Chapter 13
Impact of Heavy Metal Carcinogens on Human Health

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Abstract During the development of human activities, it has been noticed that such activities contribute to the discharge of toxic chemicals like metals and metalloids into the atmosphere. These toxic metals are accumulated in the dietary articles of human beings. Food chain polluted with toxic metals and metalloids is a significant path of human exposure and thus may cause a number of hazardous effects on human health. Nevertheless, cancer is a leading cause of morbidity, mortality, and premature death worldwide. Certain approaches like less exposure to carcinogenic factors can reduce the risk of most cancer types in human. Epigenetic variations in the etiology of cancer have led to increasing of cancer research studies in the recent years. Although epigenetic effects of these elements have more prominent role than their genetic effects, these elements are able to alter the pattern of cancer-related genes' expression profiles. Hence, an understanding of the principal epigenetically mechanisms of these trace elements and the compounds that could reduce their toxicities or the number of cancer cases is necessary. Conceivably, the toxic effects of these elements in many regions are anticipated but antioxidant supplements may eradicate the reactive oxygen species as foremost effects of these elements. In this chapter, we tried to focus on various studies dealing with epigenetic effects of carcinogens on human health.

Keywords Bioavailability · Cancer prevention · Stem cell · Epigenetic effects of carcinogens · Heavy metals and metal toxicity

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13.1 Introduction

Almost thirty chemical elements are constantly found in bio-organisms, participating in fundamental biochemical and physiological functions, and documented as necessary elements for life (Barnham and Bush 2014). Greater part of the identified metals and metalloids are very toxic to bio-organisms and even those measured as crucial can be toxic if present in excess (Mudgal et al. 2010; Jaishankar et al. 2014) as a consequence of human activities. They can perturb significant biochemical processes, constituting an important threat for the health of plants and animal systems, including human beings (Mudgal et al. 2010; Tiwari et al. 2017). Plants and animals take up these elements from soils, sediments, and water by contact with their external surfaces, through ingestion and inhalation of airborne particles and vaporized metals. The assimilation of an element (i.e., the bioavailable fraction) depends on a number of physicochemical factors such as chemical speciation, solubility in organic medium, pH, etc. (Namieśnika and Rabajczyk 2010). In soils, metals and metalloids can arise in both solid and aqueous phases. In solution, these elements can exist either as free ions or as various complexes associated with organic or inorganic ligands or as suspended colloidal particles. In the solid phase, they can be adsorbed or absorbed on organic and inorganic soil components (Track 2010). In general, ions in solution are more available for plant uptake and entering into the food chain. Metal ions present in the solid phase available under certain biological and physicochemical conditions, such as exudation of special chelators, desorption, redox, and pH changes. Animals are exposed to these toxicants through respiratory, the skin, and digestive systems (Prashanth et al. 2015). After entering the body, the metal deposited in nasopharyngeal, tracheobronchial, or pulmonary compartments may be transported by mucociliary action to the gastrointestinal tract. Macrophages phagocyted the wandering metals. Food is the most important route for entering essential and toxic elements. Some elements like mercury (Hg) are biologically magnified at higher trophic level. The dietary contribution for toxic metal intake has been extensively studied by Santos et al. (2004). If the body is deficient in minerals and trace elements, it will absorb heavy metals in their place. Every cell membrane breaks down and rebuilds every two weeks but does not release the heavy metals if essential fats are not ingested or if bad fats are ingested. The liver, which performs detoxification 100% of the time, cannot perform this important task without all the essential nutrients.

Chemical elements present as free ions and those readily ionized are almost completely absorbed by the body. Transition metals readily form stable covalent complexes and usually interact as parts of macromolecules (proteins, enzymes, hormones, etc.) according to their chemical characteristics including oxidation state (Mudgal et al. 2010; Tchounwou et al. 2012; Sharma et al. 2014). These metals are complexed with amino acids (glutathione (GSH), cysteine, and histidine) and proteins (metallothioneins, transferrin, ferritin, lactoferrin, hemosiderin, ceruloplasmin, and melanotransferrin) (Table 13.1). Health damage triggered by toxic metals may be less (irritation) or acute (teratogenic, mutagenic, and carcinogenic).

Table 13.1 Major toxic metals and their reactive forms

Metal	Toxicity
Cd	All forms are toxic and need attention
Pb	Organic forms are more toxic and easily absorbed by the gastrointestinal tract
As	Inorganic arsenate [As(+5)] or [As(+3)] is more toxic
Hg	Hg(II) organomercurials mainly methylmercury, biologically magnified

These reactive elements of food present as complexes with fiber have a low solubility within the intestinal lumen and are poorly absorbed (Table 13.2). Absorption of these minerals promotes by low concentration of fiber and absence of phytates, oxalates in the diet (Hazell 1985; Tiwari et al. 2012). Micronutrients can interact with toxic metals at several points in the body like absorption, transport, binding to target proteins, metabolism, sequestration, excretion of toxic metals and finally, in secondary symptoms of toxicity such as oxidative stress (Jan et al. 2015). Thus, a diet poor in micronutrients can have an important influence on the toxicity. In biological fluids and tissues, most metals and metalloids are not present as free cations. In blood, they are usually bound to red cells or to plasma proteins. Lead (Pb) and cadmium (Cd) are almost completely bound to red blood cells. The chemical elements bound to plasma proteins constitute the fraction available for transport into and out of the tissues (Silva et al. 2005).

Albumin, a plasma protein, has a pronounced capacity to bind several metals. In order to avoid undesirable health effects as resulted from "excessive" intake of toxicants (including toxic metals), international and national scientific organizations such as FAO/WHO, FDA, European Union, etc. have used the safety guidelines for establishing acceptable or tolerable intakes of substances that exhibit threshold toxicity. The acceptable daily intake (ADI) or tolerable daily intake (TDI) or provisional tolerable weekly intakes (PTWI) are used to describe "safe" levels of intake for several toxicants including toxic metals (Kroes and Kozianowski 2002; Oforka et al. 2012). For majority of toxicity, it is thought that there is a dose below the recommended level that has no adverse effect. For chemicals that give rise to such toxic effects, a TDI, i.e., an estimate of the amount of a substance in food, is expressed on a body weight basis (mg kg^{-1} or mg kg^{-1} of body weight) that can be ingested over a lifetime without appreciable health risk.

Table 13.2 Food sources of toxic metals

Metal	Food source
Cd	Egg, fish, mushroom, garlic, spinach, wheat, rice, oat, corn, soybean, peanuts, mushroom
Pb	Egg, cocoa powder, rice, wheat, potato, calcium supplement, smoked food, wine, beer, milk, carrot, raisins
As	Green papaya, rice, tomato, carrot, seafood, Indian mustard, bovine and chicken meat, wine, milk
Hg	Egg, mushroom, seafood, fish oil

Exposure greater than the TDI value for short period should not have deleterious effects upon health. However, acute effects may occur if the TDI is substantially exceeded even for short periods of time. Additionally, contaminants possessing very long half-lives can be accumulated in the body and chronic effects are most often observed when critical concentrations are reached in target tissues, ultimately resulting in cancer that is a foremost reason of morbidity, mortality, and premature death worldwide (Kanavos 2006; Thun et al. 2010; Santos et al. 2013).

13.2 Heavy Metals Versus Cancer

This continual and emergent burden of cancer in the world's populations' warrants finely tuned public health awareness. Prevention, early detection, and therapy have all established parameters in checking certain types of cancer and in thus dropping down the burden of premature death and advanced disease (Mishra et al. 2010; Mudgal et al. 2010; Rebecca et al. 2017). The occurrence and mortality as a result of multifactorial polygenic diseases such as varieties of cancer diverge depending upon genetic susceptibility and environmental precursors as they have certain mendelian subsets. Speedy alterations in diet and lifestyle may affect heritability of the variant phenotypes, which are dependent on the nutraceutical supplementation for their expression (Mishra et al. 2010; Mudgal et al. 2010). It is likely to distinguish the interaction of specific nutraceuticals, with the genetic code possessed by all nucleated cells (Mudgal et al. 2010). In many countries, though, these well-recognized approaches to cancer check have not been applied to their complete potential and in many countries are not applied at all. In addition, immense disparities still exist in cancer check in reference to gender, race, ethnicity, and socioeconomic status.

A variety of carcinogens have already been recognized, and the pertinent information regarding these agents is accessible, although humans make use of many food and beverage items, assuming that they are harmless. One example is the potentially harmful presence of heavy metals, which can cause serious health problems (Mudgal et al. 2010). People may be exposed to heavy metals during the course of their lifetime. The heavy metals in drinking water create the greatest threat to public health in this context. This necessitates setting appropriate quality control measures. The major source of heavy metals in drinking water is contamination of surface and ground waters by industrial sewage and agricultural runoff (Karavoltsos et al. 2008; Hariprasad and Dayananda 2013). In the areas where water delivery network is made of alloys containing heavy metals, some people may not afford bottled or mineral water with restricted heavy metal concentrations and thus consumes tap water; therefore, the likelihood of contamination of drinking water with heavy metals increases to a great extent (Leivadara et al. 2008). According to some WHO information, the concentration of these elements in groundwater is elevated in several countries including Bangladesh, India, and Argentina (WHO 1987, 2003). Heavy metals in drinking water are toxic and can easily penetrate the body.

The genetic and epigenetic impacts of these elements are coupled with an increased risk of varieties of cancer (Bower et al. 2005; Caffo et al. 2014; Jaishankar et al. 2014).

Epigenetic mechanisms play a significant role than genetic events in carcinogenesis. These effects take place most often during the early stages of tumor development. Epigenetic events consist of reversible alteration of histone proteins and CpG islands of gene promoters, which affect not only gene expression of germ and somatic cells but also cause indirect gene sequence alterations (Jones and Baylin 2002; Vaziri Gohar et al. 2007). CpG islands (5′-CG-3′ sequence) subsist in about 40% of mammalian genes. Hypermethylation or hypomethylation of C5 position of the cytosine base is implicated in the inhibition of expression of tumor suppressor genes or the raise of the oncogene expression, both of which contribute to cancer development as well as progression (Ehrlich 2009; Jin et al. 2011; Subramaniam et al. 2014). Gene silencing can also occur through methylation of lysine 9 in histone-H3 (H3-K9) that results in a cascade of clustering of a number of proteins including HP1 protein, SUV39H1 histone methyltransferase, histone deacetylases, DNA methyltransferases, and lastly methyl-C binding proteins (MBD) (Jackson et al. 2002; Tamaru and Selker 2001; Vogelstein and Kinzler 2004). Methylated cytosine may be spontaneously deaminated to create a thymine, leading to a specific transition mutation in CpG islands, for example, in the TP_{53} tumor suppressor gene as a protector of genome. Besides, hypermethylation of histone proteins results in alterations in the chromatin configuration, predisposing cells to allelic loss at a specific locus in the chromosomes (Egger et al. 2004). Such genetic and epigenetic changes in growth-control genes such as DNA repair genes, tumor suppressor genes, oncogenes, and apoptotic genes come close together to determine the cellular phenotype and demarcation (Vaziri Gohar et al. 2007; Mohammadi et al. 2008).

As far as ranking the carcinogens is concerned, heavy metals have been classified by the International Agency for Research on Cancer (IARC) and Environmental Protection Agency (EPA) as the first group, excepting selenium, which has been listed within group 3 (not carcinogen to humans) of the IARC classification (Mishra et al. 2010). The main aim of this chapter is to focus on comparison of the epigenetic effects caused by various heavy metals in cancer-concerned genes in biological systems, including human. In addition, it was also discussed that incidence of cancer can be reduced by adopting prevention behavior especially in terms of drinking water considering the following elements concomitant with their conjugative.

13.2.1 Lead (Pb)

Pb is used in storage batteries, cable coverings, plumbing, ammunition, manufacturing of tetraethyl Pb, sound absorbers, radiation shields around X-ray equipment, nuclear reactors, and paints, while the oxide is used in producing fine “crystal glass”

and “flint glass” with a high refractive index for achromatic lenses, solder, and insecticides (Chidananda and Jagadeesh 2015). Pb enters the human body in many ways. It can be inhaled in dust from lead paints or waste gases from leaded gasoline. It is found in trace amounts in various foods, notably fish, which are heavily subjected to industrial pollution plants that can absorb Pb from soils and from a $PbEt_4$ traffic-induced air pollution (90% of total Pb emissions into the atmosphere). Pb can contaminate water and consequently enter the aquatic food chains (Kaste et al. 2003; Verma and Dwivedi 2013; Weber et al. 2013). Pb is a toxic metal and most people and animals receive the largest portion of their daily Pb intake via food. Pb can enter food during storage and manufacture, e.g., in canned food and in alcoholic drinks (Eticha and Hymete 2014). Cosmetics are also an important source of Pb contamination. The amount of Pb absorbed depends on age and the extent to which Pb particles are dissolved in the stomach. The proportion of Pb absorbed from the gastrointestinal tract is about 10% in adults, whereas levels of 40–50% have been reported for infants. Milk, fasting, low levels of calcium, vitamin D, and iron have been shown to increase Pb absorption in laboratory animals (WHO 2001). Children under 6 years are especially susceptible to the adverse effects of Pb, as the blood–brain barrier is not yet fully developed in young children; hematological and neurological adverse effects of Pb occur at lower threshold levels than in adults. Pb has effects on erythropoiesis and heme biosynthesis. Chronic Pb intoxication in adults resulted in anemia, some types of cancer, reproductive harm in males while in young children hormonal imbalance of metabolite of vitamin D, namely 1,25-dihydroxy-vitamin D, and drop in IQ (Siddiqui et al. 2002; Tandon et al. 2001; Tiwari et al. 2012).

13.2.2 Cadmium (Cd)

Compounds of Cd are highly toxic to humans. Cd is used in several industrial processes such as protective coatings (electroplating) for metals like iron, preparation of Cd–Ni batteries, control rods, and shields within nuclear reactors (Malik et al. 2014). Some compounds are used as stabilizers for PVC. For nonsmoking population, the major exposure pathway is through food. Cd is readily taken up by plants. Potential source of Cd toxicity is the use of commercial sludge to fertilize agricultural fields. Some root crops (carrots and parsnip) and some leafy crops (lettuce and spinach) are able to accumulate more Cd than other plant foods. Grain crops like rice and wheat can accumulate relatively high amounts of Cd (Kibria et al. 2006).

Its absorption is increased by calcium, protein, and vitamin D. Internal organs of mammals such as liver and kidneys may also contain high amounts of Cd. The dietary Cd absorption rate in humans has been estimated at 5% of its total intake. The metal transporter protein Nramp2, known also as DMT1, seems to be involved in Cd absorption (Tallkvist et al. 2001). The daily intake of Cd was estimated as 25–60 μg for a 70 kg person from uncontaminated areas but values may rise up to

10–61 μg day^{-1}. Cd is a normal constituent of tobacco, because *Nicotiana* species is able to concentrate Cd independent of soil Cd content. The Cd content in tobacco ranged between 1 and 2 μg g^{-1} dry weight, equivalent to 0.5–1 μg $cigarette^{-1}$ (Hui et al. 2015). Approximately, 10% of the inhaled Cd oxide is deposited in lung tissues, and another 30–40% is absorbed into systemic blood circulation of smokers. Smokers have 4–5 times higher Cd levels in blood and 2–3 times greater amounts of Cd in their kidneys than do nonsmokers. Itai–Itai disease was caused by large amounts of Cd in the village's water supply of Toyama city, Japan, from 1939 to 1954 (Oudeh et al. 2002; Bishak et al. 2015).

Cd is a cumulative toxicant that affects kidneys, produce various toxic effects in the body, and disturbed bone metabolism and the reproductive system, endocrine system, and also carcinogenic (Rachdaoui and Sarkar 2013). It develops several morphopathological changes in the kidneys due to long-term exposure to Cd. Increasing intakes of zinc can reduce the renal toxicity of Cd. Cd exposure increases calcium excretion, thus causing skeletal demineralization, which may lead to increase in bone fragility and risk of fractures (Wu et al. 2001). Cd and its compounds are currently classified by IARC as a Group 1 carcinogen for humans. Occupational human exposure has been linked to lung cancer. Cd exposure, during human pregnancy, led to reduced birth weights and premature birth (Henson and Chedrese 2004; Jaishankar et al. 2014; Rengarajan et al. 2015). Besides, Kippler et al. (2012) found evidence of a sex difference in the association between maternal Cd exposure and birth size that was noticeable only in girls. Outcomes add support for the need to reduce Cd pollution to improve public health.

13.2.3 Aluminum (Al)

The certain specific compounds of Al have been used in wide range of applications in different industries including cosmetics and food additives (Darbre 2005; Stahl et al. 2017). Al-mediated carcinogenesis is due to its binding ability to the estrogen receptor and imitates estrogen functions, thus named metallo-estrogen. Metallo estrogen triggers the expression of genes found in estrogen-responsive elements (EREs). There is evidence that definite salts of Al such as those found in anti-aspirants can remain in applied regions of axillae and mammary glands for prolonged periods if not washed properly thus providing the probability for continuous exposure to Al and enhancement of risk of breast cancer due to increasing replication errors in cancer related genes (Sun et al. 2007). It has been demonstrated that if antiperspirants containing Al applied on the skin around the underarm and breast areas, it is not washed off completely, some Al salts remain in the area. This results in continuous exposure and ultimately increases the risk of breast cancer (Stellman et al. 2000). There are two different groups of estrogen receptors (ER). The first group exists in cytosol/nucleus (ER-α and ER-β) and acts as transcription factors by directly binding to ERE, whereas the second one exists in plasma membrane as transmembrane G-protein coupled receptors. These ERs can also

control gene expression by means of interaction with other transcription factors, without binding directly to ERE. Plasma membrane located ER46 is involved in endothelial nitric oxide synthase (eNOS) phosphorylation and rapid nitric oxide (NO) release through phosphatidylinositol 3-kinase in endothelial cells. Another plasma membrane located ER family called ER66 manages reporter gene expression (Darbre 2005). Al can bind to both nuclear and membrane of ERs, and ERE; as a consequence, it can trigger both ER signal transductions. Consequently, as expected, Al^{3+} treatment assists in intracellular NO generation (Satoh et al. 2007; Joshi et al. 2013). Al may produce pro-oxidant effect in rats and could be of interest for understanding the controversial role of Al in assessing toxicity (Joshi et al. 2013).

In addition to breast carcinogenesis, estrogen can activate telomerase gene expression as a gene containing ERE, in ER-α-positive cell, but not in ER-negative cells, these results in endometrial cancer (Harley 2008). The epigenetic effects of Al take place through the binding of trivalent (Al^{3+}) to the phosphate groups of double-stranded DNA under physiologic pH, thus changing DNA topology from B to Z in $(CCG)_{12}$ repeat regions (Zhang et al. 2002). The expansion of the triplet repeats is named as "dynamic mutation", and may be localized in both coding and noncoding regions. A minimum of 5–10 triplet repeats increases the probability of hairpin formations, principally in the lagging strand. Movement of DNA polymerase along the hairpin structure leads to the replication slippage and genomic instability, causing deletion mutations. Expansion of more than 200 copies of these repeats leads to excessive methylation of cytosines in the promoter of FMR1 gene that results in fragile X syndrome (Lukusa and Fryns 2008).

13.2.4 Arsenic (As)

Arsenic is generally known as an epigenetic carcinogen metalloid when in the form of an inorganic compound. In the environment, arsenic is usually found combined with other elements as inorganic and organic forms. Inorganic arsenic is more poisonous than organic one (Hughes et al. 2011). Arsenic trioxide (As_2O_3) is the most common inorganic form of arsenic found in air, while arsenates (AsO_4^{-3}) or arsenites (AsO_2) occur in water, soil, or food. Arsenic may be also necessary ultra-trace element for red algae, chickens, rats, goats, and pigs and its deficiency inhibited growth (Pimparkar and Bhave 2010). Arsenic concentration is high in marine food. In fishes, arsenic ranged between 5 and 100 μg g^{-1} and reach up to 100–250 μg g^{-1} in species at the top of the food chain (Hughes et al. 2011).

Trivalent arsenite (As^{+3}) has more carcinogenic properties than the pentavalent arsenate (As^{+5}) (Patterson et al. 2003; Alkahtani 2009). Trivalent arsenic can bind with high affinity to thiol groups of proteins and reduced glutathione (GSH) (Suzuki et al. 2004). Longtime uptake of drinking water containing low levels of arsenite induces carcinogenesis in skin, lung, bladder, and kidney tissues, resulting from alteration in multiple signaling pathways. The risk of bladder cancer is more in

people who drink water with an arsenic level above 100 ppb, and it increases the risk by more than 15 times compared with people living in areas with less than 10 ppb. Arsenic is methylated for detoxification and excretion from the body. This reaction gives rise to the carcinogenic properties of arsenic through the epigenetic transformations. This is contrary to the general belief about methylation, which is considered important way for detoxification. The toxicity of monomethyl arsenic (MMAs) and dimethyl arsenic (DMAs) is more than arsenite (Patterson et al. 2003; Suzuki et al. 2004). Arsenic methylation generally occurs by Glutathione S-transferase (GST), arsenic III methyltransferase (AS3MT), and S-adenosyl methionine (SAM). These enzymes compete with DNA methyltransferase (DNMT) for DNA methylation, hence inhibiting DNA methyltransferase indirectly and inducing the reactivation of silenced tumor suppressor genes (Huang 2002). Interaction with arsenic induces the ROS formation (through its reduction) as an inescapable reaction of regular cell metabolism (Galanis et al. 2008). ROS, acting as a second messenger, is involved in the activation of PI3 K/Akt pathway and the succeeding stimulation of transcription factor hypoxia-inducible factor-1 (HIF-1α) but not HIF-1β and vascular endothelial growth factor (VEGF) stimulation (Gao et al. 2004; Sharma et al. 2009). An additional essential mechanism of arsenic-induced carcinogenesis is through enhancing the genotoxicity of other carcinogens, together with ultraviolet radiation (UVR), ionizing radiation, alkylating agents, or oxidants. UVR induces nonmelanoma skin cancer. Strands of DNA exposed to photons of UVA and UVB break, and cyclobutane pyrimidine dimers (CPDs) are produced (Ravanat et al. 2001; Melnikova and Ananthaswamy 2005; Ramasamy et al. 2017). UVRs can trigger a zinc-finger protein family, poly (ADP-ribose) polymerase (PARP), and predominantly one member of this family, named PARP-1, has a vital role in the regulation of nucleotide excision repair (NER). CPDs have been recognized in p53 and PTCH tumor suppressor genes and ras oncogenes. Arsenite stimulates inducible nitric oxide synthase (iNOS) expression and NO production via mammalian mitogen-activated protein kinases p38 and activation of nuclear transcription factor-kappa B (NF-κB) (Ding et al. 2008; Ramasamy et al. 2017). Between 40 and 60% of arsenic intake is excreted into the urine (Fujihara et al. 2009). A foremost proportion (60–80%) of urinary arsenic is composed of dimethylated arsenic (Vahter 2000).

In humans, arsenic toxicity has been occured due to ingestion of As-containing powders or solutions accidentally, for suicide, homicide, or consumption of contaminated food or drinking water. Arsenic has been associated with hypertension and has serious effects on the cardiovascular system, and at high doses it causes hepatic damage (Lee et al. 2003; Yoshida et al. 2004). It has a suppressive effect on spermatogenesis and gonadotrophin and testosterone release in rats (Sarkar et al. 2003). There is correlation between arsenic exposure and diabetes mellitus (type II) (Walton et al. 2004). Different dermal effects are caused by inorganic arsenic ingestion like hyperkeratosis (formation of hyperkeratotic warts on the palms and soles), hyperpigmentation and hypopigmentation periorbital swellings, the occurrence of spontaneous abortion, and damage of nervous system (at high doses).

With advances in technology and the recent development of animal models for arsenic carcinogenicity, understanding of the toxicology of arsenic will continue to improve (Martine et al. 2011).

13.2.5 Chromium (Cr)

Trivalent chromium is an epigenetic carcinogen factor since it can form stable compounds with macromolecules such as DNA and cysteine residue of proteins and glutathione (Zhitkovich et al. 1995). The trivalent form of chromium cannot pass the cell membrane; however, the hexavalent salts are able to enter the cell and are converted to the trivalent form. Therefore, depending on the situation, reducing agents can affect carcinogenic properties of chromium inside the cell, and chromium (VI) can be converted to a carcinogen. During Cr (VI) reduction, many compounds such as oxygen radicals, DNA interstrand cross-links (ICLs), and single-strand breaks (SSBs) may form. ICLs act as physical barriers to DNA replication and transcription events, consequently, inducing apoptosis (Schnekenburger et al. 2007). The chromium carcinogenicity, particularly in lung epithelial cells and fibroblasts, is imposed through hypermethylation of CYP1a1 promoter. Chromium recruits histone deacetylase 1 (HDAC1) and DNMT1, especially to CYP1a1 promoter, and this assembly recruits BP1 and inhibits CYP1a1 gene expression (Wei et al. 2004). CYP1A1 is essential in the metabolism of carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines, which are extensively distributed widely in the environment via automobile exhausts, cigarette smoke, charcoal-broiled cooking, and industrial waste. Contrary to other cytochrome P450, enzymes such as epoxide hydrolase and dihydrodiol dehydrogenase, which are involved in PAH- and Benzo(a)pyrene-induced carcinogenesis, CYP1A1 inhibits PAH carcinogenesis. Hence, inhibition of CYP1A1 by chromium leads to the production of a PAH (Wu et al. 2009). PAHs have a significant role in the activation of cytosolic ligand-activated transcription factor named aromatic hydrocarbon receptor (AhR) (Nebert et al. 2000). After formation, the PAH–AhR complex is transferred into the nucleus. In the nucleus, PAH is detached from the complex and AhR binds to its nuclear partner, Arnt. This new complex acts as a transcription factor and interacts with DRE of CYP1A1 gene, leading to the activation of CYP1A1 gene expression, consequently causing bioactivation of exogenous procarcinogens of both hepatocellular and lung carcinomas (Li et al. 2009).

It is appealing that PAH through binding to transcription factor AhR activates CYP1a1 gene expression, and CYP1A1 inhibits PAH carcinogenesis, but in the presence of Cr, the promoter of CYP1a1 is inactivated and PAH can act as carcinogens. Benzo(α) pyrene is also a member of polycyclic aromatic hydrocarbon (PAHs) family that is metabolically transformed from its pro-carcinogenic status to the carcinogenic metabolite (BP-7,8-dihydrodiol-9,10-epoxide (BPDE)), which can bind covalently to DNA and form BPDE–DNA adducts and reactive oxygen

species. BPDE activates apoptosis through p53-independent and p53-dependent manner (Drukteinis et al. 2005). P53-dependent Cr-induced apoptosis occurs as a consequence ofincreasing p53 phosphorylation at serine, as well as up-regulation of proapoptotic gene bcl-XS, and caspase-7, and down-regulation of several anti-apoptotic genes from Bcl2 family (bcl-W and bcl-XL), and bax. These apoptotic events result in the destruction of the mitochondria and release of cytochrome c (Carlisle et al. 2000; Ha et al. 2003; Ceryak et al. 2004). Moreover, Cr induces the ATM protein production that phosphorylates and activates Chk_2 protein. The phosphorylated Chk2 in turn phosphorylates and activates p53. The phosphorylated p53 does not bind to MDM2 protein (Ha et al. 2003). Cr exposure at very high concentrations activates all subclasses of MAPK through phosphorylation; thus, Cr acts as a MAPK kinase and enhances survival/proliferation in a dose-dependent manner. This function is connected with its capability in ROS generation (Gao et al. 2002).

13.2.6 Nickel (Ni)

Water-insoluble nickel compounds including nickel sulfides, disulfides, and oxides readily enter the cell and are very potent carcinogens (Gao et al. 2002). In contrast, water-soluble nickel compounds including acetate, chloride, nitrate, and sulfate do not enter the cells as readily as water-insoluble nickel compounds (Ke et al. 2008). The increase in the usage of nickel compounds and the spread of nickel due to its dissolution from nickel ore-bearing rocks are the main causes of nickel presence in the environment. The primary source of nickel in drinking water is the leaching of metals in water network. However, food is the major source of nickel exposure in the nonsmoking, non-occupationally exposed population, but nickel absorption from water was considerably higher than absorption of nickel from beverages like tea, coffee, or orange juice and milk (Ke et al. 2008). Ni^{2+} induces carcinogenesis through several processes including DNA hypermethylation (H3K9 mono- and dimethylation), DNMT inhibition, DNA mutation, ROS generation, inhibiting histone H2A, H2B, H3, and H4 acetylation, converting the tumor suppressor genes to the heterochromatin, and considerable enhancements of the ubiquitination of H2A and H2B (Gao et al. 2002). Hence, nickel plays a pivotal role in the suppression or silencing of genes (Gao et al. 2002; Ke et al. 2008).

Nickel has been observed to bind to DNA in different positions. It binds to phosphate backbone of DNA in place of Mg and promotes the conversion of suppressor genes to the heterochromatin (Cangul et al. 2002). Moreover, its binding to histone H4 leads to the inhibition of lysine acetylation, and subsequently DNA hypermethylation (Broday et al. 2000). These events play an important role in silencing of tumor suppressor genes and the other genes that are involved in carcinogenesis pathways.

13.2.7 Selenium (Se)

Selenium is an essential trace element with a narrow range between toxic and therapeutic doses; its activity for that reason is highly dose-dependent. Enzymes containing selenium such as glutathione peroxidase, like other antioxidant elements, can protect body from oxidative damage and reduce the risk of cancer incidence and mortality through several pathways such as apoptosis and alteration of some collagen types (Rayman 2000).

Since selenium, like arsenic, is detoxified by methylation through S-adenosylmethionine pathway, competition between arsenic, selenium, and DNMT1 for methyl donated by S-adenosylmethionine leads to DNA hypomethylation, and an increase in arsenic retention in tissues (Xiang et al. 2008). Organic selenium compounds such as selenomethionine, Se-methyl-selenocysteine (Se-MSC), and particularly selenocystine (SeC) have shown more anticarcinogenic activity than inorganic compounds in lung cancer model systems. However, in contrast to selenomethionine, selenocystine decreases cellular reduced thiol agents like *N*-acetylcysteine (NAC) and GSH, thus increasing the ROS formation (Zou et al. 2008).

Selenium-containing proteins can induce apoptosis pathway through caspase activation. But, selenite, SeC, and selenomethionine mostly activate apoptosis by caspase-independent pathways through p53 activation and antiapoptotic inactivation and release of cytochrome c from mitochondria as follows. First, these compounds increase production of reactive oxygen species. ROS-mediated modified products such as DSBs are detected by ATM and ATR proteins, which in turn can activate p53 in MCF-7 human breast cancer cells and human prostate cancer. These DSBs can even synergistically increase the intracellular ROS production. Second, they induce p53 phosphorylation at Ser_{15}, Ser_{20}, and Ser_{392} residues, thus decreasing p53-MDM2 protein interaction and p53 stability (Chen and Wong 2008).

The Se-MSC shows its anticarcinogenic activity through down-regulation of some extracellular matrix proteins such as collagen type I alpha 1 (COL_1A1), COL_1A_2, and COL_7A_1, and up-regulation of COL_6A_1 and COL_4A_5 genes in human prostate cell line (Evans 2008; Hurst et al.2008).

13.2.8 Mercury (Hg)

Hg and its compounds are highly toxic, wide dispersion through the atmosphere. It is biomagnified through the food chain (Mendola et al. 2002). Hg is commonly used in dental amalgams, thermometers, barometers, and the development of large-scale industrial processes (e.g., chlor-alkali plants and PVC production) and release into the environment. Hg occurs in nature in mineral, cinnabar, metacinnabar, and hypercinnabar. Diet can be the main source of inorganic and organomercury compounds especially seafood, while dental amalgams are the main

exposure source to elemental Hg. Mercury is organomercurial in the form of methylmercury which has toxicological characteristics. Minamata disease name given for the cause of methylmercury in seafood in Minamata and Niigata in Japan in the 1950–1960s resulting in the death of thousands of people (Costa et al. 2004). There are a number of key neurological symptoms of high-dose exposure to methylmercury in adults. As there is no specific medical test for the diagnosis of Minamata disease, a combination of these salient symptoms is used to identify cases. The principal effects are noticed to include motor disturbances, such as ataxia and tremors, as well as signs of sensory dysfunction, such as impaired vision (Gopinath et al. 2013). The predominant neuropathological feature is the degenerative changes in the cerebellum, which is likely to be the mechanism involved in many of the motor dysfunctions. The microscopical examination of the brain of patients that died in Minamata showed entire regions devoid of neurons, granular cells in the cerebellum, Golgi cells, and Purkinje cells. The most common clinical symptoms observed in adults in Minamata were paresthesia, ataxia, sensory disturbances, tremors, impairment of hearing, and difficulty in walking. Children showed similar symptoms but with a higher incidence and at lower Hg exposure levels. On the other hand, the predominant symptom in adults in Iraq was paresthesia, which usually occurred after a latent period. Children showed cerebral palsy, altered muscle tone, and deep tendon reflex, as well as delayed developmental stages. In humans, disruptions of higher functions have also been noted, as evidenced by depression and irritability (Sarkar et al. 2003; Costa et al. 2004). Some studies suggest that even minor increases in methylmercury exposures can cause harmful effects on the cardiovascular system, blisters in the upper gastrointestinal tract, vomiting, abdominal pain, constipation, and gastritis. Renal toxicity of organic forms is expressed by glomerulonephritis with proteinuria (glomerular and tubular) and nephritic syndrome (Pazhayattil and Shirali 2014).

Elemental Hg can be oxidized to Hg^{2+}, which accumulates preferentially in the kidneys. The increased excretion of low molecular weight proteins is demonstrated at low-level exposure and related to damage to the renal tubes. It is a potent neurotoxin to human due to their ability to cross the blood–brain barrier. It is absorbed in the gastrointestinal track, immediately entering the bloodstream. It readily passes the placental barrier affecting the developing nervous system of the fetus. Continuous exposure conditions to elemental Hg can lead to its accumulation in the thyroid. The acute exposure to elemental Hg vapors can cause "pink disease" or acrodynia (Bernhoft 2012).

13.3 Conclusions

Conclusively, the heavy metals play important role in the production of ROS and NF-kB, also human genetic differences through polymorphisms in GST, metallothioneins and heavy metal methyltransferase genes induce carcinogenesis. Noticeably, heavy metals are epigenetic carcinogen, solely responsible for tumors

presentation and progression. Taken together, the data presented herein and the ongoing research provides new insights and biochemical and molecular mechanisms involved in the development of pathological conditions in human.

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