**Consequences of Toxic Heavy Metals on Environment and Human Health: A Review**

**Abstract:**

Heavy metals are significant environmental pollutants that persist in various ecosystems due to their toxicity and ability to remain in the atmosphere, contaminating soil, water, and living organisms. These contaminants can bioaccumulate in the human body, posing serious health risks. While some heavy metals are generated by human activities, the majority occur naturally. Living organisms can be exposed to heavy metals through the food chain as they interact with environmental elements such as soil, water, and air, which can amplify their harmful effects. Humans are particularly vulnerable to the combined effects of multiple heavy metals rather than exposure to a single substance. This combination can lead to oxidative stress and inflammatory processes, resulting in damage to various organs. This review highlights the fate of heavy metals and their toxicological effects on different organ systems. Some metals influence developmental and biological processes, while others accumulate in specific organs, potentially leading to a range of illnesses. In this work, we have reviewed the toxicity of several heavy metals such as lead, cadmium, chromium, mercury, their impact on the environment and human health,

**Key words:** Heavy metals, health risks, environment, oxidative stress

**Introduction:**

Naturally occurring heavy metals are found in the earth's crust, but most environmental contamination and human exposure stem from human activities like mining, smelting, industrial production, and the use of metal-containing compounds (Wang et al.,2020). The increasing exposure to heavy metals poses significant health risks, as contamination of water, air, and food with these toxic substances has become a global concern affecting millions worldwide (Tchounwou et al., 2016). While the harmful effects of heavy metals are well-known, recent research suggests that certain metals like nickel, copper, and zinc are essential for human health and occur naturally whereas, elements such as Lead (Pb), Mercury (Hg), Arsenic (As), Chromium (Cr) and Cadmium (Cd), have no known biological role and, are harmful to the animals beyond a certain range. Occupational exposure refers to the contact humans have with toxic substances in the workplace, while non-occupational or environmental exposure pertains to the same chemicals encountered by the general public (Dixit et al., 2015). Non-occupational exposure can occur through ingestion of contaminated food and water or through skin contact. Monitoring heavy metal levels in water sources, air, and food is essential for safeguarding the health of both humans and animals (Luo et al., 2020; Azeh Engwa et al., 2019). Food crops grown in environments contaminated with heavy metals causes these elements to bioaccumulate in human food chains via geo-chemical cycles. Chronic poisoning effects on animals have been commonly observed if adequate every day intake amounts are surpassed. Most metallic elements are harmful due to their tendency to accumulate in the soft tissues of animals. Each metal operates through distinct mechanisms and biological pathways within the target system (Qasem et al., 2021).

Chronic exposure to low levels of toxic heavy metals in the environment can result in long-term health issues, as symptoms may not manifest immediately unlike in cases of acute poisoning. While chronic exposure to heavy metals can elevate the risk of cancer, their carcinogenic potential is not always definitive. Some heavy metals may have a limited ability to cause mutations in DNA but can still disrupt gene expression, potentially impacting cell growth and development (Ekere et al., 2017). Furthermore, these metals can impede DNA repair mechanisms and alter the functioning of genes. The International Agency for Research on Cancer (IARC) classifies certain heavy metals according to their potential to induce cancer in humans.

**Method:**

This review aims to provide an in-depth examination of the current research regarding the toxic mechanisms of heavy metals, with a particular focus on mercury, lead, cadmium, chromium, and arsenic. It delves into their respective adverse effects and underlying toxic pathways. The analysis involves a comparison and discussion of pertinent findings sourced from diverse scientific databases like PubMed, Web of Science (ISI), Scopus, and Google Scholar, utilizing search terms such as mercury, lead, cadmium, chromium, toxicity, poisoning, and intoxication.

**Heavy metals in the environment**

Heavy metals are considered trace elements due to their presence in very low concentrations (ranging from parts per billion to less than ten parts per million (Goyer et al., 2001). in various environmental sources. Factors such as temperature, phase association, adsorption, and sequestration can affect their bioavailability. Lead, a non-biodegradable metal that occurs naturally in limited amounts, is on the rise in the atmosphere due to human activities like manufacturing, mining, and burning fossil fuels. Exposure to high levels of lead is harmful to the human body, with children being especially susceptible. Children are at greater risk of lead poisoning from contact with lead-contaminated dust in their surroundings (Loh et al., 2016).

Cadmium is a heavy metal that poses significant environmental and occupational risks. It is naturally found in black shale and is primarily sourced from volcanic activity, parent materials, marine sedimentary rocks, and phosphates (Bakshi et al., 2018).. The earth's crust contains an average cadmium concentration of about 0.1 mg/kg, with marine phosphates containing the highest levels at about 15 mg/kg. Cadmium is released into the atmosphere through natural processes and human activities, leading to exposure for animals and humans through various pathways. Pollution of aquatic ecosystems by cadmium is primarily caused by absorption, industrial discharge, and surface runoff, impacting soil and sediment quality. Human and animal poisoning from cadmium can occur through the ingestion of contaminated food, inhalation of polluted air, or consumption of cadmium-rich water. Due to its lack of benefits for plant growth and metabolic activities, cadmium is not conducive to ecological processes (Hayat et al., 2018).

**Table 1: Toxic Metal in Industrial Sewages**

|  |  |
| --- | --- |
| Metal | Manufacturing Industries |
| Cadmium | Electronics, Phosphate Fertilizer, Pigments and Paints  |
| Lead | Paints, Battery |
| chromium | Metal Plating, Tanning, Rubber and Photography |
| copper | Plating, Rayon and Electrical |
| Mercury | Chlor-Alkali, Scientific Instruments, Chemicals |
| Nickel | Electroplating, Iron Steel |
| Arsenic | Metal Hardening, Phosphate and Fertilizer, Paints and Textile |

Chromium is a potentially harmful element that can be found in two main forms in the environment: chromium (III) and chromium (VI). Chromium (III) is considered less dangerous than chromium (VI), with the two forms being able to convert into each other during industrial processes (Coetzee et al., 2020). While elemental chromium [Cr (0)] is not naturally occurring, it is introduced into different environmental components such as air, water, and soil through a combination of natural sources and human activities. Industrial operations, particularly in metal processing, tanneries, chromate production, stainless steel welding, and the manufacturing of chrome pigments, contribute significantly to the release of chromium. This element is commonly used in various commercial applications like industrial welding, chrome plating, dyes and pigments, leather production, wood preservation, and as an anticorrosive agent in cooking systems and boilers (Wang et al., 2006)

Manganese, the most common hazardous heavy metal, can be found in various oxidation states in the environment. When methylcyclopentadienyl manganese tricarbonyl (MMT), an additive in gasoline, is burned, manganese oxides are emitted into the air. Although manganese is essential for many bodily functions, consuming too much can result in serious toxicity according to O'Neal and Zheng (2015).

Arsenic is a common element found in trace amounts in various environmental sources. It can exist in different forms, including trivalent and pentavalent arsenate inorganic forms, as well as organic methylated metabolites like monomethylarsonic acid (MMA), dimethyl arsenic acid (DMA), and trimethyl arsine oxide. Arsenic pollution comes from both natural causes such as volcanic activity and soil erosion, as well as human activities (Tellez-Plaza, et al., 2013).

**Heavy metals Toxicity on human health**

**Cardiovascular toxicity**

Cadmium is a hazardous metal recognized for its toxic nature and carcinogenic properties. Being exposed to cadmium can result in various health concerns, such as kidney disease, bone abnormalities, and cardiovascular issues (Toxicological Profile for Cadmium, 2002). Exposure to cadmium at low to moderate levels has been associated with various health conditions, including hypertension, diabetes, atherosclerosis, peripheral arterial disease, chronic kidney disease, heart attacks, strokes, and heart failure (Hellström et al., 2001; Peters et al., 2010). Lead toxicity is a commonly reported issue related to exposure to heavy metals, particularly affecting children. Lead serves no beneficial purpose in human metabolism. Exposure to lead can occur through various sources, including lead-containing paint, food stored in lead containers, and contaminated water. Prolonged exposure to lead can result in numerous health problems, such as arteriosclerosis, hypertension (Tellez-Plaza et al., 2008) thrombosis, atherosclerosis, and heart disease. These conditions are influenced by factors like oxidative stress (Kianoush et al.,2013), reduced nitric oxide availability, elevated levels of vasoconstrictor prostaglandins, changes in the renin-angiotensin system, decreased vasodilator prostaglandins, disruption of calcium signalling in vascular smooth muscle cells, increased inflammation and endothelial dysfunction, and altered vascular responses to stimuli. Prolonged lead exposure can lead to higher blood pressure levels, while mercury has been found to cause harm to the nerves, kidneys, liver, and heart. Recent studies have also shown cardiovascular damage from mercury, as levels in hair have been associated with elevated oxidized LDL levels in arterial plaques, acute coronary events, and atherosclerosis (Boskabady et al.,2016). Cobalt exposure can result in temporary weakening of the heart's pumping ability, a form of heart muscle damage called systolic cardiac depression. While cobalt-induced cardiomyopathy can progress slowly and be life-threatening, survivors typically experience recovery of their heart function. Additionally, there may be an increase in T cell proliferation associated with these toxic exposures (Packer, 2016). Some of the necessary metals (Co, Cu, Cr, Ni, and Se) and toxic metals (As, Cd, Pb, and Hg) are metallo-estrogens and may raise the risk of CVD by disrupting hormones (Choe et a.,2003).

**Hepatotoxicity**

Cadmium exposure primarily affects the kidneys and liver. Acute exposure leads to cadmium accumulation in the liver, causing dysfunction. This disrupts cellular redox balance, inducing oxidative stress and liver cell damage. Both acute and chronic exposure can cause hepatotoxicity, potentially leading to liver failure and increased cancer risk, as noted by Hyder et al. (2013). "Chronic lead exposure damages liver cells, inducing oxidative stress. When paired with organic solvents, lead's harmful effects on the liver can intensify due to shared toxicological properties (Malaguarnera et al., 2012). Prolonged exposure to lead may deplete glycogen and cause cellular infiltration in the liver, potentially leading to chronic cirrhosis. (Hegazy and Fouad, 2014). Arsenic exposure can lead to liver lesions and increased risk of liver cancers, including hepatocellular carcinoma and angiosarcoma (Lu et al., 2001; Liaw et al., 2008). Copper accumulation in the liver, as seen in Wilson's disease, can cause oxidative stress and liver damage. Elevated hepatic copper levels are also associated with cholestatic liver diseases, primarily due to impaired biliary excretion rather than infection (Yu et al., 2019).

 

 **Figure 1: Effect of heavy metals on human health ( Harischandra et al., 2019)**

**Nephrotoxicity**

The presence of lead can have harmful effects on different organs, with the kidneys being especially vulnerable. Acute exposure to lead can result in lead nephropathy, which may manifest as proximal tubular dysfunction resembling Fanconi syndrome. Conversely, chronic lead nephropathy is defined by tubular atrophy, interstitial fibrosis, renal failure, hyperplasia, and glomerulonephritis (Wang et al., 2013). In rats, the subcutaneous administration of PbA at a dose of 100 mg/kg body weight resulted in increased levels of lipid peroxidation markers such as MDA and 4-HDA in the liver and kidneys when compared to control animals. Furthermore, PbA led to a decrease in levels of SOD and total GSH in the liver and kidneys of rats as reported by El-Sokkary et al. in (2005)**.** Additionally, exposure to PbA at a concentration of 500 mgPb/L in drinking water was found to induce apoptosis by triggering the release of mitochondrial cytochrome C, inhibiting Bcl-2 proteins, and activating caspase-3 in the kidneys of exposed rats, as indicated by Liu et al. in (2012).

Cadmium (Cd) is a naturally-occurring but rare element found in soil and minerals in the form of sulfide, sulfate, carbonate, chloride, and hydroxide salts as well as in water. When present in contaminated water, cadmium can disrupt essential bodily mechanisms, potentially causing short-term or long-term health issues (Cao et al., 2018). Exposure to cadmium has been linked to nephrotoxicity, which can manifest in severe clinical symptoms like glucosuria, Fanconi-like syndrome, phosphaturia, and aminoaciduria (Reyes et al., 2013). When the proximal tubular epithelium in the kidneys is directly exposed to cadmium, it can lead to increased cadmium levels in urine, aminoaciduria, 32-microglobulinuria, and glucosuria. This exposure can also lead to impaired reabsorption of renal tubular phosphate. Prolonged exposure to cadmium can be linked to conditions such as renal tubular acidosis, renal failure, and hypercalciuria, according to Friberg et al. in (2019). Investigation of kidney tissues of Wistar rats exposed to 1 mg/m3 Hg vapor per day revealed histological alteration of the kidneys after 45 days (Akgül et al., 2016). The gastrointestinal tract (GIT) and kidneys are the main organs impacted by mercury (Hg) salts. Prolonged exposure can lead to conditions such as acute tubular necrosis, immunological glomerulonephritis, or nephrotic syndrome, primarily due to the preferential accumulation of Hg ions in the renal tubule epithelial cells. As a result, elevated Hg levels can cause significant renal damage. Additionally, chronic exposure to elemental mercury vapors, inorganic mercury, and ingestion of Hg2+ salts has been associated with nephrotic syndrome, which is characterized by acute tubular necrosis, proteinuria, and albuminuria (Sanchez et al., 2018)

**Neurotoxicity**

Neurotoxicity refers to the damaging effects of toxic substances like lead, arsenic, and mercury on the nervous system. Lead exposure impacts both central and peripheral nervous systems, with peripheral effects being more pronounced in adults. Notably, neurotoxicity can occur from both high and low doses of exposure (Rehman et al., 2018). Lead exposure, especially in early childhood when the brain is still developing, can cause permanent neurological harm (Hosni et al, 2013), with the brain being the most vulnerable organ to its effects. Neurodegenerative defects, including amyotrophic lateral sclerosis, Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis, result from neurotoxicity induced by cadmium (Branca et al., 2018). Studies involving primary cultures of neurons and glia, isolated mitochondria from mouse brains, and non-neuronal cell lines have demonstrated a strong link between oxidative stress and decreased levels of glutathione (GSH) (Tönnies et al., 2017). Central nervous system (CNS) damage was indicated by increased expression of the key signalling molecule c-fos in the cortex and hippocampus, along with evidence of mercury (Hg) accumulation in the brains of treated rats (Bijoor et al., 2012). Additionally, administering lead acetate (PbA) at a dose of 15 mg/kg to pregnant Wistar female rats led to the induction of pro-inflammatory cytokines, such as TNF-α and IL-1β, in the hippocampus and forebrain of immature rat brains. These findings suggest that prolonged exposure to lead promotes inflammation in the developing CNS of rats, likely due to the activation of glial cells [54]. Furthermore, lead exposure resulted in necrotic changes in the kidneys, liver, and brain [55].

Cadmium's neurotoxicity stems from neural cell death via apoptosis, triggered by factors such as impaired neurogenesis, inhibited neuron gene expression, epigenetic effects, and endocrine disruption (Wang and Du, 2013). Wilson's disease, caused by excess copper retention, leads to neurobehavioral abnormalities resembling schizophrenia. Zinc deficiency hinders neurodevelopment, though effects of excessive zinc are unclear (Cai et al., 2005). Research suggests copper exacerbates zinc-induced neurotoxicity (Tanaka & Kawahara, 2017). Additionally, studies show low-dose chromium exposure can cause brain damage in animal models (Salama et al., 2016).

**Carcinogenicity**

Lead is a toxic substance known for its carcinogenic properties, which can disrupt the body's DNA repair processes. It also impacts genes that regulate tumour growth and alters the structure and sequence of chromosomes by generating reactive oxygen species (ROS). Furthermore, lead interferes with transcription by displacing zinc from certain regulatory proteins (Silbergeld et al., 2000). Mercury produces reactive oxygen species (ROS) that can enhance tumorigenic signalling and support the proliferation of cancerous cells. These ROS contribute to carcinogenesis by damaging cellular proteins, lipids, and DNA, resulting in significant cellular harm (Reczek and Chandel, 2017). Chromium (Cr) is a naturally occurring heavy metal found in the Earth's crust and seawater, often released during industrial activities. A recent meta-analysis indicated that exposure to chromium (VI) may lead to increased mortality and a higher incidence of various cancers, including lung, larynx, bladder, kidney, testicular, bone, and thyroid cancers in humans (Deng et al., 2019). Arsenic, on the other hand, induces epigenetic changes, damages DNA, alters the expression of the p53 protein, modifies histones, affects DNA methylation, and decreases p21 expression (Park et al., 2015). Arsenic poisoning heightens cancer risk by binding to DNA-binding proteins and impeding the DNA repair process (Garcia-Esquinas et al., 2013).

**Immunological toxicity**

Chromium can adversely affect the human immune system in several ways. High levels of hexavalent chromium can reduce the capacity of alveolar macrophages to engulf particles and weaken the body's humoral immune response. Additionally, chromium can induce two types of hypersensitivity reactions: type I (anaphylactic) and type IV (delayed). Research has established a connection between chromium exposure and the onset of allergic contact dermatitis in multiple studies (Bruynzeel et al., 1988). Both acute and chronic exposure to lead can have detrimental effects on the immune system, resulting in various immune responses, including heightened allergies, increased vulnerability to infectious diseases, autoimmune disorders, and a potential risk of cancer (Hsiao et al., 2011). Certain demographic groups with a history of lead exposure may be at a higher risk for lung, stomach, and bladder cancers. Lead exposure can enhance the production of B and T cells and influence major histocompatibility complex (MHC) activity (Kasten-Jolly et al., 2010). This toxic substance can disrupt both cellular and humoral immune responses, potentially impairing T-cell function and raising the likelihood of developing autoimmunity and hypersensitivity reactions (Mishra, 2009).

**Conclusion:**

Exposure to heavy metals can arise from both environmental and external sources. Ingesting these metals can result in severe toxicity and potentially life-threatening consequences. Our analysis indicates that oral ingestion is a prevalent route for heavy metal exposure. Elevated levels of heavy metals can inflict significant damage on various organs, leading to immunological issues, respiratory problems, increased cancer risk, kidney complications, osteoporosis, and more. It is essential to avoid products containing high levels of toxic heavy metals. Raising awareness about the dangers of heavy metal exposure can empower individuals to minimize their contact with these harmful substances. Additionally, further research is necessary to enhance our understanding of the molecular mechanisms underlying human exposure to combinations of toxic metals and their potential public health implications.

**References:**

Akgül, N., Altunkaynak, B. Z., Altunkaynak, M. E., Deniz, Ö. G., Ünal, D., and Akgül, H. M. (2016). Inhalation of mercury vapor can cause the toxic effects on rat kidney. Ren. Fail. 38 (3), 465–473

Azeh Engwa, G., Udoka Ferdinand, P., Nweke Nwalo, F., Unachukwu, N.M., (2019). Mechanism and health effects of heavy metal toxicity in humans. Poisoning Mod. World- New Tricks an Old Dog?

Bijoor AR, Sudha S and Venkatesh T (2012). Neurochemical and neurobehavioral effects of low lead exposure on the developing brain. Indian J Clin Biochem. 27:147-151.

Boskabady, M. H., Tabatabai, S. A., and Farkhondeh, T. (2016). Inhaled lead affects lung pathology and inflammation in sensitized and control Guinea pigs. Environ. Toxicol. 31 (4), 452–460.

Branca, J.J.V., Morucci, G., Pacini, A., 2018. Cadmium-induced neurotoxicity: Still much ado. Neural Regen. Res. 13, 1879–1882.

Bruynzeel, D.P., Hennipman, G., van Ketel, W.G., (1988). Irritant contact dermatitis and chrome-passivated metal. Contact Dermatitis 19, 175–179.

Cao, Z. R., Cui, S. M., Lu, X. X., Chen, X. M., Yang, X., Cui, J. P., et al. (2018). [Effects of occupational cadmium exposure on workers’ cardiovascular system]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 36(6), 474–477.

Cai, L.u., Li, X.-K., Song, Y.e., Cherian, M.G., 2005. Essentiality, toxicology and chelation therapy of zinc and copper. Curr. Med. Chem. 12 (23), 2753–2763.

Choe SY, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H and Kim Y (2003). Evaluation of estrogenicity of major heavy metals. Sci Total Environ. 312:15-21.

Coetzee, J.J., Bansal, N., Chirwa, E.M.N., (2020). Chromium in environment, its toxic effect from chromite-mining and ferrochrome industries, and its possible bioremediation. Expo. Heal. 12 (1), 51–62.

Deng, Y., Wang, M., Tian, T., Lin, S., Xu, P., Zhou, L., et al. (2019). The effect of hexavalent chromium on the incidence and mortality of human cancers: a meta-analysis based on published epidemiological cohort studies. Front. Oncol. 9, 24.

Dixit R, Wasiullah X, Malaviya D, Pandiyan K, Singh UB, Sahu A and Paul D (2015). Bioremediation of heavy metals from soil and aquatic environment: an overview of principles and criteria of fundamental processes. Sustainability. 7:2189-2212.

Egorova, K. S., and Ananikov, V. P. (2017). Toxicity of metal compounds: Knowledge and myths. *Organometallics* 36, 4071–4090.

 [Ekere JN, Ukoha IP and Ekere NR (2017) Ecological and human health risk assessment of heavy metal contamination in soil of a municipal solid waste dump in Uyo, Nigeria. Environ. Geochem. Health, 39(3): 497–515.](https://jlc.jst.go.jp/DN/JLC/20054089271?type=list&lang=ja&from=J-STAGE&dispptn=1)

Fay, M. J., Alt, L. A. C, Ryba, D., Salamah, R., Peach, R., Papaeliou, A., et al. (2018). Cadmium nephrotoxicity is associated with altered microRNA expression in the rat renal cortex. Toxics 6 (1), 16.

Friberg, L., Kjellström, T., Elinder, C.-G., Nordberg, G.F., (2019). Cadmium and health: a toxicological and epidemiological appraisal. Cadmium Heal. A Toxicol. Epidemiol. Apprais.

Garcia-Esquinas, E., Pollán, M., Umans, J.G., Francesconi, K.A., Goessler, W., Guallar, E., Howard, B.V., Yeh, J., Best, L., Navas-Acien, A., 2013. Arsenic Exposure and Cancer Mortality in a US-based Prospective Cohort: the Strong Heart Study. ISEE Conf. Abstr. 2013 (1), 3037.

Hayat, M.T., Nauman, M., Nazir, N., Ali, S., Bangash, N., (2018). Environmental hazards of cadmium: past, present, and future. Cadmium Toxic. Toler. Plants Physiol. Remediat. 163–183

Hegazy, A.M.S., Fouad, U.A., (2014). Evaluation of lead hepatotoxicity; histological, histochemical and ultrastructural study. Forensic Med. Anat. Res. 02 (03), 70 79.

Hosni H, Selim O, Abbas M and Fathy A (2013) Semen quality and reproductive endocrinal function related to blood lead levels in infertile painters. Andrologia 45 (2), 120–127.

Hou, S., Yuan, L., Jin, P., Ding, B., Qin, N.a., Li, L.i., Liu, X., Wu, Z., Zhao, G., Deng, Y., (2013). A clinical study of the effects of lead poisoning on the intelligence and neurobehavioral abilities of children. Theor. Biol. Med. Model. 10 (1).

Hsiao, C.-L., Wu, K.-H., Wan, K.-S., (2011). Effects of environmental lead exposure on T-helper cell-specific cytokines in children. J. Immunotoxicol. 8 (4), 284–287.

Hyder, O., Chung, M., Cosgrove, D., Herman, J.M., Li, Z., Firoozmand, A., Gurakar, A., Koteish, A., Pawlik, T.M., (2013). Cadmium exposure and liver disease among US adults. J. Gastrointest. Surg. 17 (7), 1265–1273.

Kabata- Pendia A 3rd, editor. Trace Elements in Soils and Plants. Boca Raton, FL: CRC Press; 2001

Karbowska, B., (2016). Presence of thallium in the environment: sources of contaminations, distribution and monitoring methods. Environ. Monit. Assess. 188 (11).

Kasten-Jolly, J., Heo, Y., Lawrence, D.A., (2010). Impact of developmental lead exposure on splenic factors. Toxicol. Appl. Pharmacol. 247 (2), 105–115.

Liaw, J., Marshall, G., Yuan, Y., Ferreccio, C., Steinmaus, C., and Smith, A. H. (2008). Increased childhood liver cancer mortality and arsenic in drinking water in northern Chile. Cancer Epidemiol. Biomarkers Prev. 17 (8), 1982–1987

Liu, C.-M., Ma, J.-Q., and Sun, Y.-Z. (2012). Puerarin protects rat kidney from leadinduced apoptosis by modulating the PI3K/Akt/eNOS pathway. Toxicol. Appl. Pharmacol. 258 (3), 330–342.

Loh, N., Loh, H.-P., Wang, L.K., Wang, M.H.S. (2016). Health effects and control of toxic lead in the environment. Nat. Resour. Control Process. 233–284.

Luo, L., Wang, B., Jiang, J., Huang, Q., Yu, Z., Li, H., et al. (2020). Heavy metal contaminations in herbal medicines: determination. comprehensive risk assessments. Front. Pharmacol. 11, 595335. doi:10.3389/fphar.2020.595335

Malaguarnera, G., Cataudella, E., Giordano, M., Nunnari, G., Chisari, G., Malaguarnera, M., (2012). Toxic hepatitis in occupational exposure to solvents. World J. Gastroenterol. 18, 2756–2766.

Mishra, K.P., (2009). Lead exposure and its impact on immune system: A review. Toxicol. Vitr. 23 (6), 969–972.

O’Neal, S.L., Zheng, W., (2015). Manganese toxicity upon overexposure: a decade in review. Curr. Environ. Heal. reports 2 (3), 315–328.

Packer, M., (2016). Cobalt cardiomyopathy: a critical reappraisal in light of a recent resurgence. Circ. Hear. Fail. 9 (12).

Park, Y.-H., Kim, D., Dai, J., Zhang, Z., 2015. Human bronchial epithelial BEAS-2B cells, an appropriate in vitro model to study heavy metals induced carcinogenesis. Toxicol. Appl. Pharmacol. 287 (3), 240–245.

Peters, J.L., Perlstein, T.S., Perry, M.J., McNeely, E., Weuve, J., (2010). Cadmium exposure in association with history of stroke and heart failure. Environ. Res. 110 (2), 199–206.

Qasem NA, Mohammed RH and Lawal DU (2021). Removal of heavy metal ions from wastewater: A comprehensive and critical review. Npj Clean Water. 4:1-15.

Reczek, C.R., Chandel, N.S., (2017). The two faces of reactive oxygen species in cancer. Annu. Rev. Cancer Biol. 1 (1), 79–98.

Rehman K, Fatima F, Waheed I and Akash M S (2018) Prevalence of exposure of heavy metals and their impact on health consequences. J. Cell. Biochem. 119, 157-184.

Reyes, J.L., Molina-Jijón, E., Rodríguez-Muñoz, R., Bautista-García, P., Debray-García, Y. Namorado, M.D.C., (2013). Tight junction proteins and oxidative stress in heavy metals-induced nephrotoxicity. Biomed Res. Int.  1–14.

Salama, A., Hegazy, R., and Hassan, A. (2016). Intranasal chromium induces acute brain and lung injuries in rats: assessment of different potential hazardous effects of environmental and occupational exposure to chromium and introduction of a novel pharmacological and toxicological animal model. PLoS One 11 (12), e0168688.

Sanchez T (2018). Effects of mercury, lead, arsenic and zinc to human renal oxidative stress and functions: a review. Arch Med. 4.

Silbergeld, E.K., Waalkes, M., Rice, J.M., (2000). Lead as a carcinogen: Experimental evidence and mechanisms of action. Am. J. Ind. Med. 38, 316–323

Sun, H., Brocato, J., Costa, M., (2015). Oral chromium exposure and toxicity. Curr. Environ. Heal. Rep. 2 (3), 295–303.

Tanaka, K.I., Kawahara, M., 2017. Copper enhances zinc-induced neurotoxicity and the endoplasmic reticulum stress response in a neuronal model of vascular dementia. Front. Neurosci. 11.

Tchounwou PB, Wilson B, Ishaque A (1999). Important considerations in the development of public health advisories for arsenic and arsenic-containing compounds in drinking water. Rev Environ Health. 14(4):211–229.

Tchounwou PB, Yedjou, CG, Patlolla AK, and Sutton DJ (2012). Heavy metal toxicity and the environment. Mol Clin Environ Toxicol.133-164.

Tellez-Plaza, M., Guallar, E., Howard, B.V., Umans, J.G., Francesconi, K.A., Goessler, W., Silbergeld, E.K., Devereux, R.B., Navas-Acien, A., (2013). Cadmium exposure and incident cardiovascular disease. Epidemiology 24 (3), 421–429.

Tellez-Plaza, M., Navas-Acien, A., Crainiceanu, C.M., Guallar, E., (2008). Cadmium exposure and hypertension in the 1999–2004 National Health and Nutrition Examination Survey (NHANES). Environ. Health Perspect. 116 (1), 51–56.

Tönnies E and Trushina E (2017). Oxidative stress, synaptic dysfunction, and Alzheimer’s disease. J Alzheimer's Dis. 57:1105-1121.

Toxicological Profile for Cadmium, (2002). ATSDR’s Toxicol. Profiles.

Velma V, Vutukuru SS, Tchounwou PB (2009). Ecotoxicology of hexavalent chromium in freshwater fish: a critical review. Rev Environ Health. 24(2):129–145.

Wang XF, Xing ML, Shen Y, Zhu X, Xu LH (2006). Oral administration of Cr (VI) induced oxidative stress, DNA damage and apoptotic cell death in mice. Toxicology. 228:16–23.

Wang, J., Zhu, H., Yang, Z., and Liu, Z. (2013). Antioxidative effects of hesperetin against lead acetate-induced oxidative stress in rats. Indian J. Pharmacol. 45 (4), 395–398.

Wang Y, Tang Y, Li Z, Hua Q, Wang L, Song X, Zou B, Ding M, Zhao J and Tang C (2020). Joint toxicity of a multi-heavy metal mixture and chemoprevention in sprague dawley rats. Int J Environ Res Pub Health. 17:1451.

Wilson DN Association Cadmium. Cadmium - market trends and influences; London. Cadmium 87 Proceedings of the 6th International Cadmium Conference; 1988. pp. 9–16.

Wu X, Cobbina SJ, Mao G, Xu H, Zhang Z, Yang L. A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environ Sci Pollut Res Int. 2016;23(9):8244-59.

Yoshizawa, K., Rimm, E.B., Morris, J.S., Spate, V.L., Hsieh, C.C., Spiegelman, D., Stampfer, M.J., 2002. Mercury and the risk of coronary heart disease in men. N. Engl. J. Med. 347, 1755–1760.

Yu, L., Liou, I.W., Biggins, S.W., Yeh, M., Jalikis, F., Chan, L.-N., Burkhead, J., 2019. Copper deficiency in liver diseases: a case series and pathophysiological considerations. Hepatol. Commun. 3 (8), 1159–1165