The Morbid Impact of Environmental Toxins on the Human Nervous System: Peripheral Neuropathy Nexus with Organic Solvents, Pesticides, and Heavy Metals

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Abstract

Peripheral neuropathy is a complex disorder characterized by damage to the peripheral nerves, resulting in various sensory, motor, and autonomic symptoms. This review offers a detailed examination of
Peripheral neuropathy, covering its prevalence, effects on individuals and society, causes, diagnosis, mechanisms, treatment, and management, focusing on its association with environmental toxins.

The etiology of peripheral neuropathy is multifactorial, encompassing diverse causes such as diabetes mellitus, autoimmune diseases, infections, vitamin deficiencies, toxic exposures, and genetic factors. Notably, environmental toxins, including organic solvents, pesticides, and heavy metals, have been implicated in the pathogenesis of peripheral neuropathy.

Environmental toxins exert their neurotoxic effects through various mechanisms, including disruption of neuronal membrane integrity, interference with neurotransmission, induction of oxidative stress, and promotion of inflammatory responses.

Accurate diagnosis of peripheral neuropathy involves a comprehensive medical history, neurological examination, electrophysiological studies, imaging tests, and laboratory investigations to identify underlying causes, including environmental toxin exposure.

Treatment strategies for environmental toxin-induced peripheral neuropathy focus on eliminating exposure, managing symptoms, and preventing further nerve damage. Pharmacological interventions, adjunctive therapies, nutritional support, regular monitoring, and patient education are integral to management.

A multidisciplinary approach is fundamental for diagnosing and managing peripheral neuropathy effectively, emphasizing identifying and mitigating environmental toxin exposure to alleviate symptoms and improve quality of life.

**Keywords:** E-Waste, Mycotoxins, Nanoplastics, Oxidative Stress, Paresthesia, Peripheral Nerve Damage.

**Abbreviations:** BBB: Blood-Brain Barrier; EMG: Electromyography; GABA: Gamma-Aminobutyric Acid; MRI: Magnetic Resonance Imaging; NCSs: Nerve Conduction Studies; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; PFAS: Per- and Polyfluoroalkyl Substances; QoL: Quality of Life; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species.


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**Introduction**

Peripheral neuropathy is a disorder characterized by damage to the peripheral nerves, leading to symptoms such as numbness, tingling, and weakness in the extremities. This condition can affect sensory, motor, and autonomic nerves, resulting in a range of symptoms and functional impairments (Galiero et al., 2023).

The term “peripheral neuropathy” combines “peripheral” from the Greek word “periphereia,” which means “circumference” or “periphery,” referring to the peripheral nervous system (nerves outside the brain and spinal cord), and “neuropathy” from the Greek words “neuron” (nerve) and “pathos” (disease)—thus, meaning a disease affecting peripheral nerves.
The underlying causes of peripheral neuropathy are diverse. These causes include diabetes mellitus, autoimmune diseases, infections, vitamin deficiencies, toxic exposures (such as heavy metals or certain medications), and genetic factors. The pathological mechanisms involved in peripheral neuropathy often involve nerve damage, inflammation, and dysfunction of nerve signaling pathways (Laddad, Kakade, & Kumbhar, 2024; Staff & Windebank, 2014).

Diagnosis typically involves a thorough medical history and neurological examination, which may include nerve conduction studies (NCSs) and imaging tests to assess nerve function and identify underlying causes. Treatment aims to manage symptoms, address root causes, and prevent complications, often through medications, physical therapy, and lifestyle modifications (Laddad et al., 2024).

**History of Peripheral Neuropathy**

The history of peripheral neuropathy dates back to ancient times, describing similar symptoms found in ancient Egyptian, Greek, and Indian medical texts (Heydari et al., 2015). Notable figures in the study of neuropathy include Thomas Willis, who made significant contributions to the study of the nervous system in the 17th century, and Jean-Martin Charcot, who advanced the understanding of neurological disorders in the 19th century (Kumar, Aslinia, Yale, & Mazza, 2010; Molnár, 2004). Research studies over the years have contributed to advancements in diagnosing and treating peripheral neuropathy, including the discovery of specific nerve conduction abnormalities and the development of medications targeting neuropathic pain (Compston, 2009).

**Epidemiology and Prevalence**

Peripheral neuropathy is a common neurological disorder with a significant global health burden. Its prevalence varies with age, sex, and underlying conditions. According to Hicks and Selvin (2019), diabetes mellitus is a leading cause of peripheral neuropathy, affecting up to 50% of adults with diabetes during their lifetime. Other causes include autoimmune diseases, infections, and toxic exposures. The prevalence of peripheral neuropathy has increased due to the rising incidence of diabetes and aging populations. Underreporting and misdiagnosis challenge accurate assessment (Galiero et al., 2023; Hicks & Selvin, 2019).

Research by Castelli, Desai, and Cantone (2020) indicates that peripheral neuropathy affects 1% to 7% of the general population, with higher rates in those over 50. In people with diabetes, the prevalence ranges from 6% to 51% depending on age, duration of diabetes, glucose control, and type of diabetes (Hicks & Selvin, 2019).

Toxic neuropathies, a preventable cause of peripheral neuropathy, arise from environmental, occupational, recreational, or iatrogenic sources. While rare, toxic neuropathies are notable in workplace exposures and can stem from a wide range of agents, from prescribed medications to recreational drugs. Prevalence depends on geographical location, exposure levels, and economic factors (Little & Albers, 2015; Valentine, 2019).

**Peripheral Neuropathy’s Impact on Individual and Society**

Peripheral neuropathy can have a profound impact on the quality of life (QoL) of affected individuals and impose significant societal and healthcare burdens. Symptoms such as chronic pain, sensory loss, and motor dysfunction can impair daily activities, mobility, and overall well-being, leading to decreased QoL (Girach et al., 2019).

Peripheral neuropathy contributes to substantial healthcare costs, including expenses related to diagnostic tests, medications, hospitalizations, and rehabilitation services. The economic burden extends to insurance companies, disability insurance programs, and employers, who may bear the costs of lost productivity and work hours due to disability and absenteeism (Sadosky et al., 2014).
Discussion

Environmental Toxins: Impact on Human Body Systems

As an aggregate, environmental toxins exhibit a pervasive impact on the spectrum of human body systems (Annexure 1), contributing to a wide range of medical conditions (Annexure 2). These environmental toxins include airborne microplastics, mycotoxins, nanoplastics, per- and polyfluoroalkyl substances (PFAS), organic solvents, pesticides, heavy metals, and electronic waste (e-waste; Ruggles & Benakis, 2024).

E-waste from electrical and electronic devices is a growing contributor to hazardous environmental toxins. Table 1 lists specific types of environmental toxins associated with e-waste and their adverse effects on human health (Ankit et al., 2021; Needhidasan, Samuel, & Chidambaram, 2014).

<table>
<thead>
<tr>
<th>Specific Types of E-Waste</th>
<th>Adverse Effects on Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Can cause skin lesions, cancer, and cardiovascular diseases</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Exposure can cause lung disease and cancer</td>
</tr>
<tr>
<td>Brominated Flame Retardants</td>
<td>Disrupt endocrine function; can affect the nervous system</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Toxic to kidneys; can cause bone damage</td>
</tr>
<tr>
<td>Hexavalent Chromium</td>
<td>Carcinogenic; can cause respiratory problems</td>
</tr>
<tr>
<td>Lead</td>
<td>Damage to the nervous system, blood disorders, and kidney damage</td>
</tr>
<tr>
<td>Mercury</td>
<td>Affects the brain and kidneys; particularly harmful to developing fetuses</td>
</tr>
<tr>
<td>Polychlorinated Biphenyls</td>
<td>Carcinogenic; affects the immune, reproductive, nervous, and endocrine systems</td>
</tr>
</tbody>
</table>

Sources: Ankit et al., 2021; Needhidasan et al., 2014

Notably, three particular environmental toxins—organic solvents, pesticides, and heavy metals (from industrial and e-waste)—have not only been connected with diverse medical conditions but also explicitly linked to peripheral neuropathy (Table 2; Mitra et al., 2022; Rao, Jortner, & Sills, 2014).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Organic Solvents</th>
<th>Pesticides</th>
<th>Heavy Metals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Cardiac arrhythmias</td>
<td>Cardiac arrhythmias</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>Ischemic heart disease</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction (heart attack)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hormonal imbalances</td>
<td>Hormonal imbalances</td>
<td>Hormonal imbalances</td>
</tr>
<tr>
<td></td>
<td>Thyroid dysfunction</td>
<td>Thyroid dysfunction</td>
<td>Thyroid dysfunction</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastritis</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal irritation</td>
<td>Diarrhea</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Liver toxicity</td>
<td>Gastrointestinal irritation</td>
<td>Gastrointestinal irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Immune</td>
<td>Immunotoxicity</td>
<td>Immunotoxicity</td>
<td>Autoimmune disorders</td>
</tr>
</tbody>
</table>

Table 2. Adverse Effects of Organic Solvents, Pesticides, and Heavy Metals on Human Body Systems - Diverse Conditions and Distinct Link to Peripheral Neuropathy
Increased susceptibility to infections & Immunotoxicity

<table>
<thead>
<tr>
<th>Integumentary</th>
<th>Increased susceptibility to infections</th>
<th>Increased susceptibility to infections</th>
<th>Immunotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis</td>
<td>Dermatitis</td>
<td>Dermatitis</td>
<td></td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Skin irritation</td>
<td>Skin irritation</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle atrophy</td>
<td>Muscle atrophy</td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Muscle weakness</td>
<td>Muscle weakness</td>
<td></td>
</tr>
<tr>
<td>Nervous</td>
<td>Cognitive impairment</td>
<td>Cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Dizziness</td>
<td>Developmental delays</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Headaches</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Neutrotoxicity</td>
<td>Neurotoxicity</td>
<td>Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Neurotoxicity</td>
<td>Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Kidney damage</td>
<td>Kidney damage</td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>Hormonal disturbances</td>
<td>Birth defects</td>
<td></td>
</tr>
<tr>
<td>Reduced fertility</td>
<td>Developmental abnormalities</td>
<td>Developmental abnormalities</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td></td>
</tr>
<tr>
<td>Respiratory irritation</td>
<td>Pulmonary fibrosis</td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory irritation</td>
<td>Respiratory irritation</td>
<td></td>
</tr>
</tbody>
</table>

Sources: Mitra et al., 2022; Rao et al., 2014

Environmental Toxins Linked to Peripheral Neuropathy: Mechanisms of Action

Organic solvents, commonly found in industrial settings, can damage peripheral nerves through direct neurotoxic effects, disrupting neuronal membrane integrity and function. Pesticides, widely used in agriculture, can cause peripheral neuropathy through mechanisms leading to impaired nerve signal transmission. Heavy metals like arsenic, cadmium, lead, and mercury, prevalent in industrial pollutants and e-waste, can induce peripheral neuropathy by disrupting neuronal ion channels, promoting oxidative stress, and triggering inflammatory responses. These toxins’ cumulative and prolonged exposure exacerbates the risk and severity of peripheral neuropathy (Mitra et al., 2022; Rao, Jortner, & Sills, 2014).

Environmental toxins can induce peripheral neuropathy through mechanisms involving direct penetration of the blood-brain barrier (BBB; Annexure 3) or actions occurring outside the central nervous system (Valentine, 2019; Wu et al., 2023).

**Organic Solvents**

At the cellular level, these organic solvents interfere with lipid bilayers, causing membrane fluidity and permeability alterations. This disruption compromises the structural integrity of neuronal membranes, leading to increased susceptibility to damage and impaired cellular signaling (Ayala, Muñoz, & Argüelles, 2014; Van Thriel & Boyes, 2022).

At the functional level, organic solvents interfere with vital neuronal processes such as neurotransmitter release, synaptic transmission, and ion channel function. These solvents disrupt the balance of neurotransmitters, including gamma-aminobutyric acid (GABA) and glutamate, which are crucial for
maintaining neuronal excitability and inhibition. Also, organic solvents interfere with ion channels’ activity, including voltage-gated sodium and potassium channels—essential for generating action potentials and propagating neuronal signals (Van Thriel & Boyes, 2022).

Organic solvents induce oxidative stress within neurons by promoting the generation of reactive oxygen species (ROS) and impairing antioxidant defense mechanisms. This oxidative stress leads to neuronal damage, protein and lipid oxidation, and mitochondrial dysfunction, exacerbating neuronal injury and dysfunction. Collectively, organic solvents’ disruption of neuronal membrane integrity and function underscores their neurotoxic potential (Van Thriel & Boyes, 2022).

**Pesticides**

At the cellular level, pesticides disrupt neuronal communication by targeting critical neurotransmission components, such as neurotransmitter synthesis, release, and receptor activation. Pesticides can interfere with neurotransmitter synthesis by inhibiting enzymes—tyrosine hydroxylase, tryptophan hydroxylase, choline acetyltransferase, and glutamic acid decarboxylase—responsible for neurotransmitter production, leading to imbalances in neurotransmitter levels within the synaptic cleft (Wen et al., 2023).

Pesticides can disrupt neurotransmitter release by interfering with exocytosis, whereby neurotransmitter-containing vesicles fuse with the presynaptic membrane and release their contents into the synaptic cleft. This disruption impairs neurons’ ability to transmit signals across synapses, leading to aberrant neuronal communication (Vester & Caudle, 2016).

At the functional level, pesticides can interfere with neurotransmitter receptor activation by binding to receptors on the postsynaptic membrane and either mimicking or blocking the actions of endogenous neurotransmitters—dopamine, norepinephrine, serotonin, acetylcholine, and GABA. By altering neurotransmitter receptor activity, pesticides can disrupt the propagation of nerve signals, leading to synaptic dysfunction and impaired neuronal communication (Vester & Caudle, 2016; Wen et al., 2023).

Oxidative stress is another significant mechanism by which pesticides disrupt nerve signal transmission. Pesticides generate ROS and reactive nitrogen species (RNS), which can damage cellular components, including lipids, proteins, and DNA. This oxidative damage impairs mitochondrial function, leading to energy deficits in neurons, which are highly dependent on oxidative phosphorylation for energy production. Dysfunctional mitochondria cannot sustain the high energy demands of neuronal activity, resulting in impaired nerve signal transmission (Sule, Condon, & Gomes, 2022).

**Heavy Metals**

**Disrupting Neuronal Ion Channels**

At a cellular level, heavy metals interfere with ion channels, specialized proteins in the cell membrane that regulate the flow of ions such as sodium, potassium, calcium, and chloride. These ions play crucial roles in maintaining the electrical potential across the neuronal membrane, essential for proper nerve function, signal transmission, and neurotransmitter release (Carmona, Roudeau, & Ortega, 2021).

Heavy metals disrupt ion channel function by binding to specific sites on the channels or altering their structure, leading to aberrant ion flux. This disruption impairs the generation and propagation of action potentials along the nerve fibers, resulting in altered neuronal excitability and impaired signal transmission (Carmona et al., 2021).

At the functional level, heavy metals’ perturbation of ion channels contributes to nerve hyperexcitability, aberrant firing patterns, and impaired synaptic transmission, ultimately leading to peripheral neuropathy. These mechanisms highlight the intricate relationship between heavy metal exposure and the pathogenesis of peripheral neuropathy, emphasizing the importance of mitigating environmental heavy
metal contamination to prevent associated neurological disorders (Carmona et al., 2021; Pamphlett & Bishop, 2023).

**Promoting Oxidative Stress**

At a cellular level, heavy metals disrupt the balance between ROS production and antioxidant defenses within neuronal cells. Excessive ROS generation overwhelms the cell’s antioxidant systems, leading to oxidative damage to cellular components such as proteins, lipids, and DNA. This oxidative damage impairs neuronal function, disrupts cellular signaling pathways, and compromises cellular integrity (Carmona et al., 2021).

At the functional level, heavy metals promote oxidative stress, exacerbating neuronal injury and dysfunction and further contributing to the pathogenesis of peripheral neuropathy. Additionally, oxidative stress induced by heavy metals, involving the release of pro-inflammatory cytokines and activation of immune cells in the nervous system, triggers inflammatory responses. These inflammatory processes further exacerbate neuronal damage and contribute to the progression of peripheral neuropathy (Carmona et al., 2021; Pyatha, Kim, Lee, & Kim, 2022).

**Triggering Inflammatory Responses**

At the cellular level, exposure to heavy metals stimulates immune cells, including microglia and astrocytes in the nervous system, as well as peripheral immune cells. These immune cells release pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, in response to heavy metal-induced cellular stress and damage. These cytokines propagate inflammation by recruiting additional immune cells to the injury site and amplifying the inflammatory response (Carmona et al., 2021; Pamphlett & Bishop, 2023; Pyatha et al., 2022).

At the functional level, the inflammatory cascade initiated by heavy metals leads to tissue damage, including neuronal injury, demyelination, and axonal degeneration. Moreover, chronic inflammation contributes to the perpetuation of neuropathic pain and the progression of peripheral neuropathy by sensitizing nociceptive neurons and altering synaptic transmission within the central nervous system (Koszewicz et al., 2021; Pamphlett & Bishop, 2023).

**Differential Diagnosis: Causes of Peripheral Neuropathy**

**Inherited Causes of Peripheral Neuropathy**

Inherited peripheral neuropathies encompass a diverse group of disorders characterized by dysfunction of the peripheral nervous system, resulting in progressive sensory, motor, and autonomic deficits. These conditions often arise from genetic mutations affecting various nerve structure and function components (Van Lent et al., 2024).

Identification and testing for inherited peripheral neuropathies involve a comprehensive evaluation encompassing clinical history, physical examination, electrophysiological studies, and genetic testing. Clinical assessment aims to identify characteristic features such as onset, pattern of progression, distribution of symptoms, and associated systemic manifestations (Korinthenberg et al., 2021; Lehmann, Wunderlich, Fink, & Sommer, 2020).

Physical examination may reveal neurological deficits, including muscle weakness, sensory loss, and abnormalities in reflexes. Electrophysiological studies, such as nerve conduction studies and electromyography (EMG), aid in assessing nerve conduction velocity and muscle activity and detecting demyelination or axonal damage (Korinthenberg et al., 2021; Lehmann, Wunderlich, Fink, & Sommer, 2020).

Genetic testing is pivotal in confirming the diagnosis by identifying specific mutations associated with hereditary neuropathies (Table 3). Advancements in genetic sequencing technologies have facilitated
targeted testing for known mutations and expanded the understanding of genotype-phenotype correlations (Korinthenberg et al., 2021; Lehmann et al., 2020).

### Table 3. Specific Hereditary Neuropathies and Their Mutations and Biomarkers

<table>
<thead>
<tr>
<th>Hereditary Neuropathy</th>
<th>Specific Mutation</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charcot-Marie-Tooth type 1A (CMT1A)</td>
<td>PMP22</td>
<td>Increased PMP22 gene dosage, PMP22 protein detection in nerve biopsy</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth type 2A (CMT2A)</td>
<td>MFN2</td>
<td>Mutation in MFN2 gene</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth type 1B (CMT1B)</td>
<td>MPZ</td>
<td>Mutation in MPZ gene</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth type 2E (CMT2E)</td>
<td>NEFL</td>
<td>Mutation in NEFL gene</td>
</tr>
<tr>
<td>X-linked Charcot-Marie-Tooth (CMTX)</td>
<td>GJB1</td>
<td>Mutation in GJB1 gene</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth type 2F (CMT2F)</td>
<td>HSPB1</td>
<td>Mutation in HSPB1 gene</td>
</tr>
</tbody>
</table>

Sources: Korinthenberg et al., 2021; Lehmann et al., 2020; Morena, Gupta, & Hoyle, 2019; Van Lent et al., 2024; Van Paassen et al., 2014

A multidisciplinary approach integrating clinical, electrophysiological, and genetic assessments is essential for accurate diagnosis and tailored management of inherited peripheral neuropathies.

**Acquired Causes of Peripheral Neuropathy**

Diverse medical conditions can cause peripheral neuropathy, each affecting the peripheral nerves differently. Some of the primary conditions associated with peripheral neuropathy include the following:

- **Alcoholism**: Chronic alcohol abuse can lead to nutritional deficiencies and direct nerve toxicity, causing alcoholic neuropathy (Lehmann et al., 2020).

- **Autoimmune diseases**: Conditions like rheumatoid arthritis, lupus, and Guillain-Barré syndrome can cause inflammation that damages peripheral nerves (Lehmann et al., 2020).

- **Cancers and paraneoplastic syndromes**: Some cancers and associated paraneoplastic syndromes can cause neuropathy through direct nerve invasion or immune-mediated mechanisms (Anwar, Jafri, Ashraf, Jafri, & Fanucchi, 2019; Lehmann et al., 2020).

- **Chemotherapy**: Certain chemotherapy drugs, such as cisplatin, vincristine, and paclitaxel, can cause toxic neuropathy as a side effect of cancer treatment (Lehmann et al., 2020; Pollard, Bolon, & Moore, 2021).

- **Chronic inflammatory demyelinating polyneuropathy**: A chronic autoimmune disorder that results in nerve inflammation and damage (Lehmann et al., 2020; Rodríguez et al., 2019).

- **Chronic kidney disease**: Uremia, a condition associated with advanced kidney disease, can lead to peripheral nerve damage due to the accumulation of toxins (De Camargo et al., 2019).

- **Diabetes mellitus**: The most common cause of peripheral neuropathy. High blood sugar levels can damage nerves, particularly in the hands and feet, leading to diabetic neuropathy (Lehmann et al., 2020).

- **Hypothyroidism**: An underactive thyroid gland can lead to peripheral neuropathy due to metabolic changes (Brzozowska, Banthia, Thompson, Narasimhan, & Lee, 2021).

- **Infections**: Certain infections, such as Lyme disease, HIV/AIDS, shingles (herpes zoster), and hepatitis C, can directly infect and damage peripheral nerves (Brizzi & Lyons, 2014; Lehmann et al., 2020).
• Trauma and nerve compression: Physical injury, repetitive stress, and conditions like carpal tunnel syndrome can cause localized peripheral neuropathy (Omole et al., 2023).

• Vitamin deficiencies: Deficiencies in vitamins B1 (thiamine), B6 (pyridoxine), B12 (cobalamin), and E can lead to nerve damage (Lehmann et al., 2020; Staff & Windebank, 2014).

• Exposure to toxins: Industrial and e-waste heavy metals (e.g., arsenic, cadmium, lead, and mercury), organic solvents, and some pesticides can cause nerve damage (Lehmann et al., 2020; Staff & Windebank, 2014).

Thus, it is crucial to differentially diagnose accurately—utilizing medical screening, laboratory work, and diagnostic tests—to identify the root cause of peripheral neuropathy and determine the most effective treatment.

It is essential to consider that multiple factors can contribute to peripheral neuropathy symptoms, such as environmental toxin exposure and one or more conditions associated with peripheral neuropathy (per above).

**Environmental Toxin Exposure: Linked to Peripheral Neuropathy**

An approach to identify potential toxins and assess nerve damage in patients with peripheral neuropathy includes medical screening, laboratory work, and diagnostic tests. This process typically begins with a thorough medical history and physical examination, focusing on occupational and environmental exposures to organic solvents, pesticides, or heavy metals (Castelli et al., 2020; Lehmann et al., 2020; Smyth, Kramarz, Carr, Rossor, & Lunn, 2023).

Clinical evaluation involves neurological examinations to assess sensory, motor, and autonomic nerve functions, potentially revealing symptoms such as numbness, tingling, weakness, and pain. Laboratory tests may include screening for specific solvent metabolites, pesticide biomarkers, or heavy metal levels in the body (Castelli et al., 2020; Lehmann et al., 2020; Smyth, Kramarz, Carr, Rossor, & Lunn, 2023).

- **Organic solvents:** Laboratory tests may incorporate blood and urine analyses to detect levels of specific solvents and their metabolites, such as acetone, benzene, dichloromethane, ethanol, ethyl acetate, methyl ethyl ketone, tetrachloroethylene (perchloroethylene), toluene, trichloroethylene, and xylene, though these tests may not always accurately reflect recent exposures (Joshi & Adhikari, 2019; Xiao & Levin, 2000).

- **Pesticides:** Laboratory tests may comprise a complete blood count to evaluate for leukocytosis or anemia, liver function tests to assess hepatic involvement, and renal function tests to detect kidney damage. Blood and urine samples may also be analyzed for pesticide metabolites or biomarkers to confirm exposure (Bunsri, Muenchmann, Naksen, & Ong-Arthorirak, 2023; Castelli et al., 2020; Smyth et al., 2023). These pesticide metabolites or biomarkers include 3-phenoxynbenzoic acid, dichlorodiphenyldichloroethylene, dichlorodiphenyltrichloroethane, dialkyl phosphates, dimethoate, ethylene thiourea, and glyphosate (Ueyama et al., 2022).

- **Heavy metals (industrial and e-waste):** Laboratory work includes blood and urine tests to measure levels of heavy metals, with blood tests assessing recent or acute exposure and urine tests detecting ongoing or chronic exposure. Specific heavy metals, such as arsenic, cadmium, lead, and mercury, are measured using atomic absorption spectrometry, inductively coupled plasma mass spectrometry, or other specialized analytical techniques. Hair and nail samples may also be analyzed to assess long-term exposure. Imaging studies, such as X-rays and bone density scans, may be performed to evaluate the skeletal accumulation of specific heavy metals (Lehmann et al., 2020; Saadatzadeh et al., 2019; Smyth et al., 2023).
Diagnostic tests for peripheral neuropathy include nerve conduction studies (NCSs) and EMG to assess nerve function and detect abnormalities in electrical signaling. These tests are crucial for evaluating nerve conduction velocity and identifying signs of peripheral neuropathy (Lehmann et al., 2020; Smyth et al., 2023). Imaging modalities such as magnetic resonance imaging (MRI) or nerve ultrasound may be utilized to assess nerve structure and rule out other potential neuropathy causes (Lehmann et al., 2020).

A comprehensive, multidisciplinary approach integrating clinical evaluation, laboratory investigations, and specialized neurophysiological testing is essential for diagnosing peripheral neuropathy associated with organic solvents, pesticides, and heavy metals. These diagnostic strategies aim to identify the presence of toxins and assess their contribution to neuropathy, guiding appropriate management and intervention strategies.

**Peripheral Neuropathy Caused by Environmental Toxins: Treatment and Management**

Treatment and management of peripheral neuropathy caused by environmental toxins involve a multifaceted approach targeting the underlying cause, alleviating symptoms, and preventing further exposure.

**Identify and Eliminate the Source of Environmental Toxin Exposure**

Identifying and eliminating the source of environmental toxin exposure often involves modifying workplace practices, using protective equipment, and ensuring adequate ventilation in industrial settings. Removing the patient from the contaminated environment is critical in severe exposure (National Research Council, 2011).

**Pharmacological Interventions**

Pharmacological interventions are used to manage symptoms and improve quality of life (QoL). Pain relief is typically achieved using medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants (e.g., gabapentin and pregabalin), and FDA-approved and off-label use of antidepressants— duloxetine and amitriptyline, respectively (Cohen, Shinkazh, Frank, Israel, & Fellner, 2015; Rafiullah & Siddiqui, 2022).

In cases of severe pain, opioids may be considered, although their use is generally limited due to the risk of dependency. Topical treatments, such as capsaicin cream or lidocaine patches, can provide localized pain relief (Cohen et al., 2015; Rafiullah & Siddiqui, 2022). More contemporaneously, BOTOX injections and patches are sometimes used to eliminate or lessen peripheral neuropathy symptoms (Kerna et al., 2024).

**Adjunctive Therapies**

Adjunctive therapies include physical and occupational therapy, which help maintain muscle strength, improve coordination, and adapt daily activities to minimize discomfort. These therapies often incorporate exercises to enhance balance and prevent falls, common in patients with peripheral neuropathy (French, Abbott, & Galvin, 2022; Williams et al., 2018).

**Nutritional Support**

Nutritional support is crucial, particularly if deficiencies in essential vitamins and minerals compound the neuropathy. Supplementation with vitamins B1 (thiamine), B6 (pyridoxine), B12 (cobalamin), and E can support nerve health and function. Dietary modifications to ensure adequate intake of these nutrients are often recommended (Calderón-Ospina & Nava-Mesa, 2019; Staff & Windebank, 2014).

**Monitoring and Regular Follow-Up**

Monitoring and regular follow-up are essential components of management, as they allow for the adjustment of treatment plans based on the patient’s progress and response to therapy. Routine
assessments of nerve function and periodic evaluations of the patient’s occupational environment are necessary to minimize exposure risk (Pop-Busui et al., 2022).

**Education and Counseling**

Education and counseling play a vital role in the long-term management of patients with environmental toxin-induced peripheral neuropathy. Patients should be informed about the nature of their condition, the importance of avoiding further exposure, and strategies for managing symptoms effectively. Referral to support groups and mental health services can provide additional support, helping patients cope with the psychological impact of chronic pain and disability (Joypaul, Kelly, McMillan, & King, 2019).

Table 4 depicts the treatment and management strategies for environmental toxin-induced peripheral neuropathy.

<table>
<thead>
<tr>
<th>Category</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify and Eliminate Source</td>
<td>Modify workplace practices, use protective equipment, ensure ventilation, remove patients from contaminated environments if severely exposed</td>
</tr>
<tr>
<td>Pharmacological Interventions</td>
<td>NSAIDs, anticonvulsants (gabapentin, pregabalin), antidepressants (duloxetine, amitriptyline), opioids (limited use), topical treatments (capsaicin cream, lidocaine patches), BOTOX</td>
</tr>
<tr>
<td>Adjunctive Therapies</td>
<td>Physical and occupational therapy to maintain muscle strength, improve coordination, adapt daily activities, enhance balance, and prevent falls</td>
</tr>
<tr>
<td>Nutritional Support</td>
<td>Supplement vitamins B1, B6, B12, and E; dietary modifications to ensure adequate intake of these nutrients</td>
</tr>
<tr>
<td>Monitoring and Regular Follow-Up</td>
<td>Routine assessments of nerve function, periodic evaluations of occupational environment, adjust treatment plans based on progress</td>
</tr>
<tr>
<td>Education and Counseling</td>
<td>Inform about condition, avoiding further exposure, managing symptoms, referral to support groups and mental health services for coping with chronic pain and disability</td>
</tr>
</tbody>
</table>

Overall, environmental toxin-induced peripheral neuropathy treatment and management involve eliminating exposure, pharmacological and non-pharmacological interventions, nutritional support, regular monitoring, and patient education to alleviate symptoms, improve quality of life, and prevent further nerve damage.

**Conclusion**

Peripheral neuropathy presents a multifaceted challenge characterized by damage to peripheral nerves, manifesting in various sensory, motor, and autonomic symptoms. Its underlying causes are diverse, spanning from metabolic disorders to toxic exposures, as well as hereditary causes.

A detailed understanding of the mechanisms by which environmental toxins induce neuropathy reveals intricate cellular and functional disruptions, highlighting potential targets for therapeutic interventions. Diagnosis requires a meticulous approach, integrating clinical evaluation, laboratory investigations, and specialized neurophysiological testing to identify the underlying cause accurately.

Treatment and management strategies for environmental toxin-induced neuropathy encompass a comprehensive approach, including eliminating exposure, pharmacological interventions for symptom management, adjunctive therapies, nutritional support, and regular monitoring. Patient education and
counseling enhance long-term management outcomes and enable individuals to understand their condition better and reduce further risk.

A collaborative strategy in addressing peripheral neuropathy caused by environmental toxins integrates scientific understanding, clinical expertise, and patient-centered care to mitigate its impact on individuals and society.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References


Annexures

Annexure 1. Human Body Systems Exposed to Environmental Contaminants

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</tbody>
</table>

**Legend:** ● distinctly linked to adverse effects in specific human body systems

**Abbreviations:** MP: Microplastics; PFAS: Per- and Polyfluoroalkyl Substances

**Sources:** Ali et al., 2024; Ankit et al., 2021; Fenton et al., 2020; Joshi & Adhikari, 2019; Mitra et al., 2022; Nicolopoulou-Stamati, Maipas, Kotampasi, Stamatis, & Hens, 2016; Omotayo, Omotayo, Mwanza, & Babalola, 2019; Prata, 2018; Van Thriel & Boyes, 2022; Verma & Sharma, 2017

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**References**


### Annexure 2. Environmental Toxins and Specific Related Medical Conditions

<table>
<thead>
<tr>
<th>Environmental Toxin</th>
<th>Medical conditions</th>
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<tbody>
<tr>
<td>Airborne Microplastics</td>
<td>Asthma, lung inflammation</td>
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<tr>
<td>Heavy Metals (Industrial)</td>
<td>Hypertension, atherosclerosis, neurological disorders, cognitive impairment</td>
</tr>
<tr>
<td>Heavy Metals (E-Waste)</td>
<td>Gastritis, liver damage, neurological disorders, developmental delays</td>
</tr>
<tr>
<td>Mycotoxins</td>
<td>Allergic rhinitis, asthma, neurological disorders, headaches</td>
</tr>
<tr>
<td>Nanoplastics</td>
<td>Skin irritation, dermatitis, hormonal imbalance, infertility</td>
</tr>
<tr>
<td>Organic Solvents</td>
<td>Neurological disorders, memory impairment, dermatitis, skin sensitization</td>
</tr>
<tr>
<td>Pesticide</td>
<td>Hormonal imbalance, thyroid disorders, muscle weakness, neuromuscular disorders</td>
</tr>
<tr>
<td>PFAS</td>
<td>Liver damage, kidney damage, suppressed immune function, autoimmune disorders</td>
</tr>
</tbody>
</table>

**Sources:** Ali et al., 2024; Ankit et al., 2021; Dick, 2006; Fenton et al., 2020; Haider, Fatema, Shoily, & Sajib, 2023; Hyvönen et al., 2020; Kori, Singh, Jain, & Yadav, 2018; Nicolopoulou-Stamati et al., 2016; Saha & Saha, 2024; Ueyama et al., 2022

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### References


Annexure 3. Mechanisms by Which Specific Environmental Toxins Cross the Blood-Brain Barrier

Environmental toxins penetrate the blood-brain barrier (BBB) through several mechanisms, which include:

1. **Passive Diffusion**: Small, lipophilic (fat-soluble) molecules can diffuse directly through the endothelial cells of the BBB. This process does not require energy and depends on the toxin’s concentration gradient and lipid solubility (Alajangi et al., 2022; Sun et al., 2023).

2. **Transporter-Mediated Processes** (Alajangi et al., 2022; Barar, Rafi, Pourseif, & Omidi, 2016):
   - **Active Transport**: Certain toxins can utilize transporters that typically carry essential nutrients or other molecules into the brain.
   - **Carrier-Mediated Transport**: Some toxins mimic substances naturally transported across the BBB, such as glucose or amino acids, and use the corresponding carrier proteins to gain entry.

3. **Endocytosis and Transcytosis** (Alahmari, 2021; Alajangi et al., 2022):
   - **Receptor-Mediated Endocytosis**: Toxins that can bind to specific receptors on the endothelial cells can be engulfed and transported across the BBB.
   - **Adsorptive-Mediated Transcytosis**: Positively charged toxins can bind to negatively charged sites on the cell surface, leading to endocytosis and subsequent transcytosis across the BBB.

4. **Disruption of the BBB** (Alajangi et al., 2022; Takata, Nakagawa, Matsumoto, & Dohgu, 2021): Some toxins can cause damage to the BBB, making it more permeable. This damage can happen through:
- **Inflammation**: Toxins that induce an inflammatory response can produce cytokines and other inflammatory mediators that disrupt tight junctions between endothelial cells.

- **Oxidative Stress**: Reactive oxygen species (ROS) generated by certain toxins can damage endothelial cells and tight junction proteins, increasing BBB permeability.

5. **Leukocyte-Mediated Transport**: Toxins can also enter the brain by attaching to or being carried by immune cells. During inflammation, immune cells can cross the BBB, carrying toxins into the brain (Alajangi et al., 2022; Fukuta, Oku, & Kogure, 2022; Li et al., 2021; Takata et al., 2021).

![Transport Routes Facilitating Access Across the Blood-Brain Barrier](image-url)


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References


