International Journal for Research in Applied Sciences and Biotechnology

ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

www.ijrasb.com

Effect of Heavy Metal Toxicity on Environment & Health

Narendra Singh Sisodia
Department of Applied Sciences, Eshan College of Engineering, Mathura, INDIA.

Corresponding Author: narendrasingh.sisodia@gmail.com

ABSTRACT

Heavy metals are naturally occurring elements having a high atomic weight and a density higher than five times that of water. Because of their diverse industrial, household, agricultural, medicinal, and technological applications, they are widely dispersed in the environment, generating concerns about their possible impacts on human health and the environment. A variety of factors influence the toxicity of these substances, including the dosage, route of exposure, chemical species, and the age, gender, genetics, and nutritional state of those exposed. Because of their extreme toxicity, arsenic, cadmium, chromium, lead, and mercury are among the priority metals of public health concern. These metallic elements are considered systemic toxicants that can affect various organs even at low levels of exposure. They are also classified as human carcinogens by the International Agency for Research on Cancer. The prevalence, manufacturing, and use of these chemicals in the environment, as well as the potential for human exposure and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity, are all investigated in this study.

Keywords- Heavy metals, human exposure, toxicity, organ harm, genotoxicity, carcinogens.

I. INTRODUCTION

Heavy metals are defined as metallic elements with a density greater than water. Heavy metals also include metalloids like arsenic, which can produce toxicity at low levels of exposure, based on the idea that heaviness and toxicity are related [1]. In recent years, environmental contamination caused by these metals has become a rising environmental and global public health hazard. Furthermore, human exposure has expanded significantly due to an exponential development in their use in a range of industrial, agricultural, residential, and technological applications. Heavy environmental metals can be found in geogenic, industrial, agricultural, pharmaceutical, residential effluents, and atmospheric sources. Mining, foundries and smelters, and other metal-based industrial operations, are extremely contaminated point sources [2]. Although heavy metals are naturally found throughout the earth's crust, anthropogenic activities such as mining and smelting, industrial production and use, as well as domestic and agricultural use of metals and metal-containing compounds, are responsible for the majority of environmental contamination and human exposure [3]. Environmental contamination can be caused by metal corrosion, air deposition, soil erosion of metal ions and leaching of heavy metals, sediment re-suspension, and metal evaporation from water sources to soil and groundwater. Natural processes such as weathering and volcanic eruptions have been connected to heavy metal pollution, plastics, textiles, microelectronics, wood preservation, and paper-producing companies [4]. Metals including cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), selenium (Se), and zinc (Zn) have been recognized as essential nutrients for a number of biochemical and physiological functions. Deficiency diseases and syndromes are caused by a lack of specific micronutrients [5]. Heavy metals are classed as trace elements because they occur in tiny concentrations (ppb range to less than 10ppm) in a variety of environmental matrices. Temperature, phase association, adsorption, and sequestration are the physical factors influencing their bioavailability [6]. Chemical variables, including speciation at thermodynamic equilibrium, complexation kinetics, lipid solubility, and octanol/water partition coefficients, play a role. Biological factors such as species characteristics, trophic relationships, and biochemical/physiological adaptation play a role [7].

II. HEAVY METALS OF SIGNIFICANCE TO PUBLIC HEALTH

Various factors, including the dose and mode of exposure, affect the amount of danger a metal provides. Metals have a variety of effects on animals. Within a single species, age, gender, and genetic predisposition all have a role in toxicity [8]. On the other hand, certain heavy metals are a major source of concern since they can affect various organ systems even at modest doses. These metals include:

- Copper
- Arsenic
- Cadmium
- Chromium
- Lead
- Mercury

III. ROLE OF COPPER ON ENVIRONMENT AND HEALTH

Important heavy metals have biochemical and physiological functions in plants and animals. They are

ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

important components of several key enzymes and play important roles in a number of oxidation-reduction reactions [9]. Copper is required as a cofactor for several oxidative stress-related enzymes, including catalase, superoxide dismutase, peroxidase, cytochrome c oxidases, ferroxidases, monoamine oxidase, and dopamine -monooxygenase. As a result, it is present in a number of metalloenzymes involved in the production of hemoglobin, glucose metabolism, catecholamine biosynthesis, collagen, elastin, and hair keratin cross-linking [10]. Copper's ability to cycle between an oxidized state, Cu(II), and a reduced state, Cu(I), is used by Cuproenzymes in redox reactions (I). Copper, on the other hand, is potentially harmful because transitions between Cu(II) and Cu(I) might result in the creation of superoxide and hydroxyl radicals [11]. In humans, excessive copper exposure has been linked to cellular damage, culminating in Wilson disease. Several other important elements, such as copper, are required for biological function; nevertheless, excessive concentrations of these metals harm cells and tissues, resulting in a variety of negative consequences and human disorders [12]. For certain elements, such as chromium and copper, the concentration range between beneficial and harmful effects is relatively narrow [13].

Heavy metals have been found to alter cell membranes, mitochondria, lysosomes, endoplasmic reticulum, nuclei, and numerous enzymes involved in metabolism, detoxification, and damage repair in biological systems [14]. Metal ions have been demonstrated to interact with cell components, including DNA and nuclear proteins, causing DNA damage and conformational changes that can result in cell cycle regulation, cancer, or death.

According to several studies, oxidative stress and the production of reactive oxygen species (ROS) have a crucial role in the toxicity and carcinogenicity of metals such as arsenic, cadmium, chromium, lead, and mercury from our lab [15]. Due to their extreme toxicity, these five elements are among the priority metals with substantial public health concerns. They're all systemic poisons that, even at modest levels, have been demonstrated to affect a variety of organs.

The United States Environmental Protection Agency (US EPA) and the International Agency for Research on Cancer (IARC) have classified these metals as "known" or "probable" human carcinogens based on epidemiological and experimental studies showing a link between exposure and cancer incidence in humans and animals [16] [17]. A multitude of processes, some of which are unknown, compound heavy metal-induced toxicity and carcinogenicity. On the other hand, each metal has unique physicochemical properties that contribute to its unique toxicological modes of action. The presence, production, and use of arsenic, cadmium, chromium, lead, and mercury in the environment, as well as the potential for human exposure and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity, are all investigated in this study [18].

IV. ROLE OF ARSENIC ON ENVIRONMENT AND HEALTH

Arsenic is a common element that may be found in trace amounts in nearly all environmental matrices. Trivalent arsenite and pentavalent arsenate are the two most common inorganic forms of arsenic. Monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and trimethylarsine oxide are the organic forms of methylated metabolites [19]. Arsenic poisoning in the environment is caused by natural phenomena such as volcanic eruptions, soil erosion, and human activities. Insecticides, herbicides, fungicides, algicides, sheep dips, wood preservatives, and dyestuffs are a few examples of arsenic-containing compounds used in industry [20]. They've also been used in veterinary medicine to eliminate tapeworms in sheep and cattle. Arsenic compounds have been used in medicine for at least a century to treat syphilis, yaws, amoebic dysentery, and trypanosomiasis. Arsenic-based drugs are still used to treat tropical diseases, including African sleeping sickness and amoebic dysentery, as well as parasitic infections like filariasis in dogs and blackhead in turkeys and chickens [21]. Arsenic trioxide was recently approved by the Food and Medication Administration as an anticancer drug for the treatment of acute promeylocytic leukaemia. The therapeutic benefits of leukaemia cells are assumed to be due to the induction of programmed cell death (apoptosis) [22]. Contamination with high levels of arsenic is a cause for concern, as arsenic has a number of harmful health effects. Several epidemiological studies have discovered a significant association between arsenic exposure and an increased risk of cancer and other systemic health repercussions [23]. Large populations in West Bengal, Bangladesh, Thailand, Inner Mongolia, Taiwan, China, Mexico, Argentina, Chile, Finland, and Hungary have been exposed to high levels of arsenic in their drinking water, resulting in a variety of clinicopathological conditions such as cardiovascular and peripheral vascular disease, developmental anomalies, neurologic and neurobehavioral disorders [24].

The cardiovascular, dermatologic, neurological, hepatobiliary, renal, gastrointestinal, and pulmonary systems are all affected by arsenic poisoning. According to the study, several places with arsenic exposure had considerably higher standardized mortality rates for bladder, kidney, skin, and liver cancers [25]. The severity of arsenic's negative health effects is determined by the chemical type, time, and dose. Although there is substantial evidence that arsenic causes cancer in humans, the mechanism by which it does so is uncertain [26].

V. ROLE OF CADMIUM ON ENVIRONMENT AND HEALTH

Cadmium is a pulmonary and gastrointestinal irritant that can be lethal if breathed or consumed. Abdominal discomfort, burning feelings, nausea, vomiting, salivation, muscular cramps, vertigo, shock, loss of consciousness, and convulsions are common 15 to 30 minutes after acute consumption [27]. Acute cadmium poisoning can cause gastrointestinal tract erosion, lung, hepatic, or renal damage, and coma, depending on the route of poisoning. Chronic cadmium exposure reduces brain levels of norepinephrine, serotonin, and acetylcholine. According to a study, chronic cadmium inhalation causes lung adenocarcinomas in animals. It can cause proliferative prostatic lesions, including adenocarcinomas, after systemic or direct exposure [28].

Cadmium compounds have been classified as human carcinogens by a number of regulatory agencies. According to the International Agency for Research on Cancer and the National Toxicology Program of the United States, cadmium is a human carcinogen. Several findings linking occupational cadmium exposure to lung cancer and exceptionally strong rodent data identifying the pulmonary system as a target location has led to this categorization as a human carcinogen [29]. As a result, in humans, cadmium carcinogenesis is most clearly shown in the lungs. The adrenals, testes, and hemopoietic system are all targets of cadmium carcinogenesis in animals and injection sites. Several studies have connected cadmium exposure at work or in the environment to prostate, kidney, liver, hematological system, and stomach cancers. DNA damage induced by base-pair mutation, deletion, or oxygen radical assault on DNA has been related to arsenic, cadmium, chromium, and nickel, among other carcinogenic metals [30]. Animal studies have shown that it has reproductive and teratogenic effects. In limited epidemiologic studies, cadmium levels in cord blood, maternal blood, and maternal urine have been associated with neonatal weight and length [31].

VI. ROLE OF CHROMIUM ON ENVIRONMENT AND HEALTH

Chromium (Cr) is a naturally occurring element that has oxidation states ranging from chromium (II) to chromium (III) (VI). Chromium compounds in the trivalent [Cr(III)] form are stable and may be found in ores like ferrochromite. The hexavalent [Cr(VI)] form is the second most stable state. In nature, the element chromium [Cr(0)] does not exist [32] [33]. Chromium is released into the environment via a variety of natural and anthropogenic sources (air, water, and soil), with industrial businesses releasing the most. The industries that contribute the most to chromium release include metal processing, tannery facilities, chromate manufacture, stainless steel welding, and ferrochrome and chrome pigment production [34][35]. Chromium emissions into the air and wastewater, especially from the metallurgical, refractory, and chemical industries, have been linked to rising chromium concentrations in the environment. The hexavalent form is the most prevalent form of chromium released into the environment by human activities [Cr(VI)]. Hexavalent chromium [Cr(VI)] is a harmful industrial contaminant that has been recognized by a number of regulatory and non-regulatory bodies as a human carcinogen [36]. The oxidation state of chromium determines the health risk associated with exposure, ranging from negligible toxicity in the metal form to severe toxicity in the hexavalent form. Because only Cr(III) occurs naturally in air, water, soil, and biological materials, all Cr(VI)-containing compounds were thought to be man-made at first [37].

However, naturally occurring Cr(VI) at levels greater than the World Health Organization's drinking water guideline of 50 g Cr(VI) per liter has recently been detected in ground and surface waters [38]. Because chromium is widely used in a variety of industrial processes, it is a contaminant in many environmental systems. Chromium compounds are used commercially in industrial welding, chrome plating, dyes and pigments, leather tanning, and wood preservation. Chromium is also an anticorrosive in cooking systems and boilers [39] [40].

High levels of chromium (VI) in the air might irritate the nasal lining and lead to ulcers. The most prevalent health issues documented in animals after eating chromium (VI) compounds are stomach and small intestine irritation and ulcers, anemia, sperm destruction, and male reproductive system damage [41][42]. Chromium (III) compounds are far less poisonous and do not appear to cause the same problems. Certain persons who are extremely sensitive to chromium(VI) or chromium(III) have experienced allergic symptoms such as severe redness and swelling of the skin [43][44]. Humans and animals exposed to chromium(VI) drinking water were more likely to develop stomach cancer. People who died or lived as a consequence of medical treatment had severe respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, and neurological symptoms after ingesting extraordinarily high doses of chromium (VI) compounds. Despite abundant evidence of chromium's carcinogenicity in humans and terrestrial animals, the precise mechanism by which it causes cancer remains unclear [45][46].

VII. ROLE OF LEAD ON ENVIRONMENT AND HEALTH

Lead is a bluish-grey metal found in tiny amounts throughout the earth's crust. Although lead is naturally prevalent in the environment, human activities such as fossil fuel combustion, mining, and manufacturing contribute to the release of high quantities [47]. Lead has a wide range of applications in industry, agriculture, and the household. It is presently used to make lead-acid batteries, ammunition, metal goods (solder and pipes), and X-ray shielding devices [48].

The main pathways of lead exposure include inhalation of lead-contaminated dust particles or aerosols and consumption of lead-contaminated food, drink, and paints [49]. Adults absorb 35 to 50% of the lead in their drinking water, while children may absorb up to 50%. Lead absorption is influenced by a variety of factors, including age and physiological condition. The kidney absorbs the most lead in the human body, followed by the liver and other soft tissues, including the heart and brain; nonetheless, the skeleton absorbs the bulk of the lead [50]. The neurological system is the most sensitive when it comes to lead toxicity. Headaches, low attention span, irritability, memory loss, and dullness are some symptoms of lead poisoning in the central nervous system [51].

VIII. ROLE OF MERCURY ON ENVIRONMENT AND HEALTH

Mercury is a heavy metal that belongs to the periodic table's transition element series. It's one of a kind in that it may be found in three different forms in nature (elemental, inorganic, and organic), each with its own toxicity profile [52]. Elemental mercury is a liquid with a high vapour pressure that is discharged into the atmosphere as mercury vapour at ambient temperature mercury also exists as a cation with oxidation states of +1 (mercurous) or +2 (mercurous) (mercuric). Methylmercury is the most frequent form of mercury found in the environment, and microorganisms produce it in soil and water, methylating inorganic (mercuric) forms of mercury [53]. Mercury is a prevalent toxin and pollutant in the environment that produces major alterations in human tissues and many detrimental health effects. People and animals are exposed to a variety of chemical forms of mercury in the environment. Among these are mercury vapour (Hg0), inorganic mercurous (Hg+1), mercuric (Hg+2), and organic mercury compounds. Humans, plants, and animals are exposed to mercury in some way since it is so widespread in the environment [54][55].

Humans are exposed to numerous kinds of mercury through accidents, environmental pollution, food contamination, dental treatment, preventative medical procedures, industrial and agricultural operations, and occupational activities. The two most prevalent chronic, low-level mercury exposure sources are dental amalgams and fish consumption. Natural off-gassing from the earth's crust and industrial pollution introduce mercury into water [56] [57]. Algae and microorganisms in the streams methylate mercury. Methyl mercury then makes its way up the food chain, eventually ending up in fish, shellfish, and humans [58].

IX. CONCLUSION

A comprehensive review of published evidence shows that heavy metals such as arsenic, cadmium, copper, chromium, lead, and mercury are naturally present. On the other hand, anthropogenic activities have a significant influence on polluting the environment [59]. These metals are systemic poisons that have been associated in humans with heart disease, developmental abnormalities, neurologic and neurobehavioral difficulties, diabetes, hearing loss, hematologic and immunologic diseases, and a variety of cancers. The most prevalent exposure modes are ingestion, inhalation, and skin contact [60]. The severity of negative health effects varies based on the type of heavy metal used, its chemical form, period, and dose. In metal toxicokinetics and toxicodynamics, speciation is essential because it is influenced by valence state, particle size, solubility, biotransformation, and chemical form, among other things [61]. Several studies have connected toxic metal exposure to long-term health consequences in people. Although the acute and chronic effects of specific metals are well documented, less is known about the health consequences of dangerous combinations. According to recent research, these harmful ions may interfere with the metabolism of nutritionally essential metals such as iron, calcium, copper, and zinc [62]. However, studies on heavy metals' combined toxicity are scarce. Exposure to many heavy metals simultaneously can have additive, antagonistic, or synergistic negative effects. According to a recent assessment of several individual studies that addressed metal interactions, co-exposure to metal/metalloid mixes of arsenic, lead, and cadmium had more severe effects at both relatively high and low dosages levels in a biomarker-specific manner [63][64]. These effects were influenced by dose, exposure time, and genetic factors.

Furthermore, co-exposure to cadmium and inorganic arsenic in humans resulted in more severe kidney damage than either element alone. Chronic low-dose exposure to many elements in many metal-contaminated areas represents a severe public health danger [65][66]. The molecular foundation of heavy metal interactions must be known to detect health concerns and control chemical combinations. As a result, further research is needed to understand better the molecular mechanisms involved in human exposure to dangerous metal combinations and the public health implications [67].

REFERENCES

[1] Fergusson JE, editor. The Heavy Elements: Chemistry, Environmental Impact and Health Effects. Oxford: Pergamon Press; 1990.
[2] Duffus JH. Heavy metals-a meaningless term? Pure Appl Chem. 2002;74(5):793–807.

ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

[3] Bradl H, editor. Heavy Metals in the Environment: Origin, Interaction and Remediation Volume 6. London: Academic Press; 2002.
[4] He ZL, Yang XE, Stoffella PJ. Trace elements in agroecosystems and impacts on the environment. J Trace Elem Med Biol. 2005;19(2–3):125–140.
[5] Goyer RA. Toxic effects of metals. In: Klaassen CD, editor. Cassarett and Doull's Toxicology: The Basic Science of Poisons. New York: McGraw-Hill Publisher; 2001. pp. 811–867.
[6] Herawati N, Suzuki S, Hayashi K, Rivai IF, Koyoma H. Cadmium, copper and zinc levels in rice and soil of Japan, Indonesia and China by soil type. Bull Env Contam Toxicol. 2000;64:33–39.
[7] Shallari S, Schwartz C, Hasko A, Morel JL. Heavy metals in soils and plants of serpentine and industrial sites of Albania. Sci Total Environ. 1998;19209:133–142.
[8] Nriagu JO. A global assessment of natural sources of atmospheric trace metals. Nature. 1989;338:47–49.
[9] WHO/FAO/IAEA. World Health Organization. Switzerland: Geneva; 1996. Trace Elements in Human Nutrition and Health.
[10] Kabata- Pendia A 3rd, editor. Trace Elements in Soils and Plants. Boca Raton, FL: CRC Press; 2001.
[11] Hamelink JL, Landrum PF, Harold BL, William BH, editors. Bioavailability: Physical, Chemical, and Biological Interactions. Boca Raton, FL: CRC Press Inc; 1994.
[12] Verkleji JAS. In: The effects of heavy metals stress on higher plants and their use as biomonitors In Plant as Bioindicators: Indicators of Heavy Metals in the Terrestrial Environment. Markert B, editor. New York: VCH; 1993. pp. 415–424.
[13] Stern BR. Essentiality and toxicity in copper health risk assessment: overview, update and regulatory considerations. Toxicol Environ Health A. 2010;73(2):114–127.
[14] Harvey LJ, McArdle HJ. Biomarkers of copper status: a brief update. Br J Nutr. 2008;99(S3):S10–S13.
[15] Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Copper. Atlanta, GA: Centers for Disease Control; 2002.
[16] Tchounwou P, Newsome C, Williams J, Glass K. Copper-induced cytotoxicity and transcriptional activation of stress genes in human liver carcinoma cells. Metal Ions Biol Med. 2008;10:285–290.
[17] Chang LW, Magos L, Suzuki T, editors. Toxicology of Metals. Boca Raton. FL, USA: CRC Press; 1996.
[18] Wang S, Shi X. Molecular mechanisms of metal toxicity and carcinogenesis. Mol Cell Biochem. 2001;222:3–9.
[19] Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol. 2008;82(8):493–512.
[20] Yedjou CG, Tchounwou PB. Oxidative stress in human leukemia cells (HL-60), human liver carcinoma cells ($HepG_2$) and human Jerkat-T cells exposed to arsenic trioxide. Metal Ions Biol Med. 2006;9:298–303.
[21] Yedjou GC, Tchounwou PB. In vitro cytotoxic and genotoxic effects of arsenic trioxide on human leukemia cells using the MTT and alkaline single cell gel electrophoresis (comet) assays. Mol Cell Biochem. 2007;301:123–130.
[22] Tchounwou PB, Centeno JA, Patlolla AK. Arsenic toxicity, mutagenesis and carcinogenesis - a health risk assessment and management approach. Mol Cell Biochem. 2004;255:47–55.
[23] Tchounwou PB, Ishaque A, Schneider J. Cytotoxicity and transcriptional activation of stress genes in human liver carcinoma cells ($HepG_2$) exposed to cadmium chloride. Mol Cell Biochem. 2001;222:21–28.
[24] Patlolla A, Barnes C, Field J, Hackett D, Tchounwou PB. Potassium dichromate-induced cytotoxicity, genotoxicity and oxidative stress in human liver carcinoma ($HepG_2$) cells. Int J Environ Res Public Health. 2009;6:643–653.
[25] Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development Studies. Oncologist. 2001;6(2):22–28.
[26] Puccetti ES, Guller S, Orleth A, Bruggenolte N, Hoelzer D, Ottmann OG, Ruthardt M. BCR-ABL mediates arsenic trioxide-induced apoptosis independently of its aberrant kinase activity. Cancer Res. 2000;60(13):3409–3413.
[27] Seol JG, Park WH, Kim ES, Jung CW, Hyun JM, Kim BK, Lee YY. Effect of arsenic trioxide on cell cycle arrest in head and neck cancer cell-line PCI-1. Biochem Biophys Res Commun. 1999;265(2):400–404.
[28] Alemany M, Levin J. The effects of arsenic trioxide on human Megakaryocytic leukemia cell lines with a comparison of its effects on other cell lineages. Leukemia Lymphoma. 2000;38(1–2):153–163.
[29] Deaglio S, Canella D, Baj G, Arnulfo A, Waxman S, Malavasi F. Evidence of an immunologic mechanism behind the therapeutic effects of arsenic trioxide on myeloma cells. Leuk Res. 2001;25(3):237–239.
[30] Tully DB, Collins BJ, Overstreet JD, Smith CS, Dinse GE, Mumtaz MM, Chapin RE. Effects of arsenic, cadmium, chromium and lead on gene expression regulated by a battery of 13 different promoters in recombinant $HepG_2$ cells. Toxicol Appl Pharmacol. 2000;168(2):79–90.
[31] Lu T, Liu J, LeCluyse EL, Zhou YS, Cheng ML, Waalkes MP. Application of cDNA microarray to the study of arsenic-induced liver diseases in the population of Guizhou, China. Toxicol Sci. 2001;59(1):185–192.
[32] Harris CC. Chemical and physical carcinogenesis: advances and perspectives. Cancer Res. 1991;51:5023s–5044s.
[33] Graham-Evans B, Colhy HHP, Yu H, Tchounwou PB. Arsenic-induced genotoxic and cytotoxic effects in human keratinocytes, melanocytes, and dendritic cells. Intl J Environ Res Public Health. 2004;1(2):83–89.
[34] Stevens JJ, Graham B, Walker AM, Tchounwou PB, Rogers C. The effects of arsenic trioxide on DNA

synthesis and genotoxicity in human colon cancer cells. Intl J Environ Res Public Health. 2010;7(5):2018–2032.
[35] Walker AM, Stevens JJ, Ndebele K, Tchounwou PB. Arsenic trioxide modulates DNA synthesis and apoptosis in lung carcinoma cells. Intl J Environ Res Public Health. 2010;7(5):1996–2007.
[36] Yedjou CG, Tchounwou PB. Modulation of p53, c-fos, RARE, cyclin A and cyclin D1 expression in human leukemia (HL-60) cells exposed to arsenic trioxide. Mol Cell Biochem. 2009;331:207–214.
[37] Yedjou C, Sutton LM, Tchounwou PB. Genotoxic mechanisms of arsenic trioxide effect in human Jurkat T-lymphoma cells. Metal Ions Biol Med. 2008;10:495–499.
[38] Brown E, Yedjou C, Tchounwou PB. Cytotoxicty and oxidative stress in human liver carcinoma cells exposed to arsenic trioxide. Metal Ions Biol Med. 2008;10:583–587
[39] Yedjou CG, Thuisseu L, Tchounwou C, Gomes M, Howard C, Tchounwou PB. Ascorbic acid potentiation of arsenic trioxide anticancer activity against acute promyelocytic leukemia. Arch Drug Inf. 2009;2(4):59–65.
[40] Yedjou C, Rogers C, Brown E, Tchounwou P. Differential effect of ascorbic acid and n-acetyl-cysteine on arsenic trioxide - mediated oxidative stress in human leukemia (HL-60) cells. J Biochem Mol Tox. 2008;22:85–92.
[41] Yedjou GC, Moore P, Tchounwou PB. Dose- and time-dependent response of human leukemia (HL-60) cells to arsenic tic trioxide treatment. Intl J Environ Res Public Health. 2006;3(2):136–140.
[42] Miller WH, Schipper HM, Lee JS, Singer J, Waxman S. Mechanisms of action of arsenic trioxide - review. Cancer Res. 2002;62:3893–3903.
[43] Smith JB, Dwyer SC, Smith L. Lowering extracellular pH evokes inositol polyphosphate formation and calcium mobilization. J Biol Chem. 1989;264:8723–8728.
[44] Th'evenod F, Jones SW. Cadmium block of calcium current in frog sympathetic neurons. Biophys J. 1992;63:162–168.
[45] Suszkiw J, Toth G, Murawsky M, Cooper GP. Effects of Pb^{2+} and Cd^{2+} on acetylcholine release and Ca^{2+} movements in synaptosomes and subcellular fractions from rat brain and Torpedo electric organ. Brain Res. 1984;323:31–46.
[46] Dally H, Hartwig A. Induction and repair inhibition of oxidative DNA damage by nickel (II) and cadmium (II) in mammalian cells. Carcinogenesis. 1997;18:1021–1026.
[47] Abshire MK, Devor DE, Diwan BA, Shaughnessy JD, Jr, Waalkes MP. In vitro exposure to cadmium in rat L6 myoblasts can result in both enhancement and suppression of malignant progression in vivo. Carcinogenesis. 1996;17:1349–1356.
[48] Durnam DM, Palmiter RD. Transcriptional regulation of the mouse metallothionein-I gene by heavy metals. J Biol Chem. 1981;256:5712–5716.
[49] Hwua Y, Yang J. Effect of 3-aminotriazole on anchorage independence and mutagenicity in cadmium- and lead-treated diploid human fibroblasts. Carcinogenesis. 1998;19:881–888.
[50] Landolph J. Molecular mechanisms of transformation of CH3/10T1/2 C1 8 mouse embryo cells and diploid human fibroblasts by carcinogenic metal compounds. Environ Health Perspect. 1994;102:119–125.
[51] Nishijo M, Tawara K, Honda R, Nakagawa H, Tanebe K, Saito S. Relationship between newborn size and mother's blood cadmium levels, Toyama, Japan. Arch Environ Health. 2004;59(1):22–25.
[52] Zhang YL, Zhao YC, Wang JX, Zhu HD, Liu QF, Fan YG, et al. Effect of environmental exposure to cadmium on pregnancy outcome and fetal growth: a study on healthy pregnant women in China. J Environ Sci Health B. 2004;39:2507–2515.
[53] Jacobs JA, Testa SM. Overview of chromium(VI) in the environment: background and history. In: Guertin J, Jacobs JA, Avakian CP, editors. Chromium (VI) Handbook. Boca Raton, Fl: CRC Press; 2005. pp. 1–22.
[54] Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Chromium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
[55] IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 49. Lyon, France: IARC Scientific Publications, IARC; 1990. Chromium, nickel and welding.
[56] U.S. EPA. Environmental Criteria and Assessment Office. Cincinnati, OH: United States Environmental Protection Agency; 1992. Integrated Risk Information System (IRIS
[57] Velma V, Vutukuru SS, Tchounwou PB. Ecotoxicology of hexavalent chromium in freshwater fish: a critical review. Rev Environ Health. 2009;24(2):129–145.
[58] Cohen MD, Kargacin B, Klein CB, Costa M. Mechanisms of chromium carcinogenicity and toxicity. Crit Rev Toxicol. 1993;23:255–281.
[59] Norseth T. The carcinogenicity of chromium. Environ Health Perspect. 1981;40:121–130.
[60] Wang XF, Xing ML, Shen Y, Zhu X, Xu LH. Oral administration of Cr (VI) induced oxidative stress, DNA damage and apoptotic cell death in mice. Toxicology. 2006;228:16–23.
[61] Guertin J. Toxicity and health effects of chromium (all oxidation states) In: Guertin J, Jacobs JA, Avakian CP, editors. Chromium (VI) Handbook. Boca Raton, FL: CRC Press; 2005. pp. 216–234.
[62] Occupational Safety and Health Administration (OSHA) Federal Register. Vol. 71. Washington, DC: Final rule; 2006. Occupational exposure to hexavalent chromium; pp. 10099–10385.

ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

[63] Singh J, Pritchard DE, Carlisle DL, Mclean JA, Montaser A, Orenstein JM, Patierno SR. Internalization of carcinogenic lead chromate particles by cultured normal human lung epithelial cells: Formation of intracellular lead-inclusion bodies and induction of apoptosis. Toxicol Appl Pharmacol. 1999;161:240–248
[64] Langård S, Vigander T. Occurrence of lung cancer in workers producing chromium pigments. Br J Ind Med. 1983;40(1):71–74.
[65] Agency for Toxic Substances and Disease Registry (ATSDR) U.S. Department of Health and Human Services. Atlanta, GA: Public Health Service; 2008. Toxicological Profile for Chromium.
[66] Costa M. Toxicity and carcinogenicity of Cr(VI) in animal models and humans. Critical Reviews in Toxicology. 1997;27:431–442.

