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REVIEW ARTICLE

Priority Heavy Metals' Toxicities on Internal Organs: a Review

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Abstract

***Background*:** Heavy metals toxicities have been implicated in many biochemical, physiological, and hematological changes, some leading to the development of many organ pathologies. Miners, and even non-miners living in mining areas, are constantly exposed to these toxicities and therefore, possible sufferers of organ failures. Some mechanisms involved in the development of these changes are already elucidated, while some are not.
***Methods*:** This review brings together many findings on the effects of these heavy metals on both occupationally and environmentally exposed individuals, and attempts to suggest some modes of action of these metals in bringing about the adverse effects. Published articles on the effects of heavy metals and priority heavy metals were randomly sourced from the internet using search terms like "toxicity of priority heavy metals", "effects of heavy metals on miners", biochemical changes in liver, kidney, heart of heavy metal miners", "hematological changes in occupationally and non-occupationally exposed lead miners", "priority heavy metals in ethno-medicinal plants. Also, unpublished work and personal experiences were used but not referenced.
***Results*:** The results showed wide adverse effects of heavy metals on internal organs, especially the kidney, liver, and heart, of both occupationally and environmentally exposed subjects.
***Conclusion*:** Artisanal system of mining in developing and underdeveloped countries can be a major culprit in the development of these organ pathologies. Therefore, government regulation and legislation will be a saving grace to the miners and other occupants of mining areas.

Keywords: Heavy metals; Toxicities; Internal organs

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INTRODUCTION

Priority heavy metals are generally environmental toxicants that are encountered in many human activities, including industrial, agricultural, and pharmaceutical, and often domestic activities [1]. First of the industrial activities is the mining of these metals. Among these metals are Lead (Pb), Arsenic (As), Mercury (Hg), Cadmium (Cd), and Chromium (Cr), known to be persistent in the environment and have a high degree of toxicity in the body. They are commonly considered as priority heavy metals that are of public health importance [2, 3], causing different degrees of health problems. In different areas of activity, these metals, especially lead, as the most studied, are proven to be mainly available in inorganic states or as compounds in soils, water bodies, locally grown food items, and even ethno-medicinal plants [4-8]. As they are ingested, inhaled, or absorbed into the body system, they are distributed into different organs where they accumulate to cause toxic, mutagenic, carcinogenic, and teratogenic changes (figure 1) [9].

In addition to being cumulative in concentration, they are also non-biodegradable in nature, hence they tend to accumulate unnoticed and gradually cause untold deleterious effects on internal organs and other biological systems. The gradual accumulation makes their effects insidious and dangerous because, before the effects are noticed, the affected organs might have gone beyond recovery. Therefore, the increase in the levels of these environmental pollutants from different sources calls for great concern and adequate care to take care of the health of both occupationally and environmentally exposed people, especially in mining communities. Already, many biochemical, physiological, nutritional, and behavioral changes caused by these priority heavy metals (individually and collectively) in the human body have variously been reported [10-13]. We present some of these reports and consider their overriding effects on some internal organs.

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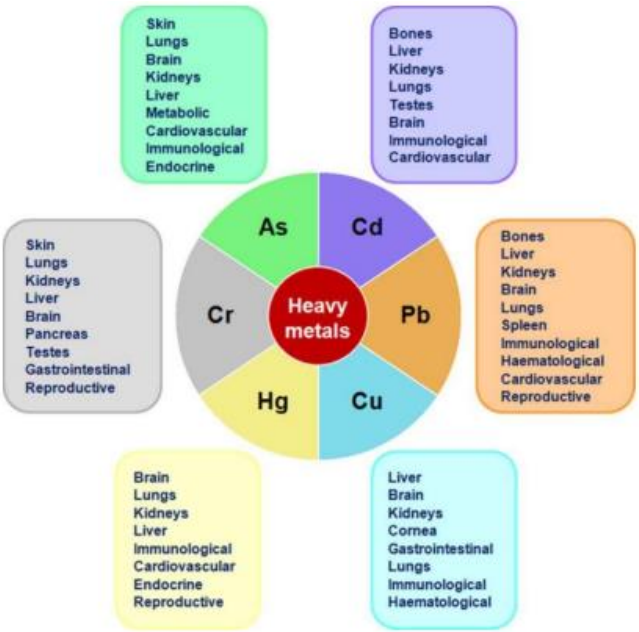

Figure 1. Organs and Systems Mostly Affected by Different Heavy Metals (Badkour, 2018)

Most mining activities in developing countries are artisanal, non-mechanized, non-regulated, and uncontrolled. This is actually illegal mining, which has been seen as one of the foremost causes of environmental pollution [14]. Artisanal miners usually start the work in their early lives when they are highly energetic, and work almost daily to meet their daily needs. They are usually never trained on how to perform the work in terms of modern methods of mining or the necessary precautions to avoid physical and health accidents. And these people continue to do this work as long as they can make a living out of it, even when married, unless something better offers itself later. Therefore, out of the usual practice, they come home with their mining tools containing the remnants of these metals and litter them in their residences [15]. The tools release these remnants into the surrounding environment, thereby exposing the living things in the environment, both plants and animals, to the health hazards of the metals [16]. These remnants inadvertently spread and contaminate utensils and other materials used for domestic activities, thus exposing non-miners in the homes either through inhalation or ingestion.

Heavy metal toxicities are assessed in terms of the many biochemical, physiological, hematological, and even histological changes they cause in internal organs, leading to the development of many organ pathologies. Thus, metal toxicities predispose miners to organ pathologies, making them highly susceptible to organ failures. More worrisome is the possibility that even non-miners, who are only environmentally exposed, may be prone to these induced changes, especially in communities involved in artisanal mining. Thus, while the effects of these metals on miners can be suspected and concerns raised (mostly by labour unions), their effects on non-miners may not attract much attention. It is also suspected that while some of these adverse changes in miners can occur within a few years of activities and are mostly readily observable, adverse effects on non-miners may be insidious, chronic, and take a longer time to manifest. In this case, before these effects can manifest and be detected, enormous damage might have been done to the health of these individuals. We review some of the reported biochemical, physiological, hematological, and organ changes attributed to the toxicities of these heavy metals on both occupationally and environmentally exposed individuals in mining communities.

METHODS

Sources of materials: Published journal articles on the effects of heavy metals and priority heavy metals were randomly sourced from the internet for this. Some of the search terms include "toxicity of priority heavy metals", "effects of heavy metals on miners", biochemical changes in liver, kidney, heart of heavy metal miners", "hematological changes in occupationally and non-occupationally exposed lead miners", "priority heavy metals in ethno-medicinal plants. Search engines included ScienceDirect, PubMed Central, Google Scholar, Scopus, and Web of Science. We also used unpublished work, personal contacts with miners, and personal experiences, but did not reference them.

Inclusion criteria: The basic criteria for inclusion of the materials obtained were emphasis on the effects of these metals, individually or collectively, on internal organs, especially the liver, kidney, and heart. Also included were articles that dealt with biochemical, hematological, and physiological changes, which in turn have effects on any of the mentioned organs, directly or indirectly.

Exclusion criteria: Articles and materials that dwelt on the social life/interaction of the subjects were excluded. Also, materials that dealt with the effect on environments or parameters that do not have a direct effect on internal organs were either totally excluded or just mentioned in passing.

Time frame: Reviewers restricted their search to articles and texts that were not more than 20 years old at the time of review, except for a few (6) that were very critical to the review.

Data analysis: Results of the search were presented together with the discussions; hence, figures and tables were included in the text where they were mentioned.

RESULTS

Heavy metals and the liver

Figure 2 shows the correlation between liver function parameters and serum concentration of lead. The activities of all the studied liver enzymes, aspartate transaminase, alanine transaminase, and alkaline phosphatase have significant positive correlation with serum concentration of lead ($p < 0.01$, $r = 0.193$; $p < 0.001$, $r = 0.474$; $p < 0.001$, $r = 0.261$, respectively), likewise the total bilirubin and total protein concentrations ($p < 0.001$, $r = 0.270$; $p < 0.001$, $r = 0.507$, respectively). Only albumin concentration did not show any correlation with lead concentration.

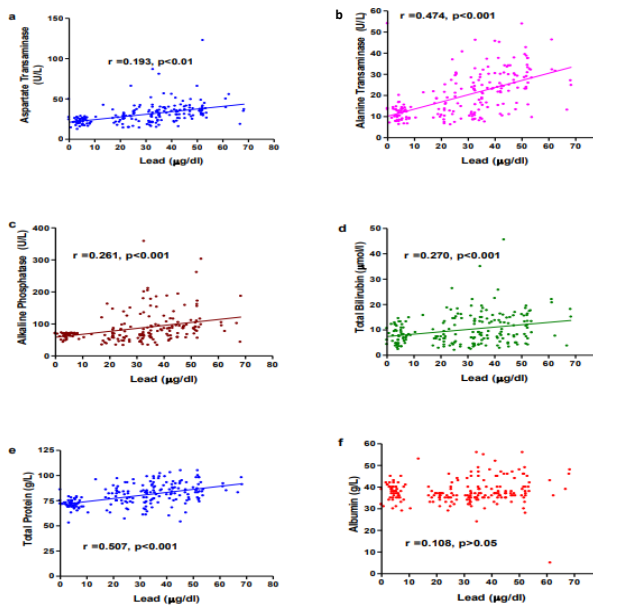

Figure 2. Correlation Between Blood Lead Levels and Liver Biomarkers in Human (Ogbodo et al, 2022)

Heavy metals and the kidney

Table 1 shows the means ± SDs of kidney function parameters in both occupationally and environmentally exposed subjects. The results indicate that all the parameters from occupationally-exposed subjects were significantly increased when compared with those from both environmentally-exposed and control subjects. Likewise, the values from environmentally-exposed subjects were significantly increased when compared with those from control subjects, implying that both occupationally and environmentally exposed subjects are equally at risk.

Heavy metals and the heart

Figure 3 shows the means ± SDs of lipid parameters in both lead-exposed subjects and controls. The results showed significant increases in the concentrations of LDL-cholesterol and triglycerides, while total cholesterol and HDL-cholesterol did not change significantly, implying the susceptibility of these individuals to cardiovascular diseases.

DISCUSSION

The liver is regarded as the powerhouse of the body because it is the site of most of the bio-transformations that occur in the body [17]. These bio-transformations range from simple metabolic processes to complex detoxifications of deleterious particles that find their way into the body. Hence, the inhalation or ingestion of heavy metals activates the liver cells, often ending in inflammation of the liver cells. The biomarkers of liver toxicity, and therefore the diagnostic tools for the assessment of the integrity of the liver cells, are the liver enzymes, including aspartate transaminase, alanine transaminase, and alkaline phosphatase [18]. Presently, there are differing opinions on the effects of heavy metals on the liver. While some studies reported only an apparent increase in liver biomarkers of heavy metal miners [16, 19], some researchers had earlier reported significantly increased liver biomarkers in rats exposed to lead and cadmium poisoning, respectively [20, 21]. Likewise, such significant increases and positive correlations have also been reported in humans involved in heavy metal mining [17, 22-24], indicating cellular damage and alteration in liver tissue histogram and plasma membrane permeability [25].

Liver cell steatosis arising from the effect of lead on lipid metabolism is also known to cause metabolic-associated fatty liver disease – MAFLD [26]. Likewise, epidemiological studies have shown that chronic exposure to arsenic causes different liver diseases like hepatomegaly, hepatoportal sclerosis, liver fibrosis, and liver cirrhosis [27], making liver one of the important internal organs affected by exposure to arsenic [28]. The effects of arsenic on the liver are almost obvious, that it has been suspected that even levels that are not enough to cause hepatotoxicity can cause stimulated inflammatory response in the liver, increasing the risk of serious chronic liver diseases [29]. Furthermore,

Table 1. Blood Levels of Kidney Function Parameters in Both Occupationally and Environmentally Exposed Subjects in a Mining Area (Tilako et al, 2020a)

Parameters	Occupationally exposed n = 89 Mean (SD)	Environmentally exposed n=61 Mean (SD)	Control n = 65 Mean (SD)
Creatinine (μmol L^{-1})	78.24 (34.20)**	75.12 (25.96)**	66.21 (8.40)
Urea (mmol L^{-1})	2.22 (0.96)**	2.20 (1.01)**	2.95 (0.90)
Sodium (mmol L^{-1})	139.37 (18.30)**	139.29 (12.55)**	131.55 (4.63)
Potassium (mmol L^{-1})	4.86 (0.86)**	4.20 (0.62)**	3.78 (0.40)
Chloride (mmol L^{-1})	98.52 (12.52)*	97.34 (8.51)*	91.25 (15.78)
Bicarbonate (mmol L^{-1})	21.47 (2.02)*	22.25 (2.11)**	21.13 (1.13)
Calcium (mmol L^{-1})	1.93 (0.24)**	2.11 (0.44)**	2.22 (0.33)

With controls: *p < 0.01, ** p < 0.001, Occupationally vs. Environmentally, [a]p < 0.05

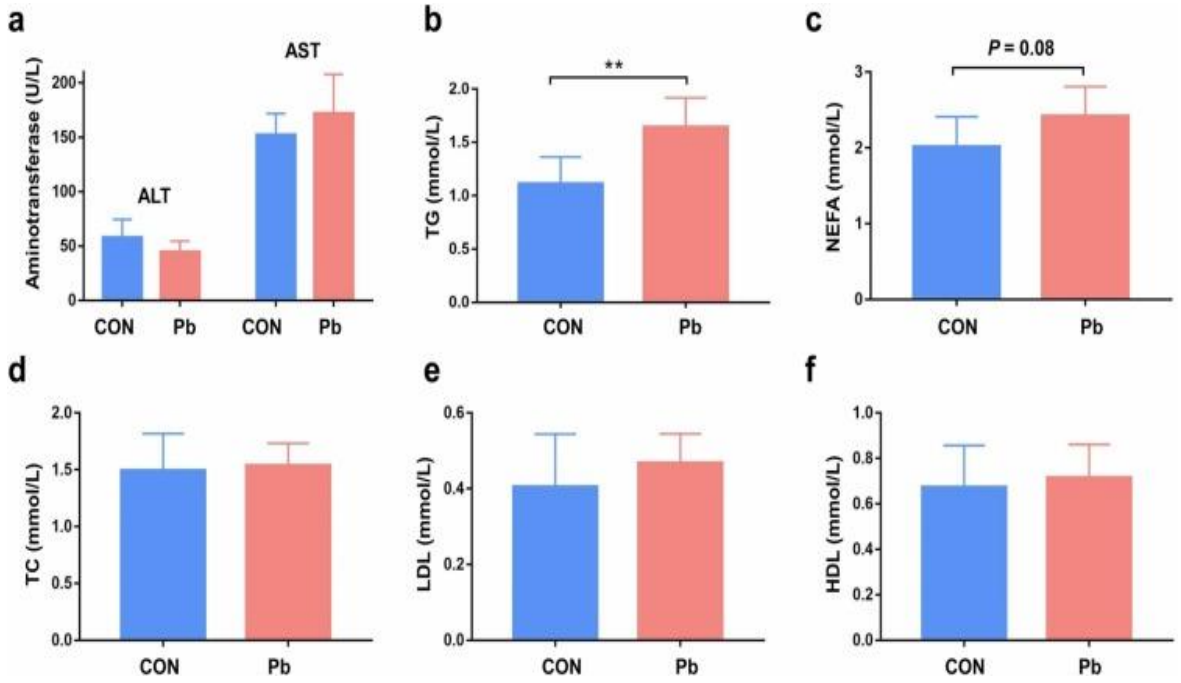

Figure 3. Effects of blood lead level on lipid profile of exposed subjects and controls (Wan et al., 2022)

other studies have reported that elevated blood mercury is associated with a 35% risk of hepatotoxicity, especially the non-alcoholic fatty liver disease found in non-obese population [30, 31]. Though chromium is known for its positive health effects [32], chromium compounds can cause mild to severe liver abnormalities [8].

More worrisome, however, is the finding that these liver biomarkers significantly increased in environmentally-exposed individuals when compared to the control subjects [17]. This alone is an indication of the health hazard of the heavy metals. The effect of these metals on liver cells is further confirmed by the finding of significantly lower serum albumin level and a significant increase in serum globulin level in occupationally-exposed subjects when compared to the control subjects [17]. Albumin is almost exclusively produced in the hepatocytes [33], and its reduced level will indicate reduced synthetic function of the liver. Likewise, increased globulin level implies up-regulation of hepatocyte activities that can activate immune response, and cause increased production of immunoglobulin [34], probably by activating the full functions of lymphoid tissues to produce more γ-globulins. Therefore, even when the activities of the biomarker enzymes in the miners are lower than the reference values, the possibility of the development of hepatotoxic effects is certain, either in the short term or the long term. The mechanisms of this hepatotoxicity have not been fully elucidated. However, some researchers have pointed to the possibility of elicitation of oxidative stress and reduced activity of cytochrome P450 [35]. This is a link to earlier findings that heavy metals up-regulate superoxide-generating enzymes and induce production of reactive

oxygen species that deplete antioxidants and attack fatty acids of the cell membrane [36-38].

The kidney is the organ involved in the removal of wastes and excess fluids from the body. According to the National Kidney Foundation, other functions of the kidney include the removal of drugs from the body, the release of hormones that regulate blood pressure, production of an active form of vitamin D that promotes strong and healthy bones, and the control of the production of red blood cells [39]. In trying to remove excess fluids, kidney controls volumes of fluids in the body and therefore fluid osmolality and acid-base balance (buffering function). It is also involved in the removal of toxins (including heavy metals) from the body, making the kidney a destination point for most toxins, including heavy metals. These heavy metals are non-biodegradable and virtually serve no purpose in the body, especially lead [40]. Therefore, they are almost always eliminated without being metabolized, thus retaining full potential to inflict injuries on the organ involved in their elimination – the kidney. Though some earlier studies [41, 42] did not find many renal changes in lead-exposed workers, recent epidemiological studies [43, 44] have shown that these environmental toxicants play considerable roles in the development of renal diseases. The different effects of these heavy metals on the kidneys have been variously reported. Many researchers [16, 21,45-47] have reported adverse effects of lead on kidney functions in lead miners following an observed increase in renal parameters, especially increased creatinine concentration. Particularly, lead is a known risk factor in the development of high blood pressure and kidney disease to an extent that some have observed that what has been taken as its blood threshold (10µg/dl) was capable of causing kidney disease [48-50], prompting the American Center for Disease Control to declare that there is no safe blood level of lead [51]. More worrisome is the finding that these adverse effects were also noticed in non-miners who were only environmentally exposed to the metals [12]. Though this study was not based on individual metals, it is possible that any of them that affect the occupationally-exposed can do so on environmentally-exposed. Therefore, it is possible that mining areas that have more than one heavy metal will cause more adverse effects on exposed individuals.

These effects include acute and chronic nephrotoxic effects, including generalized deficit of tubular transport mechanisms and degenerative changes in the tubular epithelium [12, 40]. Importantly, these changes have been noted in both occupationally and environmentally exposed individuals, though the extent of effects is not exactly the same [12]. Though lead toxicity has been reduced in many developed countries due to occupational control and legislation [52], it has not been so in developing and underdeveloped countries where artisanal mining is rampant. Cadmium, which has a long half-life and therefore accumulates over age [43], is known to cause decreased renal function, proximal tubular damage and abnormal paracellular tight junctions in the glomeruli of adult rats whose mothers were exposed to cadmium during gestation [53]. Likewise, assessment of the effects of arsenic on kidney functions showed low molecular weight proteinuria, aminoaciduria, glycosuria, phosphaturia, and progressive deterioration of renal functions indicated by increased blood urea and creatinine [12,54]. On the other hand, the known primary site of accumulation and intoxication of mercury is the kidney [55]. Mercury can be found in metallic, inorganic, and organic forms, and its exposure, which is mainly in organic form, can be occupational, environmental, and dietary [56-58]. Though exposure to any form of mercury is known to affect kidney functions [59, 60], its organic conjugates have severe effects than others [55].

Pollution is one of the drivers of non-communicable diseases, and this is said to be more common in low-income and middle-income countries [50], exceeding other metabolic and behavioral risk factors [61]. In these low and middle income countries, heavy metal mining is mainly artisanal and uncontrolled, and miners' implements are unconsciously lithered around their households. This lithering ensures that environmentally-exposed individuals are at risk of long-term development of any disease caused by these heavy metals. Heavy metals have been variously implicated as risk factors of cardiovascular diseases. This is because of various reports of the relationship between these metals and blood pressure and cholesterol level – the major causative agents of cardiovascular disease [9, 62]. In addition, heavy metals are known to accumulate in the kidney and inactivate catecholamine-O-methyltransferase (COMT), an enzyme involved in the regulation of epinephrine, norepinephrine, and dopamine in the brain, and generally result in hypertension [63-66].

Cardiovascular diseases are known to be the leading cause of death in the industrialized world, probably due to environmental toxicants among other predisposing factors. Though this prevalence cannot be substantiated in the developing and underdeveloped countries due to a dearth of statistics, non-regulation and artisanal mode of mining of heavy metals are expected to make heavy metals the leading causes of cardiovascular diseases than they may cause in developed countries. Moreover, since mining in these countries is mainly artisanal and rarely regulated, monitoring of the effects of the mining products on the miners is barely non-existent. Development of cardiovascular disease is also believed to be a complex interplay between genetic and environmental factors [9]; therefore, environmental toxins like heavy metals cannot be exonerated. However, this does not preclude the part played by lifestyles like alcohol consumption, dietary patterns, and physical activity in the generation of cardiovascular disease.

Lead has long been recognized as a risk factor for cardiovascular diseases, including hypertension and stroke [67, 68], to the extent that it is believed that even low levels may raise the risk of these disease conditions. Between 2005 and 2015, cardiovascular diseases were said to have

increased by 12.5% as a result of increased use of lead in domestic and occupational exposures [69]. This was said to be due to its effect on heart rate and cardiac contractility, affecting cardiac functions and parameters, as well as its tendency to replace calcium in some signaling reactions and inhibiting the effects of calmodulin in nitrous oxide synthesis [70]. Likewise, increased blood levels of total cholesterol (Tchol) and low-density lipoprotein (LDL), also called bad cholesterol, have been linked to high levels of blood lead and other heavy metals [71-74]. The association between heavy metal exposure and high serum lipid levels is biologically plausible; this could be due to either increased synthesis or impaired feedback inhibition of lipids [75].

From the foregoing, there seem to be a definite association between cardiovascular disease and heavy metals toxicity. Though the mechanisms for this relationship have not been fully elucidated, most suggestions point to oxidative stress (figure 4).

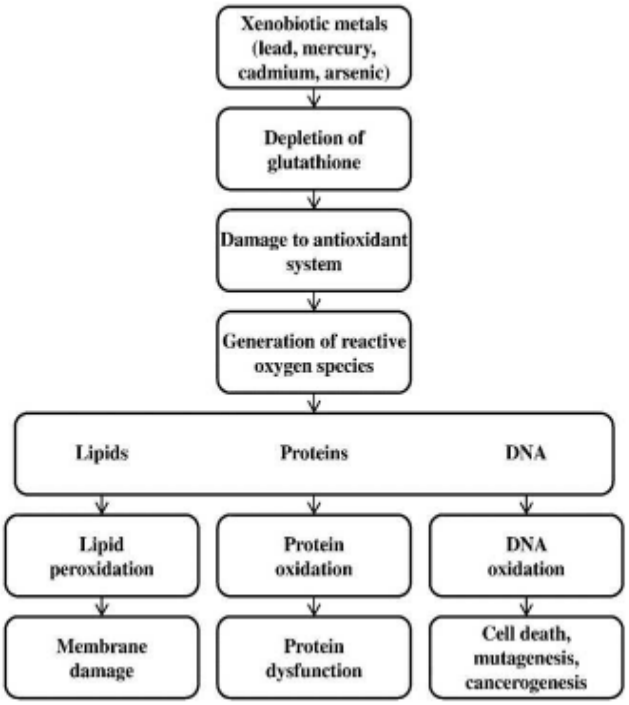

Figure 4. Oxidative Mechanism Cascade of Heavy Metal Toxicity (Badkour, 2018)

In one of the possible mechanisms [76, 77], there is inhibition of superoxide dismutase, an antioxidant enzyme, which catalyzes the conversion of superoxide to oxygen and hydrogen peroxide. The inhibition of this enzyme will lead to an increase in superoxide, which leads to a chain reaction that ends with lipid peroxidation (oxidative degradation of lipids) that will release its product, cholesterol, into the bloodstream. These metals are also known to cause oxidative stress by depleting glutathione [12], leading to oxidative stress. Another mechanism [78, 79] is through the inhibition of cytochrome P450, a group of enzymes which plays an important role in lipid metabolism through enhancing the transformation of cholesterol into bile acids. Inhibition of this enzyme will stall the transformation of cholesterol into bile acids, making it more available in circulation. A third possible mechanism [80, 81] is based on the carcinogenicity of heavy metals. Heavy metals are thought to induce DNA double-strand breaks and inhibit critical proteins from different DNA repair systems. It is known that derangements in other macromolecules, particularly proteins, can be repaired through information from DNA but any derangement in DNA and its repair system ultimately leads to mutation. DNA damage from oxidative stress, metal toxicities or any other cause has been found to play important role in the etiology of cardiovascular diseases [82,83]. Unfortunately, DNA double strand break (mutation) can be inherited by the off-springs. Therefore, this mutation (DNA strand break caused by heavy metal toxicity) is transferable from one generation to another, possibly leading to familial inheritance of the problem, cardiovascular diseases. This third mechanism of action of heavy metals puts the children of occupationally-exposed as well as environmentally-exposed parents in danger of inheriting deranged DNA molecules and therefore cardiovascular diseases. This is supported by the fact that over 40 cardiovascular disorders are known to be directly caused by single-gene defects, including familial hypercholesterolemia [84], and about 40% of siblings of those with CVA have increased risk of developing the disease, while the siblings of those with premature CVA have a 60 to 70% risk of developing the disease [85].

The limitations of this study included the lack of funding for this work and the fact that some of the articles and texts required for this review fell outside the open-access criteria. This hindered access to certain materials.

CONCLUSION

Heavy metals are very toxic to internal organs, causing many biochemical, physiological, hematological, and histological changes in these organs. These toxicities occur in both occupationally and environmentally exposed subjects, though it is certain that such toxicities will occur earlier in occupationally exposed than environmentally exposed, given that the level of toxicity will likely depend on duration and intensity of exposure.

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