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REVIEW ARTICLE

# Neurological implications of heavy metals toxicity in relation to exposure source and explicated mechanisms

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**Abstract**

Heavy metal toxicity is world-wide alarming problem now-a-days. Some metals play important roles in the body like neurotransmission, gene expression and other mechanisms of the body. These are required in traces and excess amount leads to toxicity in the body. Most toxic heavy metals lead to toxicity in different body organs and may cause neurological disorders. Human beings are mostly exposed to heavy metals through food, water and environment. Heavy metal sources include both natural and by human activities i.e. industrialization, mining etc. Heavy metals are mostly non-biodegradable and remain in the environment for years, concentrated in the environment and enter into biological cycle to cause toxic effects. Toxicity of these metals leads to reduced cerebral activity, low IQ levels, sluggish learning and infections like Parkinson's disease, Amyotrophic lateral sclerosis, Autism disease and Wilson disease. Like some studies shows that aluminum has role in causing Autism disease and Parkinson's disease. Mostly heavy metals induce their toxic effect, through oxidative stress by enhancing the production of ROS, impaired mitochondrial function, inhibition of enzyme activity while few others like aluminum can cause disturbances in metal homeostasis. Most of the heavy metals can cross the blood brain barrier (BBB) without difficulty and prompt their toxic effects in brain. The consequences of heavy metals differ depending upon age, development and other physiological factors. This review addresses brief introduction of heavy metals, their neurotoxic effects and their possible mechanism of action associated with toxicity.

**Keywords**

Heavy metals
Neurological disorders
Neurotoxicity
Oxidative stress

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## Introduction

Metals are the substances that having good electrical conductivity, ductility, shiny surfaces and mostly present in the earth's crust with different composition at various locations (Jaishankar *et al*., 2014). Metals have two main groups, essential metals like selenium, copper, lithium, manganese, iron and chromium etc. and non-essential metals which examples are lead and cadmium (Chen *et al.*, 2016). Some metals have high density and more potential of causing toxicity at lower concentrations like arsenic, lead, mercury, copper and cadmium etc. However, some are necessary for the normal body functioning, few are essential micronutrients required in traces (Govind & Madhuri, 2014). i.e. Fe deficiency may leads to restless leg syndrome, breath holding spells, cranial nerve palsy etc. (Chen *et al*., 2016). Lead is non-essential metal to humans and accumulation of large amounts in the body may leads to nervous system disorders and diseases of other systems (Li *et al*., 2014).

All the heavy metals are not detrimental some are beneficial for human health and normal body functions like protein modification, electron transport, cell adhesion, immune response, synthesis of neurotransmitters. Others like nickel, lead, mercury, chromium and cadmium are toxic to human health above

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certain levels. Due to their non-biodegradable nature, they are present for prolonged periods of time in the environment and accumulate in human body and cause toxic effects (Gaur *et al*., 2014; Bosch *et al*., 2016). Heavy metals have many toxic effects like as central nervous system (CNS) depressant, decrease in ATP levels and cellular activities like oxidative stress, autophagy, DNA fragmentation and cognitive problems which lead to numerous neurodegenerative diseases like Gullien-Barree disease, amyotrophic lateral sclerosis and Alzheimer's disease and Parkinson's disease (Chen *et al*., 2016; Mohod & Dhote, 2013).

Some metals cause silent pandemic like arsenic, mercury and lead due to their long time exposure that consequence of neuro-developmental disorders, antisocial behaviors and decrease IQ level in children (Rodríguez-Barranco *et al*., 2013). Lead metal disturb the nitric oxide synthesis and learning abilities by effecting on the hippocampus (Nava-Ruiz *et al*., 2012). Similarly, concentration and learning abilities are decreased due to cadmium along with headache, vertigo and Parkinson's like symptoms (Wang & Du, 2013). In Alzheimer's disease iron accumulates in neurofibrillary and tangles amyloid senile plaques (Batista-Nascimento *et al*., 2012). Copper (Cu) and manganese (Mn) also have role in Alzheimer's and Parkinson's diseases and cause CNS damage due to their greater levels in the plasma (Dusek *et al*., 2015). Maternal environment is more suitable for developing ASD (autism spectrum disorder) environmental risk factors for this disease include obesity, any maternal infection, and exposure to toxicants like heavy metals, plasticizers, valproic acid and ethanol (Nuttall, 2017).

The main sources of heavy metals are drinking water, air and food (Govind & Madhuri, 2014). Human activities play significant contribute in heavy metals pollution by different industries like large scale use of pesticides and fertilizers (Gall *et al*., 2015). Crops and vegetables are contaminated by high levels of heavy metals polluted water (Lokeshappa *et al*., 2012). A combination of different heavy metals is released from pharmaceutical waste and textile effluents *(*Akhtar et al., 2016; Sharif et al., 2016). Numerous other sources also have considerably important like copper from electroplating and mining, mercury from hospital waste and thermal power plants and lead comes from lead batteries and paint industry (Verma & Dwivedi, 2013).

In this review we will discussed the potential sources, mechanism of toxicity and their role in various neurodegenerative disorder of different types of heavy metals in detailed.

**Iron:** Iron (Fe) is mostly present in +2 or +3 oxidative states in earth's crust and its exposure is occurred mostly by food intake (Farina *et al*., 2013). It is mostly present in all the cell of the body and act as co-factor for various types of enzymes and proteins (Batista-Nascimento *et al*., 2012). Iron has vital roles in oxygen transport, cellular respiration, differentiation and growth of the cells. It also have role in neurotransmitters production, myelin synthesis and maintaining high energy levels (Belaidi & Bush, 2016). For maintaining the proper functions of brain cells iron homeostasis is required but higher concentration of Fe shows neurotoxic effect like oxidative damage and cells death (Ward *et al*., 2014). Most of the neurological disorders are related with cascades of molecular events like accumulation of iron with symptoms like memory decline and locomotion impairments (Dhakshinamoorthy *et al*., 2017). Fe in free form can cause lipid per-oxidation which leads to cellular and mitochondrial damage (Jaishankar *et al*., 2014). Neurodegenration diseases like PD, AD, ALS, and NBIA are caused due to accumulation of iron in brain *(*Chen *et al*., 2016). AD can be better explained by two major pathological pathways: aggregated amyloid beta peptide accumulation, major part of the extra neuronal senile plaques and formation of intracellular neuro-fibrillary tangles consisting of aggregates of hyperphosphorilated tau proteins. The amyloid beta peptide theory is more important and is dominated by researchers. Iron is also involved in production of ROS and postmortem confirms the oxidative stress. Parkinson's is characterized by intracellular inclusions and increased level of iron in *substantia nigra* dopaminergic neurons. Iron also increase the Alpha-syncline is increase due to iron that lead to death of dopaminergic neurons (Batista-Nascimento *et al*., 2012). Studies shows that deposition of iron is increased with age that lead to neurodegeneration and Parkinson's disease (Ayton & Lei, 2014). In case of NBIA, iron is deposits in the basal ganglia and affect the cortex and cerebellum (Arber *et al*., 2016).

Regarding its treatment Iron chelators are mostly used for removal of excessive iron from the brain and other body parts. High doses of these chelators may be toxic effects (Ward *et al*., 2015).

***Lead*:** The main sources of lead (Pb) include paints, lead smelting, petroleum industry, transport industry, lead arsenate and lead acid batteries (Eqani *et al*., 2016). Chronic toxicity of lead is mostly due to occupational exposures at blood levels of 40-60 ug/dL and patient shows signs like delirium, vomiting, convulsions and coma (Flora *et al*., 2012). Lead exposure is mostly occurred by food intake and environment. Lead (Pb) is absorbed through GIT after oral intake and due to high affinity of erythrocytes for lead, it remain 90% in blood. Lead mostly causes renal and cardiovascular systems distress in adults while in children CNS is more affected that result in encephalopathy, decreased nerve conduction and cognitive defects (Rebelo & Caldas, 2016).

Lead can cause neurological disorders through directly by pharmacological and morphological effects. Pharmacologically Pb replaces calcium in the brain and disturbs the GABA function by altering the dopaminergic and cholinergic effects. While,

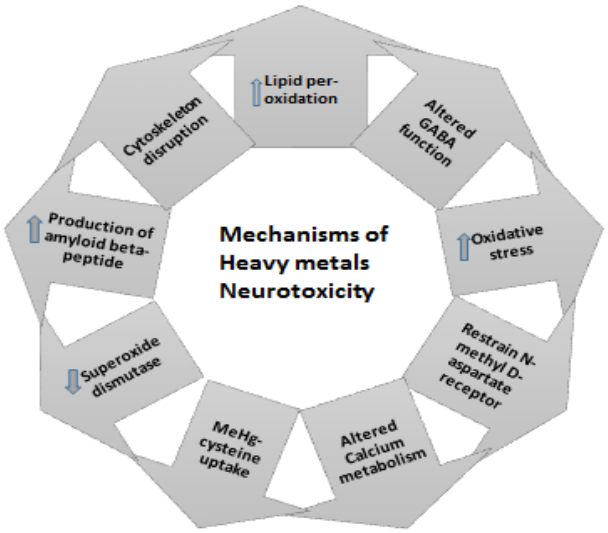


**Figure 1: Mechanisms of neurotoxicity induced by heavy metals.**

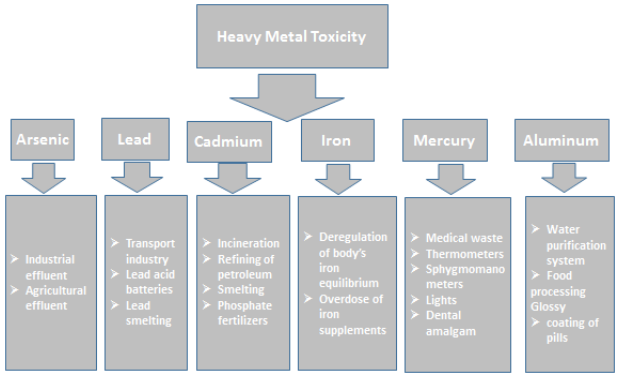


**Figure 2: Potential sources of heavy metal exposure.**

morphologically lead interfere the nervous system. Lead indirectly effects the brain by inducing changes on other body parts (Mason *et al*., 2014). Lead may induce NRF2-dependent transcriptional factor in neural stem cells recognize *SPP* up regulation and relating Pb exposure with stem cells function and neurological development in children (Wagner *et al*., 2017). AD may cause due to lead exposure during development stage (Chin-Chan *et al*., 2015). Lead may accumulate in grey matter after crossing BBB. Children's are more prone to neurological toxicity of lead because it easily crosses BBB due to its immaturity and cause decrease in hearing loss, IQ level and encephalopathy. The high level of lead may cause enduring brain damage and even death (Flora *et al*., 2012). Lead targets the memory and learning center through preventive N-methyl-D-aspartate receptor, which is vital for learning process of hippocampus. Pb also inhibit the neurological voltage-gated channels and disturbs the neurotransmitters release (Neal & Guilarte, 2013). After accumulation of Pb in mitochondria endothelial cells are first to be exposed and damage which lead to brain edema and brain damage (Nava-Ruiz et al., 2012). EDTA, $CaNa_2$ and meso-2, 3-dimercaptosuccinic are used as chelators for the excretion of lead from body but may have some side effects like nausea, loss of appetite and diarrhea (Zhai *et al*., 2015).

***Mercury*:** US Agency enlisted the mercury as third toxic metal substance. The main sources of mercury exposures include medical waste, batteries, lights, thermometers, sphygmomanometers, dental amalgam, fire stations running on coal, mining of silver and gold and incineration etc. (Kim *et al*., 2016). Mercury vapors absorbed in blood circulation through respiratory system (Rice *et al*., 2014).

Mercury toxicity may be acute or chronic and characterized with coughing, diarrhea, gingivitis, hallucination, memory loss, low IQ, cognitive dysfunction, motor polyneuropathy, tremors, neuro-cognitive and neurodegenerative diseases like Parkinson's, Autism, Autism spectrum disorder (ASD) and Alzheimer's diseases (Gauba *et al*., 2014; Mostafa *et al*., 2016). High levels exposure of mercury may have developmental and teratogenic effects with low birth weight and abortion (Dursun *et al*., 2016).

Mercury exposure is also associated with ALS (Amyotrophic Lateral Sclerosis) (Carocci *et al*., 2014). Molecular mechanisms which are involved in mercury toxicity are oxidative stress, altered thiol metabolism, interference with cell signaling, effect on neurons and imbalance of calcium homeostasis (Gauba *et al*., 2014). Mercury converts into methyl mercury (MeHg) by methylation (Carratù & Signorile, 2015). It can cross the BBB and accumulated in the brain. Long term exposure of inorganic Hg can damage the nervous system with pathological signs like PD by production of ROS and AD that result in "neurofibrillary tangles" formation in brain which is diagnostic feature of AD which promotes brain cell damage (Chakraborty, 2017). The level of 0.02ng of Hg/g can cause the destruction of intracellular microtubule axon degeneration by oxidative stress in Autism disease (Gauba *et al*., 2014). Dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropane-1-sulfonate DMPS can be used intravenously for the treatment of mercury as chelates (Bernhoft, 2012).

***Cadmium*:** The main sources of cadmium (Cd) includes smelting, phosphate fertilizers, mining of metals, cigarette, occupation exposure like welding, incineration and fossil fuels can contaminate the food and water (Rodríguez-Barranco *et al*., 2014; Unsal *et al*., 2015). It enters in the body through inhalation up to 10-15% and 5-10% by ingestion. The levels of Cd is reported higher in liver and kidney of smokers than normal (Bernhoft, 2013).

Cadmium toxicity may cause abnormalities in kidney, liver, skeletal, cardiovascular and reproductive systems (Zhai *et al*., 2015). In neonates may cause abnormalities like reduced height, birth weight, level of

thyroid hormone and may effect growth rate of the body (Al-Saleh *et al*., 2014). A relationship between Cd toxicity and cancers of different body organs like liver, lung, kidney, prostate and testes also have been reported. It also interfere in the normal functions of CNS which includes headache, poor concentration, learning abilities, olfactory dysfunction, vertigo and Parkinson's disease symptoms (Wang & Du, 2013).

Cadmium cause toxicity by enzyme inhibition that is involved in proof reading and rectifying incorrect matches during DNA replication development (Gumpu *et al*., 2015).

Cadmium may causes neuro-toxic effects because it can cross BBB and induced oxidative stress in brain tissues which leads to cellular-degeneration and protein damage (Bernhoft, 2013). The CNS abnormalities by cadmium toxic metal includes membrane disturbances, increases oxidative markers, reduced acetyl cholinesterase activity, glutathione depletion and cortical cells apoptosis in CNS due to induction of free radicals in the brain cells (Bernhoft, 2013; Unsal *et al*., 2015). Genistein can be used against cadmium induced toxicity with good results (Gong *et al*., 2015).

***Arsenic*:** Arsenic (As) is 20$^{th}$ most present element on earth crust and over 226 million people effected due to water pollution by arsenic worldwide mostly in underdeveloped countries (Bardach *et al*., 2015; Chakraborti *et al*., 2017). Water is polluted by arsenic from agriculture and industrial sources. Most arsenic water polluted countries are India, Argentina, Denmark, Taiwan, Bangladesh, Taiwan, China and United States (Lu *et al*., 2014). Chronic exposure of arsenic may cause cancers like skin, lung and kidney etc. and other disorders like cardiovascular, neurological and diabetes mellitus (Lu *et al*., 2014; Bardach *et al*., 2015). Mostly exposure of arsenic is occurred through inhalation, ingestion and skin contact (Abdul *et al*., 2015).

Arsenic is ranked 1$^{st}$ in toxicants to produce toxicity. It may accumulate in brain tissues mainly in pituitary after crossing BBB (Tyler & Allan, 2014). Arsenic exposure is related with autism in children (Tarro *et al*., 2017) and in early life may cause low IQ, memory loss, performance and motor function (Rodríguez-Barranco *et al*., 2016). On the other hand, arsenic is largely used in the treatment of cancers like leukemia as medicine (Sun *et al*., 2014). Arsenic toxicity may be acute or chronic in which sensory nerves are more affected as compared to motor nerves with symptoms like pain, paresthesia and foot numbness (Abdul *et al*., 2015). Arsenic and lead have combine affects like anxiety, decrease learning and memory loss but arsenic metal is more toxic as compared to lead metal (Aktar *et al*., 2017). There is also association between Arsenic toxicity and neurological ailments like PD and AD that is evident from experimental studies (Escudero-Lourdes, 2016).

Arsenic toxicity is caused by mostly three mechanisms following:

(i) There is increase in ROS, lipid peroxide and reduced activity of superoxide dismutase by oxidative stress that result in neurotoxicity.

(ii) Brain damage due to induction c-Jun N-terminal kinase (JNK) and Mitogen-activated protein kinase (p38 MAPK) pathways.

(iii) Axonal degeneration and neurotoxicity due to destabilizing and disruption of cytoskeleton (Abdul et al., 2015).

Results of different studies shows that in chicken brain tissues, with treatment of $As_2O_3$ there is an increase in inflammatory-related factors like NF-kB and pro-inflammatory. As toxicity in chicken activates the host defense and induces inflammatory responses by expression of inflammatory genes (Sun *et al*., 2017). Arsenic disturbs the oxidant-antioxidant balance in chicken. In chicken model, it shows decreased Glutathione peroxidase and catalase as compared to control. These findings are suggestive of arsenic poisoning in chicken (Zhao *et al*., 2017). Sensory neuron and skeletal muscle formation could be inhibited by low levels of methylated arsenic species. This is also related to low birth weight and neurological disorders in exposed chicken (McCoy *et al*., 2015; Khairul *et al*., 2017).

Selenium is used in the treatment of arsenic toxicity as an anti-carcinogenic agent which helps in excretion of arsenic from body after conjugation. Along with used high protein diet, antidepressants and exposure to enriched atmosphere (Tyler & Allan, 2014).

***Aluminum*:** Aluminum (Al) metal is mostly present in cosmetic, medicines, vaccines, coatings of pills and food processing (Shaw *et al*., 2014). Mostly in human beings aluminum exposure is occurred by food, water and skin (Bondy, 2014) and intensely affected renal and circulatory systems (Wu *et al*., 2012; Shaw & Tomljenovic, 2013). Aluminum is also used in food industry as emulsifying agents, in baking powder, food colors, cosmetics and in water purification in different concentrations (Bondy, 2016). Aluminum is toxic to all kinds of life and have harmful effects due to its non-bioavailability nature in atmosphere (Han *et al*., 2013).

High concentrations of Al in the body leads to toxic effects like interference in essential metal homeostasis like magnesium (Mg), calcium (Ca) and iron (Fe), disturbance in mitochondrial enzymes, enhanced production of lipids and neurological disorders (Lemire & Appanna, 2011). Al may cause anemia by deregulation of Fe homeostasis and skeletal diseases like osteomalacia (Han *et al*., 2013). Exposures to Al via drinking water may reduce acetylcholine instead of free available choline, and this reduction is due to decreased recycling of acetylcholine. This may leads to decreased cognitive and memory deficits (Farhat *et al*., 2017).

Al toxicity mechanism includes Deregulation of metal homeostasis. Al binds with phosphate group by replacing the Mg on cell membrane i.e. ATP and DNA. Al is a neurotoxin which cause neurodegenerative diseases like Autism Spectrum Disorders (ASD), Alzheimer's disease (AD) and Amyotrophic lateral sclerosis (ALS) although there is no direct causal role of aluminum is yet proven, however high levels of Al may progress the disease in the brain (Shaw & Tomljenovic, 2013; Yüce *et al*., 2017; Han *et al*., 2013). Intracellular free iron exposure leads to increased formation of ROS. In Al toxicity, there was observed increase production of amyloid beta-peptide, reduced degradation and its deposition in AD disease (Wang *et al*., 2016).

**Conclusion:** The heavy metals toxicity to human health is well established. The exceeding levels of heavy metals can lead to moderate to severe neurotoxicity depending upon the age and physiological factors. With increased concentrations in the environment heavy metals are entering into biological cycle and causing neuro-toxic disorders like PD, AD, ALS, Guillain-Barre Syndrome etc. Failure to minimize the exposure can lead to severe and more complicated conditions. Occupational exposure can be minimized by adopting safety procedures and engineering. Exposure monitoring, and interventions for reducing the heavy metals exposure in humans and environment are significant steps regarding prevention. National as well as international cooperation and legislation is very important for right tactics to minimize the heavy metals toxicity.

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