

Exposure and Toxic Effects of Chromium on Human Health: A Review

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Abstract-Chromium (Cr) metal and Cr compounds are primarily used in applications like making stainless steel, polishing, and leather tanning. Chromium naturally occurs in air, water, rocks, and soil, via natural or anthropogenic sources. It exists in different oxidation states ranging from +6 to -2. The most stable forms are the trivalent Cr(III) and the hexavalent Cr (VI), which are interconvertible with each other. Chromium is an important trace element for human beings as it stimulates the breakdown of fatty acids and cholesterol. However, if exposed to a higher dose of chromium particles for a longer period, it can lead to human health toxicity and fatality. It is introduced into the environment through chemical and physical processes or even by biological transport systems in living organisms. Over the past decades, chromium contamination has become a significant threat with a negative influence on the environment, especially soil and water, and its accumulation affects human health, plant metabolism, and animal tissues. By gathering information from various published literature, we have highlighted the adversities caused by Chromium toxicity, for example, acute and chronic toxicity among human beings like carcinogenic potential, apoptosis, oxidative stress, and DNA adducts. This review focuses on the complex chemistry of chromium, its exposure routes, and hazardous effect of chromium on human health, and the mechanism of chromium toxicity upon entering the cells. Therefore, it is now important to investigate and develop various useful sustainable remediation strategies to balance and reduce the increased levels of chromium in the environment.

Keywords: Chromium, carcinogenesis, human health, toxicity, DNA adducts.

I. INTRODUCTION

Heavy metals are compounds that are naturally occurring metals that have a high atomic weight and density five times that of water. Heavy metals are widely used in industries, businesses, households, agriculture, and healthcare sectors, resulting in a wide range of distribution in the environment. Due to their increased concentration and numerous exposure routes, most heavy metals have been reported to become hazardous. Among these, Chromium is highly toxic to the environment and human beings. According to the International Agency for Research on Cancer (IARC), Chromium is placed as a group 1 carcinogen and is pervasive in the environment (IARC, 1980) (National Toxicology, 2002).

Chromium is a transition metal that has 7 oxidation states, with the metallic Cr(0), trivalent, and hexavalent states being the most stable and prevalently found in the environment and industrial areas (Zhitkovich, 2011). The anthropogenic release of chromium in the environment has caused global exposure of chromium and accumulation by the inhalation of contaminated air, or ingestion by contaminated water and food (Pellerin & Booker, 2000; Bhattacharya, et al., 2019).

Trivalent chromium is present in food and dietary supplements and is widely used by the general population all over the world. Many reports have proved that there is no such significant dietary use of Trivalent chromium, hence proving that it is not essential for human growth, therefore it always becomes a necessary question whether trivalent chromium must be included in nutritional diets or gym products, etc (National Toxicology, 2002; IARC, 1980).

Cr (III) has the capability of entering the food chain as it is a part of the human diet (Uddin, et al., 2007). Various industrial settings and processes use chromium namely metal refining, chrome plating, leather tanning, stainless steel production, chemical dye manufacturing, etc (Wilbur, 2012). These industrial settings are the main cause of the production and release of Hexavalent chromium in the atmosphere and the hydrosphere (Vimercati, et al., 2017). Many reports have documented that workers in these industries are more prone to occupational illnesses due to the higher exposure level than the general population (National Toxicology, 2002). Because chromium-containing substances cause inherent toxicity and carcinogenicity, the US Environmental Protection Agency and US Occupational Safety and Health Administration have determined exposure limits of 100µg/L of total

chromium for standard drinking water and $5\mu\text{g}/\text{m}^3$ of Cr (VI)- timed weighted average for a normal work day (Wilbur, 2012). In this literature, we have highlighted the health risks in humans caused by hexavalent chromium and the several routes of exposure in the human body for both non-occupational and occupational populations in discussed in detail, we have compiled the most recent data acquired from published sources.

II. EXPOSURE ROUTES OF CHROMIUM IN HUMANS

According to the CDC (Control, 2013), the entry of chromium into the human body is through the skin, inhalation, and ingestion as mentioned in Figure 1. However, a substantial proportion of exposure in the general population occurs through the ingestion of contaminated drinking water and edibles. Also, the main route of exposure for the general population is by ingestion. As stated by Wilbur (Wilbur, et al., 2012), in people exposed to Cr occupationally, the route of exposure occurs through inhalation or skin absorption. Skin absorption chromium exposure is not considered carcinogenic; nonetheless, when the body meets chromium-containing substances, it can penetrate the skin. Cr (VI) can leach into the skin faster than Cr(III) since it has high solubility in water (Coetzee, et al., 2018). According to a study, some Cr(VI) are capable of forming burns on the skin due to their corrosive nature (Guertin, 2004).

Chromium exposure by inhalation is by the air, in which Cr exists in the form of fumes, aerosol, and dust particles. A study conducted by WHO revealed that the daily intake of chromium through inhalation is ($<0.2-0.6\mu\text{g}$) approximately (WHO, 2003). Chromium is highly non-volatile. Chromium can linger in the lungs for years and become a probable cause of cancer. About 53-85% of Cr enters into the lungs and gets absorbed (Guertin, 2004; ATSDR, 2015). It causes nasal infections, asthma, bronchitis, and respiratory problems. Ferrochrome production and chromite plating workers are more prone to cancers caused by Cr (VI) inhalation (Coetzee, et al., 2018).

Chromium exposure by ingestion is the most common route for the general population, nevertheless, children are mostly exposed to chromium because of contaminated dirt particles. According to an investigation, it is reported that an elevated amount of Cr (VI) (0.06-156g/L) in breast milk was observed, implying that exposure is also possible through breast milk (Casey & Hambidge, 1984; ATSDR, 2015). Some

fruits, meat, and vegetables also contain high levels of chromium. Some utensils can also introduce Cr (VI) into food and drinking water with a Cr concentration of more than 25g/L can cause chromium poisoning (Coetzee, et al., 2018). After Cr (VI) enters the body through contaminated food and water, gastric juices convert Cr (VI) to Cr(III) and only 2-3% of Cr enters into the gastrointestinal system (Guertin, 2004). However, there is not much evidence about chromium being carcinogenic when ingested, yet some literature has mentioned an increase in gastrointestinal complications related to Cr (VI) in Chromium contaminated areas (Sharma, et al., 2012). Cr (VI) compounds can induce stomach and intestinal ulcers as stated by the Agency for Toxic Substances and Disease Registry (ATSDR, 2015).



Figure 1 Various routes of exposure to Chromium in human beings

III. MECHANISMS OF CHROMIUM TOXICITY

The chemical composition of chromium plays a significant role in its cellular entry and toxic effects. Cr (VI) is mostly found in the environment as the chromate oxyanion (CrO_4). Since the Chromate oxyanion is structurally identical to the sulfate oxyanion (SO_4), it enters the cell through the generic sulfate transporters present on the cell surface (Bagchi, et al., 2001). Once within the cell, Cr (VI) causes toxicity after being reduced by ascorbate and thiols like glutathione or cysteine amino acid residues (Zhitkovich, 2011; Quievryn, 2003). Hexavalent chromium is reduced to pentavalent chromium by glutathione by one-electron reduction, and with the same process, eventually, Cr (VI) is reduced to Cr (III) (Stearns, et al., 1995). This process of reduction by glutathione can produce hydrogen peroxide and other highly reactive free radical species leading to high levels of oxidative stress, causing cell damage, DNA damage, protein degradation, etc (Bagchi, et al., 2001; Salmikow & Zhitkovich, 2008). Moreover, the addition of ascorbate

back in the cell induces DNA strand breakage and the formation of DNA Adducts comprising Cr (III) cross-linked with ascorbate, cysteine, Glutathione, or histidine (Zhitkovich, 2005; Martin, 2006; Reynolds, 2007). These differently impaired DNA adducts cannot be easily repaired and therefore become the main factor in inducing Chromium mutations in cellular transformations (Quievryn, 2003).

Cr(VI) not only induces Oxidative stress but also causes autophagy and apoptosis (Yan, et al., 2023). It can also trigger pyroptosis, Cr (VI) elevates inflammation markers in the human bronchial epithelial cells like (BEAS-2B), TNF-, and COX-2 as stated by (Roy, et al., 2016). A study was conducted in 2019, which proved that Cr (VI) induces the pyroptosis of DF-1 cells, and the mechanism of interaction is potentially connected to CaSR activation (Zhu, et al., 2021). Several studies conducted on chicken and mice of chromium exposure triggered oxidative pathways and led to the loss of their biological functioning (Scharf, et al., 2014).

To summarize, hexavalent chromium entrance into the cell causes several reactions like oxidative stress, apoptosis, and autophagy, and their responses are closely linked, Yet the mechanism of action of these linkages is still not understood and requires deep and critical research.

IV. HEALTH EFFECTS OF CHROMIUM

Chromium's biological adverse effect is heavily dependent on its redox potential (Pradhan, et al., 2017; Bharagava & Mishra, 2018). Cr (III) is a trace element that is required in the human diet and is nontoxic at low levels. Cr (III) picolinate is a common dietary supplement (Tumolo, et al., 2020). It enhances insulin activity functioning as receptor binding and decreases the risk of diabetes mellitus as stated by (Shanker, 2019) (Son, et al., 2018). As a result, its deficiency can cause problems related to glucose metabolism (Pellerin & Booker, 2000). Considering the absorption value of 25%, the daily need for absorbable Cr (III) is estimated to be 0.5-2ug according to the study by Nordberg (Nordberg & Cherian, 2013). Nevertheless, exceeding the permissible amount of Cr (III) may result in long-term adverse toxicity and may induce carcinogenesis or cellular damage (EFSA, 2010).

Hexavalent chromium is known to be the most hazardous type (Pellerin & Booker, 2000), causing kidney and liver damage, and cellular and respiratory

damage. Cr (VI) can enter the cells by air, through the skin, through drinking water, and through contaminated food. Even if our body has defense mechanisms like saliva, gastric juice, bacteria, and humoral and cell-mediated immunity due to B and T cell receptors, the toxicity of Chromium depends on the exposure, doses, and the duration spent in its exposure (Pellerin & Booker, 2000; Korallus, et al., 1984; Ray, 2016).

A study conducted by Korallus (Korallus, et al., 1984) displayed that the human plasma could spontaneously convert Cr (VI) ions of 2mg to Cr (III) and that this capability may be improved by assuming ascorbic acid. However, the intake of Cr (VI) over plasma and red blood cell lowering capacity produces hematological alterations (Ray, 2016). Similarly, greater doses of Cr (VI) suppress the phagocytosis of alveolar macrophage and the humoral immune response (Shrivastava, et al., 2002).

Likewise, there is a considerable amount of literature justifying the health consequences of the several routes of exposure for Cr (VI). Many studies have stated that chromium exposure has been linked with adverse respiratory effects (Osman, et al., 2019). The amount of Cr (VI) inhaled at industry sites can induce lung cancer. Prolonged inhalation exposure can cause damage to the nasal septum, creating ulcers and perforations, bronchitis, asthma, pneumonia, discomfort, reduced oxygen uptake, and soreness (Saha, et al., 2011). Concerning skin absorption, chromium can cause dermatitis, ulcers, burns, etc (Pellerin & Booker, 2000; Fowler, et al., 1999). According to several studies, ingestion is the most common route of exposure leading to kidney failure, reduced immune response, and gastrointestinal infections (Ray, 2016) (Shrivastava, et al., 2002). Ingesting up to 2gm of hexavalent chromium can cause kidney damage but ingesting 2-5g of soluble Cr (VI) can be lethal to human beings (Sharma, et al., 2008). **Table 1** provides the necessary information on Chromium (VI) and its health effect on humans, it has been gathered from various published sources depicting the level of exposure: Acute (less than 14 days), Intermediate (up to 15-365 days) and Chronic (more than 365 days). (ATSDR, 2000).

Table 1 Overview of Chromium exposure and health effects on humans and animals

Cr(VI) dosage per day(in	Expo sure level	Effect on Human body	Refere nces
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mg/kg /day)			
37	Chronic	The lowest recorded dosage causes growth issues in mice.	(Gerald, 2011)
13.5	Intermediate	Kidney damage inhibits membrane enzymes in rats	(ATSDR, 2015)
7.8	Intermediate	Adversely affects hematological sites in mice.	(Gerald, 2011)
3.5	Chronic	Cause cytoplasmic damage and hepatocytes in mice.	(ATSDR, 2000; Gerald, 2011)
0.57	Chronic	The lowest dosage recorded for causing abdominal pain, vomiting, and damage of leukocytes in humans.	(ATSDR, 2000)
0.036	Acute	Skin contact dermatitis in humans.	(ATSDR, 2000)

V. CHROMIUM CARCINOGENICITY

Hexavalent chromium has also been linked with causing carcinogenicity in animal tissues and the human body, also Prolonged or excessive exposure to Cr (VI) can raise the risk of cancer. Long-term exposure and higher levels of exposure to chromium-containing compounds can raise the risk of developing lung, stomach, blood, and pancreatic cancers in human beings (Yan, et al., 2023). In a study conducted in 1987 in Liaoning Province, China, Researchers investigated the link

between CR and Cancer. Statistics indicated that the mortality rate of patients with stomach cancer was higher in Liaoning Province between 1970 and 1978 than in the surrounding uncontaminated areas (Beaumont, et al., 2008). Moreover, the death rate due to lung cancer also increased in the chromium-contaminated area (Jomova & Valko, 2011). Similarly, workers exposed to Cr (VI) have an estimated 7.00% greater risk of cancer and an increased risk of respiratory disease when compared to the entire general population of the same age and sex (Deng, et al., 2019).

Similarly, A National Toxicology Program (NTP) conducted a two-year drinking water study in which male and female rats were exposed to sodium dichromate dihydrate which increased the incidence of squamous cell neoplasms of the oral cavity (NTP, 2008). There was also an increase in the incidence of neoplasms of the small intestine (NTP, 2008). Therefore, these results suggested that Cr (VI) may act as a potential carcinogen, thereby raising concerns for the general population exposed to Cr(VI) (Chen, et al., 2019). Studies have proved that molecular mechanisms including ER stress and DNA damage are the main reasons leading to carcinogenic activity (Chen, et al., 2019).

VI. CHROMIUM DNA ADDUCTS

Cr(VI) has long been acknowledged as a genotoxic chemical. Numerous published pieces of literature have described its potential for genotoxicity (Flora, et al., 1990). Oxidative stress, chromium DNA adducts, DNA strand breakage, and other chromosomal abnormalities are all examples of chromium damage. The chemical complexes form when a chemical attaches to a biological molecule like DNA, RNA, or protein, and then that complex is known as an adduct.

According to many sources, Chromium has been shown to form Cr-DNA adducts, Cr-DNA crosslinks, or Cr-protein adducts, all of which can cause DNA polymerase arrest, mutations, and alterations in the gene expressions (Singh, et al., 1998). Moreover, the repair of such defects can result in DNA single-strand breaks (SSB) and Double-strand Breakage (DSB). And it is a tedious task to isolate and detect particular Cr-DNA adducts. Cr (VI) can generate bulky Cr (III) binary adducts as well as ternary adducts during intracellular reduction. Cr (VI) reduction occurring due to ascorbic acid indicates that ternary ascorbate-Cr(III)- DNA crosslinks are more mutagenic than binary Cr-DNA

crosslinks, with ternary complexes accounting for more than 90% of mutagenic defects (Quievryn, 2003).

Despite the heavy and detailed work being done at laboratories and various research institutions, the detection and mechanism of the Cr-DNA adduct is not well known in detail. Existing measures of assessment rely on isolating DNA and determining the amount of Cr linked with DNA through quantitative analysis techniques. As a result, whether Cr binds directly to DNA bases or just electrostatically associates with the phosphate remains unknown. Even though there is no such specific answer to this yet, it may provide some scientific input, the ultimate summary is that Chromium's relationship with DNA; whether causing a permanent alteration or a complex(adducts) is significant as such interactions lead to severe consequences like DNA strand breakage through lesions or mutagenesis, dimer formation, chromosomal aberrations (Wise, et al., 2008).

CONCLUSION

The prime aim of the review was to investigate the routes of exposure as well as the negative health impacts of chromium on human beings. While surveying various literature, this study revealed that entry of chromium into the human body occurs majorly through skin absorption and inhalation or ingestion of contaminated drinking water and food. The adverse health impacts on human beings of various ages have been reported to occur through different mechanisms depending on the oxidation state of the chromium, As stated earlier Cr (VI) is more toxic and induces carcinogenicity when exposed to high doses for longer periods, whereas Cr (III) is less toxic, and is usually introduced in dietary supplements to the human body. But the problem arises when Cr (VI) reduces into Cr(III) with the help of ascorbate and forms Cr-DNA adducts or Cr-DNA crosslinks, inside the cell leading to intracellular chromium toxicity through the formation of free radicals. Cr (VI) is a frequently utilized heavy metal, and its pollution has become a global concern. It is fatal to plants, animal tissues, and humans in numerous ways. Cr (VI) is capable of inducing oxidative stress, apoptosis, and autophagy, but the mechanisms are not known in much detail. Therefore, this gives us a heading that learning about chromium toxicity mechanism should become our next stage in research. Furthermore, researchers have employed a wide variety of practical approaches to reduce Cr (VI) from the surroundings, but each strategy has its pros and cons. As a result, combining all these approaches we must now look at

feasible, cost-effective, and efficient practices to decontaminate our environment from these toxic heavy metals.

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