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NEUROTOXIC AGENTS AND THEIR IMPACT ON THE NERVOUS SYSTEM

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ABSTRACT

In the review paper, we have studied about Neurotoxic agents, a wide range of chemical, biological, and environmental substances, which pose significant threats to the integrity and function of the nervous system. This review provides a comprehensive overview of major neurotoxic compounds including heavy metals, pesticides, pharmaceuticals, and industrial chemicals, and their mechanisms of action on neuronal cells. It highlights how these agents induce oxidative stress, disrupt neurotransmission, impair synaptic plasticity, and lead to neuroinflammation and apoptosis. Particular emphasis is placed on the vulnerability of specific brain regions and cell types, as well as the long-term implications for neurodevelopmental and neurodegenerative disorders. The paper also discusses current methodologies for neurotoxicity assessment and emerging research tools such as in silico models and biomarkers. By integrating recent findings and perspectives, this review aims to deepen the understanding of neurotoxic risks and guide future strategies for diagnosis, prevention, and therapeutic intervention.

KEYWORDS: Neurotoxic agents, Eco-toxicity, Arsenic, Neurodegenerative disorders.

1. INTRODUCTION

The human nervous system is an intricate and highly sensitive network responsible for coordinating bodily functions, processing sensory information, and maintaining cognitive abilities. However, this complex system is particularly vulnerable to a wide array of harmful substances known as neurotoxic agents.[1] These agents, which include certain chemicals, drugs, heavy metals, and environmental pollutants, can cause direct or indirect damage to

neural tissues, leading to structural, functional, and behavioural impairments. Neurotoxicity has emerged as a critical public health concern due to its association with a variety of neurological disorders such as Parkinson's disease, Alzheimer's disease, developmental delays, and neurobehavioral deficits. Both acute and chronic exposures to neurotoxic substances can disrupt neuronal signaling, induce oxidative stress, impair neurotransmitter function, and trigger neuroinflammation.[2] Moreover, vulnerable populations such as children, the elderly, and individuals with genetic predispositions are at a heightened risk.[3] This review aims to provide a comprehensive overview of major neurotoxic agents, their mechanisms of action, and the pathological consequences they have on the nervous system. By understanding the pathways through which these agents exert their toxic effects, we can improve diagnostic strategies, develop targeted therapies, and implement effective preventive measures.[4] Additionally, the review highlights recent research advancements, regulatory challenges, and future perspectives in the field of neurotoxicology According to estimates from the World Health Organization (WHO), over 200 million people globally are exposed to arsenic at levels higher than those recommended for safety.[5] Although airborne exposures contribute to exposure, particularly near mines, smelters, and industrial "hot spots," contaminated groundwater is the primary exposure pathway. Humans are primarily exposed to arsenic through contaminated drinking water.[6] There have been reports of widespread arsenic pollution in groundwater in Bangladesh, West Bengal, China, Taiwan, Thailand, Ghana, Argentina, Chile, Mexico, Hungary, Canada, the United Kingdom, and other parts of the world.[7]

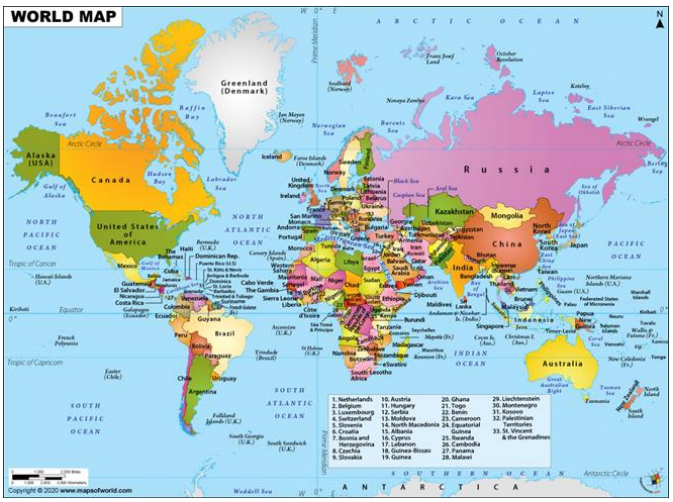

Fig. 1: Globel future perspectives in the field of neurotoxicology.

Both natural and man-made sources, such as mining, industrial waste, and the usage of fertilizers containing arsenic, can contribute to its presence in the environment.[8] Natural

causes include erosion and geological leaching. Incineration of arsenic-preserved wood products and burning coal are two additional, less frequent causes of arsenic exposure. Consumption of tainted foods, ingestion of kitchen dust, inhalation of indoor air polluted by coal combustion and tobacco smoke, and hand-to-mouth ingestion of soil have been cited as additional exposure pathways to arsenic.2,3 Additional factors include airborne exposures, particularly near mines, smelters, and industrial "hot spots."[9]

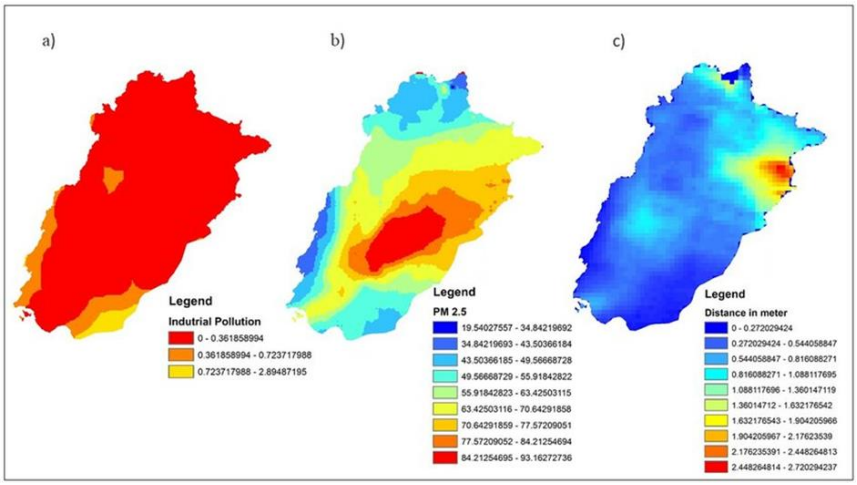

Fig. 2: Natural causes include erosion and geological leaching.

Studies have indicated that exposure to arsenic may occur during pregnancy and that it can pass the placenta. In one investigation, pregnant mice were given arsenic-labeled arsenate and arsenite.[10] Using autoradiography and gamma counting, it was found that the arsenic traveled from the mother to the lethal circulation through the placenta. Other studies have also shown transplacental arsenic transfer in animal models.[5,6] Similar findings have been described in humans. Strong positive correlations have been found between cord and Arsenic levels in the blood of pregnant women exposed to arsenic are nearly identical to those in their babies' umbilical cord blood.[11] This indicates arsenic readily crosses the placenta. Similar levels of arsenic metabolites (dimethylarsinate, monomethylarsonate, arsenite, and arsenate) are found in both. Therefore, the developing fetus is at risk. While breast milk is another potential route, animal studies haven't shown arsenic transfer via this route.[12] A study on mice exposed to low-dose arsenic in drinking water found no arsenic in their milk. Human studies also suggest arsenic doesn't pass into breast milk, potentially protecting Bangladeshi infants. However, once in a baby, arsenic can cross the blood-brain barrier, directly impacting the central nervous system. This barrier, formed by tight junctions in brain capillaries and

choroid plexus cells, prevents many substances from entering the cerebrospinal fluid. A toxicant's neurotoxicity thus depends.[13]

Table No. 1: Mechanistic Pathways of Neurotoxicity.

Key pathway	Principal molecular events	Representative evidence
Oxidative stress & redox dyshomeostasis	Excess ROS/RNS, Nrf2–ARE dysregulation, lipid peroxidation, DNA oxidation	Methylmercury up-regulates ROS and depletes antioxidant enzymes in brain tissue Ag-nanoparticle exposure triggers Nrf2 and NF-κB signaling[14]
Excitotoxicity & Ca^{2+} overload	Persistent activation of NMDA/nACh receptors → Ca^{2+} influx → calpain activation	Neonicotinoids cause sustained α7-nAChR activation and hippocampal damage Methamphetamine and cocaine heighten glutamate release[15]
Mitochondrial dysfunction	ΔΨm collapse, impaired oxidative phosphorylation, mtDNA damage	Ketamine and nitrous oxide disrupt ETC complexes in cortical neurons[16]
Neuroinflammation	Microglial activation, cytokine/chemokine surge, BBB impairment	TMT elevates hippocampal Cxcl10/12 and TNF-signaling transcripts before neurofilament-light release[17]
Apoptosis & autophagy dysregulation	Caspase-3 activation, PARP cleavage, autophagosome accumulation	Ag-NPs induce apoptotic and autophagic markers via Ca^{2+}-NF-κB/Nrf2 crosstalk[18]
Epigenetic modification	DNA methylation, histone acetylation, miRNA perturbation	Environmental toxins drive differential DNA-methylation patterns linked to AD, PD, ALS [19]

Animal studies show a dose-response relationship between arsenic in drinking water and brain arsenic levels, indicating the blood-brain barrier (BBB) doesn't effectively block arsenic's passage to the central nervous system (CNS). Furthermore, arsenic may directly harm the BBB. A study on mixed metals' effects on the BBB showed that various metals, including arsenic, compromised its integrity, possibly via effects on astrocytes, increasing its permeability to toxins like arsenic.[20] Nanotechnology, a rapidly growing field, significantly impacts various industries and society. The National Nanotechnology Initiative defines nanomaterials as having at least one dimension between 1 and 100 nm. Their small size gives them unique chemical, physical, optical, and electrical properties, different from their bulk counterparts. Nanotechnology uses engineered nanoscale materials to exploit these properties.[21]

Impairment of mineral metabolism

Humans have been exposed to many nanoparticles (NPs) originating from various activities such as combustion, welding, and biomedical applications. People working in certain in dustries, for example, automobile, aerospace, The electronics, communications, chemical, and paint industries face significant exposure to numerous nanoparticles (NPs).[22] Environmental persistence of these NPs increases human exposure, particularly for those living nearby. Significant human exposure to NPs like copper, zinc, iron, cerium, silver, gold, manganese, titanium, aluminum, silica, and various carbon-based nanomaterials is linked to health problems, including neurotoxicity. The rise in neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's diseases in recent years may be connected.[23]

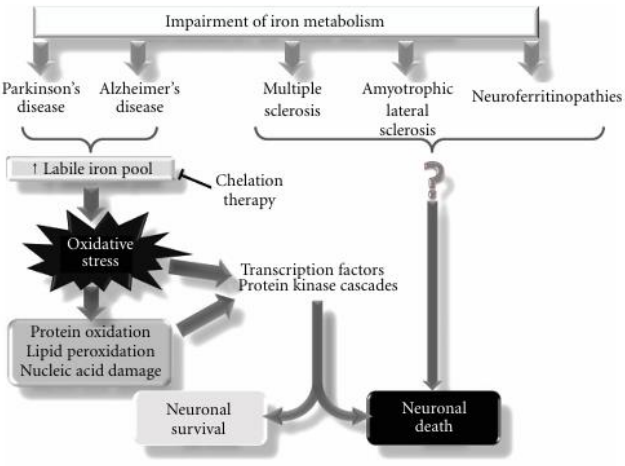

Fig. 3: Connection between the disruption of iron metabolism and neurodegenerative disorders.

Disrupted iron metabolism is a characteristic feature in various neurodegenerative disorders like Parkinson's (PD) and Alzheimer's (AD) diseases, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and neuroferritinopathies. In the cases of PD and AD, iron has been shown to significantly influence neuronal outcomes. Based on the level and severity of oxidative stress stemming from the rise in the labile iron pool, it affects transcriptional activities and signaling pathways that may contribute to neuronal survival or demise. While the involvement of iron has been noted in MS, ALS, and neuroferritinopathies, the molecular processes resulting in neuronal death remain unclear. The rise in environmental pollutants, such as NPs, might contribute to the growing prevalence of these neurodegenerative disorders.[24] The function of the blood-brain barrier (BBB) is essential for comprehending NP toxicity within the brain. BBB distinguishes between blood and cerebrospinal fluid within

the central nervous system (CNS). The BBB is an expanded plasma membrane that features tight junctions linking the neighboring endothelial cells of the cerebral capillaries. The permeability characteristics of the BBB are noteworthy. In contrast to noncerebral capillaries, the cerebral endothelium lacks vesicles for transporting macromolecules. Astrocytic end feet envelop the majority (85%) of the endothelial cells in cerebral capillaries, and they also feature a robust basement membrane.[25]

Research indicates that the intravenous, intraperitoneal, or intracerebral delivery of Ag, Cu, or Al NPs (50-60 nm) is said to compromise the BBB, as demonstrated by staining with albumin-bound Evans blue. NPs may also promote vesicular transport to penetrate the CNS microenvironment and induce toxic effects within the CNS. The distinctive dimensions and surface alterations of NPs may transport drugs or therapeutic agents to the brain in the advancement of nanomedicine. Further investigation is, nonetheless, essential to completely comprehend how NPs are transferred from the bloodstream to the brain.[26]

Neurobehavioral Effects in Animal

Models Research has shown that arsenic affects the CNS function in experimental animals during behavioral and cognitive assessments. In a study involving weanling rats, spatial learning capabilities were assessed following arsenic exposure through various tests, such as hidden platform acquisition tests and visible platform trials. The findings indicated that arsenic exposure correlated with deficits in spatial memory, as evidenced by lower performance on hidden platform acquisition assessments.[27] A comparable investigation into arsenic exposure from the prenatal stage to about 4 months of age indicated that affected rats made more mistakes in a delayed alternation task that necessitated sensory information,14 while another study revealed that offspring exposed to arsenic exhibited impairments in spatial working memory and responses to new stimuli. Further research has examined the impact of arsenic on learning and conditioning in young animals. In a certain study, a range of operant conditioning tests was administered to both adult and infant rats. The research showed that developing rats subjected to arsenic exhibited learning impairments, needing more sessions to master a learned task compared to unexposed controls.[28] Arsenic exposure did not impact the acquisition of new skills in adult animals. This varying impact on learning in young animals versus adult animals suggests the presence of vulnerability windows, indicating that the developing brain may be more vulnerable to the neurotoxic effects of arsenic Moreover, even following a 100-day rehabilitation period without exposure,

developing rats still exhibited learning deficits, indicating a degree of irreversibility.[29] In a different trial assessing the extinction of acquired behavior, evidence indicated that both adult and developing subjects exhibited increased synthesis and metabolism of neurotransmitters due to arsenic exposure. In another investigation, the intake of inorganic arsenic by rat pups from postnatal day 2 to 60 days resulted in a reduction of acetylcholinesterase (AChE) activity, which is vital for the metabolism of acetylcholine, another key neurotransmitter. Decreases in AChE were observed even after a recovery phase without continuous arsenic exposure, indicating a degree of irreversibility.[25] Additionally, another study discovered that arsenic induces regional changes in the concentrations of glutamate, gamma-aminobutyric acid, and various other biogenic amines in the brain.[30]

The complete biological implications of these variations in neurotransmitter levels caused by arsenic remain unclear, yet an earlier study13 indicated that these alterations might occur prior to the onset of cognitive effects. This research performed learning and spatial memory assessments on weanling rats subjected to arsenic, while also examining the glutamate receptor N-methyl-D-aspartate receptor (NMDAR) and ultrastructural alterations in the hippocampus. NMDAR was studied due to its involvement in synaptic plasticity and learning, with both NMDAR and the hippocampus believed to contribute to memory. The researchers determined that exposure to arsenic correlated with dose-dependent reductions in the expression of specific NMDAR subunits and also with ultrastructural alterations in the hippocampus. Importantly, while only the group with the highest arsenic exposure exhibited a deficiency in the spatial memory assessment, the ultrastructural and molecular alterations observed were dose-dependent and detected even with low arsenic exposure.[31] These interesting results indicate that the alterations in ultrastructure and protein expression were more sensitive indicators of arsenic exposure compared to the neurobehavioral changes,13 potentially occurring before the noticeable neurobehavioral effects. Along with the neurotransmitter system, the hormonal system might also be influenced. Mice exposed to perinatal conditions exhibit elevated baseline levels of the steroid hormone corticosterone relative to control groups.[29] Additionally, research indicates that such exposure results in decreased glucocorticoid receptor levels in the hippocampus.[24] A study involving glucocorticoid receptor knockout mice identified deficits in spatial memory,30 suggesting that the decline in glucocorticoid receptor levels could carry cognitive consequences.[32]

Epidemiological studies: Epidemiological research has started to indicate that prolonged and low-level exposure to arsenic is linked to significant impacts on cognitive function

throughout a wide age spectrum. Twenty epidemiological studies evaluated neurocognitive or behavioral effects linked to arsenic; 17 concentrated on neurocognitive results, and among these, 15 indicated deficits in neurocognitive or intellectual functions related to arsenic exposure, while 2 did not demonstrate any effect. Three epidemiological studies concentrated entirely on behavioral outcomes, and one, part of the 17 mentioned, evaluated both behavioral and intellectual outcomes, with none demonstrating significant behavioral impacts from arsenic exposure. In children, negative neurobehavioral effects have been linked to both short-term and long-term arsenic exposure.[33,34] A meta-analysis regarding children exposed to arsenic revealed intelligence deficits; examining four cross-sectional studies from China on the effects of arsenic exposure on IQ, this analysis determined that the average IQ score of children residing in arsenic-contaminated areas was over 6 points lower than that of children not exposed. Indeed, an increasing number of studies are corroborating the intellectual deficits linked to arsenic exposure in children as young as 5 years old.[35] A cross-sectional study involving an older demographic similarly identified neurobehavioral impacts associated with long-term arsenic exposure in adolescents.47 Results showed that adolescents who had been exposed to arsenic-laden well water during early life scored lower in 3 out of 4 neurobehavioral subtests when compared to unexposed controls, indicating that early exposure to arsenic may influence neurobehavioral development in later years.[36] In distinct meta-analyses focused on studies measuring arsenic levels in urine (n ¼ 6) and in drinking water (n ¼ 4), results indicated that a 50% rise in urinary arsenic correlates with a decrease of 0.39 points in full-scale IQ (P ¼ .09), while a similar increase in arsenic from water is linked to a significant reduction (P ¼ .052) of 0.65 points in full-scale IQ.52 Numerous investigations have also explored the behavioral impacts of arsenic exposure. A study focusing on elementary school students in the United Arab Emirates revealed no substantial connection between arsenic exposure levels and the likelihood of having attention-deficit hyperactivity disorder (ADHD).[37,38]

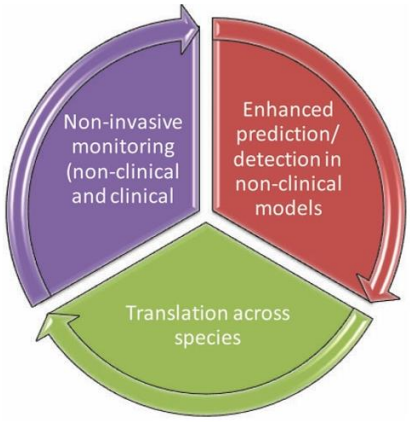

Fig. 4: A schematic depicting the interdependency among enhanced detection preclinically, enhanced capability in translation of nonclinical data to the clinic, and enhanced capability for noninvasive monitoring in the clinic.

A research study in Bangladesh did not find any behavioral deficits in 7-month-old infants exposed to arsenic prenatally. In Torreón, Mexico, a study of 526 children aged 6 to 7 years indicated that, while arsenic markers were not linked to parental behavior ratings, increased urinary arsenic levels were related to higher scores on oppositional, cognitive issues, and ADHD subscales.[39]

Neurotoxicity and mechanism of nanomaterials

Titanium dioxide nanoparticles Among various metal-derived nanoparticles, those that come from titanium have been extensively utilized and in significant amounts. Titanium dioxide (TiO2) is the most prevalent titanium compound and has various applications in our daily lives. TiO2 is a white, odorless, water-insoluble substance that was thought to possess low toxicity.[40] TiO2 is a fairly stable, non-flammable substance that occurs naturally in several ore types, including rutile, anatase, and brookite. TiO2 can additionally be obtained from an iron-rich mineral (FeTiO3) referred to as ilmenite [32e36]. TiO2 has specific physiochemical characteristics that render it valuable for various uses. Some appealing qualities that have facilitated the widespread use of TiO2 include corrosion resistance, biocompatibility, mechanical strength, whiteness, opacity, and photocatalytic, optical, and electrical functionalities.[41] The National Nanotechnology Initiative in the United States identifies nanoparticulate TiO_2 particles as one of the most extensively produced nanoparticles worldwide. In industry, 80% of TiO_2(worldwide), is utilized for manufacturing paints, coatings, plastics, and paper products.[42] The toxicity of nano-sized TiO2 remains not fully comprehended, even though it is widely used. Recent toxicological research has shown the detrimental impacts of TiO_2 NPs on biological systems, raising significant concern. It has recently been acknowledged that inhaling TiO_2 could be carcinogenic to humans.[43] As noted in the 149 Journal of Food and Drug Analysis 22 (2014), understanding the risks and hazards, such as neurotoxicity, linked to nanoparticulate TiO2 exposure and its dose-dependent response is crucial.[44]

Levels of malondialdehyde

An oxidative marker rose following the transnasal instillation of TiO2 NPs. A comparable effect was observed with the intra-abdominal injection and intratracheal instillation of TiO2

NPs in mice. Reactive oxygen species (ROS) like superoxide, hydrogen peroxide, and hydroxyl radical were also observed to be elevated in animals exposed to TiO2 NPs. Elevated cytokine levels, signaling inflammatory responses in the brain, were observed in animals that received TiO2 NPs.[45,46]

Neurotoxic effects. Numerous studies examined the (neurotoxic) impacts of polystyrene and polyethylene micro- and nanoplastics on invertebrates like nematodes, bivalves, and crustaceans, whether or not co-exposed to additional substances.[47] Exposing the nematode Caenorhabditis elegans to five varying sizes of spherical polystyrene microplastics (0.1 to 5 µm) through the culture medium (1mg/L) led to excitatory toxicity affecting locomotor activity, a decreased survival rate, and a shortened average lifespan, especially after exposure to 1.0 µm polystyrene particles. In addition, the expression of several neuronal genes was decreased, which aligned with the dysfunction of cholinergic and GABAergic neurons as well as oxidative stress.[48,49]

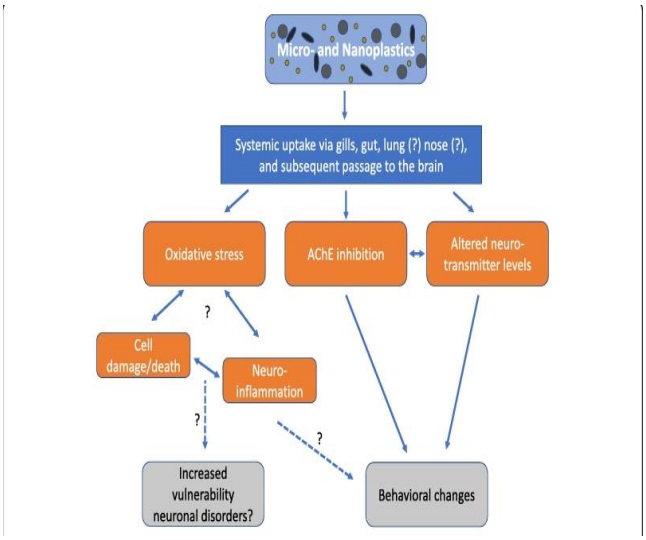

Fig. 5: Behavioral changes by the Micro-Nano plastics.

In this above fig. of the neurotoxic impacts of micro- and nanoplastics. Plastic particles may enter the systemic circulation and eventually the brain by being absorbed through the gills, gut, and potentially the lungs or directly through the nasal cavity. Upon entering the brain, micro- and nanoplastics can trigger oxidative stress, possibly causing cellular harm and neuroinflammation, which might eventually lead to the onset and progression of neurodevelopmental and/or neurodegenerative conditions.[50] Micro- and nanoplastics in the brain may lead to the inhibition of AChE and alterations in neurotransmitter levels, potentially contributing to the noted behavioral alterations. It is important to point out that

much of the evidence is incomplete and derived from various, predominantly aquatic species, emphasizing the necessity for comprehensive systematic studies to thoroughly clarify the neurotoxic potential of micro- and nanoplastics.[51,52]

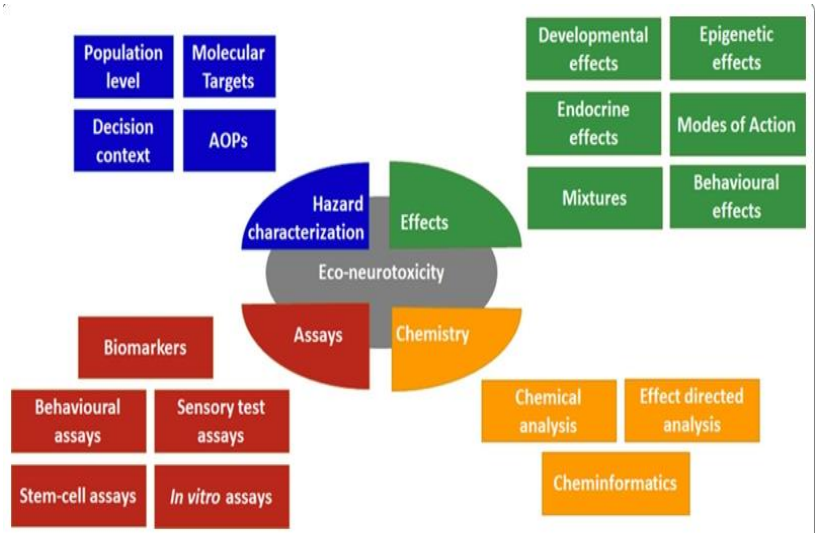

Fig. 6: In this figure shows eco-neurotoxicity.

Key components of eco-neurotoxicity assessment

Exposure of Mediterranean mussels to polystyrene microplastics (0.11 μm, 0.005–50 mg/L) for 96 hours led to notable changes in the expression of genes linked to biotransformation, cell stress response, and innate immunity in the gills (hsp70, at 50 mg/L) and digestive gland (cyp11, at 0.5 mg/L; cyp32, at 5 mg/L; cat, at 0.05 and 0.5 mg/L; lys, at 5 mg/L).[53] Paul-Pont, I., Lacroix, C., Fernández, C. G., Hégaret, H., Lambert, C., Le Goïc, N., ... & Soudant, P. (2016). Exposure of marine mussels Mytilus spp. to polystyrene microplastics: toxicity and influence on fluoranthene bioaccumulation. *Environmental pollution*, *216*, 724-737.no additional indications of neurotoxicity were noted. Regrettably, there was no evidence presented showing the actual absorption of the polystyrene microplastics.[54,55] Exposure of Mediterranean mussels (Mytilus galloprovincialis) to virgin and pyrene-contaminated polyethylene and polystyrene microplastics (100 μm, 1.5 g/L) for 7 days resulted in plastic particles being present in the hemolymph, gills, and gut, as identified by polarized light microscopy.[56] Microplastics from polyethylene and polystyrene caused nuclear changes and DNA damage, along with a decrease in AChE activity in the clams' gills, but not in the hemolymph.[57] The contamination with pyrene did not worsen the inhibition of AChE activity. When Asian freshwater clams (Corbicula fluminea) were exposed for 96 hours to Red Fluorescent Polymer Microspheres (composition not disclosed; sizes 1–5 μm,

concentrations of 0.2 or 0.7 mg/L), plastic particles were found in the gut, digestive gland lumen, connective tissue, hemolymphatic sinuses, and gill surfaces, as identified through light and fluorescence microscopy.[58,59] Exposure to 0.2 but not 0.7 mg/L polymer microspheres significantly reduced cholinesterase activity, with co-exposure to florfenicol worsening the effect. In a similar investigation, Asian freshwater clams were subjected to Red Fluorescent Polymer Microspheres (1–5 μm, 0.13mg/L) for 8 days, leading to the detection of particles in the gills and digestive tract. Contact with the polymer microspheres decreased.[60,61]

SUMMARY

In summary, the diverse array of neurotoxic agents—ranging from environmental contaminants like heavy metals and pesticides to endogenously produced excitotoxins—exerts profound and often irreversible effects on the structure and function of the central and peripheral nervous systems. Through mechanisms that include oxidative stress, mitochondrial dysfunction, disruption of neurotransmitter homeostasis, and inflammatory cascades, these compounds compromise neuronal integrity at multiple levels. For instance, chronic exposure to lead and methylmercury has been shown to impair synaptic plasticity and cognitive development, while organophosphates interfere with cholinergic signaling, leading to acute neurobehavioral disturbances and long-term neurodegeneration. Moreover, endogenous excitotoxins such as glutamate, when dysregulated, precipitate excitotoxic cell death, further illustrating how both exogenous and intrinsic factors converge on common pathophysiological pathways. Advancements in high-throughput screening and in silico modelling have greatly enhanced our capacity to predict neurotoxic potential before human exposure, yet significant gaps remain. Current in vitro assays often fail to recapitulate the complex cellular interactions of the brain's microenvironment, and animal models, while informative, do not always translate seamlessly to human risk assessment. Consequently, there is an urgent need to develop more physiologically relevant three-dimensional neural cultures, organoid systems, and computational frameworks that integrate multi-omics data to capture the multifaceted nature of neurotoxicity.

Finally, public health initiatives must prioritize monitoring of known neurotoxic agents in vulnerable populations particularly children and occupational cohorts and enforce stricter regulatory limits. Future research should also explore the role of genetic susceptibility and epigenetic modifications in modulating individual responses to toxic exposures. By

combining mechanistic insights with innovative screening platforms and robust epidemiological surveillance, the scientific community can better elucidate the underpinnings of neurotoxic injury and devise targeted interventions. Ultimately, protecting neural health demands a concerted, multidisciplinary effort that bridges basic research, translational science, and policy-driven prevention strategies.

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