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Exposure routes and health effects of heavy metals on children

Muwaffak Al osman · Fei Yang · Isaac Yaw Massey

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Abstract Heavy metals are naturally existing elements that have relatively high atomic weight and a minimum density five times the density of water. Heavy metals have extensive applications in industries, homes, agriculture and medicine, leading to their wide distribution in the environment. Most heavy metals are reported to be highly toxic. They also have numerous exposure routes, including ingestion, inhalation, and dermal absorption, subsequently inducing some health effects resulting from human and heavy metals contact. The implications of heavy metals with regards to children's health have been noted to be more severe compared to adults. The element's harmful consequences on children health include mental retardation, neurocognitive disorders, behavioral disorders, respiratory problems, cancer and cardiovascular diseases. Much attention should be given to heavy metals because of their high toxicity potential, widespread use, and prevalence. This review therefore examines the exposure routes and health effects of mercury (Hg), lead (Pb), chromium (Cr), cadmium (Cd), and barium (Ba) on children. In addition, their toxic mechanisms are elucidated.

Keywords Mercury (Hg) · Lead (Pb) · Chromium (Cr) · Cadmium (Cd) · Barium (Ba) · Health effects · Exposure routes · Mechanisms of toxicity

M. Al osman · F. Yang (✉) · I. Y. Massey
Department of Occupational and Environmental Health, Xiangya School of Public Health, Central South University, 110 Xiangya Road, Changsha 410078, China
e-mail: phfyang@csu.edu.cn

M. Al osman
e-mail: muwaffak83@csu.edu.cn

I. Y. Massey
e-mail: mriymassey@ymail.com

F. Yang
Key Laboratory of Biometallurgy, Ministry of Education, School of Mineral Processing and Bioengineering, Central South University, Changsha 410083, China

F. Yang
Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing 210009, China

Introduction

Heavy metals refer to metals with relatively high densities, atomic numbers or atomic weights. Heavy metals include mercury (Hg), lead (Pb), chromium (Cr), cadmium (Cd), barium (Ba), aluminum (Al) and copper (Cu). There have been increasing environmental and public health concerns resulting from heavy metals contamination in recent times. Human exposure to these metals is also on the rise due to their growing applications in manufacturing, agriculture, homes and technology (Tepanosyan et al. 2018). Though heavy metals exist naturally, human activities

such as mining smelting, farming and manufacturing significantly contribute to their release into the environment (Tchounwou et al. 2012). Contamination may also occur due to their corrosion, atmospheric deposition, erosion of their ions, leaching, sediment re-surfacing and the evaporation of the metals from a contaminated water source into the soil and groundwater (Cai et al. 2019). Natural events such as volcanic explosions and weathering also play a role in its environmental contamination (Wu et al. 2018).

Studies indicate elements such as chromium and copper are essential components of diverse biochemical and physical purposes and their insufficient supply cause deficiency diseases or syndromes (Sawut et al. 2018). As such, heavy metals are either essential or non-essential. Essential metals employ biochemical and physical functions in plants and animals. For instance, copper is essential for hemoglobin formation and carbohydrates metabolism. In excess, however, it causes cellular damage (Tchounwou et al. 2012). Non-essential metals include barium, lead, cadmium, aluminum and mercury.

Heavy metals are known to inhibit cellular organelles and mechanisms including cell membrane, mitochondrial, lysosome, endoplasmic reticulum, nuclei and some enzymes used in metabolism, body cleansing and damage reparation (Tchounwou et al. 2012). They also interact with DNA and protein-damaging the DNA and causes conformational alterations which may lead to cycle modulation, carcinogenesis or apoptosis (Tchounwou et al. 2012).

For their high toxicity levels, mercury, lead, chromium, cadmium and barium pose an urgent challenge to public health. Accordingly, they are classified as systemic toxicants. Though there are numerous other heavy metals, the paper focuses on these five because of their (1) widespread use, (2) harmfulness of some of their forms and (3) prevalence in the environment. It is worth-knowing that these metals are capable of damaging the various human organs even at lower exposure degrees. This is either classified as "confirmed" or "probable" human carcinogens where their poisoning potency depends on diverse mechanics. It is noted that, each of them has exclusive characteristics and chemical properties that define its harmfulness. Some of these elements lack adequate explanation to their taxological mechanisms and actions. There is therefore the need for a concise body of knowledge that can guide the implementation of countermeasures to mitigate health complications in children arising from heavy metals exposures. Thus, this paper reviews mercury, lead, chromium, cadmium and barium's exposure routes, their negative effects on children's health and mechanisms of toxicity.

Heavy metals' exposure routes, health effects on children and mechanisms of toxicity

Mercury

Exposure routes of mercury

Mercury exists in three forms: elemental, organic and inorganic mercury compounds (CDC 2007). These forms have different properties, usage and degree of toxicity. The distribution of mercury into the environment occurs through the natural degassing of the earth's crust (Berlin et al. 2015). Mercury pollution can also arise because of human activities. Estimates indicate that human activities account for thousands of tons of mercury released into the environment (Streets et al. 2017). It exists as mercury vapor in the atmosphere, which is the primary passageway of global transport of the pollutant. While in the atmosphere, it remains unaltered for about one year. After that, it changes into a water-soluble form and returns back to the earth surface. It is then converted back to mercury vapor or mono-methyl mercury compounds by micro-organisms, mainly bacteria. Mono-methyl mercury is capable of entering the aquatic food chain through aquatic organisms including planktons and fish. Thus, human tend to be exposed to mercury through the consumption of these animals (Habiba et al. 2017; Díez et al. 2009; Sagiv et al. 2012). Again, through eye and skin contact, skin absorption and inhalation, human may be exposed to mercury (NIOSH n.d.).

Health effects of mercury

The impact of mercury exposure in children can be examined in two dimensions. First, fetal exposure of mercury through mothers' intake of contaminated shellfish and fish has been associated with adverse developmental outcomes such as impaired neurological development in children (Kampa and Castanas 2008; Rice et al. 2014). Impaired nervous and

cognitive development is also linked to the neurotoxicity of mercury (Myers et al. 2009). Children exposed to mercury via their mothers have been found to have low verbal Intelligence Quotient (IQ) scores and suboptimal scores in social development, fine motor skills and prosocial behavior (Oken and Bellinger 2008).

Exposure to mercury in children has also been found to lead to mental retardation (Huang et al. 2014; Mohamed et al. 2015; Mahmud et al. 2016; Ye et al. 2017). According to Liu et al. (2010), the toxicity of mercury can be manifested through growth disorders, epilepsy, excessive salivation, deformity of limbs, chorea and athetosis, dysarthria, damaged cerebellum, misalignment of the eyes and primitive reflexes. Further, the World Health Organization (WHO 2017) reported that, inhalation of mercury's vapor is capable of causing impairment of vital body organs such as the kidneys, lungs, digestive and immune systems, as well as the nervous system. Mercury exposure has also been noted to cause eye and skin corrosion, leading to neurocognitive disorders such as impaired memory (Tang et al. 2015; Aaseth et al. 2018; Kaur et al. 2018), insomnia (Zhou et al. 2014; Do et al. 2017) and tremors (WHO 2017; Calabresea et al. 2018).

Mercury poisoning has also been linked to increased cases of type 2 diabetes (Schumacher and Abbott 2017; Jeon et al. 2015; Wallin et al. 2017; Jeppesen et al. 2015). According to Schumacher and Abbott (2017), methylmercury exerts detrimental impacts on pancreatic beta (β) cell development and function. Impaired pancreas functioning therefore may lead to hyperglycemia and insulin resistance eventually resulting to diabetes. Jeon et al. (2015) also reported that mercury poisoning leads to oxidative stress which results in the death of the pancreatic beta cells as well as their dysfunctioning. Mercury-stimulated oxidative stress has also been established to disrupt insulin signaling pathway. Further, Jia et al. (2015) noted that, mercury poisoning is again capable of causing cardiorenal metabolic syndrome since it can affect the structure and normal functioning of the mitochondria. Consequently, renal, metabolic, and cardiovascular abnormalities have been found in individuals exposed to mercury (Jia et al. 2015).

Mechanisms of mercury toxicity

The entry of mercury ions into the body produces toxic impacts through generalized corrosion, inhibition of enzymes and precipitation of proteins. Mercury ions bind proteins with different groups including amine, amide, carboxyl and phosphoryl. Proteins made up of these groups have a high susceptibility to mercury reaction. After binding with mercury, these proteins become inactive. Mercury toxicity depends on its oxidative state and chemical form. For instance, elemental Hg is highly soluble in lipids hence; it readily crosses the plasma membranes. In its divalent oxidized state, Hg is more toxic than in the monovalent state. Additionally, organic forms of mercury have higher absorption rates (90%) than inorganic forms (10%). Organic compounds of mercury are therefore reported to have greater corrosive impacts on the gastrointestinal mucosa (Broussard et al. 2002).

Lead

Exposure routes of lead

According to the WHO (2018), the primary routes of exposure to lead are ingestion of lead-contaminated substances and inhalation of lead particles that come from the burning of lead-containing materials, such as gasoline and residential paint (Roy et al. 2009).

Entrance by inhalation is most common through fumes that play the largest role in lead transmission. While the absorption of lead through the skin is rare and children are most prone to lead because of their frequent oral activity and chewing things (non-food) containing lead such as paint chips and furniture coated and toys (He et al. 2009).

Health effects of lead

The impacts of lead exposure on humans depend on the level or severity of exposure. Exposure to very high levels of lead in children has been found to decrease attention span, increased irritability, increased dullness and shorter attention span in the central nervous system sebsequently resulting to seizures, headache, coma and even death (Pfadenhauer et al. 2014).

Lanphear et al. (2005) indicated that, the negative impact of lead on human health occurs when the

concentration of lead in the blood exceeds 10 µg/dL. Lead exposure above this limit has been linked to lowered intelligence in children. Rodrigues et al. (2016) determine the relationship between environmental exposure to lead and neurodevelopmental impacts among Bangladeshi children and reported that, children exposed to high levels of lead had lower cognitive scores on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Similarly, Hong et al. (2015) found exposure to low levels of lead negatively affects intelligence and increased impulsivity in school-age children. Again, blood lead concentration has inversely been related to academic achievement where, reading and mathematics failure is attributed to children's exposure to lead (Evens et al. 2015). Further, Skerfving et al. (2015) also noted exposure to lead was negatively associated with school performance. The highest negative impact of lead on academic achievement was found in lead blood levels of 50 µg/L than for higher levels (Skerfving et al. 2015). In a recent study, Reuben et al. (2017) indicated childhood lead exposure is linked to impaired cognitive functioning, decreased intelligence and lower socio-economic status at adulthood.

Lead exposure has also been associated with behavioral and emotional problems in children. According to ('Lead Exposure in Children Affects Brain and Behavior,' n.d.), lead exposure has adverse health consequences on children's development and behavior. Children exposed to lead have been reported by Evens et al. (2015) to show inattentiveness, hyperactivity and irritability. Again, exposure to high levels of lead has been found to cause learning and reading problems, stunted growth as well as hearing losses (Roy et al. 2009). Furthermore, lead is capable of damaging the central nervous system and may result in death at high levels. In a related study, Kim et al. (2016) hypothesized that, high levels of lead concentrations in the blood result to autistic behaviors, such as poor communication and socialization, low levels of interests, and stereotypical behaviors among school-age children. Consequently, emphasis is being placed on the need for continued reduction of lead exposure in children. In addition, children exposed to lead have been reported to have a higher risk of developing the attention deficit hyperactive disorder (ADHD) (CDC 2015). Children under this condition are more likely to display symptoms such as daydreaming, disorganization, inability to complete tasks due to lack of persistence and distractibility.

The CDC (2015) further reported that poor academic achievement of children exposed to ADHD is linked to impaired executive functioning. This is because dopamine neurotransmitter system is damaged by lead. Since dopamine plays a vital role in cognitive abilities, exposure to lead results to deficits in executive functioning. In children with high exposure to lead, CDC (2015) discovered the low levels of performance in tasks that require focused attention and flexible thinking. In addition to impairment in executive functioning, children exposed to lead show deficiency in the visual-spatial domain and have manifested through mathematical and reading difficulties. Furthermore, children exposed to lead exhibit conduct disorder symptoms, poor self-regulation, disruptive behaviors, destructive behaviors and antisocial behaviors. Impaired neurocognitive function in children exposed to lead is also manifested through speech and language deficits as well as gross-motor and fine-motor dysfunctions.

Mason et al. (2014) also demonstrated that, exposure to lead is associted with anxiety, depression and increased aggression in children. Lead exposure has also been linked to externalizing behaviors such as bullying which increases the risk of jail time and truancy in school-going children. Other behavioral problems that develop in children exposed to lead include increased emotional reactivity, somatic complaints, insomnia, hyperactivity and affective problems (Zhou et al. 2014). Reyes (2015) found that lead exposure is capable of predicting antisocial and risky behavior among children and adolescents. Higher scores in attention deficit hyperactive disorder and increased social problems have also been reported in children exposed to lead (Roy et al. 2009). Children exposed to lead are reported off criminal behavior in adolescence and adulthood (Meyer and Rogers 2018; Beckley et al. 2018), delinquent behavior (Dietrich et al. 2001; Sampson and Winter 2018) and higher rates of arrests for violence as well as total arrests (Fergusson et al. 2008; Wright et al. 2008; Feigenbaum and Muller 2016).

Mechanisms of lead toxicity

Even though the mechanisms of lead toxicity have not yet been fully known, Flora et al. (2012) identified

heme-biosynthesis enzymes and antioxidants as the primary targets of lead poisoning. At low concentrations in the blood, lead can inhibit the activity of these enzymes and stimulate the formation of oxygen species as well as intensifying oxidative stress. Oxidative stress has been reported to be the most crucial factor in the pathogenesis of lead-related toxicity. Nemsadze et al. (2009) noted the central nervous system as the principal target of lead-induced poisoning. Lead toxicity has been linked to various mechanisms in the nervous system including stimulation of oxidative stress, elevation of nerve cell death and interference of calcium ion-dependent enzymes (Nemsadze et al. 2009). Further, lead is reported to be primarily stored in the bones and teeth which accumulate over time to affect the bones, kidney and liver (WHO 2018).

Chromium

Chromium exposure routes

Chromium exists in three stable oxidation states: Cr (0), Cr(III), and Cr(VI). Noteworthy, Cr(III) is an essential dietary nutrient whose deficiency is associated with infertility, cardiovascular conditions and diabetes while Cr(VI) causes cancer. According to the CDC (2013), entry of chromium into the body occurs through skin absorption, inhalation and ingestion. Skin contact and inhalation is the primary means of occupational exposure to chromium. However, a prominent proportion of exposure in the general population occurs through the ingestion of contaminated water and food.

Chromium health impacts

Chromium exposure has been linked to adverse respiratory effects. Neghab et al. (2015) explored the pulmonary impacts of chronic exposure in the electroplating industry as well as the pulmonary effects of chronic and reported that, the participants exposed to occupational chromium poisoning had more incidents of adverse respiratory impacts of chromium including shortness of breath wheezing, phlegm and productive cough than the workers who were not exposure to chromium. Additionally, Neghab et al. (2015) noted that workers with occupational exposure to the metal had lower parameters of pulmonary function compared to the non-exposed workers. In a related study, Hamzah et al. (2016) found that, the inhalation of chromium metal dust was associated with the deterioration of lung function. Individuals who are highly sensitive to Cr(VI) compounds have also been identified to develop respiratory-related complications such as asthma and decrease in the forced expiratory volume linked to other respiratory complications including wheezing, coughing, nasal blockage and facial erythema (Wilbur et al. 2012). Chromium exposure is seen to manifest through nasal septum mucous membrane perforations, irritable larynx and pharynx, edema, constriction of bronchial airways, and co-occurrence of asthma and acute bronchitis (Rasoul et al. 2017). Other respiratory impacts of chronic inhalation of hexavalent chromium include nasal itching and soreness, pneumonia, impaired pulmonary functioning, and bronchitis (Saha et al. 2011). The evidence thus indicates that, occupational exposure is capable of leading to impaired respiratory functioning.

Chromium exposure has also been associated with the increased risk for cancer. Halasova et al. (2009) examined the impact of hexavalent chromium exposure on human lung cancer and established that exposure to chromium is capable of causing lung cancer and cell lung carcinoma. Zhitkovich (2011) also reported that human exposure to chromium through drinking water mutations and chromosomal breaks are associated with cancer development. Further, increased mortality related to cancer has also been indicated among people exposed to higher concentrations of hexavalent chromium through drinking water (Beaumont et al. 2008).

Again, the exposure to chromium has been related to adverse gastrointestinal, hematological, immune, kidney and liver effects (Saha et al. 2011). Additionally, chromium has been found to cause skin ulcers, increased skin sensitivity and dermatitis (Shelnutt et al. 2007; Yoshihisa and Shimizu 2012; Buters and Biedermann 2017). A recent study conducted by Ray (2016) revealed the hematological effects of chromium on blood cell. Sharma et al. (1978) and Ramzan et al. (2011) demonstrated that, chromium exposure is capable of decreasing total red blood cells count, low volume of packed red cells, decreased mean corpuscular hemoglobin concentration, elevated levels of leucocytes and increased the number of immature

erythrocytes following ingestion illustrating intravascular hemolysis.

Mechanisms of chromium toxicity

Laboratory and clinical evidence link chromium toxicity to hexavalent chromium. Much of its toxicity can also be explained through chromium-induced molecular damage associated with intracellular reduction. Hexavalent chromium exposure has been found to cause many types of point mutations in deoxyribonucleic acid as well as to induce chromosomal damage. Moreover, its toxicity has been identified to induce oxidative protein changes and adduct formation (Dayan and Paine 2001). The reduction of hexavalent chromium to trivalent chromium inside the cells has also been related to the toxicity of chromium compounds. Intracellular chromium toxicity has also been linked to damage of the cellular components during the reduction of Cr(VI) to Cr(III). This damage occurs through the formation of free radicals including deoxyribonucleic acid damage (ATSDR, n.d.).

Cadmium

Exposure routes of cadmium

Cadmium consists of eight naturally occurring isotopes which do not naturally occur in its elemental form but rather exists as a compound (Xie and Shaikh 2006; Prozialeck and Edwards 2012). The most common cadmium compounds have been identified as carbon oxide, cadmium carbonate and cadmium sulfide. It is capable of entering the human body through consuming contaminated foods such as shellfish, inhalation of cigarette smoke, improper handling of the metal itself, and drinking of cadmium-contaminated water. Noteworthy, cadmium exposure may also primarily occur indirectly through plants. Plants absorb cadmium from soil contaminated through cadmium-enriched fertilizers, irrigation water containing cadmium, and cadmium fallout from the air (Olympio et al. 2018).

Health effects cadmium

According to Chunhabundit (2016), exposure to Cadmium may cause renal damages manifested through the impairment of proximal convoluted tubule which has been demonstrated to be associated with mitochondrial dysfunction (Takaki et al. 2004), formation of free radicals (Safhi et al. 2016), injury to the proximal tubular epithelial cells (Boonprasert et al. 2018), and apoptosis induction (Xie and Shaikh 2006; Prozialeck and Edwards 2012).

Another adverse health impact related to cadmium exposure in children is osteoporosis. Schoeters et al. (2006) reported that, exposure of children to cadmium at a tender age may lead to the accumulation of cadmium in their bodies because; its excretion is limited from the body. Osteoporosis and increased risk of fracture are manifested when a person attains adulthood (Sughis et al. 2011). Cadmium exposure has also been associated with pediatric cancer. Sherief et al. (2015) determined whether or not children cancer patients have higher exposure to cadmium than their non-cancer counterparts. Measuring the cadmium levels in nails, hair, urine, and serum among cancer patients and their healthy counterparts using Sing Atomic Absorption Spectrophotometer, it was noted that the cancer patients had higher cadmium levels than non-cancer children. This indicates that there is a positive relationship between cadmium status and malignancy. Cancer development resulting from cadmium exposure has also been documented in several other studies (Goyer et al. 2004; Nawrot et al. 2006; Absalon and Slesak 2010; Hartwig 2013).

In addition, the detrimental impact of cadmium exposure is an increased risk factor for cardiovascular diseases. In a prospective cohort study involving American Indian adults, long-term cadmium exposure was linked to elevated cardiovascular mortality as well as elevated incidence of cardiovascular disease including heart failure, stroke, and coronary heart disease (Tellez-Plaza et al. 2013). Further, cadmium exposure has been related to stunted growth in children. Gardner et al. (2013) indicated cadmium exposure is negatively associated with infant size at birth (height and weight) while Kippler et al. (2012) reported cadmium exposure's negative effect on child's IQ.

Mechanisms of cadmium toxicity

According to Rani et al. (2014), the mechanisms of cadmium toxicity is related to its ability to induce genomic instability through complex and

multifactorial mechanisms. One of the most vital mechanisms is its interaction with deoxyribonucleic acid repair mechanisms, stimulation of cell death, and production of reactive oxygen species. Additionally, the toxicity of cadmium is associated to its stimulation to form inflammatory cytokines and down-regulation of the protective role of nitric oxide formation (Navas-Acien et al. 2004). Cadmium-induced toxicity has also been linked to increased oxidative stress through its catalytic role in the production of reactive oxygen species, increased lipid peroxidation, to deplete protein-bound glutathione and sulfhydryl groups (Navas-Acien et al. 2004).

Barium

Exposure routes of barium

Barium exists mostly in its compound form and significantly occurs as barium carbonate and barium sulfate (CDC 2007). Exposure of barium is mainly through the inhalation of contaminated air and intake of contaminated food and water. CDC (2007) reported that, through direct contact with the skin, barium may enter the body in small quantities. The absorption of barium compounds into the bloodstream depends on the solubility of the compound. Highly soluble compounds (barium chloride and barium nitrate) are readily absorbed into the bloodstream than the insoluble compounds (barium carbonate and barium sulfate).

Health effects of barium

The adverse health impact of barium varies depending on the extent of solubility of barium compounds in water or the stomach. CDC (2007) reported that insoluble barium compounds such as barium sulfate and carbonate have minimal or no adverse health effect while soluble barium compounds including barium sulfide, hydroxide, chloride, nitrate and acetate exert harmful health consequences through consuming contaminated water and food. This may subsequently result to impaired heart rhythm, paralysis or death if medical attention is not sought immediately. In addition, gastrointestinal problems such as diarrhea, abdominal cramps and vomiting may also be induced. Further, CDC (2007) noted that, exposure to small amounts of water-soluble barium is capable of causing respiratory difficulties manifested through breathing and cardiovascular effects including reduced blood pressure or increased blood pressure leading to hypokalemia.

Mechanisms of barium toxicity

Even though the mechanisms of action for barium toxicity is not yet fully known, it has been associated with barium's action as a competitive K^+ channel antagonist that leads to the blockage of the passive efflux of intracellular K^+. This cause a shift in K^+ from extracellular to intracellular compartments resulting in reduced resting membrane potential which induces reduced capacity of neuronal cells to stimulation respond. Barium also inhibits the metabolic regulation of K^+ levels (ATSDR, n.d).

The stimulation of hypokalemia occurs through two synergistic mechanisms. First, barium ions are competitively blocked by potassium rectifier channel which is required to pump intracellular K^+ out of the cell actively. Additionally, barium toxicity is also linked to its ability to increase the permeability of the plasma membrane to Na^+. This is followed by a secondary increase in sodium–potassium pump bioelectrogenesis resulting in a shift of extracellular K^+ into the cell. Intracellular trapping of K^+ has been related to depolarized membranes as well as paralysis.

Conclusion

The current paper was aimed at investigating the routes of exposure as well as the negative health impacts of heavy metals on children. Findings of this paper revealed that entry of heavy metals to the body occurs through inhalation of contaminated air, dermal absorption, consumption of contaminated food, and drinking of contaminated water. Exposure of children to heavy metals has adverse impacts on their health. The negative health consequences have been reported to occur through various mechanisms depending on the heavy metal, and the health concerns are even more urgent regarding mercury, lead, chromium, cadmium, and barium. This is because of their widespread use, high toxicity levels, and prevalence.

The adverse effects of heavy metal toxicity are manifested differently depending on the metal concerned. However, most of the heavy metals show

commonalities in their negative health impacts. For instance, most of these metals have been found to cause mental retardation and neurocognitive disorders in children such as impaired memory and lower IQ in children. In turn, the neurological damages impede a child's academic performance besides causing behavioral disorders. Moreover, mercury, lead, and cadmium impair children's growth. Further, chromium and cadmium cause cancer, including sinus, lung, and nasal cancers while mercury and chromium cause diabetes. Heavy metal poisoning also causes respiratory problems, such as irritation of air passages, obstruction of airways, and respiratory diseases such as rhinitis, bronchitis, and asthma. They also cause cardiovascular diseases such as heart failure, stroke, coronary heart disease, and elevated or decreased blood pressure. Because of the detrimental health effects of heavy metal poisoning, efforts should be made to curb their pollution or release to the environment. This can be achieved through stringent laws and regulation.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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