ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Mercury, lead and arsenic: impact on environment and human health

Gagan Matta[1*] and Laura Gjyli[2]
[1]Department of Zoology & Environmental Science, GurukulaKangri University, Haridwar, India
[2]Faculty of Professional Sciences, University "Aleksander Moisiu" Durres, Albania
***Corresponding Author: E-Mail: drgaganmatta@gkv.ac.in**

ABSTRACT

Current article describes the occurrence, exposure; dose detected in food and human health effects. Many of the cases are identified as the harmful effects of mercury, lead and arsenic on human health, in several parts of the world. Those incidents have prompted numerous investigations into the metabolism and toxic effects of these three elements. This review paper outlines their metabolic factor and describes the major routes of entry and the relative scale of such incidents. Main attention is paid to the environmentally important chemical species of mercury and arsenic, the overall health significance of early biochemical effects and the limitations of certain epidemiological studies.

KEY WORDS: Mercury, Lead, Arsenic, Human Health, Environment, toxicity.

1. INTRODUCTION

Heavy metals is the generic term for metallic elements having an atomic weight higher than 40.04 (the atomic mass of Ca). Heavy metals enter into the environment by natural and anthropogenic means. Such sources include: natural weathering of the earth's crust, mining, soil erosion, industrial discharge, urban runoff, sewage effluents, pest or disease control agents applied to plants, air pollution fallout, and a number of others (Morais, 2012). Although some individuals are primarily exposed to these contaminants in the workplace, for most people the main route of exposure to these toxic elements is through the diet (food and water). The contamination chain of heavy metals almost always follows a cyclic order: industry, atmosphere, soil, water, foods and human (Matta, 2015). Although toxicity and the resulting threat to human health of any contaminant are, of course, a function of concentration, it is well-known that chronic exposure to heavy metals and metalloids at relatively low levels can cause adverse effects (Castro and Mendez, 2008). While focusing on developing countries the conditions is getting more disastrous due to increase in industrial complexes with minimal follow up of environmental and pollution control guidelines (Matta, 2015; 2014; Arora, 2014).

Despite the fact that these metals have crucial biological functions in plants and animals, sometimes their chemical coordination and oxidation-reduction properties have given them an additional benefit so that they can escape control mechanisms such as homeostasis, transport, compartmentalization and binding to required cell constituents. These metals bind with protein sites which are not made for them by displacing original metals from their natural binding sites causing malfunctioning of cells and ultimately toxicity. Previous research has found that oxidative deterioration of biological macromolecules is primarily due to binding of heavy metals to the DNA and nuclear proteins (Flora, 2008).

The most commonly found heavy metals in waste water include arsenic, cadmium, chromium, copper, lead, nickel, and zinc, all of which cause risks for human health and the environment (Lambert, 2000). On the other hand, however, deficiencies of essential heavy metals, such as zinc (Zn), copper (Cu) and manganese (Mn) and metalloids, such as selenium (Se) in agricultural soils are affecting agricultural productivity and human health in many countries (Alloway, 2013). Neurotoxic effects of heavy metals are also well documented, especially for mercury and lead, with numerous reports of neurobehavioral changes after occupational exposure and of developmental effects in children with pre- or early postnatal exposure (Davidson, 2004; Lidsky and Schneider 2003). However experimental studies suggest that arsenic could also interfere with the nervous system and that all three metals may influence the dopaminergic system in different ways (Pohl, 2003). There is, however, a need to clear which exposure levels are likely to cause these effects, and to what extent the three metals could interfere in mixed exposures.

Occurrence: Mercury is one of the most toxic heavy metals in the environment (Castro and Mendez, 2008). Higher levels are often found in marine foods. Up to 90% of most organic mercury compounds are absorbed from food. Mercury can be detected in most foods and beverages, at levels of < 1 to 50 μg/kg (Reilly, 2007).

Like many other contaminants, lead is ubiquitous and can be found occurring as metallic lead, inorganic ions and salts (Harrison, 2001). Anthropogenic activities such as fossil fuels burning, mining, and manufacturing contribute to the release of high concentrations. Lead amounts in Deep Ocean waters is about 0.01-0.02 μg/L, but in surface ocean waters is ca.0.3 μg/L (Castro and Mendez, 2008).

Arsenic is a metalloid. It is rarely found as a free element in the natural environment, but more commonly as a component of sulphur-containing ores in which it occurs as metal arsenides. Arsenic is quite widely distributed in natural waters and is often associated with geological sources, but in some locations anthropogenic inputs, such as the use of arsenical insecticides and the combustion of fossil fuels, can be extremely important additional

sources. Arsenic occurs in natural waters in oxidation states III and V, in the form of arsenous acid (H_3AsO_3) and its salts, and arsenic acid (H_3AsO_5) and its salts, respectively.

In foods, the major source of arsenic is mainly fish and seafood. The organic arsenic in food and seafood appears to be much less toxic than the inorganic forms (Uneyama, 2007). The presence of arsenic in fish has been detected in several species such as; sardine, chub mackerel, horse mackerel (Vieira, 2011) blue fish, carp, mullet tuna, and salmon (Castro and Mendez, 2008).

Concentrations in air in rural areas range from <1 to 4 ng/m3, whereas concentrations in cities may be as high as 200 ng/m3. Much higher concentrations (>1000 ng/m3) have been measured near industrial sources. Water concentrations are usually <10 µg/l, although higher concentrations may occur near anthropogenic sources. Levels in soils usually range from 1 to 40 mg/kg, but pesticide application and waste disposal can result in much higher concentrations.

Uses: The mercury compound cinnabar (HgS), was used in pre-historic cave paintings for red colours, and metallic mercury was known in ancient Greece where it (as well as white lead) was used as a cosmetic to lighten the skin. In medicine, apart from the previously mentioned use of mercury as a cure for syphilis, mercury compounds have also been used as diuretics [calomel (Hg_2Cl_2)], and mercury amalgam is still used for filling teeth in many countries (WHO, 1991).

Lead still has a number of important uses in the present day; from sheets for roofing to screens for X-rays and radioactive emissions (Harrison, 2001). It is currently used in the production of lead-acid batteries, ammunitions and metal products (solder and pipes). An estimated 1.52 million metric tons of lead were used for various industrial applications in the United Stated in 2004. Of that amount, lead acid batteries production accounted for 83 percent, and the remaining usage covered a range of products such as ammunitions (3.5 percent), oxides for paint, glass, pigments and chemicals (2.6 percent), and sheet lead (1.7 percent) (Gabby, 2003; 2006).

In recent years, the industrial use of lead has been significantly reduced from paints and ceramic products, caulking, and pipe solder.

Several arsenic-containing compounds are produced industrially, and have been used to manufacture products with agricultural applications such as insecticides, herbicides, fungicides, algicides, sheep dips, wood preservatives, and dye-stuffs. They have also been used in veterinary medicine for the eradication of tapeworms in sheep and cattle (Tchounwou, 1999). Arsenic compounds have also been used in the medical field for at least a century in the treatment of syphilis, yaws, amoebic dysentery, and trypanosomaiasis (Tchounwou, 1999; Centeno, 2005). Arsenic-based drugs are still used in treating certain tropical diseases such as African sleeping sickness and amoebic dysentery, and in veterinary medicine to treat parasitic diseases, including filariasis in dogs and black head in turkeys and chickens (Centeno, 2005). Recently, arsenic trioxide has been approved by the Food and Drug Administration as an anticancer agent in the treatment of acute promeylocyticleukemia (Rousselot, 1999). Its therapeutic action has been attributed to the induction of programmed cell death (apoptosis) in leukemia cells (Yedjou and Tchounwou, 2007).

Exposure: The general population is primarily exposed to mercury *via* food, fish being a major source of methyl mercury exposure27, and dental amalgam. Several experimental studies have shown that mercury vapour is released from amalgam fillings, and that the release rate may increase by chewing28. Mercury in urine is primarily related to (relatively recent) exposure to inorganic compounds, whereas blood mercury may be used to identify exposure to methyl mercury. A number of studies have correlated the number of dental amalgam fillings or amalgam surfaces with the mercury content in tissues from human autopsy, as well as in samples of blood, urine and plasma26. Mercury in hair may be used to estimate long-term exposure, but potential contamination may make interpretation difficult.

The sources of lead exposure include mainly industrial processes, food and smoking, drinking water and domestic sources. The sources of lead were gasoline and house paint, which has been extended to lead bullets, plumbing pipes, pewter pitchers, storage batteries, toys and faucets (Thurmer, 2002). Plant food may be contaminated with lead through its uptake from ambient air and soil; animals may then ingest the lead contaminated vegetation. In humans, lead ingestion may arise from eating lead contaminated vegetation or animal foods. Another source of ingestion is through the use of lead-containing vessels or lead-based pottery glazes. In humans, about 20 to 50% of inhaled, and 5 to 15% of ingested inorganic lead is absorbed. In contrast, about 80% of inhaled organic lead is absorbed, and ingested organic Pb is absorbed readily. Once in the bloodstream, lead is primarily distributed among blood, soft tissue, and mineralizing tissue.

Arsenic is the twentieth most abundant element on earth and its inorganic forms such as arsenite and arsenate compounds are lethal to the environment and living creatures. Humans may encounter arsenic by natural means, industrial source, or from unintended sources. Drinking water may get contaminated by use of arsenical pesticides, natural mineral deposits or inappropriate disposal of arsenical chemicals. Deliberate consumption of

arsenic in case of suicidal attempts or accidental consumption by children may also result in cases of acute poisoning (Mazumder, 2008; Saha, 1999).

The adverse effects of arsenic in groundwater used for irrigation water on crops and aquatic ecosystems are also of major concern. The fate of arsenic in agricultural soils is less characterized compared to groundwater. However, the accumulation of arsenic in rice field soils and its introduction into the food chain through uptake by the rice plant is of major concern mainly in Asian countries (Bhattacharya, 2007; Duxbury, 2003).

Effects on human health: Also methylmercury is a well-known potent neurotoxin which causes adverse impacts on the developing human brain. It passes readily through the placental barrier and the blood-brain barrier making any exposure during pregnancy of great concern. Methylmercury is considered possibly carcinogenic by the International Agency for Research on Cancer (IARC, 1993) and classed as group 2B.

The children born of exposed parents (congenital cases) showed a higher level of symptoms than the parents. Symptoms included severe disturbance of nervous functions and highly delayed developmental skills. Common symptoms of the disease include sensory disorders in hands and feet, ataxia, narrowing field of vision, hearing impairment, balance impairment, speech impediment, trembling in hands and feet and disorders in ocular movement.

It is estimated that 8 to 10% of American women have mercury levels that would induce neurological disorders in any child they gave birth to, according to both the Environmental Protection Agency and National Academy of Science (Haley, 2005).

The brain remains the target organ for mercury, yet it can impair any organ and lead to malfunctioning of nerves, kidneys and muscles. It can cause disruption to the membrane potential and interrupt with intracellular calcium homeostasis. Mercury binds to freely available thiols as the stability constants are high (Patrick, 2002).

According to the Environmental Protection Agency (EPA), lead is considered a carcinogen. Lead has major effects on different parts of the body. Lead distribution in the body initially depends on the blood flow into various tissues and almost 95% of lead is deposited in the form of insoluble phosphate in skeletal bones (Papanikolaou, 2005).

The bones and teeth of adults contain more than 95% of the total body burden of lead. Children are particularly sensitive to this metal because of their more rapid growth rate and metabolism, with critical effects in the developing nervous system (Castro and Mendez, 2008). Toxicity of lead, also called lead poisoning, can be either acute or chronic. Acute exposure can cause loss of appetite, headache, hypertension, abdominal pain, renal dysfunction, fatigue, sleeplessness, arthritis, hallucinations and vertigo. Acute exposure mainly occurs in the place of work and in some manufacturing industries which make use of lead. Chronic exposure of lead can result in mental retardation, birth defects, psychosis, autism, allergies, dyslexia, weight loss, hyperactivity, paralysis, muscular weakness, brain damage, kidney damage and may even cause death (Martin and Griswold, 2009).

Lead is a toxic heavy metal even at very low levels of exposure in humans. Its effect on the human body can be both acute and chronic depending on dose and exposure scenarios. Lead targets multiple organs in the body due to its systemic toxicity which can cause neurological, cardiovascular, renal, gastro-intestinal, haematological and reproductive effects. Human exposure to lead is usually tested through blood sampling. However this approach does not always accurately reflect the intoxication level of the individual as lead moves from the vascular system and is deposited in the bones of the human body. Blood tests do not assess historic exposure to lead which is stored in bones at the time of the blood test. The lead stored in the bones can emerge as a remobilised form of lead exposure late in the life of the individual (UNEP, 2008).

One of the critical human health impacts of lead is neuro-developmental effects in children. Very low levels of lead exposure to children aged between 0-5 years can lead to developmental impacts and subsequent lowering of IQ. The activities and behaviour of children (particularly ‘pica’ behaviour where small children deliberately or incidentally ingest significant quantities of soil) can magnify the exposure of children beyond an adult exposure in the same setting. Children playing in a garden with lead contaminated soil and ingesting that soil may have a greater relative exposure than an adult occupying the same garden space. For children, exposure begins in-utero due to lead passing the placental barrier and therefore exposure of pregnant women is also a key concern (UNEP, 2008).

Testing biological samples for arsenic in an individual with suspected toxicity must be done more than 48 hours after the individual abstains from eating seafood; otherwise, the test may be confounded by the presence of arsenobentaine, a relatively harmless form of arsenic that is contained in fish at high levels of concentration. Once absorbed into the body, arsenic undergoes some accumulation in soft tissue organs such as the liver, spleen, kidneys, and lungs, but the major long-term storage site for arsenic is keratin-rich tissues, such as skin, hair, and nails---making the measurement of arsenic in these biological specimens useful for estimating total arsenic burden and long-term exposure under certain circumstances. Acute arsenic poisoning is infamous for its lethality, which stems from arsenic’s destruction of the integrity of blood vessels and gastrointestinal tissue and its effect on the heart and brain. Chronic exposure to lower levels of arsenic results in somewhat unusual patterns of skin

hyperpigmentation, peripheral nerve damage manifesting as numbness, tingling, and weakness in the hands and feet, diabetes, and blood vessel damage resulting in a gangrenous condition affecting the extremities (Col, 1999).

Chronic arsenic exposure also causes a markedly elevated risk for developing a number of cancers, most notably skin cancer, cancers of the liver (angiosarcoma), lung, bladder, and possibly the kidney and colon. The dose necessary to increase the risk for cancer has recently become the focus of particularly intense scrutiny in the U.S. because of proposed efforts to lower standards governing general population's exposures to arsenic. Among environmental scientists studying this problem, the most common view is that the current standard for the allowable amount of arsenic in U.S. drinking water-50 mg/liter-is probably not adequate to sufficiently safeguard the general population from arsenic's cancer risk.

Toxicity: Methylmercury is a neurotoxic compound which is responsible for microtubule destruction, mitochondrial damage, lipid peroxidation and accumulation of neurotoxic molecules such as serotonin, aspartate, and glutamate (Patrick, 2002). The toxicity of mercury depends on its chemical form (ionic < metallic < organic) (Clarkson, 2006). These forms of mercury are present widely in water resources such as lakes, rivers and oceans where they are taken up by the microorganisms and get transformed into methyl mercury within the microorganism, eventually undergoing bio magnifications causing significant disturbance to aquatic lives. Consumption of this contaminated aquatic animal is the major route of human exposure to methyl mercury (Trasande, 2005). Organic mercury compounds easily pass across bio membranes and are lipophilic. Therefore elevated mercury concentrations are mainly found in liver of lean species and in fatty fish species. Methyl mercury has a tendency to accumulate with fish age and with increasing trophic level. This leads to higher mercury concentrations in old fatty predatory species like tuna, halibut, redfish, shark, and swordfish (Oehlenschlager, 2002).

Lead is a highly toxic metal whose widespread use has caused extensive environmental contamination and health problems in many parts of the world. Lead is a bright silvery metal, slightly bluish in a dry atmosphere. It begins to tarnish on contact with air, thereby forming a complex mixture of compounds, depending on the given conditions (Sharma and Dubey, 2005).

Lead as a toxicologically relevant element has been brought into the environment by man in extreme amounts, despite its low geochemical mobility and has been distributed worldwide (Oehlenschlager, 2002). Lead metal causes toxicity in living cells by following ionic mechanism and that of oxidative stress. Many researchers have shown that oxidative stress in living cells is caused by the imbalance between the production of free radicals and the generation of antioxidants to detoxify the reactive intermediates or to repair the resulting damage. Antioxidants, as e.g. glutathione, present in the cell protect it from free radicals such as H_2O_2. Under the influence of lead, however, the level of the ROS increases and the level of antioxidants decrease. Another biomarker for oxidative stress is lipid peroxidation, since the free radical collects electron from lipid molecules present inside the cell membrane, which eventually causes lipid peroxidation (Wadhwa, 2012; Flora, 2008). At very high concentrations, ROS may cause structural damage to cells, proteins, nucleic acid, membranes and lipids, resulting in a stressed situation at cellular level (Mathew, 2011).

The ionic mechanism of lead toxicity occurs mainly due to the ability of lead metal ions to replace other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations like Na^{+}, which ultimately disturbs the biological metabolism of the cell. The ionic mechanism of lead toxicity causes significant changes in various biological processes such as cell adhesion, intra- and inter-cellular signaling, protein folding, maturation, apoptosis, ionic transportation, enzyme regulation, and release of neurotransmitters. Lead can substitute calcium even in picomolar concentration affecting protein kinase C, which regulates neural excitation and memory storage (Flora, 2008).

Arsenic is one of the most important heavy metals causing disquiet from both ecological and individual health standpoints (Hughes, 1988). It has a semi metallic property, is prominently toxic and carcinogenic, and is extensively available in the form of oxides or sulfides or as a salt of iron, sodium, calcium, copper, etc. (Singh, 2007). Arsenic is a protoplastic poison since it affects primarily the sulphydryl group of cells causing malfunctioning of cell respiration, cell enzymes and mitosis (Gordon and Quastel, 1948).

In arsenic biotransformation, harmful inorganic arsenic compounds get methylated by bacteria, algae, fungi and humans to give mono methyl arsonic acid (MMA) and dimethyl arsinic acid (DMA). In this biotransformation process, these inorganic arsenic species (iAs) are converted enzymetically to methylated arsenicals which are the end metabolites and the biomarker of chronic arsenic exposure.

iAs (V) → iAs (lll) → MMA (V) → MMA (lll) → DMA (V)

Bio methylation is a detoxification process and end products are methylated inorganic arsenic such as MMA (V) and DMA (V), which excreted through urine, are bio indication of chronic arsenic exposure. However MMA (III) is not excreted and remains inside the cell as an intermediate product. Mono methyl arsonic acid (MMA III), an intermediate product, is found to be highly toxic compared to other arsenicals, potentially accountable for arsenic-induced carcinogenesis (Singh, 2007).

The toxic effects of arsenic depend specially on oxidation state and chemical species, among others. Inorganic arsenic is considered carcinogenic and is related mainly to lung, kidney, bladder, and skin disorders. The toxicity of arsenic in its inorganic form has been known for decades under the following forms: acute toxicity, subchronic toxicity, genetic toxicity, developmental and reproductive toxicity (Chakraborti, 2004), immune toxicity (Sakurai, 2004), biochemical and cellular toxicity, and chronic toxicity (Mudhoo, 2011; Schwarzenegger, 2004).

Drinking water is one of the primary routes of exposure of inorganic arsenic (Mudhoo, 2011; National Institute of Health, 2001). Ingestion of groundwater with elevated arsenic concentrations and the associated human health effects are prevalent in several regions across the world. Arsenic toxicity and chronic arsenicosis is of an alarming magnitude particularly in South Asia and is a major environmental health disaster (Bhattacharya, 2007; Chakraborti, 2004; Kapaj, 2006).

Chronic arsenic ingestion from drinking water has been found to cause carcinogenic and non-carcinogenic health effects in humans (Mudhoo, 2011).The results show that arsenic concentration is low in most fish, being always its highest concentration in muscle (Vieira, 2011). The JECFA (2004), established a PTWI for inorganic arsenic as 0.015 mg/kg body weight. Organo-arsenic intakes of about 0.05 mg/kg body weight/day seemed not to be associated to hazardous effects (Uneyama, 2007).

The toxicity of an arsenic-containing compound depends on its valence state (zero-valent, trivalent, or pentavalent), its form (inorganic or organic), and factors that modify its absorption and elimination. Inorganic arsenic is generally more toxic than arsenic, and trivalent arsenite is more toxic than pentavalent and zero-valent arsenic. These nuances are important.

Regulatory limits:

For Mercury: Because of the extreme health effects associated with mercury exposure, the current standards for drinking water were set by EPA and WHO (2004), at the very low levels of 0.002 mg/L and 0.001 mg/L, respectively.

- EPA – 2 parts per billion parts (ppb) in drinking water
- FDA – 1 part of methylmercury in a million parts of seafood.
- OSHA – 0.1 milligram of organic mercury per cubic meter of workplace air and 0.05 milligrams per cubic meter of metallic mercury vapor for 8-hour shifts and 40-hour work week.

For Lead: The Joint FAO/ World Health Organization Expert Committee on Food Additives (JECFA, 2004), established a provisional tolerable weekly intake (PTWI) for lead as 0.025 mg/kg body weight (bw).

- The WHO (2004), provisional guideline of 0.01 mg/L has been adopted as the standard for drinking water.
- EPA – 15 parts per billion (ppb) in drinking water, 0.15 micrograms per cubic meter in air.

For Arsenic: The growing awareness of arsenic-related health problems has led to a rethinking of the acceptable concentration in drinking water. Following a thorough review and in order to maximize health risk reduction, the USEPA in 2001 decided to reduce the drinking water maximum contaminant limit (MCL) to 0.010 mg/L, which is now the same as the WHO guidelines.

- Environmental Protection Agency (EPA) - 0.01 parts per million (ppm) in drinking water.
- Occupational Safety and Health Administration (OSHA) – 10 micrograms per cubic meter of workplace air (10 μg/ m^3) for 8 hour shifts and 40 hour work weeks.

REFERENCES

Alloway B.J, Heavy Metals in Soils, Trace metals and metalloids in soils and their bioavailability, Environmental Pollution, 22, 2013, 3-9.

Arora Tushar, Mishra Anand, Matta Gagan, Chopra A.K, Kumar Ajendra, Khanna D.R, and Vinod Kumar, Human health risk assessment of temporal and spatial variations of ground water quality at a densely industrialized commercial complex at Haridwar, India, Journal of applied and natural science, 6 (2), 2014, 825 – 843.

Bhattacharya P, Welch A.H, Stollenwerk K.G, Mc Laughlin M.J, Bundschuh J, & Panaullah G, Arsenic in the environment: Biology and Chemistry, Science of the Total Environment, 379, 2007, 109–120.

Castro-Gonzalez M.I, & Mendez-Armenta M, Heavy metals: Implications associated to fish consumption, Environmental Toxicology & Pharmacology, 26, 2008, 263-271.

Centeno JA, Tchounwou PB, Patlolla AK, Mullick FG, Murakat L, Meza E, Gibb H, Longfellow D, Yedjou CG, Environmental pathology and health effects of arsenic poisoning: a critical review, In: Naidu R, Smith E, Smith J, Bhattacharya P, Managing Arsenic In the Environment: From Soil to Human Health, Adelaide, Australia: CSIRO Publishing Corp., 2005.

Chakraborti D, Sengupta M.K, Rahaman M.M, Ahamed S, Chowdhury U.K, & Hossain M.A, Groundwater arsenic contamination and its health effects in the Ganga–Megna–Brahmaputra Plain, Journal of Environmental Monitoring, 6, 2004, 74–83.

Clarkson T, The toxicology of mercury and its chemical compounds, Critical Reviews in Toxicology, 36, 2006, 609–662.

Col M, Col C, Soran A, Sayli BS, Ozturk S, Arsenic-related Bowen's disease, palmar keratosis, and skin cancer, Environ Health Perspect., 107, 1999, 687-689.

Davidson PW, Myers GJ, Weiss B, Mercury exposure and child development outcomes, Pediatrics, 113, 2004, 1023–1029.

Duxbury J.M, Mayer A.B, Lauren J.G, & Hassan N, Food chain aspects of arsenic contamination in Bangladesh: effects on quality and productivity of rice, Journal of Environmental Science Health Part A, Environmental Science Engineering & Toxic, 2003.

Flora SJS, Mittal M, Mehta A, Heavy metal induced oxidative stress & its possible reversal by chelation therapy, Indian J Med Res., 128, 2008, 501–523.

Gabby PN, Lead, Environmental Defense, Alternatives to Lead-Acid Starter Batteries, Pollution Prevention Fact Sheet, 2003.

Gabby PN, Lead: in Mineral Commodity Summaries, Reston, VA: U.S, Geological Survey, 2006.

Gordon JJ, Quastel GH, Effect of organic arsenicals on enzyme system, Biochem J., 42, 1948, 337-350.

Haley BE, Mercury toxicity: genetic susceptibility and synergistic effects, Medical Veritas, 2 (2), 2005, 535–42.

Harrison N, Inorganic contaminants in food, In: Food Chemical Safety Contaminants, Watson, D.H.(Ed.), 2001, 148-168. Hazard Substance Control, 38, 61–69.

Hughes JP, Polissar L, Van Belle G, Evaluation and synthesis of health effects studies of communities surrounding arsenic producing industries, Int J Epidemiol., 17, 1988, 407–413.

IARC, IARC monographs on the evaluation of carcinogenic risks to humans, Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry, Lyon, International Agency for Research on Cancer, 58, 1993.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), Safety evaluation of certain food additives and contaminants, WHO Food Additives Series, No 52, 2004.

Kapaj S, Peterson H, Liber K, & Bhattacharya P, Human health effects from chronic arsenic poisoning - a review, Journal of Environmental Science Health Part A, Environmental Science Engineering Toxic Hazard Substance Control, 41, 2006, 2399–2428.

Lafuente A, Gonzalez-Carracedo A, Romero A, Esquifino AI, Effect of cadmium on 24-h variations in hypothalamic dopamine and serotonin metabolism in adult male rats, Exp Brain Res., 149, 2003, 200–206.

Lambert M, Leven BA, Green RM, New methods of cleaning up heavy metal in soils and water, Environmental science and technology briefs for citizens, Kansas State University, Manhattan, KS, 2000.

Lidsky TL, Schneider JS, Lead neurotoxicity in children: basic mechanisms and clinical correlates, Brain, 126, 2003, 5–19.

Martin S, Griswold W, Human health effects of heavy metals, Environmental Science and Technology Briefs for Citizens, 15, 2009, 1–6.

Martin, Sabine, and Griswold, Wendy, Human Health Effects of Heavy Metals, Center for Hazardous Substance Research, 15, 2009.

Mathew BB, Tiwari A, Jatawa SK, Free radicals and antioxidants: A review, Journal of Pharmacy Research, 4 (12), 2011, 4340–4343.

Matta Gagan, Kumar Ravindra, Kumar Avinash, and Gjyli Laura, Heavy metal analysis of industrial effluent allied with groundwater, ESSENCE – International Journal for Environmental Rehabilitation and Conservation, VI (1), 2015, 33 – 40.

Matta Gagan, Kumar Ravindra, Kumar Avinash, and Kumar Ajendra, Effect of industrial effluent on ground water quality with special reference to DO, BOD and COD, J of Sus. Env Res., 3 (2), 2014, 183-186.

Matta Gagan, Srivastava Sachin, Pandey R.R, and Saini K.K, Assessment of physicochemical characteristics of Ganga Canal water quality in Uttarakhand, Environment development and Sustainability, 2015.

Mazumder G, Chronic arsenic toxicity & human health, Indian J Med Res., 128 (4), 2008, 436–447.

Morais S, Costa FG, Pereira ML, Heavy metals and human health, in Environmental health – emerging issues and practice, Oosthuizen J. ed., 2012, 227–246.

Mudhoo A, Sharma S.K, Garg V.K, & Tseng C.H, Arsenic: an overview of applications, health, and environmental concerns and removal processes, Critical Reviews in Environmental Science & Technology, 41, 2011, 435–519.

National Institute of Health, Biomarkers Definitions Working Group. Biomarkers and Surrogate endpoints: preferred definitions and conceptual framework, Clinical Pharmacology & Therapeutics, 69, 2001, 89-95.

Oehlenschlager J, Identifying heavy metals in fish In: Safety and Quality issues in fish processing, Bremner H.A, (Ed), Woodhead Publishing Limited, Cambridge, 2002, 95-113.

Papanikolaou NC, Hatzidaki EG, Belivanis S, Tzanakakis GN, Tsatsakis AM, Lead toxicity update, A brief review, Med Sci Monitor., 11 (10), 2005.

Patrick L, Mercury toxicity and antioxidants: Part 1: role of glutathione and alpha-lipoic acid in the treatment of mercury toxicity, Altern Med Rev., 7 (6), 2002, 456–471.

Pohl HR, Roney N, Wilbur S, Hansen H, De Rosa CT, Six interaction profiles for simple mixtures, Chemosphere, 53, 2003, 183–197.

Reilly C, Pollutants in Food —Metals and Metalloids, In: Mineral Components in Foods, Szefer P, and Nriagu J.O, (Eds), 2007, 363-388.

Rousselot P, Laboume S, Marolleau JP, Larghero T, Noguera ML, Brouet JC, Fermand JP, Arsenic trioxide and melarsoprol induce apoptosis in plasma cell lines and in plasma cells from myeloma patients, Cancer Res., 59, 1999, 1041–1048.

Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC, A review of arsenic poisoning and its effects on human health, Crit Rev Env Sci Technol., 29 (3), 1999, 281–313.

Sakurai T, Kojima C, Ochiai M, Ohta T, & Fujiwara K, Evaluation of *in vivo* acute immune toxicity of a major organic arsenic compound arsenobetaine in seafood, International Immuno pharmacology, 4, 2004, 179–184.

Schwarzenegger A, Tamminen T, & Denton J.E, Public health goals for chemicals in drinking water arsenic, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 2004.

Sharma P, Dubey RS, Lead toxicity in plants, Brazilian Journal of Plant Physiology, 17 (1), 2005, 35–52.

Singh N, Kumar D, Sahu A, Arsenic in the environment: effects on human health and possible prevention, J Environ Biol., 28 (2), 2007, 359–365.

Tchounwou PB, Wilson B, Ishaque A, Important considerations in the development of public health advisories for arsenic and arsenic-containing compounds in drinking water, Rev Environ Health, 14 (4), 1999, 211–229.

Thurmer K, Williams E, Reutt-Robey J, Autocatalytic oxidation of lead crystallite surfaces, Science, 297 (5589), 2002, 2033–2035.

Toxicological Profile for Arsenic, U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control, Atlanta, 2003.

Toxicological Profile for Cadmium, U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control, Atlanta, 2008.

Toxicological Profile for Copper, U.S. Department of Health and Humans Services, Public Health Service, Centers for Diseases Control, Atlanta, 2004.

Toxicological Profile for Lead, U.S. Department of Health and Humans Services, Public Health Humans, 2007.

Toxicological Profile for Mercury, U.S. Department of Health and Humans Services, Public Health Humans Services, Centers for Diseases Control, Atlanta, 2003.

Trasande L, Landrigan PJ, Schechter C, Public health and economic consequences of methyl mercury toxicity to the developing brain, Environ Health Perspect., 113 (5), 2005, 590–596.

UNEP, Draft final review of scientific information on lead, Chemicals Branch DTIE, 2008, 36-7.

Uneyama C, Toda M, Yamamoto M, & Morikawa K, Arsenic in various foods: Cumulative data, Food Additives & Contaminants, 24, 2007, 447-534.

Vieira C, Morais S, Ramos S, Delerue-Matos C, & Oliveira M.B.P.P, Mercury, cadmium, lead and arsenic levels in three pelagic fish species from the Atlantic Ocean: intra- and inter-specific variability and human health risks for consumption, Food & Chemical Toxicology, 49, 2011, 923-932.

Wadhwa N, Mathew BB, Jatawa S, Tiwari A, Lipid peroxidation: mechanism, models and significance, Int J Curr Sci., 3, 2012, 29–38.

WHO, Guidelines for drinking-water quality, Sixty-first meeting, Rome, 10-19 June 2003, Joint FAO/WHO Expert Committee on Food Additives, 2004.

WHO, Inorganic Mercury, Environmental Health Criteria, Geneva: World Health Organization, 118, 1991.

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., 301, 2007, 123–130.

Zhang I, & Wong M.H, Environmental mercury contamination in China: sources and impacts, Environment International, 33, 2007, 108-121.