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Chapter 1

Heavy Metals and Cancer

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Abstract

There has been increased concern surrounding exposure to heavy metals due to the evolving understanding of their role in the development of cancer. This review highlights research related to the impact that heavy metals aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel and radium have on human health. Research was collected through PubMed, and it was compiled to assess the current knowledge of exposure sources, types of cancers induced and therapeutic measures for these metals. Furthermore, it was designed to assist in guiding future research efforts with respect to heavy metals and cancer.

Keywords: heavy metals, carcinogenesis, exposure, treatment

1. Introduction

Exposure to heavy metals represents significant health concerns in the human population. These elements have the ability to induce a number of adverse health effects, but one of their more serious actions is their role in carcinogenesis. There exists a plethora of information on the research database, PubMed, regarding various exposure patterns and cancers induced by these heavy metals. However, this information has remained largely disconnected at this point, which necessitates the consolidation of this research. Our work reviews studies for how humans are exposed to heavy metals as well as what specific body systems are targeted.

2. Aluminum

Aluminum is a unique heavy metal with numerous pathways of exposure. Exposure to this element has been documented in contaminated food, vaccines to elicit a more powerful immune response and aluminum salts used in industrial processes and commercial products [1, 2].

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Specific commercial products containing aluminum salts include certain antacids and antiperspirant deodorants [1–3].

Aluminum exposure has been strongly correlated with carcinogenesis in the breast tissue. Mice subjected to $AlCl_3$, the same aluminum salt used in antiperspirant deodorants, displayed malignant growth of mammary gland epithelial cells [1]. This same result was observed in studies performed on samples of human breast cells [1–3]. This heavy metal was also hypothesized to have a role in the development of sarcomas [4]. Additionally, in one patient, it was proposed that the chronic exposure of aluminum containing heavy metal salts resulted in the development of an atypical neuroectodermal tumor [4].

There have been several determined mechanisms for the carcinogenic activity of aluminum. After exposing samples of human breast cells to this element, one study observed diminished concentrations of mRNA for the recognized tumor suppressor gene BRCA1 in addition to mRNA concentrations for other essential DNA maintenance genes [3]. Another study determined that subjecting human breast cells to aluminum had the potential to induce uncontrolled growth [2]. In this study, aluminum was observed to act as a metalloestrogen, which behaves as an agonist for estrogen receptors, and represents a known risk for carcinogenesis in the breast [2]. In another area of the body, analyzed samples of bladder carcinomas displayed statistically higher levels of aluminum, among other heavy metals [5]. Although a mechanism has not been established currently, this evidence suggests that this metal plays at least a supportive role in malignant growth in the bladder [5]. Standard therapy following aluminum poisoning has been the use of chelators. Aluminum in the human body has been demonstrated to bioaccumulate in soft and skeletal tissues, which are target areas for the removal of aluminum [6]. The common chelator used therapeutically has been desferrioxamine [6]. This chelator has proven effective in eliminating aluminum from the body; however, there are a number of toxic side effects associated with its use [6]. There have been several promising candidates to replace desferrioxamine, but none have proved to be as effective thus far [6]. The most successful method in limiting the toxic effects of aluminum is to reduce exposure to the metal. One potential solution for reducing public exposure is the use of reverse osmosis filtration. This technology has demonstrated the ability to remove significant levels of aluminum from copper mining waste at the experimental stage [7].

3. Arsenic

Arsenic is a cytotoxic element, and exposure to this metal presents serious risks to human health. Contact with arsenic generally results from ingesting contaminated food and water, occupational exposure and environmental pollution [8–11] Common occupations where arsenic exposure is common include smelting and arsenic based pesticide industries [12]. One noted source of environmental exposure to this heavy metal is contact with contaminated soil, which has the potential to enter the human food chain [13].

This heavy metal has been detected in an extensive variety of malignant growths. Research strongly supports role of arsenic in the development of lung, bladder and skin cancer [8, 11, 12]. Another study determined a strong positive association between exposure and mortality rates

of cancers including colon, gastric, kidney, lung and nasopharyngeal [13]. Epidemiological studies have also suggested an association between chronic low-level exposure to arsenic and development of pancreatic cancer and non-Hodgkin's lymphoma [14, 15].

Well-documented carcinogenic mechanisms for this heavy metal include generation of reactive oxygen species (ROS), epigenetic alterations and damage to the dynamic DNA maintenance system [8, 9, 12]. Key epigenetic changes induced by arsenic include alterations to the status of DNA methylation, histones, and miRNA, which are all changes that have the potential to cause malignant growth [9, 12]. Another study found that this toxic metal could induce inappropriate growth cycles for macrophages in addition to lung epithelial cells [16]. Furthermore, it was observed that macrophages exposed to ROS generated by arsenic responded by activating through the M2 phase, which is correlated with potential lung carcinogenesis [16]. Arsenic displayed a specific mechanism of action against human lung epithelial cells. This heavy metal was determined to alter the expression of the p53 protein, which resulted in decreased expression of p21, one downstream target [17]. The observed inappropriate proliferation was attributed to this mechanism [17]. Further examination of arsenic revealed its ability to reduce intracellular concentrations of glutathione, a natural antioxidant [18]. This carries the potential for carcinogenic activity by subjecting the cell to oxidative stress [18]. An additional carcinogenic mechanism proposed for this heavy metal lies in its ability to influence base excision repair [19]. The enzyme DNA polymerase beta was involved with this repair system, and arsenic was observed to inhibit its activity at high concentrations [19]. Another novel pathway for tumorigenic activity was discovered in human bladder cells. This study determined that chronic arsenic exposure had the potential to induce morphology changes and alter gene expression for proteins that regulate proliferation [20]. The use of chelators has remained the most effective way to eliminate arsenic from the body. Rac-2,3-dimercaptopropanol, or British anti-lewisite, contains two thiol functional groups, and it is one prominent chelator for this metal [21]. Although lacking clinical data at this point, 2,3-dimercaptopropane-1-sulphonate was used in one individual with acute arsenic poisoning [22]. This therapy resulted in successful treatment with limited side effects, which suggests the importance of future study [22]. Following arsenic exposure, dietary antioxidants have been recommended to mitigate carcinogenic effects of this metal, such as oxidative stress [23]. Developing novel prevention methods is essential for limiting human exposure. Rice and apple juice have been recognized as two common sources of exposure [24]. Safety standards of 5 μg/L of arsenic have been recommended for apple juice, due to its extensive ingestion by children [24]. Current research to limit its presence in rice includes genetic modifications to inhibit arsenic uptake, and the use of microbes that compete for arsenic in the environment [24]. It has also been observed that the use of sprinkler irrigation has the potential to significantly reduce the concentration of arsenic in rice by inducing its precipitation [24, 25].

4. Beryllium

Beryllium is a heavy metal that has uses in industrial processes and technology production. The primary environmental contamination source for this element is thought to be power plants, which leech beryllium in the form of dust [26, 27]. Due to inhalation being the

general method of exposure for this contaminant, current research is investigating its role in lung carcinogenesis [27–29]. There are mixed reviews supporting the extent of the role for beryllium in lung cancer, but recent research has determined a more significant correlation between the two [28–30]. Furthermore, an increased risk of lung cancer was observed in individuals exposed to exceptionally high concentrations of beryllium, which suggests that this element does induce some carcinogenic mechanism [29]. The use of beryllium in the dental industry creates additional occupational risk for exposure [29]. It was determined that the use of protective equipment significantly reduced the level of exposure in individuals [31]. Additionally, elevated concentrations of beryllium were detected in patients with stage III breast cancer [32]. However, beryllium was one of several heavy metals detected, so a defined role has not been identified at this point [32]. Exposure to beryllium is also recognized as a risk for the potential development of osteosarcomas [33].

Currently, there has not been much research relevant to beryllium's carcinogenic mechanisms. Most literature that exists now is related to action against the lungs. For instance, one potentially carcinogenic mechanism identified was its role in inducing a higher level of tumor necrosis factor alpha (TNF-α) cytokine secretion from CD4+ T-cells in the lungs [30, 34]. Both of these proteins have a role in the inflammation process, and their elevated presence was suspected to have action in chronic inflammation [30, 34]. Beryllium also has the potential to induce inappropriate genetic changes. For instance, this heavy metal was observed to methylate the *p16* gene, a known tumor suppressor gene, and induce its inactivation [30]. Chelators are common forms of therapy used to eliminate beryllium from the body and reduce its toxic effects. Relevant chelators include 4,-dihydroxy-1,3-benzene disulphonic acid disodium salt (Tiron) and D-penicillamine (DPA), which proved to be effective when tested in animals [35–37]. Also, the chelator meso-2,3-dimercaptosuccinic acid (DMSA) was used in a case study to successfully save a child suffering from heavy metal poisoning [38]. This result suggested potential clinical significance and requires further investigation [38]. There have been significant efforts to reduce exposure to this metal, especially occupational exposure [39, 40]. These efforts include company programs instituted to screen blood samples for beryllium sensitization during employment as well as providing refined ventilation and dust control to processes where exposure is common [40]. Attention was also given to educating employees about the importance of using protective equipment, and illuminating the potential risks involved with chronic beryllium exposure [39, 40].

5. Cadmium

Cadmium is an immensely toxic heavy metal, and it is associated with significant health implications as an environmental contaminant. Cadmium contamination generally results from emissions from industries that utilize this element including mining, metal research, development of certain batteries and preventing precipitation in pigments [41]. Soil pollution is a serious issue from cadmium emissions, and human exposure typically occurs from inhalation, smoking and ingesting contaminated food and water [41, 42]. Another source of environmental contamination is landfills, which have been observed to contain levels of cadmium exceeding safety standards in certain cases [43]. Additionally, ingesting this metal from contaminated food has been noted as a typical source of exposure [14, 44].

Exposure to cadmium has been associated with carcinogenesis in multiple tissues including breast, esophagus, stomach, intestines, prostate, lungs and testes [41, 45, 46]. Cadmium also has a proposed role in the development of cancer in the gallbladder. The composition of gallstones, which are recognized as a risk factor for carcinogenesis, were analyzed from patients with this type of cancer [47]. Statistically higher concentrations of cadmium, along with other heavy metals, were observed [47]. Although a causal link involving cadmium was not observed, it does suggest a potential role in malignant growth of the bladder [47]. Cadmium has also demonstrated carcinogenic activity on liver cells in a laboratory setting [44]. Additionally, increased concentrations of cadmium were detected in patients with malignant gliomas, suggesting a potential role of carcinogenesis in the brain [48]. Another organ where cadmium is suggested to exert carcinogenic influence is the pancreas [15, 49]. This metal also has a suspected association with the development of chronic myeloid and lymphoblastic leukemia. It was determined that, when compared to controls, patients with these forms of leukemia displayed significantly elevated concentrations of cadmium and lower levels of magnesium in blood and serum samples [50]. Further work with this metal determined that increased concentration of cadmium in urine was strongly correlated with risk of developing gastrointestinal cancer [51].

Similar to other heavy metals, carcinogenic mechanisms associated with cadmium include generation of ROS, epigenetic alterations, inhibiting DNA repair processes and apoptosis [41, 46, 52, 53]. It has been demonstrated that both chronic and acute cadmium exposure has the ability to induce changes in gene regulation, which generates an increased risk for malignant growth [44]. Key proteins that displayed upregulated expression include DNAJB9, a protein involved in regulating cell destruction, and metallothioneins [44]. Important regulatory proteins also displayed downregulated expression, such as EGR-1, a protein involved in regulating transcription [44]. There are not currently any standard therapeutic measures for the treatment of cadmium poisoning [54]. However, there is ongoing research to develop compounds that reduce the toxic effects of this metal. For example there has been research to develop unique peptoid ligands with selective affinity for cadmium [54]. It has also been determined that flavonoids, compounds present in most plants, have antioxidant properties and can chelate cadmium atoms [55]. Further study is recommended to determine how the structure of flavonoids relates to its action on cadmium [55]. There is also investigation into the use of stem cells as a therapeutic measure for cadmium induced damage. For one study, rat testes were subjected to damaging levels of cadmium [56]. Upon treatment with bone marrow mesenchymal stem cells, it was observed that the rat testes displayed more appropriate levels of proteins related to apoptosis regulation [56]. Additionally, these cells were determined to restore damaged testes tissue, and it was suggested that a possible mechanism is associated with mitochondrial apoptosis [56].

6. Lead

Lead is a toxic heavy metal and exposure constitutes significant risks to health. One common source of environmental pollution has been found in the soil, which can enter the human food

cycle through contaminated produce [57–59]. Despite being banned from use in commercially available gasoline in 1995, lead is still added to aviation fuel [59]. This source of environmental pollution has been determined to contribute high emission levels of lead [59]. It was also determined that smokers contained elevated levels of blood lead, representing an additional source of environmental exposure [60]. Certain occupations also play a role in lead exposure, such as mining [57].

Various epidemiological studies have been performed to determine if increased lead exposure is associated with any forms of cancer. Additionally, current research has indicated at this point that lead may not have a causal role in cancer, but it may play a more supportive role [61]. Along with cadmium, lead was detected in significantly higher concentrations in glioma patients, suggesting these two metals combined may produce excessively toxic effects [48]. One study has determined strong correlation between lead exposure and the development of kidney cancer [58]. Another study concluded that patients with higher levels of blood lead had an increased risk of developing renal cell carcinoma [60]. Lead was one of several heavy metals observed in statistically higher concentrations in gallstones [47]. This suggests exposure to this metal represents an increased risk of malignant growth in the gallbladder [47]. In a study performed on lead exposed workers, positive correlation was observed between exposure to this heavy metal and increased risk of carcinogenesis in lung tissue and marginal positive correlation for malignant growth in brain, larynx and bladder tissues [62]. Along with several additional heavy metals, lead was reportedly detected in elevated levels in individuals with exocrine pancreatic cancer, suggesting an unknown mechanism in the development of this cancer [15].

Current literature has not displayed a comprehensive understanding of carcinogenic mechanisms of lead; however, plausible mechanisms have been proposed. Based on the present understanding of lead, it was hypothesized to support the carcinogenic process by disrupting cellular tumor regulation genes, the DNA repair system and inducing DNA damage [63]. In a study performed on mice, there was evidence to support lead's role in generating ROS and altering chromosomal structure and sequence [63]. It was also determined that lead had the potential to disrupt the transcription process by replacing zinc in certain proteins that regulate this system [63]. In an epidemiological study, it was determined that elevated levels of serum calcium were correlated with lower risk of developing renal cell carcinoma, which suggested the need for a clinical trial to determine significance [60]. Chelation therapy is the recommended course of action for individuals with lead poisoning [64]. Common chelators for reducing levels of lead in the body include British, Anti-Lewisite, calcium disodium ethylenediaminetetraacetic acid, D-penicillamine and Meso-2,3-dimercaptosuccinic acid, and use of a specific chelator depends on the situation of the individual [64]. There has also been research into the effectiveness of less toxic therapies. For instance, when garlic was administered in a clinical setting, it was found to reduce blood lead levels in non-severe lead poisoning and alleviate symptoms [64]. The most effective strategy for keeping blood concentration of lead low is prevention of exposure [58]. This includes ensuring that industries that generate significant levels of lead emissions and employees follow safety guidelines for limiting exposure [64]. It has also been suggested that identification of lead contamination

sources, followed by removal or avoidance, constitutes the ideal solution to reduce exposure to this heavy metal [64].

7. Mercury

Mercury is another toxic heavy metal with the potential for serious health complications. Although this element can be found in trace amounts in mineral form, most present in the environment is due to human induced pollution from processed mercury [65]. Mercury has a wide range of uses that result in occupational and environmental contamination. Several sources of this heavy metal have been identified as thermometers, fossil fuel emissions, dental fillings, certain batteries and burning medical waste [65, 66]. Mercury compounds have the potential to be vaporized and enter the atmosphere or leech into soil or water systems [65, 67]. Consuming large quantities of seafood has been identified as a primary method for environmental exposure to methyl mercury [65]. Although the pathway through which mercury enters the ecosystem has not been discovered, bioaccumulation of this heavy metal has been observed in shellfish and tuna [65, 68, 69].

Although a causal role has not been established at this time, it has been proposed that mercury exposure may be associated with renal cancer due to this organ being a target for this element [65]. Another study observed that increased mercury exposure has been correlated with liver cancer, and it also has the carcinogenic potential to induce gastric cancer [70]. Mercury was another heavy metal detected in gallstones in statistically higher concentrations from patients with gallbladder cancer [47]. A causal association was not observed with this metal, but a role in carcinogenic development was hypothesized [47].

Comparable to most of the other heavy metals discussed in this study, mercury has the potential to induce malignant growth through several specific mechanisms. These include the ability to generate free radicals as well as disrupt DNA molecular structure and the maintenance system [66]. However, there have been several proposed carcinogenic mechanisms of mercury that are either unique to this metal or not observed in most heavy metals. One mechanism that enhances the carcinogenicity of mercury is its role in reducing the body's concentration of glutathione, a natural antioxidant [71]. This could potentially contribute to increasing susceptibility of essential cellular components to oxidative stress. Oxidative stress on cells has been shown to elevate rates of lipid peroxidation, another mechanism associated with carcinogenesis [65]. It has also been proposed that mercury can affect the microtubules in cells, which, among other processes, can disrupt cellular division [66]. The use of chelators is the common therapeutic strategy for eliminating mercury from the body. It has been determined that the two most effective chelators in a clinical setting are dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS) [72, 73]. There has also been research to investigate untested chelators for their effectiveness against mercury. For instance, deferasirox and deferiprone were combined and tested on rats [74]. It was observed that this combination was able to successfully chelate mercury and reduced toxic effects of mercury [74]. One unique experimental chelator was thiol-modified nanoporous

silica material [75]. Following animal testing, it was observed that this material displayed tremendous potential for eliminating mercury, along with several other heavy metals, with marginal toxicity [75].

8. Nickel

Nickel, a heavy metal present in Earth's core, has garnered research attention due to increased understanding of carcinogenic properties. This metal can produce toxic effects upon exposure in an environmental or occupational setting. Several industries involving potential occupational exposure to nickel include mining, metal alloys and the refinement of nickel [76–78]. Pollution of this heavy metal can enter the environment and bioaccumulate in organisms that enter the human food chain, such as fish [79]. Contaminated soil represents another method of contacting this toxic metal [76]. Emissions from oil refineries have also been established as a significant source of nickel pollution, creating risk for environmental exposure to residents in close proximity [80].

There are a variety of cancers that have been associated with nickel exposure. Epidemiological studies have revealed a significant correlation between exposure and the incidence of carcinogenesis in lung, nasal and sinus tissues [13, 77, 81, 82]. In another study, high levels of serum nickel were determined to be statistically significant in patients with breast cancer, suggesting that exposure has potentially carcinogenic consequences [83]. Exposure to this heavy metal has also been associated with the development of acute myeloid and lymphoblastic leukemia. It was determined that urine contained higher levels of nickel and 8-hydroxy-2′-deoxyguanosine in children with this leukemia [84]. These results suggested a role of nickel in acute leukemia by inducing oxidative damage as a mechanism of action [84]. Research has also revealed the presence of elevated nickel concentrations in individuals with exocrine pancreatic cancer [15]. Although there were other heavy metals present, these findings suggest carcinogenic action from nickel [15]. Another study proposed a link between chronic allergic stimulation from several heavy metals, including nickel, and the development of cutaneous T-cell lymphoma [85]. Furthermore, significant correlation was observed between exposure and mortality rates of liver cancer [13].

Nickel has an extensive range of carcinogenic mechanisms. One such mechanism involves its role in affecting the expression of specific long noncoding RNAs. It has been determined that nickel possesses the ability to induce the downregulation of maternally expressed gene 3 (MEG3) through the methylation of its related promoter [81]. This process was shown to inhibit expression of PHLPP1 and upregulate hypoxia-inducible factor-1α, two proteins recognized for their role in carcinogenesis [81]. It has also been demonstrated that nickel can generate free radicals, which contributes to the carcinogenic process [86]. Exposure to this heavy metal also has the ability to alter the regulation status for the transcription of various mRNAs and microRNAs [78]. The expression of these transcripts has roles in immunity as well as inflammation, which both have proposed roles in the development of malignant growth [78].

The role of nickel in chronic inflammation was investigated in animals and samples of human cells. It was concluded that exposure elevated expression of proteins SQSTM1 and TNF, which have roles in maintaining levels of inflammation, and induced carcinogenesis [82]. Like other heavy metals, nickel has the potential to induce epigenetic changes such as alterations in DNA methylation. For instance, it was observed that nickel ions (Ni2+) had the potential to induce the tri-methylation of histone H3K4 [87]. This process has been correlated with inappropriate transcriptional activation, which suggests another carcinogenic mechanism for nickel [87]. Compared to other heavy metals, the use of chelators involving nickel has been markedly different. Sodium diethyldithiocarbamate has proven to be an effective chelator in response to nickel carbonyl, but a chelator associated with nickel cancer has not been recommended at this point [88]. Despite this fact, there has been research into the use of chelators to remove nickel from the environment. For instance, it was observed that ethylene diamine tetraacetic acid (EDTA) induces the uptake of nickel from contaminated soil in *Arundo donax* L. [89]. This carries tremendous potential for use in areas where nickel is present in dangerous concentrations. It was also determined that CaNa(2) EDTA reverses the damage induced by nickel chloride as well as eliminate the metal from Cirrhinus mrigala [90].

9. Radium

Radium is a radioactive heavy metal that can negatively impact health. This ionizing radiation results from radium decaying into toxic radon gas [91]. Occupational and environmental presence of radium generates opportunities for exposure to ionizing radiation. Coal mining has been noted as one of the most relevant occupations with risk for exposure [92]. Wastewater drained from mines also carries potential for environmental radium contamination [92]. Radium presents further occupational hazards from exposure sources that include soil, building materials and water systems [93]. A study performed in Italy suggested radon gas tends to concentrate in confined spaces of buildings, such as basements or storage areas [91]. Due to radon's ability to bind to cigarette smoke, it was observed that this act increased the accumulation of radon inside buildings [93]. This suggests that smoking increases radium's impact as an environmental contaminant.

Radium is a known carcinogen that is associated with several cancers. Since a primary method of exposure to radon gas has been identified as inhalation, radium has been strongly correlated with the development of lung cancer [91]. Due to the radioactive nature of this metal, chelators are generally not necessary. Nevertheless, it has been determined to have several unique uses. For example, radium has been used as a therapy for patients with ankylosing spondylitis. However, injection of this metal was determined to be associated with increased risk of various forms of leukemia [94]. Injection of mice with radium was determined to cause the generation of osteosarcomas [94]. In another particular case, it was proposed that a patient developed a cutaneous squamous cell carcinoma in response to treatment with radium-223 that extravasated [95]. This study suggested that patients with extravasated radioactive substances require the oversight of a dermatologist [95].

10. Conclusion

Heavy metals exhibit an immense range of toxic effects in humans with regard to carcinogenesis. The research available at this point has illuminated several areas of emphasis for future work. It is clear that a refined understanding of carcinogenic mechanisms is necessary. This could help generate personalized therapeutic or prevention measures for specific heavy metals. Continued consolidation of information is another essential factor moving forward. Effective educational programs are also needed in high-risk areas to raise awareness of the risks associated with exposure to heavy metals.

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