higher LDH (18–30%) in TDCPP + MPs groups; lower AChE (10–19%) in TCEP + PE groups; changes in metabolites related to amino acid and energy metabolism	24
Adult zebra fish (<i>Danio rerio</i>)	50 nm	PS NPs: 3 $\mu\text{g/g}$ (w/w), 20 $\mu\text{g/g}$ (w/w), 43 $\mu\text{g/g}$ (w/w), and 85 $\mu\text{g/g}$ (w/w)	1 and 3 days of exposure	Exposure through water	Synergistic	BPA and dopamine	BPA and PS NPs accumulation in fish tissue; co-exposure increases BPA uptake in the head and viscera; neurotoxic effects observed in central nervous system and dopaminergic systems	25
Blood clam (<i>Tegillarca granosa</i>)	490 $\pm$ 11 nm	PS MPs: 25 mg/mL	14 days	Oral ingestion	Synergistic	BPA	Increase in <i>in vivo</i> contents of neurotransmitters (e.g., GABA, DA, and AChE); decrease in the expression of genes encoding modulatory enzymes and receptors for neurotransmitters	26
Immature mice	NA	PP MPs	NA	NA	Additive or synergistic	DEHP	Neurocognitive and memory deficits, damage to CA3 region of the hippocampus, increased oxidative stress, decreased AChE activity, and additive or synergistic effects	28
Mice	50 nm, 500 nm, and 5 μm	PS (50 nm)	NA	Oral	Synergistic	DEHP 100 μM	Cytotoxicity observed in nerve cells; brain identified as a target organ; increased accumulation of DEHP in the brain; elevated levels of inflammatory factors in serum; neurotoxic effects; systemic inflammation	29
Juveniles of gilthead seabream	(<5 mm) MPs	MPs (10% of MPs in the diet for all treatments (control, virgin, and exposed)	90 days	Ingestion through diet	NA	Pollutants adhered to MPs, including aromatic hydrocarbons, food and paint additives, and plastic and industrial antioxidants	Increased activity of oxidative stress biomarkers (e.g., CAT and GST); alterations in dopaminergic and serotonergic system activity in seabream brains; potential neurofunctional effects associated with MPs and pollutants ingestion	30

Abbreviations: AChE: Acetylcholinesterase; BPA: Bisphenol A; CAT: Catalase; DA: Dopamine; DEHP: Di(2-ethylhexyl) phthalate; GABA: Gamma-aminobutyric acid; GST: Glutathione-S-transferase; LDH: Lactate dehydrogenase; MP: Microplastic; NA: Not available; NP: Nanoplastic; PE: Polyethylene; PP: Polypropylene; PS: Polystyrene; TCEP: Tris(2-chloroethyl) phosphate; TDCPP: Tris(1,3-dichloro-2-propyl) phosphate.

modulation of antibiotic toxicity.³⁵

These sorption-driven interactions underscore the urgent need for mechanistic studies on desorption kinetics under gut conditions and for remediation strategies targeting plastic-contaminant complexes to protect neurodevelopment across trophic levels (Table 4).

6. Sorption chemistry of environmental contaminants on plastic surfaces and associated ecotoxicological impacts

6.1. Interactions between environmental contaminants and plastic surfaces

Plastic pollution has become a global environmental concern due to its widespread contamination and detrimental effects on ecosystems. The interaction between environmental contaminants and plastic surfaces plays a crucial role in the transport and fate of pollutants in the environment. MPs/NPs have high surface reactivity, allowing them to adsorb various hazardous chemical contaminants from the surrounding environment.³⁶ This adsorption process occurs on the “plastisphere,” a novel man-made ecosystem formed by the close interface of plastic litter and the microbiome.³⁷ The adsorption of contaminants on plastic surfaces can lead to the enrichment of contaminants on MPs/NPs, posing risks to both environmental and human health.³⁶

The sorption of pollutants onto plastic surfaces is affected by several factors, such as surface interactions, dimensions, morphology, and crystalline structure of the plastic particles.³⁴ Weathering processes, such as exposure to UV radiation and mechanical stress, can alter the physical and chemical properties of plastics, affecting their adsorptive attributes.²⁹ These weathering-induced changes can lead to enhanced surface complexation and the introduction of functional groups on plastic surfaces, influencing the sorption capacity of contaminants.³⁶

The sorption of contaminants onto plastic surfaces carries substantial implications for ecosystems. Plastic particles serve as reservoirs for environmental pollutants, amplifying their toxicity and endangering both biota and human health.³⁷ The release of contaminants from the plastisphere into the environment can threaten the health of organisms and disrupt ecosystem dynamics.³⁸ Furthermore, the adsorption dynamics of different contaminants on plastic surfaces may vary, depending on the interactions with environmental factors and the physicochemical properties of the plastic particles.^{37,38}

One area of concern is the potential neurotoxic effects of ingested MPs/NPs on humans and wildlife. Studies have demonstrated that exposure to plastic particles can result

in neurotoxicity, oxidative damage, and disruptions in energy metabolism in organisms.³⁷ For example, Barboza *et al.*¹⁵ demonstrated that MPs/NPs can modulate the bioaccumulation of mercury in European seabass, leading to neurotoxic effects. Moreover, the emerging threat of NP exposure to endocrine disruption and reproductive toxicity presents a significant global public health concern.³⁹

In summary, the interactions between environmental contaminants and plastic surfaces play a significant role in the transport and fate of pollutants in ecosystems. Understanding the adsorption mechanisms of contaminants on plastic particles and the effects of weathering processes is essential for mitigating the impacts of plastic pollution on the environment. Further research is needed to elucidate the detailed mechanisms underlying pollutant adsorption on plastic surfaces and to develop effective remediation strategies to address plastic-related pollution.

6.2. Plastic-mediated sorption of environmental contaminants

The sorption of environmental contaminants onto plastic surfaces, especially MPs/NPs, plays a pivotal role in determining the fate and distribution of pollutants in the ecosystem. Studies have demonstrated the strong adsorption of emerging contaminants like tetracycline onto organic montmorillonite surfaces, exhibiting patterns consistent with the non-linear Freundlich model commonly applied in sorption chemistry on plastic surfaces.⁴⁰⁻⁴² Moreover, the integration of plastics into carbon-based nano-adsorbents has been found to enhance the efficiency of environmental remediation, underscoring the potential advantages of incorporating plastics into remediation strategies.³⁶

The COVID-19 pandemic has led to a surge in plastic waste from increased use and disposal of personal protective equipment and packaged goods. Mismanagement of personal protective equipment waste poses risks to ecosystems and public health, with materials like PET and PP degrading into MPs and NPs, thereby increasing chemical adsorption on plastispheres.³⁶

The interactions between environmental contaminants and plastic surfaces are influenced by several factors, including surface chemistry, size, shape, and crystallinity of the plastic particles. Weathering processes, such as UV radiation exposure and mechanical abrasion, can alter the physicochemical properties of plastic surfaces, thereby affecting the adsorption and desorption mechanisms of pollutants.⁴³

Environmental weathering processes substantially modify the physicochemical properties of MPs and NPs, thereby altering their capacity to sorb and release

Table 4. Summary of studies investigating the combined neurotoxicity of microplastics and nanoplastics with other co-contaminants

Model	Size of MPs/ NPs	Type of MPs/ NPs with concentrations	Duration of exposure	Route of administration	Type of interactions	Co-contaminant	Effect	References
Common carp (<i>Cyprinus carpio</i>)	200 nm	PS MPs: 0.5 mg L ⁻¹	42 days	Water	NA	Triphenyltin	Induce lipid metabolism disorder; immunosuppression; immunotoxic effects; effects on the gut-brain axis	32
Zebrafish larvae	95.33 ± 3.28 nm	NPs	3 days	NA	Synergistic effect	Avobenzone	Affects genes related to nervous system development; genes associated with retinal system development; alters activities of acetylcholinesterase and antioxidant enzymes; changes in enzymatic and gene expression	33
Corbicula fluminea	PS MPs: 6 µm; PS NPs: 80 nm	PS MPs/ PS NPs: 10 mg/mL	10 days	NA	NA	Ciprofloxacin: 0.5 µg/g, 5 µg/g, and 50 µg/g	oxidative damage, neurotoxicity, decline in filtration rates, and interactions modulating toxicity	34
Red tilapia (<i>Oreochromis niloticus</i>)	0.1 µm	PS MPs: 100 µg L ⁻¹	14 days	Waterborne	Additive and synergistic effects	ROX: 500 µg/L	Enhanced ROX bioaccumulation with MPs; reduced neurotoxicity; enhanced ROX bioaccumulation with MPs; reduced neurotoxicity and oxidative damage by MPs; altered ROX metabolism in red tilapia; increased ROX accumulation with MPs; limited egestion and persistence of small MPs	35

Abbreviations: NP: Nanoplastic; NA: Not available; NP: Nanoplastic; PS: Polystyrene; ROX: Roxithromycin.

co-contaminants. Exposure to UV radiation, mechanical abrasion, thermal stress, and oxidative aging increases surface roughness, porosity, and the abundance of oxygen-containing functional groups on plastic particles, enhancing their affinity for metals, hydrophobic organic compounds, and endocrine-disrupting chemicals.^{44,45} These weathering-induced changes also increase surface area and promote electrostatic interactions, hydrogen bonding, and hydrophobic partitioning, resulting in higher contaminant loading compared with pristine plastics. Consequently, aged plastics often act as more efficient vectors for contaminant transport within aquatic and terrestrial ecosystems.⁴⁶

In parallel, the formation of plastisphere biofilms, which are complex microbial communities that colonize plastic surfaces, further modifies sorption behavior. Biofilms introduce extracellular polymeric substances rich in polysaccharides, proteins, and lipids, which provide additional binding sites for metals, antibiotics, and organic pollutants. Microbial metabolism within the plastisphere can also chemically transform sorbed contaminants, altering their speciation, persistence, and toxicity.⁴⁵ Importantly, biofilm-coated plastics exhibit altered surface charge and hydrophobicity, which can either enhance or inhibit contaminant adsorption depending on environmental conditions such as salinity, pH, and organic matter content.^{46,47}

Collectively, the combined effects of plastic weathering and biofilm colonization underscore the dynamic role of MPs and NPs as active vectors rather than inert carriers, highlighting the need to incorporate aging and plastisphere processes into neurotoxicity risk assessments and regulatory frameworks.

7. Possible neurotoxic pathways induced by micro-/nanoplastics with co-contaminants

The neurotoxic pathways associated with MPs/NPs and co-contaminants have been extensively investigated, providing valuable insights into the complex mechanisms through which these pollutants affect the nervous system and behavior of organisms. Studies have elucidated how MPs and co-contaminants disrupt neurotransmitter function in the brain, upsetting the delicate balance of signaling molecules crucial for mood regulation, cognition, and behavior.^{48,49} This interference with neurotransmitter pathways can result in abnormal neurobehavioral responses in exposed organisms.

Moreover, combined exposure to MPs and co-contaminants triggers neuroinflammation, characterized by the activation of microglia and the

release of pro-inflammatory cytokines.⁵⁰ Chronic neuroinflammation, resulting from this interaction, is implicated in various neurodegenerative disorders. Additionally, the integrity of the BBB can be compromised by MPs and co-contaminants, facilitating the penetration of toxic substances into the brain and amplifying neurotoxic effects, thereby increasing susceptibility to neurological disorders.⁵¹

Additionally, exposure to MPs and co-contaminants induces oxidative stress in the brain and nervous system.⁵¹ Oxidative stress, characterized by an imbalance between ROS production and cellular antioxidant defenses, leads to neuronal damage and dysfunction. The subsequent inflammatory responses triggered in the brain, as observed in studies by Han *et al.*,²⁸ can further exacerbate neurotoxic effects, influencing behavior.

Moreover, the endocrine-disrupting properties of co-contaminants associated with MPs/NPs highlight their impacts on hormone regulation and neuroendocrine pathways.^{14,39} Disruption of these pathways can affect stress responses, reproductive behaviors, and circadian rhythms, ultimately leading to neurotoxic effects and behavioral changes.

Furthermore, the bioaccumulation of co-contaminants carried by MPs/NPs in the brain and neural tissues directly affects neurobehavioral functions.¹⁹ The accumulation of neurotoxic substances within neuronal cells disrupts their function and integrity, resulting in altered behavior, cognitive impairment, and changes in neuronal signaling⁵² (Figure 2).

8. Conclusion

In conclusion, the interaction between MPs/NPs and co-contaminants poses a significant risk to neurotoxicity in organisms. The synergistic effects, bioaccumulation, disruption of neurotransmission, inflammatory responses, and oxidative stress induced by combined exposure to MPs/NPs and co-contaminants can have detrimental effects on neurological health. Understanding these complex interactions is crucial for assessing the risks posed by these pollutants to both human health and the environment. Further research is warranted to elucidate the mechanisms underlying neurotoxicity induced by MPs/NPs and co-contaminants, as well as to develop strategies to mitigate their impact on neurological health.

9. Knowledge gaps and future research needs

Despite growing evidence that MPs and NPs can potentiate the neurotoxicity of co-contaminants, substantial gaps

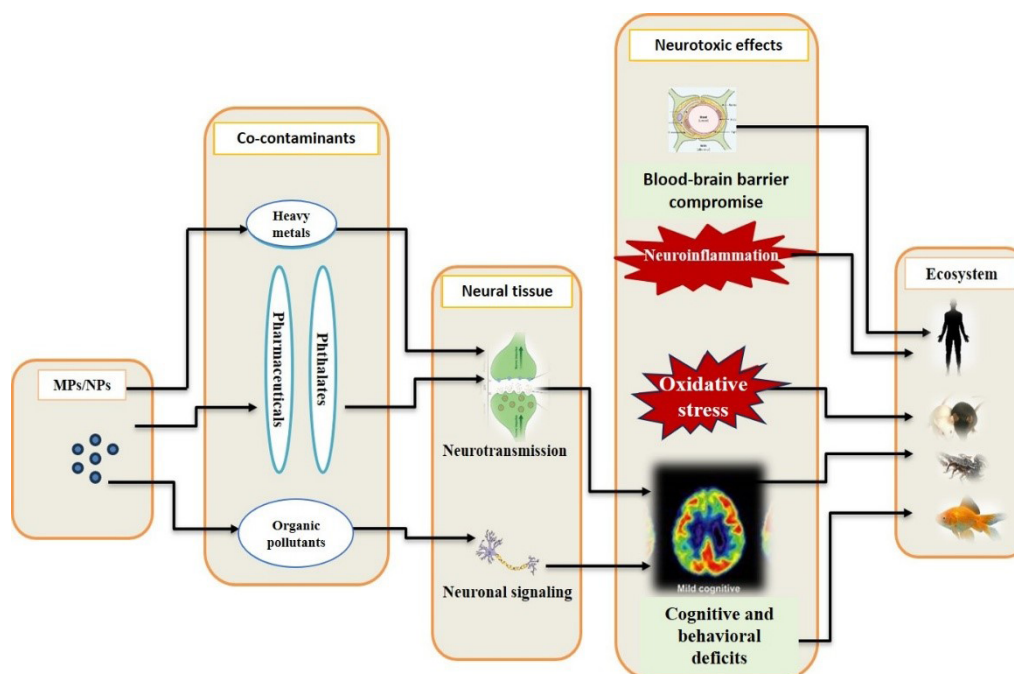


Figure 2. Neurotoxic pathways induced by microplastics (MPs), nanoplastics (NPs), and co-contaminants in organisms within the ecosystem. Created with BioRender. Sharma, K (2026). <https://BioRender.com>.

remain in the literature. Chronic, low-dose exposure studies that reflect environmentally relevant concentrations are scarce, particularly across critical developmental windows and aging models. Mammalian studies remain limited compared to aquatic models, thereby restricting translational relevance to human neurological health. Mechanistic understanding is also incomplete, with insufficient integration of molecular, cellular, and behavioral data to clearly delineate causal pathways linking plastic-contaminant interactions to neurotoxicity. Key unresolved questions include the kinetics of contaminant desorption from plastic surfaces under physiological conditions, region-specific brain vulnerability, reversibility of neurobehavioral effects, and the long-term consequences of cumulative exposures. Future studies should prioritize harmonized exposure protocols, chronic mammalian models, sex-specific analyses, and multi-omics approaches to better resolve mechanistic pathways. Expanding research in these areas will be essential for accurate risk assessment and for informing regulatory and mitigation strategies addressing combined microplastic and co-contaminant neurotoxicity.

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