

# Heavy Metal Causing Neurotoxicity in Human Health

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**ABSTRACT:** Human exposure to heavy metals is a worldwide major health problem. Heavy metals which cause neurological toxicity, such as Pb, Hg, Cd, Cu, Zn, As, Fe and Cd considered as most neurotoxic agent which affect humans. They having particular concern due to the long-lasting and possibly irreversible nature of their effects. The heavy metal exposure in childhood can result in cognitive and behavioral deficits in children. Neurotoxicological disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common but dangerous as it can cause lifelong disability. Metals are universal and take dangerous part in neurobiology. Heavy metals generate toxic effects on different organs of body and by this differently affect Humans. Heavy metals contaminate in water, air, soil etc. and affect human beings by different ways.

**KEYWORDS:** Neurotoxicity, Heavy Metal, Effect, etc.

## I. INTRODUCTION

Heavy metal poisoning has become an increasingly major health problem, especially since the industrial revolution, effect may be either acute or chronic [1, 2]. Additionally, mental disability prevalence rates were twice as high in developing countries as found in developed countries. Environmental factors, such as maternal and child health care, immunizations, and environmental pollution, can influence the prevalence of mental disability [3]. Thus, poorer health quality and higher contamination levels of pollutants in developing countries may contribute to the higher prevalence rates. A prime agent implicated in cognitive and neurological deficits is environmental exposure to heavy metals. Heavy metal exposure can occur through contaminated air, food, water, or in hazardous occupations. While the levels of heavy metal contamination of the environment have decreased in recent decades in the developed world, the developing world experiences high levels of metal pollution. In particular, Asian and African countries have high levels of metal contamination, especially in urban environments [4, 5]. The excess quantities of heavy metals are detrimental as these destabilize the ecosystems because of their bioaccumulation in organisms, and elicit toxic effects on biota and even death in most living organisms [6]. Nearly all organ systems are involved in heavy metal toxicity; however, the most commonly involved systems include the (central nervous system) CNS, (peripheral nervous system) PNS, hematopoietic, renal, and cardiovascular. The other problems include carcinogenicity, nephrotoxicity, nervous system toxicity, respiratory system toxicity, endocrine and reproductive effects [7]. With prenatal or neonatal developmental insults, dietary deficits and stress damage the brain structures and down regulate essential neurotransmitters, because toxic metals are retained in bone urine, feces and astroglial cells in the brain [8]. Small amounts of toxic metals appear in hair, nails, sweat, saliva and breast milk [9, 10]. Uptake during fetal development and early childhood has long lasting effects on development and behavior. Although ligand formation is the basis for much of the transport of heavy metals throughout the body, some metals may compete with ionized species such as calcium and zinc to move through membrane channels in the free ionic form. For example, lead follows calcium pathways in the body [11, 12, 13].

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## Neurotoxicity of Iron (Fe)

Iron(Fe) and neurodevelopment has focused primarily on the effects of Fe deficiency anemia. Nevertheless, there is evidence that excess Fe stores in pregnancy and newborns may be toxic. Several studies have noted a “U”-shaped association between maternal hemoglobin or serum ferritin (SF) and low birth weight. This association has been attributed by some investigators to a failure of normal plasma volume expansion in pregnancy or to inflammation from undiagnosed perinatal infection, as serum ferritin is a well-known acute-phase reactant [14, 15]. Showed that high trimester-2 maternal Fe stores not only predicted low birth weight and prematurity but also predicted decreases in IQ in children who were followed until age 5 y. More recently [16]. Demonstrated a U-shaped association between infant umbilical cord SF and lower IQ scores at age 5 y in an Alabama birth cohort. Subjects in the highest quartile of SF at birth were 3.3-fold more likely than the middle 2 quartiles (95% confidence interval: 1.2–9.1) to score below the 15th percentile in full-scale IQ. Similar findings were reported for subjects in the lowest quartile for SF, suggesting that both high and low Fe stores are associated with poor developmental outcomes. Animal studies also support these findings. Fe supplementation of rats produced a decrease in motor activity and exploratory and stereotyped behaviors similar to that of late iron deficiency (ID) anemia [17]. Another report by Fredriksson et al. showed that mice administered large oral doses of Fe at postnatal d 10–12 had long-term effects on spontaneous motor behavior, with the animals showing a lack of habituation of spontaneous activity and poorer performance in the radial maze test at 3 mo of age [18]. Such findings, if validated, will undoubtedly complicate public health efforts at eradicating Fe deficiency but should not be dismissed as confounding from the effects of ferritin as an acute phase reactant. Excess Fe is known to be neurotoxic in adults, and the possibility that it may also produce health effects in pregnant women and newborns must also be investigated [19].

## Neurotoxicity of Lead (Pb)

The lead exposure is a public health concern, especially in early childhood as children are more at risk because of increased hand to mouth activity and absorb about half of an oral dose of water-soluble lead [20]. Childhood lead exposure is estimated to contribute to 600,000 new cases of children with intellectual disabilities every year with 99 % of them living in developing countries [21]. The lead exposure in utero, infancy or early childhood can slow mental development and cause lower intelligence later in childhood that can persist beyond childhood. The effects of lead are more toxic on developing nervous system of children than on a mature brain. Lead-associated deficits have been documented in most fields including verbal intelligence quotient (IQ), performance IQ, academic skills such as reading and mathematics, visual/spatial skills, problem-solving skills, executive functions, fine and gross motor skills, memory and language skills. Meta-analyses have indicated that children’s IQ scores decline 2–3 points per 10 ug/dl increase in blood lead level and identified no threshold for the effects of lead on IQ [22, 23]. In fact academic performance of children exposed to lead has been observed to be subservient in comparison to controls. Children (6–10 year old) with blood lead levels of 5–10 ug/dl scored significantly lower than children with levels of 1–2 ug/dl on academic skills such as word reading, reading comprehension, listening comprehension, math reasoning and math calculations [22]. Another large American study documented inverse association between blood lead levels as low as 2 ug/dl, measured up to 5 years of age, and end-of-grade reading and mathematics achievement scores [24]. In National Health and Nutrition Examination Survey (1999–2002), the risk of parent-reported diagnosis of attention deficit hyperactivity disorder increased, in a dose-dependent manner with blood lead level [22]. Similar findings have been reported by a recent Indian study which emphasizes the detrimental effect of lead on executive and attention domain in neurobehavioral function [25]. The mechanisms underlying lead-induced neurotoxicity are complex. Oxidative stress, membrane bio-physics alterations, deregulation of cell signaling, and the impairment of neurotransmission are key aspects involved in lead neurotoxicity. It can cause toxicity by oxidative stress directly or indirectly by lipid peroxidation resulting in the generation of reactive oxygen species (ROS), including hydroperoxides, singlet oxygen, hydrogen peroxide and direct depletion of antioxidant reserves. Lead renders enzymes nonfunctional by binding to their sulfhydryl groups further contributing to an impairment in oxidative balance [26]. The ability of lead to pass through the blood–brain barrier is mainly due to its ability to substitute for calcium ions. Within the brain, lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, and possibly Alzheimer’s disease, Parkinson’s disease and schizophrenia [27]. Lead substitutes for calcium

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and to a lesser extent zinc, inappropriately triggers processes dependent on calmodulin. Lead also restricts neurotransmitter release, disrupting the function of GABAergic, dopaminergic and cholinergic systems as well as inhibiting NMDA-ion channels during the neonatal period. Indeed experimental studies have shown that lead activates protein kinase C in capillary cells and inhibits Na<sup>+</sup>/K<sup>+</sup>-ATPase thus interfering with energy metabolism. Within the cell, lead appears to interfere with calcium release from the mitochondria resulting in formation of permeability transition pore and primes for programmed cell death processes leading to mitochondrial self-destruction [28]. Hence direct neurotoxic actions of lead include apoptosis, excitotoxicity affecting neurotransmitter storage, release and modifying neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, astroglia and oligodendroglia. Mechanisms underlying cognitive deficits resultant of lead exposure have been reported using cellular models of learning and memory. There is convincing evidence that exposures to lead have adverse effects on the central nervous system (CNS), environmental factors augment lead susceptibility and exposures in early life can cause neurodegeneration in later life. Magnetic resonance spectroscopy (MRS) has revealed reductions in the N-acetylaspartate-to-creatine and phosphocreatine ratios in the frontal gray matter of lead-exposed children, consistent with increased neuronal loss. Similarly in adults an association between greater cumulative lead exposure and higher myoinositol-to-creatine ratios in the hippo-campus, reflecting glial dysfunction has been seen [22].

### **Neurotoxicity of Copper (Cu) and Zinc(Zn)**

Like Fe, most of the literature on the neurotoxicity of Cu and Zn centers around nutritional deficiency and its effect on brain [29]. Also, as for Fe, there is evidence of neurotoxicity when these metals are found in excess in the brain. Cu is a transition metal, and consequently, its metabolism and toxicity are similar to those of Fe and Mn. As for Fe, genetic diseases of excess Cu retention are well described and have significant neurologic sequelae. Wilson's disease is the most common of these diseases, and the presenting complaint for this genetic disorder frequently includes neurobehavioral changes resembling schizophrenia [30]. These neurologic findings may even precede other findings such as liver disease. Descriptions of environmental or excess dietary Cu producing subclinical neurobehavioral effects are very rare, but these have not been systematically studied. Excess brain Cu is a common finding in neurodegenerative diseases such as Alzheimer's disease. Zn deficiency has long been known to impact neurodevelopment adversely, but the effects of excess Zn on neurodevelopment are essentially unknown. Excess Zn, like excess Fe and Cu, is a common finding in neurodegenerative disease [31]. Zn finger proteins are key transcriptional elements that regulate the cellular response to metal toxicity among other processes. Excess Zn is involved in the neuronal injury observed in cerebral ischemia, epilepsy, and brain trauma. Toxic Zn accumulation may result from either trans synaptic Zn movement or mobilization from intracellular sites, such as Zn flux through receptor associated calcium channels, voltage-sensitive calcium channels, or Zn-sensitive membrane transporters [32]. The mechanisms by which Zn exerts its neurotoxicity include mitochondrial production of reactive oxygen species and the disruption of metabolic enzymes, ultimately leading to activation of apoptotic processes. As with Cu, Fe, and Mn, an exciting new area of research is the role of Zn metabolism in Alzheimer's disease as a trigger for amyloid-b aggregation and neuronal plaque formation. As we previously noted, excess Fe, particularly during pregnancy, has been associated with neurodevelopmental outcomes later in life, and similar studies of Cu and Zn in pregnancy are sorely needed [19].

### **Neurotoxicity of Cd**

The neurotoxicity of Cd in children was investigated in several studies in the 1970s and 1980s but has received little attention since. In most of these studies, the biomarker of exposure was the concentration of Cd in hair. In case-control studies in which the hair concentration of Cd of a clinically defined group was commonly encountered as mixtures in the environment. Initial studies merely reported correlations among markers of internal metal dose, including a positive correlation between blood Pb and Mn and a positive correlation between urine As and blood Pb among children [33-35]. With respect to neurologic outcomes, we are unaware of any clinical data investigating joint exposures to Mn and Pb. However, animal studies provide compelling evidence that exposure to both Mn and Pb lead to synergistic neurological effects. Among rats orally exposed to both Mn and Pb, motor activity and neurotransmitter levels were

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significantly increased, compared with rats exposed to only 1 metal [36]. Exposure to Pb and Mn decreased learning of conditioned avoidance responses more than either Pb or Mn alone, and gestational exposure to both Pb and Mn reduced brain weight to a greater extent than either metal alone [37]. Each of these studies also showed that co-exposure to Mn and Pb led to increased brain Pb levels, perhaps because of changes in affinity of Pb-binding proteins in the brain [38]. In addition, multiplicatively greater changes in monoaminergic neurotransmitter levels occur in the brains of rats exposed to Pb and As jointly, compared either metal alone or to combinations of Pb, Mn, and As [39]. observed that Mn and As had greater accumulation in rat brains relative to controls with single metal exposures [40]. The 3 metal concentrations when combined were associated decreases in dopaminergic metabolites and increases in serotonergic metabolites. Overall, these findings are complex, but the data support the concept that co-exposure to multiple metals may cause neurotoxic effects not seen with exposure to a single metal at the same dose [19].

## Neurotoxicity of Methylmercury

Toxic effects on the brain due to methylmercury were first established in men with occupational exposure [41]. The developmental toxicity of this organic mercury compound became evident in the 1960s in Minamata, Japan, where an epidemic of spasticity, blindness and profound mental retardation was seen in infants born to mothers who consumed fish from contaminated waters. After many years of clinical and experimental studies, the source proved to be mercury compounds released into Minamata Bay by a plastics plant [42]. Methylmercury accumulated and reached high concentrations in locally caught fish. Exposed adults, including mothers of poisoned children, were less seriously affected, if at all [43]. Similar outbreaks of profound neurodevelopmental disorders in the infants of seemingly unaffected mothers have arisen after maternal consumption during pregnancy of seed grain treated with methylmercury fungicides [44, 45]. Studies of a serious poisoning incident in Iraq established a crude dose-response association between mercury concentrations in maternal hair and risk of neurological abnormalities in the children of the women [46]. Recent studies have focused on prenatal exposures to reduced concentrations of methylmercury. They have examined populations with a high intake of seafood and freshwater fish with various degrees of methylmercury contamination. Prospective examination of a New Zealand cohort noted a three-point decrement in intelligence quotient (IQ) and changes in affect in children born to women with mercury concentrations in hair of greater than 6 µg/g. A large prospective study in the Faroe Islands noted evidence of dose-related impairments in memory, attention, language, and visuospatial perception in exposed children [47]. A third prospective cohort study in the Seychelles provided no support for prenatal neurotoxicity after adjustment for postnatal exposures [48]. Several cross-sectional studies recorded significant associations between methylmercury exposure and neurobehavioral impairment in young children [49].

## Neurotoxicity of Arsenic (As)

Ingestion of arsenic-contaminated drinking water has long been recognised to cause peripheral neuropathy in adults [50]. Developmental neurotoxicity due to arsenic was reported in 1955 in Japan, where consumption of powdered milk contaminated with arsenic led to over 12 000 cases of poisoning and 131 deaths. A follow-up study of three groups of adolescents born during the time of the milk contamination included one group that was fully breast-fed, one that was exposed to the tainted milk product, and one that received other supplements, but no tainted formula. Compared with national rates, a ten-fold increase in mentally-retarded individuals was seen in the tainted milk group. Poor school records, emotional disturbances, and abnormal or borderline electro-encephalogram findings were also more common in the exposed group. Since these findings were initially reported in Japanese journals not easily available elsewhere [51,52], they have often been overlooked, even in the most thorough risk assessments of environmental arsenic exposure [53,54]. Arsenic is present in ground water worldwide, and industrial pollution is widespread. Cross-sectional studies of school-age children showed cognitive deficits associated with drinking water contamination [52] and raised urinary arsenic concentrations [54,55]. Similar results were obtained in children with arsenic exposure from a smelter [56]. Possible combined adverse effects on IQ caused by arsenic and manganese exposures was suggested by metal concentrations in hair in children living near a hazardous waste site [57]. Although evidence for subclinical neurodevelopmental neurotoxicity of arsenic is less well established than for lead and methylmercury, the data are

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consistent and fit with the high-exposure findings from Japan. Still, regulatory action does not emphasize the need to protect the developing brain against this neurotoxic substance [53,58].

## III. DISCUSSION

Heavy Metals are recognized as causes of developmental neurotoxicity. The major impact of heavy metals is on the peoples who were directly in exposure of industries. Nowadays the major reason of neurotoxicity by which human affected is due to toxicity from mixture of heavy metal instead of single metals. The effect of human exposure to mixtures of heavy metals is presently an major research area in neurotoxicology. This proposes that contact to multiple metals may result in higher order of neurological effects than to single metals and this enhance need to understand the toxicology of complex mixtures. Analysis of concentration of heavy metals in chemicals before allowing them to be marketed is concerned to prevent toxicity, but has been seen active only in recent years. These consisted of employees who were exposed to high doses of elements either by inhalation or accidental ingestion, and began to develop permanent neurologic damage. Some of these information originated in industries where heavy metals exposure was common.

## IV. CONCLUSION

This paper reviewed the neurotoxicity Effect of Human Health. The growing effects of Heavy metals on cognition and behavior in children may be linked to this common theme of toxicity. The emerging brain is predominantly sensitive to agents that disrupt synaptic activity. The practice of Heavy Metals detection should be continued to avoid possible consumption of contaminated eatables. Neurological symptoms are recognized, early and appropriate treatment and removal from exposure is provided, neurotoxicological and or psychological function can remain steady or actually improve despite the earlier exposures. This is mostly prominent with peripheral neurotoxicity.

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