



Workplace Carcinogens: Metals

Part II: Detoxification of metals

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INTRODUCTION

Cadmium (Cd), chromium (Cr), arsenic (As) and nickel (Ni) are some of the most widely-studied heavy metals, for their roles in oxidative stress.¹ These metals are classified as Group 1 carcinogens to humans, according to the International Agency for Research on Cancer (IARC).² The major cancer sites are lung, bladder, skin, nasal cavity and sinuses. Together with environmental pollution that causes excessive exposure to heavy metals, occupational exposure increases heavy metal body burden. Detoxification methods should be investigated, and implemented as part of medical surveillance programmes.

OXIDATIVE STRESS

Oxidative stress is an imbalance between the production of reactive oxygen species (oxygen free radicals) and antioxidant defences.³ The balance between free radicals and antioxidants is essential for proper physiological function. A free radical is any molecule that contains an unpaired electron in an atomic orbital. Free radicals can derive from normal metabolic processes (endogenous) or from external (exogenous) sources, such as water, food or occupational exposure. Oxidative stress is associated with damage to a wide range of molecular species, such as lipids, proteins and nucleic acids.⁴

ANTIOXIDANTS

An antioxidant is a molecule stable enough to donate an electron to a free radical, thus reducing its capacity to damage.⁴ Antioxidants inhibit or delay cellular damage. Some antioxidants are produced during normal metabolism in the body, including glutathione, uric acid and ubiquinol. Vitamin E (α -tocopherol), Vitamin C (ascorbic acid), and B-carotene are antioxidants that the body cannot manufacture and which must be supplied in the diet.⁴

Cadmium

Cd is a highly toxic metal. It is unable to generate free radicals directly, but it indirectly generates various free radicals⁵ and can cause free radical-induced DNA damage, affecting gene expression.⁶ The effect of aspirin and Vitamin E on Cd toxicity was investigated on COS-7 cells; it was shown that they can protect cells from Cd-induced toxicity.⁷ Aspirin is an anti-inflammatory drug and this property allows it to partially reduce the cytotoxicity of hydrogen peroxide in cells, suggesting that it can function as an antioxidant.⁷ Vitamin E is classified into eight forms, referred to as tocopherols. α -Tocopherol is considered to be the most active compound and functions as a chain-breaking antioxidant, preventing free radical reactions.⁸

Chromium

Cr (III) is an essential trace element that plays an important role in regulating blood glucose levels. However, Cr (VI) is potentially toxic, and carcinogenic at high doses.² Until recently, it was believed that only Cr (VI) could penetrate cell membranes, but more recent models have considered the uptake of reduced species of Cr. Once inside the cell, Cr is able to generate free radicals.⁴ Vitamin C is a powerful antioxidant, converting free radicals to harmless molecules, and reducing Cr (VI) to Cr (III). When the reducing action of Cr (VI) to Cr (III) is extracellular, it is protective, but a series of studies has presented evidence that intracellular reduction of Cr (VI) by Vitamin C results in extensive Cr-DNA adducts.⁹ Inside the cell, Cr (VI) causes a wide variety of DNA lesions. Intracellular Vitamin C reduces Cr (VI) to Cr (V) and Cr (III). Cr (III)-mediated DNA cross-links of cysteine, histidine, glutathione and ascorbate represent a major class of DNA modifications.⁵ A recent study demonstrated that the toxicity of Cr (III) is largely dependent on the ligand when two dietary supplements, Cr (III)-picolinate and Cr (III) niacin, were compared. It was reported that Cr (III)-picolinate produces more oxidative stress and DNA damage than Cr (III)-niacin.⁶

Arsenic

As is a well-known poison and carcinogen.⁵ Many studies in humans have confirmed the generation of free radicals from As. As compounds bind to -SH groups and inhibit various enzymes. Studies support the hypothesis that As may act as a co-carcinogen – not causing cancer directly, but enabling other substances, such as ultra violet light and cigarette smoke, to cause DNA mutations. As is one of the few species other than vinyl chloride that causes angiosarcoma,⁵ and is a cardiovascular toxicant.¹⁰ As impairs mitochondrial function and increases apoptosis by promoting reactive oxygen species. The majority of antioxidants that counteract the toxic effect of As on mitochondria in cardiovascular tissue are phenolic compounds.¹⁰ Findings from studies on microsomal functions in liver and kidney cells provide evidence that Vitamin C and E supplementation can improve the As-induced altered microsomal functions.⁶

Nickel

Ni is a human carcinogen that can alter gene expression.⁵ Exposure to Ni can also result in elevated expression of the proteins, SQSTM1 and TNF, which play a role in maintaining levels of inflammation and induce carcinogenesis¹¹. Chelation therapy can also be used to reduce the toxic effect of metals. A chelating agent has the ability to form complex structures that are easily excreted, by removing metals from intracellular and extracellular



Vitamin E and C supplementation can improve As-induced altered microsomal functions in liver and kidney cells

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spaces.¹² The use of chelators involving nickel is different to that for other heavy metals; a chelator associated with Ni-induced cancer is not currently recommended.¹¹ However, research has been conducted to identify methods to remove Ni from the environment. It has been observed that ethylene diamine tetraacetic acid (EDTA) induces the uptake of Ni from contaminated soil,¹¹ which can be potentially beneficial as a control mechanism in Ni-contaminated areas.

CONCLUSION

Heavy metals exhibit a wide range of toxic effects on humans with regard to carcinogenesis. Research has made it apparent that antioxidants can play an important role in detoxifying free radicals. It is, however, important to understand the different carcinogenic mechanisms of each metal, as this could help to personalise therapeutic or preventive measures. Although antioxidants can assist with detoxifying the effects of metals, the main aim should be to implement sufficient control mechanisms to prevent exposure to these carcinogens in the workplace.

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