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PROSPECTS

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Prevalence of exposure of heavy metals and their impact on health consequences

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Abstract

Even in the current era of growing technology, the concentration of heavy metals present in drinking water is still not within the recommended limits as set by the regulatory authorities in different countries of the world. Drinking water contaminated with heavy metals namely; arsenic, cadmium, nickel, mercury, chromium, zinc, and lead is becoming a major health concern for public and health care professionals. Occupational exposure to heavy metals is known to occur by the utilization of these metals in various industrial processes and/or contents including color pigments and alloys. However, the predominant source resulting in measurable human exposure to heavy metals is the consumption of contaminated drinking water and the resulting health issues may include cardiovascular disorders, neuronal damage, renal injuries, and risk of cancer and diabetes. The general mechanism involved in heavy metal-induced toxicity is recognized to be the production of reactive oxygen species resulting oxidative damage and health related adverse effects. Thus utilization of heavy metal-contaminated water is resulting in high morbidity and mortality rates all over the world. Thereby, feeling the need to raise the concerns about contribution of different heavy metals in various health related issues, this article has discussed the global contamination of drinking water with heavy metals to assess the health hazards associated with consumption of heavy metal-contaminated water. A relationship between exposure limits and ultimate responses produced as well as the major organs affected have been reviewed. Acute and chronic poisoning symptoms and mechanisms responsible for such toxicities have also been discussed.

KEYWORDS

cancer, diabetes mellitus, heavy metals, oxidative stress, reactive oxygen species

1 | INTRODUCTION

Heavy metals are found naturally in earth's crust but technology-based and/or research-related activities have caused drastic changes in their geochemical cycles. These heavy metals then accumulate in different parts of plants thus causing various harmful effects on human health.[1] Some metals such as zinc, copper, iron, manganese, and cobalt are required by human body,[2] however, they may be toxic if ingested at higher concentrations.[3] There are some other

heavy metals such as lead and mercury which are not known to have any beneficial effects on human health but in fact are deleterious to human health if accumulated in body over time.[3]

Heavy metals can disturb body's metabolic functions through various ways. Moreover, they may accumulate in vital body organs such as liver, heart, kidney, and brain disturbing normal biological functioning. Once heavy metals are within the biological systems they block their vital activities in body. However, it is an utmost fact that it is impossible to have an environment totally free of heavy metals. Entrance of these heavy metals into human body could occur in a number of ways such as through consumption of contaminated food, drinking water and/or air.[1] In Pakistan (Fig. 1), heavy metals such as cadmium, arsenic, lead, mercury, and nickel have been found in ground as well as in surface water all over the country. Crops irrigated with this contaminated water are also found to have toxic concentration of such heavy metals. To support the development of human technology, metals were being discovered and extracted to be used as a tool for the purpose of fulfilling the needs of humans. But now, as metals wastes are polluting the water and soil surfaces thus are leading toward detrimental human health effects. Living systems do not degrade heavy metals which ultimately leads to their accumulation up to harmful levels.[4]

Various carcinogenic pathways induced by heavy metal exposure have been established by researchers. Various studies have investigated that carcinogenicity and mutagenicity of heavy metals are associated with induction of oxidative stress. In this regard, researchers found that within the biological systems redox reactions are being performed by carcinogenic metal ions such as chromium, nickel, vanadium, cobalt, and arsenic. Thus free radicals produced as a result of these reactions lead toward oxidative damage of proteins as well as DNA. In spite of producing direct DNA damage, species produced as a result of redox reactions also have two important functions causing carcinogenic effects in humans. One of which is activation of transcription factors which are redox sensitive whereas other function involves its role as mitogenic signals.[5] Likewise, another pathway for heavy metals to cause carcinogenicity has been considered as the process of DNA repair interference.

2 | GENERAL MECHANISM OF HEAVY METALS TOXICITY

Accumulation of heavy metals in body has shown to exert adverse human health effects. The prominent heavy metals which are mostly involved in causing such health effects include cadmium, aluminum, mercury, iron, lead, and arsenic. These metals may enter the body through various routes such as dermal or inhalational route or by ingestion of heavy metals either through contaminated food and/or drinking water. Due to increased industrialization processes, heavy metal exposures have been increased worldwide and as a result increased deleterious human health effects associated to metal exposure are being observed in last few years. Heavy metals actually react with some of body's compounds such as chloride and oxygen and exert their toxic effects.[6] Continuous exposure to heavy metals may lead to internal imbalance in body, they start accumulating in body where the body start using them as substitute of essential elements. Examples of some heavy metals which substitute for body's essential elements include calcium substituted by lead, zinc substituted by cadmium and majority of trace elements are substituted by aluminum. Moreover, stored heavy metals destroy major metabolic processes of body, along with creating antioxidant imbalance. Similarly, activity of various hormones and essential enzyme's function are also influenced.[7] Susceptibility of body toward infection is increased as a result of alterations in carbohydrate, protein and lipid metabolism.[8] All of the above mentioned mechanisms ultimately alter the synthesis of neurotransmitters and their use in body thus altering Central Nervous System (CNS) functions.[9]

Hence, the literature clearly indicates that whatever the molecular pathway is influenced by exposure to heavy metals, they ultimately induce generation of reactive oxygen species which produces oxidative stress that may lead toward different kind of cancers, neurological disorders, damage of kidney function, and other endocrine abnormalities.[10]

3 | CADMIUM

3.1 | Occurrence and exposure

Cadmium (Cd) is a heavy metal and is found naturally in ores. Cd is used generally as stabilizer in different products like color pigments, several alloys and in Polyvinyl chloride (PVC)-related products. Another major source of Cd exposure is phosphate fertilizers. Moreover, during the twentieth century, the production of Cd, its usage and emission to the environment has been increased throughout the world. When Cd containing waste is incinerated, it heavily contaminates the environment. For example, soil contamination occurs when phosphate fertilizer and sewage sludge is applied to crops where Cd is up taken by the crops and vegetables which are ultimately consumed by humans.[11] Another major source of Cd exposure could be cigarette smoking. However, studies have found that this accounts for a little of total Cd concentration of body.[12]

3.2 | Cadmium handling by body

Once Cd enters in to the blood, it is transported by proteins such as albumin and metallothionein (MT) in a bound form.

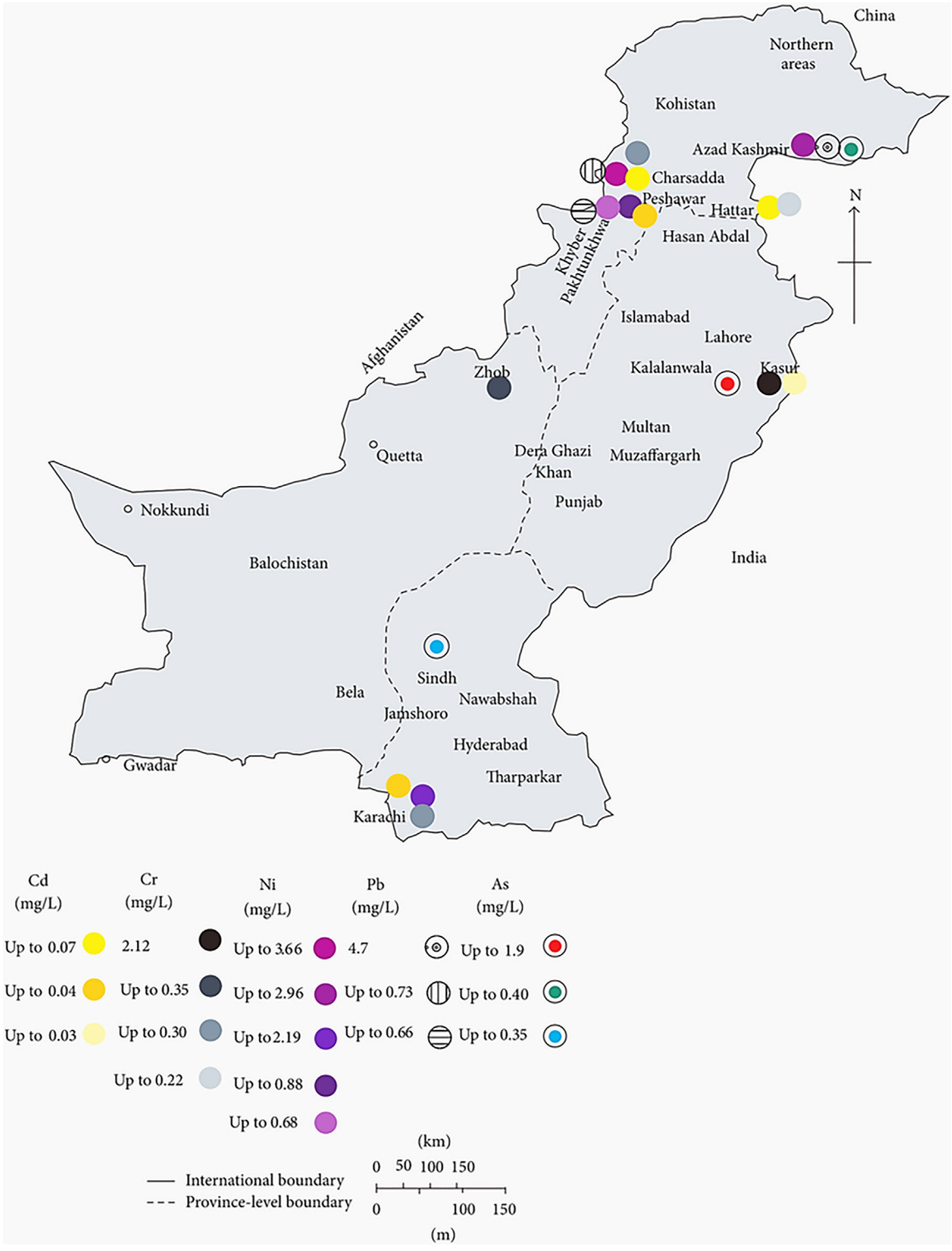

FIGURE 1 Map of Pakistan showing Cd, Cr, Ni, Pb, and As concentration in ground water (mean values; where mean value is not available, the highest values are used). This figure represents the four provinces of Pakistan with colored dots showing the areas with highest concentration of heavy metals, whereas, dark colors are showing upper range and lighter colors showing the lower range of concentration of heavy metals. Source: *Biomed Res Int*. 2014;2014

After reaching gastrointestinal tract, Cd enters liver where it initiates the production of metallothionein and Cd metallothionein is released into sinusoidal blood. Cd may enter the enterohepatic cycle as cadmium-glutathione conjugates after being secreted into the biliary tract. Whereas, in biliary tract, these Cd conjugates are broken into cadmium-cysteine complexes and Cd can again enter into the small intestine.[13] Moreover, it has been observed that Cd can be stored for a long time in kidney[14] which can lead toward tubular necrosis. A measure of blood Cd concentration provides a more accurate estimate of recent exposures while measurement of renal Cd concentration is recognized to indicate past exposure and body burden of Cd.[15]

3.3 | Cadmium in drinking water

One of the basic needs for human survival is drinking water. In present era, the overall population of world is more than one billion people. Majority of the population from this one billion resides in rural areas. According to world health report 1998, with respect to different areas and countries the supply of water has been seen to vary widely. Still the majority of population especially those in developing countries is at risk of developing hazardous diseases because of unsafe drinking water containing heavy metals like lead, mercury, cadmium, and arsenic.[16]

In Pakistan, it has been found that Cd is present both in earth's crust and also in ocean water. According to International Agency for Research on Cancer (IARC), ocean water on an average has concentration of Cd ranging from less than 5-110 ng/L.[17] According to World Health Organization (WHO), Cd concentration which is considered to be tolerable in drinking water is 0.003 mg/L[18] (Table 1). A survey was conducted in Pakistan to measure the concentration of heavy metals in drinking water. According to this survey, Cd concentration was found to be 0.001-0.21 mg/L in samples collected from different regions of Pakistan.[19] As a result the highest value of Cd averaging about 0.02 mg/L were found in water samples collected from a tube well water source of Hayatabad Industrial Estate in Khyber Pakhtunkhwa province in Pakistan.[20]

A study conducted in Southwest Nigeria for assessing ground water quality showed that Cd and levels of some other heavy metals were exceeded to those as specified by WHO in drinking water.[21] In Nigeria, drinking water was found to be contaminated with Cd at a concentration of 0.06-1.1 μg/L.[22] Similarly, a survey conducted in Sweden for drinking water taken from shallow wells resulted in Cd concentration ranging upto 5 μg/L.[23] Likewise, samples taken from private wells in Saudi Arabia showed mean Cd concentration of 1-26 μg/L.[24] Concentration of cadmium in drinking water samples of Netherlands was ranging up to 0.1-0.2 μg/L.[25] This high Cd concentration is caused by various natural as well as anthropogenic sources such as smelter waste, sewage sludge, phosphate fertilizers, and municipal waste.[17] This shows a global contamination of drinking water with Cd that might have harmful effects on human. The major health concerns related to exposure of Cd particularly through drinking water are discussed in the proceeding sections.

3.4 | Cadmium-associated health effects

3.4.1 | Acute intoxication

Even acute exposure to cadmium has been observed for causing severe adverse consequences. Inhalation of Cd fumes may cause severe damage to respiratory system causing shortness of breath; it can also disrupt the mucous membranes and lead toward lung edema. For instance, it has been reported in a case study that a previously healthy 78-year-old man who used to work in a brazing industry, was exposed to Cd fumes while brazing through Cd containing silver solder. Latter he was found to develop severe sudden pneumonitis and died within 25 days of Cd exposure.[26]

3.4.2 | Cadmium effect on respiratory system

Particles having a diameter of smaller than 100 nm are considered to be nanoparticles. Cd containing nanoparticles are inhaled most frequently by humans working in industries where they may have acute or chronic exposure to Cd fumes. This exposure can adversely affect different body organ

TABLE 1 Permissible limits of heavy metals in drinking water

Standards	Cadmium (μg/L)	Arsenic (μg/L)	Lead (μg/L)	Nickel (μg/L)	References
IARC	Group 1	Group 1	Group 2B	Group 1	Breslow and Day[289]; IARC[17]
US-EPA	5	10	15	–	US-EPA[290]
WHO	3	10	10	70	WHO[18]
NSDWQ-PAK	10	50	50	20	Waseem et al[291]
EU	5.0	10	10	20	Council[292]

IARC (International Agency for Research on Cancer) classification and permissible limits of Heavy Metals in Drinking water regulated by WHO (World Health Organization); US-EPA (U.S. Environmental Protection Agency); NSDWQ-PAK (National Standards for Drinking Water Quality-Pak) and EU (European Union).

system, however, the most commonly effected one is the respiratory system specially the lungs.[27–30] In this regard, a study was being conducted to monitor the effect of inhaled Cd oxide nanoparticles on target organs mainly respiratory system. Ultra-structural changes were observed in lungs including congested capillaries, enlarged pulmonary septa, and small areas of atelectasis. When observed through experimentation, nanoparticles were found in cytoplasm of bronchiolar cells and also in alveolar spaces. Hence, it can be seen that inhaled Cd oxide nanoparticles may cause serious damage not only at a tissue/organ but also at cellular level.[31]

3.4.3 | Neurotoxic effects of cadmium

Long ago a study was conducted to observe the neurotoxic effects of Cd. It was concluded that CNS is one of the sensitive parts of biological system that can become easily damaged during the early phase of neonatal development. Moreover, it has been recognized that Cd has the ability to cross the placental barrier and reach fetal tissue exerting harmful effects including neurotoxicity. Similarly, Cd has also found to be excreted in breast milk.[32] However, it was found that unlike neonates and fetal tissues, a much developed blood brain barrier in adults allows only a limited exposure of brain to Cd.[33] However, if Cd exposed for a long period of time, it may also show adverse effect on adult brain as evident by various investigations where changes in behavioral alterations and learning ability were observed after chronic Cd exposure. Similarly, in children, Cd exposure showed to alter their perceptual ability.[34] Besides, chronic exposure to Cd may also result in development of peripheral polyneuropathy (PNP) particularly.[35]

Recently, according to the results of a research study, it was observed that persons having motor neuron disease (MND) and/or sporadic motor neuron disease (SMND) possessed high blood Cd levels as compared to control groups.[36] Interestingly, a cross-sectional study of China involving children aged between 7 and 16 years concluded that high frequency of attention and social problems can be directly associated with higher levels of Cd in their body.[37] Moreover, another interesting evidence has been found where Cd was recognized as a major causative factor for neurodegenerative disorders including Parkinson's disease (PD) and Alzheimer's disease (AD).[38]

3.4.4 | Mechanisms of cadmium neurotoxicity

Metallothionein (MT) is a protein and out of its various isoforms, Metallothionein-3 (MT-III) has been found to be expressed in brain. MT proteins are also found to be expressed in choroid plexus, moreover, experiments performed revealed that as MT has high cysteine level and possesses great binding affinity for metals like Cd, as a result rats exposed to Cd metal showed high Cd accumulation in their choroid plexus.[39] Similarly, increased peroxidation of lipids have also been observed in several brain areas such as cerebellum and cortex after Cd exposure.[40] Interestingly, Cd has been observed through various experimental studies for its disturbing effects on the level of enzymes maintaining oxidation reduction reactions (Fig. 2). As a result of this disturbance, progression

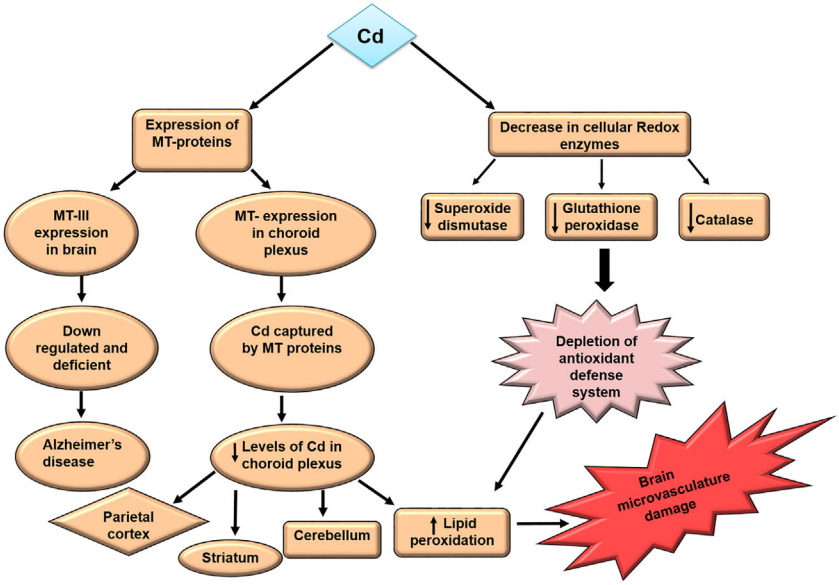

FIGURE 2 Figure illustrating the schematic pathways of Neuronal toxicity caused by cadmium exposure. Increased cadmium exposure lead toward increase in lipid peroxidation and causing harm to the microvasculature of brain. See text for detail

of lipid peroxidation occurs that may ultimately lead to microvasculature damage in the brain.[41]

Recent studies have suggested oxidative stress as an underlying cause for neuronal toxicity (Fig. 3). Investigations showed that two neuronal cell type; PC12 and cells of SH-SY5Y have been found to have increased generation of ROS as a result of Cd exposure.[42] Two signaling pathways namely; mTOR (mammalian target of rapamycin) and MAPKs (mitogen activated protein kinases) were found to be activated as a results of ROS generation thus leading to cellular apoptosis.[43,44]

3.4.5 | Cadmium-associated kidney damage

Cd has been known to have a prolonged half-life and if it is exposed at low concentrations, it still tends to accumulate in renal cortex and may cause renal damaging effects where decrease in GFR and proteinuria are considered to be major indicators of Cd-induced nephrotoxicity.[45]

Cadmium metallothionein (Cd-MT) is the form in which Cd enters the kidneys. Kidney glomerulus then filters this complex and this is ultimately absorbed again into the proximal tubules. Stored amount of Cd in renal tubules is increased day by day in person having chronic exposure to Cd especially those working in silver and zinc handling industries.[46] A study was conducted in European population to investigate Cd associated kidney damage. In this study, urinary Cd levels were tested in general population and found that urine Cd level of 2-3 μg Cd/g of creatinine was found to be responsible for kidney damage.[47] Recent studies have suggested that chronic Cd exposure is found to be associated with end stage renal disease (ESRD).[48] Two of the major kidney issues namely; formation of kidney stones and tubulointerstitial nephritis are found common in workers working in industries where they are exposed to Cd and/or lead.[49]

An investigation conducted in China and Australia involved diabetic population groups who showed increased susceptibility to kidney disease induced by Cd exposure.[50] Another study found that in blood plasma of patients having type II diabetes mellitus (T2DM), high levels of autoantibodies were found against MT along with increased level of urinary Cd. This also indicated increased risk of kidney damage in such patients.[50]

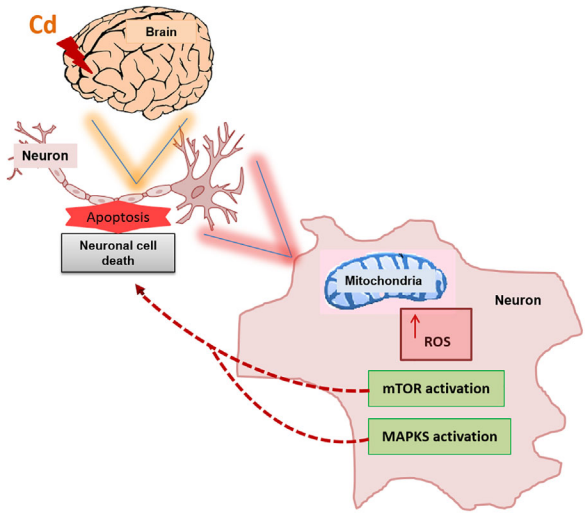

FIGURE 3 Figure representing apoptotic neuronal cell death after cadmium exposure. Death of neuronal cells occur when two signaling pathways namely; mTOR (mammalian target of rapamycin) and MAPKs (mitogen activated protein kinases) are activated due to increased generation of ROS (reactive oxygen species) caused by cadmium exposure to in mitochondria

3.4.6 | Cancer risk induced by cadmium

Recently, a review has been compiled classifying 100 chemicals, biological and physical agents which are known to be carcinogenic to human health by IARC.[51] Moreover, numerous studies have recognized the ability of Cd for contributing in induction and propagation of different kind of cancers and tumors. Waalkes[52] conducted an animal study concluding that inhalational Cd exposure results in lung carcinomas whereas ingested or injected Cd results in development of prostate cancer. Several in vitro studies in mammalian cells as well as bacterial assays were performed to expose the underlying mechanisms of Cd induced carcinogenicity. Similarly, numerous observations including genetic mutations as well as chromosomal aberrations whereas DNA strands breakage have been found after in vitro mammalian cell study. However, Cd compounds were not found to be mutagenic in results revealed by bacterial assay.[52] Cd has been found not to be directly involved in redox reactions of body. However, oxidative stress has been proposed to be a relevant mechanism for Cd related genotoxicity. It has been found after investigations that major body's antioxidant enzymes such as glutathione reductase and superoxide dismutase are inhibited by Cd exposure.[53,54]

Breast cancer

Recently, reports have suggested that Cd has been associated with estogenicity.[55] It has been reported that changes in gene expression may occur after exposure to Cd when it competes with estradiol for its binding to estrogen receptors and thus activation of receptors in this way can lead toward alteration in many essential and regulatory gene expressions. Similarly, Cd has also been seen to act as estrogen in uterus.[56] Likewise, presence of Cd in a biological system may influence the body's mechanism for keeping androgen-estrogen balance as Cd exposure was

seen to increase the levels of testosterone within body.[57] This increased level of testosterone is known to be associated with high risk for development of many disorders and diseases including breast cancer. A recent meta-analysis revealed the risk of breast cancer development when the testosterone levels were found to be doubled.[58]

Prostate cancer

Recent evidences suggest that because of increased industrialization and almost no proper recycling, Cd is being considered a major causative factor for prostate cancer.[59] Study results have shown that Cd is capable to cause malignant transformations in human prostatic epithelial cells.[60] A continuous exposure to Cd for a prolonged time was found to be associated with malignant transformations in prostate gland mainly because of the probable progressive accumulation of Cd in human prostate.[59] Evidences have also suggested that Cd may lead to cell cycle arrest owing to the damage caused to DNA.[61]

Renal cancer

Some evidence also suggests that renal cancer in human is thought to be caused by Cd exposure.[62] Ultimately, Cd has now been classified in Group I human carcinogens by IARC. Similarly, data supports that only inhalational Cd exposure is capable of carcinogenicity.[15]

3.4.7 | Cadmium effects on reproduction

Along with other organs such as kidney, lung, and pancreas, the reproductive organs of mammalian group such as prostate, ovary, and placenta are also adversely affected by Cd exposure.[63,64] Studies have demonstrated that free radicals such as hydrogen peroxide produced by Cd have capability to disturb the spermatogenesis.[54,65]

Oxidative stress produced by Cd results in cellular damage (which is caused by interaction of ROS with macromolecules) such as protein structure as a result normal functioning of organelles is disrupted and DNA mutations are produced leading toward gene expression changes that can ultimately lead to cellular apoptosis.[54] An experimental study of animals showed that a major cause of male infertility is decreased number of sperms and their impaired motility which may be due to the pathological lesions caused by Cd exposure.[66,67]

3.4.8 | Cadmium and bone demineralization

Interestingly, low level of Cd has also shown damaging effects on bones including high risk of bone fracture because of increased bone fragility.[45,68] Increased prevalence of osteomalcia and osteoporosis is being identified because of increased Cd exposure and its accumulation in bones.[11]

Different pathways have been suggested through which bones can be affected directly via Cd exposure, including interference of Cd with collagen synthesis in bones and/or direct stimulation of prostaglandin synthesis by the body which ultimately stimulates the resorption processes of bones. Moreover, calcium incorporation into bone cells has also been observed to be altered after Cd exposure.[47]

3.4.9 | Cadmium and diabetes risk

It has now been considered that environmental toxins are contributing toward increased rates of diabetes specially T2DM. Several experimental studies have been conducted which concluded that several body organs including pancreas, liver as well as adipose tissues are affected with Cd. Experiments revealed that Cd has diabetogenic effects on these organs.[69] A survey conducted by NHANES revealed that Cd exposure has been found to be a cause of pancreatic cancer thus supporting the fact that there exists a relationship between Cd exposure and diabetes. In a cross sectional study, it was observed that a link was found between impairment of fasting glucose and levels of Cd found in urine.[70]

Studies investigated the link between diabetes and Cd exposure by performing experiments on rats who were exposed to Cd at a dosing rate of 0.5-2 mg/kg/day. Results found that pancreas of these rats were found to have significant levels of Cd accumulated in tissues. This study revealed that homeostasis of glucose was found to be disturbed whereas the secretion of insulin from pancreatic β cells of experimental animals was impaired.[69,71]

A study conducted by Chang et al[72] concluded that pancreatic β cells undergo apoptosis via the activation of JNK pathway as a result of oxidative stress induced by Cd exposure. Recent investigations on Cd and diabetes found that a cause of type 1 diabetes mellitus due to insulin deficiency is mutation in mitochondrial DNA thus leading toward death of pancreatic β cells. Study concluded that all this occurs because of sensitivity of mitochondria toward oxidative damage induced by Cd exposure.[73,74]

Investigations reported that mitochondrial dysfunction and resulting cellular apoptosis occurs as a result of heavy metals exposure. Studies revealed that mitochondrial dysfunction is caused as a result of MMP (matrix metalloproteinase) disruption. Increased release of death effectors of mitochondria including AIP, Endo G as well as cytochrome c is another result of mitochondrial dysfunction. All this leads ultimately toward the activation of caspase cascade signals thus causing cell death.[75,76]

4 | ARSENIC

4.1 | Occurrence and exposure

Human encounter with Arsenic (As) may occur as a result of drinking water contaminated by industrial waste or agro-chemical waste.[77] Contaminated fumes or mists of As may be another source of water contamination. As poisoning may also occur by eating contaminated food containing pesticides or by food that may be grown using high levels of As metal or through food grown in As rich-soil.[78,79] Surprisingly, milk has also become a source of As poisoning after adulteration of milk occurs through mixing of As containing water. Other than these sources, route of As entry into body include inhalational and dermal exposure.[80] Humans are facing occupational health problems that may be the result of As compounds available commercially. In some occupational circumstances, exposure to arsine gas is of great risk to human health because arsine exposure may result in rapid deterioration of red blood cells (RBC's) resulting in kidney failure. Moreover, use of acid and crude metals is another major source of As poisoning.[81]

Energy production from fossil fuels and metal smelting may result in air, soil, and water contamination.[82] However, human exposure to organic As compounds such as arsenobetaine may result from fish eating which contain organic As. Determination of As exposure can be done by measuring As concentration in urine and also in hair and nails. As exposure in past may be indicated best by As measurement in hair and nails. Recent As exposure may be best determined by measurement of As in urine samples.[18]

4.2 | Global presence of arsenic in drinking water

According to a survey conducted in 2007, about 137 million people are affected because of exposure to As contaminated drinking water in more than 70 countries.[83] Arsenic compounds (organic and inorganic) have been classified as carcinogenic to human health in Group 2B (organic) and Group 1 (inorganic) by IARC[17] (Table 1). According to a survey, As was found in high concentrations in ground waters of USA, Taiwan, Argentina, China, Hungary, Vietnam, and the Ganges Plain during 1990's.[84] According to WHO, the permissible limit of As concentration in drinking water is 10 μg/L, some countries like United States of America (USA) has also developed As concentration guidelines for drinking water because of the growing risk of health effects caused by As through exposure by drinking water.[18]

If we talk about ground water As contamination then high As levels were found in the ground waters of Chile, Mexico, China, Argentina, and in the Indian state of West Bengal, Vietnam, and Bangladesh.[85–87] According to a survey conducted by Ravenscroft, it has been estimated that about 150 million people are thought to be affected with As exposure around the world.[88] One of the Asian countries which are affected badly with ground water As contamination is India. It is believed that As is being derived naturally from eroded Himalayan sediments which then enters into solution from solid phase after its reductive release when the conditions are anaerobic.[89] Recently, a report suggested alarming levels of As in ground waters of West Bengal. Ground water As concentration was found to be higher than 50 μg/L in nine districts of West Bengal.[90]

In Bangladesh, because the levels of As in drinking water are much higher than the permissible limits of WHO and people are chronically exposed to this As contaminated drinking water that's why about 57 million people in Bangladesh are at risk for arsenicosis and other As induced health effects.[91] Almost 80% of Bangladeshi population use As contaminated tube well water for drinking and cooking purposes.[92] A study conducted on 150 patients in Bangladesh revealed that about 82% population was suffering from moderate or severe skin lesions.[93]

The areas located in Chaco Pampean Plain of Central Argentina such as La Pampa, Cordoba, Santa Fe, San Luis, Tucuman, and Buenos Aires were found to be highly contaminated with As in drinking water.[84] In Argentina, La Pampa has been investigated to produce water that contains 4-5300 μg of As/L.[94] Salta and Jujui provinces of Argentina revealed high levels of As in surface water, shallow wells and springs where samples were taken from five rivers which resulted in As levels ranging from 52 to 1045 μg/L.[95] Similarly, High concentration of As was found in regions of China such as Inner Mongolia, Shanxi, and Xinjiang.[96] Up till now eight provinces of China are being affected with higher As levels in drinking water thus resulting in an increased number of patients of arsenicosis. The highest As levels found in China were between 0.05 and 2.0 mg/L.[97]

A study investigated by Cáceres et al[98] revealed that in Chile, the regions of Antofagasta, Tocopilla and Calama resulted in higher As concentration and As exposure was found to be ranged between 40 and 860 μg/L and the period of highest exposure was found to be 1958-1970. Southwick et al[99] performed a survey which concluded that about 250 people were drinking As contaminated well water with As concentration ranging between 180 and 210 μg/L in West Millard County the United States of America. Participants were found to have signs of As toxicity especially dermal toxicity.[99] In the United States of America in Fairbanks, Alaska the well water was found to be contaminated with As concentration exceeding up to 50 μg/L.[100] A study conducted in Pakistan revealed that two main provinces that resulted in higher As concentration were Punjab and Sindh. Water resources having As concentration higher than 50 μg/L were found in Sindh and Punjab.[101,102] A survey was conducted for

35 districts of Pakistan in 2001 which resulted in As concentration above 10 μg/L in 9% samples and above 50 μg/L in 0.70% of samples out of 8712 samples.[103] One of the As enriched areas identified was Muzaffargarh as a result of survey conducted by The Public Health Engineering Department of Pakistan in collaboration with The United Nations International Children's Fund (UNICEF) in 2001.[104] Farooqi et al[105] analyzed a survey conducted in 2007 which concluded the high concentration of As in four villages of Punjab that is 883 μg/L in Shamkey Bhatian, 681 μg/L in Waran Piran Wala, 2400 μg/L in Kalalanwala and Kot Asad Ullah, and 672 μg/L in Manga Mandi. Likewise, As concentration in Southern part of Punjab is also of concern as it is causing health problems because of being used for drinking and irrigation purposes. Another study resulted in As concentration ranging between 35.2-158 μg/L in Manchar Lake (Southern Part of Sindh).[106,107]

When soil samples were tested for As, surface soil samples showed higher As concentration than deep soil even when samples were taken from the same area. As concentration was found to be 46.2 mg/kg in samples taken from soils of agricultural areas of Sindh which are irrigated with lake water having higher As concentration.[106,107] Some other Samples collected from soils of Punjab resulted in As concentration of 35 mg/kg.[108]

4.3 | How arsenicals metabolized by body

As complex with sulfur is referred to as red Arsenic (As_2S_2) also known as Sandaraca. As also exist in the form of yellow Arsenic (As_2S_3) also known as Auripigment.[109] It is very rare that you may find As in free state because mostly it exists in trivalent and pentavalent oxidation states or in the form of calcium or sodium salts.[110] Trivalent forms of As such as sodium arsenite or arsenic trioxide react with many of biological ligands having sulfur groups and because of these reactions arsenicals inhibit many enzymes. As in its pentavalent form is known for its uncoupling property of mitochondrial oxidative phosphorylation.[111]

Most of the As that is ingested in inorganic form is removed via urine and a small amount of As may be bio transformed in first step after methylation of As it is converted into mono methyl arsonic acid and in second step it is converted into dimethyl arsinic acid. These processes generally detoxify the organic As but some metabolites of As which are organic in nature may contribute to As toxicity.[112]

4.4 | Arsenic-associated health effects

Ingestion of large quantities of As may result in acute intoxication causing gastrointestinal disturbances then it may affect cardiovascular system that may cause toxicity to CNS and ultimately death may occur. In people who survive, may be seen suffering from other long-term conditions such as melanosis, bone marrow depression, hepatomegaly, and encephalopathy. Studies conducted on such populations having inhalational As exposure particularly in miners and smelter workers demonstrated increased rates of lung cancers. Increased As exposure via drinking water show increased mortality rates from kidney, lung, and bladder cancer. Increased risk of cancer has been associated with increased As exposure via drinking water. According to the latest evaluation performed by WHO, kidney, skin and bladder cancers are caused mainly by As exposed to humans via drinking water (Table 2).[18]

4.4.1 | Arsenic-induced acute poisoning incidents

Cullen et al conducted a survey for determining acute poisoning from As and concluded that if toxic quantities of As are ingested they usually produce their results only with in half to one hour and it has been reported that only a little quantity of about 1 mg of As_2O_3 can produce severe toxicity.[113]

Studies have revealed two clinical presentations of acute As poisoning one of which is acute gastrointestinal syndrome which is found to be initiated with a garlic like taste that may cause burning lips, dry mouth, dysphagia, and severe vomiting may then result in hematemesis.[114] Second clinical presentation of acute As poisoning is acute paralytic syndrome which is manifested by cardiovascular collapse in first step CNS will be depressed in the next phase resulting in death of the patient with in a few hours.[114]

4.4.2 | Arsenic related social health effects

A study conducted with special reference to Bangladesh concluded that mental health is also affected by arsenicosis diseases which may produce psychological effects on human.[115] Arsenicosis has been associated to cause a number of social issues such as people suffering from arsenicosis are isolated socially and suffer from social uncertainty.[113,115] Economic burden on poor people has been increased by arsenicosis. Society considers such victims as a burden to their family. About 20-70% of arsenicosis patients remain untreated because of financial crisis in Bangladesh. Brinkel et al[115] performed a survey which concluded that people in Bangladesh hesitate to marry to a person suffering from arsenicosis. Young people who have arsenicosis in their families are advised not to marry.[115] Arsenicosis related superstitions are very common among Bangladeshi population e.g they believe that arsenicosis is a God's curse or it is an act done by evil spirits. A total of 30-80% of people in Bangladesh are not being treated because of these types of superstitions.[115]

TABLE 2 Route of heavy metals exposure and major health impacts

Name of metal	Route of exposure	Major sources	Health impacts
Arsenic	Ingestion via drinking water, food, smoking, occupational	Smelting, fossil fuel burning, agricultural pesticides, industrial waste[77,82]	Arsenicosis, psychological effects,[115,293,294] decreased mental performance,[120] hypertension, cardiovascular disease risk, carotid atherosclerosis and diabetes mellitus,[50,127,136,295] lung cancer,[296] carcinogenesis.[297]
Cadmium	Ingestion via drinking water and food like fish	Incineration fumes (from cadmium containing products, phosphate fertilizers, color pigments, PVC products, cigarette smoking[11,12]	Neurodegenerative disorders,[38] ESRD,[48] breast cancer,[58] prostate cancer,[59] demineralization of bones,[298] diabetes.[70]
Lead	Water ingestion, paint, soil	Mining, fossil fuel burning, manufacturing of lead—acid batteries, oxide synthesis forv paint, and pigments[148,149]	Neurotoxic effects on intelligence,[194] decreased memory,[195] hemolytic anaemia,[198] CVS diseases,[199] reproductive toxicity,[202] lung cancer, bladder cancer[204]
Nickel	Ingestion through drinking water and food, inhalation exposure, occupational exposure	Chemical industries, food processing industries, forest fires, volcanic emissions, incineration of waste, combustion of coal[207,212,216]	Allergic contact dermatitis,[256] oral hypersensitivity and risk of gingival hyperplasia,[266] oral cancer,[273] skin cancer,[274] lung cancer,[299] asthma, bronchitis,[277] reproductive toxicity,[279] carcinogenesis[297]

4.4.3 | Neurotoxicological effects induced by arsenic

Neurotoxicological effects caused by As include disturbances in speech, psychomotor speech problems with visual perception and reduced cognitive performance.[116] The actual mechanism for neurotoxicological effects by As are not yet clear but Agency for Toxic Substances Disease Registry (ATSDR) concluded that neurotransmitters which have effects on depression are interfered by exposure to As via drinking water. White matter in brain is affected by As which crosses blood brain barrier. Monoamine oxidase (MAO) activity in brain is enhanced as As inhibits acetylcholine synthesis.[116,117] Toxicity by As may also cause reduction in locomotor activity that ultimately disturbs the CNS.[118] Calderon et al[119] conducted a study in children which concluded that children showing higher As concentration were found to show a low verbal intelligence.

In Taiwan, high school students were compared between areas who were affected with As and those of non-affected areas. Study results showed that in children from As affected areas neurobehavioral performance were found to be low compared to areas which were not affected by As.[120]

4.4.4 | Arsenic and risk of high blood pressure

Chen et al[50] conducted a study in Bangladesh which concluded that positive associations were found between systolic hypertension and As exposure and the participants with less folate and vitamin B levels were showing these associations at higher rate.

Greater left ventricular mass and more carotid intimal-medial thickness were found in people having higher pulse pressure than those having lower pulse pressure whereas the mean diastolic blood pressure was found to be same in both cases.[121] Study concluded that a major cause of cardiovascular disease associated deaths is high systolic blood pressure. The proposed mechanism for As causing high blood pressure may involve inflammatory process initiated by As. In porcine aortic endothelial cells super oxides will be accumulated due to low arsenite concentrations.[122] Studies also investigated that endothelial nitric oxide production may be impaired by As.[123–125] Because of low level of nitric oxide blood pressure will be disturbed because it is very important for maintenance of vascular tone.[123,126]

4.4.5 | Arsenic exposure and cardiovascular disease

Results of some studies have revealed that synthesis of ROS is being increased by As exposure.[122,127] The oxidative stress which is produced by As may have effects on inflammatory processes, expression of genes, and on homeostasis of endothelial nitric oxide[128] all of the above mentioned processes are very important for the maintenance of vascular tone.[129]

In a highly exposed area of Taiwan, a study was conducted taking 79 people with HTN and 213 as controls for understanding the role of NOS3 which is a gene for

enzyme endothelial nitric oxide synthase, SOD2 the gene for enzyme manganese superoxide dismutase and CYBA a gene for p22 phox a superoxide producing enzyme. Study concluded that all above genes were associated with risk of hypertension in people exposed to As.[130] A study conducted in Northeastern Taiwan taking 605 residents in areas of low-moderate exposure of As concluded that As induced polymorphism of glutathione-S-transferase P1 (GSTP1) was associated with higher prevalence rates of carotid atherosclerosis.[131,132]

4.4.6 | Arsenic and diabetes prevalence

In a strong heart study (SHS) conducted during 1989-1991 in American-Indians from rural communities in Arizona, Oklahoma, and north and south Dakota to investigate the relation between inorganic As exposure and prevalence of diabetes.[133,134] The population taken had a low intake of sea food[113] so the As in urine is all because of exposure to inorganic As.[119]

Another study conducted in the United States found that As in drinking water especially in Southwest and Northeast areas is a major risk factor for developing diabetes.[133] Likewise, As levels measured in Arizona were ranging from less than 10-61 μg/L and in areas of North and South Dakota As concentration was found to be less than 1-2 μg/L in public water systems.[134] These measurements of As in drinking water of these areas were found consistent with As levels in urine of subjects involved in this study. In some other studies in Taiwan and Bangladesh, the higher rates of diabetes incidence[113] its prevalence[135] and death rates[136,137] were found to be associated with higher As exposure via drinking water.[138]

Researchers concluded that one of the mechanisms involved for inducing diabetes mellitus is decreased sensitization of insulin resulting after low PPAR-γ (Peroxisome proliferator-activated receptor gamma) expression caused by aesenicals exposure.[139] Watts et al[96] concluded that process of gluconeogenesis is impaired due to decreased expression of glucocorticoid receptor present in adipose as well as in hepatic tissues (Fig. 4). In vitro experimental studies investigated that stimulation of glucose uptake process is impaired because of decreased insulin secreted as a result of altered signal transduction factors including MAPK (mitogen-activated protein kinase), NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), TNF-α (tumor necrosis factor-α), and IL-6 (Interleukin-6).[99,140]

Other studies have proposed the mechanism for As causing diabetes uptake of glucose which is stimulated by insulin is suppressed by trivalents of arsenicals by causing interference at two levels. First one is that it interferes with transcription factors responsible for gene expression related to insulin.[141] Secondly, it interferes with mobility of glucose transporters present in adipose cells.[96]

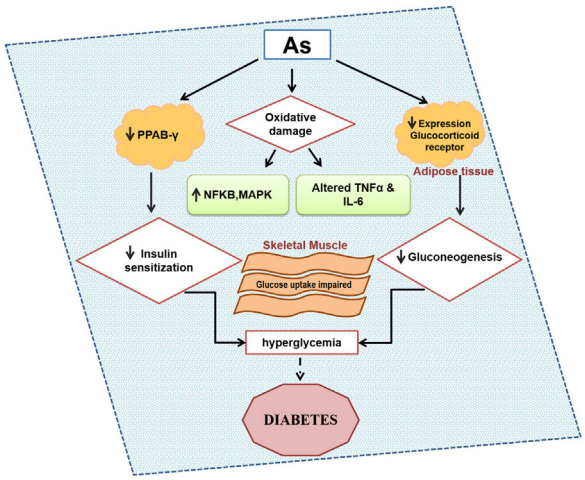

FIGURE 4 Pathological mechanisms of arsenic-induced diabetes mellitus. Decreased PPAR-γ (Peroxisome proliferator-activated receptor gamma) expression causing reduced insulin sensitivity as well as decreased glucocorticoid receptor (responsible for gluconeogenesis) expression and thus inducing diabetes mellitus. Whereas, alteration of signal transduction factors MAPK (mitogen-activated protein kinase), NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), TNF-α (tumor necrosis factor-α), and IL-6 (Interleukin-6) is another pathway responsible for induction and propagation of diabetes mellitus

4.4.7 | Arsenic and risk of cancer

Arsenic has been recognized as carcinogenic to human health. Researchers have found that As exposure via drinking water can result in various type of cancers.[142] Researchers concluded that when compared to inorganic As, monomethyl arsonous [MMA(III)], and dimethyl arsinous [DMA(III)] acid (trivalent methylated metabolites of As) were found to have more genotoxic potential.[143–145] Schoen et al[146] conducted a studys using human lymphocytes as well as cultured cell lines of mammals namely; A549 and V79. These investigations revealed that even at low As concentrations DNA damage (strand breakage and oxidative stress) were observed.[146] The ability of As to react with thiol groups has been recognized by numerous studies as a possible mechanism for its toxic effects. As may react with thiol groups which are present in various zinc binding structures that have been found to be present in many transcription factors as well as in proteins that control cell cycle. In a recent study, different effects were observed for arsenite and MMA(III) when a zinc finger peptide of XPA that contained thiol was applied and zinc was observed to complex with four cysteines. Thiol oxidation was observed as a result of arsenite reaction with apopeptide thus resulting in production of disulphide bonds. In contrast, two different species were produced as a result of MMA(III) reacting with XPAzf. Either it resulted in production of complexes with two MMAs or one

MMA having or no oxidation of two remaining cysteine. Thus, zinc binding structures have been recognized as target points for As to attack and produce DNA repair inhibition.[147]

5 | LEAD

5.1 | Occurrence and exposure

Lead (Pb) is found in the crust of earth as a bluish gray metal. Pb has been used for many years in many agricultural and industrial applications as well as for domestic purpose. A number of anthropogenic activities are causing increase in Pb exposure such as mining, burning of fossil fuels and various manufacturing processes. Pb exposure occurs because of use of Pb in production of lead-acid batteries also used for synthesis of oxides for paints and pigments.[148]

A survey concluded that out of 16.4 million US homes, 25% of homes are still found to have deteriorated paints or adjoining bare soil that is contaminated with Pb.[149] Children are more prone to Pb poisoning because while playing they are exposed to deteriorated Pb paints on soil surfaces, dust and chips.[150] Charney et al[151] concluded in a survey that blood levels of Pb were found to be about 20 μg/dL or higher in blood of children who have damaged Pb paints in their homes. Studies have investigated that amount of Pb which is used in present decade exceeds the amount of Pb that has been used in all previous decades.[152]

Two main routes of Pb exposure include ingestion of food and water contaminated with Pb and inhalation of aerosols or particles of dust which are contaminated with Pb.[153,154] Studies have investigated that 35-50% of Pb absorption occurs through the use of drinking water with increased rates of absorption for children which is more than 50%. The highest percentage of Pb is absorbed in kidneys then liver and other tissues such as brain and heart in the body of human.[155] Investigations have proved that most prominent target for Pb poisoning is nervous system. The major symptoms of lead poisoning on CNS include lack of attention, headache and memory loss.

Pb has been exposed to humans via a number of routes including the household paints which are deteriorated, crystal and ceramic containers made of Pb and also by Pb which is used in cosmetics and medicines.[153,156] Ong et al[157] investigated that Pb consumed by pregnant women is transferred to the fetus, so it should be a case of special concern. Researchers have investigated the presence of brain developmental abnormalities in children whose mothers were exposed to Pb during pregnancy.[158]

5.2 | Mechanism of lead toxicity

The major biochemical processes that are responsible for induction of Pb toxicity include capability of Pb to inhibit calcium actions and ability of Pb to react with proteins.[154] Once inside the body Pb is being incorporated into minerals instead of calcium. It then interact with biological molecules thereby interfering with their normal actions. Pb diminishes the activity of various enzymes by causing changes in their structure such as sulfhydryl and amide enzymes. Pb also inhibits enzyme activity by competing with essential cations for binding sites.[159]

Pb induced oxidative stress is the major mechanism responsible for its toxicity. Changes in membranes fatty acid composition is the major intrinsic mechanism for Pb induced oxidative damage to membranes.[160] The lateral phase separation induced by Pb affects the processes related to membranes such as exocytosis and endocytosis and processes of signal transduction.[161] Recently, researchers have found that Pb cause gene expression alterations.[162] An important human DNA associated protein Protamine is involved in Pb toxicity because of gene expression alterations induced by it and then it interact with zinc binding sites on protamine.[163] Studies have investigated the effects of Pb on activity of glucose-6-phosphate dehydrogenase (G6PD). Studies were conducted on Pb treated rats and on workers exposed to Pb which concluded that activity of G6PD was increased in RBC's of these rats and human workers.[164,165]

White et al[166] investigated that anemia is caused because of Pb exposure as it disrupts the membrane integrity and due to such disrupted membranes RBC's show more fragility. It has further been investigated that synthesis of heme is interfered by Pb exposure.[167] Pb inhibits δ-aminolevulinic acid dehydratase (δ-ALAD) enzyme thus leading to increased blood levels of δ-aminolevulinic acid (δ-ALA) (Fig. 5).[167,168] Another pathway of heme interference by Pb include inhibition of enzyme ferrochelatase and thus reducing the incorporation of iron (Fe) into heme. Moreover, Pb induced oxidative damage is found to be a result of disturbance in balance of Glutathione (GSH) and glutathione disulfide (GSSG) as Pb is known to have high binding affinity for sulfhydryl rich proteins like GSH. Likewise, increased blood levels of δ-aminolevulinic acid (δ-ALA) also contribute in increasing the ROS level after Pb exposure.

Various molecular mechanisms have been suggested for lead toxicity. Studies revealed that major mechanism by which lead induces neurotoxic damage is through its influence on events which are regulated by calcium.[169,170] Another proposed mechanism for lead toxicity includes its effect on calmodulin and cAMP phosphodiesterase both of which have been observed to be stimulated by the presence of lead. This phenomenon results in increased phosphorylation of proteins with in the synaptic vesicles, which can be further enhanced by stimulated calmodulin which itself is stimulated by lead. Thus, release of neurotransmitters is interfered.[171] Presence of lead in body may cause depletion of body's antioxidants. On other hand, it may increase the production of

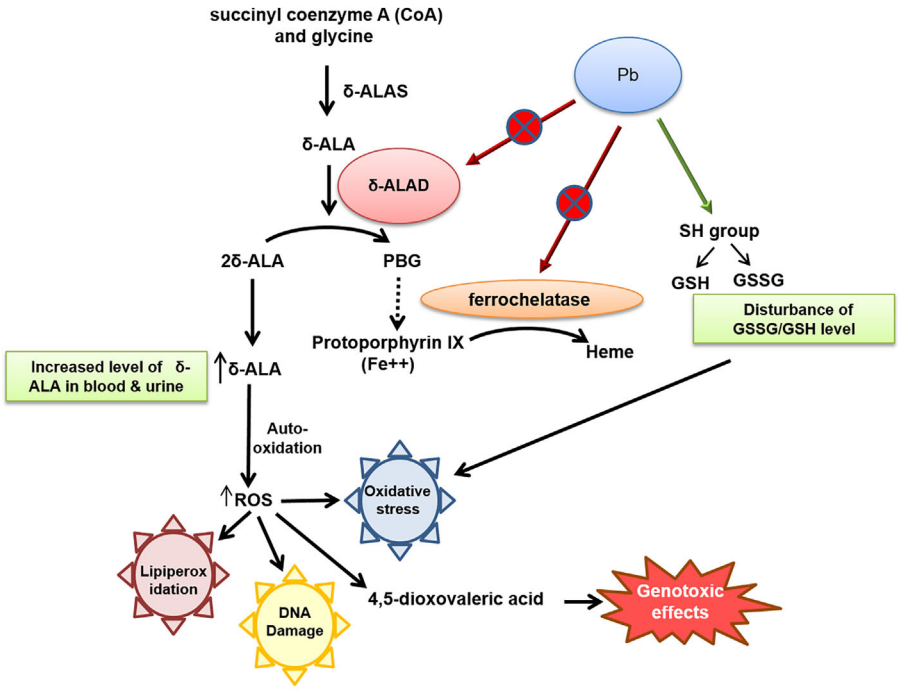

FIGURE 5 Mechanisms of lead induced toxicity. Lead exposure causes anemia because of interference with heme-synthesis. δ-aminolevulinic acid dehydratase (δ-ALAD) enzyme is inhibited resulting in increased δ-aminolevulinic acid (δ-ALA) levels which can cause oxidative stress and may result in the production of genotoxic effects

reactive oxygen as well as reactive nitrogen species.[172] The proposed mechanism for this enhanced oxidative stress is reduction in glutathione reductase levels thus leading to decreased levels of major body antioxidants that is glutathione. This results because of the ability of lead to bind directly with thiol groups.[173]

5.3 | Lead occurrence in drinking water globally

In Pakistan, Pb concentration was found to be ranging from <0.001 to 4.7 mg/L in various areas in most of water samples and this concentration exceeds the permissible limit which is 0.01 mg/L a standard set by WHO for drinking water. Some of water samples collected from Azad Jammu Kashmir Pearl valley showed Pb concentration ranging between 1.8 and 4.7 mg/L.[174] Likewise, water samples tested from Hattar Industrial Estate (KPK), showed Pb concentration averaging about 0.26 mg/L which also exceeded the permissible limits.[20] Similarly, all water samples tested from Sialkot Punjab exceeded the critical limit for Pb in drinking water.[175] More than 50% studies conducted to test Pb levels in waste water concluded that Pb levels were higher than permissible range (0.50 mg/L) of Pb in waste water as set by National Environmental Quality Standard Pakistan (NEQS).[176] These high levels of Pb in waste water are hazardous for our soil, crops, plants and also for human beings. Similarly, when soil Pb concentration was measured in Kohistan Region in Gilgit Baltistan province the Pb concentration detected was 103 000 mg/kg in contaminated soil.[177] Pb levels of 121 mg/kg were present in coastal sediments of the Arabian Sea along the urban Karachi.[178] When Pb levels were tested in superficial sediments of Lyari River they were found to be 49.5 mg/kg.[179]

Pb is considered a toxic constituent because of emission resulting from coal and oil combustion in industries at level of 450 million kg per annum whereas Pb levels emitted as a result of natural sources were found to be 30 million kg per annum.[180] Pb levels were found to be ranging between 0.03 and 44 mg/kg in various vegetable species of Pakistan.[181] A study conducted in Gilgit (Northern Punjab) found that highest Pb concentrations were found in *M sylvestris*.[182,183]

If we observe globally, a study conducted in an Indian area Assam found that Pb is a heavy metal which is found in high concentration in drinking water of Assam.[184] Also, in Bangladesh Pb concentration in drinking water of tube wells was higher than the permissible limits.[185] Another study conducted in Tarkwa, Ghana areas of Africa found that drinking water was heavily contaminated with Pb and other heavy metals.[186] Similarly, in a survey conducted by Wyatt et al[187] in Northern Mexico showed Pb concentration ranging between 50 and 120 μg/L. Moreover, a study in Australia in Lake Burragorang Pb concentration was found to be 332 μg/g.[188] Likewise, Chinese researchers investigated that Pb was a major toxic metal found in river waters of China.[189]

5.4 | Effect of Lead exposure on health

Numerous toxic events have been associated with exposure to various concentrations of lead that have produce a significant burden on health care system (Table 2), some of which are discussed in the following sections.

5.4.1 | Neurotoxicological effects of lead

There are a number of mechanisms by which Pb metal which is accumulated in body causes damage to the human nervous system. There are two types of effect that Pb has on nervous system. One of which is morphological and other is pharmacological.[111] Some of the morphological changes that are believed to affect the nervous system include reduced synthesis of neuronal sialic acid that interferes with synapse formation[190] and also it is believed that some key molecules are damaged during migration of molecules and their differentiation.[191] Another morphological change includes early glial cells differentiation.[192] Pharmacological effects of Pb causing neurotoxicity include its substitution for calcium and zinc. Functions of three main brain systems which include cholinergic, dopaminergic and GABAergic systems are disorganized as a result of interference with neurotransmitter release caused by Pb accumulation.[111] Other pharmacological effects include N-methyl-D-aspartate (NMDA) ion channels inhibition during neonatal period.[193]

5.4.2 | Lead-associated neurotoxicity on intelligence

A program conducted by WHO for determining the effects of inorganic Pb concluded by reviewing all related literatures that if humans show a blood level of Pb less than 25 μg/dL it showed a reduction in intellectual functioning and further the study concluded that a decrease in intelligence quotient (IQ) from 1 to 5 points has been shown with every 10 μg/dL increment. Khalil et al[194] conducted a study for showing dose dependent effects on intelligence. Study concluded that low levels of cognitive functions were observed with increase in Pb exposure.[194]

5.4.3 | Memory reduction with lead exposure

Researchers have revealed that capability of a person to memorize the visual stimuli and the visuospatial capabilities are disturbed due to Pb exposure. Studies revealed that long term Pb exposure results in progressive decrease both in verbal and non-verbal memory. A study conducted on individuals with peak Pb exposure of 20 μg/g showed that executive functional abilities are reduced due to Pb exposure.[195] Stollery et al[196] concluded in a study that individuals showing Pb concentration in blood up to 40 μg/dL or higher than this showed that ability of decision making and speed for classifying the things was deficient in such individuals.[196]

5.4.4 | Lead effects on language

Studies have revealed the effects of Pb exposure on human reading capabilities. Researchers have demonstrated the effects of Pb exposure on human language in a study conducted in older men. The ability of defining the words and capacity to name the drawings by visualizing them has been shown to be markedly affected by Pb exposure.[197]

5.4.5 | Risk of hemolytic anemia caused by lead exposure

There are three important enzymes in body which are involved in synthesis of heme. Studies investigated that activity of these three enzymes including aminolevulinic acid synthetase (ALAS), Aminolevulinic acid dehydratase (ALAD), and ferrochelatase is blocked by long-term lead exposure. ALAD is most affected out of these three enzymes. Therefore, ALAD is being used as a biomarker for testing Pb toxicity.[101] Vij concluded in a study that acute hemolytic anemia is caused by high levels of Pb exposure.[198]

5.4.6 | Cardiovascular effects induced by lead

Researchers have investigated that risk of cardiovascular disease has some correlation with increased blood pressure caused by Pb exposure.[199] A study investigated that death caused by cardiovascular diseases have found some association between blood Pb levels and death due to cardiovascular disease.[200] Sirivarasai et al[201] found that the mechanism involved in Cardiovascular system (CVS) diseases caused by Pb exposure is somewhat associated with oxidative stress caused by Pb toxicity.

5.4.7 | Reproductive toxicity in male and females

Pb has been found to be associated with male and female infertility. Pb exposure in men is associated with reduced sperm count and vigor as well as decreased libido is also found to be caused by Pb in blood. In females, Pb exposure is investigated to be a major risk factor for causing still births and miscarriages.[202]

5.4.8 | Vitamin-D deficiency caused by lead

A study conducted by Kemp et al[203] found that reduction in amount of vitamin D in body is associated with Pb exposure. As pathways involved in conversion of vitamin D into

1,25-dyhydroxyvitamin D (which is biologically active form of vitamin D) are disrupted by Pb.[203]

5.4.9 | Lead and cancer risk

Evidence has been collected from animal testing and some from human studies for classifying inorganic Pb to be carcinogenic for humans (Group 2A) by IARC (Table 1). Cancers of bladder, stomach and lung is known to be caused by Pb exposed to humans.[204]

5.4.10 | Pregnancy and lead exposure effects

Study conducted by Potula found that some adverse events induced by Pb exposure during gestational period can lead to premature baby birth and low weight of fetus at birth. Study also revealed that fetal growth of bones has also been impaired because of Pb. This is because of same chemical characters of Pb and calcium, so Pb competes with calcium for deposition into bones.[156]

5.4.11 | Increased risk of lead poisoning in children

There are two main reasons because of which children are at greater risk of developing Pb toxicity. First, of all because children have a smaller body size than adults so chances of rapid absorption of lead in children are more than adults. Secondly, because babies use to crawl on floors so they are more exposed to Pb containing materials. Some of symptoms caused by Pb toxicity in children include stomach pain, reduced learning abilities, anemia and incidence of vomiting. Studies revealed that symptoms of leukonychia striata have been seen in children who are exposed to higher levels of Pb.[205]

6 | NICKEL

6.1 | Occurrence and exposure

A total of 3% of earth crust consists of nickel (Ni) as this metal is the 24th most abundant element in earth.[206–208] Increased industrialization is the major source of increment in environmental pollutants including Ni and their increased health hazards. There are two sources (Anthropogenic and natural release) for increased Ni in environment and its increased exposure to human beings thus reaching toxic levels. Ni is considered to be an important element for various vital body functions. But its increased exposure may lead to toxic levels in human body.[209–211]

Two main sources of oral Ni exposure include water and food contaminated with Ni compounds.[207,211] There are many industrial and commercial applications of this metal. Some of chemical and food processing industries use Ni and its alloys as a result of which it is exposed to workers working in such industries.[212] Natural sources for its emission into atmosphere include forest fires, volcanic emissions, and windblown dust. Coal combustion and waste incineration are sources of Ni emission into air.[207,212,213] Another source of Ni exposure to humans is tobacco smoke. From medical point of view, dental and orthopedic implants are source for Ni toxicity in humans. Researchers have investigated that women are exposed to Ni by using stainless steel kitchen utensils and by wearing inexpensive jewelry.[214]

Bencko concluded by conducting studies at different work places such as those related to welding and battery manufacturing that Ni concentration as a result of occupational exposure may vary widely from micrograms to milligrams of Ni.[215] Leaching or corrosion processes are main reason by which Ni present in pipes and containers gets dissolved in drinking water and beverages. These processes may lead to daily oral Ni intake of 1 mg/day.[216,217] There are a number of applications where Ni compounds are used involving electroplating, nickel-cadmium alkaline batteries, and electronic equipment. White gold, sterling silver, and German silver are examples of Ni containing alloys. Because of this increased use of Ni and its alloys it is being released into atmosphere during manufacturing processes and cause toxicity in humans.[218] Likewise, in industries during welding, cutting, and grinding operations Ni is exposed to workers either by ingestion or by inhalation of Ni or because of skin contact with Ni.[219,220]

6.2 | Mechanism of nickel toxicity

Inhalational exposure and Ni absorption through oral route results in acute toxicity symptoms in human body. Das and Buchner[221] conducted a study for reviewing the mechanism of how it induces toxic effects. In human body, Ni combines with thiol resulting in the formation of Ni-Thiol complexes. When these complexes react with molecular oxygen it results in free radicals production that ultimately causes Ni toxicity. Study showed a similar reaction of Ni complexes with lipid hydroperoxides.[222]

Experimental studies have proved that Ni binds to a group of proteins called sulfhydryl proteins and cause reduction in glutathione levels of body which causes toxicity of Ni in body.[223] Researchers investigated that because of Ni exposure to human body its physiological chemistry is altered because of decreased excretion of calcium ions via urinary routes and also because retention of nitrogen is decreased following Ni exposure.[224] The pathway for oxidative phosphorylation is damaged because of decreased level of Nicotinamide followed by chronic Ni exposure.[225] A study conducted by M'Bemba-Meka et al[226] on RBC's of humans that were cultured concluded that oxidative stress was

produced in these cells as a result of Ni exposure. Evidences also suggested that Ni is capable of inducing hematotoxicity. Salnikow et al conducted a study in rats and mice by inducing inhalational Ni exposure. Study results revealed that some of parameters of study showed elevated levels such as count of RBC's in blood, packed cell volume (PCV) %, and the concentration of hemoglobin was seem to be increased. Study found that all these parameters were increased because of increased synthesis of erythropoietin and this happened in response to tissue hypoxia produced by Ni exposure.[218,219]

Immune system toxicity is also evident to be caused by Ni metal exposure. Studies revealed that immunotoxic effects are being induced in humans because of Ni induced damage to immune system. Skin allergy such as dermatitis is known to be caused by Ni exposure.[227] Researchers investigated that one of the mechanisms of Ni toxicity is by damage to DNA which occurs as a result of binding of Ni to nuclear proteins and also because of its binding to DNA.[228] Some studies investigated that base excision repair property of DNA is being interfered by Ni thus resulting in its toxicity. Repair process of DNA adducts is being impaired by Ni.[229] Further studies revealed the fact that proto-oncogenes are activated as a result of enhanced proliferation of cells because of altered expression of genes. And the reason behind this altered expression is carcinogenic metals.[4] A study conducted by Cortijo et al[230] concluded that membrane of placenta is disrupted because of peroxidation of lipids induced by prenatal Ni exposure. Because of this peroxidation pathway permeability of placenta is increased and toxic damage is induced in fetus.[230]

6.3 | Nickel presence in drinking water globally

Nickel is a metal that is found to have a wide distribution in nature. Drinking water is a major source of Ni exposure to humans. According to WHO,[18] maximum concentration of Ni that is permitted to be present in drinking water is 0.07 mg/L.

In Pakistan, 0.02 mg/L is the permissible limit of Ni to be present in drinking water defined by National Standards for Drinking Water Quality, Pakistan (NSDWQ-Pak).[231] A Survey found that variation is found in Ni concentration of ground water from <0.001 to 3.66 mg/L. In surface water of Pakistan, Ni concentration is found to be <0.001-1.52 mg/L. Another survey concluded that in various regions of Pakistan Ni concentration exceeds the permissible limit defined by NSDWQ-Pak. This survey found that ni concentration exceeds the permissible limit in drinking water of Karachi.[232] The limit of Ni concentration to be permitted by National Environmental Quality Standards of Pakistan in waste water is 1.0 mg/L. A study was conducted in Lahore to investigate the Ni concentration in waste water of Lahore city in Pakistan and concentration of Ni was found to be ranging between 0.91 and 5.94 mg/L which is higher than the permissible limit.[176,233] Areas in Lahore that were found to be contaminated with Ni showed concentration of Ni 324 mg/kg in soil samples. Samples collected from Kohistan represented with 70 mg/kg of Ni soil concentration. Both of these concentrations were found to be higher than the permissible limits.[233,234] Also in samples collected from soil of Jhangar Valley in Punjab maximum concentration of Ni in soil was found to be 81 mg/kg.[183] In Karachi, in Lyari area when Ni concentration was measured in samples taken from Malir River its concentration was found to be 74 mg/kg.[179] Recent analysis concluded the Ni concentration in atmosphere ranges between 0.01 and 0.15 μg/m^3. The highest concentration was found in atmosphere of Islamabad.[235] Researchers found that in area of Hasan Abdal Punjab Ni concentration was measured in Spinach that was being irrigated with sewage water contaminated with Ni. Concentration of Ni was found to be 28 mg/kg.[19]

Drinking water pollution is a major concern in North American countries. A survey conducted in Canada revealed the presence of high concentration of Ni in water sold in bottles for drinking purpose. Survey found that Ni concentration was 16-35 μg/L.[236] Also some researchers investigated bottled samples and water samples taken from taps to analyze the presence of heavy metals in Denmark. Results showed that Ni concentration in drinking water exceeded the local limit that is 20 μg/L in Denmark.[237] Similarly, a study conducted in China investigated that river water of China were found to have high concentration of Ni and other heavy metals.[238]

6.4 | Effect of nickel exposure on health

Health effects of Ni may be classified according to the duration of Ni exposure as exposure of 1 day to Ni may produce acute toxic health effects whereas if a person is exposed for 100 days or more then the toxic health effects may be classified as chronic effects. The IARC has classified this metal as a carcinogenic substance to human health based on studies performed on workers exposed to Ni occupationally.[239]

Acute effects are produced in two stages after Ni inhalational exposure (Table 2). The two stages are named as immediate and delayed effects. First of all, only after few hours of Ni accidental inhalation immediate effects including feeling of vomiting, irritation, headache, and insomnia may appear. After that patient may feel an interval of 1-5 days. Then, second phase that is delayed symptoms such as vertigo, palpitations, cough, cyanosis, tightness of chest and lassitude may appear.[240] A case was reported in which cause of death of a baby girl was arrest of cardiac system after ingesting Ni sulphate in an amount of 15 g.[241] Another study conducted by Kasprzak et al[242] revealed the injury of kidney and chances of

haematuria to be observed as signs of acute toxicity after Ni exposure. Mostly, the cause of chronic Ni toxicity is its exposure through the occupation of person particularly for workers working in welding industries. Mostly, respiratory system disorders such as pneumoconiosis and asthma are caused by chronic inhalational exposure.[216] Experimental studies on rats revealed the incidence of myocardial fibrosis after the rats were exposed to Ni for a period of eighteen months.[243] Experiments performed by Chashschin et al[244] found that developmental toxicities were observed in workers exposed to Ni for a long time because of their occupational responsibilities.

A number of experimental and epidemiological studies have been conducted on metallic forms of Ni and its compounds. These studies revealed Ni as a carcinogen.[245,246] Recently, Ni containing products named as nickel based nanoparticles has been used extensively in various industries.[247] These nanoparticles show different types of bioactivity and thus pose various challenges to health of human.[248] In the last 30 years, different toxicological test systems have been used to assess the genotoxicity induced by Ni.[249] Park et al[250] worked by comparing the results from experiment conducted on alveolar epithelial cells which were exposed to nickel nanoparticles (100 nm) as well as to titanium oxide which a compound already is known to cause genotoxicity. Two studies were conducted on these cells. Results revealed more damage of alveolar cells (which were exposed to nickel nanoparticle as compared to titanium oxide) induced by apoptosis. Similar pattern of results were observed for DNA fragmentation in the cells.[250] Researchers observed that these effects were due to generation of ROS where DNA was observed to be cleaved into internucleosomal fragments.[251] Investigations were also conducted on other nanoparticles which summarizes that the key role player is oxidative stress.[252] A study was conducted by Zhao et al[253] on mouse. He performed experiment on epithelial (JB6) cell line. This study also revealed the apoptotic damages in the study cells after Ni exposure.

6.4.1 | Nickel-induced allergic contact dermatitis

Investigations revealed that the incidence of Ni allergy is 10-30% in females, whereas in males 1-3 % of men are affected with these allergies.[254,255] A survey conducted by Möller et al[256] found a correlation between ingestion of Ni orally and induction of contact skin dermatitis in individuals who are sensitive to its compounds. Some research data found that there exist sufficient evidence for the fact that some individuals are genetically predisposed to Ni induced skin allergies.[257–259] But in most cases, Ni caused skin dermatitis is due to its occupational exposure. Researchers investigated the chances of eczema of hands in individuals who are chronically exposed to Ni.[260,261]

As Ni is used in formation of coins so workers dealing with coins or working in coin manufacturing industries have chances to develop skin dermatitis. A study conducted by Pedersen et al[262] observed that Ni was found in varying concentrations on hands of workers who deal with coin counting at their work place. Studies have investigated the chance of occurrence of dermatitis and hand eczema with coin handling. A case study of two individuals found that nature of job of these individuals was the reason for their hand eczema. They were doing a job in which they have to change money in form of paper into coins.[263]

6.4.2 | Nickel and orthodontics

Sensitivity of Ni and its allergic incidences are gaining importance in orthodontics because of increased use of orally used piercings.[264] Cell mediated delayed hypersensitivity reactions occur when Ni is released and enter into oral cavity of mouth because of appliances used by dentists.[265] Shelley concluded in a study that sign and symptoms of gingival hyperplasia are induced by Ni compounds.[266] Another health concern caused by Ni exposure is occurrence of metallic taste in mouth.[267,268]

6.4.3 | Nickel-induced carcinogenicity

Researchers investigated the Ni toxic mechanisms and suggested that oxidative stress and damage to DNA is a common mechanism for Ni induced toxicity.[269] Studies revealed that a major defense against metals induced carcinogenicity is nuclear factor erythroid-2 (Nrf2) (Fig. 6).[270] This factor prevents metal induced oxidative damage.[271,272] Ni is found to knockdown Nrf2 as a result of which oxidative damage is increased. Also, certain genes are up regulated and others are down regulated resulting carcinogenicity. Up regulated genes include CAV 1 (Caveolin 1), FOSL2 (FOS-like antigen 2), MICA (MHC class I polypeptide-related sequence A), PIM2 (Pim-2), RUNX1(runt-related transcription factor 1), and SLC7A6 (solute carrier family 7, member 6) leading toward several type of cancers.

Oral cancer

A study conducted in Taiwan by Chen et al[120] concluded that third most common type of cancer in males is oral cancer. Recently, researchers investigated that in Taiwan the risk of oral cancer is being increasing rapidly. This study concluded that from 1982 in male and females of Taiwan the risk of oral cancer was increased from two to threefolds in last 2 decades.[273]

Skin cancer

A study was conducted by Uddin et al[274] in mice to investigate the co-carcinogenic effect of Ni. It was found that nickel

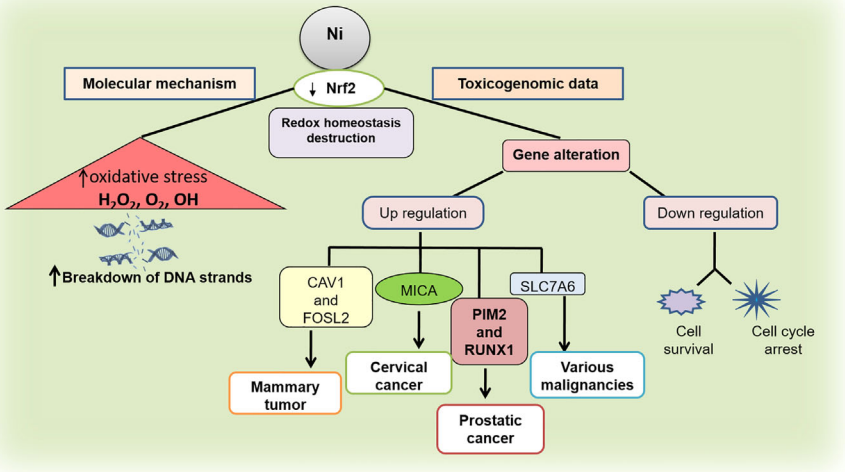

FIGURE 6 Schematic illustration of nickel induced cytotoxic pathways. Nickel exposure reduces the level of nuclear factor erythroid-2 (Nrf2) as a result the body defense against oxidative damage is diminished resulting in up and down regulation of genes that ultimately lead toward cytotoxicity

chloride when combines with ultra violet radiation and mice were exposed to this a synergistic effect was found for both to induce skin cancer in mice.[274] Uddin concluded that because humans have exposure to Ni mostly via drinking water as well as through the food or may have environmental exposure. So, when orally ingested Ni in human body combines with ultra violet radiation it may cause a hazardous effect of skin cancer.[274]

Lung cancer

A survey conducted by Silvera and Rohan in 2007 concluded that workers working in such industries that deal with Ni and its compounds had increased incidence of cancers such as cancer of lungs and cancer of larynx as well as nose cancer was also found to be caused by Ni exposure.[275] In another study conducted by Kuo et al in 2006 found that Ni metal is a cause of increased incidence of lung cancer. A case control study was performed on resected lung tissues taken both from lung cancer and normal patients to estimate the amount of metals present in these tissues. Among all metals included in the study the concentration of Cr and Ni was found to be higher in tumor containing tissues than normal tissues.[276]

6.4.4 | Respiratory disorders induced by nickel

Various studies has been conducted worldwide on workers working in welding industries and estimated that about 1 million workers are exposed to welding processes during performing their work related responsibilities. Mostly, welding materials include Ni and its alloys to which workers are exposed during duty hours and suffer from various respiratory diseases. Studies investigated that along with lung cancer other respiratory disorders found in welders include asthma and risk of bronchitis. Evidence also suggests the incidence of siderosis in welders. Animal studies demonstrated the incidence of inflammation and resulting lung injury in workers exposed to welding fumes of stainless steel containing higher levels of Ni. And also these fumes are investigated to be retained for longer time in lungs than the fumes of mild steel.[277]

6.4.5 | Toxic reproductive effects of nickel

An experimental study was conducted by Forgacs et al[278] on cell lines of mammals and their cell cultures. Results of study revealed that at hypothalamic pituitary gonadal (HPG) axis Ni compounds cause toxicity of reproductive pathways at neuroendocrine levels as well as at level of gonads by producing varying hormone effects. Molecular level studies indicated an alteration in protein functions. Ni has ability to form a link between amino acids and DNA. Also, oxidative stress is produced and mimic hypoxia. As a result of all these changes some of signaling pathways are activated. Subsequently, expression of genes is altered thus leading to reproductive toxicity.[278] Weischer et al[279] performed a study in rats that were exposed to Ni at very high levels through inhalational route during prenatal period. Results of this study found that weight of new born was low at birth.[279]

6.4.6 | Neurotoxic effects induced by nickel

Studies concluded that sign and symptoms of neurotoxicity were observed after chronic Ni exposure. A survey found two neurological effects one of which was giddiness and the other

was weariness in individuals who were having drinking water contaminated with Ni.[280]

6.4.7 | Nickel effects on liver

A study found some workers who were found to be hospitalized after drinking water being contaminated with nickel sulphate. These workers were observed to have increase in their serum bilirubin levels after Ni exposure.[219,280] A study was conducted on rats by injecting them nickel sulphate via intraperitoneal route of administration. Study concluded that liver tissues were found to be degenerated after having exposure to nickel sulphate. Study also found the presence of signs of hypertrophy of kupffer cells. This happened because of changes in normal architecture of liver cells.[222] An experiment performed on rats showed that activity of transaminase enzymes of liver was found to be decreased after the rats were treated with Ni.[221] Other changes found after nickel sulphate exposure was the reduced level of ascorbic acid in liver. Also, the levels of cholesterol were found to be decreased.[281]

6.4.8 | Nickel effects on lungs

Various studies have investigated the harmful effects of Ni exposure on human lungs and found that Ni exposure is a cause of various respiratory disorders. A survey conducted by ATSDR found that lung inflammation was observed in experiments conducted on rats which are found to be the reason for respiratory disorders after acute and chronic exposure to Ni and its compounds.[282] Another study conducted by Gupta et al[283] found that after ten days of Ni exposure to experimental animals the functionality of some antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) in lungs were reduced as compared to the control group. An experimental study of rat lung tissues by Gupta et al[283] concluded that alveolar surfaces of kidneys were found to be congested whereas hyperplasia of cells of alveoli was also observed. This study further investigated bronchiolar inflammation and in some areas lumen was also found to be congested.[283]

6.4.9 | Nickel effects on kidneys

Experimental study in rats to observe Ni-induced toxic effects on kidneys concluded that weight of kidneys was increased after thirteen weeks of exposure whereas urine volume was found to be decreased.[284]

7 | SUMMARY AND FUTURE PROSPECT

This review pointed out the presence of heavy metals in drinking water in Pakistan (Table 3) and worldwide. This review found that concentration of heavy metals is not under the permissible limits and a number of health concerns are associated with this issue (Tables 1 and 2). Ingestion and inhalation are two major routes for exposure to heavy metals. Other routes of exposure may include dermal contact.

The article discusses the major health hazards posed to human health by ingestion of heavy metals mainly through drinking water. Individuals with high concentration of heavy metals in body have potential threats for major diseases such as risk of cardiovascular disorders, neurotoxicity, renal

TABLE 3 Heavy metals concentration in different cities of Pakistan

		Water concentration of heavy metals				
Name of province	**Major cities**	**Cd (mg/L)**	**As (mg/L)**	**Pb (mg/L)**	**Ni (mg/L)**	**References**
Punjab	Hasan Abdal	0.001	–	0.03	0.03	Lone et al[19]
	Lahore	–	–	0.002	0.036	Akhter et al[300]
	Kasur	0.001	–	0.003	0.001	Tariq et al[301]
	Kalalanwala	–	1.889	–	–	Farooqi et al[302]
	Sialkot	–	–	0.81	0.22	Ullah et al[175]
Sindh	Korangi	0.041	–	0.24	0.656	Saif and Midrar-Ul-Haq[303]
	Nawabshah	0.002-0.017	–	0.006-0.053	0.013-0.09	Majidano and Khuhawar[304]
	Jamshoro	–	0.013-0.106	–	–	Baig et al[16]
	Hyderabad	–	0.0045-0.010	–	–	Baig et al[305]
	Karachi	–	–	0.006	0.037	Karim[306]
Khyber Pakhtunkhwa	Peshawar	0.0-0.04	–	0.38	0.0-0.68	Ilyas and Sarwar[307]
	Charsadda and Risalpur	0.01-0.07	–	0.02-0.73	0.002-3.66	Midrar-Ul-Haq and HajikanPunu[232]
	Hattor	0.001-0.21	–	0.001-2.34	0.009-0.585	Manzoor et al[20]
Baluchistan	Zohab River Basin	–	–	002-0.06	–	Umar et al[308]

damage, risk of diabetes, and infertility. Such individuals must be screened and treated to ensure public health. Two major vulnerable groups include pregnant women and children. Adverse effects on human reproduction such as increased risk of abortion and still births have been observed. Investigations also found that heavy metals ingestion is one of the reasons for increased rates of infant mortality. Thereby, cautions must be taken by pregnant women to avoid fetal neurological damage. As deteriorated lead paints has been a major risk factor for children. It is important to aware public about the exposure routes and educates them to avoid further exposure. According to previous research data, many people have already exceeded the limits as set by regulatory authorities and are at threshold for developing major organs toxicity. There exists a very narrow margin for such individuals. Therefore, important measures are necessary to be taken to save general population from such health hazards. People must be advised to avoid fish varieties containing high arsenic and mercury levels. From an agricultural safety point of view, herbicides containing arsenicals such as mono-sodium methanearsonate (MSMA) should be replaced with safer alternatives. Instead of mercury containing amalgam filling always choose composite fillings for dental use.

Steps must be taken to ensure availability of safe drinking water to public. Contaminated water must be treated before it is discharged to the environment. Different methods used for eradication of heavy metals from water include ion exchange,[285] adsorption,[286] membrane filtration,[287] and electrodialysis method.[288] Thus there is a strong need to develop defensive mechanisms against the oxidative damage caused by increased level of ROS in human body as a result of exposure to heavy metals. In future, more research is required to be conducted to ensure a complete understanding of disease pathology as well as molecular and cellular pathways involved in this regard.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest for this article.

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