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Review

Neurotoxicity Following Exposure to Micro and Nanoplastics

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Abstract

The pervasive presence and enduring existence of micro and nanoplastics in the environment render their exposure to humans and aquatic creatures unavoidable. Research indicates these tiny plastic particles can be taken in by aquatic beings and mammals. Once within the body, micro and nanoplastics have the capability to infiltrate the brain, although the level of penetration and the subsequent neurotoxic effects are not fully explored. Previous studies indicate that metal (oxide) nanoparticles can enter the brain and induce neurotoxic effects. Given the chemical resemblances between plastic particles and inert metal (oxide) nanoparticles, this review aims to summarize existing studies on the neurotoxic implications of nanoplastics across various species and in vitro settings. The current evidence, although incomplete, suggests that exposure to nanoplastics may lead to oxidative stress, potentially causing cell damage and raising the risk of developing neurological disorders. Moreover, such exposure could inhibit acetylcholinesterase activity and alter neurotransmitter levels, potentially contributing to observed behavioral changes. There is a notable lack of systematic comparison regarding the neurotoxic effects stemming from different particle types, shapes,

and sizes at various concentrations and durations of exposure. Understanding these aspects is essential for further evaluating the neurotoxic danger and risk associated with nanoplastics.

Keywords
Neurotoxicity; microplastic; nanoplastic; oxidative stress; nanoparticles

1. Introduction

Plastics are crucial in producing various products, including packaging materials, pharmaceuticals, cosmetics, textiles, masks, and surgical instruments [1-3]. Their widespread application can be attributed to their adaptability, strength, water resistance, cost-effectiveness, and ease of production with minimal energy use [1, 2]. These attributes make plastics an excellent choice for fabricating medical devices such as syringes, IV bags, medical packaging, artificial joints, and prosthetics, as well as food storage solutions and other plastic goods [4]. Despite these benefits, plastics face criticism due to environmental and health concerns stemming from their long-lasting nature, widespread presence, and potential to contaminate food and water sources for animals [1, 4]. Plastics gained traction alongside the Industrial Revolution, expanding significantly as a consumer product since the 1930s and 1940s. Between 1975 and 2012, global plastic resin production jumped by 620%, reaching 288 million tons [5]. Consequently, plastic waste surged from 275 million tons in 2010 to 335 million tons by 2017 [5, 6], posing a grave threat to human health due to its largely unsustainable usage patterns [4]. In the U.S., the recycling rate for plastics is merely 8.8% [7]. Plastics' slow decomposition remains problematic, as single-use plastics like LDPE bags may take up to 250 years to break down in landfills or natural environments [8]. By 2025, it is expected that 192 countries' coasts within 50 km will accumulate around 250 million tons of poorly managed marine plastic waste [5]. Over time, these enduring plastics fragment into microplastics and nanoplastics—tiny particles with variable chemical structures formed through degradation processes [9-11]. Microplastics and nanoplastics, present everywhere, from the atmosphere to aquatic systems, pose threats due to their minute size and diverse shapes, including fibers, foams, beads, and fragments [12]. Interestingly, spherical microplastics may cause fewer gut health issues than irregular ones [13]. Although there is debate over the size categories of plastic debris, classifications typically include macroplastics (2.5-100 cm), mesoplastics (0.1-2.5 cm), microplastics (1000 μm–1 μm), and nanoplastics (<1 μm) [14-16], with some sources defining micro- and nanoplastics as slightly different ranges “small microplastics” (1 μm to <100 μm), “sub-micron plastics” (100 nm - <1 μm), “nanoplastics” (1 nm to <100 nm) [17, 18], or 100 nm–1 nm [19, 20]. However, there is a significant gap in understanding regarding the dimensions, architecture, and cost of micro- and nanoplastics. The toxicological impacts of micro- and nanoplastics on human organs, their cellular absorption pathways, and the underlying molecular mechanisms remain underexplored due to the scant and often inconsistent scientific literature. This study aims to provide an overview of the potential entry of microplastics and nanoplastics into the body and then into the brain and to link exposure and the physicochemical properties of the particles with neurological diseases. In addition, it also provides insights into the mechanisms of the effects of microplastics and nanoplastics on the diseases above.

2. Methodology

A systematic search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, using keywords such as combinations such as Neurotox AND Nanoplastic, Neurotox AND Microplastic, and Neurotox AND plastic particles, neuroinflammation, and oxidative stress markers. The review includes studies published between 2015 and 2024, ensuring that the most current findings are represented. The inclusion criteria were focused on peer-reviewed articles that involved both animal and human models and specifically examined micro and nanoplastics's effects on oxidative stress and neuroinflammation. Studies unrelated to micro and nanoplastics, those involving other pollutants classes, or those lacking molecular insights were excluded. The selected studies were synthesized to assess consistent findings on micro and nanoplastics's ability to induce oxidative stress, including the production of reactive oxygen species (ROS) and lipid peroxidation, as well as its endocrine-disrupting effects on the hypothalamic-pituitary-adrenal (HPA) axis, thyroid function, and other hormonal pathways. Special attention was given to studies addressing micro and nanoplastics's persistence in the environment and their potential for cumulative toxicity through prolonged exposure.

3. Comparison with Prior Studies

While micro and nanoplastics's toxicological effects have been well documented, previous reviews have not thoroughly addressed micro and nanoplastics's interaction with other environmental contaminants or its long-term impact at sub-lethal doses. This review fills these gaps by focusing on micro and nanoplastics's dual role in oxidative stress and endocrine disruption. It also provides a more detailed exploration of micro and nanoplastics's molecular mechanisms, which have mainly been underexplored in earlier work. The integration of recent findings on micro and nanoplastics's environmental persistence and the risks of chronic exposure further distinguishes this review from past analyses, offering a more comprehensive understanding of micro and nanoplastics toxicity.

4. Ways to Microplastics and Nanoplastics Exposure

Recently, the frequent use of plastic has been pinpointed as a substantial contributor to micro and nanoplastics pollution, capturing the focus of environmentalists and medical scholars [21]. This pollution is a pressing global issue due to its threat across ecosystems. It includes humans, who face exposure through food, drinking water, inhaled air, and skin contact via cosmetic and pharmaceutical products [22]. Research indicates that micro- and nanoplastics are harmful in environmental and laboratory contexts, impacting experimental animal models, cellular assays, and various aquatic and land animal species [23-25]. Humans face exposure to these micro- and nanoplastics predominantly through consuming marine animals and other food commodities contaminated with these particles, including everyday consumer products like toothpaste, beer, honey, salt, and sugar [26, 27]. In addition to food sources, humans ingest these plastics through water consumption, mainly mineral and drinking water stored in plastic bottles and cartons [26, 27]. Beyond ingestion, inhalation poses another exposure route, as micro- and nanoplastics can be released from textiles, synthetic rubber tires, and plastic coatings [26-28]. Rodent studies over the years have documented the presence of these minuscule particles, particularly those 0.3 μm or

smaller, which have been shown to transit to vital organs like the liver and spleen, and systems like the lymphatic system, though at minimal levels [29-31]. There is compelling evidence indicating that micro-scale plastic fibers have made their way into human lung tissues, implying the possibility of these micro- and nanoplastic particles entering the body through inhalation processes [32, 33]. This concern extends further, as certain studies have documented the slight absorption of biodegradable polymeric microparticles when ingested via the gastrointestinal tract [34]. While these investigative efforts collectively underscore the potential for micro- and nanoplastic entry into the human body through both inhalation and ingestion [35], there remains a significant shortfall in research that meticulously examines how these particles are dispersed throughout the body, specifically across various organs, based on differences in particle dose and size. Moreover, the health implications associated with exposure to, absorption of, and the transport mechanisms of micro- and nanoplastics within the human body have not been thoroughly explored, making this a central issue in current scientific discussions and debate [24, 26, 36].

5. Microplastics and Nanoplastics Effects on the Nervous System

Due to the constraints in obtaining human tissue samples, the repercussions of microplastics and nanoplastics on human health remain inadequately comprehended [37]. The human nervous system, a sophisticated network with numerous neurons, oversees various physiological functions [38]. Despite the limited research on how microplastics and nanoplastics impact the nervous system, there is potential for nanoplastics to breach physiological barriers like the BBB [39]. The transport and build-up of these particles in the brain can result in different types of damage, heightening the brain's susceptibility to neurological disorders by causing oxidative stress [40]. Research indicates that microplastics and nanoplastics have detrimental effects on the nervous system, potentially leading to neurodegeneration. Studies have observed that nanoplastics contribute to neurotoxicity by disrupting typical neuron arrangements and characteristics in the cerebral cortex, signified by nuclear pyknosis. In particular, mouse brain tissues exposed to PS-NH2 showed increased caspase-3 signals, a marker for neuron cell apoptosis. Additionally, cytokines like TNF-α and IL-6 were upregulated in these tissues, hinting at inflammation caused by cytokine presence [41]. In the case of European seabass, exposure to microplastics reduced the release of the enzyme acetylcholinesterase (AChE), triggered oxidative stress and lipid peroxidation, and forced a shift towards anaerobic energy pathways, which subsequently led to irregular swimming behavior [42]. When neural cells were subjected to these particles, toxicity was induced and the metabolic rate decreased. These adverse effects of microplastics and nanoplastics appear to stem from the build-up of immune cells activated within the brain, oxidative stress, and heightened levels of inflammatory cytokines in circulation, particularly TNF-α and IL-6 [41, 43]. Other research supports the neurotoxic impact of these particles [44, 45], such as findings by O'Donovan et al., [46] which demonstrated that LDPE microplastic particles in clams could lead to neurotoxicity by altering acetylcholinesterase activity or by infiltrating the brain and causing oxidative stress, culminating in cellular damage that can cause neurodegenerative and neurodevelopmental issues [47].

6. Neurotoxicity of Nanoparticles

Metal (oxide) nanoparticles are prevalent in various fields, including food production, personal care products, cosmetics, and biomedical therapy, where they're utilized for drug delivery and gene

therapy [48-51]. The impact of these nanoparticles has been extensively studied, with the central nervous system identified as a crucial target for their toxic effects [52-54]. These nanoparticles can infiltrate the brain, primarily by traversing the blood-brain barrier (BBB) or through retrograde transport via the olfactory nerve endings [47, 55-57]. The properties of different metal and metal oxide nanoparticles vary widely; intriguingly, some of their physicochemical properties are akin to those observed in plastic particles. Notably, specific metal nanoparticles exhibit high reactivity, capable of inciting oxidative stress and subsequent damage. Notable examples include iron oxide [58, 59], silver [60, 61], and copper oxide [62, 63]. Gold (Au) and titanium dioxide (TiO_2) nanoparticles closely align with the criteria for hemistry. This is a critical trait when evaluating metal (oxide) nanoparticles alongside plastic micro- and nanoparticles [28, 64, 65]. Studies have demonstrated that gold nanoparticles can penetrate brain tissues in adult zebrafish and rats. Within these tissues, they are capable of causing oxidative stress, altering energy and mitochondrial metabolism, affecting acetylcholinesterase (AChE) activity, and influencing neurobehavioral functions [66-68].

Similarly, among the various types of TiO_2 nanoparticles, the most extensively researched are those that enter the brains of aquatic creatures like fish. Here, they can trigger oxidative damage, increase cell mortality, impact neurotransmitter levels, affect motor activity, and alter spatial recognition abilities [69-72]. In rodent models, exposure through the oral, intranasal, or intratracheal routes to TiO_2 nanoparticles (sizing between 5 to 100 nm) has been linked to oxidative stress and neuroinflammation [73, 74]. Such exposure disrupts glutamatergic pathways, modifies neurotransmitter levels [73, 75, 76], changes AChE activity [74, 75], hinders motor skills [77], reduces long-term potentiation, and hampers learning and memory recall [75, 78]. Further in vitro experiments have reinforced the capability of TiO_2 nanoparticles to incite oxidative stress and neuroinflammation [79-82]. Despite specific effects of gold and TiO_2 nanoparticles being observed only after substantial doses or non-natural administration methods (like injections), these nanoparticles can nonetheless reach the brain and impose an array of neuroprotective impacts. The degree to which these findings are relevant to micro- and nanoplastics remains largely unexplored. Given the prevalent nature of micro- and nanoplastics and considering the evident neurotoxic effects tied to gold and TiO_2 nanoparticles of comparable size and chemical neutrality, this review delves into the potential of these plastics to offer neuroprotection.

7. Microplastics and Nanoplastics Neurotoxic Effects on Marine Invertebrates

Caenorhabditis elegans were subjected to five different spherical polystyrene microplastic sizes (0.1–5 µm) in a culture medium at 1 mg/L concentration. This led to excitotoxicity affecting their movement, lowered survival rates, and decreased average lifespan, with the most pronounced effects observed with exposure to 1.0 µm size particles. Additionally, the expression of several neuronal genes declined, which was linked to disruptions in cholinergic and GABA neurons and increased oxidative stress. However, there is no direct proof of the ingestion of these microplastics by C. elegans [83, 84]. Earthworms (Eisenia fetida) exposed to low-density polyethylene particles ranging from 100–200 µm (0.1–1.5 g/kg soil) for a period of up to 28 days within artificial soil, exhibited skin damage, particularly at 1.5 g/kg soil exposure level. Upon analyzing and quantifying polyethylene particles, their uptake (after 14–28 days at 1.5 g/kg soil) was confirmed, yet the detailed distribution of the particles inside the earthworms remains unclear. When exposed to

polyethylene particles at a level of 1.0 g/kg soil for 28 days, an increase in catalase activity and malondialdehyde levels was noted, suggesting oxidative stress in these organisms. Notably, exposure levels of 1.0 and 1.5 g/kg soil for 21 and 28 days, respectively, also led to higher AChE activity [85]. Freshwater zebra mussels, known as Dreissena polymorpha, were exposed to pristine polystyrene microbeads of two sizes (1 µm and 10 µm) at concentrations of 1 and 4×10^6 MPs/L for six days. This led to the accumulation of particles within the gut lumen and further movement to tissues and hemolymph, as observed with confocal microscopy. Importantly, these polystyrene microbeads did not cause genotoxic effects. While both bead sizes boosted dopamine levels, other parameters such as serotonin, glutamate levels, and activities of monoamine oxidase and AChE remained unchanged. Interestingly, the lower-dose mix enhanced catalase activity, lowering glutathione peroxidase and pointing towards moderate cellular stress [86]. In a different study involving the bivalve Scrobicularia plana, exposure to 20 µm polystyrene microplastics at a concentration of 1 mg/L resulted in particles being detected in the hemolymph, digestive gland, and gills using light microscopy and infrared spectroscopy. A 7-day exposure to these microplastics in the gills led to sustained increases in superoxide dismutase (SOD) activity and a rise in Glutathione-S-transferase (GST) activity by the end of the exposure, suggesting oxidative stress. During the exposure period of 3 to 14 days, along with post-excretion, a decrease in AChE and lipid peroxidation (LPO) activities was noted in the gills. In the digestive gland, from day 14, SOD activity was elevated, whereas catalase activity was reduced [87]. Myetilus gallopro-vincialis (Mediterranean Mussels) were subjected to polystyrene microplastics (0.11 µm, 0.005–50 mg/L) for 96 hours, resulting in notable deviations in the genes' expression linked to biotransformation, cellular stress response, and innate immunity. Distinct responses were observed in the gills (hsp70 at 50 mg/L) and digestive glands (cyp11 at 0.5 mg/L, cyp32 at 5 mg/L, cat at 0.05 and 0.5 mg/L, lys at 5 mg/L). While there wasn't an evident pattern of dose dependence, the mean DNA damage increased with exposure concentrations ranging from 0.05–50 mg/L. There was a reduced cholinesterase activity in the hemolymph at concentrations between 0.05–0.5 mg/L, though no further signs of neurotoxicity were noted. However, there’s a lack of evidence concerning the actual uptake of polystyrene microplastics [88]. Exposure of the same species to both unpolluted and pyrene-contaminated polyethylene and polystyrene microplastics (100 µm, 1.5 g/L) over seven days led to the introduction of plastic particles within the hemolymph, gills, and intestines, identified through polarized light microscopy. This exposure decreased AChE activity in the gills but not in the hemolymph, also inducing nuclear alterations and DNA damage. Pyrene did not amplify the AChE activity inhibition [89]. Corbicula flumina (Asian Freshwater Mussels), when exposed to red fluorescent polymeric microspheres (composition unspecified; 1–5 µm, 0.2 or 0.7 mg/L) for 96 hours, showed plastic particles inside the digestive tract, gland’s lumen, connective tissue, hemolymphatic sinuses, and the surface of the gills using light and fluorescent microscopy. Exposure at 0.2 mg/L significantly reduced cholinesterase activity, heightened with florfenicol exposure [90]. In another study, these mussels exposed to red fluorescent polymeric microspheres (1–5 µm, 0.13 mg/L) for eight days had increased presence of particles in their digestive tract and gills. The exposure diminished cholinesterase activity and elevated LPO levels, signifying oxidative damage. The effects were reversible after six days of recovery and, surprisingly, were mitigated by simultaneous mercury exposure [91]. The exposure of both striped shrimp (Amphibia lanu amphitrite) and brine shrimp (Artemia Franciscan) larvae to 0.1 µm fluorescent polystyrene microparticles, at concentrations ranging from 0.001 to 10 mg/L, over periods of 24 to 48 hours led to plastic particles being

detectable within them through fluorescence microscopy. Yet, it remains uncertain whether these particles can penetrate further into surrounding tissues. When exposed to microplastics at concentrations of 1 mg/L or higher for 48 hours, noticeable alterations in the larvae's swimming speeds were observed. Furthermore, the microplastic exposure resulted in various influences on enzyme activities. Notably, there was a significant increase in catalase activity, more evident at a higher concentration of 1 mg/L. In contrast, the influence on cholinesterases, such as acetylcholinesterase and propionylcholinesterase, showed no clear pattern of dose dependency [92].

Exposure of brine shrimp larvae (Artemia Francesca) to amino-modified polystyrene nanoparticles, with a size of 50 nm, at concentrations of 0.1 to 10 µg/mL over either 48 hours or 14 days caused a decrease in GST and catalase activity. This reduction suggests oxidative stress, along with inhibition of carboxylation and ChE carboxylation processes, particularly at a 1 µg/mL concentration. Unfortunately, despite these effects, there was no substantial evidence to confirm the actual uptake of these polystyrene nanoparticles by the larvae [93].

8. Microplastics and Nanoplastics Neurotoxic Effects in Rodents

In contrast to the extensive rodent in vivo research available for metal(oxide) nanoparticles, studies delving into the micro- and nanoplastics neurotoxicity in rodents are notably scarce, with only two such investigations. This scarcity is particularly surprising when considering the documented neurotoxic consequences of micro- and nanoplastics exposure in marine and fish invertebrates. In the solely published mice in vivo study, adult mice were subject to chronic exposure over 30 days to polystyrene microplastics, with sizes of 5 and 20 µm and doses ranging from 0.01 to 0.5 mg per day (approximately 0.5 to 25 mg/kg body weight daily), administered through oral gavage. The exposure to polystyrene microplastics led to the absorption and presence of particles in the mice's gut, liver, and kidneys, confirmed via fluorescence spectrometer analysis of freeze-dried tissues. During the initial week of exposure, particle concentrations in the tissues rose swiftly and stabilized at approximately 0.2, 1.0, and 1.4 mg/g for 5 µm particles in the liver, kidney, and gut, respectively. For 20 µm particles, the concentration was more consistent across the organs, reaching a plateau at about 0.8. Examination of the liver revealed dose-dependent alterations in energy metabolism, including reduced ATP levels and elevated LDH activity, alongside oxidative stress markers such as increased GSH-Px and SOD and decreased CAT. Curiously, liver AChE activity rose, and metabolomic shifts implied possible neurotransmitter level changes. Notably, the difference in effect size between 5 µm and 20 µm particles was minimal when considered on a mass basis. Regrettably, the study did not explore brain tissue [42]. Another in vivo study involved chronic exposure, over five weeks, of male rats to significant doses of polystyrene nanoplastics measuring 40 nm, with dosages between 1 and 10 mg/kg body weight per day. However, this exposure did not impact behavior or weight gain, and no evidence was provided of actual polystyrene nanoplastic uptake [94].

9. Factors Affecting the Microplastics and Nanoplastics Neurotoxic Potential

Several factors can affect the neurotoxic potential of micro- and nanoplastics. One major factor is the extent of exposure organisms have to these particles, significantly impacting the potential neurotoxic effects [95]. In real-life scenarios, the levels of exposure are notably lower than those

typically used in laboratory experiments. Conversely, the length of exposure in experimental situations is usually far less than what would be encountered in human exposures. Some research indicates that the neurotoxic impacts of micro- and nanoplastics are dependent on how long one is exposed [93, 96, 97]. Besides concentration and exposure time, the temperature at which exposure occurs may also play a role in neurotoxicity, especially in fish, with toxicity levels rising as temperatures increase [98, 99]. Apart from these locational factors, the intrinsic properties of the particles themselves may heavily influence their neurotoxic potential. Particle size is considered one of the key characteristics influencing toxicity, with nanoparticles generally being absorbed more readily and have more significant toxicity than microparticles [95, 100]. However, for plastic particles specifically, there is only limited data supporting the idea that smaller particles exhibit higher toxicity [42, 83, 101]. The hydrodynamic diameter of particles, reflecting the size of secondary particles, could play a significant role in their neurotoxic effects. Though smaller particles tend to exhibit more significant neurotoxicity, they are also prone to aggregation, forming larger clusters. While this aggregation theoretically mitigates neurotoxic potential by increasing the particle size, there is limited research on this phenomenon. Notably, a study discovered that nanoplastics aged for six months expanded from 65 nm to over 1300 nm, amplifying toxicity in comparison to the initial particles, implying that larger aggregated particles might exhibit increased neurotoxicity [102]. The extent of particle aggregation is influenced by surface charge and the suspension medium [71, 79, 80, 92, 93]. Moreover, a particle's surface charge is directly implicated in its neurotoxic potential and biological activity, whether micro- or nanoplastics [28, 65]. Specifically, nanoparticles with a negative surface charge tend to undergo greater cellular uptake [103], whereas a positive charge leads to increased disruption of the plasma membrane and more significant mitochondrial harm [104]. Unfortunately, scant research analyzing the micro- and nanoplastics surface charge investigations into this aspect remains nascent. The particles' zeta potentials span from +40 mV to -50 mV, yet their neurotoxic implications are beginning to be examined. For metal (oxide) particles, the elemental composition has a bearing on toxicity. Likewise, the specific chemical makeup of micro- and nanoplastics is anticipated to influence their neurotoxic potential. The shape of plastic particles, though not exhaustively compared, could substantially impact neurotoxic potential. Variations in shape—such as spheres, fibers, and rods—lead to differences in surface area and potential internalization [65]. Therefore, comprehensive research is necessary for comparing neurotoxic effects across various particle types, shapes, and sizes, considering aggregation impacts, through both in vitro and in vivo model systems. Another complexity is the potential for microplastics and nanoplastics to act as carriers for pathogens and chemicals. Although not fully understood, these particles may adsorb different environmental substances [105] and potentially even pathogens [106]. These adsorption capabilities might inadvertently enhance exposure to these harmful agents, aggravating their neurotoxic impact. Therefore, further investigation is essential to elucidate the detailed role of these factors in particle-induced neurotoxicity.

10. Mechanisms of Microplastics and Nanoplastics Entry into the Brain

Micro- and nanoplastics predominantly infiltrate the brain by traversing the BBB through a permeation process [107]. Generally, micro- and nanoplastic internalization involves two primary mechanisms: passive permeation and active endocytosis, which include pinocytosis and

phagocytosis [108]. Endocytosis can proceed through kaolin-mediated pathways (typically for larger particles) and clathrin-mediated pathways (typically for small nanoplastics) [109]. The permeation processes of micro- and nanoplastics are affected by their physicochemical characteristics, such as the shape and size of the particles, their chemical makeup, and their surface charge [110, 111]. There's minimal research regarding how nanoplastic size affects their penetration through the BBB. This is primarily because conducting such experiments is complex, requiring labeled nanoplastics of varying sizes to be detectable within the intricate environments of biological systems [112]. Research has demonstrated that smaller, fluorescently labeled polystyrene particles (100 nm) can more effectively penetrate the brain of zebrafish embryos compared to larger particles (500 and 1000 nm), leading to increased entry and neurotoxicity of the smaller particles [113]. In the domains of medical and environmental research, numerous studies have utilized various metal nanomaterials to demonstrate the crucial role that particle size plays in the capacity of these nanomaterials to traverse the BBB [111]. For example, one investigation established that smaller-sized nanoplastics more readily infiltrate the brain, posing greater toxicity than larger microplastics [114]. Another study assessed different sizes of silica nanomaterials regarding their ability to pass through brain endothelial cells in mice [115]. The findings indicated that smaller particles, specifically those measuring 25 nm, were absorbed by the brain more effectively than those measuring 50 nm and 100 nm [109, 116]. It has been posited that larger nanomaterials mainly penetrate using active mechanisms such as pinocytosis and phagocytosis. While applying this knowledge directly to nanoplastics is debatable because of variations in particle chemistry and density—factors that greatly influence cellular penetration—these investigations provide a foundational comprehension and form a basis for conducting comparable experiments with nanoplastics [117]. The configuration of nanoplastics also has potential ramifications on their penetration through the BBB into the brain, as it can influence their interaction with cellular structures. Research has examined the toxic effects of both spherical and rod-shaped polystyrene nanoplastics in mice. Findings demonstrate that rod-shaped nanoplastics may exhibit a more robust binding ability than their spherical counterparts [118]. Further evidence regarding the influence of particle shape on BBB penetration exists for other nanoparticles. For instance, a study highlighted that gold rod-shaped nanomaterials possess a heightened affinity and efficiency for endothelial cells, leading to increased uptake [119]. An essential factor affecting the ability of nanoplastics to bypass the BBB is their chemical structure. This aspect also helps distinguish between various types of nanoparticles. Recent investigations indicate that nanoplastics made from polystyrene and polyvinyl chloride (PVC) can move across the BBB, albeit at minimal concentrations. The research further highlights that a biological corona, comprised of proteins and metabolites, significantly alters the permeability efficiency of these nanomaterials through the BBB. The corona’s development is directly influenced by the particle's chemical attributes [39]. Studies have also demonstrated that polypropylene, polyethylene, polystyrene, and PVC can access the central nervous system (CNS), with polypropylene and polyethylene possibly inducing greater inflammation [120]. Chemical composition, even with identical particle sizing, can differentially impact the behavior of zebrafish embryos [121]. This recognition complicates efforts to comprehend how the composition may affect the biological outcomes and toxicity of nanoparticles [122]. The particles' surface charge is crucial in defining their capacity to penetrate the BBB. Nanoplastics with negative charges are typically less likely to cross the membrane because of electrostatic forces. Nevertheless, studies have indicated that cellular membrane ionic imbalances may allow these negatively charged particles to penetrate

directly [123]. Our prior research has evidenced that nanoparticles from diesel exhaust can creep through the BBB [31, 48, 54]. Nanoplastics with a positive charge, however, show a heightened capacity to infiltrate the BBB and become localized within cells [124]. Negatively charged polystyrene particles measuring 50 nm have been shown to cross the BBB by impacting tight junctions [125]. Furthermore, these negatively charged nanoplastics are more inclined to settle in rodent brains than their positively charged counterparts of identical size [126]. Conversely, positively charged polystyrene particles, ranging from 20–100 nm, are prone to increasing the permeability of the BBB [127]. This increase is partly due to potential membrane damage inflicted by structural disruption [128]. While there is evidence that nanoplastics permeating the BBB may lead to neurodegenerative changes, conclusive data remains elusive [47]. It should be noted that the literature on polystyrene nanoparticles surpasses that of other plastic varieties in terms of extent and depth.

11. Conclusions

Despite the widespread presence of micro- and nanoplastics in the environment, information on their absorption and toxicity remains limited. Research shows these particles can enter various organisms, including humans, fish, and mammals, through different exposure pathways. There's a significant lack of knowledge about the neurotoxic potential of these plastics. However, studies indicate that they might induce oxidative stress, inhibit the activity of AChE, impact neurotransmitter levels, and alter behavior in some species. It's still unclear if these effects relate to neurodevelopmental or neurodegenerative disorders in humans, unlike metal nanoparticles. Most experimental exposures to date don't mimic real human exposure situations, as they occur over short periods with high doses. In contrast, humans are exposed chronically to lower levels. Moreover, many studies use particle types and shapes that are not typical of environmental conditions. There's also a significant gap in systematically comparing various particle types, shapes, sizes, and concentrations. Most research so far has concentrated on aquatic species. To thoroughly understand the neurotoxin and exposure risks from micro- and nanoplastics, several actions are necessary:

1. Improved Monitoring: A better assessment of exposure levels for humans is needed, focusing on different exposure routes like inhalation, ingestion, and retrograde transport after nasal exposure, along with particle characteristics.

2. Focused Assessments: Research should investigate absorption through the lungs, nasal epithelium, or gut, potential crossing into the bloodstream, blood-brain barrier penetration, and organ accumulation, including the brain. It must determine direct transfer to the brain via nerve endings or indirect bloodstream transport, helping to identify the most dangerous particles for human health and the most vital exposure reduction measures.

3. Enhanced Risk Identification: Exposure time and particle dose standardization should incorporate dose-response curves, considering particle weight and number. Research should utilize various particle types, sizes, shapes, and surface charges, preferably those prevalent in the environment. For realistic assessments, aged and contaminated particles should be studied alongside virgin manufactured particles despite the complex toxicity.

4. Diversified Species Use: It's crucial to include different species, particularly mammals, given the variability in exposure routes. Laboratory assays can significantly aid hazard identification,

increasing throughput, reducing costs, and providing mechanistic insights. However, the focus should be on subtle, functional effects beyond overt (neuro)toxic endpoints, as such effects may occur only at unrealistic exposure levels. Ultimately, irrespective of the findings from these hazard and risk evaluations of nanoplastics, measures should be implemented to minimize their further contamination and release into the environment.

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Competing Interests

The authors declare that they have no competing interests.

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