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A Perspective Review on Role of Environmental Pollutants in Developing Neurodegenerative Diseases

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Abstract

As human society progresses towards industrialization, an excess number of environmental pollutants are released into our ecosystem, which significantly contributes to causing various health issues primarily associated with neurodegenerative diseases such as cognitive disorder, dementia, anxiety, Alzheimer's, Parkinson's, etc. Because of their high global occurrence, these diseases have attracted attention in recent decades, however, the etiology of these diseases remains unclear. Pollutants are discharged into the environment by natural events such as volcanic eruptions and wildfires, as well as by man-made activities such as industrial and laboratory waste, pesticide residues, automotive exhaust and the burning of terrestrial waste that pollute the water, air and soil, causing neurological diseases in inhabitants. These pollutants enter the body by inhalation, oral absorption and ingestion and reach to the central nervous system (CNS), where they induce tissue damage and disrupt molecular and cellular processes. Recent epidemiological studies have focused on the neurodevelopmental effects of organic solvents and pesticides on children born to female workers, highlighting potential neurobehavioral impairments. Despite the lack of evidence for other presumed neurotoxicants, prioritizing the protection of pregnant workers remains crucial, urging a precautionary approach to neurodevelopmental toxicity in occupational health. Numerous investigations on humans, animal models and cell cultures have shown how these pollutants affect the blood-brain barrier, causing neuroinflammation, CNS oxidative stress, neurodegeneration and cerebrovascular system damages. The current review discusses diverse sources of pollutants, their neurotoxic effect, molecular mechanisms of distinct pollutants involved in the etiology of various neurological diseases, and their management strategy. In addition, this study intends to address the current understanding of the relationship between environmental toxins and human health to bridge this knowledge gap.

Keywords: Pollutants, sources, neurodegenerative diseases, human health, management strategy

INTRODUCTION

The alarming rise in the rapid industrialization of rural areas and the excessive use of toxicants, including pesticides, hazardous solvents, heavy metals and automobile exhausts, have imposed a chemical load on society and shown significant risk factors for the progression of environmental pollution [1,2]. Environmental pollution refers to any deterioration in the physical, chemical and biological quality of the environment [3]. Environmental pollutants, also known as xenobiotic substances, are released into the environment by humans at higher quantities than "natural levels". Pollutants are typically categorized as biodegradable or non-biodegradable. Biodegradable pollutants include sewage effluents and organic waste that degrade easily under normal conditions. Heavy metals, plastics and detergents are examples of non-biodegradable compounds

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because microbes do not digest them [4]. Toxic chemicals are widely released into nature due to increased industrial growth and urban migration [5]. These toxic chemicals, whether they are released directly or indirectly, have a harmful impact on human health [6]. Many people worldwide are constantly exposed to pollutants at levels that exceed permissible ranges [7]. Environmental pollutants have a substantial effect on human disease, climatic change and public health, leading to higher death and morbidity rates. There is a lack of information on pollution exposure in less developed nations due to poor waste management, poverty and restricted adoption of new technologies. Further research is needed to understand the link between pollutants and health impacts. In many affluent countries, remedies are only identified after harm has occurred and protections are no longer necessary. The relationship between environmental toxins and health remains unclear due to challenges in estimating exposure levels and insufficient systematic monitoring. Pollutants can cause both acute and chronic diseases [8]. Acute consequences include nose, eyes, skin and throat coughing, irritation, headaches, dizziness and nausea, as well as serious illnesses such as asthma, bronchitis and lung/heart difficulties. Chronic diseases include reproductive, cardiovascular, respiratory and neurological [9]. These pollutants mostly damage the heart and lungs, which can lead to several respiratory and cardiovascular issues. Nonetheless, it is well-established that these are linked to neurological conditions like epilepsy, Parkinson's disease, stroke and Alzheimer's [10].

Neurodegenerative diseases typically impair both mental and physical abilities. The majority of neurodegenerative diseases are intrinsically tied to aging, with the chance of gradually expanding as one gets older [11,12]. Neurodegenerative disorders are categorized based on clinical presentation, with extrapyramidal and pyramidal movement abnormalities, which include the most common, cognitive or behavioral impairments [13]. Neurodegeneration refers to the loss of neural structure and function, which are linked to a wide range of disorders such as dementia, Parkinson's disease (PD), epilepsy, stroke, Alzheimer's disease (AD), schizophrenia and amyotrophic lateral sclerosis (ALS) [13,14]. AD affects one in every 10 people over 65 years old, and its prevalence rises with age [13]. In the present era, medical advances have significantly boosted the average life expectancy. As a result, the incidence of neurological diseases is expected to increase at a certain point in age, mostly in older age. The majority of such diseases continue to have two primary concerns: 1) determining the root cause in the majority of cases, and 2) discovering therapeutic medications. Unfortunately, after extensive research, none of these issues have been resolved [15].

Environmental, genetic and social factors play a significant role in behavior and cognitive development. Heredity is responsible for around 50% of the variability in cognitive, behavioral and personality traits. This confirms that environmental factors may account for 50% of the variance [16]. Pollutants in the environment have been linked to higher rates of unfavorable pregnancy results, including low birth weight, preterm delivery, intrauterine growth retardation and birth abnormalities [10]. During the first few weeks of fetal development, when the organs primordial are forming, susceptibility is most noticeable. During this vulnerable time, exposure to environmental toxins may cause long-term changes in behavior, metabolism and anatomy. At any given stage of a person's life, from infancy to aging, this abnormality may develop as a short- or long-term condition. According to WHO 2022, environmental contaminants cause about 7 million deaths annually and contribute to 24% of diseases [17]. According to a report published by the Global Burden of Disease (GBD) 2015, neurological disorders are now the second leading cause of death after cardiovascular diseases, i.e., 16·5% of all deaths. They are also a major cause of disability globally, with attributable disability-adjusted life years reaching 11·6% [18]. In an effort to minimize the aforementioned sources of environmental pollution, the governments have established techniques for preventing or limiting any existing repercussions by proper disposal and/or burying of garbage [19]. Further research is required to address methodological and practical issues to regulate the impact of pollutants on pathophysiologic processes that contribute to disease onset and progression.

The present chapter emphasizes the nervous system's susceptibility to environmental toxicity and seeks to gather information on human neurotoxicity from toxic chemicals. The link between pollutants

and neurological diseases has gained attention in recent years. This chapter discusses environmental pollutants, their types, sources, neurological consequences, pathways, processes, preventive strategies and experimental links between exposure and neurological diseases. It also seeks to analyze and research the potential effects of environmental toxins on an individual's neural functions and discuss how neurodegenerative diseases impact humans' social and economic status and emphasize the importance of balancing environmental pollutants uses with health concerns.

POLLUTANTS: SOURCES AND THEIR ROUTES

A xenobiotic or pollutant is a foreign chemical compound that exceeds acceptable concentrations in an organism or the environment. These pollutants are present everywhere, but it's crucial to know how and where they release themselves into the environment. Improved knowledge of their sources and their routes of exposure will enable us to create novel strategies to reduce their release or emission [20]. In general, these pollutants come from both natural and man-made sources. Natural sources are those that occur naturally in the environment, such as volcanic eruptions, forest fires, dust storms and decay of organic matter. Man-made sources are those that result from human activities, such as industrial emissions, agricultural runoff, urban waste and transportation [21]. Environmental pollutants can come from air, water, land, food, noise, and through radioactive emissions. The primary sources include power stations, automotive emissions, pesticides, medical laboratories, burning trash, chemical industries and released volcanic eruption gases such as sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen monoxide (NO), heavy metals, ozone, biological pollutants, tobacco and smoke are discharged into the environment and affect targets and non-target species, including humans [22, 8].

Developing countries often use very harmful chemicals generated by industries to increase yields from agriculture [23]. Most environmental pollutants come from five major industrial sectors: chemical and synthetic industries, petroleum refining, coal conversion and steel mining, textile manufacturing and paper milling [24,25]. The environment's exposure to chemicals is not just the fault of industry but consumers also have some responsibility. Customers who use pesticides, fertilizers, aerosol sprays and petrol discharge toxins into the environment directly [26, 4]. The response to different pollutant exposures is determined by the individual's genetic traits. This complicated relationship is linked to the development and progression of allergy disorders; however, the timing, amount of exposure and route of allergen exposure also have an impact on disease progression and symptom intensity [27]. Humans can be exposed to environmental pollutants through various exposure routes, such as inhalation, ingestion, dermal contact, or injection. The route of exposure determines the amount and duration of the pollutants in the body, as well as the potential health risks [28]. Some factors that influence the route of exposure are the physical and chemical properties of the xenobiotic, the environmental conditions, and the behavior and characteristics of the exposed individual. For example, volatile organic compounds (VOCs) can easily evaporate and enter the air, where they can be inhaled by humans. Heavy metals, such as mercury and lead, can accumulate in soil and water, where they can be ingested by humans or animals. Pesticides and herbicides can be absorbed through the skin or mucous membranes when humans come into contact with treated crops or surfaces. Drugs and vaccines can be injected into the bloodstream or muscles, where they can have direct effects on the target organs or tissues [29,30]. Over the past 30 years, there has been a growing global concern over environmental pollutants impact on public health [31]. Environmental pollutants are considered to be the second greatest cause of noncommunicable diseases after smoking, contributing to the progression of various diseases related to respiratory, cardiovascular and neurological diseases, as well as cancer [32].

MAJOR POLLUTANTS CAUSING NEURODEGENERATIVE DISEASES

In recent decades, advancements in healthcare have led to increasing life expectancy [33]. However, due to these advancements in modern era, various pollutants are consecutively released into the environment [16]. This has led to an increase in the chronic neurotoxicity conditions such as Alzheimer's, cognitive disorders, Parkinson's neurovascular disease, i.e., brain aneurysms, autism spectrum disorder (ASD), attention deficit hyperactive disorder (ADHD) and intellectual disability [34].

Neurodegenerative diseases are influenced by both genetic and environmental factors, highlighting the need for further research to identify environmental risk factors that contribute to their development [33]. Air pollutants promote inflammation in the lungs and brain, disrupting the CNS's healthy function [15]. The nervous system is the most important organ in the body, with complex and complicated links to all other organs and systems. Trauma, genetic abnormalities and exposure to environmental toxins affect normal nerve conduction in the body, leading to neurotoxicity. According to reports, around 70,000 compounds are known to be neurotoxic, although only about 10% have their toxicological pathways properly understood [35]. Environmental pollutants such as heavy metals, particulate matter, pesticides, automotive exhaust, laboratory waste, plastics and their additives are the leading causes of neurotoxicity [36, 8]. The overview of present study is represented in Figure 1.

Heavy Metals

Heavy metals are a primary cause of neurotoxicity and have caused numerous environmental issues globally. Heavy metals are naturally present in lower amounts, but their use in industry leads to higher concentrations and an increased risk of occupational neurotoxicity [37]. Neurotoxic heavy metals can accumulate in the food chain due to their presence in water as well as in industry. Many environmental scientists have been interested for the past few decades in the toxicity of heavy metals to plants and microorganisms because they tend to uptake hazardous metals and metalloids [38,39]. Metal contamination occurs when humans disturb biogeochemical cycles or concentrate metals [4]. Major metals, including mercury, cadmium, manganese, lead and arsenic, can enter the body via inhalation, cutaneous, or orally and have varying degrees of neurotoxicity [34].

Lead (Pb)

Pb toxicity targets the brain's memory and learning processes and can be mediated through three mechanisms. Pb can damage memory and learning ability in the brain by: 1) inhibiting the N-methyl-d-aspartate receptor (NMDAR), as well as blocking neurotransmission by inhibiting the release of neurotransmitters, 2) blocking neuronal voltage-gated calcium (Ca^{2+}) channels (VGCCs), and 3) reducing brain-derived neurotrophic factor (BDNF) expression [40].

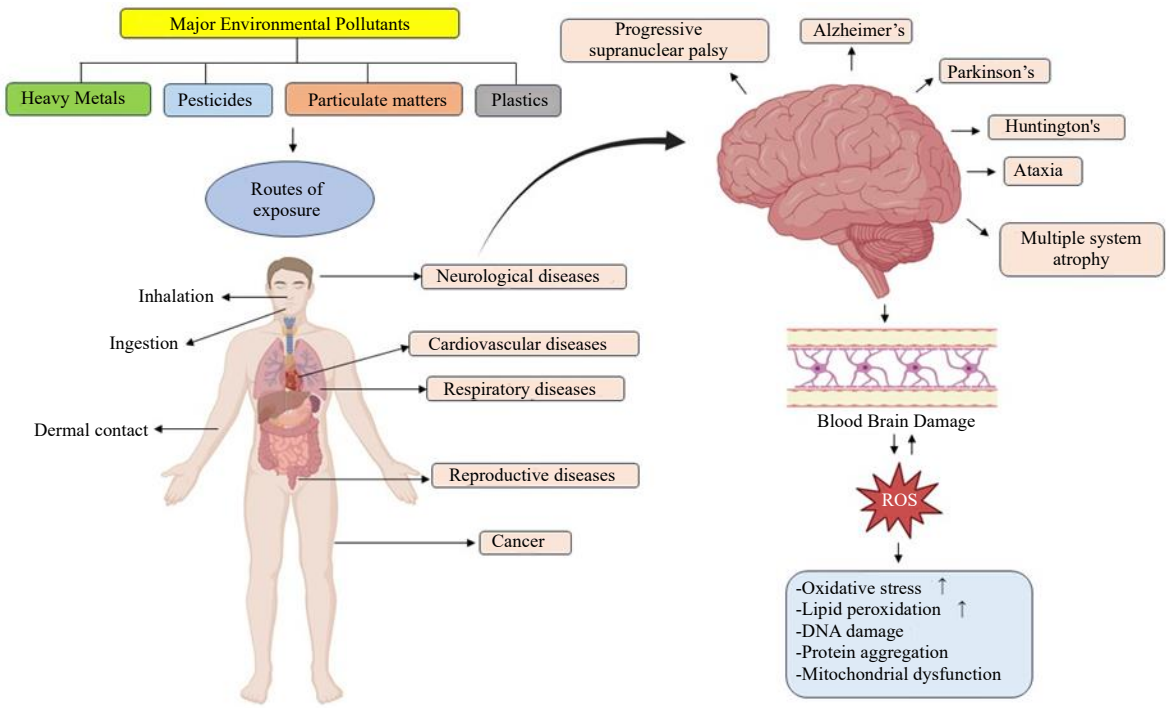

Figure 1. Overview of the present study.

Mercury (Hg)

The toxic heavy metal Hg is well known for causing tragedies in Japan's Minamata Bay [41]. Hg is a commonly used component in the chemical form of thiomersal, used to preserve the DPT and hepatitis B vaccines [42]. Despite being well-known for its neurotoxicity, methyl mercury is nevertheless frequently employed in the pharmaceutical industry [40]. Methyl mercury enters the brain and agonistically interacts with the dopamine D1, D2, and M1, M2 receptors of acetylcholine. Then, inhibits the catalytic activity of glutamic acid decarboxylase (GAD), which converts glutamine into GABA. Overall, the effect causes increased oxidative and nitrative stress, which causes neurotoxic symptoms, as well as defective neurotransmitter-mediated processes [34].

Manganese (Mn)

Mn, a vital component of the human nutrition and is found naturally in the earth's crust. In contrast, Mn plays numerous beneficial roles in human physiology while Pb has no recognized physiological effect in the body. According to the National Academy of Sciences (NAS), the daily recommended intake dose for men is 2.3 mg, while for women, it is 1.8 mg. However, if the homeostatic regulation of Mn absorption and/or excretion is overwhelmed or interrupted, increased Mn levels in the bloodstream can cause neurotoxicity in humans. Workers who are exposed to high levels of airborne are more likely to develop a neurological disease similar to Parkinson's disease [43]. Its exposure in the brain causes damage to the substantia nigra, globus pallidus, basal ganglions, striatum and mitochondria. Damaged nervous system components lead to aberrant synaptic function, while Mn disrupts F_0/F_1 synthase in mitochondria, resulting in reduced ATP generation, increased intracellular calcium levels and increased oxidative stress. The overall effect results in neuronal death, inflammation, ataxia and cognitive impairment [44].

Arsenic (As)

As is receiving global interest due to its tremendous toxicity. As contaminated drinking water affects at least 140 million people in 50+ nations. Over the past century, As has been utilized in the production of pesticides, medications and ingredients in various products [45]. The exact mechanism of As-induced neurotoxicity is still unknown; however, animal research has led to numerous suggested mechanisms. Metabolites affect cells by deactivating enzymes involved in energy metabolism, DNA synthesis and repair. As-induced neurotoxicity is linked to various processes, including oxidative stress, thiamine shortage and reduced AChE activity [46].

Particulate Matter (PM)

Particulate air pollution from both natural and manmade sources causes significant illnesses, including neurological and behavioral impairments, resulting in millions of early deaths. Particulate matter (PM) varies in size, from 10 μm to less than 0.1 μm. Fine PM particles ($PM_{2.5}$) vary in size from 2.5 to 0.1 μm, whereas ultrafine particles (UFP) are smaller ($PM_{0.1}$) [47]. Fine and ultrafine PM can enter the brain via several paths after entering the circulatory system [48]. Ultrafine particles ($PM_{0.1}$) can enter the brain via the vagal nerves after crossing the blood-brain barrier. PM can enter the brain bypassing the blood-brain barrier through the olfactory bulb and fifth cranial nerve when inhaled directly through the nose. These particles enter the central nervous system and trigger the immunological response in astrocytes, microglia and neurons to create ROS (reactive oxygen species), leading to increased lipid peroxidation and neuroinflammation throughout the brain. Neurological diseases often involve many pathogenic processes, including disruption of the blood-brain barrier, protein aggregation, oxidative stress, mitochondrial dysfunction and DNA damage [49, 50]. According to epidemiological studies, being exposed to particulate matter increases the possibility of acquiring neurological conditions like Alzheimer's [51].

Pesticides

Pesticides are chemical substances used to control or kill pests. They constitute a class of chemical substances with numerous subclasses that are typically categorized according to the pests they target.

Pesticides are classified into insecticides, herbicides, fungicides and rodenticides. Each class may have subclasses based on chemical identity, physical state/application method and origin of derivation [52]. Pesticides play an important role in agricultural and public health, but their molecular targets are frequently shared by pest and non-target species, including humans [53]. Several pesticides target the neurological systems of insect pests. These chemicals may produce neurotoxicity in humans due to their similarities in neurochemical mechanisms. The developing human brain is more susceptible to harm from toxic chemicals than adult brains, making this a significant worry [54]. Pesticides that disrupt mitochondrial complex I are increasingly utilized to control mites and acaricides (mites and ticks). Although herbicides and fungicides should not have been targets for mammals, several have been shown to harm the mammalian brain [53]. The most widely and majorly used pesticide are insecticides. A wide range of insecticide classes have been introduced over the last 70 years. Organochlorines (OCs), which were introduced to the market in the early 1940s, were the first insecticides (DDT) to be effective against a wide range of pests over long periods, but later it was banned in 1972 due to excessive toxicity in the US; however, some countries, including India, still use DDT in limited proportion for vector control purposes. These were succeeded by organophosphates (OPs), carbamates (CAs), pyrethroids (PIs), and most recently in the 1990s, by neonicotinoids [55,56].

Organophosphorus (OP) and carbamate insecticide's mechanisms of action are similar and are predominantly mediated by cytochrome P450 enzymes in the liver, but there is also evidence of bioactivation in target organs such as the brain and lungs [57,53]. The primary action of organophosphate insecticides is their ability to inhibit carboxyl ester hydrolases, specifically acetylcholinesterase (AChE) [58]. Both the peripheral and central nervous systems contain the neurotransmitter acetylcholine, which is broken down by this enzyme. The organophosphate insecticide inhibits AChE activity causes synapses to accumulate acetylcholine (present in the terminal endings of all postganglionic parasympathetic nerves) which overstimulates the nervous system and impairs transmission in both the peripheral (PNS) and central nervous systems (CNS). The CNS and PNS are the primary targets of OP action, although many researchers believe that these chemicals disrupt the redox processes and altering the functions of antioxidant enzymes and increase lipid peroxidation in numerous organs [59].

Pyrethroids class of insecticides primarily affect sodium and chloride channels, which transport ions across the cell membrane. Pyrethroids reduce the action potential thresholds of nerve and muscle cells, resulting in recurrent activation. In excessive quantities, salt can prevent the formation of the action potential, obstruct conduction and cause paralysis. Small doses are enough to alter nerve cell sensitivity [60].

In neonicotinoid insecticides action of mechanism, acetylcholine plays an important role as they maintain the intracellular to extracellular concentrations of K^+ and Na^+, which is necessary to start the electric signal in the postsynaptic neuron, by opening and closing the channels. Nicotinic acetylcholine receptors regulate the movement of K+ and Na+ via the channels in neural postsynaptic membranes [61]. The nicotinoids insecticides target mammals and insects' central nervous systems, irreversibly blocking postsynaptic nicotinergic acetylcholine receptors and leading to toxicity [62].

Most insecticides used in agriculture and health care sectors are designed to affect pest's nervous systems. As a result, pesticide exposure causes neurotoxicity in humans due to similarities in neurochemical processes. Typical neurodevelopmental abnormalities include learning disabilities, attention deficit hyperactivity disorder, autism spectrum diseases, developmental delays and behavioral issues [9].

Plastics

Plastic pollution is a persistent challenge worldwide with the first reports evidencing its impact on the living and non-living components of the environment dating back more than half a century. Plastic

pollution provides serious risks to both living and non-living systems, as well as causing environmental stress [63]. Plastics are composed of several polymers, and the type of polymer utilized determines the plastic's chemical characteristics [64]. Plastics come in a wide variety and are frequently made for one-time usage. Polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyamide and polyethylene terephthalate are the most common polymers [65]. Because the majority of plastic polymers produced today are so resistant to breaking down, an accumulation of these complex and long-lasting materials is seriously harming neural human health [66]. UV radiation, natural weathering, and biodegradation transform plastic particles into microplastics (MPs) and nanoplastics (NPs). Microplastics induce extensive neurotoxicity, aberrant animal behavior, and depression. Microplastics accumulate in the human brain and inhibit the function of AChe; penetrate the epidermis into the muscular tissue, and causing nerve fiber atrophy [67].

EXPERIMENTAL STUDIES

Environmental contaminants have been a known threat since 1940. Epidemiological research, case studies and cohort studies have assessed their impact on lifestyle, cognitive dysfunction, neonatal development and teratogenic effects [34]. Literature evidenced that heavy metals (aluminum, cadmium and fluoride) induced neurotoxicity, which caused Alzheimer's disease in rats [68]. Various past studies have been conducted on different experimental models after exposure to pollutants that caused neurotoxicity, as mentioned in Table 1. One study examined the effects of cadmium chloride and mercury chloride on zebrafish behavior, oxidative stress, gene expressions and brain histopathology after 21 days of exposure, which showed the behavioral alterations and neurotoxicity [69, 70]. Studies were conducted on African giant rats to assess the neurotoxicological effects of different heavy metals, such as vanadium, lead and low metals, which revealed the destruction of different neuronal cells sensitive to neuroinflammation and oxidative stress [71]. After two decades of research, it is widely accepted that heavy metals cause cellular toxicity through a variety of mechanisms, including oxidative stress, lipid peroxidation, mitochondrial dysfunction, apoptosis, DNA damage, disruption of ATP synthesis, DNA methylation, thiamine deficiency, reduction of acetylcholinesterase activity, generation of free radicals and reactive oxygen species, epigenetic changes, upregulation of hypoxia-inducible factor-1α, and disruption of the DNA repair system, all of which seem to be mostly conserved across species [72]. Previous studies on neurological consequences from heavy metal exposure lacked a specific route of exposure. However, just a few studies have looked into the link between inhaling PM component metals and brain health [47]. Many studies have been conducted on mice, rats and BV2 cell lines that address the negative effect of inhaled particulate matter on the brain and/or mental health [47, 48, 49].

The organophosphate insecticide, i.e., chlorpyrifos as a neurotoxic chemical, targets non-cholinergic neurotransmitters such as serotonin, dopamine, glutamate and hormones that leading to Parkinson's disease (PD) and Alzheimer's disease (AD) [73, 74]. Neurotoxic effects of organophosphate exposure can alter the brain and plasma ChE activity of *Eptesicus fuscus* (Big brown bats) and in prepubertal guinea pigs, it causes long-term memory deficits as well as significant reductions in hippocampal myo-inositol levels [75,76]. Chlorpyrifos exposure can cause motility in various species of such as *D. melanogaster, Brachionus koreanus and* Honey bees *(Apis mellifera)* [77-79]. In previous studies, malathion toxicity has been assessed in *Drosophila and Ophiocephalus punctatus* which showed locomotion impairment and degenerative changes [80, 81]. Some research has revealed that neonicotinoid insecticide such as imidacloprid is neurotoxic to honey bees (*Apis mellifera), Japanese quails, Australoheros facetus* and *Danio rerio* (zebrafish) [82-85]. Further research examined the neurotoxicity of micro or nanoplastics in combination with pyrene (3 times), mercury (2 times), 17-α-ethinylestradiol (EE2), Bisphenol-A (BPA), cadmium, carbamazepine, Cefalexin, chromium, Florfenicol, gold nanoparticles and roxithromycin [65]. In addition, numerous studies have found histological abnormalities in the CNS of fishes following exposure to microplastics and other chemicals [86].

Table 1. Experimental evidence of neurotoxicity caused by major environmental pollutants and their action of mechanism.

Environment Pollutants	Man-made Sources	Mechanism of action	Experimental Model	Doses & Exposed Duration	Outcome	References
Lead (Pb)	Paints	Inhibiting N-methyl-d-aspartate receptor & release of neurotransmitter	Pregnant Wistar female rats	15 mg/kg for 2 weeks	Production of pro-inflammatory cytokines such as IL-1 and TNF-α in the hippocampus and IL-6 in forebrain of immature rat brain	8, 100, 101
	Lead contaminated dust	Blocking neuronal voltage-gated calcium channels	Mice model	100 ppm Pb acetate for 10 weeks	Induce learning & memory impairment in mice by activation of microglia & NLRP3 inflammasome	8, 100, 102
	Lead acid-batteries	Reducing neurotrophic factor (BDNF) expression	SH-SY5Y cell line	15–50 ppb for 96 hours	Induce significant changes in percentage of mature neurons as well as neurite lengths	8, 100, 103
Mercury (Hg)	Medical waste	Interacts with the dopamine D1, D2 and M1, M2 receptors of acetylcholine	Sprague-Dawley rat	28 days	Abnormal histopathology of Purkinje cells, TEM revealed axonal damage, chromatin condensation, indistinct nucleoli and mitochondrial damage	8, 34, 104
	Industrial waste	Inhibits the catalytic activity of GAD which converts glutamine into GABA	*Danio rerio* (Zebrafish)	30 µg/l for 21 days	Development of anxiety- behavior, oxidative damage and decreased glutathione levels in brain	8, 34, 69
	Mining & Coal combustion	Increased oxidative & nitrative stress	*Caenorhabditis elegans*	0–125lM grown for 48 h at 20C	Dopamine neuron degeneration	34, 107, 108
Manganese (Mn)	Steel miles	Damaged brain components lead to aberrant synaptic function	$APP^{SWE}/PSEN1^{\Delta E9}$ transgenic mice	3 ×50 mg/kg for 7 days	Accumulation in brain tissue, alters glutamate in primary cortical astrocytes, increases susceptibility to seizure leads to AD	44, 109, 110
	Chemical industries	Mn disrupts F_0/F_1 synthase in mitochondria, reduced ATP generation,	C57BL/6 mice and hippocampal neuronal HT22 cells	2 ml/kg per week (6 weeks)	Induces the accumulation of impaired SVs at pre-synapse & impairs learning memory and synaptic plasticity in hippocampal tissue of mice	44, 109, 111

	Mining	Increased oxidative stress	*Danio rerio* (Zebrafish)	2 mM for 21 days	Induced oxidative stress, neuroinflammation and brain neuronal apoptosis and induced PD	44, 109, 112
Arsenic (As)	Pesticides, fertilizers	Cells used to deactivate enzymes involved in energy metabolism, DNA synthesis and repair.	*Danio rerio* (Zebrafish)	30, 60, and 100 µg/g for 60 days	Leads to oxidative stress, disrupts dopaminergic signalling, impairs cognitive performance	8, 107, 108
	Wood preservatives	Increased oxidative stress, thiamine shortage	Mice	0, 5, 10, 25, and 50 mg/L for 30 days	Induces BBB dysfunction and T lymphocyte infiltration, affects $CD4^+$ T lymphocyte differentiation, which may be associated with Nrf2 activation impaired learning and memory	8, 113
	Industrial & Mining	Reduced AChE activity	*Drosophila melanogaster*	0.5 mM, 1 mM, 1.5 mM, 2 mM, 3 mM, 4 mM, and 5 mM	Affected their locomotor abilities, pupae size, cognitive functions and neurobehavioral impairment	105,106, 107
Particulate matter	Agriculture waste	ROS production	3D cultured human brain model in microfluidic system	Chronic PM2.5 exposure	Neuronal damages, such as synaptic impairment, phosphoric tau accumulation and neuronal death	8, 51, 114
	Automobile emission, combustion	leading to increased lipid peroxidation leads to neuroinflammation	Male mice (C57BL/6)	10 weeks	Neuroinflammation and oxidative stress, which can induce neuronal and white matter damage via apoptotic pathways	8, 51, 115
Organophosphorus (OP) and carbamate	Agriculture	inhibit carboxyl ester hydrolases, specifically acetylcholinesterase (AChE)	*Drosophila melanogaster*	7 days exposure to chlorpyrifos	Induced developmental lethality but also significantly impaired coordination & motor behavior	8, 59, 116
	Medical sectors	causes synapses to accumulate acetylcholine which impairs transmission in both the peripheral (PNS) and central nervous systems (CNS)	*Lumbricina* (Earthworm)	100 mg/kg methiocarb (1%); 60 worms	Significant differences in the 2D trajectories of the fractal, 44 where the exposed earthworms followed altered trajectories compared to the control group	8, 59, 117

Pyrethroids	Agriculture, Medical & Veterinary field, Textile industry	affect sodium and chloride channels, which transport ions across the cell membrane	Adult male Wistar rats	tefluthrin [2.2, 4.4 and 5.5 mg/k] for 6 days	Altered the DA and 5-HT neurotransmitter, decreased DA, 5-HT & caused neurotoxicity	60, 118, 119
Neonicotinoid	Agriculture & Medical sectors	blocking postsynaptic nicotinergic acetylcholine receptors	*Danio rerio* (Zebrafish)	clothianidin (1–100 µM) and dinotefuran (1–100 µM)	Reduced locomotor activity in the novel tank in adolescence and adulthood, altered the diving response in a dose-age and time-block-dependent manner	62, 120, 121
Plastics	Polyethylene, polypropylene, polystyrene,	plastic particles transform into microplastics (MPs) and nanoplastics (NPs)	*Caenorhabditis elegans,*	0.1–100 µg/L	damage to neurons & dopamine, glutamate, serotonin and GABA) were altered	65, 67, 122
	poly-vinyl chloride, polyamide and polyethylene terephthalate	inhibit the AChe; penetrate the epidermis into muscular tissue, causing nerve fibre atrophy	*Danio rerio* (Zebrafish)	20 µg/mL for 21 days	induced oxidative damage in gill and intestinal cells & induced AChE activity	65, 67, 123

GLOBAL BURDEN

The burden of diseases and mortality caused by environmental pollution is becoming a global public health concern, particularly in emerging countries. Environmental pollution causes up to 22% of the world's disease burden and 24% of fatalities; the general population is inevitably exposed to environmental toxins [87,88]. Over the next 25 years, the industrial sector is projected to utilize energy at a rate of 1.8 to 3.5%. Industrialization has led to a rise in pollution levels [89]. South Asia faces high population growth and environmental challenges. The majority of countries in this area are experiencing quicker growth than the worldwide average. Since 2013, India has had economic growth of over 7%, making it the world's biggest economy. South Asia, home to 60% of the world's population, is primarily reliant on non-renewable energy sources, resulting in significant CO_2 emissions [89,90]. Gautam et al. (2009) nominated Indian cities among the most polluted cities in the world. In India, Maharashtra and Uttar Pradesh were revealed to be the states with the highest pesticide consumption [91,92]. Heavy metal contamination in peri-urban regions is mostly caused by metal-laden dust and aerosols that infiltrate the soil and are absorbed by vegetables and plants. Methylmercury can be hazardous to the brain and central nervous system, even at low concentrations of 3.0 µg/kg in humans [93]. Furthermore, 70% of all agricultural land worldwide is impacted by the usage of pesticides. Known to be the most often used pesticides, chlorpyrifos, carbaryl and terbuthylazine have detrimental effects on an organism's ability to thrive and create respiratory issues that eventually lead to neurotoxicity [94]. Roughly 70,000 compounds have been claimed to be neurotoxic; however, only 10% of these substances' effects and toxicity mechanisms have been determined [34]. Air pollution, mostly due to PM, was expected to cause 11.65% of deaths globally [95]. $PM_{2.5}$ exposure was linked to all-cause dementia (pooled odds ratio 1.30), Alzheimer's disease (pooled ratio: 1.65) and Parkinson's disease (pooled ratio: 1.17) [96].

The global production of plastics reached a remarkable 400.3 million metric tonnes in 2022, up nearly 1.6 percent from the previous year. Plastics manufacture has continuously increased since the 1950s because of its extraordinary adaptability [97]. The global production of heavy metals, pesticides and plastics is graphically shown in Figure 2. According to 2022 reports, China leads the way in plastic

production and distribution, accounting for 32% of global output volume. India has the highest plastic recycling rate in the world, reportedly recycling up to 60% of its plastic garbage [98].

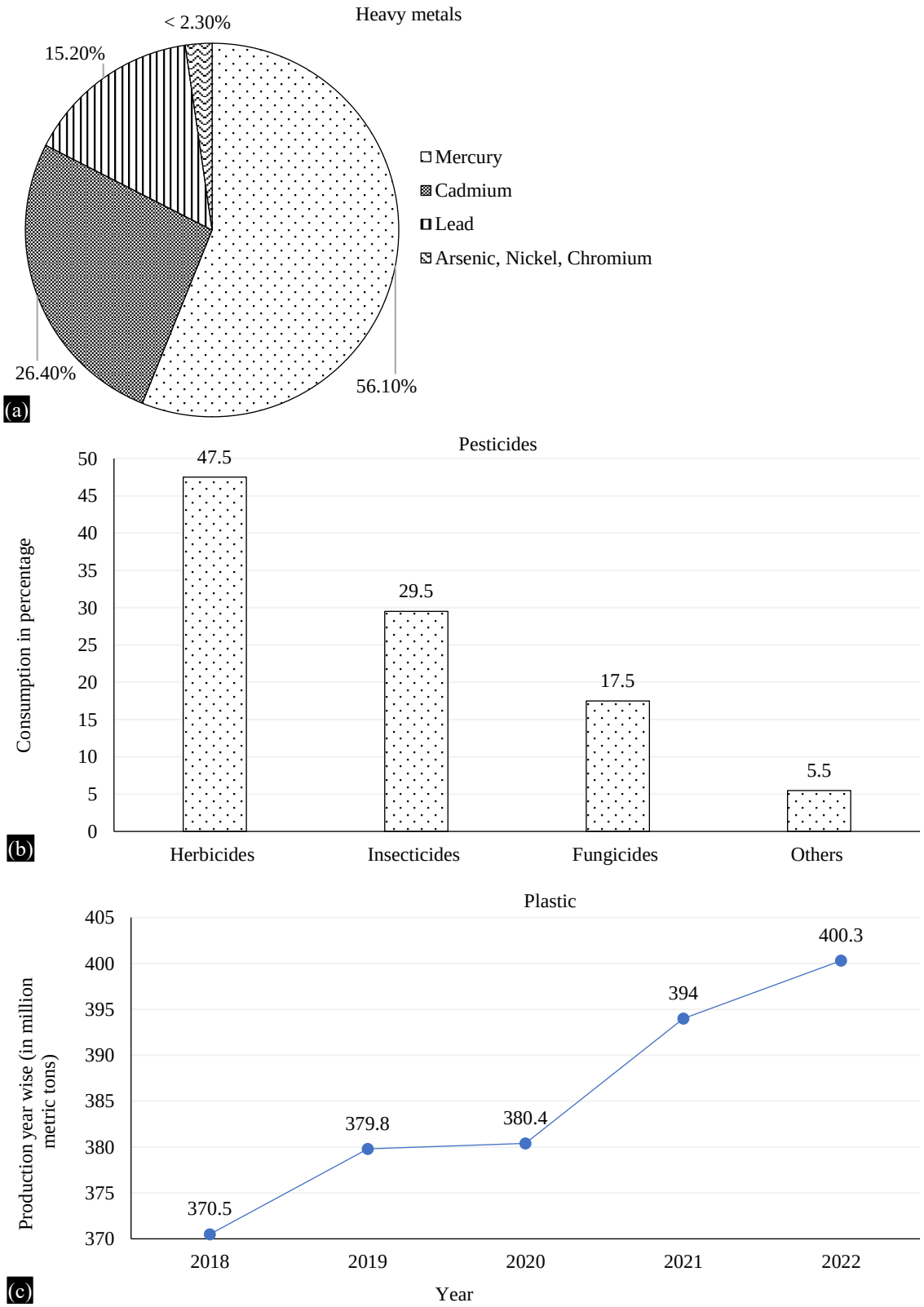

Figure 2. Global data distribution of (a) heavy metals; (b) pesticides; and (c) plastic production of last five years.

Similar circumstances exist in many industrialized nations, where the need for precautions has diminished and solutions are found only after damage has already been done. Given the challenges associated with measuring exposure levels and the absence of systematic monitoring, a deeper understanding of the relationship between environmental toxins and health is necessary. Distinct contaminants are responsible for both acute and chronic neurological diseases [5,8]. According to WHO 2023 data, SDG (Sustainable Development Goal) targets a 3.9 reduction in the number of deaths and diseases caused by hazardous substances and air, water, and soil pollution and contamination [88]. For a long time, pollution was assumed to be a local issue that could be dealt with by local or national rules; nevertheless, it is now very evident that pollution is a planetary threat and requires worldwide intervention [99].

CONCLUSION

It is clear from the preclinical, clinical and previously published studies that one of the main causes of neurotoxicity is environmental pollutants. Due to the exposure to these pollutants, the entire age range i.e., children, adults and pregnant women is impacted by neurotoxic symptoms. However, there are also unmet needs for reducing industrial emissions and the use of heavy metals, pesticides and plastics, which can help to improve the environmental conditions. Strict global regulations and the development of neuroprotective medications are necessary to address this issue. To prevent neurotoxicity, new compounds should undergo rigorous laboratory testing before commercialization. Based on earlier research, we expect that our study will provide updated and informative knowledge about the harmful effects of different environmental pollutants on causing neurodegenerative diseases, which emphasizes the importance of preventing developmental and neurodegenerative toxicity.

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Conflict of Interest Statements

The author declares there are no competing interests.

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