

Environmental Neurotoxicants And Autism Spectrum Disorder: From Toxic Metals And Pesticides To Neuroimmune Dysregulation Narrative Review

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ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder resulting from interactions between genetic susceptibility and environmental factors during critical periods of brain development. Increasing evidence implicates environmental neurotoxicants, particularly toxic metals and pesticides, in ASD risk through oxidative stress, mitochondrial dysfunction, blood–brain barrier impairment, epigenetic alterations, and persistent neuroinflammation. Neuroimmune dysregulation, including chronic microglial and astrocyte activation, cytokine imbalance, and altered peripheral immune responses, may contribute to abnormal neuronal development and connectivity. These effects may be amplified by gene–environment interactions, increasing individual susceptibility. This review summarizes epidemiological and experimental evidence linking toxic metals and pesticides to ASD, with emphasis on molecular and neuroimmune mechanisms, emerging biomarkers, and preventive strategies. Despite advances in understanding these pathways, causal relationships and clinical translation remain challenging. Integrating epidemiology, toxicology, molecular neuroscience, and multi-omics approaches may help identify susceptible populations, validate biomarkers, and improve targeted prevention and early intervention.

Keywords: Autism spectrum disorder; Environmental neurotoxicants; Toxic metals; Pesticides; Neuroimmune dysregulation.

INTRODUCTION

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder characterized primarily by persistent differences in communication and social interaction, as well as by restricted or repetitive behaviors, interests, or activities. ASD encompasses a wide range of clinical presentations, with considerable variation in symptoms, abilities, and support needs from one individual to another. According to the World Health Organization (WHO, 2025), autism affects approximately one in 127 people worldwide, making it a major global public health issue [1].

The etiology of ASD is multifactorial, involving complex interactions between genetic susceptibility and environmental influences acting during critical periods of prenatal and early postnatal brain

development. Although numerous susceptibility genes and copy number variants have been identified, genetic factors alone cannot fully explain the complexity of ASD or its significant phenotypic variability [2, 3]. Consequently, increasing attention is being paid to environmental determinants that may influence neurodevelopment through epigenetic, metabolic, and immunological mechanisms [4].

Among these environmental determinants, developmental exposure to neurotoxicants has emerged as a major area of research. Toxic metals, pesticides, air pollutants, endocrine-disrupting chemicals, and other environmental contaminants have been linked to ASD risk in epidemiological and experimental studies [5–8]. These agents can disrupt fundamental neurodevelopmental processes by inducing oxidative stress, mitochondrial dysfunction, altered calcium signaling, blood–brain barrier

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dysfunction, and persistent neuroinflammation. Collectively, these alterations can affect neuronal differentiation, synaptogenesis, synaptic plasticity, neuronal connectivity, and brain maturation [9, 10].

A growing body of evidence indicates that neuro-immune dysregulation may be a key mechanism linking environmental exposures to atypical neurodevelopment. Chronic activation of microglia and astrocytes, excessive production of pro-inflammatory cytokines, and dysregulation of peripheral immune responses can contribute to sustained neuroinflammation and impaired neuronal circuit formation [11, 12]. These biological disruptions can be modulated by gene–environment interactions and epigenetic regulation, potentially contributing to inter-individual differences in susceptibility and clinical presentation [13].

Taken together, these findings support the need to examine specific environmental neurotoxins and the biological pathways through which they may influence ASD susceptibility. The following section therefore focuses on the major classes of environmental contaminants that have been associated with ASD, with particular attention to toxic metals, pesticides, and other emerging neurotoxins.

2. Environmental neurotoxins associated with autism spectrum disorder

Environmental neurotoxins have attracted increasing attention as potential contributors to ASD susceptibility, particularly when exposure occurs during prenatal life and early childhood, which are critical periods for brain development. Although genetic predisposition remains a major determinant of ASD, environmental exposures may modify neurodevelopmental risk through mechanisms including oxidative stress, mitochondrial dysfunction, neuroinflammation, immune dysregulation, and epigenetic alterations [6, 13]. Epidemiological studies, supported by experimental evidence, suggest that early-life exposure to several classes of environmental contaminants may adversely affect neurodevelopment [5, 8].

2.1 Toxic metals

Toxic metals are among the most extensively investigated environmental risk factors for ASD because of their persistence, bioaccumulation, and ability to cross both the placental and blood–brain barriers. Lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), and excessive manganese (Mn) have all been associated with neurodevelopmental impairment [9, 10]. These metals converge on common pathogenic mechanisms, including oxidative stress, mitochondrial dysfunction, calcium dyshomeostasis, neuroinflammation, impaired synaptic plasticity, and epigenetic dysregulation [8, 9]. Although the strength of epidemiological evidence varies among individual metals, experimental studies consistently demonstrate their capacity to interfere with neuronal differentiation, migration, and brain maturation during vulnerable developmental windows [5].

Lead exposure during pregnancy and early childhood has been associated with cognitive impairment, behavioral abnormalities, and altered neurodevelopment, even at low exposure levels [8]. Mercury, particularly methylmercury, affects neuronal migration, neurotransmitter systems, and oxidative balance, while prenatal arsenic exposure has been linked to impaired cognitive development and altered gene regulation [9, 10]. Recent studies have also suggested altered metal homeostasis in children with ASD, although causality remains under investigation [5, 9].

2.2 Pesticides

Pesticides constitute another major class of developmental neurotoxins associated with ASD. Prenatal exposure to organophosphate insecticides has shown the strongest epidemiological evidence and has been linked to impaired neuronal differentiation, disrupted cholinergic signaling, mitochondrial dysfunction, and persistent neuroinflammation [12, 13, 6]. Pyrethroids have also been associated with oxidative stress, altered sodium channel activity, and behavioral abnormalities in experimental models [6, 14]. Although organochlorine pesticides are now banned in many countries, their environmental persistence continues to represent a potential risk because of their long biological half-lives and effects on neurotransmission and endocrine function [5, 9].

Neonicotinoids have recently emerged as potential developmental neurotoxicants, although current human evidence remains limited [15].

2.3 Other environmental contaminants

Beyond toxic metals and pesticides, air pollution, endocrine-disrupting chemicals (EDCs), and emerging contaminants have attracted increasing attention. Prenatal exposure to particulate matter, nitrogen dioxide, diesel exhaust, and polycyclic aromatic hydrocarbons has been associated with ASD risk through oxidative stress, placental inflammation, blood–brain barrier disruption, and microglial activation [7, 16, 17]. EDCs, including bisphenol A, phthalates, polychlorinated biphenyls, dioxins, and PFAS, may disrupt endocrine, epigenetic, and immune processes [6,8,18]. Emerging contaminants such as microplastics and brominated flame retardants

are also of concern, although their contribution to ASD remains insufficiently established [19, 20].

Overall, diverse environmental neurotoxicants appear to converge on common pathways, particularly oxidative stress, mitochondrial dysfunction, neuroimmune activation, and epigenetic dysregulation. These interacting mechanisms may increase ASD susceptibility, especially during critical periods of brain development and in genetically predisposed individuals [11, 13].

Table 1 summarizes the major environmental contaminants implicated in ASD, their principal mechanisms, and the current epidemiological and experimental evidence. The strength of evidence varies across contaminant classes, highlighting the need for further standardized and prospective studies.

Environmental neurotoxicant	Principal mechanisms involved	Strength of evidence in ASD	Representative human evidence
Lead (Pb)	Oxidative stress, mitochondrial dysfunction, calcium dysregulation, synaptic dysfunction, neuroinflammation, epigenetic alterations	Strong association	Meta-analyses and systematic reviews reporting higher Pb exposure or levels in children with ASD [5,9,10]
Organophosphate pesticides	Acetylcholinesterase inhibition, oxidative stress, mitochondrial dysfunction, cholinergic dysregulation, microglial activation	Strong association	CHAMACOS, CHARGE, and California population studies reporting associations between prenatal exposure and ASD risk [12,13]
Pyrethroid pesticides	Sodium channel dysfunction, oxidative stress, neuroinflammation, neuronal dysfunction	Moderate association	Limited epidemiological evidence supported by experimental studies [21]
Organochlorine pesticides	Oxidative stress, endocrine disruption, altered neurotransmission, neuroinflammation	Moderate association	Biomonitoring and epidemiological studies suggesting associations with ASD [5,9]
Neonicotinoid pesticides	Nicotinic receptor modulation, oxidative stress, developmental neurotoxicity	Limited–Moderate	Mainly experimental evidence, with limited human epidemiological data [6,15]

Air pollutants (PM _{2.5} , NO ₂ , diesel exhaust particles, PAHs)	Oxidative stress, placental inflammation, blood–brain barrier disruption, neuroinflammation, mitochondrial dysfunction	Moderate–strong association	Large cohort studies and meta-analyses reporting associations between prenatal exposure and ASD [7,16,17]
Endocrine-disrupting chemicals (BPA, phthalates, PCBs, PFAS)	Endocrine and epigenetic dysregulation, oxidative stress, immune dysfunction, altered synaptic development	Moderate association	Prospective birth cohorts and systematic reviews reporting associations with ASD-related outcomes [6,8,18]
Emerging contaminants (microplastics, brominated flame retardants)	Oxidative stress, neuroinflammation, endocrine disruption, mitochondrial dysfunction, blood–brain barrier impairment	Limited–Emerging	Predominantly experimental evidence; insufficient human data to establish an association or causality [6,19,20]

Table1. Environmental neurotoxins and autism spectrum disorder

3. Molecular and neuroimmune mechanisms linking environmental neurotoxins to Autism Spectrum Disorder

Environmental neurotoxins affect brain development through interconnected pathways, including oxidative stress, mitochondrial dysfunction, neuronal dysregulation, neuroimmune activation, and epigenetic alterations. Their convergence may disrupt neuronal connectivity and increase susceptibility to ASD [5, 6, 8].

3.1 Oxidative stress and mitochondrial dysfunction

Environmental neurotoxins, including toxic metals, pesticides, air pollutants, and endocrine-disrupting chemicals, can increase reactive oxygen and nitrogen species while weakening antioxidant defenses. This promotes lipid and protein oxidation, DNA damage, and disruption of cellular signaling [9, 22].

Mitochondria are particularly vulnerable, with toxicant exposure impairing respiration, ATP production, calcium homeostasis, and mitochondrial DNA integrity. These alterations may compromise neuronal differentiation, axonal growth, synaptogenesis, and synaptic plasticity, particularly in the metabolically demanding developing brain [28,

29]. Mitochondrial abnormalities and increased oxidative damage have also been reported in ASD, suggesting a potential link between environmental stressors and genetic susceptibility [24, 29].

3.2 Disruption of neuronal homeostasis

Environmental neurotoxins can disturb calcium signaling, neurotransmission, and synaptic function, thereby altering neuronal excitability and circuit formation. They may also impair blood–brain barrier integrity, facilitating the entry of inflammatory mediators and toxic compounds into the central nervous system [8, 9, 22].

Epigenetic alterations, including changes in DNA methylation, histone modification, and non-coding RNAs, may produce persistent changes in gene expression affecting neuronal differentiation, synaptic organization, and immune regulation [25, 26].

3.3 Neuroimmune dysregulation

Developmental exposure to environmental toxicants may induce persistent microglial and astrocytic activation, increasing the production of pro-inflammatory mediators and disrupting neuroimmune homeostasis [11, 12]. Because glial cells regulate neuronal survival, synaptic formation, maturation, and pruning, their sustained activation during critical

developmental periods may impair neural circuit formation.

Environmental neurotoxicants may also alter peripheral immune responses, including cytokine production and immune-cell activity. Communication between peripheral and central immune systems may further amplify neuroinflammatory processes [27]. In genetically susceptible individuals, persistent neuroimmune alterations may affect neuronal connectivity and contribute to ASD-related phenotypes [11, 12].

These mechanisms are closely interconnected: oxidative stress and mitochondrial dysfunction can promote glial activation and inflammation, while chronic neuroinflammation can further impair mitochondrial and neuronal function. Their convergence provides a plausible framework linking environmental neurotoxicant exposure to altered neurodevelopment during critical periods of brain maturation [6, 13].

4. Biomarkers and clinical implications

Reliable biomarkers may improve the assessment of environmental neurotoxicant exposure and ASD risk. Although no single biomarker is sufficiently specific or sensitive for clinical use, combining exposure, oxidative stress, and immune markers may better identify susceptible individuals [9, 32].

Exposure biomarkers include toxic metals and pesticide metabolites measured in blood, urine, hair, nails, or deciduous teeth, providing information on cumulative or developmental exposure [10, 30]. Oxidative stress and neuroimmune biomarkers, including lipid peroxidation, reduced antioxidant capacity, mitochondrial dysfunction, inflammatory mediators, and microglial activation, further indicate biological alterations associated with ASD [11, 12, 32].

Advances in genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiome research have enabled the identification of potential molecular signatures of exposure and susceptibility. However, clinical application remains limited by methodological heterogeneity, small cohorts, and insufficient validation [31, 33]. Integrating exposure and molecular biomarkers may ultimately improve

risk stratification and support personalized prevention strategies [21].

5. Prevention and future perspectives

Reducing exposure to environmental neurotoxicants during pregnancy and early childhood is essential to minimize preventable neurodevelopmental risks. Public health measures should strengthen the control of toxic metals, pesticides, air pollutants, and endocrine-disrupting chemicals, particularly in vulnerable populations [1, 8].

Antioxidant, anti-inflammatory, and microbiota-targeted interventions may mitigate toxicant-induced effects, but their clinical efficacy requires further validation [32]. Future research should focus on large prospective birth cohorts combining precise exposure assessment with genetic, epigenetic, immunological, and multi-omics data to clarify gene–environment interactions and support biomarker discovery and precision prevention strategies for ASD [2, 6, 13].

CONCLUSION

Accumulating evidence indicates that environmental neurotoxicants may contribute to ASD susceptibility, particularly when exposure occurs during critical periods of brain development. Toxic metals, pesticides, air pollutants, and endocrine-disrupting chemicals can converge on common pathways involving oxidative stress, mitochondrial dysfunction, epigenetic alterations, and persistent neuroimmune activation. These interconnected mechanisms may disrupt neurodevelopment and contribute to ASD risk in genetically susceptible individuals.

Despite progress in understanding these mechanisms, important challenges remain in establishing causality and translating experimental findings into clinical and public health applications. Future multidisciplinary research integrating epidemiology, molecular neuroscience, toxicology, and systems biology should focus on validating biomarkers, identifying susceptible populations, and developing effective prevention strategies. A better understanding of environmental influences on neurodevelopment may support improved public health policies and contribute to earlier intervention and better outcomes for individuals with ASD.

COMPETING INTEREST

The author declares that she has no competing interests

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