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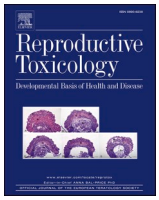

Review

Micro- and nanoplastics and brain sexual differentiation: An emerging neurodevelopmental threat within the DOHaD framework

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ABSTRACT

Micro- and nanoplastics (MNPs) have been increasingly detected in human tissues, including the placenta and, more recently, the brain. Their capacity to cross biological barriers such as the placenta and the blood–brain barrier raises significant concern for sexually dimorphic neurodevelopment. Brain sexual differentiation, orchestrated by steroid hormones, neuroimmune signaling, and epigenetic programming during early life, represents one of the most hormonally sensitive and developmentally critical targets of environmental disruption. In this narrative review, we synthesize evidence positioning MNPs as potential endocrine and epigenetic disruptors that may reprogram hypothalamic circuits governing reproduction and socioemotional behavior within a DOHaD framework. Evidence is stronger in animal and cellular models, implicating oxidative stress, neuroinflammation, apoptosis, and disrupted neurotransmission as central mechanisms; however, sex-specific endpoints remain underexplored and human data are still limited. This review adds a novel integrative perspective by focusing on sexually dimorphic hypothalamic nuclei and by outlining testable, sex-informed hypotheses. We highlight key methodological priorities for future research, including environmentally relevant exposures, explicit consideration of sex as a biological variable, multi-omics approaches, and longitudinal designs.

1. Introduction

Micro- and nanoplastics (MNPs) are emerging contaminants of global concern for human and environmental health. These particles have been detected in human blood, placenta, lungs, breast milk, and recently, in brain tissue, underscoring their systemic bioavailability [1–5]. Their diminutive size, surface reactivity, and chemical composition allow translocation across biological barriers, including the placenta and the blood–brain barrier (BBB) [6,7].

Among developing organs, the brain is particularly vulnerable. Sexual differentiation of the brain, orchestrated by steroid hormones and epigenetic cues during perinatal and pubertal windows, establishes sexually dimorphic neural circuits underlying reproductive and behavioral functions [8]. Environmental toxicants, especially endocrine- disrupting chemicals (EDCs) present in plastics such as bisphenols, phthalates, and polybrominated diphenyl ethers (PBDEs), can perturb

Abbreviation: ADHD, Attention-Deficit/Hyperactivity Disorder; AMH, Anti-Müllerian Hormone; ASD, Autism Spectrum Disorder; AVPV, Anteroventral Periventricular Nucleus; BBB, Blood–Brain Barrier; BPA, Bisphenol A; Cd, Cadmium; CNS, Central Nervous System; DDT, Dichlorodiphenyltrichloroethane; DNMTs, DNA-Methyltransferases; DOHaD, Developmental Origins of Health and Disease; EDC, Endocrine-Disrupting Chemical; EDCs, Endocrine-Disrupting Chemicals; ERα/ERβ, Estrogen receptors alpha/beta; GnRH, Gonadotropin-Releasing Hormone; HPG, Hypothalamic–Pituitary–Gonadal axis; HPT, Hypothalamic–Pituitary–Thyroid axis; IL-1β, Interleukin 1 beta; LH, Luteinizing Hormone; MNPs, Micro- and Nanoplastics; MPOA, Medial Preoptic Area; MPs, Microplastics; NPs, Nanoplastics; PA, Polyamide; PBDEs, Polybrominated Diphenyl Ethers; PC, Polycarbonate; PCP, Personal Care Product; PE, Polyethylene; PET, Polyethylene Terephthalate; PGE_2, Prostaglandin E_2; Pb, Lead; POMC, Proopiomelanocortin; POPs, Persistent Organic Pollutants; PP, Polypropylene; PS, Polystyrene; PS-MPs, Polystyrene Microplastics; PS-NPs, Polystyrene Nanoplastics; PU, Polyurethane; PVC, Polyvinyl Chloride; ROS, Reactive Oxygen Species; TNF-α, Tumor Necrosis Factor alpha; VMH, Ventromedial Hypothalamus.

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these finely tuned developmental processes [9].

The Developmental Origins of Health and Disease (DOHaD) framework provides a conceptual lens through which early-life exposures are understood to permanently shape health trajectories [10,11]. Within this paradigm, MNPs emerge as novel developmental programming agents, capable of inducing inflammation, oxidative stress, and epigenetic reprogramming. Despite growing evidence of MNP neurotoxicity [12], sex-specific effects during brain sexual differentiation remain critically underexplored, limiting our understanding of how early exposures may generate lifelong neuroendocrine and behavioral outcomes.

In this narrative review, we synthesize current evidence on the interactions between MNP exposure and sexually dimorphic brain development, highlighting hormonal, neuroimmune, and epigenetic mechanisms within the DOHaD framework. We also propose research priorities to bridge current mechanistic gaps and to promote sex-informed, translational approaches for future studies. Although this is a narrative, mechanistic-focused review, we adopted a transparent and targeted literature search strategy. Publications were identified through PubMed, Web of Science, and Scopus (2008–2025), using keyword combinations including "microplastics," "nanoplastics," "neurodevelopment," "sexual differentiation," "hypothalamus," "endocrine disruptors," and "DOHaD." Additional articles were obtained through citation tracking.

Foundational studies published before 2008 (e.g., classic works from 1998 and 2006 addressing steroid-dependent brain sexual differentiation and neuroendocrine organization) were intentionally included when essential for mechanistic context and historical framing. Studies were selected based on relevance to MNP-induced neurotoxicity, neuroendocrine disruption, and sex-dimorphic outcomes. No formal systematic criteria or quality scoring were applied, consistent with the aims of a narrative review.

2. Micro- and nanoplastics: sources, properties, and exposure

Plastic debris is commonly classified by size into macroplastics (>5 mm), large microplastics (1–5 mm), **microplastics (MPs; 0.1 μm–5 mm)**, and **nanoplastics (NPs; <0.1 μm)** [13,14]. This classification is crucial for understanding their biological impact, as particle size dictates their capacity to cross biological barriers. While MPs are typically measured in micrometers and are found ubiquitously in the environment and human tissues, NPs are measured in nanometers (i.e., less than 100 nm or 0.1 μm) and possess increased surface reactivity and a greater ability to translocate across the BBB and the placenta [6,7]. The term **micro- and nanoplastics (MNPs)** is used throughout this review to collectively refer to both size fractions, acknowledging their shared polymeric nature and the complexity of distinguishing between them in environmental and biological samples. These particles may originate as secondary fragments derived from the degradation of larger items or as primary particles intentionally produced for commercial use in cosmetics, paints, textiles, and industrial abrasives [15]. Due to their minute size and high surface-area-to-volume ratio, MNPs exhibit increased reactivity, colloidal stability, and environmental persistence, enhancing their bioavailability and toxicological potential [16].

MNPs are ubiquitous in marine, freshwater, terrestrial, and atmospheric compartments, and have been detected in various food products, such as seafood, table salt, honey, and bottled water, underscoring the inevitability of chronic human exposure [17,18]. Beyond particle size, plastics differ by polymer composition. The most prevalent synthetic polymers are polypropylene (PP), polyethylene terephthalate (PET), polyethylene (PE), polyvinyl chloride (PVC), polyamide (PA), and polyurethane (PU). These materials dominate packaging, textiles, and construction industries, reinforcing their environmental ubiquity and biological relevance [19].

Plastics are further divided by their thermomechanical behavior. Thermoplastics, such as fragmented packaging, synthetic fibers, and cosmetic microbeads, can be melted and reshaped, whereas thermosetting plastics possess cross-linked structures that prevent remelting. This latter group includes tire rubber, insulating foams, and ship coatings. Importantly, environmental aging (photo-oxidation, mechanical abrasion) increases surface oxidation and roughness, enhancing the adsorption of EDCs and persistent organic pollutants (POPs) and potentially magnifying neurotoxic responses [20].

The global proliferation of MNPs is driven by escalating plastic production and ineffective waste management. Between 1950 and 2015, about 4.9 billion metric tons of plastic waste accumulated in landfills and natural environments, with projections exceeding 12 billion tons by 2050 [21]. Over time, photodegradation, mechanical abrasion, and microbial activity fragment macroplastics into smaller particles that persist for decades, generating heterogeneous mixtures with evolving surface chemistry and biological reactivity [22].

In addition to intrinsic polymer properties, the toxicological behavior of MNPs is profoundly influenced by their chemical context. During manufacture, plastics incorporate additives such as phthalates, bisphenols, and flame retardants, while in the environment they adsorb metals and persistent pollutants. These intrinsic and extrinsic factors jointly form complex chemical mixtures that determine bioavailability and toxicity [23–26]. The combination of additive leaching and pollutant sorption enhances MNP reactivity, promoting oxidative and endocrine-disrupting responses across biological systems. This so-called "Trojan horse" phenomenon, in which MNPs act as vectors for co-contaminants, is summarized in Box 1 [27–29].

Collectively, polymer heterogeneity, environmental aging, and contaminant sorption define the "chemical identity" of MNPs in biological systems. Thus, risk assessment cannot rely solely on polymer type or size: mixture composition and environmental history must also be considered to understand biological responses, particularly in neural and endocrine targets.

2.1. Routes of human exposure: oral, inhalational, and olfactory pathways

Humans are exposed to MNPs through ingestion, inhalation, and, to a lesser extent, dermal absorption. Among them, ingestion and inhalation represent the dominant exposure routes across all age groups [30,31]. Ingestion occurs through the consumption of contaminated seafood as well as products such as salt, honey, and sugar [32], and is particularly elevated in individuals who consume bottled water, which may contain substantially higher MP loads than tap water [33]. In addition to dietary sources, MNPs have been detected in household dust, indicating that food preparation and consumption in indoor environments may contribute to exposure. Furthermore, MPs can enter food during processing, packaging, storage, and transportation, highlighting the ubiquity of contamination across the agri-food supply chain [32].

Inhalation of airborne MNPs, now documented worldwide, represents another major pathway. These particles have been detected in lung tissues, bronchoalveolar lavage fluid [2], as well as in placental and fetal tissues [33], raising concerns about their ability to reach deep biological compartments. Notably, indoor environments appear to be a major exposure source, with infants and children presenting the highest estimated inhalation doses of airborne MNPs [34]. Although dermal uptake contributes minimally to total body burden, NPs can penetrate the stratum corneum through follicles, sweat glands, or microlesions, inducing oxidative stress, mitochondrial dysfunction, and cellular senescence in keratinocytes and fibroblasts [35].

Emerging evidence identifies a direct olfactory pathway as an additional route to the central nervous system (CNS). Experimental models show that ultrafine PS particles can migrate along the olfactory and trigeminal nerves, bypassing the BBB and accumulating in the olfactory bulb and hypothalamus [36,37]. This neuroanatomical shortcut may represent a critical yet under-recognized route for MNP entry into brain regions governing neuroendocrine regulation and sexual differentiation,

Box 1
Additives and Sorbed Contaminants: Why Mixtures Matter.

MNPs rarely act as isolated entities; their toxicological profile is shaped by both intrinsic additives incorporated during manufacturing and environmental contaminants adsorbed post-production.

- Additives include plasticizers (such as phthalates), flame retardants (PBDEs), stabilizers, colorants, and bisphenol A (BPA), all recognized EDCs [23,24].
- Sorption processes allow MNPs to concentrate heavy metals, microorganisms, and POPs on their surface.
- Acting as "Trojan horses," MNPs deliver these co-contaminants into biological systems, amplifying toxicity beyond that of the polymer core [27–29].
- Example: aged PS particles with sorbed PBDEs markedly increase reactive-oxygen-species (ROS) and cytokine release in hypothalamic neuron–astrocyte co-cultures *in vitro*, highlighting mixture-driven neuroinflammatory risk.

Implication: Toxicity assessments must consider the mixture effect -the interactive roles of polymer type, additives, adsorbates, and aging -to estimate exposure risk accurately.

particularly during perinatal development [38].

Once internalized, MNPs circulate through the bloodstream and lymphatic system, accumulating in organs such as the lungs, liver, heart, placenta, and brain [33]. Their biodistribution is influenced by particle size, surface charge, polymer type, and exposure route. Fetuses and neonates exhibit higher vulnerability because physiological barriers, including the placenta and BBB, are still immature, facilitating maternal–fetal transfer and early-life accumulation [39].

Early-life exposures - including transplacental transfer, lactational exposure, and ingestion of contaminated breast milk or meconium - represent a major concern within the DOHaD framework. Section 2.2 explores these pathways in detail, emphasizing the implications of maternal–fetal MNP transfer for neurodevelopment and sexual differentiation.

2.2. Exposure during development: transplacental, perinatal, and early-life routes

Pregnancy and early postnatal life represent critical windows of susceptibility to MNP exposure [40], with direct implications for neurodevelopmental programming and long-term health (Fig. 1). Because both the placenta and the BBB are still developing during these stages, the maternal-fetal interface is highly permeable to environmental contaminants [41]. MNPs have been detected in human placenta, amniotic fluid, breast milk, and meconium, providing clear evidence of both transplacental and postnatal transfer routes [1,4]. Quantitative analyses

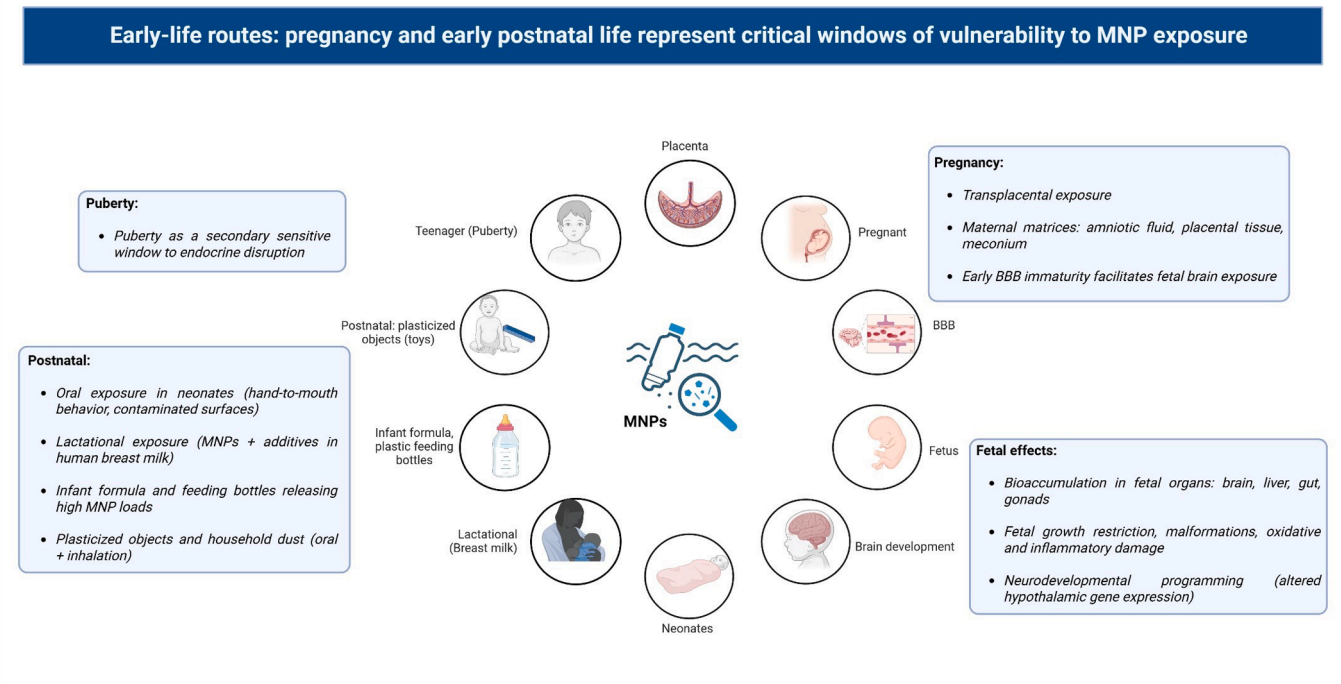

Fig. 1. Early-life exposure routes to micro- and nanoplastics (MNPs) during pregnancy, postnatal life, and puberty. Created with BioRender. MNPs may reach the developing organism through transplacental transfer, amniotic fluid, placental tissue, and meconium, with early blood-brain barrier (BBB) immaturity facilitating fetal brain exposure. Postnatal routes include oral ingestion in neonates, lactational transfer via breast milk, MNP release from infant formula and polypropylene feeding bottles, and contact with plasticized objects and household dust (oral and inhalation). Puberty represents an additional vulnerable window due to increased endocrine sensitivity. These exposures contribute to fetal bioaccumulation, growth restriction, oxidative and inflammatory injury, and neurodevelopmental programming.

report MNP concentrations in placental tissues ranging from 0.28 to 9.55 particles per gram, with PE, PS, PA, PU, and PVC polymers identified in both maternal and fetal compartments [7,42–44]. These findings demonstrate that the placenta, once considered an effective barrier, is in fact a selective but leaky interface that allows nanoscale particles and associated additives to enter fetal circulation and accumulate in developing organs, including the brain [41].

Both *in vitro* and *in vivo* studies corroborate these observations, demonstrating that MNPs can traverse the placenta and BBB during critical periods of development, bioaccumulating in fetal tissues and persisting postnatally, thereby maintaining biological activity during periods of heightened neuroendocrine sensitivity [45–47]. Following transplacental transfer, MNPs have been detected in fetal tissues and associated with multiple adverse outcomes, including fetal growth restriction, oxidative stress, inflammation, skeletal malformations, intestinal dysbiosis, endocrine disruption, and altered hypothalamic gene expression, consistent with early neuroendocrine reprogramming [33,48–50].

In addition to transplacental exposure, early-life contact with MNPs occurs through maternal breast milk, infant formula, plastic feeding bottles, and other plasticized objects [51,52]. MNPs have been identified in human breast milk samples, with PP, PE, and PVC representing the most common polymers [5,53]. Lactational exposure delivers not only polymer particles but also MNP-associated additives and metabolites, reinforcing the infant's body burden proportionally to maternal exposure and breastfeeding duration [1].

While ingestion represents a dominant postnatal route, inhalation emerges as an equally relevant pathway during infancy and childhood. Infants may ingest between 7.2×10^2 and 4.5×10^4 plastic particles per day - approximately 1.8 times more than adults - due to higher food intake relative to body weight and frequent hand-to-mouth behaviors [54]. Feeding bottles and pacifiers made of PP can release substantial quantities of MNPs into formula milk, while airborne household dust contributes additional particles to infant inhalation [52,55]. Due to elevated respiratory rates and more time spent close to the ground, where particulates accumulate, infants may experience higher cumulative inhalation exposure than adults under similar conditions [28].

The COVID-19 pandemic has further increased human contact with plastic-derived materials, particularly single-use packaging and polypropylene face masks, expanding opportunities for MNP exposure in daily environments [55]. Although dermal absorption remains less characterized, it may become relevant in the context of damaged skin barriers or chronic topical contact with contaminated surfaces or personal-care products containing plastic microbeads [31].

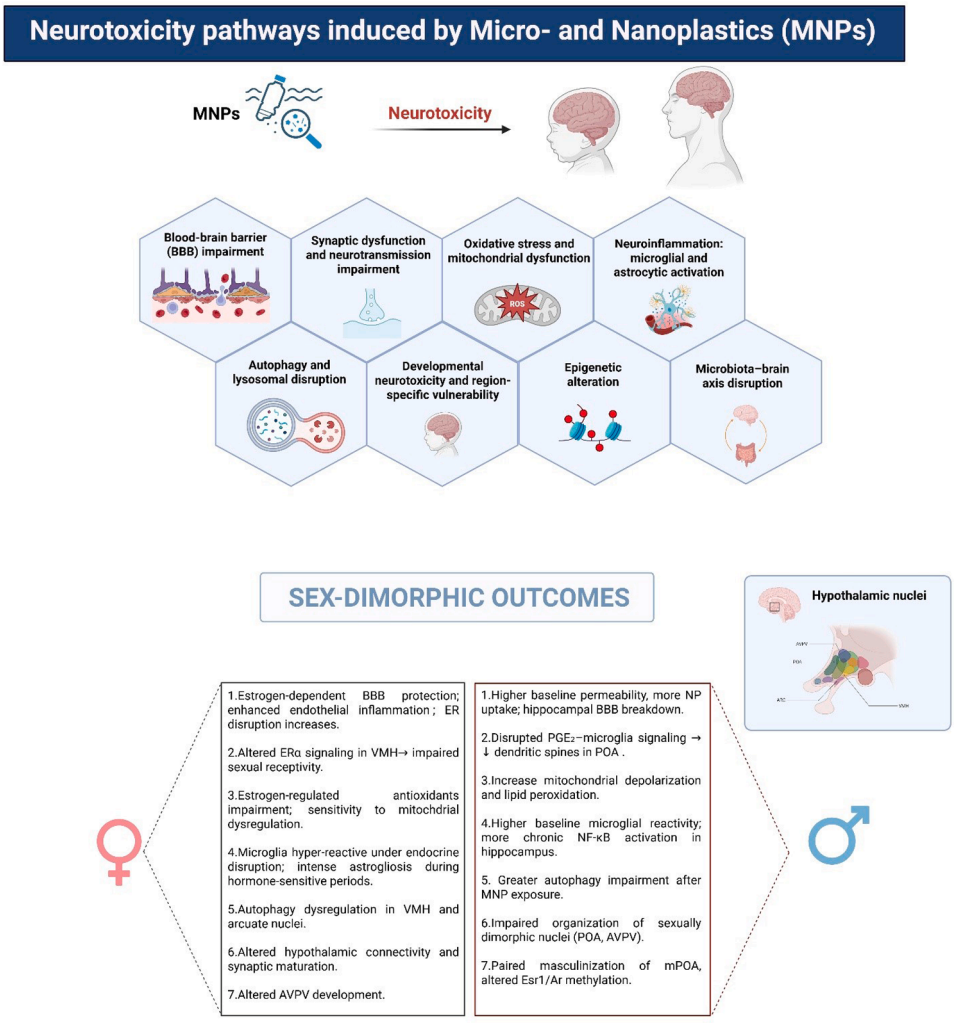

Fig. 2. Mechanistic pathways underlying Micro- and nanoplastic (MNP)–induced neurotoxicity and sex-dimorphic outcomes. Created with BioRender. Schematic representation summarizing the major cellular and molecular mechanisms by which MNP exposure disrupts neurodevelopment. Key pathways include oxidative stress, neuroinflammation, blood–brain barrier (BBB) disruption, altered neurotransmission, endocrine disruption affecting the HPG/HPT axes, and epigenetic reprogramming. These processes converge to impair neuronal differentiation, synaptic organization, and hypothalamic sexual differentiation, resulting in sex-specific neurobehavioral and reproductive alterations.

3. Neurotoxic potential of micro- and nanoplastics

MNPs are increasingly recognized as neurotoxicants capable of crossing biological barriers and accumulating in the brain, where they induce neural dysfunction through multiple mechanisms (Fig. 2). They have been detected in cerebrospinal fluid and neural tissues after crossing the BBB or migrating through retrograde olfactory transport [12,56]. These findings indicate that nanoscale particles, in particular, possess physicochemical properties - such as high surface reactivity and the capacity to acquire biologically active coronas - that enable interactions with neural and neuroendocrine structures, especially when biological barriers are immature or compromised [12].

MNPs, especially particles < 100 nm, can cross the BBB via transcytosis, endocytosis, or paracellular passage. The nasal olfactory epithelium and the gut–brain axis provide additional routes of entry into the CNS [57,58]. Once within systemic circulation or neural interfaces, these particles may be internalized by microglia, astrocytes, and neurons, where limited degradative pathways facilitate intracellular retention and progressive accumulation [59].

Experimental evidence shows that exposure to MNPs compromises BBB integrity, increasing permeability and facilitating particle entry into the CNS. Polystyrene microplastics (PS-MPs) induce BBB leakage and disrupt endothelial tight junctions in rodents (0.5–50 mg/kg PS-NPs for 7 days) and *in vitro* models [60,61], and similar effects have been observed in avian and fish species, suggesting a conserved cross-species vulnerability [62,63]. Olfactory exposure to NPs can further exacerbate BBB dysfunction by promoting oxidative stress and pro-inflammatory signaling along the olfactory–hypothalamic axis [57].

Once within the CNS, MNPs trigger neurotoxicity through interconnected molecular pathways, including BBB impairment, neurotransmission disruption, oxidative stress, neuroinflammation, apoptosis-autophagy imbalance, microbiota-brain axis disruption, and epigenetic programming. These alterations converge on hypothalamic and limbic circuits critical for endocrine regulation, stress responses, and sexual differentiation [64,65]. Table 1 summarizes the main mechanistic pathways of MNP-induced neurotoxicity, highlighting molecular targets and delineating sex-dimorphic vulnerability across developmental contexts.

3.1. Developmental neurotoxicity

Exposure to MNPs during sensitive developmental windows—gestation, lactation, and early postnatal life - can interfere with neurodevelopment, resulting in long-lasting and potentially sex-specific cognitive and behavioral outcomes [66]. The route of exposure shapes CNS biodistribution: oral exposure primarily involves BBB translocation, whereas inhaled or intranasal exposures enable direct transport along the olfactory pathway, producing region-specific vulnerability in the olfactory bulb and hypothalamus [32,36]. Studies in rodents have demonstrated that oral administration leads to MNP distribution in central brain regions, including the cortex and hippocampus [55,60,67]. In contrast, neuronal transport pathways may allow MNPs to reach the olfactory bulb, cortex, cerebellum, and brainstem [36], and particles may subsequently migrate to additional brain regions [55].

Notably, a subset of studies has begun to adopt environmentally relevant dosing strategies. For example, in a chronic oral exposure model, mice received PS-MPs in drinking water (1 mg/L). Based on recorded water intake, the estimated daily dose was 167 μg/kg/day, closely approximating the lower range of daily human MP ingestion (174 μg/kg/day) reported by Cox et al. [68]. Such designs help bridge the gap between traditional high-dose toxicology and real-world chronic low-level exposures, providing a more realistic framework for detecting subtle and potentially sex-dependent neurodevelopmental effects.

However, a major limitation of the current literature remains the frequent use of exposure concentrations that exceed estimated human intake levels [28,68]. While high-dose experimental designs are valuable for mechanistic discovery, they may not accurately reflect chronic, low-dose human exposure scenarios [28]. Evidence from studies employing environmentally relevant exposure estimates suggests that even low-level, chronic exposure to microplastics may be sufficient to induce subtle neurodevelopmental and neuroendocrine alterations [68]. These findings underscore the importance of aligning experimental paradigms with realistic exposure metrics, particularly when assessing developmental and sex-specific outcomes.

Beyond physical deposition, converging evidence implicates oxidative stress, apoptosis, neuroinflammation, microglial activation, impaired neuronal differentiation, disrupted neural stem cell maintenance, and altered neurodevelopmental signaling pathways [66,69,70]. These processes may modify critical developmental trajectories, although further validation in human populations is urgently needed.

The timing of exposure is crucial, as the developing brain undergoes sequential and highly sensitive periods of differentiation, growth, and circuit formation [66]. Gestational exposure to MNPs is associated with alterations in brain metabolism and vascular function, reduced expression of proteins essential for myelination and neuronal survival, and increased oxidative stress, inflammation, and apoptosis. These molecular and structural changes can be accompanied by long-term behavioral effects, such as anxiety-like behavior and impaired social interaction [71,72]. Continued exposure during lactation further disrupts neuronal architecture and hippocampal neural stem cell function, induces sex-dependent cognitive and behavioral impairments, alters monoamine and amino acid neurotransmission, and impairs cortical development and neuronal migration [66,73]. Moreover, perinatal exposure has been shown to impair retinal development, reducing retinal ganglion and bipolar cell populations and compromising vascularization [74].

Chronic exposure from fetal life through adulthood inhibits neuronal growth, alters cell proliferation, increases apoptosis, and downregulates neurodevelopmental genes such as *GABRA2*. Neonatal exposure also disrupts microglial autophagy and synaptic pruning, leading to persistent anxiety-, depression-like, and social behavior abnormalities [75,76].

Since hypothalamic sexual differentiation depends on precise temporal coordination of gene expression and neuronal migration, MNP-induced developmental perturbations may interfere with the establishment of sexually dimorphic hypothalamic nuclei. Such disruptions may impair gonadotropin-releasing hormone (GnRH) network formation and neuroendocrine circuit organization, resulting in long-term, sex-specific consequences [38,77]. These mechanistic intersections are further elaborated in Section 4.

3.2. Micro- and nanoplastics as neuroendocrine disruptors

MNPs function as complex endocrine-disrupting mixtures, exerting biological activity through intrinsic physicochemical properties and through associated additives such as BPA, phthalates, PBDEs, and heavy metals. These compounds can mimic or antagonize endogenous hormones, disrupt receptor signaling, and alter steroidogenic enzyme activity even at low concentrations [23,54,78].

Studies with different animal models have been demonstrated that MNP exposure reduces circulating testosterone levels, suppress aromatase expression, and alter estrogen receptors alpha/beta (ERα/ERβ) signaling in neural and gonadal tissues [78–80]. Such disruptions are particularly concerning during perinatal and pubertal windows, when sex steroid hormones orchestrate hypothalamic sexual differentiation and the establishment of neural circuits controlling reproduction and social behavior [38].

The hypothalamus represents a primary neuroendocrine target for MNP-associated EDCs. Additives commonly absorbed or released by MNPs, including PBDEs, phthalates, BPA, PCBs, and heavy metals, can impair both the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–thyroid (HPT) axes by disrupting hormonal feedback, inducing oxidative stress, promoting astrocyte-mediated

Table 1
Mechanisms of Micro- and Nanoplastic (MNP)–Induced Neurotoxicity and Sex-Dimorphic Outcomes, indicating experimental model (*in vivo* or *in vitro*) and species/cell type.

Mechanism	Experimental Model	Species/Cell type	Molecular/Cellular Effects	Representative Markers /Pathways	Sex-Dimorphic Susceptibility	Key References
Blood-brain barrier (BBB) impairment	*In vivo/In vitro*	Mouse, rat; human brain endothelial cells	Tight junction loss (Claudin-5, Occludin, ZO-1); endothelial inflammation; increased BBB permeability; NP translocation	Claudin-5, Occludin, ZO-1, NF-κB, MAPKs, VE-cadherin, ICAM-1, VCAM-1	*Males:* Higher baseline permeability, more NP uptake; stronger hippocampal BBB breakdown under oxidative load *Females:* Estrogen-dependent BBB protection disrupted by EDCs; enhanced endothelial inflammation during high-estrogen phases (puberty, estrous peaks); ER disruption increases ICAM-1 / VCAM-1 sensitivity, more leukocyte infiltration	[60,91,124]
Synaptic dysfunction and neurotransmission impairment	*In vivo/In vitro*	Mouse, rat; neuronal cultures	↓ synaptic proteins, imbalance of neurotransmitters (GABA, 5-HT, dopamine), altered Ca^{2+} homeostasis	Synapsin, PSD-95, AChE, dopamine/ serotonin signaling	*Males*: Disrupted PGE_2–microglia signaling → ↓ dendritic spines in POA (impaired masculinization) *Females:* Altered ERα signaling in VMH → impaired sexual receptivity	[12,91,97, 124, 141–143]
Oxidative stress and mitochondrial dysfunction	*In vivo/In vitro*	Mouse, rat; neuronal and glial cells	ROS generation; mitochondrial depolarization (ΔΨm↓); ATP depletion; oxidized DNA, proteins and lipids	ROS, MDA, 8-OHdG; ΔΨm, Cox IV; Nrf2/ Keap1, SOD, CAT, GPx	*Males:* Increase mitochondrial depolarization and ATP loss; stronger lipid peroxidation, higher MDA/4-HNE; weaker Nrf2 response, deficient recovery from oxidative injury *Females:* Estrogen-regulated antioxidants (Nrf2, GPx, SOD) impairment → oxidative vulnerability; more mtDNA damage when estrogen cycling is high; higher sensitivity to mitochondrial Ca^{2+} dysregulation	[124,131, 144]
Neuroinflammation: microglial and astrocytic activation	*In vivo/In vitro*	Mouse, rat; microglial and astrocyte cultures	Microglial and astrocyte activation; cytokine upregulation; complement-mediated synaptic pruning	Iba-1, GFAP, IL-1β, TNF-α, IL-6, NF-κB, MAPK, C1q/C3, CD68	*Males:* Higher baseline microglial reactivity due to stronger TNF-α production; more chronic NF-κB activation in hippocampus; increased complement C1q, C3 → more synaptic pruning *Females:* Stronger IL-6 / IL-1β response; microglia hyper-reactive under endocrine disruption; intense astrogliosis during hormone-sensitive periods	[12,60,145, 146]
Autophagy and lysosomal disruption	*In vivo/In vitro*	Mouse; neuronal cell lines	Impaired degradation of damaged proteins; accumulation autophagosomes; altered LC3 and p62 expression	LC3, p62, LAMP-1, Beclin-1	*Males:* Greater autophagy impairment after MNP exposure *Females*: Autophagy dysregulation in VMH and arcuate nuclei → impaired energy balance and maternal behavior	[135, 147–150]
Developmental neurotoxicity and region-specific vulnerability	*In vivo*	Mouse, rat, zebrafish	Downregulation of neuronal differentiation markers; disruption of developmental signaling pathways; altered neuronal migration and synaptogenesis; region-specific deposition of MNPs (hippocampus, cortex, olfactory bulb, brainstem)	Notch, atoh1a, DCX, GnRH, NeuN, MAP2	*Males:* Impaired organization of sexually dimorphic nuclei (POA, AVPV) *Females:* Altered hypothalamic connectivity and delayed synaptic maturation	[70,117, 138,151]

(*continued on next page*)

Table 1 (*continued*)

Mechanism	Experimental Model	Species/Cell type	Molecular/Cellular Effects	Representative Markers /Pathways	Sex-Dimorphic Susceptibility	Key References
Epigenetic alterations (cross-cutting)	*In vivo/In vitro*	Mouse, rat; neuronal progenitor cells	DNA methylation and histone modifications, altered miRNA; persistent transcriptional changes in neurodevelopmental and steroid-responsive genes	DNMTs, HDACs, miR-132, miR-9	*Males:* Impaired masculinization of mPOA, altered Esr1/Ar methylation *Females:* Altered AVPV development, disrupted estrogen-regulated miRNA networks *Transgenerationality:* Potential cross-generational programming via germline methylation changes	[82,118, 123,139, 152,153]
Microbiota–brain axis disruption	*In vivo*	Mouse, rat	Gut dysbiosis; ↓ Lactobacillus, ↓ SCFA and serotonin; ↑ pro-inflammatory species and LPS ("leaky gut"); altered HPG and steroid metabolism	SCFAs, 5-HT, GABA, LPS, IL-6, TNF-α, HPG axis genes	*Males:* Greater susceptibility to systemic inflammation *Females:* Altered estrogen metabolism and maternal microbiota transmission	[122,123, 154,155]

Notes: Model classification reflects the predominant experimental approaches reported in the cited literature; detailed study-specific information is provided in the referenced articles.

Abbreviations: 5-HT - 5-hydroxytryptamine (serotonin); 8-OHdG - 8-hydroxy-2′-deoxyguanosine; AChE - acetylcholinesterase; ATP - adenosine triphosphate; atoh1a - atonal homolog 1a; AVPV - Anteroventral Periventricular Nucleus; Ca^{2+} - Calcium ion; CAT - Catalase; C1q/C3 - Complement component 1q and 3; CD68 - Cluster of Differentiation 68; Cox IV - Cytochrome c Oxidase Subunit IV; DCX - Doublecortin; ΔΨm - mitochondrial membrane potential; DNA - deoxyribonucleic acid; DNMTs - DNA methyltransferase; ER - Estrogen receptor; GABA - γ-aminobutyric acid; GFAP - Glial Fibrillary Acidic Protein (expressed in astrocytes); GnRH - gonadotropin-releasing hormone; GPx - Glutathione Peroxidase; HDACs - Histone deacetylases; Iba-1 - Ionized calcium-binding adaptor molecule 1 (microglia marker); ICAM-1 - Intercellular Adhesion Molecule 1; IL-1β - interleukin-1-beta; IL-6 - Interleukin-6; LAMP-1 - Lysosome-Associated Membrane Protein 1; LC3 - Microtubule-associated protein 1 A/1B-light chain 3; LPS - Lipopolysaccharide; MAP2 - Microtubule-associated protein 2; MAPKs - Mitogen-Activated Protein Kinases; MDA - Malondialdehyde; miR-9 - microRNA-9; miR-132 - microRNA-132; NeuN - Neuronal Nuclear antigen; NF-κB - Nuclear Factor-kappa B; Nrf2/Keap1 - Nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1; p62 - Sequestosome 1; PGE2 - Prostaglandin E2; POA - preoptic area; PSD-95 - Postsynaptic Density protein-95; ROS - Reactive Oxygen Species; SCFAs - Short-Chain Fatty Acids; SOD - superoxide dismutase; TNF-α - Tumor Necrosis Factor-alpha; VCAM-1 - Vascular Cell Adhesion Molecule-1; VE-cadherin - Vascular Endothelial cadherin; VMH - Ventromedial Hypothalamus; ZO1 - Zonula occludens-1.

neuroinflammation, and contributing to neuronal loss [54]. In zebrafish, exposure to environmentally relevant concentrations of PS-NPs has been shown to induce brain lesions, inflammatory responses, oxidative stress activation, hormonal imbalance, gonadal damage, and disruption of the HPG axis, with evident sex-specific susceptibility [81]. Comparable findings in mammalian models show dysregulated HPG signaling, neuroinflammation, oxidative stress, and impaired reproduction in male mice exposed to environmentally relevant concentrations of PS-MPs (100–1000 μg/L) [82].

Beyond receptor-mediated effects, epigenetic reprogramming has emerged as a key mechanism linking MNP exposure to persistent neuroendocrine and behavioral outcomes. Studies in neural progenitor cells and rodent models show that MNPs modify DNA methylation, histone modifications, and microRNA expression, influencing gene networks that regulate neurodevelopment, steroidogenesis, and reproductive physiology [69,83]. For instance, PS-NPs alter methylation of genes controlling synaptogenesis and steroid metabolism, while transgenerational models reveal heritable changes in sperm DNA methylation accompanied by altered offspring neurobehavior [84].

The dual role of MNPs as EDCs and epigenetic modulators positions them as powerful developmental programming agents. Perturbations in steroid-hormone signaling and chromatin remodeling during critical developmental windows may impair the organization of sexually dimorphic hypothalamic nuclei such as the medial preoptic area (mPOA), anteroventral periventricular nucleus (AVPV), and ventromedial hypothalamus (VMH) [38,85]. Disruption of these nuclei, which govern gonadotropin release, sexual motivation, and maternal behavior, can yield long-lasting sex-biased alterations in neuroendocrine homeostasis and social behavior [38].

Collectively, these mechanisms reinforce the central tenet of the DOHaD framework: early-life MNP exposure constitutes a developmental programming event that durably inscribes molecular, neuroendocrine, and behavioral trajectories. Operating at the intersection of endocrine disruption and epigenetic reconfiguration, MNPs collapse traditional disciplinary boundaries, underscoring the need to consider toxicology, neuroendocrinology, and developmental neuroscience as deeply interdependent domains.

4. Brain sexual differentiation as a critical target

One of the most hormonally sensitive and developmentally critical processes affected by environmental insults is the sexual differentiation of the brain. This process establishes the structural and functional dimorphism of neural circuits that regulate reproduction, behavior, and neuroendocrine control, making it highly vulnerable to endocrine and epigenetic disruption [66,86].

Brain sexual differentiation begins early in life, when transient surges of gonadal hormones orchestrate large-scale organizational changes in the CNS, and is later refined during puberty. In male rodents, a sharp neonatal rise in testosterone triggers its aromatization to estradiol within the brain by the enzyme P450 aromatase [87]. Estradiol acts primarily through ERα and ERβ, nuclear transcription factors that regulate gene expression in a region-specific manner [88]. ERα functions as the principal regulator of male-typical brain organization, whereas ERβ contributes mainly to female reproductive physiology, including fertility, lactation, and sexual receptivity [89].

In addition to steroidal signaling, brain sexual differentiation relies on a tightly timed neuroimmune program in which microglia and astrocytes orchestrate synaptogenesis via prostaglandin E_2 (PGE_2) and cytokine-dependent pathways. This developmentally programmed inflammatory cascade is essential for the establishment of male-typical circuit assembly in the mPOA and its associated behaviors [90]. MNPs can subvert this program: *in vivo*, PS-NPs cross the BBB and activate microglia, elevating pro-inflammatory signaling and inducing neurotoxicity [60]. Maternal exposure to PS-NPs produces neuroinflammatory and oxidative disturbances that persist into adolescence and adulthood, consistent with developmental programming within the DOHaD framework [91]. Mechanistically, MNPs activate microglia and trigger ERK/MAPK and NF-κB pathways, leading to increased IL-1β and TNF-α expression and redox imbalance [60]. Such effects provide biologically

plausible routes through which excessive or mistimed neuroinflammation may distort sex-specific circuit formation [92].

The structural and functional differentiation of sexually dimorphic nuclei depends on transient hormonal surges that coordinate region-specific gene expression, neuronal pruning, and synaptogenesis [93]. Key nuclei - among the most extensively studied, though not exclusive - include the mPOA, which governs male copulatory behavior; the AVPV, responsible for the female pre-ovulatory LH surge; and the VMH, which modulates female sexual receptivity, energy balance, and aggression. Disturbances in steroid signaling during these organizational windows can irreversibly alter neural wiring and behavioral outcomes [94,95].

Emerging findings indicate that environmental toxicants, including MNPs and their associated endocrine-disrupting additives, can interfere with this finely tuned process. MNP exposure suppresses aromatase activity, reduces ERα expression, and disrupts hypothalamic estrogen signaling, impairing masculinization of the mPOA and feminization of the VMH and AVPV [96,97]. In parallel, MNPs provoke chronic microglial activation and neuroinflammatory signaling [60], conditions that can amplify or derail the PGE_2-dependent inflammatory cascade required for sexual differentiation.

Epigenetic mechanisms also play a fundamental role in establishing and maintaining sexually dimorphic gene expression in the brain. Steroid hormones dynamically regulate DNA methyltransferases (DNMTs) and histone-modifying enzymes in a region-specific manner [85], while microglia and astrocytes sculpt synaptic architecture through PGE_2--mediated pathways [98]. Perturbations during these critical windows - when microglia-driven synaptic refinement is both hormonally and epigenetically gated - make these circuits particularly susceptible to environmental interference [90,92].

Altogether, brain sexual differentiation emerges as a convergence point for hormonal, immune, and epigenetic regulation - precisely the pathways perturbed by MNP exposure. Because MNPs and their additives can mimic, antagonize, or dysregulate steroid signaling while simultaneously inducing inflammatory and epigenetic remodeling, they may distort the formation of sex-specific neural and behavioral phenotypes. Such early-life perturbations represent developmental programming events within the DOHaD paradigm, linking environmental pollution to long-term neuroendocrine and behavioral risk.

4.1. Sexual dimorphism and differential effects of micro- and nanoplastics

Accumulating evidence indicates that gestational and perinatal exposure to MNPs and their chemical additives can simultaneously affect gonadal development and hypothalamic organization, establishing the basis for long-term reproductive and behavioral dysfunction. Experimental studies in rodents have shown that maternal ingestion of PS-MPs during pregnancy leads to transplacental transfer and accumulation of particles in the fetal brain and gonads, disrupting steroidogenesis, GnRH neuron development, and HPG-axis signaling [50,99]. In humans, MNPs and plastic additives such as BPA, phthalates, and PBDEs have been detected in the placenta, amniotic fluid, and fetal tissues, suggesting potential interference with neuroendocrine programming during critical developmental windows [33,78]. Mechanistically, these exposures activate oxidative and inflammatory pathways in the fetal hypothalamus and induce epigenetic remodeling of genes that regulate reproductive and neuroendocrine circuits, such as GnRH, Kiss1, and Esr1 [97,99]. Such alterations may reprogram both gonadal differentiation and hypothalamic circuitry, generating sex-specific phenotypes consistent with the DOHaD paradigm, in which early-life environmental insults shape reproductive and neurobehavioral trajectories across generations.

Due to their endocrine-disrupting potential, MNPs can interfere with both reproductive and neuroendocrine axes in males and females [54]. Their small size and hydrophobicity facilitate penetration into reproductive tissues, where they accumulate in gametes, gonads, and accessory glands, altering morphology, histoarchitecture, and physiological function [54,100]. Exposure to classical EDCs - such as DDT, cadmium (Cd), and lead (Pb) - has long been associated with impaired reproductive health. In males, DDT induces testicular degeneration and transgenerational genetic effects, while elevated Cd and Pb impair HPG-axis regulation, reducing sperm quality and fertility [101]. Similarly, mice exposed to PS-MPs for six weeks exhibit increased sperm deformities, reduced motility, and decreased testosterone levels, alongside reduced activity of key enzymes involved in sperm metabolism [102,103].

In females, MPs accumulate within ovarian and granulosa cells, inhibiting folliculogenesis, reducing anti-Müllerian hormone (AMH) and estradiol levels, and producing irregular estrous cycles and abnormal oocyte maturation [80]. These effects likely involve apoptosis of ovarian granulosa cells through NLRP3/caspase-1 activation linked to oxidative stress [99]. Evidence from pregnant women and animal models indicates that MPs can cross the placental barrier and have been associated with neurodevelopmental abnormalities in offspring [104].

Although most studies have focused on gonadal endpoints, the neuroendocrine dimensions of these alterations should not be overlooked. The same endocrine disruptions that impair spermatogenesis and folliculogenesis also perturb hypothalamic circuits governing gonadotropin release, sexual motivation, and maternal behavior [105]. Thus, reproductive and neural outcomes likely share a common mechanistic origin rooted in MNP-induced hypothalamic dysregulation. Disruption of steroid-hormone signaling in the developing hypothalamus affects both the HPG axis and the organization of sexually dimorphic nuclei such as the mPOA and AVPV - regions essential for LH release and reproductive behavior, whose structural and molecular programming depends on balanced estrogen-androgen signaling [38,94]. Consequently, MNP exposure during perinatal life may simultaneously affect gonadal differentiation and hypothalamic circuit formation, generating parallel reproductive and behavioral phenotypes that persist into adulthood.

Endocrine disruptors - including PBDEs, BPA, phthalates, PCBs, tributyltin (TBT), mercury, and chromium - elicit similar neuroendocrine disturbances by targeting hypothalamic regulatory circuits and endocrine axes. Collectively, these compounds disrupt the HPG, HPT, and HPA axes, resulting in altered secretion of GnRH, LH, FSH, and thyroid hormones [78]. Experimental data show neuronal loss, astrocyte activation, and neuroinflammation within hypothalamic nuclei, accompanied by oxidative stress, reduced acetylcholinesterase activity, and impaired metabolic signaling. At the molecular level, these disruptors modulate expression of KiSS1, GPR54, GnRH, IGF-1, Insr, and MT-3, and interfere with peptide synthesis in proopiomelanocortin (POMC) neurons [92,106–110]. These changes provoke precocious puberty, irregular estrous cycles, and reproductive hormone imbalance in females, as well as impaired spermatogenesis and androgen signaling in males. Pathways involving NF-κB, NLRP3/caspase-1, and ROS-mediated oxidative injury contribute to hypothalamic apoptosis and persistent endocrine dysregulation.

Consistent with these mechanistic findings, male offspring often display more pronounced impairments in spermatogenesis and androgen-dependent behaviors [82,99], whereas female offspring exhibit disrupted follicular maturation and irregular estrous cycles [47,100]. These sexually dimorphic outcomes reflect differences in steroid hormone milieus as well as epigenetic and neuroimmune modulation, particularly within hypothalamic and limbic regions [111,112]. Such data support the concept that chronic exposure to diverse endocrine disruptors - either as environmental contaminants or MNP-associated additives - elicits sex-specific neuroendocrine and reproductive toxicity rooted in hypothalamic dysfunction and the collapse of hormonal feedback control [78,97].

These findings highlight that MNP exposure should be considered a systemic endocrine–neuroendocrine insult rather than an isolated reproductive toxicant. By acting across gonadal and neural axes, MNPs

may reshape sex-dependent physiology, leading to persistent alterations in reproductive function, stress responsivity, and social behavior.

4.2. Micro- and nanoplastics and sex-biased neurodevelopmental disorders

During brain sexual differentiation, steroid hormones act across multiple regions to guide neuronal migration, synaptogenesis, and circuit formation, shaping the sexually dimorphic behaviors and cognitive functions observed in adulthood [113]. Comparative studies of male and female neurodevelopment have demonstrated how these organizational events diverge, producing lasting differences in social behavior, stress responsivity, and susceptibility to neurological and psychiatric disorders [38].

Epidemiological and preclinical data indicate that many neurodevelopmental and psychiatric conditions display marked sex differences in prevalence and severity. Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) occur more frequently in males, whereas anxiety and affective disorders disproportionately affect females [114,115]. These dimorphisms emerge partly from sex-specific patterns of hormone exposure, microglial activity, gene regulation, and synaptic refinement during early development -precisely the processes susceptible to disruption by MNPs.

MNPs may function as neuroendocrine disruptors capable of interfering with the same signaling pathways that orchestrate brain sexual differentiation. By altering gonadal steroid synthesis, aromatase activity, and receptor-mediated transcription, MNPs can remodel neural circuits in a sex-dependent manner [99,100]. Such endocrine and epigenetic perturbations may not only impair reproductive function but also increase vulnerability to sex-biased neurodevelopmental disorders, including ASD, ADHD, and anxiety [116].

Preliminary human evidence reinforces these concerns: MPs have been identified in human placenta, meconium, and, more recently, brain tissue, suggesting early-life exposures that coincide with critical windows of neurodevelopment [5,43]. Although causal links remain to be established, converging mechanisms such as oxidative stress, neuroinflammation, and epigenetic dysregulation provide a biologically plausible framework linking MNP exposure to the developmental origins of neurobehavioral disorders.

Sex differences in microglial function, chromatin accessibility, and steroid receptor expression may further amplify MNP effects. Male microglia exhibit heightened sensitivity to pro-inflammatory stimuli, whereas female astrocytes display enhanced resilience via estrogen-dependent antioxidant pathways [86,98]. Consequently, MNP-induced inflammation may unmask or intensify intrinsic sex differences in neural plasticity and stress responsivity, skewing developmental trajectories toward disorder-specific vulnerabilities.

Within the DOHaD framework, these interactions exemplify how environmental exposures can differentially shape male and female susceptibility to neurodevelopmental and psychiatric disorders. By disrupting the hormonal and epigenetic cues that sculpt sexually dimorphic circuits, MNPs may embed persistent, sex-specific signatures into the brain's developmental blueprint.

5. DOHaD perspective: fetal programming and long-term risks

The DOHaD paradigm emphasizes that exposures during critical periods of development - particularly gestation and early postnatal life - can permanently program physiological systems and predispose individuals to disease later in life [10,11]. Within this framework, MNPs have emerged as potent developmental stressors capable of altering endocrine, epigenetic, and neuroimmune pathways that collectively shape long-term health trajectories.

Experimental evidence shows that these effects are sex-biased, reflecting the distinct hormonal and epigenetic environments governing male and female development. The fetal period - when brain sexual differentiation, placental function, and endocrine feedback are simultaneously active - represents a particularly vulnerable window for MNP-induced programming [117]. Some studies report persistent effects extending into the F2 generation, supporting the possibility of heritable epigenetic alterations consistent with DOHaD and transgenerational inheritance paradigms [50,99]. This suggests that early-life MNP exposure can reprogram germline epigenetic marks, transmitting increased vulnerability across generations.

These exposures coincide with critical periods of neuroendocrine differentiation, during which steroidal, inflammatory, and epigenetic cues organize hypothalamic and limbic circuits that regulate reproduction, metabolism, and socioemotional behavior [38]. Disruption of these signaling networks by MNPs can yield lasting alterations in neuroendocrine homeostasis, reproductive capacity, and behavioral function. Notably, maternal inflammation and oxidative stress during pregnancy further heighten vulnerability by modifying placental permeability and fetal hormone balance [118].

Epigenetic modulation represents a central mechanism linking MNP exposure to DOHaD-related outcomes. MNPs have been shown to alter DNA methylation, histone acetylation and methylation, and non-coding RNA profiles in neural and germline cells [68,119]. Such molecular changes may become stably inherited across cell divisions and, in some cases, across generations. Transgenerational models demonstrate that NP exposure modifies sperm DNA methylation and induces neurobehavioral alterations in F2 offspring [119,120], supporting the hypothesis that MNPs can encode environmental information into the germline epigenome [121]. This mechanism exemplifies how environmental contaminants can redefine developmental plasticity, influencing gene–environment interactions and disease susceptibility well beyond the initial exposure window.

Beyond direct toxicodynamic and epigenetic mechanisms, MNP exposure also impacts the microbiota–brain axis, an emerging pathway linking maternal environment, gut homeostasis, and neurodevelopment [122]. Alterations in the maternal gut microbiome during pregnancy and lactation can be vertically transmitted to offspring, shaping immune maturation, steroid metabolism, and stress responsivity [123]. Because both microbial composition and immune–endocrine crosstalk are sexually dimorphic [124], dysbiosis may exacerbate sex differences in MNP susceptibility. Experimental models have shown that gut-derived inflammation and microbial metabolites can influence hypothalamic microglia, providing an additional link between peripheral and central responses to plastic exposure [65].

Together, these interconnected mechanisms - including endocrine disruption, oxidative stress, epigenetic reprogramming, and microbiota–brain axis perturbation—position MNPs as multifactorial developmental hazards. Early-life exposure to these particles can generate sex-biased neuroendocrine, reproductive, and behavioral phenotypes consistent with the DOHaD paradigm. Such programming may increase lifetime risk of metabolic syndrome, infertility, affective disorders, and cognitive dysfunction, representing a cross-generational health burden. Fig. 3 illustrates this integrative conceptual model, depicting how MNP-induced disturbances converge to reshape developmental trajectories across molecular, cellular, and systemic levels.

6. Human data, clinical implications, and translational perspectives

Although the mechanistic evidence for MNPs neurotoxicity and endocrine disruption is robustly established in i*n vitro* and animal models, the direct evidence linking MNP exposure to adverse human reproductive and neurodevelopmental outcomes remains appropriately limited and primarily observational [125]. Nevertheless, a growing body of translational research has established the systemic bioavailability of MNPs in humans, providing a critical context for the experimental findings discussed in this review.

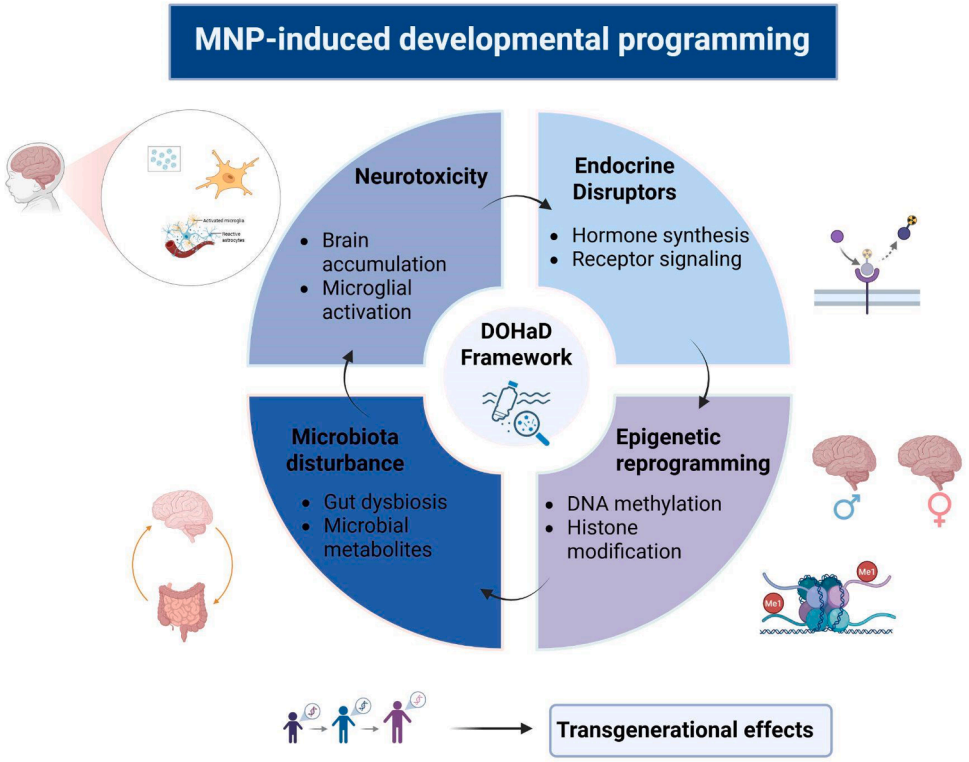

Fig. 3. Integrated mechanistic pathways linking Micro- and nanoplastic (MNP) exposure to developmental programming within the DOHaD framework. Created with BioRender. Early-life exposure to MNPs activates multiple interconnected mechanisms - including neurotoxicity (brain accumulation and microglial activation), endocrine disruption (altered hormone synthesis and receptor signaling), epigenetic reprogramming (changes in DNA methylation and histone modifications), and microbiota disturbance (gut dysbiosis and microbial metabolites). These pathways converge to shape long-term neuroendocrine, reproductive, behavioral, and metabolic trajectories in a sex-dimorphic manner. Disturbances occurring during critical windows of development may also propagate across generations, leading to transgenerational effects mediated by germline epigenetic inheritance.

6.1. *Evidence of human exposure and fetal vulnerability*

The most compelling human data confirms the widespread presence of MNPs in tissues relevant to the DOHaD framework. MNPs have been detected in the human placenta ("plasticenta") [4], umbilical cord blood [126], breast milk [127], and meconium [128], confirming both transplacental and postnatal transfer routes. This bioaccumulation during critical windows of development underscores the vulnerability of the fetus and neonate, whose physiological barriers, such as the BBB, are still immature. Furthermore, recent autopsy-based studies have also detected MNPs in the human brain, with PP fragments identified in regions such as the olfactory bulb, suggesting a direct nose-to-brain translocation pathway [129]. Although higher MNP burdens have been reported in individuals with neurodegenerative conditions, these findings are correlational and do not establish causality, serving primarily to reinforce biological plausibility and concern.

6.2. *Clinical implications for reproductive and birth outcomes*

Emerging observational studies suggest a potential association between MNP exposure and adverse reproductive or perinatal outcomes, reinforcing the clinical relevance of the experimental data. Higher MP loads in placental or umbilical cord samples have been associated with reduced birth weight, shorter neonatal length, and lower 1-minute Apgar scores [130,131]. Moreover, the presence of specific polymers (e.g., PE and PC) in the umbilical cord has been linked to an increased risk of pregnancy-induced hypertension [126], a condition associated with placental dysfunction and adverse maternal-fetal outcomes. These findings suggest that MNP-induced inflammation and oxidative stress, as demonstrated in animal models, may translate into clinically significant placental dysfunction and fetal growth restriction in humans.

6.3. *Epidemiological signals and spectrum of neurotoxic processes*

Large-scale, longitudinal epidemiological studies establishing a direct causal link between MNP exposure and increased incidence of defined neurodevelopmental disorders are currently lacking. Importantly, no population-based studies have demonstrated that MNP exposure is associated with a single, specific neurological disease entity.

Instead, available evidence supports the concept that MNP exposure may contribute to a broad spectrum of neurotoxic processes, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and disruption of protein homeostasis, rather than being linked to a single clinical diagnosis [28,38,115]. These shared pathogenic pathways are relevant across multiple neurodevelopmental and neurodegenerative conditions and are consistent with a DOHaD-based model of increased vulnerability following early-life environmental exposure.

6.4. *Knowledge gaps and translational priorities*

Despite growing evidence of human exposure, the current understanding of MNP-related neurodevelopmental risk remains largely inferential. Much of the biological plausibility derives from the established neurotoxicity of plastic-associated EDCs, such as BPA and phthalates, which can leach from MNPs (the “Trojan horse” effect) [132].

Key priorities for advancing translational understanding include:

- **Direct causality:** Establishing whether MNP particle burden, independent of associated EDCs, causally contributes to adverse human neurodevelopmental outcomes.

- **Sex-specific outcomes:** Explicitly designing human studies to assess sex as a biological variable, in line with experimental evidence on sexually dimorphic brain development.
- **Standardized methodologies:** Developing validated, high-throughput approaches for detecting and quantifying nanoplastics in human biofluids (e.g., serum, cerebrospinal fluid) and tissues.
- **Longitudinal cohorts:** Establishing prospective cohorts tracking MNP exposure from conception through childhood and adolescence, with integrated neurodevelopmental and reproductive endpoints.

6.5. *Strategies for exposure minimization and biological modulation*

Given the confirmed presence of MNPs in the maternal–fetal environment, a precautionary approach is warranted. Strategies to reduce exposure and mitigate potential biological effects are particularly relevant during sensitive developmental windows.

6.5.1. *Exposure minimization (precautionary measures)*

- **Infant feeding practices:** Avoid heating infant formula or breast milk in PP bottles, as heat can markedly increase particle release; glass or stainless-steel alternatives are preferable [133].
- **Food preparation:** Avoid microwaving food in plastic containers, particularly fatty or acidic foods, which can accelerate the release of both MNPs and associated EDCs [134].
- **Water consumption:** Where tap water quality is assured, prioritize its use over bottled water, which may contain higher microplastic loads [135].

6.5.2. *Biological modulation (experimental evidence)*

Experimental studies indicate that natural antioxidants, including lycopene, citric acid, and astaxanthin, can attenuate MNP-induced oxidative stress and neurotoxicity in animal models [136,137]. Increased dietary fiber intake has also been suggested to reduce gastrointestinal uptake of MNPs, potentially lowering systemic body burden [138]. These findings derive exclusively from experimental models and should not be interpreted as evidence-based clinical interventions.

7. Gaps, challenges, and priorities for future research

Despite the rapidly growing body of evidence linking MNP exposure to developmental and neuroendocrine toxicity, major knowledge gaps remain regarding dose–response relationships, particle heterogeneity, and sex-specific outcomes. Most experimental studies rely on simplified exposure models, frequently using high doses of uniform polystyrene particles that do not reflect real-world mixtures or chronic low-level exposures [28,139–141]. Only a few studies have attempted to model environmentally relevant exposure levels by aligning experimental doses with human intake estimates, such as those derived from dietary microplastic consumption assessments [68]. Expanding such approaches will be critical to improving translational relevance and to identifying subtle, cumulative, and sex-dependent effects that may be missed under supraphysiological exposure conditions.

A critical methodological gap in the current literature concerns the limited alignment between experimental exposure levels and environmentally relevant human intake estimates [28,68,139]. Many *in vivo* studies continue to rely on relatively high concentrations of MNPs to elicit detectable effects, which, while informative for mechanistic exploration, may not accurately represent chronic, low-dose exposure scenarios experienced by human populations [28]. This mismatch limits the extrapolation of experimental findings to human health risk assessment, particularly for developmental and neuroendocrine endpoints shaped by early-life programming.

Future studies should therefore prioritize exposure paradigms that more closely approximate real-world conditions, incorporating chronic, low-level dosing strategies grounded in human intake estimates, as well as realistic exposure routes [26,68]. Such approaches are particularly important for detecting subtle, sex-dependent neurodevelopmental and neuroendocrine effects that may be overlooked under high-dose experimental designs [38,115]. Addressing this gap will be essential for improving translational relevance within the DOHaD framework and for informing human health risk assessment [10,11].

Critical physicochemical parameters—including particle size distribution, polymer type, surface charge, and the presence of additives or sorbed pollutants—are frequently underreported or inconsistently characterized, despite their strong influence on cellular uptake, biodistribution, and toxicokinetics. This lack of standardization hampers cross-study comparability and obscures dose–effect relationships, underscoring the need for harmonized reporting and experimental design. Standardization of MNP characterization and dosimetry is therefore essential for establishing reliable thresholds of developmental toxicity [26].

The timing of exposure also remains an underexplored determinant of outcome. Developmental windows such as gametogenesis, implantation, organogenesis, and the perinatal period are marked by intense endocrine and epigenetic remodeling and may represent heightened vulnerability to MNP-induced programming. Yet, many studies continue to focus primarily on adult exposures. Longitudinal and multigenerational experimental designs that follow offspring into maturity are urgently needed to identify persistent and transgenerational effects within the DOHaD framework [72,73].

A persistent limitation in the current literature is the inadequate consideration of sex as a biological variable. Few studies disaggregate results by sex or evaluate sexually dimorphic endpoints such as hormone levels, hypothalamic gene expression, or sex-specific behavioral patterns. Given the fundamental sex differences in endocrine signaling, neuroimmune responses, and epigenetic dynamics, sex-informed experimental designs are indispensable for capturing the full spectrum of MNP toxicity [38,115].

Future studies should therefore incorporate balanced sex representation, analyze outcomes in both gonadal and neural tissues, and integrate hormonal, molecular, and behavioral endpoints. Such integrative approaches will help clarify whether MNP exposure amplifies preexisting biological differences between sexes or actively generates new dimorphisms through developmental reprogramming.

Advancing the field requires a transition from largely descriptive studies toward mechanistic and integrative research frameworks. The incorporation of multi-omics strategies -including transcriptomics, epigenomics, and metabolomics - will facilitate mapping of molecular perturbations across tissues and developmental stages. When combined with neuroimaging, endocrine profiling, and behavioral assessments, these datasets can reveal cross-level connections linking MNP exposure to neurodevelopmental and reproductive outcomes.

Standardized *in vitro–in vivo* extrapolation models, incorporating realistic exposure levels and biological barriers (e.g., placenta and BBB), will also be essential to bridge mechanistic toxicology and human risk assessment. Moreover, routine inclusion of environmentally aged particles and chemical mixture effects (polymer core plus additives and adsorbates) should become standard practice to better reflect the complexity of human exposure scenarios.

Finally, addressing these research gaps demands interdisciplinary collaboration—bringing together toxicologists, developmental biologists, endocrinologists, environmental chemists, and data scientists—to develop predictive and integrative models of MNP-induced developmental toxicity. Such collaboration will enhance reproducibility, mechanistic clarity, and translational value.

In summary, closing current knowledge gaps demands a paradigm shift toward realistic, sex-informed, and mechanistically integrated approaches. Only through rigorous methodological refinement and cross-disciplinary synthesis can the field determine whether MNPs act as subtle modulators of developmental physiology or as pervasive drivers

of long-term neuroendocrine dysfunction.

8. Conclusions

MNPs represent a multifactorial and persistent threat to both neurodevelopmental and reproductive health. Acting through interconnected endocrine, oxidative, inflammatory, epigenetic, and microbial mechanisms, they influence molecular and cellular processes that extend well beyond classical toxicology. Within the DOHaD paradigm, MNPs emerge as environmental programming agents capable of altering brain sexual differentiation and neuroendocrine organization in a sex-specific and potentially transgenerational manner.

Collective evidence from cellular, animal, and emerging human studies underscores the need for a conceptual shift: MNPs should no longer be regarded as inert environmental debris but as bioactive agents with the capacity to reprogram developmental trajectories. Recognizing their intersection with neuroendocrine, immune, and epigenetic pathways provides a strategic opportunity to integrate toxicology, endocrinology, and environmental health under a unified developmental framework.

Preventing MNP-induced outcomes will require a dual approach - mitigating environmental contamination through coordinated global policy efforts, and advancing mechanistic, sex-informed, longitudinal research to delineate the true scope of developmental neurotoxicity. Addressing these challenges is essential to safeguard human health across generations and to ensure that the legacy of the plastic age is not written into the neurodevelopmental code of the future.

CRediT authorship contribution statement

Hamilton Hisano: Writing – original draft, Funding acquisition. **Julia Stein:** Writing – original draft. **Cândida Aparecida Leite Kassuya:** Writing – review & editing, Writing – original draft. **Bárbara Campos Jorge:** Writing – review & editing, Writing – original draft. **Beatriz de Matos Manoel:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation. **Arielle Cristina Arena:** Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition, Data curation, Conceptualization.

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Declaration of Competing Interest

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

Data availability

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

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