Cobalt in the hard metal production industry - exposure via inhalation and skin and the inflammatory response in human keratinocytes

av

Maria Klasson

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Opponent: Professor Kristina Jacobsson
Arbets- och miljömedicin, Institutionen för medicin,
Sahlgrenska akademin, Göteborgs Universitet
Sverige

Örebro universitet
Institutionen för MedicinskaVetenskaper
701 82 ÖREBRO

Abstract

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Cobalt is a strong sensitizer and can cause contact allergy upon both direct contact or from airborne exposure on the skin. In the skin, keratinocytes are the first cells to come in contact with the metal and will react and respond to the danger by triggering an alarm system resulting in an inflammatory response in the skin. Keratinocytes have been shown to produce IL-1β, which is one of the most potent inflammatory agents in our body and is associated with a variety of diseases.

The aims of this thesis was to investigate cobalt air concentrations for different particle fractions for possible use as proxies for other article measures and to examine if cobalt skin and inhalable air exposure contributes to uptake. Also, to investigate the effect of cobalt on cultured human keratinocyte cell viability, pro-inflammatory cytokine/chemokine release and NLRP3 inflammasome activation using cells cultured at low or high calcium (the latter yielding a more differentiated cell type).

Air exposure to cobalt was found in all departments and for all work tasks in the hard metal production facility and exposures were in general below the Swedish OEL for inhalable cobalt. The highest exposure levels were found in the powder production department and for laboratory and furnace work. Good correlations for the mass based measures enable us to use the findings for future references. When personal inhalable air levels of cobalt, cobalt skin levels skin and biological monitoring of cobalt in blood were analysed, the skin exposure was determined to be import as a route of uptake. Skin exposure to cobalt in the hard metal industry, could further affect the total uptake in the same order of magnitude as air exposure. *In vitro* investigations of cobalt using the human keratinocyte cell line HaCaT, showed that $CoCl_2$ triggered an alarm system in cells where the proinflammatory cytokines/chemokines IL-6, CXCL8 and CCL2, known to be involved in skin inflammation, were secreted in a time- and dose-dependent manner. Comparing HaCaT cells of high- and low differentiation stages indicated that the effect of cobalt chloride on cell toxicity occurs throughout the living epidermis. $CoCl_2$ exposure also resulted in secretion of the pro-inflammatory cytokines IL-1β and IL-18, and caspase-1, which indicates activation of the NLRP3 inflammasome in the cells. $CoCl_2$ regulates the inflammasome both as primer and as an activator. Our mRNA results indicates a negative feedback mechanism in the inflamamsome due to the exposure. The inflammatory response in general is more dose than time dependent, which be important for understanding the mechanisms of allergic sensitization.

Keywords: cobalt, cobalt chloride, skin, HaCaT, in vitro, cell viability, pro-inflammatory cytokines, NLRP3 inflammasome.

Maria Klasson, Faculty of Medicine and Health
Örebro University, SE-701 82 Örebro, Sweden, maria.klasson@oru.se