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HEAVY METAL TOXICITY-IMPLICATIONS ON METABOLISM AND HEALTH

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ABSTRACT

Heavy metal toxicity leads to major threats to the environment, causing adverse effects on the living beings. Since ages, heavy metals are been used by the humans. The threatening health disorders of heavy metals are known, but still exposure continues. The increased global population, industrialization and urbanization are some of the major reasons for the contamination. The release of heavy metals occurs from various anthropogenic activities, agronomic practices and dumping of various types of wastes. Heavy metals such as arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg) are the most toxic heavy metals, according to WHO ranking of the top ten potential chemicals of major public health concern. They alter the food chain by disturbing the biochemical apparatus of the living organisms, leading to life threatening disorders. This paper reviews the impact on the metabolism occurred by the exposure to these top four harmful heavy metals for public health concern.

KEYWORDS: ***Heavy metal toxicity, environmental contamination, health disorders.***

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INTRODUCTION

Metals are the substances that possess higher malleability, electrical conductivity and luster properties. These are known to be found naturally in the earth's crust. Their compositions and distribution in the atmosphere depends upon the various environmental factors and their respective physical and chemical properties.[1] Heavy metals are considered to be the metallic elements that have a higher atomic weight and specific density of five times greater than that of water. With the assumption of heaviness of heavy metals, the impact of toxicity could be inter-related. The impact of heavy metal toxicity mainly depends upon the absorbed dose, route of exposure and duration of exposure of the respective form of heavy metal. [1,2]Various heavy metals such as cobalt (Co), chromium (Cr), iron (Fe), manganese (Mn), copper (Cu), nickel (Ni), magnesium (Mg), selenium (Se), molybdenum (Mo) and zinc (Zn) are considered to be the essential nutrients that are required for the maintenance of the biochemical and physiological functions, whereas, exposure to certain heavy metals such as arsenic (As), lead (Pb), chromium (Cr), cadmium (Cd), antimony (Sb) could cause adverse effects in the living organisms. [3, 4] The heavy metals after certain threshold levels are considered to cause deleterious effects by altering the mechanisms of the biochemical apparatus of the exposed living organisms. Therefore, it is acknowledged that heavy metals are considered to be the potential toxicants which further bio accumulates in the environment and cause life-threatening disorders to the population. According to several reports, the heavy metals are known to bind to the protein sites by displacing the required metal complexes or cause oxidative deterioration, leading to the malfunctioning of the cells and thus, toxicity. [2,5,7,8] The heavy metals are known to enter into the environment naturally or through human activities. Environmental contamination naturally occurs through weathering and volcanic eruptions [9]. The major sources of heavy metals induced toxicity in the environment include industrial, agricultural, pharmaceutical, domestic effluents, and atmospheric sources. Environmental pollution is very prominent in point source areas such as mining, foundries and smelters, and other metal-based industrial operations. [10,11,12] According to WHO ranking of the top ten toxic pollutants, heavy metals such as arsenic (As), mercury (Hg), lead (Pb) and cadmium (Cd) have been considered as the most potential chemicals of major public health concern. [13] This review focusses mainly on the impact of the mentioned heavy metals on the biochemical apparatus of the humans leading to deadening diseases.

HEAVY METALS AND THEIR TOXICITY MECHANISMS

ARSENIC

Arsenic, a metalloid, is a ubiquitous element present in the natural environment. Its toxicity has become a major concern for the living beings. [1] It is found in two forms: inorganic and organic. The major inorganic forms include arsenite (AsIII) and arsenate (AsV); and organic forms include monomethylarsenic acid (MMA) and dimethylarsenic acid (DMA), while the inorganic forms are known to be highly toxic as compared to other forms. [1] Various arsenic containing compounds are produced industrially by the manufacturing of the products such as silicon based chips, homeopathic medicine, shipdips, insecticides, wood preservatives, herbicides, fungicides and algicides. Occurrence of arsenic containing compounds in the environment also occurs by the natural phenomena like volcanic eruptions and soil erosion. Various anthropogenic activities like mining, smelting play an important role in the arsenic contamination. Also, the sources of arsenic contaminants get linked to ground water, it being the prime source of arsenic contamination. Ground water is majorly used for agricultural purposes and drinking water. Also, the usage of pesticide and fertilizers on the crops play a major role in arsenic contamination. Henceforth, drinking water and crops play a significant role of introduction of arsenic into the food chain.[16,17,18] According to WHO, the recommended limit for the maximum concentrations of arsenic in drinking water is 10µg/L and 20 µg/day of intake of arsenic contaminated food is considered to be safe. But due to high contamination of ground water, the concentration has reached to 100µg/L leading to high risk of contamination in one's body. According to several reports, population exposed to arsenic via drinking water show high risk of mortality from kidney, bladder, lung and skin cancer and the risk increases with the increase in the exposure. [19] The concentration of arsenic in air in cities is considered to be as high as 200ng/m3, although even higher concentrations could occur near anthropogenic sources. As per various studies, populations exposed to arsenic by inhalation such as pesticide,manufacturing and mining, smelting, the workers show an excess of clinical symptoms of lung and skin cancers. [19,2] Though the population could be exposed to other chemicals as arsenic, but no common factor could explain the results. According to an epidemiological study, occupational exposures of arsenic have led to the accumulation of arsenic in bone, keratinized tissues and fingernails.[21,22] Although there are various other clinic pathological symptoms such as diabetes, cardiovascular disorders, cognitive development anomalies, neurological and neurobronchial disorders and different type of cancers. [17, 21, 22]

MECHANISMS OF TOXICITY

Inorganic forms of arsenic are considered to be highly toxic than the organic forms. Among the inorganic forms, AsIII (arsenate) is being considered more toxic than AsV (arsenite). AsIII (arsenate) is a lipid soluble element, readily absorbed in the intestine. So, AsV gets biotransfered into AsIII, which binds to RBCs, globulin and sulfhydryl containing proteins, or get converted to methyl arsenite and get readily eliminated as dimethyl arsenite in urine. So, the function of proximal convoluted tubule gets affected by the urinary elimination of the arsenic concentrates in the kidney. This further leads to the hepatotoxicity, manifested by the increase in the levels of total bilirubin, aspartate aminotransferase, alanine aminotransferase and malionaldehyde. [15, 20] Therefore, intake of inorganic arsenic leads to several disturbances in the metabolism of the body. Hence, causing inhibition of the cellular glucose uptake,

gluconeogenesis and fatty acid metabolism, thus, giving rise to oxidative stress

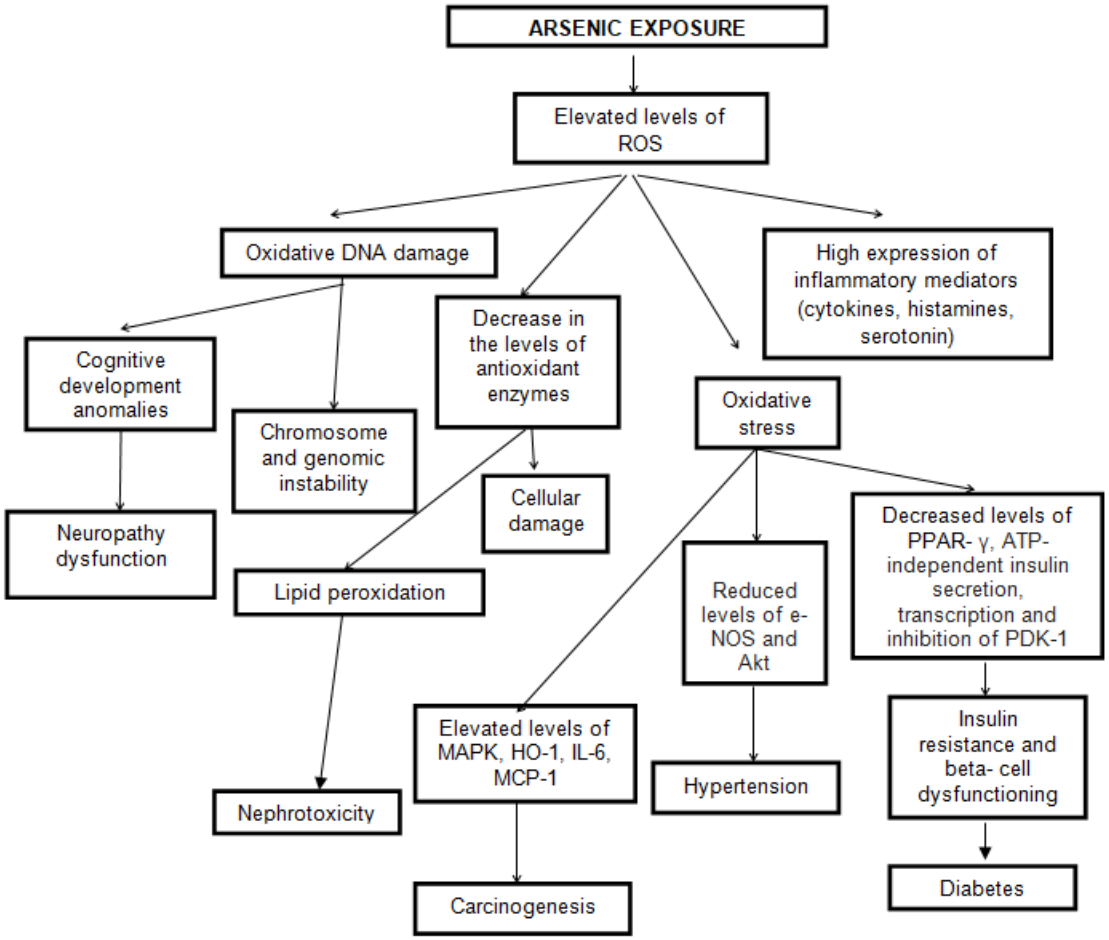

Figure 1
Possible biochemical mechanisms of arsenic induced toxicity

It further leads to the generation of reactive oxygen species (ROS) causing increase in the expression of atherosclerosis related genes such as heame-oxygenase 1 (HO-1), MAPK, interleukin-6 (IL-6), monocyte chemo-attractant protein (MCP-1), thus, causing impaired production of vasoactive mediators in blood vessels, hence, leading to hypertension. [16,18] The elevated levels of ROS lead to chromosomal and genomic instability, causing increased risks of carcinogenesis. [24] The enzyme protein kinase B or Akt plays an important role in various cellular processes, but due to arsenic exposure it leads to the significant reductions in the Akt levels, causing severe clinical symptoms. The enzyme, e-NOS, is known as the regulator of the vascular tone and possessing of antioxidant properties, but due to arsenic contamination in the body, it leads to the suppression of acetylcholine-induced vascular relaxation, which further leads to hypercontraction through calcium sensitization. These biochemical effects promote cardiovascular complications. [17,25] Also, the prolonged exposure leads to the decreased expression of PPAR-γ, altered glucocorticoid receptor mediated transcription, ATP-independent insulin secretion and inhibition of PDK-1, leading to diabetes (Figure 1). The arsenic exposure also causes thiamine deficiency by the inhibition of enzymes such as pyruvate decarboxylase, acetyl cholinesterase, thus, causing encephalopathy and other cognitive developmental anomalies. [23, 25]

CADMIUM

Cadmium is considered as the most non-essential and highly toxic heavy metal. It is the heavy metal which is situated in between of zinc and mercury in the periodic table, having similar behavior to zinc. It is usually found as the impurity in zinc or lead deposits and therefore, it is primarily produced as the by-product of zinc or lead smelting. In present day world, cadmium possess various applications such as in electroplating, batteries, plastics, paint pigments, television screens, cosmetics, galvanizing steel and metal coatings. It is also known to enter naturally through volcanic eruptions, river transport, weathering and human activities like, smelting, mining, incineration wastes and manufacturing of fertilizers. [26] Primary exposure sources of cadmium include food and tobacco smoking. The crops are able to accumulate the cadmium levels due to the high rates of soil-to-plant transfer via cation exchange and intracellular transport. Therefore, consumption of staple foods such as rice, wheat and other leafy vegetables significantly contribute to the human cadmium exposure. Also, consumption of sea foods such as fishes, oysters,

molluscs, crustaceans also lead to the human exposure. Therefore, in non-smokers, diet is the main source of environmental cadmium exposure.[26,27,28] Various activities like mining, usage of cadmium containing fertilizers and pesticides and sewage sludge on farm land and disposal of industrial wastes into the water bodies may lead to the contamination of cadmium in crops and sea foods for human exposure. Cigarette smoking is considered as the most significant source of human exposure since; one cigarette contains almost 1 to 2 µg of cadmium. The exposure by inhalation depends on the particle size and the solubility of the cadmium compounds for the absorption in the body parts. Absorption of cadmium through the skin is negligible. Regardless the route of exposure, Cd is efficiently retained in the organism and remains accumulated throughout life, as the metal cannot undergo metabolic degradation to less toxic species and is poorly excreted. The amount of Cd excreted daily in urine is however very low, representing somewhat 0.005 to 0.01 per cent of the total body burden. The target organs for cadmium toxicity in animals include the liver, kidney, lungs, testes, prostate, heart, skeletal system, nervous system and immune system.[27,28] However, prolonged human exposure to Cd results in its accumulation in the body and leading to diseases mainly affecting lungs and kidneys. Symptoms of acute cadmium poisoning usually appear after 24 hours are: shortness of breath, general weakness, fever. It can also cause pulmonary enema, pneumonia, and in severe cases, respiratory failure and death. As per several reports, women are considered to have higher cadmium body burden than men, reflected as higher concentrations of cadmium in blood, urine and kidney cortex. The main reason for the higher body burden in women is increased intestinal absorption of dietary cadmium. Blood cadmium is considered the most valid marker of recent exposure and is usually assessed in whole blood.[28, 29]

MECHANISMS OF TOXICITY

Cadmium poses a great health risk to humans even at very low concentrations in the body and because the body has limited capacity to respond to cadmium exposure. The mechanisms of cadmium induced toxicity interfere with several cellular functions of the cells (Figure 2). Cadmium is unable to catalyse redox reactions in biological systems under physiological conditions. It has been shown, however, that Cadmium increases the concentration of free redox-active metals like Fe (II), Cu (II) possibly by their replacement in various proteins, changes in mitochondrial membrane potential and inhibiting the flow of electrons from reduced ubiquinone to cytochrome c and these free redox-active metals directly enhance the production of OH (hydroxyl) radicals through the Fenton reaction. Reduction of the oxidized metal ion can be achieved by the Haber–Weiss reaction with superoxide radicals (O2 -) as a substrate, but also other reducing agents, such as ascorbate can catalyse this reaction. The cellular responses against oxidative stress balance between cell death and cell proliferation, and signalling molecules such as p38-MAPK (Mitogen-Activated Protein Kinase) and JNK (Jun N-terminal Kinase) are involved in both stress-induced processes.[16,18,27,28] The exact role of ROS in the activation of signal transduction pathways involved in defense mechanisms during Cadmium stress, still needs to be clarified. The oxidative stress that arises in cells exposed to cadmium weakens their antioxidant defense mechanisms, results in reduction of glut changes antioxidant enzyme activity, activates proto-oncogenes, which leads to excessive production of protein products that stimulate cell proliferation. Low efficiency of antioxidant mechanisms in cells exposed to cadmium may result from the interaction of cadmium with zinc, copper, iron and selenium resulting in a decrease in activity of antioxidant enzymes: superoxide dismutase, catalase, glutathione peroxidase.

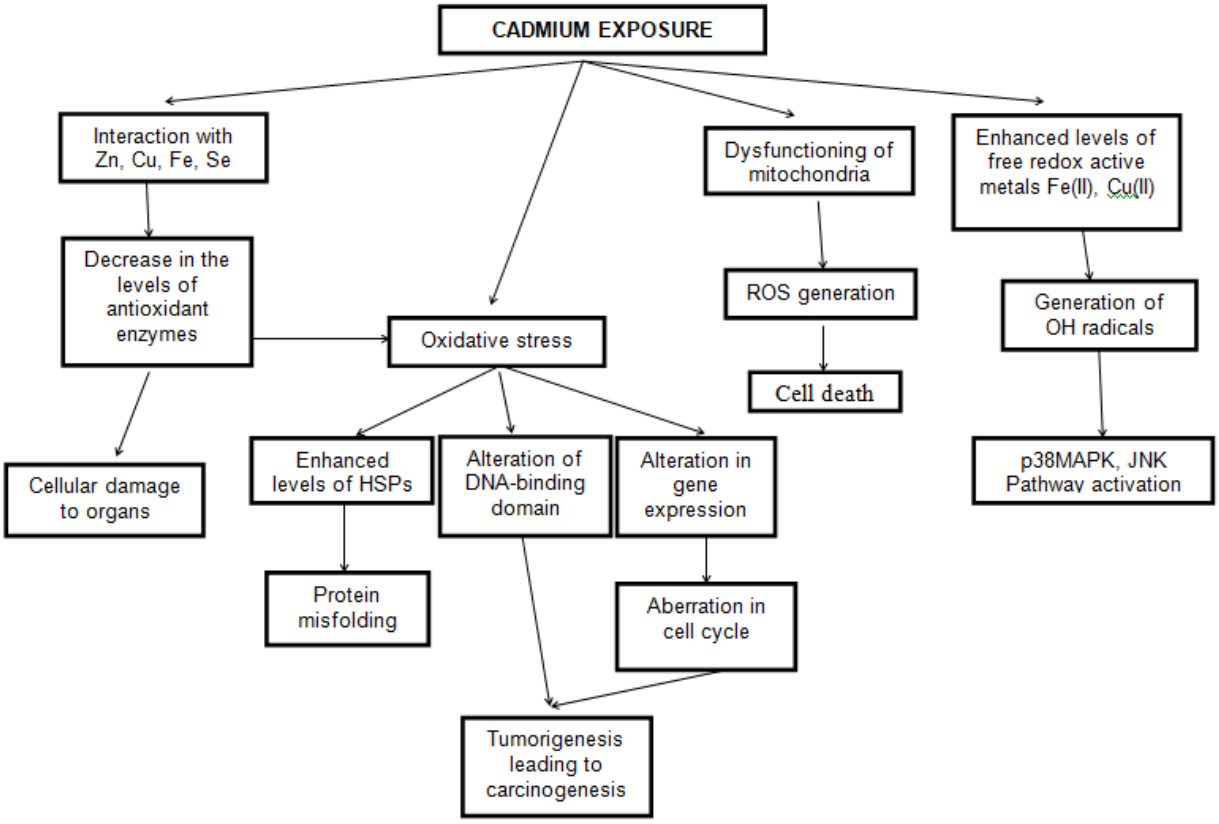

Figure 2
Possible mechanisms of cadmium induced toxicity

Regardless of the mechanism of induction of oxidative stress in cells by cadmium, increase in ROS occurs, which leads to the damage and changes in their structure and metabolism. Their excess induces mitochondrial membrane lipid peroxidation, which can cause damage to these organelles. ROS reacting with polyunsaturated fatty acids of cell membranes initiate lipid peroxidation process that results in modification of proteins, changes in membrane gradient, and this causes the loss of their integrity and irreversible damage. These biochemical changes lead to several life threatening disorders such as Fanconi syndrome, diabetes, renal impairment, cardiovascular complexities and bone sorption related diseases. [29,30,31] The major mechanisms involved in Cadmium carcinogenesis can be broadly categorized into four groups, aberrant gene expression, inhibition of DNA damage repair, inhibition of apoptosis, and induction of oxidative stress, with significant overlap among the groups. In addition, the ability of Cadmium to cause aberrant DNA methylation, endocrine disruption and cell proliferation may assume minor importance with respect to its carcinogenic potential. [26,29,30]

LEAD

Lead is considered as one of the most highly toxic heavy metal whose existence in the environment has beacome a global issue around the globe. The various human activities such as smelting, mining, plumbing, usage of fertilizers and pesticides, accumulation of wastes from battery industries and soils, excess amount of automobile usage leading to elevated levels of emissions, has led to an accumulation of lead and its compounds in the environment, including soil, air and water. [32,33] Lead is also used for the production of lead based paints, cosmetics, gasoline, solder and pipes, thus, leading to high amounts of lead exposure to humans[34]. Drinking water is also considered a potential souce of lead contamination. Since, water passing in the pipes could be made from lead, thus, leading to contamination of water. Thus, people get exposed to lead through occupational and environmental sources. Inhalation of lead particles, actively by the occupational workers or passively by the other huamn beings freom the environment or by the ingestion of lead contaminated water, food, medicines and cosmetics, are the primary sources of lead exposure, affecting human health.[35]

MECHANISMS OF TOXICITY

Various studies have been published regarding the harmful effects of lead in children and the adult population. [33,36,37] In children, these studies have shown significant link between the concentration of lead in blood and decreased IQ levels, retarding neurobehavrial development and affecting various cognitive developments in the children. [36] The adult population gets severely affected by the lead concentrations affecting the various organs of the body. The acute lead toxicity syptoms include reproductive defects, kideny damage, heamatological effects and others. [38] The mechanisms of lead induced toxicity leads to disruption

of various cellular functions (Figure 3). Toxicity caused by metal lead in living cells is mainly due to the ionic mechanism leading to oxidative stress. Various studies have shown that oxidative stress is the prime cause for the imbalance between the production of free radicals and the decrease in the levels of anti-oxidants. Various antioxidants are present in the cell, one of them being the glutathione, which protects the cells from the radicals such as hydrogen peroxide.

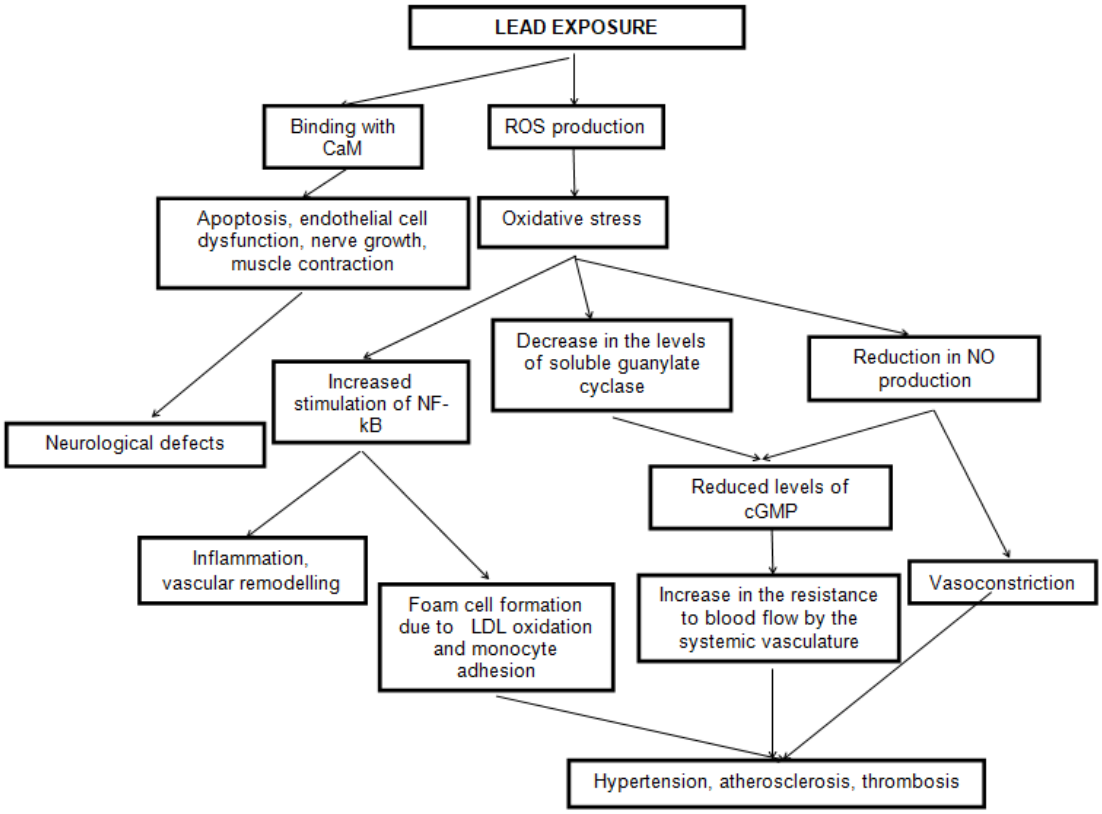

Figure 3
Possible mechanisms of lead induced toxicity

Since, glutathione is known to exist in reduced (GSH) and oxidized (GSSG) states, the reduced form of glutathione donates the reducing equivalents from the thiol groups of cysteine to ROS, thus, making it stable. The enzyme, glutathione peroxidase plays a major role catalyzing the formation of glutathione disulfide (GSSG) from the reduced form of glutathione (GSH). Under the stress levels, there is an increase concentration of GSSG, as comapared to the concentration of GSH. [38,39] Another indicator of oxidative stress is lipid peroxidation. Excess of free electrons collected from the lipid molecules, being the constituent of cell membrane, leads to lipid peroxidation. Excess of ROS can lead to serious cellular and morphological defects in the structure. Also, due to oxidative stress, transcription factors like, NF-kB which controls cell survival, cytokine production lead to the promotion of inflammation, endothelial dysfunction, fibrosis, apoptosis and oxidation of LDL, leading to foam cell formation and thus, causing thrombosis and artherosclerosis. Several studies have shown that lead exposure leads to NF-kB activation which further plays a major role in hypertension. Due to the enhanced formation of free radicals induced by metal lead, there has been a decrease in the NO production and expression of guanylate cyclase. These effects lead to the resistance of the systemic vasculature. [3,37,38,39,40]

MERCURY

Mercury is considered to be a highly hazardous heavy metal and excessively bio accumulative in the environment. It exists mainly in three forms: metallic elements, inorganic salts and organic compounds, each possessing different levels of toxicity and bioavailability. The sources of exposure to mercury poisoning are diverse. It is ubiquitously found in the environment, to which tons of mercury are added by various anthropogenic activities such as municipal waste water discharges, mining, agriculture, incineration and disposal of industrial wastes or waste water in the water bodies or soil, as the risk of entering into the food chain prevails.[41,42] Thus, mercury pollution has been hiking with the speeding rate of industrialization and man's hungry desire of technological advancement. Therefore, various forms of mercury are present widely in the water bodies. It is known that inorganic mercury is transformed to the organic form, methylmercury (MeHg) by methylation reaction occurring in water bodies. The process is believed to occur in sediments at the bottom of aquatic ecosystems where anaerobic bacteria like SRB (sulphate-reducing bacteria) and methanogens thrive. One such example is *Desulphovibrio desulfuricans*, a sulphate reducer which produces large amounts of methyl mercury by acetyl CoApathway. [43] According to several reports, methylmercury is known to

accumulate in the muscles and fatty tissues of the fish. Thus, due to bio magnifications through the food web the contamination of methylmercury by the aquatic animals is one of major route of human exposure. In present day, the metal mercury is used in thermometers, pyrometers, barometers, hydrometers, fluorescent lamps and mercury arc lamps. It is also excessively used in dental amalgams; pulp and paper, agricultural, pharmaceutical and chlorine and soda production industries; and used as a component in the batteries. Due to the various applications of mercury, the risk of its contamination prevails. [42,44]

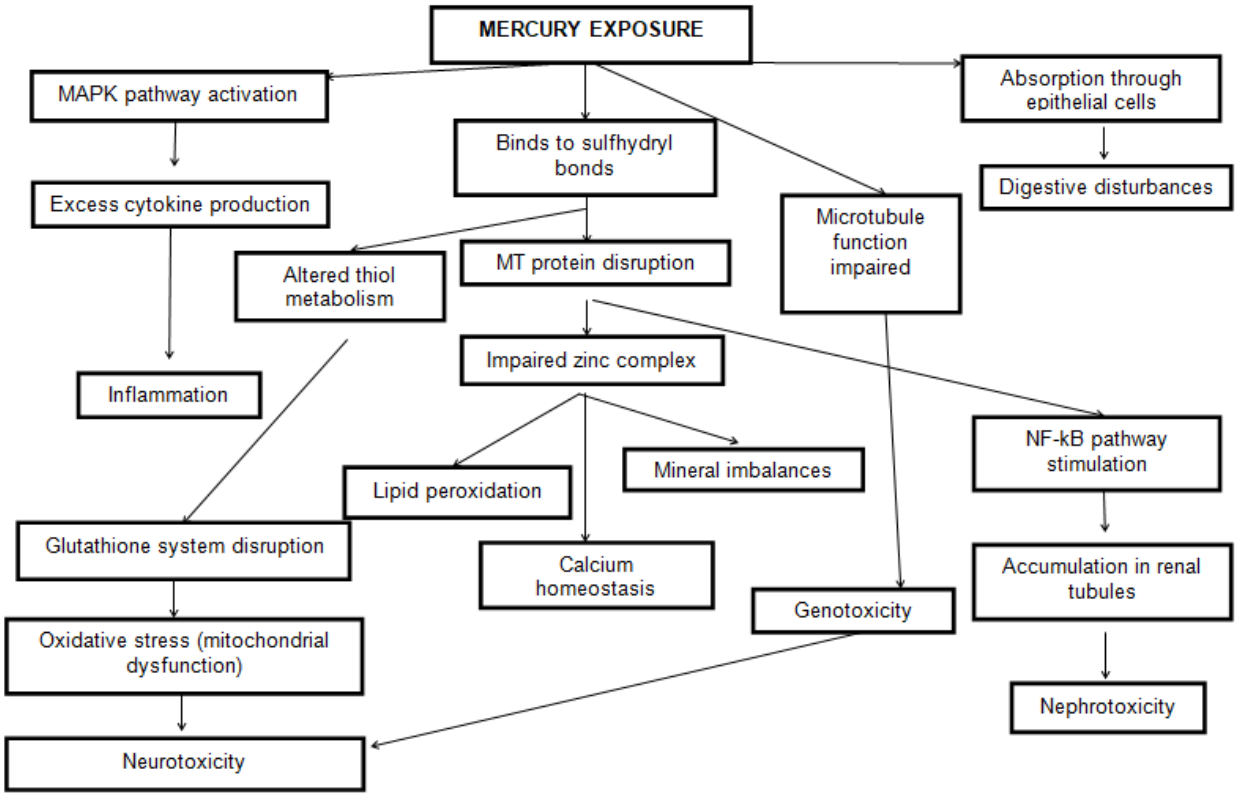

Figure 4
Possible mechanisms of mercury induced toxicity

As per several studies, exposure to elevated levels of mercury could damage the kidneys, lungs, developing foetus and mainly the nervous system, as it could alter the brain functions and further cause tremors, shyness, memory problems, irritability and problem in seeing and hearing, with the respective type of mercury toxicity. Hence, due to the dreadening health effects caused by mercury poisoning, the maximum permissible limit of mercury has been set up to 0.001-0.002 mg/l, as per WHO and USEPA.[45]

MECHANISMS OF TOXICITY

There are several molecular mechanisms, but none of which could alone explain the multitude of effects observed in mercury induced toxicity (Figure 4). Once mercury is taken up by the body in various forms, it could cross the blood brain barrier and get accumulate in the brain, lungs and the kidney on exposure to mercury in the body.[42,45] Further, it disrupts the metallothionein gene, which synthesizes the Zn-dependent metal binding protein metallothionein (MT) for the metalothionein expression which is required for the elimination of the heavy metals from the body. It also binds to sulfhydryl bonds, thus disturbing the cellular functions of the body. Also, it alters the thiol metabolism by elevated levels of ROS production, thus inducing oxidative stress which would further lead to apoptosis, inflammation, mitochondrial dysfunction, calcium homeostasis and neurological disorders. If the mercury is inhaled, it would get absorbed by the lungs and reach to the blood. Once mercury reaches the blood, the lipid solubility allows for easy passage across membranes, thus hampering the membrane potential of the cell. On entering a cell, mercury maybe oxidized and gets converted to its inorganic form. The mercury ion (Hg^{2+}) formed leads to non-uniform distribution and accumulation in renal tubules leading to nephrotoxicity. [44,45] On eating contaminated sea foods, it would directly affect the gastrointestinal tract, leading to digestive problems such as inhibition of the production of the digestive trypsin, chymotrypsin and pepsin along with the function of dipeptidyl peptidase IV and xanthine oxidase. Also, the methyl and ethyl groups present would increase the hydrophobicity leading to easy diffusion across the blood brain barrier and placenta. Methyl mercury forms water soluble complexes and gains access to its target tissue, brain via molecular mimicry mechanism. The structure of the complex between L-cysteine and MeHg resembles methionine, an essential amino acid and is thus able to gain entry into the brain, which would further lead to Alzheimer's or Parkinson's diseases, and if absorbed into placenta, it would be stored in the fetal cells and may lead to conditions like autism. Some amount of MeHg is

demethylated by microflora in the intestine and passes out of the body in the form of Hg2+.[44,45,46,47] Major fraction of absorbed Hg accumulates in the kidneys, liver and neurological tissues. Mercury poisoning is characterized by latent periods between exposure and appearance of signs and symptoms. The period varies from weeks to months and the underlying mechanism is not yet clear.

CONCLUSION

In this review the effects of some heavy metals, *i.e.* arsenic, lead, mercury and cadmium on the environment and living organisms, mainly human beings has been discussed. Effective legislation, guidelines and detection of the areas where there are higher levels of heavy metals are necessary. Failure to control the exposure will result in severe complications in the future because of the adverse effects imposed by heavy metals. Occupational exposure to heavy metals can be decreased by engineering solutions. Monitoring the exposure and probable intervention for reducing additional exposure to heavy metals in the environment and in humans can become a momentous step towards prevention. National as well as international co-operation is vital for framing appropriate tactics to prevent heavy metal toxicity.

CONFLICT OF INTEREST

Conflict of interest declared none.

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