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Review

Cobalt toxicity in humans—A review of the potential sources and systemic health effects

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ABSTRACT

Cobalt (Co) and its compounds are widely distributed in nature and are part of numerous anthropogenic activities. Although cobalt has a biologically necessary role as metal constituent of vitamin B_{12}, excessive exposure has been shown to induce various adverse health effects. This review provides an extended overview of the possible Co sources and related intake routes, the detection and quantification methods for Co intake and the interpretation thereof, and the reported health effects. The Co sources were allocated to four exposure settings: occupational, environmental, dietary and medical exposure. Oral intake of Co supplements and internal exposure through metal-on-metal (MoM) hip implants deliver the highest systemic Co concentrations. The systemic health effects are characterized by a complex clinical syndrome, mainly including neurological (e.g. hearing and visual impairment), cardiovascular and endocrine deficits. Recently, a biokinetic model has been proposed to characterize the dose-response relationship and effects of chronic exposure. According to the model, health effects are unlikely to occur at blood Co concentrations under 300 µg/l (100 µg/l respecting a safety factor of 3) in healthy individuals, hematological and endocrine dysfunctions are the primary health endpoints, and chronic exposure to acceptable doses is not expected to pose considerable health hazards. However, toxic reactions at lower doses have been described in several cases of malfunctioning MoM hip implants, which may be explained by certain underlying pathologies that increase the individual susceptibility for Co-induced systemic toxicity. This may be associated with a decrease in Co bound to serum proteins and an increase in free ionic Co^{2+}. As the latter is believed to be the primary toxic form, monitoring of the free fraction of Co^{2+} might be advisable for future risk assessment. Furthermore, future research should focus on longitudinal studies in the clinical setting of MoM hip implant patients to further elucidate the dose-response discrepancies.

1. Introduction

Cobalt (Co) is a hard, silvery gray and ductile metal element, of which the chemical properties are highly similar to iron (Fe) and nickel (Ni) (Barceloux, 1999). Cobalt compounds predominantly occur in two valence states: cobaltous (Co^{2+}) and cobaltic (Co^{3+}), the former being most commercially and environmentally available (Barceloux, 1999; Paustenbach et al., 2013a). Furthermore, cobalt metal ions are trace elements widely distributed in nature. Trace elements are − in specific quantities − essential for normal physiological function; they play a role in the prevention of nutritional deficiencies, the functioning of the immune system, the regulation of gene expression, the antioxidant defense and the prevention of chronic diseases (Strachan, 2010). The only known biological function of cobalt is its role as metal component of vitamin B_{12}, also named cyanocobalamin (Strachan, 2010; ATSDR, 2004), whereas other cobalt compounds have been described as toxic

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for the environment and the human body following excessive exposure.

Because of its widespread occurrence, humans are frequently exposed to various Co compounds in daily life. The general population is primarily exposed through inhalation of ambient air and ingestion of food and drinking water containing Co compounds (ATSDR, 2004). Occupational exposure to cobalt is another relatively frequent event, as cobalt has numerous industrial applications (production of hard metals, grinding, mining, paint) (Barceloux, 1999; ATSDR, 2004). Furthermore, cobalt is or has been used for a number of medical purposes, some of which were abandoned over the years (Barceloux, 1999; ATSDR, 2004; IARC, 2006).

The toxic potential of cobalt and the related health risks have been investigated thoroughly in animal and human toxicity studies. Previous reviews often focused on either one specific exposure setting and the related Co intake routes, toxicity mechanisms and clinical consequences (Campbell and Estey, 2013; Borowska and Brzóska, 2015; Delaunay et al., 2010; Devlin et al., 2013; Nordberg, 1994; Pizon et al., 2013; Bocca et al., 2014; Bradberry et al., 2014; Christensen and Poulsen, 1994; Gessner et al., 2015; Zywiel et al., 2016), or the effect of Co on a specific physiological system in different Co exposure settings (Catalani et al., 2012; De Boeck et al., 2003; Beyersmann and Hartwig, 1992; Fowler, 2016; Garner, 2004; Jarvis et al., 1992; Rizzetti et al., 2009). A recent extensive review of Paustenbach et al. (2013a) covered the main cobalt sources, intake routes, kinetics, underlying toxicity mechanisms and a critical evaluation of previously reported adverse health effects. Since their work already provides a comprehensive and detailed quantitative exposure and risk assessment (Paustenbach et al., 2013a; Finley et al., 2013; Tvermoes et al., 2015; Unice et al., 2014), our goal was to provide a more general and concise overview of the following areas:

(1) The historical and contemporary cobalt sources in different exposure settings, with the related intake routes.
(2) The instruments for detection and quantification of Co intake, and the recent insights regarding the interpretation of these measures.
(3) The currently known systemic human health effects.

2. Cobalt sources

For thousands of years, cobalt has been used as a coloring agent for glass, pottery and jewelry because of the characteristic blue color of certain compounds (IARC, 1991). Cobalt was isolated and identified as an element in the eighteenth century, and its use in industrial applications commenced in the beginning of the twentieth century (Barceloux, 1999). An extensive array of historical and contemporary Co sources is documented in the literature. In this review, four exposure categories were distinguished to group the different sources: (1) occupational, (2) environmental, (3) dietary and (4) medical exposure.

2.1. Occupational exposure

2.1.1. Hard metal industry

With almost 15% of the worldwide production of Co being used for hard metal production Klasson et al., 2016, the hard metal industry is believed to represent the main source of occupational Co exposure. Cobalt (Co), tungsten (W) and tungsten carbides (WC) are the major constituents of hard metal alloys and are thus commonly used in the production and processing of hard metals. Tungsten carbide (WC) is the key component of the alloy mixture ($\geq$90%), whereas Co is less represented ($\leq$10%) and used as a binder (Lison et al., 1996). The combination of Co with WC is assumed to enhance the cellular uptake of Co and modulate its biological reactivity and toxic effect (Barceloux, 1999; Lison and Lauwerys, 1992; Broding et al., 2009). Bodily cobalt uptake in the hard metal industry mainly results from inhalation of hard metal dust, although dermal uptake has also been demonstrated (Scansetti et al., 1994). When only considering the inhalation pathway, the uptake is determined by the airborne workplace concentration, the duration of the working shift, the breathing volume per minute, and the percent retention of dust in the airways. Furthermore, smoking has been shown to increase the Co intake via the dust-hand cigarette-mouth path (Hutter et al., 2016). The airborne workplace concentration typically differs between departments within a hard metal plant. For cobalt, the highest levels were measured in the powder production areas, the sintering workshop and the pressing department (Kusaka et al., 1986; Kumagai et al., 1996; Kraus et al., 2001; Stefaniak et al., 2008). Overall, the airborne workplace levels of Co and tungsten dusts have significantly decreased over the years (Hutter et al., 2016), which has been associated with improved hygiene and protection measures (Simonsen et al., 2012). This decrease can be illustrated by two recent studies: Hutter et al. (2016) reported airborne Co levels ranging between 0.001 and 8 mg/m^3 measured between 1985 and 2012 in a large Austrian hard metal plant, whereas much lower levels were found by Klasson et al. (2016) between 2007 and 2009 in a Swedish hard metal plant (range: 0.000028-0.056 mg/m^3). This trend is seen in many other industries as well (Peters et al., 2016; Coble et al., 2001; Kauppinen et al., 2012; Koh et al., 2014), and the currently measured levels are mostly well below the occupational exposure limit (OEL) as stipulated by different (inter)national institutions for occupational health (e.g. American Conference of Governmental Industrial Hygienists (ACGIH): 0.02 mg/m^3; Austrian Occupational Safety and Health Administration (OSHA): 0.1 mg/m^3; National Institute for Occupational Safety and Health (NIOSH): 0.05 mg/m^3; Swedish Work Environment Authority (SWEA): 0.02 mg/m^3) (Klasson et al., 2016; Hutter et al., 2016).

2.1.2. Construction industry

Cobalt exposure may also occur in the construction industry, primarily through skin contact with cement. Irritant and allergic contact dermatitis are considered the most frequent occupational health hazards in cement workers (Wang et al., 2011). Morrone et al. (2014) studied the clinical-epidemiological features of contact dermatitis in rural and urban areas in Northern Ethiopia. They found a strong positive correlation between the reactivity to cobalt chloride and being a construction worker. However, reactivity to Co alone is rare and is mostly associated with reactivity to chromate (Athavale et al., 2007), which was confirmed by their findings. Chromate was found to be the most common contact allergen among construction workers, followed by epoxy resin and cobalt (Wang et al., 2011; Uter et al., 2004; Condé-Salazar et al., 1995; Sarma, 2009). According to the authors, this finding indicates that the concomitant hypersensitivity to cobalt and chromate is the result of an actual simultaneous sensitization due to combined exposure, rather than a cross-reaction between both allergens (Morrone et al., 2014).

2.1.3. E-waste recycling industry

Several electric and electronic devices have been reported to contain and release cobalt, often with concentrations far above the local legal threshold (Kang et al., 2013; Nnorom and Osibanjo, 2009; Lim and Schoenung, 2010). Consequently, employees in the e-waste recycling industry might be significantly exposed to cobalt. Three main exposure routes were described by Grant, Goldizen Grant et al. (2013) in this context: inhalation, skin contact and oral ingestion. The exposure rate is assumed to be variable, depending on whether formal or informal recycling techniques are implemented. In formal recycling factories (typically in Europe and North America), the workers are mostly properly protected and the equipment is specifically designed for the recycling of e-waste (Fujimori et al., 2012). In Africa, Asia and South America, more informal recycling factories are seen, where techniques such as cutting, acid bathing and open burning are used and the workers may not be protected at all (Sthiannopkao and Wong, 2013). A Swedish study of Julander et al. (2014) characterized the metal exposure in workers performing formal recycling of e-waste compared to office workers. Regarding Co specifically, they observed a 15 times greater airborne