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Neurotoxic Chemistry: Unraveling the chemical mechanisms connecting environmental toxin exposure to neurological disorders

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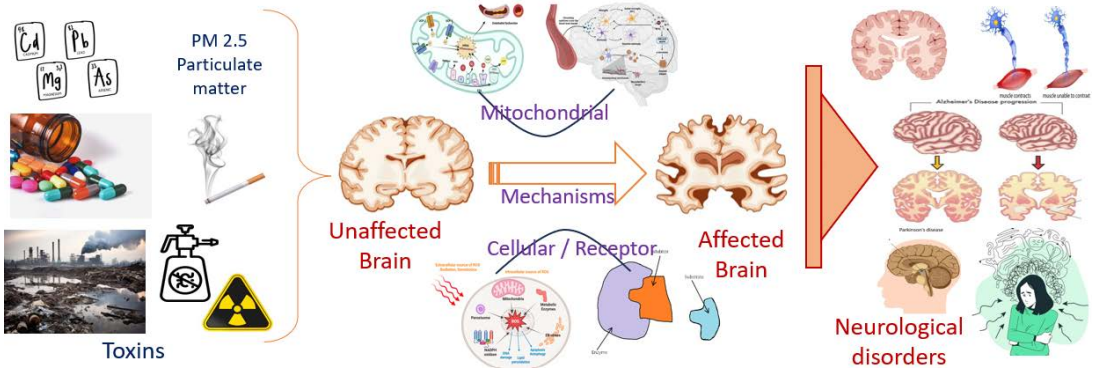
Review

ABSTRACT



The environmental pollution poses a serious global health risk, contributing to high morbidity and mortality rates. Neurological disorders, such as Alzheimer's, Parkinson's, Schizophrenia, Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease, are increasingly prevalent and are characterized by both structural and functional abnormalities in neurons of the brain and the spinal cord. Understanding neuro-impact of environmental toxins is crucial for developing effective prevention and intervention strategies. This review article investigates the complex interactions between environmental toxins and neurological health, focusing on their role in the development and progression of neurodegenerative and neuropsychiatric disorders. Key mechanisms include oxidative stress, mitochondrial dysfunction, and, disruption of neurotransmitter systems. It highlights the pathways through which these toxins exert their effects, presents epidemiological evidence linking toxin exposure to neurological disorders, and discusses the potential public health implications. By elucidating these connections, the paper aims to enhance understanding of the environmental determinants of neurological health. The Key Findings includes: • Environmental toxins like heavy metals and pesticides cause oxidative stress and inflammation, damaging the nervous system. • Reactive oxygen species (ROS) generated by toxins lead to severe oxidative damage in neurons. • Developmental stages, especially prenatal and early postnatal, are highly vulnerable to neurotoxic exposure. • Toxins are linked to diseases such as Alzheimer's, Parkinson's, schizophrenia, and, ALS.

Keywords: Neurodegenerative disorder, environment toxins, Neuroinflammation, Neurotoxicity, Neurological Diseases

INTRODUCTION

The intricate relationship between humans and their environment is fundamental to the functioning of both entities. This interconnectedness is especially evident in the relation of neurological health, where environmental factors play an important role in the development and progression of disorders affecting the brain and nervous system. Increasing evidence points to a significant association between environmental toxins and the rising prevalence of neurological disorders globally. These disorders, which include conditions such as Alzheimer's disease, Parkinson's disease, and various developmental disorders, are not only a major cause of disability but also profoundly impact the quality and duration of life.

Environmental toxins, which are pervasive in our surroundings, can originate from a variety of sources, including industrial pollution, pesticides, heavy metals, and household chemicals. Exposure to neurotoxins at any stage of development disrupts bodily functions, resulting in both microscopic and macroscopic impairments. Health impacts vary and range from acute symptoms to long-term chronic conditions depending on, the nature of the toxin, duration of exposure, and individual susceptibilities. This leads to lifelong neurological and psychiatric symptoms in humans. The brain, the most complex and vital organ in the animal kingdom, is safeguarded by the Blood-Brain Barrier (BBB) and the Blood-Axion Barrier, which protect the central nervous system (CNS) and

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peripheral nervous system (PNS).[1] However, regions such as the area postrema, hypothalamus, pineal gland, and motor and sensory nerve terminals lack this protective mechanism, making them vulnerable to the easy entry of neurotoxins and subsequent injury. These substances can disrupt normal neurological function through various mechanisms, such as inducing oxidative stress, inflammation, and direct neurotoxicity. The impact of these toxins can be particularly severe during critical periods of brain development, making prenatal, perinatal, and early postnatal exposures especially concerning.

The review examines the impact of environmental toxins on neurological health, particularly their role in the development and progression of neurodegenerative and neuropsychiatric disorders. It examines the biological pathways through which these toxins affect the nervous system, supported by epidemiological evidence linking toxin exposure to increased risks of neurological conditions.

ENVIRONMENTAL TOXINS & NEUROTOXICITY

"Any poisonous chemical substance, its by-products, or harmful organisms present in our immediate environment that adversely affect human health (e.g., causing carcinogenesis, cardiovascular, respiratory, or neurological disorders) are classified as environmental toxicants[2]."

Environmental toxin can be natural or man-made, results in the loss of balance within human body with the brain being the most affected organ. Environmental toxins are categorized into biodegradable (like waste water, etc.) and non-biodegradable (like heavy alloys, microplastics, etc.).[3] Various exogenic chemicals are considered to be the reason of increases in different common or deadly and neurological related diseases.[4] The emergence of organic toxic molecular compounds can be attributed to five major industries: petroleum refining, organic chemical and synthetic industries, steel mining and coal conversion, textile processing, and pulp and paper milling. The most dangerous chemicals include polycyclic aromatic hydrocarbons, heavy metals, nitrogen oxides, particulate matter, polychlorinated biphenyls, pesticides, dioxins, food additives, antibiotics, and hormones. However, these industries are not solely responsible for the release of these chemicals into the environment. The use of gasoline, aerosol sprays, pesticides, and fertilizers by individuals is a leading cause of environmental toxicity by consumers. Ineffective waste disposal practices are contaminating soil and its ecosystems, ultimately leading to numerous diseases caused by microorganisms. Additionally, heavy metal toxicity is prevalent in industrialized countries, further exacerbating environmental degradation.[5]

Environmental neurotoxins exert toxic effects on the human central nervous system (CNS) through mechanisms such as oxidative stress, disruption of calcium homeostasis, mitochondrial dysfunction, and chronic inflammation.[6] Many neurotoxins, including transition metals like lead, mercury, and manganese, generate reactive oxygen species (ROS), leading to oxidative damage of lipids, proteins, and DNA, particularly in neurons, which are highly metabolically active and rich in peroxidation-prone lipids.[7,8] Neurotoxins interfere with calcium signaling, crucial for synaptic transmission and neuronal plasticity, leading to excitotoxicity and cell death.[9] Mitochondrial dysfunction is another key pathway, with toxins such as mercury and pesticides impairing ATP production and enhancing ROS generation. Neurotoxins can also disrupt neurotransmitter systems, as observed with organophosphates, which inhibit acetylcholinesterase, causing excessive cholinergic activity. The CNS's vulnerability stems from its high metabolic demand, lipid-rich environment, and limited regenerative capacity, as well as the selective permeability of the blood-brain barrier, which some neurotoxins, such as methylmercury and lipophilic pesticides, can penetrate. This susceptibility is particularly pronounced during development, when critical processes such as neurogenesis and synaptogenesis are easily disrupted.[10]

Environmental neurotoxicity results from inhibition of mitochondrial activity, excess oxidative stress leading to neuroinflammation, and promoting apoptosis and neuronal cell death. The complex interchange of genetic susceptibility and life incidents developing cognitive decline and an increased potential risk of neurodegenerative disorders such as Alzheimer's disease, Parkinson disease, peripheral neuropathy, tremors, and many more.[11] High prevalence of certain cancers,[12] increased rates of various diseases, cognitive impairment in children, the incidence of type 2 diabetes, disorders of the immune and respiratory systems, and degenerative nerve diseases have all been linked to environmental toxicity.[13] Exposure to toxins during the developmental period of brain lead to development disorders and brain defects due to oxidative stress, inflammation, and changes in neurotransmitter secretion.[11]

STRUCTURAL FEATURES OF NEUROTOXICANTS

Neurotoxicants such as heavy metals, pesticides, and industrial chemicals exhibit diverse molecular structures, with specific functional groups playing a pivotal role in their reactivity and interaction with neuronal tissues. Heavy metals like lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) possess unfilled d-orbitals, enabling them to coordinate with biological molecules, particularly thiol (-SH), amine ($-NH_2$), and carboxyl ($-COO^-$) groups in proteins, enzymes, and DNA.[14,15] These metals often act as soft acids, binding strongly to sulfur-containing groups, thereby impairing enzymatic functions and redox homeostasis.[16] For instance, lead mimics calcium ions (Ca^{2+}), disrupting synaptic signaling, while mercury, especially in its organic form (methylmercury), preferentially binds to thiol groups, compromising antioxidant defenses. Pesticides, such as organophosphates, organochlorines, and carbamates, derive their neurotoxicity from functional groups like phosphate esters (P=O or P=S) and carbamate groups ($-O-C(=O)-NH_2$), which target acetylcholinesterase, leading to cholinergic overstimulation.[17] Halogenated organochlorines, such as DDT, feature aromatic rings substituted with halogens (e.g., Cl, Br), enhancing their lipophilicity and persistence in lipid-rich neuronal tissues, where they interfere with ion channels and neurotransmitter systems.[18] Similarly, industrial chemicals like polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) possess structural features that exacerbate their neurotoxicity.[19] PCBs, with their biphenyl backbone and chlorine substitutions, bioaccumulate in neuronal membranes and disrupt calcium homeostasis, while

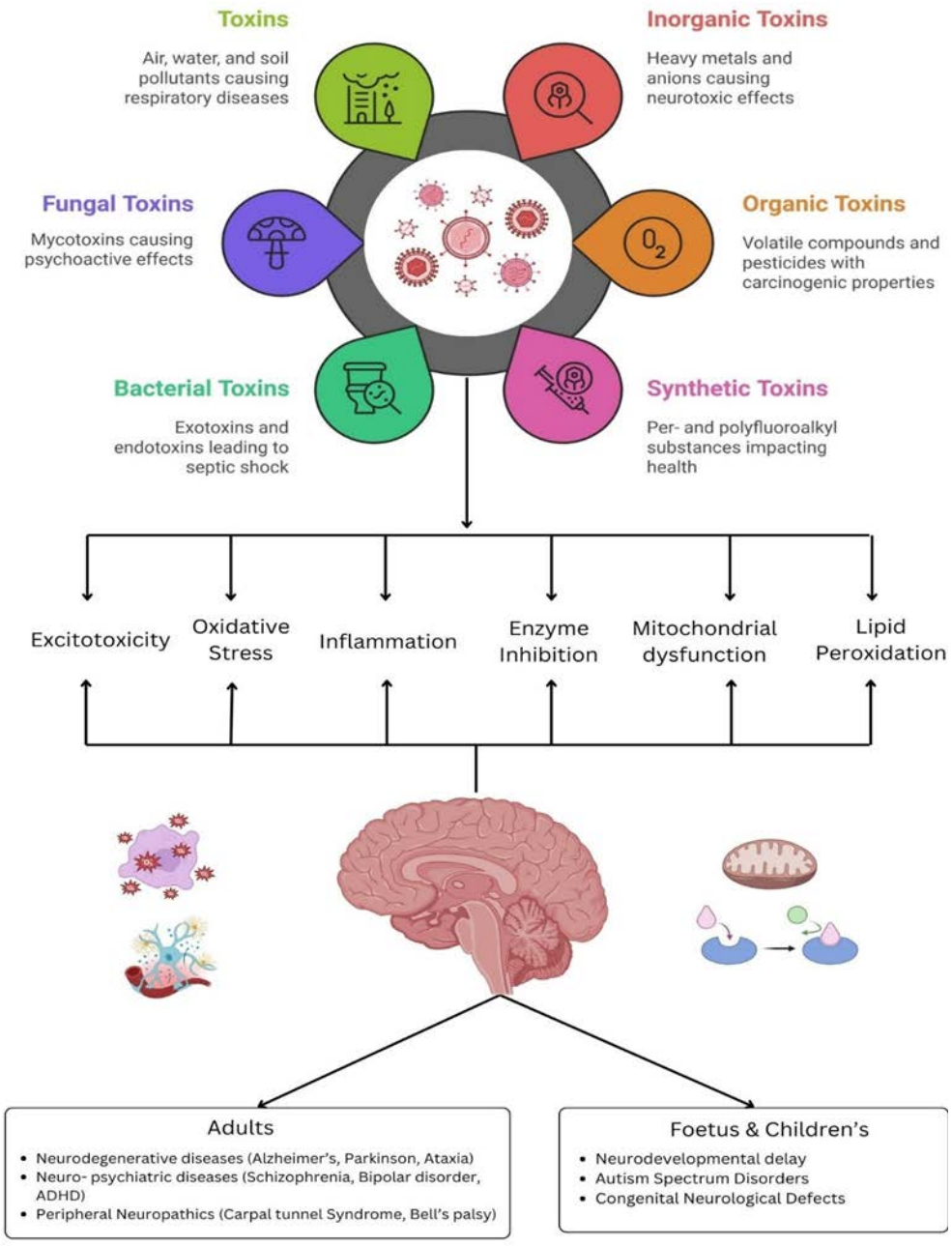

Figure 1. Various environmental toxins

PAHs, characterized by fused aromatic rings, are metabolically activated to reactive intermediates (e.g., epoxides) that generate oxidative stress and damage neuronal DNA.[20,21]

REACTIVE OXYGEN SPECIES GENERATION

Reactive oxygen species (ROS), including superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), are key mediators of oxidative stress and are generated through enzymatic and non-enzymatic pathways, with transition metals like iron (Fe) and copper (Cu)[22]. Fenton reaction, a prominent mechanism, where Fe^{2+} catalyzes the decomposition of H_2O_2 into highly reactive hydroxyl radicals (•OH)[23]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$$

Copper undergoes a similar redox cycling process. Superoxide anion ($O_2^{\bullet-}$), often produced by mitochondrial electron transport chain leakage or NADPH oxidase activity, further sustains ROS generation by reducing Fe^{3+} or Cu^{2+} to Fe^{2+} or Cu^{+}, perpetuating the Fenton cycle. These ROS chemically modify biomolecules, leading to lipid peroxidation, protein carbonylation, and DNA damage. Lipid peroxidation targets polyunsaturated fatty acids (PUFAs) in neuronal membranes, initiating a chain reaction wherein ROS abstract hydrogen atoms from lipids[24], forming lipid radicals (L•), which react with oxygen to form lipid peroxyl radicals (ROO•). This process propagates, generating aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) which are toxic in nature disrupting membrane integrity and act as secondary ROS amplifiers.[25] Proteins undergo carbonylation, either directly via ROS oxidation of amino acid side chains such as lysine and proline or indirectly through adduction with lipid peroxidation-derived aldehydes. These modifications impair protein function, promote aggregation, and overwhelm proteasomal degradation pathways. DNA is similarly vulnerable, with hydroxyl radicals inducing oxidative base lesions, such as 8-oxo-2′-deoxyguanosine (8-oxo-dG), strand breaks via cleavage of the deoxyribose backbone, and DNA-protein cross-links through secondary aldehyde products.[26,27] These ROS-induced modifications impair critical cellular processes, trigger mutations, and activate apoptotic pathways if repair mechanisms like base excision repair fail. The synergistic effects of ROS-mediated damage to lipids, proteins, and DNA contribute significantly to neuronal dysfunction and degeneration, underpinning the pathophysiology of oxidative stress-related diseases such as Alzheimer's and Parkinson's.[26]

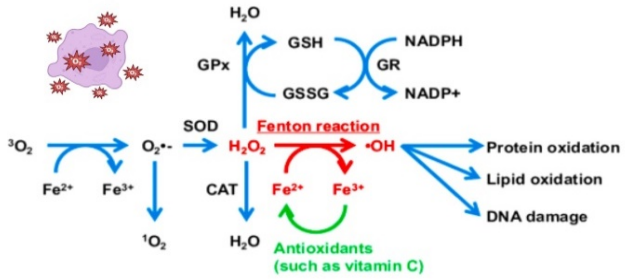

Figure 2. ROS Generation and Fenton Reaction[28]

PHYSICO-CHEMICAL PROPERTIES AND MODIFICATIONS AFFECTING NEUROTOXIN PENETRATION OF BLOOD-BRAIN BARRIERS

The ability of neurotoxins to cross the blood-brain barrier (BBB) is primarily determined by their physicochemical properties, including lipophilicity, molecular weight, polarity, charge, and molecular structure. Lipophilicity, key factor, as highly lipophilic compounds (logP between 1 and 3) readily diffuse through the lipid bilayer of endothelial cells, enabling toxins such as organochlorines to accumulate in neuronal tissue.[29,30] Molecular weight also plays a crucial role, with compounds below 400–500 Daltons more likely to cross via passive diffusion, as exemplified by methylmercury (~215 Da), which easily penetrates the BBB. Polar molecules or those with excessive hydrogen bonding capacity are typically excluded unless they utilize specific transporters.[31] For instance, L-DOPA, a polar molecule, crosses the BBB via amino acid transport mechanisms. Neutral charge further enhances permeability, as charged species are generally repelled by the barrier unless facilitated by carriers. Shape and rigidity also influence passage, with planar molecules often displaying better permeability.[32] Chemical modifications can significantly impact BBB permeability: increasing lipophilicity through alkylation or halogenation can enhance brain uptake, while reducing lipophilicity or adding polar groups can inhibit entry[29,33]. Prodrug strategies, where lipophilic moieties are enzymatically cleaved in the brain, provide another route to enhance delivery, while targeting efflux transporters like P-glycoprotein can limit toxin accumulation. Neurotoxins exploit these principles; for example, methylmercury's lipophilicity and mimicry of methionine allow transport via amino acid carriers, while polychlorinated biphenyls (PCBs) passively diffuse due to their high lipophilicity. Conversely, polar conjugation products like glutathione adducts of reactive intermediates inhibit BBB penetration, aiding detoxification.[34,35]

VARIOUS MECHANISM OF ACTION

Oxidative Stress & ROS

Oxidative stress and the production of reactive oxygen species (ROS) due to environmental toxins cause extensive cellular damage, particularly in neurons. Oxidative stress arises when there is an imbalance between ROS production and reactive nitrogen species (RNS) and the body's antioxidant defenses, resulting in an accumulation of these reactive molecules that can damage lipids, proteins, and DNA[36]. ROS, which include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), are typically byproducts of cellular metabolism in the mitochondria[37] and play essential roles in cell signaling and homeostasis[38]. Excessive ROS production can be triggered by environmental toxins, including transition metals (like mercury, cadmium, lead, and iron) and organic pollutants (such as pesticides and industrial chemicals)[39,40]. These toxins increase ROS through various mechanisms, such as redox cycling (involving metals like iron and copper), mitochondrial dysfunction, inhibition of antioxidant enzymes (e.g., superoxide dismutase), and activation of inflammatory pathways further promoting ROS release. Neurons are particularly vulnerable to ROS-induced damage due to their high oxygen consumption, abundant lipid content (which is prone to lipid peroxidation), and relatively low antioxidant defense capacity.[41] The consequences of oxidative stress in neurons include lipid peroxidation, which disrupts membrane integrity and signaling; protein oxidation, leading to protein dysfunction and aggregation (a feature in neurodegenerative diseases); and DNA damage, which increases the likelihood of mutations and cellular apoptosis, impairing transcription and translation.[36,42,43]

Enzyme Inhibition

Enzyme inhibition impair cellular function and promote toxicity. Toxins such as heavy metals (like lead, mercury, and arsenic), pesticides, and industrial chemicals can interfere with enzymes either by binding to the enzyme's active site or by altering its structure, effectively disrupting its function. Enzymes are crucial for regulating metabolic reactions, maintaining cellular homeostasis, and defending cells, so their inhibition leads to a cascade of harmful effects.[44,45] Lead and mercury, bind directly to enzyme active sites, replacing essential ions needed for function, or interact with thiol groups in cysteine residues, which alters enzyme structure and inhibits activity. Other toxins act on allosteric sites, changing the enzyme's shape and reducing its efficiency. Some toxins, like cadmium and lead, inhibit antioxidant enzymes such as superoxide dismutase (SOD), resulting in elevated reactive oxygen species (ROS) and oxidative stress[46]. Additionally, pesticides inhibits mitochondrial enzymes like mitochondrial complex I, involved in cellular respiration, impairing ATP production and causing energy deficits that impact cellular function.

Mitochondrial dysfunction

Mitochondrial dysfunction impairs cellular energy metabolism, contribute to oxidative stress, and promote various diseases, including neurodegenerative disorders, metabolic syndromes, and cardiovascular diseases[47]. Mitochondria, known as the powerhouse of the cell, produce adenosine triphosphate (ATP) through oxidative phosphorylation and regulate cellular metabolism, apoptosis, and reactive oxygen species (ROS) production. Environmental toxins, such as heavy metals (like lead, mercury, and cadmium), pesticides, and certain industrial chemicals, adversely affect mitochondrial function through several mechanisms[48]. These toxins can directly damage mitochondrial structures, disrupting membranes and proteins, and impairing the electron transport chain (ETC), which diminishes ATP production. Additionally, toxins like rotenone and cyanide inhibit specific ETC complexes, leading to increased ROS generation that further damages mitochondrial components[49]. Elevated oxidative stress

can result from the combination of impaired mitochondrial function and increased ROS production, damaging mitochondrial DNA (mtDNA), proteins, and lipids, creating a vicious cycle of dysfunction. Environmental toxins can also hinder mitochondrial biogenesis by inhibiting peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), reducing the number and functionality of mitochondria. The disruption of calcium (Ca^{2+}) homeostasis can overload mitochondria, increasing ROS production and triggering apoptotic pathways.[50–52] The impaired ATP production, increased cellular damage, inflammation, and apoptosis, which contribute to neurodegenerative diseases like Alzheimer's and Parkinson's, as well as metabolic disorders, cardiovascular diseases.[53]

Inflammation

Inflammation, a significant mechanism causing cellular damage and contribute to various diseases, including cardiovascular, respiratory, and neurodegenerative conditions. Toxins such as air pollutants, heavy metals (like lead, mercury, and cadmium), pesticides, and industrial chemicals can trigger inflammatory responses in tissues as they are often recognized by the body as harmful. Upon entering the body through inhalation, ingestion, or skin absorption, these toxins activate immune cells, which release signaling molecules called cytokines and chemokines that recruit

Table 1. Various environmental neuro-toxins and their effects

Environmental Toxin	Major Effect	Description	Mechanism of Action	Effects	References
Particulate Matter (PM2.5)	Brain Damage	Fine particles present in polluted air with diameter of 2.5 micro-meters or less	Enter through bloodstream causing oxidative stress, neuroinflammation, autonomic dysfunction, fibrinolytic system disorders	Neurodegenerative disorders, nerve damage, tumor	[129]
Cigarette Smoke	Chronic Obstructive Pulmonary Disease (COPD)	Carbon monoxide, nicotine, free radicals, other toxic chemicals	Hypoxia, inflammation of airway, oxidative stress, , blood brain barrier, lung emphysema	Neurocognitive dysfunction, structural and neurochemical abnormalities	(World Health Organization, 2022)[130–132]
Opioid	Autism, Schizophrenia	Naturally derived from poppy plants, semi-synthesized from natural opiates or synthetic	Alteration of interneuron migration in the adult cortex	Respiratory depression & hypoxia, Neuroinflammation, Neuropsychiatric effects, Hyperalgesia	[133–135]
Fluorinated organic compounds (per- and polyfluoroalkyl substances [PFAs] or perfluorinated compounds [PFCs])	Attention Deficit Hyperactivity Disorder, Autism spectrum disorders, Alzheimer's disease	Synthetic organic toxin	Oxidative stress, mitochondrial dysfunction, disruption of calcium homeostasis	Neurobiological, neuroendocrine and neurobehavioral disorders	[136,137]
Heavy Metals [Mercury(Hg), lead (Pb), manganese (Mn), cadmium (Cd)]	Peripheral neuropathies, Gliomas	Water, food, air & industrial waste by inhalation, skin contact, ingestion	Oxidative stress, mitochondrial dysfunction, Calcium homoeostasis dysfunction, impaired neuronal function	Systematic inflammation, Peripheral Neuropathy, cognitive and motor dysfunction, protein binding and enzyme inhibition	[138–141]
Industrial Chemicals	Malignant Gliomas, Neurological disorders	Benzene, formaldehyde, Dioxins	Oxidative stress & ROS, mitochondrial dysfunction	Disruption of cell cycle regulation and DNA repair mechanism	
Radiations	Acute Radiation Syndrome, Peripheral Neuropathy	Sunlight, X-rays, radio waves, particle radiation [Alpha (α), Beta (β), Gamma (γ)], Particles and Neutrons	Exposure through direct contact	Predispose to cancer, congenital disabilities, skin burns	[142,143]

additional immune cells to the site of exposure, creating a localized inflammatory response.[5455] Many toxins induce oxidative stress by increasing the production of reactive oxygen species (ROS), which damage cellular components and provoke inflammation. Environmental toxins can directly activate immune cells like macrophages and neutrophils, leading to the release of inflammatory cytokines, which can be easily seen with particulate matter in polluted air. Certain lipophilic toxins, such as pesticides, disrupt cell membranes, triggering immune responses, while mitochondrial dysfunction caused by various toxins results in excess ROS and promotes inflammatory signaling pathways.[56,57] This chronic inflammation contributes to tissue damage and a range of health issues, such as asthma, chronic obstructive pulmonary disease (COPD), neurodegenerative diseases like Alzheimer's and Parkinson's, autoimmune diseases, and cardiovascular problems.[58]

Excitotoxicity

Excitotoxicity is a process by which neurons are damaged or killed due to excessive stimulation by excitatory neurotransmitters, mainly glutamate, and environmental toxins like heavy metals (e.g., lead, mercury) and organic pollutants (e.g., pesticides and industrial chemicals) disrupting the balance of neurotransmitter release, reuptake, and receptor activity.[59,60] Many toxins increase glutamate release or inhibit its reuptake, causing an excess of glutamate in the synaptic cleft that overstimulates receptors—especially NMDA and AMPA receptors—leading to a massive influx of calcium ions (Ca^{2+}) into neurons.[61,62] Calcium overload activates various enzymes that degrade proteins, lipids, and DNA, resulting in mitochondrial damage, increased reactive oxygen species (ROS) production, and ultimately, apoptosis[63]. Toxins also interfere with astrocytes, the support cells responsible for glutamate reuptake, prolonging excitotoxic signaling.[64] Additionally, some toxins activate inflammatory pathways, releasing cytokines that worsen excitotoxicity. This synergistic effect between excitotoxicity, oxidative stress, and inflammation is particularly damaging to neurons and contributes to neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS.[6465]

Lipid peroxidation

Lipid peroxidation, refers to the oxidative degradation of lipids, occurring when reactive oxygen species (ROS) attack polyunsaturated fatty acids (PUFAs) in cell membranes, leading to the formation of toxic byproducts.[66,67] Environmental toxins, such as heavy metals (like lead, mercury, and cadmium), pesticides, and industrial pollutants, can initiate and exacerbate lipid peroxidation through several mechanisms such as oxidative stress by increasing ROS production and disrupting cellular antioxidant systems, creating an imbalance that allows ROS to attack lipid membranes[68,69]. Additionally, some toxins interact directly with lipid membranes, altering their structure and making them more susceptible to oxidative damage. The lipid peroxidation process typically involves a chain reaction; once a ROS reacts with a PUFA, it generates a lipid radical that can react with oxygen to produce peroxyl radicals, perpetuating a cycle of damage. This process results in the formation of toxic byproducts, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which can modify proteins and DNA, disrupt cellular functions, and trigger inflammatory responses.[70,71] The consequences of lipid peroxidation are profound, leading to compromised cell membrane integrity, impaired cellular functions, and increased permeability, ultimately resulting in cell death. Furthermore, the toxic byproducts can initiate inflammatory responses, contributing to chronic conditions like atherosclerosis, neurodegenerative diseases, and cancer.[72,73]

ENVIRONMENTAL TOXIN INDUCED NEURODEGENERATIVE DISORDERS

Parkinson's Disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by motor symptoms such as tremors, rigidity, bradykinesia, and postural instability, along with non-motor symptoms like cognitive impairment and mood disorders. Pesticides such as paraquat and rotenone are strongly linked to PD, inducing oxidative stress and mitochondrial dysfunction that leads to the selective degeneration of dopaminergic neurons due to dopamine metabolism, which produces reactive intermediates, and their high mitochondrial activity.[74,75] Toxins such as rotenone and MPTP inhibit complex I of the mitochondrial electron transport chain (ETC), reducing ATP production and increasing ROS generation. This creates a cycle of mitochondrial damage and energy failure, leaving neurons unable to maintain ion gradients and survive excitotoxic conditions.[75,76] Dysfunctional mitochondria also fail to regulate calcium homeostasis and release pro-apoptotic factors, triggering cell death pathways.[77] Organochlorines, commonly used in agriculture, disrupt dopaminergic signaling and induce neuroinflammation[78]. Chronic exposure to heavy metals like manganese, lead, and mercury also contributes to PD by causing oxidative stress and inflammation reducing the brain's antioxidant capacity. Industrial chemicals such as polychlorinated biphenyls (PCBs) and trichloroethylene (TCE) disrupt dopaminergic neurotransmission, impair mitochondrial function, and increase oxidative stress, all of which are implicated in PD pathogenesis. These environmental toxins often induce oxidative damage, mitochondrial dysfunction, chronic neuroinflammation, and disrupt dopaminergic signaling, exacerbating the motor and non-motor symptoms characteristic of Parkinson's disease.[79,80] The selective vulnerability of dopaminergic neurons in PD, combined with environmental toxin exposure, accelerates the emergence and progression of the disease.

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is another progressive neurodegenerative disorder marked by cognitive decline, memory loss, and behavioral changes. Chronic exposure to heavy metals like lead and mercury has been linked to neurotoxicity, disrupting neuronal function and potentially accelerating cognitive deficits through mechanisms such as oxidative stress and inflammation[81]. The role of aluminum exposure remains debated, but some studies indicate it might promote amyloid-beta plaque formation, a hallmark of Alzheimer's pathology.[82] Oxidative stress impairs mitochondrial function, as toxins disrupt the electron transport chain (ETC), reduce ATP production, and enhance ROS generation, creating a vicious cycle of mitochondrial

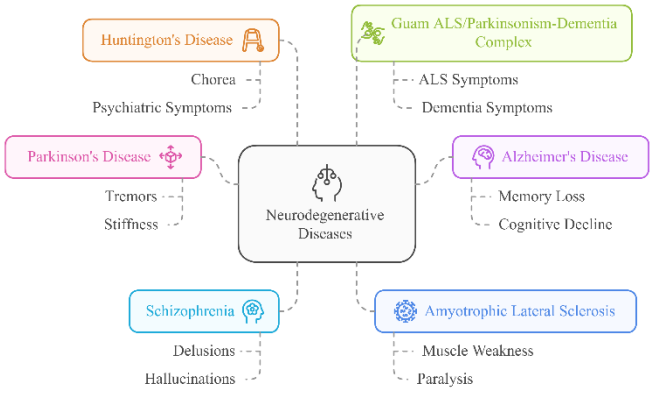

Figure 3. Neurodegenerative disorders

dysfunction.[83,84] Pesticides, including organophosphates and organochlorines, have been associated with neurodegenerative changes by inhibiting acetylcholinesterase, leading to cholinergic dysfunction, while heavy metals can impair enzymes critical for antioxidant defenses, such as superoxide dismutase (SOD) and catalase, inducing oxidative stress, mitochondrial dysfunction, and disrupting cholinergic signaling,[85–87] all of which are implicated in Alzheimer's disease.[88] Furthermore, exposure to air pollution, particularly fine particulate matter (PM2.5), and nitrogen dioxide, correlates with increased risks of cognitive decline and dementia, as these pollutants can penetrate the blood-brain barrier, leading to neuroinflammation and the accumulation of amyloid-beta and tau proteins in the brain.[89,90] Industrial chemicals such as polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) also exhibit neurotoxic effects, disrupting normal neuronal function and promoting the aggregation of neurotoxic proteins associated with Alzheimer's disease.[91] These environmental toxins often induce oxidative stress, increase the production of reactive oxygen species, and activate microglia and astrocytes, resulting in chronic neuroinflammation by activating microglia and astrocytes. These activated glial cells release pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) and ROS, which further amplify oxidative damage and promote Aβ plaque deposition disrupting synaptic plasticity and contributes to neuronal loss[92–94]. Additionally, they may promote the misfolding and aggregation of amyloid-beta and tau proteins, which are crucial pathological features of Alzheimer's disease.[95] Environmental toxins not only initiate these processes but also interfere with the brain's capacity to repair and maintain cellular homeostasis, accelerating the progression of AD.

Schizophrenia

Schizophrenia, a complex chronic mental health disorder characterized by hallucinations, delusions, disorganized thinking, and impaired cognitive function. Exposure to heavy metals like lead and mercury, particularly during critical developmental periods, disrupts neurotransmitter systems, induces oxidative stress, and causes neuroinflammation, all linked to schizophrenia.[96] Oxidative stress particularly damage the prefrontal cortex and hippocampus, regions critical for cognition and emotion regulation. Elevated ROS levels disrupt neuronal signaling and impair neurodevelopmental processes, increasing susceptibility to this neurodegenerative disorder.[97,98] Mitochondrial dysfunction in neural progenitor cells during brain development disrupt neural circuit formation, while in mature neurons, it impairs energy metabolism required for synaptic plasticity and neurotransmitter release. This dysfunction contributes to the cognitive deficits and emotional dysregulation[99,100]. Air pollution, specifically fine particulate matter and nitrogen dioxide, is associated with a higher risk of developing the disorder, as pollutants can cross the blood-brain barrier, leading to systemic inflammation, neuroinflammation, and oxidative stress. Chronic neuroinflammation disrupts synaptic pruning during neurodevelopment, potentially resulting in hyper- or hypo-connectivity.[97,100] Pesticides, especially organophosphates used in agriculture, disrupt cholinergic signaling and induce oxidative stress and neuroinflammation, contributing to neurodevelopmental disorders including schizophrenia[101]. Industrial chemicals such as polychlorinated biphenyls (PCBs) also pose risks by disrupting dopamine signaling, inducing oxidative stress, and causing neuroinflammation, all relevant to schizophrenia's neurobiology. These environmental toxins increase production of ROS, leading to oxidative damage, chronic neuroinflammation, and interference with critical neurotransmitters like dopamine and glutamate[102]. Exposure during critical stages of brain development can lead to structural and functional abnormalities in the brain, increasing the likelihood of schizophrenia.[103]

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease affecting motor neurons in the brain and spinal cord, leading to muscle weakness and eventual paralysis and death[104] . Environmental toxins have been increasingly implicated in the onset and progression of ALS, with particular focus on neurotoxic substances such as heavy metals (e.g., lead, mercury, and manganese), pesticides, and chemicals like β-N-methylamino-L-alanine (BMAA)[105–107]. These toxins contribute to neuronal dysfunction by inducing oxidative stress, mitochondrial damage, and excitotoxicity. The key mechanism involves the generation of reactive oxygen species (ROS) overwhelming the antioxidant defenses of motor neurons, which are inherently vulnerable due to their high metabolic activity, which cause oxidative damage to vital cellular components such as DNA, proteins, and lipids within neurons[104,105]. Certain environmental toxins impair the body's natural antioxidant defenses, including enzymes like superoxide dismutase (SOD1) and glutathione peroxidase, mutations of which are linked to familial forms of ALS. This disruption reduce the capacity to neutralize and exacerbates the accumulation of ROS, leading to neuronal death through apoptosis and accelerating the degeneration of motor neurons.[108,109] Environmental toxins impair mitochondrial function by disrupting the electron transport chain, reducing ATP production, and increasing ROS leakage. This creates a self-perpetuating cycle of oxidative stress and mitochondrial damage.

Huntington's Disease

Genetic neurodegenerative disorder, Huntington's disease (HD), results in the progressive loss of neurons in the brain, particularly in the basal ganglia, leading to motor impairment, cognitive decline, and psychiatric disturbances.[110] While the primary cause of

HD is a mutation in the HTT gene, environmental toxins may exacerbate the neurodegenerative processes associated with the disease by triggering mechanisms such as oxidative stress and reactive oxygen species (ROS) generation, inflammation, enzyme inhibition, and mitochondrial dysfunction. Exposure to toxins such as pesticides, heavy metals, and industrial chemicals[111,112] has been linked to increased oxidative stress, mitochondrial dysfunction, and inflammation in the brain, further damaging neurons.[113,114] Toxins (pesticides, polychlorinated biphenyls, BMAA, manganese) stimulating the production of ROS can accelerate oxidative damage in brain regions already vulnerable due to the mutant huntingtin protein(mHTT). mHTT itself triggers chronic neuroinflammation, and toxin exposure intensifies this inflammatory environment. Persistent inflammation disrupts synaptic integrity and neuronal survival. Enzymes involved in mitochondrial energy metabolism and protein degradation, such as those in the ubiquitin-proteasome system, are inhibited or impaired, leading to an accumulation of damaged proteins and further dysfunction.[115,116] These environmental stressors may also impair the brain's capacity to repair damaged neurons and maintain cellular balance, thereby contributing to the acceleration of disease progression.[117]

Guam - ALS/Parkinsonism-Dementia Complex (ALS/PDC)

Guam - ALS/Parkinsonism-Dementia Complex (ALS/PDC) predominantly observed in the Chamorro population of Guam and other Pacific islands, characterized by combination of amyotrophic lateral sclerosis (ALS), Parkinson, and, dementia. β-N-methylamino-L-alanine (BMAA), a neurotoxin produced by certain cyanobacteria, which accumulates in the local food chain, particularly in traditional foods such as flying foxes and cycad seeds.[118,119] Chronic exposure to BMAA leads to neurodegeneration through mechanisms including oxidative stress and excitotoxicity, as it promotes the generation of reactive oxygen species (ROS) that damage neurons, disrupt mitochondrial function, and trigger inflammation.[120,121]

GREEN CHEMISTRY APPROACH

Green chemistry offers innovative solutions to minimize the environmental release of neurotoxicants by focusing on the development of biodegradable pesticides, safer industrial solvents, and sustainable chemical processes. Traditional pesticides, such as organophosphates and organochlorines, are highly persistent in the environment and often accumulate in soil, water, and organisms, leading to neurotoxic risks.[122] Biodegradable alternatives, including biopesticides derived from natural organisms like *Bacillus thuringiensis* (Bt) and plant-based compounds like neem oil or pyrethrins, offer targeted pest control with minimal environmental persistence and lower toxicity to non-target species.[123,124] Additionally, nano-formulations of pesticides can enhance solubility and controlled release,[125] further reducing environmental impact.[126] In industrial applications, neurotoxic solvents such as toluene and xylene can be replaced with green solvents derived from renewable plant materials, such as d-limonene or terpenes, which are biodegradable and less harmful to human and environmental health[127]. Supercritical carbon dioxide (CO_2) and ionic liquids also represent sustainable alternatives, as they offer non-toxic, recyclable solutions for industrial processes, reducing the need for harmful organic solvents.[127,128] Green chemistry principles extend to the design of chemical processes, emphasizing solvent-free or water-based methods, as well as the use of renewable feedstocks and catalytic processes, which minimize waste and energy consumption. These strategies not only reduce the release of neurotoxic chemicals but also promote sustainability by utilizing non-toxic, renewable resources, and optimizing chemical reactions to limit byproduct formation.

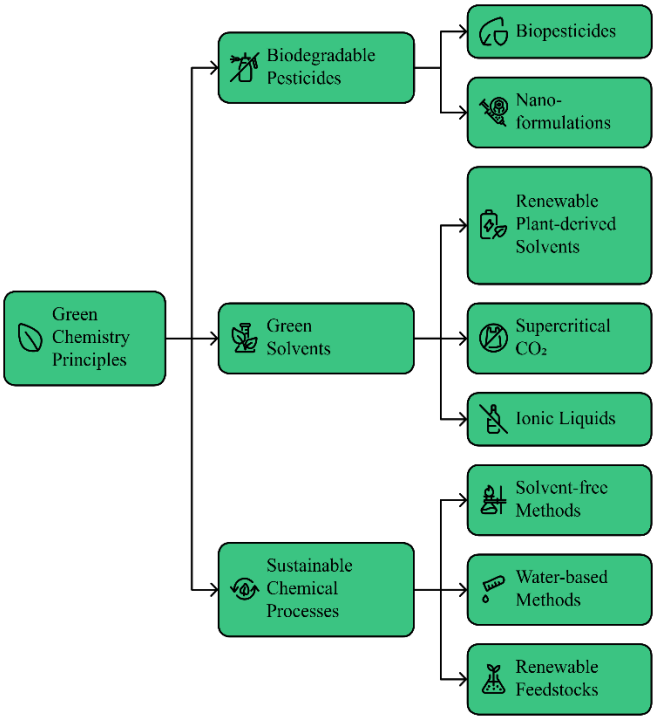

Figure 3. Green chemistry systems for environmental neurotoxins mitigation

DISCUSSION

The intricate interplay between transition metals and the generation of ROS underscores the vulnerability of the nervous system to environmental toxins. The highlights of the study include how the redox-active properties of metals such as iron, copper, and manganese, coupled with the inherent metabolic demands of neurons, create a milieu prone to oxidative damage. The susceptibility of neuronal tissues, due to their high lipid content and limited regenerative capacity, emphasizes critical role of oxidative stress in neurodegenerative and neuropsychiatric disorders.

The findings consolidate evidence that transition metals disrupt cellular homeostasis through multiple pathways, including Fenton reactions, mitochondrial dysfunction, and interference with calcium signaling. These mechanisms converge to produce ROS, triggering lipid peroxidation, protein oxidation, and DNA damage. Such damage not only impairs neuronal function but also activates apoptosis and chronic inflammation, further exacerbating neurotoxicity.

Epidemiological studies provide compelling links between metal exposure and diseases like Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS). These connections are particularly pronounced in populations exposed to industrial

emissions, contaminated water, or occupational hazards. The developmental stages, marked by heightened neuroplasticity and ongoing synaptogenesis, emerge as the most vulnerable periods, with even low-dose exposures posing significant risks.

Interestingly, bidirectional role of metals like zinc, which are essential for enzymatic processes and neuronal communication but neurotoxic in excess. The delicate balance required to maintain metal homeostasis underscores the importance of regulatory mechanisms like metallothioneins and antioxidant systems. However, their inefficacy in the face of chronic or acute exposure highlights gaps in natural defenses.

The adoption of green chemistry principles represents a proactive approach to minimizing neurotoxic risks. Developing biodegradable pesticides, replacing hazardous industrial solvents with sustainable alternatives, and implementing solvent-free or water-based chemical processes could significantly reduce environmental contamination. Such strategies not only protect human health but also promote ecological sustainability.

The implications of these findings extend to public health and policy. Strategies for mitigating neurotoxic risks must include stringent industrial regulations, improved environmental monitoring, and public education on exposure risks. From a therapeutic perspective, antioxidants, chelating agents, and interventions targeting mitochondrial function show promise, but their efficacy in clinical settings requires further exploration.

CONCLUSION

This review examines the profound effects of environmental toxins on the human nervous system, focusing on their role in the development of neurodegenerative and neuropsychiatric disorders. Mechanisms such as oxidative stress, mitochondrial dysfunction, calcium homeostasis disruption, and chronic inflammation interact in a complex manner, amplifying neuronal damage and accelerating disease progression. Environmental pollutants—including heavy metals, pesticides, industrial chemicals, and particulate matter—are highlighted as key contributors to conditions like Parkinson's disease, Alzheimer's dementia, schizophrenia, and amyotrophic lateral sclerosis (ALS), as well as more subtle impairments like cognitive deficits, headaches, and depression. Particularly vulnerable populations, such as those in critical developmental stages, face an elevated risk, underscoring the importance of early detection, intervention, and, prevention. By understanding underlying toxicological mechanisms and identifying susceptible groups, it becomes possible to develop more effective approaches to prevention and treatment. Moreover, promoting sustainable practices, such as green chemistry, offers a dual benefit: reducing exposure to harmful toxins while fostering long-term neurological health.

FUTURE DIRECTION

Future research should focus on uncovering molecular mechanisms of toxin-induced neurodegeneration and identifying early biomarkers for detection. Longitudinal studies on gene-environment interactions are crucial to understanding individual susceptibility. Advanced *in vitro* and *in vivo* models can be developed for studying chronic, low-dose toxin effects during critical developmental stages. Therapeutic strategies must leverage molecular tools for neuroprotection and repair. Strengthening global policies, public awareness campaigns, and sustainable technologies is vital to reduce exposure and mitigate the neurological burden of environmental toxins.

METHODOLOGY

A thorough search of the online available literature was conducted using electronic databases such as PubMed, ScienceDirect, Medline, Scopus, and Embase. Initially, search terms including "environmental toxins," "environmental contaminants," "air pollutants," "heavy metals," "pesticides," "neurological disorders or diseases," "neuroinflammation," "Parkinson's disease," "Alzheimer's disease," "autophagy and neurological disorders," "neurotoxicants," "pesticides" and "particulate matter" were used individually. An advanced search was then performed by combining all search fields in keywords, abstracts, and/or titles. Relevant articles were selected based on these search terms. To ensure a comprehensive review, the investigation was further supplemented by examining the reference lists of the selected articles. Finally, all chosen articles were checked for duplicates, which were excluded if detected.

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CONFLICT OF INTEREST STATEMENT

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