Chapter

Role of Heavy Metals in the Incidence of Human Cancers

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Abstract

There has been increased concern on many levels focused on the environmental and occupational exposure of heavy metals and their impact on disease, specifically the carcinogenic potential inducing cancer in humans. Because the impact of heavy metals on human health continues to be a major health concern, research continues to improve our understanding of the carcinogenic potential of these substances. Of particular concern have been human exposure to aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel, and radium and their carcinogenic potential whether contact is via environmental or occupational exposure. This updated review focuses on the carcinogenic mechanisms heavy metals use to induce malignant transformation of cells as well as addressing the overall environmental and occupational hazards of heavy metal exposure.

Keywords: heavy metals, carcinogenesis, human exposure, toxicity, mechanisms, remediation

1. Introduction

Heavy metal exposure has long been associated with major health care concerns pertaining to human health. The metals responsible for these adverse changes in human health need to include and focus on their role in carcinogenicity. As a premise, and for obvious reasons, there has been long-standing research and clinical focus among scientists and oncologists that has produced an extensive database. Using a variety of research engines, such as the National Institute of Medicine database (PubMed) and Google Search to explore the various aspects of heavy metals and their ability to induce cancer, we have attempted to review the reported studies in this area. Importantly, the information presented in the following pages represents linking heavy metal exposure to cancer, and specific human systems most susceptible to heavy metal carcinogenesis.

1.1 Aluminum

Aluminum is unique based upon the various mechanisms of action whereby it is listed based on its carcinogenic activity. More often, human exposure to aluminum is the result of contamination of food, interestingly in the process of manufacturing vaccines for human use, and when added as a chemical salt during a variety of processes used in industry for manufactured products for commercial purposes [1, 2]. The commercial products most susceptible are those in which aluminum salts are included in the list of added ingredients such as antacid tablets and antiperspirant deodorants [1–3].

Exposure to aluminum has had a direct link to the induction of human cancer, specifically breast cancer. Experimental studies performed in mice exposed to $AlCl_3$, which interestingly is the identical form of aluminum used in the manufacture of antiperspirant deodorants for humans, demonstrated an induction of malignant transformation of epithelial cells located within mammary glands [1]. Similar results were observed following exposure to human breast tissue epithelial cells [1–3]. Aluminum has been implicated in the development of neoplasia, specifically in the development of sarcomas [4]. In the same report it was noted that one patient, following consistent chronic exposure to aluminum, developed an atypical transformation resulting in a neuroectodermal malignancy [4].

Regarding the carcinogenicity of aluminum, it was of importance to best identify the potential or possible mechanism(s) of action responsible for the induction of tumors following exposure. In research studies performed *in vitro* using human breast cells exposed to aluminum, researchers observed a reduction in the levels of the tumor suppressor gene BRCA1 mRNA [3]. This effect took place concurrent with decreased levels of other maintenance genes that regulate normal DNA levels [3]. In a complementary study, researchers exposed human breast cancer cells to aluminum and measured induced uncontrolled cell growth that was consistent [2]. Upon evaluation of these results, researchers concluded the aluminum acted as a metalloestrogen, meaning the reaction acted as an antagonist for the estrogen receptor complex on these breast cells. This kind of biochemical activity has been associated with the carcinogenesis ability following aluminum exposure [2].

When other body tissues were examined following aluminum exposure, in this specific case, the development of bladder cancer, it was revealed the bladder cancer cells had higher levels of aluminum compared to other heavy metals [5]. Although these studies were not able to directly link a cause and effect between aluminum and the induction of bladder cancer, it did provide suggestive evidence that aluminum exposure may play in the development of such cancers. This hypothesis lead to a formative therapeutic modality and that is to remove the aluminum. Use of chemical chelators has been recommended standard therapeutic procedure to be performed whenever aluminum exposure, thus poisoning, has been implicated in any physiological or cellular transformation. Physiological studies have demonstrated that when introduced into the human body, aluminum accumulates in both the soft and skeletal tissues. These are the target tissues for aluminum chelation [6]. The most common chelating agent used to detoxify aluminum exposure is desferrioxamine [6]. This chelator has proven very effective in removing the heavy metal aluminum from tissues, even though use of desferrioxamine is associated with its own level of toxicity that is associated with its clinical use in humans [6]. In order to address desferrioxamine toxicity, other chelating agents have been identified that show promise as candidates to replace desferrioxamine; however, the level of chelation associated with these agents has not yet equaled what has been demonstrated using desferrioxamine. Another option in order to reduce aluminum especially if is measured to be present in high amounts in public consumption, e.g., drinking water [7]. The method used in these conditions is reverse osmosis filtration. The procedure has been demonstrated to reduce significant aluminum levels when applied in a variety of industrial settings such as in the mining of copper and in other areas of industrial usages [7].

1.2 Arsenic

Arsenic is a heavy metal with known cytotoxicity in human tissues following exposure that can result in serious illnesses to those who are exposed. In a majority of cases, the path of exposure results from ingestion of foods and sources of

drinking water contaminated with arsenic [8–11]. There are also examples of arsenic exposure that are the result of occupational exposure through environmental pollution [8–11]. Examples of occupations that provide direct risks are smelting and arsenic based pesticide industries [12]. Another well documented source of heavy metal arsenic is through contact with contaminated soil thus consumption occurs through the food chain [13].

The correlation between heavy metal arsenic exposure and human cancers is relevant because arsenic detection within tumor tissue. Specific examples of arsenic and cancer development comes from research studies demonstrating a role for arsenic in the development of bladder, lung and skin malignancies [8, 11, 12]. An additional positive correlation linking arsenic with the development of human cancers focused on the relationship between arsenic exposure and mortality rates in patients diagnosed with a variety of cancers – colon, gastric, kidney, lung and nasopharyngeal cancers [13]. Importantly, based on epidemiological data from several studies shows a clear association between the induction of both pancreatic and non-Hodgkin's lymphoma following chronic arsenic low-level exposure [14, 15].

As with all heavy metals the question is what is/are the mechanism(s) responsible for the carcinogenic activity? As it pertains to arsenic, several studies have clearly demonstrated the mechanisms responsible for arsenic induced carcinogenicity involve the formation of reactive oxygen species (ROS) that indues critical epigenetic changes leading to damaging DNA repair mechanisms [8, 9, 12]. Specifically, these important epigenetic changes induced by arsenic have included alterations in DNA methylation, histones, and miRNA, all potentially responsible for the tumorgenicity associated with arsenic exposure [9, 12]. Another postulated mechanism of action for arsenic associated carcinogenicity is arsenic's ability to induce abnormal cell growth cycles in specific cell types such as macrophages and lung epithelial [16]. This was of particular concern because in lung epithelial cells, arsenic promoted a key and significant mechanism of action inducing carcinogenesis. In this cell population arsenic was demonstrated to alter the gene expression of the tumor suppressor protein *p53,* which in turn decreased the expression of *p21,* a downstream target [17]. Thus, the result of this association between heavy metal and tumor suppression gene inactivation was increased cellular proliferation, which demonstrated the most prominent mechanism of cellular transformation. Under these conditions what develops is major oxidative stress in these cells.

In studies conducted to further understand the association between arsenic and tumor cell initiation, another important activity was attributed to arsenic. Based upon further examination, it became clear that in co-existence with changes in cell transformation, intracellular levels of glutathione, a potent ant-oxidant agent, were reduced [18]. Lowering glutathione levels thereby reduces its antioxidant activity, thus allowing altered or transformed cells to escape from being removed by suppressor T-cell lymphocytes and NK cells [18].

Another postulated mechanism of action explaining the tumorgenicity of arsenic was proposed. This alternative mechanism was identified following arsenic exposure to human bladder cells. The mechanism was attributed to the ability of chronic exposure of arsenic to inhibit proper cellular morphology attributed to altered gene expression responsible for base excision repair [19]. The key enzymatic component here is the rate limiting step catalyzed by the enzyme DNA polymerase beta, an active enzyme in the process [19]. In the presence of arsenic, the enzymatic activity was reduced in a dose-dependent manner, meaning higher concentrations of arsenic, correlating with the lack of enzymatic activity [19]. These studies demonstrated chronic exposure to arsenic influenced changes in cellular morphology and altered the gene expression for specific proteins that control cellular proliferation [20].

In order to remove arsenic from the body the use of specific chelating agents have been shown to be most effective [21]. One such example of a very effective chelating agent is 2,3-dimercaptopropanol, otherwise known as British anti-lewisite. The molecule contains 2 functional thiol groups [21]. Significant clinical data has been accumulating over the past several years demonstrating the effective chelating action of this compound. 2,3-dimercaptopropane-1-sulphonate was administered effectively with minimum side-effects to a patient diagnosed with arsenic exposure [22]. This one study provided the clear and effective use of chelators to remove excess amounts of heavy metals [22]. Based on these observations, it was proposed that incorporation of antioxidants as a component of one's dietary consumption should be recommended in order to maximize anti-cancer and reduced oxidative stress [23]. Both rice and apple juice have been found to reduce cellular stress by the presence of antioxidant compounds, in part because they contain levels of vitamin C, a potent antioxidant. Oxidative stress is a major factor leading to a number of cellular disease pathologies.

As mentioned above, safety regulators have identified apple juice and rice as two food stuffs that can often serve as source of arsenic exposure in children. The level of 5 μg/L arsenic has been set as the lowest level of toxicity exposure [24]. With these dietary links identified other alternative methods to curb the toxicity linked to food stuffs have been presented to limit arsenic uptake using genetic modifications to rice that would inhibit the absorption of arsenic [24]. Another strategy has been to use specific micro-organisms that when co-existing with arsenic in the environment reduce metal uptake [24]. Alternatively, in the cultivation of rice, use of certain watering methods in agricultural would ultimately reduce the concentration of the heavy metal when present in the environment [24, 25].

1.3 Beryllium

The heavy metal beryllium is associated with human use through its application tied to industrial processes. Thus, human consumption is linked to environmental contamination documented to most often occur from its association in power plants where it is often found in dust [26, 27]. Thus, human contact occurs via inhalation as the most common method of contact. As an environmental contaminant, it has been linked to a number of respiratory ailments including carcinogenesis of the lung [27–29]. Initially the relationship between beryllium and lung cancer was suspect, but additional studies demonstrated a clear association between exposure, especially following higher levels of beryllium exposure [28–30]. Subsequently it was shown that use of beryllium in the dental industry was another opportunity for exposure through occupational risk [29]. Thus, the intervention of personal protective equipment (PPE) had a marked ability to reduce occupational exposure related to dentistry [31]. Importantly, patients diagnosed with stage III breast cancer were found to have elevated levels of beryllium [32]. However, in this study, beryllium was not the only heavy metal to be detected thus limiting a direct cause effect situation [32]. Another cancer, osteosarcoma has also been implicated to be the result of beryllium exposure [33].

There has been a paucity of defined experimental studies conducted to determine cause and effect between beryllium and the conduction of cancer and the mechanisms involved. Much of the focus has been to address issues correlated with lung exposure. One carcinogenic mechanism studied was the link between the elevated levels of tumor necrosis factor alpha (TNF-α), which is a cytokine secreted from a specific type of T-cell ($CD4^+$) that are present in the lung [30, 34]. This factor plays an important role in the development and induction of inflammation [30, 34].

The association between TNF-α and beryllium implicates a direct link to the action of chronic inflammation exposure [30, 34].

Genetic changes are associated with beryllium exposure and have been observed to methylate the *p16* gene, which as stated previously is a known tumor suppressor gene that is activated following exposure to beryllium [30]. How to best address the removal of beryllium following exposure, in order to reduce its carcinogenetic properties, has focused on the use of chelators. Chelators are often used to remove heavy metal contamination from the body and in doing so they effectively reduce the toxic effects of exposure. Examples of effective chelators include – 4-dihydroxy-1,3-benzene disulphonic acid disodium salt [Tiron] and D-pencillamine (DPA), which demonstrated effectiveness following animal exposure [35–37]. It is of interest that a benzene derived compound would be used under any conditions because of the known carcinogenetic activity of benzene. Another chelator, meso-2,3-dimercaptosuccinic acid (DMSA) has been demonstrated to be effective when used and reported as a case-study to successfully treat a young child who was suffering from high level beryllium poisoning [38]. This experience suggested it is an effective treatment and therefore is worthy of further investigation [38]. Taken together this collective response indicates reduced exposure of beryllium will impact the overall health risks associated with its exposure [39, 40]. Addressing specific companies and other industrial sources linked to beryllium exposure should be used to support screening other methods to test employees for beryllium exposure among them. Furthermore, such companies should screen their employees using blood samples in addition to providing proper ventilation control measures in these plants and factories [40]. Along with instituting proper screening methods for employees to minimize exposure, additional strategies should be implemented, like better educating plant workers to use personal protective equipment the need arises [39, 40].

1.4 Cadmium

The heavy metal cadmium is a toxic element related to significant health consequences as an environmental contaminant. The sources of environmental exposure are generally associated with industries where it is present in their emissions. The element is used in industries such as mining, research with metallurgy, battery development, and preventing pigment precipitation when used in textiles [41]. A very serious issue regarding environmental cadmium exposure is soil contamination, as human exposure of cadmium most often is the result of ingesting contaminated food and water, inhalation and/or smoking [41, 42]. Regarding soil contamination, a specific source of cadmium contamination occurs as a result of landfills. High levels of cadmium have been found in landfills at concentrations that are much higher than recommended as tolerable in the maintenance of human health [43].Given that landfills are a major source of soil and water contamination, human exposure to cadmium more often is associated with the ingestion of contaminated foods [14, 44].

The main health issue associated with cadmium is the carcinogenicity following toxic exposure in humans, in particular, cancers of the breast, esophagus, intestines, lungs, stomach, testes [41, 45, 46], and possibly the gallbladder. The link to the gallbladder is identified in studies where gallstones have been associated as a pre-cancerous situation in many cases, when analyzed for the heavy metal contact in patients with cancer of the gallbladder [47]. When analyzed statistically significant levels of heavy metal content, cadmium and other heavy metals were found to be elevated [47]. The link between cadmium and carcinogenicity is still a significant human health concern. In other types of studies, in particular laboratory generated

experiments, the results of liver cells cultured in the presence of cadmium demonstrated the oncogenic transformation of these liver cells [44]. In patients with gliomas (cancer of the brain) heavy metal analysis detected high levels of cadmium, indicating cancer of the brain may be linked to heavy metal exposure [48].

Another body organ that has also been linked to cancer following cadmium exposure is the pancreas [15, 49]. Cadmium has also been linked to the development of blood disorders, in particular, the development of chronic myeloid and lymphoblastic leukemia. When analyzed compared to controls, patients with leukemia when tested were found to have increased concentrations of cadmium in the presence of reduced levels of magnesium in both blood and serum [50]. Another significant correlation between increased levels of cadmium and carcinogenicity is the association between cadmium in urine and the development of cancer of the gastrointestinal system [51].

As was observed with other heavy metals, the overall effects correlated with the development of a variety of cancers, focused attention to determine what were the exact mechanisms involved that led to initiation of the carcinogenic processes. With respect to cadmium, the focus of the carcinogenic mechanism involved the generation of reactive oxygen species (ROS) and epigenetic changes. Both contributed to the restriction of repair mechanisms that generated altered or damaged DNA. Both also contributed to the loss of apoptosis in affected cells [41, 46, 52, 53]. Whether the exposure to cadmium is either acute or chronic, the result targets the altered signal transduction mechanisms that induce altered gene regulation, which collectively contribute to the initiation of tumor growth [44]. In this key sequence of intracellular changes that takes place following cadmium exposure, important proteins are dysregulated either via upregulation or enhanced activity or perhaps via suppression of key molecular pathways. Such an example is the inhibition of EGR-1, which is a key protein that regulates cell destructive pathways, such as transcription [44].

Adverse toxic human exposure resulting from cadmium poisoning unfortunately is not associated with any standard therapeutic measures designed to address cadmium toxicity, if presented following acute or chronic exposure [54]. With that said, research has developed compounds that upon co-administration would be effective in reducing the toxicity of cadmium exposure. Examples of compounds developed to reduce cadmium toxicity are peptide ligands that have specificity for cadmium [54]. Importantly because of their widespread availability, meaning they occur naturally are flavonoid compounds that are present widely in fruits and in fact in most plants. Collectively whether they are fruits or vegetables, they all contain flavonoids. Flavonoids are potent antioxidants, thus chemically they reduce the development of ROS and also, they can assist in cadmium chelation [55]. With that said, it is still important to more fully understand how flavonoids, specifically via their structure inhibit the development of cadmium toxicity [55].

There is experimental evidence exploring whether the use of stem cells would be effective in ameliorating the cellular damage associated with cadmium toxicity. In a study performed using rats, the testicles were exposed to cadmium causing tissue damage [56]. Following the toxic exposure, animals received bone marrow derived mesenchymal stem cells. Upon clinical treatment it was observed that within the testes the levels of proteins responsible for apoptosis reached appropriate levels to restore apoptosis, thus effecting cell regulation [56]. Within the affected tissue there was evidence that the damaged tissue had been repaired. The implications of these observations suggested that the target of recovery delivered by mesenchymal stem cells was the restoration of mitochondrial apoptosis [56].

1.5 Lead

One of the most researched heavy metals, in part because of its well-established effects on human health is lead. It has long been recognized as a significant environmental pollutant. There have been a number of pathways that either singularly or in concert attribute to impairing human health especially after chronic lead exposure [57–59].

A very common method of human lead exposure is the result of environmental contamination that involves soil and water contamination, especially sources of drinking water. Lead levels accumulate in deposits and exposure is manifested through the human food chain, thus its eventual presence in consumed food [57–59]. Another common source of lead that contributed to its exposure to humans was the presence of lead added as additive to gasoline. However, since 1995 lead has been banned as additive to gasoline for use in automobiles, yet it is still added to the fuel used for aviation purposes [59]. Another alarming link to human lead exposure was the discovery that lead was present in cigarette smoke; therefore, the lead levels in blood of smokers was reported to be high, as there is no safe concentration of lead regarding impact on human health [60]. Other occupational hazards also exist such as mining that contributes to the presence of lead exposure in those workers [57].

What have been the studies conducted to determine the overall level of toxicity of lead exposure to human health? A number of epidemiological studies have been conducted to determine the impact of lead on human health that has implicated the heavy metal as a causative factor in a number of human cancers. Whether lead exposure functions in terms of a direct cause vs. effect on inducing a specific cancer type is still under investigation [61]. In particular, interest has centered on a supportive, perhaps an additive, role in the maintenance of cancer rather than an initiating agent [61]. Lead has been detected along with other heavy metals that are also known for their impact on human health especially in children where it can impact the development of myelin, thus causing impairment in neurological development. An example was the detection of very high levels of lead in the water systems of Flint, MI and along with cadmium when analyzed in patients with gliomas (brain cancer) [61]. This observation demonstrated an increased toxic consequence to human health when such heavy metal contaminants are found together in human tissue or body fluids [61].

A study of patients with kidney cancer came to the conclusion that the cancer developed associated with high levels of lead [58]. This observation was later supported by evidence linking the development of renal cell carcinoma as associated with the presence of lead in the blood [60]. A link to the development of liver disease as the result of high lead concentrations levels along with a number of other heavy metals when tested in gallstones [47] suggested there may be a correlation between lead levels and disease of the gallbladder, perhaps inducing a pre-cancerous lesion [47]. When examined in workers exposed to high levels of lead, it was clearly demonstrated there was a significant positive correlation between the heavy metal and the presence of cancer in the lungs, along with a positive correlation linking lead exposure to the development of cancer of the brain, larynx, and bladder tissues [62]. In patients detected with pancreatic cancer, increased levels of lead in addition to several other heavy metals were measured, suggesting heavy metal exposure may contribute to the overall carcinogenicity of these heavy metals [15, 61].

The scientific literature has been devoid of studies devoted to the understanding of the mechanisms of lead induced carcinogenicity; however, several potential mechanisms have been proposed. Based on the current understanding of how lead

can be carcinogenetic, one hypothesis has implicated lead as effectively disrupting internal genetic processes that result in the inability of tumor regulatory genes to function, inducing damage to DNA, and at the same time inhibiting repair of DNA damage [63]. In animal studies using mice exposed to lead, they showed that the heavy metal was capable of inducing reactive oxygen species (ROS) and by doing so the exposure effectively altered the sequence of specific gene function [63]. Another critical observation related to the ability of lead to disrupt normal cellular physiological processes were the results showing lead was effective in normal reactions controlling transcription. The reaction that mediates this transition was the substitution of lead for zinc that serves as a metal catalyst for several key enzymatic reactions that control DNA transcription [63]. Along with this observation was the important association of calcium in these enzymatic reactions based on epidemiological studies showing an increase in calcium correlated with a lower risk level for developing renal cell cancer. Consequently, as pointed out by the investigators, it clearly showed the need to have a clinical trial to determine the overall significance when these important cations and heavy metals come into contact with one another [60].

For clinical cases where heavy metals such as in lead poisoning are implicated in disease etiology and pathology, the therapeutic remedy recommended is chelation [64]. The most common chelators being used for reducing elevated lead levels are British, Anti-Lewsite, calcium disodium ethylenediaminetetraacetic acid (EDTA), D-penicillamine and Meso-2,3-dimercaptosuccinic acid. The use of any specific chelator depends on the individual clinical case [64]. Unfortunately, several of these chelating agents are associated with their own level of toxicity. Thus, to reduce the toxicity potential of these chelating agents, substitution using garlic in the clinically was found to effectively reduce blood levels of lead when lead toxicity was at moderate levels and also restricted lead associated symptoms when used clinically [64]. With the collective results, it goes worth saying the most effective treatment is to prevent lead exposure [58]. To achieve such a goal requires that all industries known to be associated with lead toxicity must address emissions of the toxic metal to the environment as well as to reduce with the goal to completely eliminate emissions such that workers are not exposed, which implies factories need to have established quality control guidelines for limiting lead exposure [64]. It stands to reason that the best and most effective way to remove lead contamination is to eliminate the sources of lead contamination [64]. In communities such as has been the case in Flint, MI that have been impacted because of lead leaching from old water pipes, the only remedy is to completely remove the old lead-based pipes for modern substitutes.

1.6 Mercury

Another heavy metal that has shown severe health consequences in humans following exposure is mercury. A minor portion of the heavy metal is found as a mineral in trace amounts with the major portion of mercury exposure the result of the environmental exposure following industrial use [65]. There are many different areas where mercury use has caused environmental problems. Common usage includes the long-term use of mercury in thermometers, dental fillings, in the manufacture of certain types of batteries, and in the burning of medical waste [65, 66]. Burning of fossil fuels has also been identified as a source of mercury pollution [65, 66]. Another contributing factor to environmental pollution and mercury is the fact that mercury often will be vaporized thus entering the atmosphere along with the other substances that when in the atmosphere, can then be incorporated into the soils and water systems [65, 67]. Regarding foods, consumption of large amounts of seafood,

e.g., tuna and shellfish has been identified as another link to environmental exposure especially methyl mercury [65, 68, 69]. Collectively these sources have contributed to the environmental contamination associated with mercury.

Regarding the association between the development of cancer and mercury, there has been suggestive evidence linking mercury exposure and kidney cancer. This association is based on the physiological role of kidney in removing toxic substances when present in the body, especially within the blood [65]. Several other cancers associated with mercury are both liver and gastric cancers [70]. Also related to liver and gastric cancers, in patients with cancer of the gallbladder, mercury has been detected in gallstones at significant concentrations [47].

As has been mentioned when discussing the other heavy metals, mercury has the potential to be associated with the development of malignancies that utilize specific mechanisms that regulate the control of tumor development. The mechanisms implicated are the capacity to generate free radicals (ROS), in addition to the disruption of DNA, whether it be related to transcription events, changes in or maintenance of its molecular structure [66]. With that said there are reported other carcinogenic mechanisms that are unique to mercury. One such mechanism that addresses the carcinogenic potential of mercury is its ability to reduce levels of glutathione [71]. As mentioned earlier, glutathione is a naturally occurring antioxidant and as such it can reduce the antioxidant activity of mercury via reactive oxidant species, by inhibiting the development of oxidative stress mediated through reactive oxidant production, thus minimizing its carcinogenic potential [71]. Cells that are exposed to oxidative stress have been demonstrated to have increased rates of peroxidation of lipids, which has been proposed as another functional mechanism inducing cancer [65]. Within cells mercury has been implicated to influence the function of microtubules, which by their very nature can disrupt cellular mitosis [66].

As was stated with the other heavy metals previously mentioned, the use of chelators has been a common therapeutic approach for removing mercury from the body. For mercury two of the most effective chelating agents are dimercaptosuccinic acid (DMSA) and dimercaptopropane (DMPS) [72, 73]. With that said, there are substances that have been untested in terms of their chelating abilities for their effect against mercury. Two of these substances, desferairox and deferiprone, were tested experimentally in rats where it was observed that the combination was able to effectively chelate mercury and reduce toxic effects of mercury [74]. An experimental chelating agent that has been postulated is thiol-modified nanoporous, a silica material [75]. When tested experimentally in animals, it was observed that this substance had the potential to chelate mercury with minimal toxicity [75].

1.7 Nickel

The heavy metal nickel originally discovered as a major component constituting the earth's core has in recent years been the focal point of investigations to determine if its exposure, occupational or environmental, is involved in any carcinogenic action that compromises human health, through occupational exposure occurring primarily in the mining and refinement of nickel ore and producing metal alloys [76–78]. Nickel pollution of the environment results in its accumulation in organs and tissues within exposed organisms. As an example, nickel can enter the food chain through fish [79]. Alternatively, another route can take occur once contamination of the soil takes place [76]. On an industrial scale, nickel is often present in emissions released from oil refineries that have been identified as significant sources of environmental exposure and pollution, thus increasing the risk of exposure to those residents living close to these refineries [80].

Nickel exposure in humans has been associated with the development of a variety of cancers. Through epidemiological studies, evidence has shown there is a correlation between nickel exposure and the induction of cancer development in the lungs and in nasal and sinus tissues [13, 17, 81, 82]. In a study performed in breast cancer patients, when blood serum was analyzed for nickel it was found to be elevated significantly suggesting a potential relationship between the high nickel levels and the induction of breast cancer [83]. The correlation between nickel exposure and cancer has also been linked to the development of acute myeloid and lymphoblastic leukemia [84]. Additionally, when the urine was analyzed in patients with childhood leukemia, elevated levels of both nickel and 8-hydroxydehydrogenase implicating a causative role for nickel in inducing this childhood disease [84]. The role of nickel as a carcinogenic agent is implicated because of its ability to induce oxidative cellular damage as a primary mechanism of action [84].

Patients with pancreatic cancer, when measured for nickel levels, demonstrated elevated levels suggesting there is a positive correlation, even though other heavy metals were detected [15]. In addition, a study came to the conclusion that there may be a link between chronic nickel exposure, along with concomitant exposure of other heavy metals, to the development of T-cell lymphoma [85] and also liver cancer [13]. Collectively, the implications of these reports suggest the carcinogenic action of nickel.

Discussion of nickel and cancer addresses the need to focus on potential mechanisms of action. Several have been implicated. One mechanism involves the ability of nickel to influence noncoding RNA expression. A study demonstrated that nickel was effective in inducing materially expressed gene regulation (gene 3 MEG3) by its ability to influence the methylation of its associated promoter element [81]. This process was an effective inhibitor of PHLPPI and up-regulator of hypoxia-inducible factor-1α. Both are proteins recognized for their effective role in the processes involved in carcinogenesis [81]. As has been reported for other heavy metals, nickel as well can induce the formation of free radicals, a known carcinogenic action [86]. Exposure to nickel has been demonstrated to influence the status of the transcription and regulation status of mRNAs and also involve microRNAs [78]. Implicated in these reactions is the ability of nickel to influence immunity and the immune response, especially when it involves inflammation and the immune response, which in itself has also been implicated as having a significant role in carcinogenicity [78]. Nickel and its role in influencing the inflammatory response has been researched using animals and in combination with human cells [82]. These studies came away with the observation that there is an association between nickel exposure and cancer [78].

In addition to nickel's association with cancer, inflammation has also been investigated when tested using both animal and human cells. After dose–response studies were conducted it was determined that exposure to nickel increased the expression of certain proteins, specifically SQSTM1 and TNF. Both are known to have specific functions in the inflammation process [82]. As was observed with other heavy metals, nickel has been suggested to induce cellular following exposure epigenetic changes, an example is alteration in DNA methylation [82]. This conclusion is suggested from results that demonstrated exposure to nickel induced histone H3K4 tri-methylation [87]. The reactions associated with nickel exposure have been correlated with faulty transcriptional activation that can be a blueprint for the development of cancer [87].

Although chelation has been widely applied as a mechanism to remove heavy metal contamination, when applied to alleviate nickel contamination has produced different results. A very effector for chelating nickel, especially the cancer-linked nickel carbonyl, sodium diethyldithiocarbamate to the extent that it is the

recommended remedy in the clinical setting [88]. With respect to environmental contamination, the compound ethylene diaminetetraacetic acid (EDTA) was shown to decrease the uptake of nickel when exposed to soil [89], indicating the potential for EDTA to be considered as an effective remedy for experimental exposure. The chelating compound $CaNa(^{2+})$-EDTA effectively removed nickel [90].

1.8 Radium

The heavy metal radium has had a long association with negative effects on human health. The harmful fact associated with radium is its radioactivity. Radium releases ionizing radiation through the decaying of radium into a toxic gas [91]. Radon contamination in the form of ionizing radiation can be associated through environmental and occupational exposure. Occupational exposure to radium is often associated with coal mining [92]. Coal mining exposure also implies radium contamination of any water or liquid residue used in the mining process [93]. The occupational exposure of radium can be associated with exposure through contact with building materials, soil and water systems. An Italian study demonstrated radium can accumulate when associated with confined space, such as in buildings, basements and other storage facilities [91]. Another overlooked substance that can contribute to the increased presence and concentration of radium in confined spaces is cigarette smoke [93]. This observation clearly implicates smoking and radium exposure that collectively could synergistically impact human health [93].

The development of several types of cancer have linked to radium, thus labeling it as a known carcinogen. Because the main occupational exposure of radium comes from occupations where inhalation is the primary method of exposure, the predominate form of cancer is lung cancer [91]. As a significant agent responsible for inducing cancer following radium exposure is the release of the ionizing radiation. With that said, when under controlled conditions, radium is used in the clinical treatment for human ankylosing spondylitis [94]. However, careful administration is critical because injection of radium has been associated with the development of several types of leukemia [94]. In animals, radium injections were demonstrated to induce the formation of osteosarcomas [94]. In a clinical case report, a patient being treated with radium-223 developed a cutaneous squamous cell carcinoma indicating such patients need to be followed clinically by a dermatologist [95].

2. Carcinogenicity effects on human cancer cells

2.1 Aluminum

Aluminum is known for its genotoxic profile in cosmetics, especially underarm anti-perspirant products [96]. Aluminum prevents perspiration by blocking the sweat ducts; it also absorbs through the skin. This environmental carcinogen accumulates in the human breast, transforming MCF-10A human mammary epithelial cells and inducing DNA double strand breaks (DSB). These effects have been exhibited *in vitro* with similar concentrations of aluminum to those measured in the human breast [97]. The concentrations of aluminum in the culture medium transform the MCF-10A human mammary epithelial cells, therefore enabling them to produce tumors that can metastasize [98].

To repair DSB is intrinsically mutagenic; once aluminum was removed from the culture medium, however, DSB were not reversible, therefore suggesting that mammary epithelial cells cultured in the presence of aluminum acquire mutations.

In addition, *in vitro* studies have shown that aluminum increases the migratory and invasive properties of MCF-7 or MDA-MB-231, human breast cancer cells [97].

Aluminum is a metalloestrogen, a type of inorganic xenoestrogen that is capable of binding to cellular estrogen receptors and mimicking the actions of physiological oestrogens [99]. The most commonly used aluminum-based compounds in underarm cosmetic products (UCP) are aluminum chloride and aluminum chlorohydrate. Not only do aluminum salts trigger DNA DSB, they can lead to oxidative stress, proliferation, and interference in estrogen action before and with metastasis.

A 1:1 age-matched hospital-based case–control study was performed to examine the impacts that self-reported UCP use had on breast cancer. Between a large series of breast cancer patients (aged 20–85 years) and healthy individuals, the aluminum concentrations in their breast tissue were measured and compared. The study participants were interviewed about their UCP application; their answers were categorized under "never", "1-4 times per month", "2-6 times per week", "daily" and "several times per day." A positive family history of breast cancer resulted in being the most prominent risk factor. However, self-reported use of UCP several times per day during early ages (< 30 years) showed a significant association with an increased risk of breast cancer. In addition, the aluminum in breast tissue was significantly associated with self-reported UCP use [98].

Another study showed that in an aqueous solution with a pH of 7.0, aluminum chloride and aluminum chlorohydrate yield aluminum hydroxide and are absorbed through the human skin. This suggests that with daily application of UCPs to the underarm's skin indicates a pronounced source of exposure to aluminum for the human mammary epithelium.

Aluminum has a transforming effect that is followed by the dose-dependent appearance of DNA DSB. The altered phenotype of MCF-10A cells that were cultured in the presence of aluminum chloride is not reversed by withdrawing the salt, however. These results reveal that a mutagenic effect is at least partly responsible for aluminum's transforming effect. The salt causes mutations in genes that regulate cellular proliferation, migration, metastasis and apoptosis. Mutations are also found in the genes monitoring the Max-binding protein MNT and T-lymphoma invasion and metastasis-inducing protein 2 (*Tiam2*) [1]. MNT functions as a pro-survival protein whose activity suppresses the pro-apoptotic activity of MYC, a family of proteins that contribute to oncogenesis [100]. The *Tiam2* gene serves a significant role in neuron development and human malignancies [101].

2.2 Arsenic

Arsenic is a naturally deposited metalloid that is widely distributed throughout the Earth's crust. Most arsenic-containing compounds are classified as organic and inorganic forms, with the inorganic form, specifically the trivalent arsenic (As^{3+}), being much more toxic and carcinogenic. Studies have shown that As^{3+} is an environmental etiological factor for a certain number of human cancers. There has shown to be a significant correlation between human lung cancer and environment As^{3+} exposure, either from drinking water contamination or air pollution. When As^{3+} is ingested through drinking water, it is absorbed into the bloodstream; its metabolic products, especially the methylated As^{3+}, is potentially deposited in the lung tissues due to the high partial pressure of oxygen [102].

The exact pathophysiological mechanism through which arsenic induces carcinogenesis is still to be determined; however, the increasing of oxidative stress, chromosome abnormalities (with uncontainable growth), and abnormal immune developments, are likely mechanisms. Reactive oxygen species, 8-Hydroxy-2-deoxyguanosine, is a major form of oxidative DNA damage that was acquired from

the urine and skin tissue of individuals exposed by arsenic. DNA strand breaks, micronuclei in cord blood, and nitrative DNA damage were some of the early genetic effects discovered in the arsenic exposed patients. Studies have shown that arsenic also affects DNA repair machinery, which therefore causes oxidative DNA damage and mutations by the impairment of nucleotide excision repair, DNA ligase, DNA base excision repair, and DNA strand break rejoining.

Arsenic additionally affects epigenetic regulations. Chanda *et al.* claims that DNA hypermethylation of the crucial promoter region of the *p53* and *p16* genes was present in the DNA from arsenic-exposed individuals [103]. Since high exposure of arsenic is related to DNA hypermethylation of *p53* and *p16* genes, this suggests the notion that epigenetic silencing of these key tumor suppressors genes may be a notable mechanism by which arsenic induces cancer initiation [104].

Recent evidence has been reported to show that arsenic can alter miRNA expression patterns in *in vitro* and *in vivo* models of arsenic-induced carcinogenesis. Dysregulated miRNAs contribute to cancer development and progression, with the potential of acting as a novel class of oncogenes or of tumor suppressor genes. microRNAs are significant in tumorigenesis; for example, the overexpression of miR-504 negatively regulates the *p53* gene, decreasing the *p53*-mediated apoptosis, in addition to negatively regulating the cell cycle arrest in response to stress [105]. Production of reactive oxygen species (ROS) is one of the most reviewed mechanisms in arsenic carcinogenicity; as ROS reacts with DNA and induces structural DNA damage, genetic defects result, and the overexpression of antioxidant enzymes will desensitize cells to apoptosis. Arsenic can inflict oxidative stress through two different routes: direct Fenton-type reactions to produce ROS, or indirect depletion of critical antioxidants [106].

In immortalized human keratinocytes (HaCaT cells), miR-21, miR-200a, and miR-141 are overexpressed after a 4-week treatment with 500 nM sodium arsenic. For miR-21 and miR-141, these microRNAs have exhibited strong associations with the majority of human tumors. The miR-200 family has been reported to have a role in the epithelial-mesenchymal transition and cancer progression. For lung cancer development, the overexpression of miR-155 in normal cells has been a leading cause. Results indicate that urothelial human cancer is induced by miR-200 family members; the expression of miR-200a, miR-200b, and miR-200c was down-regulated in arsenic-exposed human urothelial cells (HUC1) in comparison to nonexposed HUC1 cells. The levels of these miR-200 family members in the urine of arsenic-exposed patients were also decreased [105].

2.3 Beryllium

Beginning in 1952, a collection of case reports in the Beryllium Case Registry at the Massachusetts General Hospital and cohort studies established the basis for several overlapping epidemiological reports on how beryllium induces cancer. Elevated ratios of lung cancer were shown among workers who had experienced acute berylliosis; however, the results were not similar in workers with chronic berylliosis [107]. Acute beryllium disease is mostly considered an irritative chemical phenomenon associated with high exposures; on the other hand, chronic beryllium disease is an immune-mediated granulomatous reaction to beryllium [108]. Studies showed that the increased cancer death started to occur 15 years after the onset of beryllium exposure.

Experiments were conducted by injecting zinc beryllium silicate in rabbits intravenously. Results indicated that the administration produces consistently metastasizing osteosarcomas in the long bones. Outcomes parallel to these results were obtained with the injection of beryllium oxide, beryllium phosphate, and beryllium

metal into the medullary cavity of bones. This route of administration was the only route that led to the formation of osteosarcomas. Splenectomy was additionally shown to increase carcinogenicity with the IV-injected beryllium in bones; the spleen, being an important storage organ, most likely allowed the retention of a higher proportion in the reticuloendothelial system and bone.

Exposing the rats to beryllium sulfate, beryllium phosphate, beryllium fluoride, zinc beryllium manganese silicate, and beryl ore, through inhalation also produced carcinogenic properties. Throughout the duration of a 35-hour week exposure schedule, 10 micrograms of $BeSO_4$ was determined to be threshold for the induction of pulmonary adenocarcinoma in rats. The majority of malignancies were adenocarcinomas with a predominantly alveolar pattern.

In Chinese hamster V79 cells (lung fibroblasts) and in Chinese hamster ovary (CHO) cells, the induction of 8-azaguanine-resistant mutants by $BeCl_2$ and by $BeSO_4$, respectively, has demonstrated beryllium's ability to inflict gene mutations in cultured mammalian cells. $BeSO_4$ did not cause chromatid or chromosomal aberrations in Chinese hamster lung cells. In CHO cells and cultured human lymphocytes, however, $BeSO_4$ produced chromosomal breaks and sister-chromatid exchanges [107].

With a soluble beryllium compound and upon incubation of a continuous human cell line, there was shown to be a reduction of the expression of messenger RNA coding for DNA repair proteins. This observation was suggested to be a relevant mechanism for potential carcinogenicity of beryllium. To further study this claim, the DNA of rat primary hepatocytes was purposely damaged by incubation with a known DNA damaging agent, 2-acetylaminofluorene. In addition, the DNA was co-incubated with beryllium metal extracts. In the results, there was a reduction in DNA repair synthesis with the beryllium metal extract. Beryllium metal has not been confirmed to directly damage the DNA of cells; nevertheless, there is strong evidence that the metal can cause morphological cell transformation and the inhibition of DNA repair synthesis [109].

The carcinogenic properties of beryllium have been mostly demonstrated when in its metal form, some of its alloys, and a variation of its compounds. Lung cancer induced by beryllium is a main result from pulmonary instillation or inhalation with consequent direct action on the lung. The bone tumors that beryllium stimulates, a characteristic of osteogenic sarcoma, reflects the metal's bone seeking propensities [110].

2.4 Cadmium

Cadmium is a dangerous metal for humans as the human body is limited in its response to cadmium exposure; the metal is incapable of metabolic degradation to less toxic species [111]. Cadmium is a toxic heavy metal that is commonly known as a human carcinogen. Their main sources of exposure include food, cigarette smoking, and cadmium related industry. Reactive oxygen species (ROS) are measured to be the most prominent mechanism in cadmium-induced carcinogenesis. The intracellular oxidative stress that reactive oxygen species induce potentially damage macromolecules and eventually grow responsible in the formation of cancer.

There are two stages referred to when discussing cadmium-induced carcinogenesis. In the first stage, normal cells transition into transformed cells. The reactive oxygen species contribute in the malignant cell transformation of BEAS-2B (human bronchial epithelial) cells in their exposure to cadmium. For the second stage, morphologically transformed cells advance into tumorigenesis. Cadmium-transformed cells, *p62* and Nrf2, are activated and their downstream antioxidants and anti-apoptotic proteins are elevated, therefore causing a reduction in ROS, apoptosis

resistance (permitting cancer cells to persist and not die), and tumorigenesis. The decrease in ROS generation in the second stage provides an optimal environment for transformed cells to survive and engage in tumorigenesis [112].

Cadmium exposure is shown to induce consistent low levels of ROS production, which causes endoplasmic reticulum stress that causes defective autophagy, which protects cadmium exposed damaged cells and encourages malignant transformation in prostate carcinogenesis. In order to maintain the quality of intracellular components, autophagy, a highly complex lysosomal-mediate degradation process, is accountable for the removal and recycling of damaged organelles. This deficient form of this activity assists in cancer cell survival as autophagy protects the cells from hypoxia and oxidative damage, in addition to promoting chemoresistance [113].

The *p62* protein performs several cellular functions for autophagy, apoptosis, ROS signaling, and cancer. The protein has been found to accumulate in autophagy-deficient cells, and the overall accumulation of *p62* due to autophagy dysfunction encourages cell survival and tumorigenesis through the activating of nuclear factor, κB. The *p62* protein is highly expressed in human lung cancer. As *p62* accumulates, it activates Nrf2 and Nrf2 target gene expression. Autophagy deficiency results in the up-regulation of *p62,* which therefore leads to the transcriptional activation of the Nrf2-dependent genes, involving antioxidant enzyme genes [114].

Similar to metal arsenic, cadmium is weakly genotoxic and mutagenic. To determine whether cadmium exposure induces properties analogous to cancer stem cells, researchers exposed immortalized human pancreatic ductal epithelial (HPDE) cells to low dose cadmium for 29 weeks. Using suspension culture spheroid formation assay, the chronic cadmium-exposed HPDE cells exhibited significantly higher levels of molecular markers for cancer stem cells, yielding 3-fold more suspension spheres than the controlled cells [115].

Cadmium does not form adducts with DNA; however, it is capable of inflicting oxidative stress that could indirectly attack DNA. This process is not instigated through participation in Fenton type chemical reactions [111]. The Fenton reaction is defined by a redox pair of ferrous ion and hydrogen peroxide (H_2O_2) that ultimately generates a reactive hydroxyl radical [116]. The potential mechanisms for cadmium-carcinogenesis include aberrant gene activation and signal transduction, suppressed apoptosis and disruption of E-cadherin-mediated-cell–cell adhesion, and altered DNA repair [111].

2.5 Lead

Lead is a metal that can be classified as an environmental pollutant and is commonly known for its usage in many industrial settings worldwide. With high lead exposure, health effects can include damage to the brain and nervous system, gastrointestinal problems, anemia, liver and kidney damage, fertility problems, and developmental delays. Inorganic lead is also suggested to be a carcinogen; epidemiological evidence for carcinogenicity in industrial workers that have been exposed to inorganic lead indicates a significant relationship with cancers of the stomach, lung, kidney, brain, and meninges.

The two primary routes through which lead enters and accumulates in the body is inhalation and oral ingestion. With this being said, even though lead has the capacity to enter the bloodstream and impact other organs of the body, the lungs and stomach are what first come into contact with lead. Due to lead's ability to pass through the blood–brain barrier, the brain and nervous system are especially vulnerable to the potential toxic effects of lead. The mechanisms that lead uses in playing a role in carcinogenesis include oxidative damage, induction of apoptosis,

altered cell-signaling pathways, inhibition of DNA synthesis and repair of damage, and interaction with DNA-binding proteins [117].

In one study, results provided support for an association between occupational lead exposure and brain cancer risk. Among industrial workers who were potentially exposed to lead, the brain cancer mortality rates were greater as compared to unexposed subjects, with indications of an exposure-response trend [118]. Results, however, of many studies have showed inconsistency in determining the relationship between lead exposure and brain tumors. For results that support the association, the results suggest that lead can cross the blood–brain barrier and concentrate in the brain parenchyma due to its ability to replace calcium ions. Once the lead is absorbed, it is generally allocated to plasma, the nervous system, and soft tissues, therefore potentially developing micronucleus formation, chromosomal aberrations, and DNA damage in most mammals.

Lead's mechanism in which it causes brain cancer remains unclear; nevertheless, studies suggest the most probable mechanism is the metal's inhibiting of DNA synthesis and repair and the interacting with binding proteins that eventually hinder tumor suppressor proteins [119].

2.6 Mercury

Mercury is one of the most toxic heavy metals due to its persistence in the environment. Mercury inflicts oxidative stress and induces apoptosis. Methylmercury (MeHg) is a metalloestrogen, a small ionic metal that activates the estrogen receptor. Studies indicate that once metalloestrogens activate the estrogen receptor, there is an increase in transcription and expression of estrogen-regulated genes, therefore inducing proliferation of estrogen-dependent breast cancer [120].

The phases of cancer development are initiation, latency, promotion, and then progression. In the promotion phase, mercury has shown to cause an imbalance in the reactive oxygen species homeostasis through selectively inhibiting selenocysteine antioxidant enzymes. Mercury fulfills both the capacity to induce an inhibition of the gap junction intercellular communication and the proinflammatory cytokine release. These two mechanisms have potential to isolate cells from tissue-specific homeostasis, promoting their proliferation. In addition, they have potential to overcome the immune system defenses, checkmating the entire organism. The International Agency Research Cancer (IARC) does not classify mercury as an identified carcinogen to humans; nevertheless, if the toxic compound inhibits the gap junction intercellular communication, mercury is suggested to be a potential cancer "promoter" [121].

Animal experiments were performed to investigate the carcinogenic effects that methylmercury had on mice. They were fed with 10 mg/kg of methylmercury, and as a result, chronic kidney failure, adenoma, and carcinoma were observed. With these results, rodents that were exposed to methylmercury were reported to show a higher incidence of kidney cancer. The International Agency for Research on Cancer claims there is a satisfactory amount of evidence for methylmercury's impact in cancer on experimental animals, only classifying it as a possible carcinogenic to humans. On the other hand, the U.S. Environmental Protection Agency (EPA) judges that evidence of methylmercury's carcinogenic potential in humans was insufficient and the justification of the carcinogenicity in experimental animals was limited. Therefore, they classified methylmercury as a Group C material (possible human carcinogen) [122].

Mercury can affect multiple organ systems, especially the nervous and renal systems. One particular study wanted to determine mercury's capacity to induce

centrosome amplification. Centrosomes, microtubule organizing centers of the cell, play a crucial role in cell division; they aid in the proper segregation of chromosomes into the resulting daughter cells. When metals induce cellular and genotoxic stress, however, this can interfere with the strict coordination between the centrosome and DNA cycles that ensures the cell to enter mitosis with only two chromosomes. This disrupted linkage stimulates centrosome amplification, potentially resulting in chromosome segregation and aneuploidy. For the aneuploid cells that survive, they can eventually lead to tumor formation and cancer. The study reported that methylmercury, but not inorganic mercury, prompted both a mitotic arrest and centrosome amplification in mitotic cells, therefore suggesting a possible carcinogenic mechanism [123].

2.7 Nickel

Nickel is considered a major carcinogenic heavy metal, mainly through the mechanism of DNA damage. Demonstrated by *in vitro* and *in vivo* studies, nickel destructs DNA processes through direct DNA binding and reactive oxygen species (ROS) stimulation. Nickel's carcinogenic properties also include their repressing of DNA damage repair systems through direct enzyme inhibition and downregulation of DNA repair molecule expression. Studies have shown that Ni^{2+} has potential to induce DNA damage in certain human cell systems; some include hepatocellular carcinoma (HepG2), human TK6, Chinese hamster lung fibroblast, A375, and HCT-116 cells [124, 125].

With reactive oxygen species, when they excessively attack the DNA, this results in genomic instability, a promoter of tumorigenesis. This oxidative stress or genomic instability, being a major driving force of oncogenesis, is the basic toxicological mechanism of nickel overexposure [124]. Oxidative stress is known to occur as a result of overproduction of reactive oxygen and nitrogen species through endogenous and exogenous insults. The production of these reactive oxygen species is enabled by nickel's capacity to bind with amino acids, peptides, and proteins [125].

The metal has the ability to dissolve in the human body, releasing ionic nickel, an active and occasionally genotoxic carcinogenic form of nickel. When a carcinogen is classified as 'genotoxic', this refers to chemicals that are capable of directly altering genetic material, opposed to 'non-genotoxic' carcinogens that produce cancer through indirect or secondary mechanisms. Most of the chemical carcinogens that induce direct DNA damage are therefore categorized as 'genotoxic' in their carcinogenic mechanisms. Nickel's carcinogenic potential also originates from its capacity to raise the intracellular concentration of nickel ions [126]. The nickel ions exhaust intracellular iron by hindering the membrane ion transporters, in addition to displacing iron from the active site of dioxygenase enzymes. This all leads to the inhibition of their catalytic activity [127].

DNA hypermethylation and subsequent silencing of tumor suppressor genes potentially serve as an epigenetic mechanism responsible for nickel's carcinogenicity. Promoter hypermethylation induced by nickel was observed *in vivo* as nickel sulfide was injected into *p53* heterozygous mice to induce tumor formation. Malignant fibrous histiocytomas advanced in both wild type and *p53* heterozygous mice, with all tumors exhibiting promoter hypermethylation of *p16* (a tumor suppressor gene). Additionally, Wistar rats exhibited muscle tumors that displayed DNA hypermethylation in the promotor regions of *RARβ2*, *RASSF1A* and *p16* genes, following intramuscular injection of nickel sub-sulfide [128].

2.8 Radium

Along with X-rays, radium has a carcinogenic effect of ionizing radiation in humans. The danger of ionizing radiation involves the risk of developing cutaneous squamous cell carcinoma. Additionally, studies suggest that radium treatment for the benign skin lesions may only increase the risks of sarcoma of the bone. For example, in one particular case, a patient developed a mixed tumor of carcinoma and sarcoma at the specific site where she had received radium treatment; a malignancy that developed in the same location supports the notion that the previous radium treatment caused it [129].

At elevated concentrations, naturally occurring dissolved radium can potentially be classified as carcinogenic to the human body. Following digestion, the radium can become deposited within the body where its radioactive characteristic threatens human health through cell damage, therefore increasing the overall risk of cancer [130].

Other experiments show that intra-uterine radium application or X-irradiation of the uterus can induce rat malignant uterine tumors, usually endometrial adenocarcinomas. One rat subject's uterus was exposed to direct X-irradiation and a composite endometrial tumor, also classified as an adeno-sarcoma, was produced. The tumor was not structurally similar to the mixed endometrial tumors seen in women; nevertheless, the composite structure and the potential that the tumor may also exhibit carcinomatous areas, implies that it may strongly represent the rat counterpart of the human neoplasm. Results of the experiment strengthened the suspicion that pelvic radiation can lead to an increase in long-term incidence of uterine cancer, particularly mixed tumors [131].

3. Legalization and the national and international permissible levels for these heavy metals

In recent years the legalization of producing marijuana (cannabis and cannabis-derived products) especially in certain specific states within the United States has caused a level of alarm in part because of the presence of heavy metals within these products. As the result of the expansion in the commercialization of these products, has created the challenge to now measure heavy metals in cannabis and cannabis-infused commodities. Marijuana is now legal and approved for both medical and recreational use in 33 states within the United States and the District of Columbia (Washington, DC) [132]. However, the raw materials (cannabis and hemp plants) are known to be hyperaccumulators of contaminants such as heavy metals that may be present in the medium used to cultivate the plants, whether it is the soil, the fertilizers used, and in any other growth promoting substances used to supply needed nutrients. With that said, the alarm has been sounded to critically monitor the levels of heavy metal contaminants present in any part of the growing process to ensure that the marijuana-cannabis material and its food-associated products are safe to consume [133].One of the major remaining issues, at least in the United States, is the lack of federal government oversight regarding measuring contaminants in marijuana (cannabis and cannabis-prepared food products) produced in the United States. The U.S. federal government has removed itself from this oversight and in doing so they have delegated regulatory issues to the individual states to regulate the use of marijuana cannabis and cannabis-prepared products. This adds a financial burden to states that are often financially stressed to meet these demands.

What individual states have emphasized has been to focus on the manufacturers of these marijuana (cannabis and cannabis-prepared food products) to show

regulation by measuring for the following four major heavy metals: lead (Pb), arsenic (As), cadmium (Cd), and mercury (Hg). The levels of metals must be below maximum limits, based mainly on regulations set by the pharmaceutical industry in USP Chapter 232 and ICH Q3D guidelines [134, 135]. The state of California is usually the state that places severe restrictions on levels allowed. This policy is considered to be the gold standard in regulating cannabis and hemp. It determines the levels allowable in both the oral (edibles) and inhaled (vapes) cannabis products to be to safe to consume only if these four heavy metals are present at levels below those shown in **Tables 1** and **2**, based on typical consumption of 10 g/day of cannabis material [137].

For analytical measurements of heavy metal contaminants, the state of California requires that at least half a gram of sample must be used for testing purposes. The analytical testing methodology recommends that inductively coupled plasma mass spectrometry (ICP-MS) serve as the method of choice [136]. ICP-MS is a sophisticated multi-element analytical technique, capable of measuring levels to parts per trillion (ppt) using mass spectrometry to identify and measure positively charged ions. The testing methods occur in an extremely energetic argon plasma at approximately 6,000-7,000°C [138]. However, this method requires a solution technique, meaning any solid samples must be dissolved/digested before being analyzed. Most cannabis-related samples are solid materials, powders, concentrates and extracts, which invites several challenges. In addition, cannabinoid oils, which are mainly hydrophobic (not miscible with water), must also be digested prior to analysis.

As mentioned previously in the United States within the federal government exists the Environmental Protection Agency (EPA). The function of the EPA is to set federal standards for a variety of compounds and substances in terms of determining their presence in the environment, which includes the air, soil, ground water, lakes, and rivers. Over the past several years, based upon political influences, the minimum acceptable levels for a variety of substances such as heavy metals have been increased for no other reason than to reduced regulations without factoring the environmental impact. These changes come at the expense of potentially reducing the overall quality of air, soil, ground water, lakes and rivers, thus imposing potential harm to people (children and adults). As mentioned earlier in the discussion of sources of lead contamination, recent incidence of dramatically higher levels of lead present in the drinking water of those living in the Flint, Michigan area is an example of political incompetence when the politicians in the community changed the source of the community drinking water from Lake Michigan to the Detroit River, which was highly contaminated because of age of the lead pipes used to pump the water from the river. The rationale for the change was to reduce the overall costs of providing usable water for the community. Based upon the excessive negligence involved in this case, compensation costs to the citizens of the community has been in the hundreds of millions of dollars not to mention the total costs involved to completely remove and install a new water delivery system devoid of metal pipes of

Element	Maximum limit (edibles) mg/m	Maximum limit (inhaled) mg/g
Arsenic	1.5	0.2
Cadmium	0.5	0.2
Lead	0.5	0.5
Mercury	3.0	0.1

Table 1.
Heavy metal limits (cannabis & cannabis-hemp) by state of California [136].

Element	Maximum limit (soil) mg/kg	Maximum limit (plant) mg/kg
Cadmium	0.8	0.02
Chromium	100	1.3
Lead	85	2
Lead (water)	0.01/children, 0.015/adult	
Mercury	50	200
Nickel	35	10

Table 2.
Heavy metal limits according to the World Health Organization (https://www.who.int/ceh/capacity/heavy_metals.pdf?ua=1).

any kind. The long-term consequence of this unfortunate and unnecessary change on the overall sustained health of the community is yet to be determined.

In Europe the European Environment Agency (EEA), controls the level of pollutants such as heavy metals [139]. Regarding heavy metal emissions, across the 33 European countries the following is a short summary of recent achievements in the EU with respect to reducing heavy metals concentrations: (a) Since 1990 across all 33 countries, lead admissions decreased by 93%, mercury by 72%, and cadmium by 64%; (b) Reductions in levels of lead have occurred by 2004 due in part to the removal lead from gasoline; (c) Reductions in levels of mercury have occurred as the result of changes in energy use both in industries and other processes used in industry; and (d) Reductions in levels of cadmium are attributed to operational changes in industries across the board.

A remaining issue in a select set of areas of Europe is the continued presence of unacceptable levels of arsenic, cadmium, lead, mercury and nickel as the result of the presence of these substances still in the atmosphere [140]. The collective set of excessive metal excesses due cause local health issues, in part, because of the presence of localized industrial plants that release emissions of the pollutants. With that said, even though the emissions are concentrated in localized areas, this does not limit nor restrict the impact on health concerns because the pollutants are able to enter the food chain through ground soil and water contamination. Across the EU member countries there is the political will to do what is necessary and needed to sustain the momentum to continue to reduce pollutants in the environment.

4. Mitigation of the negative effects of these heavy metal materials

One could deduce that the presence of heavy metals in the environment combined with occupational exposure is a problem for human health. A pertinent question to ask then is "what can be done to reduce human heavy metal exposure?" Several remedies or actions can be considered that have been shown to be effective, they are:

a. Antioxidants - consume foods high in Vitamin C. Fruits and vegetables high in vitamin C can reduce the damage caused by heavy metal toxins by acting as an antioxidant. Vitamin C helps to convert toxins into a water-soluble form that can be easily eliminated from the body [141].

b. Porphyra. A logical approach would be to use naturally occurring organisms to monitor and remove toxic metals from aquatic systems. Such organisms could

be harvested at regular intervals, dried and disposed of as contaminated solid waste or used to recover valuable heavy metals. It is the feasibility and future optimization of this approach using marine macroalgae that forms the basis of the proposed studies. Bioavailability of heavy metals is highly dependent upon several environmental factors. Biomonitors utilizing plants growing under "natural" conditions where biotic and abiotic factors are intercalated reduces the need for making assumptions regarding bioavailability of metals. Plants themselves can alter the microenvironment around them, thus altering the amount of metals that are biologically available. Bulk water analysis may not measure the conditions at the membrane level where changes occur. Benthic plants can provide valuable information regarding past environmental conditions over weeks and months. This is particularly important in plants growing within the intertidal zones where the metal content of water may fluctuate continuously [142].

c. Integrated Processes. Addressing heavy metal pollution is one of the productive areas of environmental research. Despite natural existence, various anthropomorphic sources have contributed to an unusually high concentration of heavy metals in the environment. The central problem is often these metals are characterized by their long persistence in natural environment leading to serious health consequences in humans, animals, and plants even at very low concentrations (only 1 or 2 μg in some cases). Failure of restrict regulations by government authorities is also to be blamed for heavy metal pollution. Several individual treatments, namely, physical, chemical, and biological are being implied to remove heavy metals from the environment; but they all face challenges in terms of expensiveness and *in-situ* treatment failure. Hence, integrated processes are gaining popularity as it is reported to achieve the goal effectively in various environmental matrices and will overcome a major drawback of large-scale implementation. Integrated processes are the combination of two different methods to achieve a synergistic and an effective effort to remove heavy metals. Many of the articles published so far have focused on what individual methods are most effective to remove specific heavy metals concentrating on environmental exposure. Although integrated processes are being used in mediation of heavy metal extraction, there is still the need to determine the advantages and disadvantages of each integrated process. With that said, regardless of the method more research is necessary to determine what remediation method is most effective in reducing heavy metal concentrations in the environment [143].

d. Phytoremediation. Soil heavy metal pollution has become a worldwide environmental problem that has attracted considerable public attention. This attention stems largely from the increasing concern regarding the overall security of agricultural products. In this area, heavy metals refer to several metals and metalloids that possess toxicity on biological systems. The heavy metals of most concern are arsenic, cadmium, chromium, lead, and mercury. These metals pollutants enter the soil agricultural ecosystem through natural processes derived from parent materials and anthropogenic activities. As stated previously, heavy metal pollution poses a great threat to the health and well-being of all organisms not just human beings due to the risk of increased accumulation potential that takes place through bioaccumulation via the food chain. Remediation from heavy metal exposure using chemical, physical, and biological methods has been recommended to best solve the overall problem of toxic exposure in the environment. Phytoremediation has proven to be a promising alternative to conventional approaches as it is cost effective, environmentally

friendly, and esthetically pleasing. According to studies conducted, based on the natural ability of extraction, approximately 500 plants and other organisms have been identified as hyperaccumulators of one or more the heavy metals. In addition, further research integrating biotechnological approaches with comprehensive multidisciplinary research is needed to improve plant tolerance and reduce the accumulation of toxic metals in soils [144].

e. Other. As stated, heavy metals endanger overall human health. Of importance are the conditions especially when as the result of testing identifies heavy metal levels to be significantly above required standards for each. What still remains as an important factor regarding overall human health is that sustained elevated levels of heavy metals are indeed carcinogenic. The majority of studies performed designed to determine the pathway of heavy metal exposure that results in the carcinogenic effect of heavy metals in human exposure takes place via heavy metal contamination the overall food chain thereby impacting the quality agriculture, specifically the generation of agricultural products such as food and food by-products. In addition to the exposures that account for heavy metal contamination, there are additional factors that account for human exposure. This additional exposure can occur through the use of pesticides directly contaminating soil and also through waste-water run-off contamination. There are natural remediation methods that can help remediate areas of heavy metal contamination such as the presence of geological specific rock formations. With that said, it is still necessary to employ methods that address the heavy metal remediation especially when the sites of contamination are present in food products - fruits and vegetables. In addition, remediation of soil areas and water may also must be considered because these factors also contribute to heavy metal food contamination. Thus, it is imperative heavy metal remediation methods be used constructively in order to maintain overall public health [145].

5. Conclusion

The heavy metals have been shown to be responsible for a variety of human illnesses. These illnesses develop as the result of unwanted exposure whether by internal or external processes. One of the major health problems associated with heavy metal exposure is the development of a variety of cancers. The most common risk factors for developing cancer are exposure to heavy metals in the form of industrial based carcinogens, in cigarette smoke, and through foods consumed, thus via the diet. The toxicity associated with heavy metal poisoning can vary from minor conditions to major diseases, such as cancer. Both are capable of compromising overall human health. It is a fact that the major pathway responsible for human exposure, more often than not, is linked to both environmental and occupational exposure. Comparable studies have demonstrated higher levels of heavy elements, such as arsenic, aluminum, cadmium, lead, and nickel were present in cancerous tissue when compared and measured against non-heavy metal exposure in tissue from controls. Thus, limiting human exposure to heavy metals is sound public health policy; however, successful health policy must include cooperation from local, regional and national government agencies to develop, approve, implement, and then enforce those policies in order to reduce the links between heavy metal exposure and the major health concerns associated with exposure. The challenge seen for local, state, national and/or federal governments is to take these health concerns seriously and devise suitable and cost effective remedies to reduce the overall impact of heavy metals on the health consequences for its citizens.

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