Toxic and Carcinogenic Activity of Heavy metal Chromium in respect to Animals and Humans

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***Abstract*: Chromium is a common environmental pollutant because of its toxicity. Hexavalent chromium is a group 1 carcinogen that causes cancer through a variety of intricate processes. Chromosome breakage, increased oxidative stress, and DNA adduct production are a few of the main ways that Cr (VI) damages cells. The last century's industrial activities have significantly increased human exposure to heavy metals. Apoptosis, damage-repairing mechanisms, growth, proliferation, differentiation, and other cellular functions are all interfered with by heavy metals. When the methods of action of metals are compared, they are found to have comparable mechanisms of action, which include oxidative stress, ROS production, antioxidant defense weakness, and enzyme inactivation. This review will offer current research on both humans and animals to address the possible negative effects of exposure to Cr.**

***Keywords*: Chromium, Carcinogen, Cellular damage, Heavy metal, Animal study.**

INTRODUCTION

Global human health is greatly affected by the dispersion of metals in the environment. For example, chromium (Cr) is a transition metal with seven oxidation states (0eVI), the most common of which are metallic (Cr(0)), trivalent (Cr(III)), and hexavalent (Cr(VI)). According to the International Agency for Research on Cancer (IARC), chromium is a group 1 carcinogen and is found in many parts of the environment **(Zhitkovich, 2011).** Toxic metal contamination of air and water is a global environmental problem that affects hundreds of millions of people **(Uddin et al., 2007).** The health of humans and animals is also concerned about food contamination with heavy metals. In this context, the concentration of heavy metals in food, air, and water resources is evaluated **(Mousavi et al., 2013; Luo et al., 2021).**

The discovery of many metals as potential human carcinogens represents yet another significant facet of chronic exposure. Abnormal alterations in the genome and gene expression are proposed as the underlying cause, albeit the precise mechanism is unknown. Arsenic, cadmium, and chromium are examples of carcinogenic metals that can interfere with DNA synthesis and repair **(Koedrith et al., 2013).** Heavy metal toxicity and carcinogenicity are dosage dependent. According to **Gorini et al. (2014),** high-dose exposure generates severe reactions in both humans and animals, which increases DNA damage and neuropsychiatric problems. Similar mechanisms often involve the production of reactive oxygen species (ROS), the inactivation of enzymes, and the inhibition of antioxidant defences in the harmful mechanism of heavy metals. However, certain ones selectively bind to particular macromolecules and produce toxicities in a specific way. Our understanding of the detrimental effects of heavy metals on bodily organs has increased due to their various toxic mechanisms, which has improved the treatment of poisonings in humans and animals. Our goal was to review the literature on the toxicity mechanisms related to heavy metals, particularly Cr (chromium), in order to better understand how these metals affect the body's organs and treat metal poisonings.

CHROMIUM (Cr)

Cr (III) is needed in trace amounts for normal lipid and protein metabolism as well as acting as a cofactor for insulin action, Cr (VI) is linked to a number of illnesses and disorders **(Vincent, 2019).** Hexavalent chromium is categorised as a group I occupational carcinogen according to the International Agency for Research on Cancer (IARC, 2018) study **(Loomis et al., 2018).** According to **Deng et al. (2019),** a meta-analysis of 973,697 workers with 17 standardised incidence ratios (SIRs) from seven different countries and four different types of jobs revealed that 11,564 of them had cancer. For non-occupational human populations, consuming food and water containing chromium or coming into touch with chromium-containing goods through the skin are the main routes of exposure **(Nickens et al., 2010).** Moreover, a significant quantity of Cr is released into the soil, ground water, and atmosphere by the metallurgical, refractory, and chemical sectors. This leads to health problems for humans, animals, and marine life **(Fang et al., 2014).** Because of its bioaccumulation in the human body, Cr can lead to a wide range of illnesses. This includes disorders of the skin, kidneys, nervous system, and gastrointestinal tract in addition to the emergence of various cancers of the lungs, throat, bladder, kidneys, testicles, bone, and thyroid **(Fang et al., 2014).**

ANIMAL STUDIES

Wang et al. (2012) studied the carcinogenicity of Cr (VI) using a mouse model of colorectal cancer. It was discovered that tumour incidence and size increased with exposure to Cr. It was mediated by the ROS-induced Wnt/betacatenin signalling pathway **(Wang et al., 2012).** Reactive nitrogen species (RNS) and ROS interactions with cellular macromolecules such proteins, lipids, and DNA are thought to be one of the primary factors contributing to toxicity and the advancement of cancer after exposure to Cr **(Aggarwal et al., 2019).** Potassium dichromate was given intraperitoneally to Sprague-Dawley rats in one study by **Patlolla et al. (2009)** for five days at doses of 2.5, 5.0, 7.5, and 10 mg/kg body weight per day. It was revealed that there was a dose-dependent increase in superoxide dismutase and catalase activity in addition to a significant increase in ROS and malondialdehyde levels in the liver and kidney. Moreover, DNA damage was noted in a dose- and time-dependent manner 24, 48, 72, and 96 hours following treatment **(Patlolla et al., 2009).** According to **Salama et al. (2016),** intranasal exposure to low doses of Cr in Albino Wistar rats was associated with a significant risk of brain injury. Higher Cr concentrations also led to pulmonary damage. Interleukin-1β (IL-1β), phosphorylated protein kinase B (PKB), and cyclooxygenase 2 (COX-2) were the oxidative stress biomarkers that increased in response to a 2 mg/kg intranasal potassium dichromate **(Salama et al., 2016).**

HUMAN STUDIES

According to the findings of a recent meta-analysis, exposure to Cr (VI) may raise the incidence and death rate of many malignancies in humans, including those of the lung, throat, bladder, kidney, testicles, bone, and thyroid **(Deng et al., 2019).** A 2012 Indian study found that people who were exposed to groundwater contaminated by Cr (VI) had higher rates of gastrointestinal and dermatological problems **(Sharma et al., 2012).** It is acknowledged that Cr toxicity and carcinogenicity are caused by DNA damage, genomic instability, and ROS production. ROS can be produced by Cr (VI) and Cr (III) as well **(Pavesi and Moreira, 2020).** Following Cr carcinogenicity, transcription regulation disruption causes damage to DNA. According to **Urbano et al. (2012)** and **Thompson et al. (2013),** Cr-induced DNA damage comprises p53 point mutations, DNA-Cr-protein crosslinks, DNA inter/intrastrand crosslinks, and single- and double-strand breaks (SSBs and DSBs, respectively). Nucleic acid binding by Cr (III) has been shown in-vitro **(Urbano et al., 2012; Fang et al., 2014**). Binary and ternary DNA adducts are formed by Cr (III). In mammalian cells, ternary adducts are more common and significant from a toxicological standpoint (**Zhitkovich, 2011).** Four forms of ternary adducts have been identified: Cr (III) glutathione DNA adduct, Cr (III) histidine, Cr (III) cysteine, and Cr (III) ascorbate. In human lung cancer cells (A549), Cr (III) creates DNA–protein crosslinks

(Macfie et al., 2010). As the replication fork collapses during DNA replication, SSBs and DSBs are detected in rapidly dividing cells, such as cancer cells. This activation of p53 causes cell cycle arrest and apoptosis **(Wilhelm et al., 2020**). A single injection of Cr (VI) produced SSBs in the liver and kidney of male albino mice in one investigation by Ueno et al., but no appreciable amounts of DNA strand breaks were seen in the spleen, lung, or brain **(Urbano et al., 2012).** Cr-induced carcinogenicity appears to be influenced by a number of variables, including tissue type, cell type, concentration of Cr (VI), exposure duration **(Ferreira et al., 2019),** production of free radicals, and reactivity of the intermediate Cr (V) and Cr (IV). The hexavalent cation interacts with cellular reductants to form Cr (V), Cr (IV), and Cr (III) rather than binding to macromolecules or DNA by itself **(Zhitkovich, 2011).** The DNA and lipid content of cells are the targets of Cr (VI)-induced oxidative stress and high levels of ROS generation, which cause DNA damage and lipid peroxidation, respectively. Furthermore, a variety of further cellular damage and cell death, including necrosis and apoptosis, may transpire **(De Flora et al., 2008).**

CONCLUSION

A number of pathways allow heavy metals to enter the body, including food, drink, air, and sometimes even skin contact. Heavy metals are retained in the body after absorption and build up over time. Hazardous consequences can arise from the bioaccumulation of hazardous metals on a range of bodily tissues and organs. Acute or persistent symptoms are possible in cases of metal toxicity. Apoptosis, damage-repairing mechanisms, growth, proliferation, differentiation, and other cellular functions are all interfered with by heavy metals. However, compared to inhalation treatment, oral exposure results in less Cr(VI) entering target cells because of the extracellular reduction of Cr(VI) to Cr(III) in the gastrointestinal tract. Any quantity of Cr(VI) that penetrates cells has the capacity to start the development of tumour. Hence, rather than total Cr, the levels of Cr in drinking water should be based on the hexavalent form in order to safeguard the entire population.

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