INOSR APPLIED SCIENCES 13(2):39-43, 2025 ISSN: 2705-165X
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International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.3943

# Environmental and Pharmacological Neurotoxins: Shared Pathways in Oxidative Stress, Neuroinflammation, and Cognitive Decline

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## ABSTRACT

Environmental and pharmacological neurotoxins contribute significantly to the global burden of cognitive impairment and neurodegenerative diseases. Despite their differing origins, these neurotoxic agents often converge on common molecular and cellular pathways that result in neuronal dysfunction. This narrative review synthesizes evidence on how environmental toxicants such as heavy metals, pesticides, industrial solvents, and air pollutants, and pharmacological agents, including antipsychotics, chemotherapeutics, and antiepileptics induce neurotoxicity through shared mechanisms. Oxidative stress, mitochondrial dysfunction, neuroinflammation, and blood–brain barrier disruption emerge as key processes that underlie synaptic degeneration, impaired neurogenesis, and long-term cognitive decline. Both classes of neurotoxins promote the generation of reactive oxygen species (ROS), activate microglia and astrocytes, and stimulate the release of pro-inflammatory cytokines such as TNF-α and IL-1β. These responses compromise neuronal plasticity and accelerate neurodegenerative cascades. By examining the intersection of environmental exposure and iatrogenic neurotoxicity, this review highlights the urgent need for early biomarkers, preventive strategies, and regulatory frameworks. Particular emphasis is placed on protecting vulnerable populations such as children, the elderly, and individuals with pre-existing conditions who are disproportionately affected by cumulative neurotoxic burden. Understanding these shared pathways offers valuable insight into therapeutic interventions and public health policy aimed at mitigating neurotoxicity across environmental and clinical contexts.

**Keywords:** Neurotoxicity, Oxidative stress, Neuroinflammation, Cognitive decline, Environmental and drug-induced toxicity

## INTRODUCTION

Neurotoxins are exogenous agents capable of adversely affecting the structure or function of the nervous system. These substances include a wide range of environmental pollutants and pharmacological compounds that, despite differences in origin, often produce similar neurobiological outcomes [1]. Increasing evidence reveals that many neurotoxins act through converging molecular and cellular pathways, particularly those involving oxidative stress, neuroinflammation, and mitochondrial dysfunction [2]. The central nervous system (CNS) is highly susceptible to such insults due to its high lipid content, elevated metabolic demand, and limited regenerative capacity [3]. The implications of neurotoxic exposure are profound, extending from developmental neurotoxicity to late-life cognitive decline [4]. Environmental exposures, particularly during sensitive periods such as gestation and childhood, have been linked to long-term alterations in brain development, while therapeutic drugs—though often necessary—can produce iatrogenic cognitive side effects [5]. This review aims to explore the overlapping mechanisms of neurotoxicity induced by environmental and pharmacological agents, with a particular focus on shared pathways that lead to oxidative stress, chronic neuroinflammation, and impaired cognitive function. By identifying these common threads, we can better understand the etiology of neurodegenerative diseases, improve risk assessment models, and guide the development of neuroprotective interventions.

## Environmental Neurotoxins

Environmental neurotoxins are widely distributed in ecosystems and human habitats, with exposure occurring through air, water, food, and dermal contact. Common environmental neurotoxicants include heavy metals (such as lead, mercury, and arsenic), organophosphate pesticides, industrial solvents, and air pollutants like particulate matter (PM2.5) [6]. These substances are particularly harmful due to their persistence in the environment and their tendency to bioaccumulate in living organisms. Heavy metals disrupt neuronal homeostasis through multiple mechanisms. Lead impairs synaptic transmission and myelination, while mercury interferes with microtubule function and neurotransmitter release [7,8]. Arsenic has been shown to affect hippocampal neurogenesis and promote oxidative damage [9]. These metals generate reactive oxygen species (ROS) through redox cycling and Fenton-like reactions, overwhelming endogenous antioxidant defenses such as glutathione and superoxide dismutase (SOD) [10]. Pesticides like chlorpyrifos and paraquat exert neurotoxic effects by increasing ROS levels and activating glial cells [11]. Chlorpyrifos inhibits acetylcholinesterase, leading to the accumulation of acetylcholine and subsequent cholinergic overstimulation, while paraquat is structurally similar to MPP+, a neurotoxin known to selectively target dopaminergic neurons [12,13]. Airborne pollutants, especially fine particulate matter (PM2.5), can cross the blood-brain barrier (BBB) and initiate neuroinflammatory cascades [14]. These particles are associated with microglial activation, increased expression of inflammatory cytokines, and enhanced beta-amyloid deposition, linking air pollution to increased risk of Alzheimer's disease. The cumulative effect of environmental neurotoxin exposure is a sustained state of oxidative stress and inflammation that disrupts neuronal integrity and impairs cognitive function.

## Pharmacological Neurotoxins

Pharmacological agents, while developed for therapeutic purposes, can exhibit neurotoxic effects under certain conditions. Such effects may arise from high dosages, long-term administration, polypharmacy, or individual susceptibility due to age or genetic factors. Common examples include antipsychotics, chemotherapeutic agents, and antiepileptic drugs. Antipsychotic drugs such as haloperidol and risperidone have been linked to neurodegenerative changes in basal ganglia structures, potentially due to oxidative stress and mitochondrial damage [15]. Haloperidol, for example, enhances dopamine turnover and generates ROS as a by-product of dopamine metabolism [16]. This contributes to lipid peroxidation and neuronal apoptosis. Chemotherapeutic agents like methotrexate and cisplatin are known to cross the BBB and accumulate in the CNS, where they impair neurogenesis and damage white matter tracts [17]. Methotrexate disrupts folate metabolism, essential for DNA synthesis and repair, while cisplatin induces mitochondrial dysfunction and oxidative DNA damage [18] Antiepileptic drugs, such as valproate and phenytoin, affect brain function by altering ion channels and neurotransmitter levels. Long-term use has been associated with reduced hippocampal volume and cognitive deficits in both pediatric and adult populations [19]. These drugs can impair mitochondrial function, reduce levels of neurotrophic factors such as BDNF, and exacerbate neuroinflammation.

In summary, pharmacological neurotoxins compromise brain health through mechanisms similar to those of environmental agents, including mitochondrial impairment, oxidative stress, and inflammatory signaling, which collectively contribute to cognitive decline.

## Shared Pathways in Oxidative Stress

Oxidative stress is a central mechanism linking both environmental and pharmacological neurotoxins to neurodegeneration. It refers to the imbalance between the production of ROS and the capacity of the brain's antioxidant defenses to neutralize them [20]. Because of its high oxygen consumption and lipid-rich composition, the brain is particularly susceptible to oxidative damage [21]. Neurotoxins stimulate ROS generation by disrupting mitochondrial respiration, activating NADPH oxidases, and depleting antioxidant reserves such as glutathione [22]. Mitochondrial dysfunction, a hallmark of neurotoxicity, reduces ATP production and increases electron leakage from the electron transport chain, exacerbating ROS accumulation [23]. ROS cause damage to cellular components, including lipids, proteins, and nucleic acids. Lipid peroxidation compromises membrane integrity and ion channel function, protein oxidation impairs enzyme activity and receptor signaling, and oxidative DNA damage can trigger cell cycle arrest or apoptosis [24]. Furthermore, oxidative stress activates redox-sensitive transcription factors such as NF-κB, which amplify inflammatory gene expression [25]. Persistent oxidative damage disrupts synaptic function, alters neurotransmitter systems, and impairs neurogenesis, particularly in regions critical for learning and memory like the hippocampus [26]. Importantly, oxidative stress also primes glial cells for activation, laying the foundation for chronic neuroinflammation [27].

## Shared Pathways in Neuroinflammation

Neuroinflammation is a common downstream consequence of oxidative stress and a key mediator of neurotoxicity. It involves the activation of microglia and astrocytes, the primary immune cells of the CNS [28]. Under toxic conditions, these glial cells switch from a resting to an activated state and release pro-inflammatory mediators, including interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6). [29]

Although acute inflammation is a protective response, chronic glial activation leads to persistent inflammation that exacerbates neuronal damage. Activated microglia produce ROS, nitric oxide, and matrix metalloproteinases, which compromise the BBB and facilitate the infiltration of peripheral immune cells [30]. Astrocyte dysfunction impairs glutamate uptake, leading to excitotoxicity and neuronal death [31].

The inflammasome complex, particularly NLRP3, plays a pivotal role in neuroinflammation. It is activated by mitochondrial ROS and DAMPs, leading to the maturation and release of IL-1β and IL-18 [32]. Chronic inflammasome activation has been implicated in neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis [33]. Persistent neuroinflammation results in synaptic pruning, white matter loss, and hippocampal atrophy, all of which are associated with cognitive decline [34]. Thus, neuroinflammation is both a consequence and a driver of neurotoxic injury.

## Impact on Cognitive Function

Cognitive function encompasses a range of mental abilities including memory, attention, executive function, and problem-solving. Neurotoxic exposure—whether environmental or pharmacological has been linked to deficits in each of these domains, particularly when exposure occurs during critical periods of brain development [35].

Prenatal and early childhood exposure to heavy metals like lead and mercury has been associated with lower IQ scores, attention deficits, and behavioral problems [36]. Similarly, exposure to organophosphates and air pollution correlates with impaired working memory and slower cognitive processing [37]. In adults, chronic exposure to solvents and particulate matter has been linked to accelerated cognitive aging and increased dementia risk [38].

Pharmacologically, chemotherapy-induced cognitive impairment, often termed "chemo brain," affects cancer survivors with symptoms of forgetfulness, mental fog, and reduced processing speed. Studies implicate reduced hippocampal neurogenesis, white matter disruption, and neuroinflammation as underlying mechanisms [39]. Mechanistically, cognitive deficits arise from synaptic loss, reduced neurotrophic support (e.g., BDNF), impaired long-term potentiation (LTP), and disrupted neurotransmission [40]. Loss of dendritic spines and alterations in cholinergic, glutamatergic, and dopaminergic systems further compromise cognitive networks.

Collectively, these findings highlight that neurotoxic insults impair brain function through converging biological pathways, ultimately resulting in measurable deficits in cognitive performance and increased vulnerability to neurodegenerative disease.

## Translational and Public Health Implications

The convergence of environmental and pharmacological neurotoxicity necessitates integrated strategies in neuroscience research, public health, and clinical practice. Identifying shared biomarkers of early neurotoxicity, such as elevated 8-OHdG, protein carbonyls, or inflammatory cytokines could inform screening and intervention [41]. Moreover, the development of neuroprotective agents targeting oxidative and inflammatory pathways holds therapeutic promise. Policy-level action is equally critical. This includes stricter regulation of neurotoxic industrial pollutants, reevaluation of drug safety profiles, and community education on cumulative neurotoxic risks. Emphasis should be placed on protecting vulnerable populations—children, pregnant women, and the elderly through exposure reduction and monitoring.

## CONCLUSION

Environmental and pharmacological neurotoxins, though diverse in source, often target overlapping molecular and cellular pathways that culminate in oxidative stress, neuroinflammation, and cognitive impairment. Unraveling these shared mechanisms provides critical insight into the etiology of neurodegenerative disorders and opens avenues for cross-disciplinary approaches in neuroprotection, diagnostics, and policy reform. The future of neurotoxicology lies in precision environmental health, combining molecular insights with proactive public health strategies.

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**CITE AS: Taliikwa Nicholas Ceaser (2025). Environmental and Pharmacological Neurotoxins: Shared Pathways in Oxidative Stress, Neuroinflammation, and Cognitive Decline. INOSR APPLIED SCIENCES 13(2):39-43. https://doi.org/10.59298/INOSRAS/2025/13.2.3943**