Chromium (III & VI) toxicity

It works well in practice, but how does it work in theory?

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INTRODUCTION

The scientific literature contains a considerable number of studies on biological monitoring of urine chromium in occupationally exposed populations. The development in science and technology in the 21st century requires us to limit the exposure to this substance to the extent that it can be considered non-toxic to the environment and its organisms. Urine chromium concentrations have been widely used as an indicator of occupational exposure to these chemicals. However, the fact that chromium (III) is an essential micronutrient and acts as cofactor in insulin function, the maintaining of normal glucose tolerance complicates its use. Chromite ore processing and hexavalent chromium are listed as having carcinogenic potential, while lead and zinc chromates are suspected carcinogens. To identify these different species in urine or blood requires analysis techniques which can differentiate between the toxic chromium (VI) and non-toxic chromium (III) oxidation states.

With the growing recognition of the long-term hazards of heavy metals, notably cancer, that might be the result of these exposures, it has become more important to develop the analytical capabilities to analyse chromium levels to very low concentrations of exposure, accentuated by the fact that there is no safe exposure to carcinogens, and determine the trend level of chromium that can eventually be interpreted. Normal values, as it has been known for years may be erroneous, especially for trace elements / essential elements and are dramatically lower than those regarded as being correct, non-toxic or essential some years ago.

The question remains, are lower levels of total chromium considered safe or should we not determine the true the oxidation states of chromium and the impact it has on our health?

A. ABSORPTION, DISTRIBUTION AND EXCRETION

We know that trivalent chromium is poorly absorbed (<1%) from the GI-tract, whereas 50% of the hexavalent chromium can be absorbed from the gut and distributed to different organs cells and tissues. Chromium (VI) has a half life (t1/2) of 3–4 years and causes extensive damage if the levels of exposure are not limited to the lowest possible detection limit.

B. TARGET ORGAN OF CHROMIUM (VI)

Organ accumulation of chromium is extensive and includes the brain, liver, spleen, testes, bone marrow and reticuloendothelial system. Serum half life is 15–41 hours and approximately 80% of a chromium dose is excreted in the urine. The basis of chromium (VI) toxicity is its ability to penetrate the cell membrane where it produces mutagenic events which results in cell death. Organ toxicity is widespread and normally presents as respiratory tract disturbances, including acute pulmonary oedema within 72 hours of significant exposure.

Other symptoms are:
1) eczematous changes – “Blackjack disease”, painless ulcers on the hands, periumbilical region, axillae and forearms (“chrome holes”);
2) GI toxicity including severe haemorrhagic gastroenteritis;
3) hepatitis;
4) renal toxicity including tubular necrosis and glomerulonephritis.
5) haematologic disturbance – including methemoglobinemia, thrombocytopenia, anaemia and intervascular haemolysis;
6) cardiovascular disturbance including circulatory collapse and shock usually secondary to extensive GI corrosion/perforation; and
7) increased incidence of nasal cancer and bronchial carcinoma associated with occupational exposure to chromium (VI).

TREATMENT/MANAGEMENT MECHANISM

Chromium intoxication can be diagnosed through the analysis of blood or urine. Chromium (VI) exposure is more complex and can only be diagnosed through the determination of total chromium in red blood cells (see Figure 1).

Treatment of chromium (VI) ingestion includes:
1) management of hypotension or shock;
2) forced diuresis – integral part of management;
3) aggressive treatment of corrosive GI injury;
4) evaluation for intravascular haemolysis, methemoglobinemia and renal failure.

MECHANISM

The mechanism of toxicity / carcinogenicity of chromium (VI) is explained by the uptake-reduction model (Figure 1). Chromium (VI) water solubility and ionisation properties gives the compound the ability to readily enter cells by diffusion through a nonspecific anion channel, whereas due to its
non-soluble nature chromium (III) does not seem to enter the cell through these anion channels.

Glutathione appears to facilitate Cr(VI) uptake by reducing Cr(VI) to Cr(III) after it enters the cell. This process limits the concentration of Cr(VI) by reducing it to Cr(III). However, glutathione reduction action does allow the further uptake of Cr(VI) which can lead to excess chromium accumulation in the cell. There are other non-enzymatic processes like ascorbate and riboflavin, as well as enzymes like cytochrome P-450, DT-diaphorase and the mitochondrial electron chain transport. Chain complexes are all capable of reducing Cr(VI) in vitro.

Once chromium (VI) is reduced, it is capable of producing various forms of DNA damage including DNA strand breaks, DNA interstrand cross links, DNA-protein cross links as well as Cr DNA adducts. Thus, the different pathways of metabolism in tissue will influence the extent of DNA damage produced by Cr (VI). This DNA damage observed accounts for the functional changes in DNA replication and transcription which may be crucial and explains the carcinogenicity of chromium (VI) compounds.

**CHROMIUM URINE AND RED BLOOD CELLS ANALYSIS DATA 2008–2011**

The data reflect the extent of exposure to chromium in
industry. Total chromium urine results were summarised and are graphically demonstrated in Figures 2 to 4. A gradual decline in exposures has been observed for the male workers. With respect to the female exposure, data followed a very similar pattern for normal and action levels.

The data for chromium (VI) in red blood cells (Figures 5 – 7) are alarming and illustrate that a significantly high percentage of workers were actually exposed.

CONCLUSION
Over the past few years an increased awareness among occupational physicians has led to the re-evaluation of chromium exposure and in particular the long-term exposure effect of Cr (VI) and the possibly symptomatic effects such exposure has on the workers health. Biological trend line evaluations of red blood cell chromium (VI) levels is a valid method to determine possible exposure or body burden resulting from long-term exposure to chromium (VI). From the results a noticeable drop in exposure was observed. However, chromium (VI) exposure in the workplace is a reality and still under-diagnosed.