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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.

Keywords: cobalt; systemic cobalt toxicity; medical cobalt exposure; dietary cobalt exposure; occupational cobalt exposure; metal-on-metal hip implants

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) [1]. Cobalt compounds predominantly occur in two valence states: cobaltous (Co^{2+}) and cobaltic (Co^{3+}), the former being most commercially and environmentally available [1, 2]. 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 [3]. The only known biological function of cobalt is its role as metal component of vitamin B_{12}, also named cyanocobalamin [3, 4], whereas other cobalt compounds have been described as toxic 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 [4]. Occupational exposure to cobalt is another relatively frequent event, as cobalt has numerous industrial applications (production of hard metals, grinding, mining, paint) [1, 4]. Furthermore, cobalt is or has been used for a number of medical purposes, some of which were abandoned over the years [1, 4, 5].

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 [6-16], or the effect of Co on a specific physiological system in different Co exposure settings [17-23]. A recent extensive review of Paustenbach et al. [2] 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 [2, 24-26], 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 [27]. 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 [1]. 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 [28], 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 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 [29]. The combination of Co with WC is assumed to enhance the cellular uptake of Co and modulate its biological reactivity and toxic effect [1, 30, 31]. Cobalt uptake in the hard metal industry mainly results from inhalation of hard metal dust, although dermal uptake has also been demonstrated [32]. 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 [33]. 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 [34-37]. Overall, the airborne workplace levels of Co and tungsten dusts have significantly decreased over the years [33], which has been associated with improved hygiene and protection measures [38]. This decrease can be illustrated by two recent studies: Hutter et al. [33] 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. [28] 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 [39-42], 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) [28, 33].

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 [43]. Morrone et al. [44] 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 [45], 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 [43, 46-48]. 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 [44].

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 [49-51]. Consequently, employees in the e-waste recycling industry might be significantly exposed to cobalt. Three main exposure routes were described by Grant, Goldizen [52] 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 [53]. 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 [54]. A Swedish study of Julander et al. [55] 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 exposure and significantly higher blood and urine concentrations in the recycling workers versus office workers. A similar study performed in e-waste recycling factories in Ghana [56] revealed much higher exposure values to several metals, which may be attributed to the application of informal recycling methods.

2.1.4. Diamond industry

Diamond polishers often use high-speed polishing disks of which the surface is composed of microdiamonds, cemented in ultrafine cobalt metal powder. During polishing activities, Co dust is formed and may be inhaled by the diamond polisher [1], which has been shown to cause respiratory impairment [57-63].

2.1.5. Pigment production and paint industry

Cobalt is often present in certain paints or inks as siccative to facilitate the drying process [64] and in cobalt blue dyes for painting porcelain pottery [14, 65]. Skin contact and inhalation of paint fumes/dusts are the primary exposure routes [14, 66, 67].

2.2. Environmental exposure

2.2.1. Contaminated air, water & soil

Different cobalt compounds are widely dispersed in nature, generally in low concentrations. Atmospheric Co levels at unpolluted sites are generally lower than 2.0 ng/m^3 [4, 68-72]. The earth's crust has an average Co concentration of 25 mg/kg [1], and the mean soil concentration in the US is 7.2 mg Co/kg (range 1-40 mg/kg) [73, 74]. Cobalt is rarely detected in drinking water, and if so, the concentration is low (range 0.1-5 µg/l) [75]. In lakes, rivers and groundwater Co may be present in trace amounts [69], and in open ocean waters the average concentration is estimated around 0.3 µg/l [1].

Air, water and soil pollution by Co and other metal compounds typically occurs in areas near factories and in heavily industrialized cities [76]. Incineration of combustible municipal solid waste is a primary example of polluting activity. The remaining bottom ash contains heavy metals (including Co) that can leach into soil and groundwater, which may result in long-term risks to the environment [77]. Feng et al. [77] reported Co concentrations lower than 0.01 mg/l in the groundwater of such areas (called *leachates*), which is rather low in comparison with other heavy metals (e.g. zinc, lead). Also in the context of waste processing, the recycling of e-waste might contaminate the surrounding area. Lim et al. [51] developed a pathway and impact model for the heavy metals in e-waste, which may be distributed in flue gas, fly ash and bottom ash after incineration or leaching in water near landfills. Cobalt was primarily found in bottom ash (90%) and fly ash (10%) [78] and showed an ecotoxicity potential for water according to the model.

Furthermore, environmental pollution may be caused by mining activities. The Idaho Cobalt Belt (ICB) in the USA and the Katanga Copperbelt (KC) in Congo are enormous mining zones where Co concentrations in the surrounding rivers, air and soil are highly elevated above regional background levels (ICB[79]: 0.12 µg/l in water, 12 µg/g in soil ; KC[80]: <0.001 µg/l in drinking water, 20 µg/g in soil, 11 µg/g in indoor and outdoor dust) and limits posed by national agencies for environmental protection (e.g. United States Environmental Protection Agency, US EPA: target clean-up level of 80 µg/g and 86 µg/l for Co in sediment and surface water, respectively) [79-83]. A biomonitoring study of Banza et al. [84] in the KC revealed substantially increased urinary Co levels measured in people living nearby compared to control subjects. In recent work from the same group [80], the Co concentration in several environmental samples was determined and linked to biomonitoring data from people living in polluted areas and control areas. This analysis indicated that dietary Co intake (vegetables, cereals and fish) and ingestion of contaminated dust are the main human exposure routes in the polluted areas, of which the latter is especially significant in children.

2.2.2. Electronic devices

A small number of studies delivered evidence for Co release from several (depleted) electronic devices. For instance, depleted rechargeable batteries used in mobile phones were shown to contain Co levels exceeding the locally (California, USA) established toxicity threshold limit (8000 mg/kg) with a factor between 20 and 45 [49, 50]. Kang et al. [49] utilized hazard assessment models to estimate the toxicity potential of such batteries and revealed an association between cobalt (among other metals) and both ecotoxicity and human toxicity. Furthermore, Lim et al. [51] warned for the toxic potential of metals detected in new types of flat panel display (FPD) devices such as plasma TVs, LCD (liquid crystal display) TVs, LCD computer monitors and laptop computers. Compared to the other metals, Co was identified in rather small amounts and its derived toxicity potential was limited to 'ecotoxic in water'. At last, a few studies

demonstrated Co release from mobile phones [85-87]. Skin contact is assumed to be the main human intake pathway, but all abovementioned studies mainly focused on measuring the Co content and release from these devices.

2.2.3. Cosmetics & jewelry

Cosmetic products (eye pencil, eye shadow, lipstick, skin cream, soap, …) are widespread Co sources for humans with varying Co concentrations [12]. The use of Co and Co salts in cosmetics is forbidden by the EU regulation on cosmetics and intentional ingredients, but their presence is allowed as impurities when technically necessary [88, 89]. There are no fixed permissible levels for these impurities so far and forbidden metals may accidentally end up in the product, for example by use of plants and herbs contaminated with metals [90-92].

Several jewelry items may contain and release Co, but the Ni release and concentration in jewelry is much higher and Ni allergy is one of the most frequent causes of allergic contact dermatitis worldwide [93-98]. However, concomitant Ni and Co allergy is frequently seen, since cobalt is often mixed with or serves as impurity in other metals [21, 95]. Inexpensive dark-colored items were found to release more Co than the more expensive and lighter-colored variants [93, 97, 99].

The permeation process of Co through human skin is scarcely documented. In vitro experiments of Larese et al. [100] demonstrated that Co powders are oxidized into Co ions by sweat, resulting in permeation. This process appears to be easier for damaged skin than for intact skin [101], and metal nanoparticles penetrate the skin even better because of their very small size [102]. However, there are no in vivo data indicating that Co ions can permeate through the skin into the blood stream and internal organs. They were found to accumulate in the deeper layers of the *stratum corneum*, causing merely local skin reactions (i.e. allergic contact dermatitis) [101, 103-107]. However, some jewelry items (e.g. piercings) penetrate the epidermal barrier and may cause more profound trauma. Consequently, interaction between the metal

substrate and body fluids may lead to a corrosion action, causing a release of metal ions that bind to tissue and interstitial fluid proteins [97, 108].

2.2.4. Other

Recent research showed that leather goods can also contain cobalt and may subsequently cause Co allergy [109, 110]. Furthermore, Bjoernber [111] described allergic reactions due to the use of Co as a light blue tattoo pigment (azure blue and cobaltous aluminate).

2.3. Dietary exposure

For the general population, the diet is believed to be the main source of Co exposure [4, 112]. Hundreds of food items contain Co in varying concentrations [113]. The highest mean Co concentrations were found in chocolate, butter, coffee, fish, nuts, green leafy vegetables and fresh cereals [5, 114-118]. Vitamin B_{12} is mainly found in meat and dairy products [4]. Trace elements in food may originate from environmental sources (e.g. pollution from industrial or other anthropogenic activities) or from food processing and packaging [116]. In the past 10-15 years, several countries performed 'Total Diet Studies' (TDS); national surveys to assess public health risks associated with substances in food [116, 118-125]. These studies reported a mean dietary Co intake ranging from 0.13 to 0.48 µg/kg bw/day (bw=body weight) in adults and from 0.27 to 0.31 µg/kg bw/day in children, which is far below the lower limit of tolerable daily Co intake set by the Agence Française de Sécurité Sanitaire des Aliments (AFSSA) (1.6-8 µg/kg bw/day)[116].

In addition to the unintentional dietary Co intake, people may deliberately ingest cobalt in the form of Co-containing supplements or vitamin B_{12} supplements that are widely available for sale. The supplement manufacturers present Co as a contributor to protein synthesis, red blood cell production, fat and carbohydrate metabolism, and myelin sheath repair in the central nervous system [126-128]. The recommended daily intake of vitamin B_{12} for adults is 2.4 µg/d, which contains 0.1 µg of cobalt [129]. Furthermore, there are concerns about Co being misused as

blood doping agent by athletes to enhance aerobic performance [130, 131], and some energy drinks may contain high amounts of vitamin B_{12} [132].

The gastro-intestinal absorption of Co in humans was reported to be approximately 25% of the administered dose, but the inter-individual variation is considerably large (5-95%) due to its dependence of several factors: the ingested dose, the solubility of the compound and the nutritional status (e.g. iron deficiency) of the individual [1, 5, 112, 133-140]. There are no differences in gastro-intestinal absorption rates between the ionic forms of cobalt (Co^{2+} and Co^{3+}) [141]. The mechanism of gastro-intestinal Co absorption appears to occur from the proximal jejunum through a saturable process, and the intestinal Co uptake starts with mucous absorption followed by transfer from the enterocytes [141]. Furthermore, the Co gastro-intestinal absorption involves mechanisms common with Fe^{2+}, as people with iron deficiency show an increased Co absorption [139]. After absorption (from all intake routes), Co is mainly disseminated to the serum, whole blood, liver, kidneys, heart and spleen. Lower concentrations are observed in the skeleton, hair, lymphatic circulation, brain and pancreas [2, 112, 134, 142-149]. The kidneys are predominantly responsible for the excretion of absorbed cobalt [4, 116].

2.4. Medical exposure

2.4.1. Treatment of anemia

In the 1950s and 1960s, various Co preparations (e.g. cobaltous chloride or $CoCl_2$) were used in the treatment of anemia because of its stimulant effect on the hemoglobin and red blood cell production. The average daily doses (25 to 300 mg $CoCl_2$/day) were considerably high and often taken for several months [2, 150-153]. Due to frequent development of severe adverse health effects and a paucity of positive responses, this therapy is not applied anymore today [154].

2.4.2. Treatment of estrogen hyperexcretion

Menopausal or post-menopausal women often receive hormone replacement therapy. Occasionally, the therapy may fail to relieve the typical menopausal symptoms (e.g. hot

flashes). Compared to the women responding well to the treatment, these patients showed excessive excretion of estrogen, which was assumed to result from an overactivity of cytochrome enzymes. Since cobalt, among other minerals, can affect cytochrome function, Co supplements are sometimes prescribed to improve the therapeutic effect [155]. The administered doses (0.5 to 1.12 mg $CoCl_2$/day) are comparable with the averagely ingested dose of over-the-counter supplements [2, 155].

2.4.3. Metal-on-metal hip prostheses

Today, the population of metal-on-metal (MoM) hip implant patients is considered to undergo the most important Co exposure from non-dietary and non-occupational sources [25]. It was estimated that approximately 1.000.000 MoM articulations have been implanted worldwide since 1996 [156, 157]. Between 1990 and 2010, MoM implants represented approximately 10% of all hip arthroplasties in developed countries [158, 159].

Metal-on-metal hip prostheses are predominantly comprised of cobalt (64%) and chromium (Cr) (28%), but can contain small amounts (0.2-7%) of other metals (e.g. molybdenum, aluminum, nickel, manganese, iron, lanthanum) [160-162]. Currently, two types of hip replacements are performed with MoM implants: total hip arthroplasty (THA) or hip resurfacing arthroplasty (HRA). In the latter one, the patient's femur is preserved and capped with a metal component, allowing higher activity levels and better survivorship. Therefore, HRA is frequently executed in younger patients [163-165]. Cobalt and chromium ions may be formed and released as a result of two processes: friction between the articulating surfaces producing numerous nano-sized wear particles [166-168], and corrosion of the metal surfaces and wear particles [169-171]. Several factors may negatively influence this wear process and enhance the metal ion release or lead to higher metal ion levels: suboptimal surgical positioning of the implant [172, 173], mixing components from different manufacturers or different types [174], many

modular connections with friction and chemical corrosion at the taper/trunnion junction [175], impaired renal function and bilateral MoM hip replacement [164].

Chemical analysis of periprosthetic tissue samples and several *in vitro* studies revealed that nano-sized wear particles from MoM implants are mainly composed of insoluble oxidized Cr^{3+}, with practically no Co content [166, 171, 176-181]. This was confirmed by the findings of Madl et al. [182] for well-functioning hip prostheses, which also showed a low volumetric wear rate. For mal-positioned implants, however, the balance can be skewed to a higher volumetric wear rate and larger particle sizes containing higher Co levels [182]. After being released from the CoCr nanoparticles, the highly soluble Co^{2+} ions bind with synovial fluid proteins and adjacent tissue surfaces [183, 184], followed by dissemination into the peripheral blood [185].

3. Detection and quantification methods, and interpretation

3.1. Target organ level

Measuring Co levels at the target organ level is often applied in the occupational setting, where the skin and the respiratory system are the main target organs of Co toxicity. For cutaneous intake of Co, conventional skin patch tests are mostly used [44, 48, 186]. For determination of the inhaled Co concentration, analysis of the exhaled breath condensate (EBC) was proposed by Goldoni et al. [187] and Mutti et al. [188]. However, Broding et al. [31] observed that the EBC Co concentration was not significantly correlated to the airborne workplace concentration and concluded that the EBC Co concentration is not a reliable indicator for Co exposure in the workplace.

3.2. Systemic level

For measurement of the ion concentration at the systemic level, various matrices can be used, such as urine, whole blood and serum. Different analytical methods are available [112]; to determine the urinary Co concentration, sample chelation and/or acid digestion followed by graphite furnace atomic absorption spectrometry (GF-AAS) is typically applied, with detection limits ranging from 0.1 to 2.4 µg/l. These techniques can also be used for whole blood and serum analyses, with detection limits of 2 µg/l and 0.02 µg/l, respectively. Furthermore, inductive-coupled atomic emission spectrometry (ICP-AES) and inductive-coupled plasma mass spectrometry (ICP-MS) are widely available techniques since the 1990s, of which the latter exhibits lower detection limits compared to GF-AAS and allows simultaneous multi-element analysis. The results can be expressed in different units. For blood or serum, parts per billion (ppb), micrograms per liter (µg/l), nanograms per milliliter (ng/ml), nanomoles per liter (nmol/l) and micromoles per liter (µmol/l) are frequently used. The urinary concentration is

often expressed in micrograms per gram creatinine (µg/g creatinine), micrograms per liter (µg/l), and micrograms per millimole creatinine (µg/mmol creatinine).

The urinary Co concentration is most commonly used as a biomarker in occupational exposure assessment [17]. However, one should take into account that the urinary Co concentration shows a rapid increase in the first hours after cessation of the exposure, with a peak at 3 hours post-exposure [189]. Numerous studies determined the blood and urinary Co concentrations in occupationally exposed individuals, which are listed in ***Table 1***. The ACGIH established a Biological Exposure Index (BEI) of 15 µg/l of Co in urine and 1 µg/l in blood at the end of the workweek, corresponding with an atmospheric exposure level of 0.02 mg/m^3 (Threshold Limit Value – Time-Weighted Average (TLV-TWA) over 8 hours) [190].

In the medical exposure setting, which is currently dominated by MoM hip implants, whole blood and serum are the preferred matrices, since the ion concentrations in urine samples are more variable and depend on the hydration of the patient [191]. Mean serum and whole blood Co concentrations were shown to be relatively similar and well correlated [192, 193]. However, oral Co supplementation studies of Finley et al. [24] and Paustenbach et al. [194] showed considerably higher serum versus whole blood Co concentrations during dosing, which the authors attributed to a rate-limited uptake of Co in red blood cells (RBC). Additionally, the post-dosing clearance of Co from the serum appeared to be considerably faster compared to the RBC, and the serum Co levels were found to be more variable during dosing. The latter has been related to inter-individual variability in the gastro-intestinal Co uptake and differences in the time interval between Co ingestion and the blood sample collection. These differences in variability and elimination rate suggest that the whole blood concentration might be the most appropriate measure to estimate the long-term average Co exposure [185], whereas the serum concentration might give a better indication of the recent or recently changed Co exposure [38]. Furthermore,

there is no standard rate of conversion between the respective concentration values, so it was concluded that whole blood and serum levels should not be used interchangeably [192, 195].

Various studies have shown that the metal ion levels will first increase to a maximum during the 'running-in' phase of the MoM device, which takes approximately 9 to 12 months postoperatively. Subsequently, the ion concentration is expected to decrease to a steady-state, whereas in mal-functioning implants it may increase further [196-200]. Hence, after the 12-month running-in phase, the systemic Co and Cr concentration (in whole blood or serum) is recommended as a screening tool for the *in vivo* performance of MoM hip prostheses [201]. Several authors reported a distinct association of elevated metal ion concentrations with an increased degree of wear and corrosion [202-204] and with the occurrence of periprosthetic complications (e.g. loosening) [205-207]. The majority of patients with well-functioning MoM implants have Co concentrations ranging between 0.2 and 10 µg/l [185, 196, 202, 208-215]. Different organizations attempted to define threshold values for the identification of patients with adverse local tissue reactions that require clinical follow-up or intervention. The Medicines and Healthcare products Regulatory Agency recommended a 7 µg/l threshold [201], which demonstrated only a modest sensitivity (57%) and specificity (65%) [216]. Van Der Straeten et al. [217] proposed a 4 µg/l threshold for unilateral HRA (uHRA) and a 5 µg/l threshold for bilateral HRA (bHRA), resulting in a higher specificity (95% for uHRA and 93% for bHRA) but lower sensitivity (25% for uHRA and 43% for bHRA). Sidaginamale et al. [204] reported a high sensitivity (94%) and specificity (95%) of 4.5 µg/l as threshold value for the detection of abnormal wear. The Mayo Clinic stated that Co serum levels above 10 µg/l indicate significant implant wear, whereas values between 4 and 10 µg/l reflect good condition of the MoM device [218]. In summary, it is clear that metal ion levels should be interpreted carefully and serve as an adjunct to clinical and radiographic evaluations, for which different clinical algorithms have been proposed [157, 217, 219-221].

Additionally, (highly) elevated Co concentrations have been related to certain systemic manifestations of Co toxicity [2, 222]. Van Der Straeten et al. [206] collected questionnaires, validated to detect cobaltism in occupationally exposed individuals, in a MoM hip implant population. They found a significant correlation between increasing Co levels and the prevalence of several toxicity symptoms, and concluded that patients with repeated Co concentrations exceeding 20 µg/l are at risk for systemic toxicity. Likewise, a recent systematic review of the published cases of probable systemic Co toxicity from MoM hip arthroplasty reported a significant association between the Co concentration and a quantitative measure of overall symptom severity [15]. However, the measured Co levels covered an extensive range of 10-1085 µg/l. Approximately half of these cases showed Co levels above 100 µg/l, of which the majority had a fractured ceramic head before implantation of the MoM bearing. The higher Co concentrations in this subgroup probably result from abrasion of the metal surface by residual ceramic fragments [223]. Despite abovementioned evidence for systemic Co toxicity from MoM implants, there is a current lack of uniform criteria concerning blood Co concentrations to guide physicians in the detection and management of this condition.

To this purpose, efforts have been made to characterize the dose-response relationship for Co-induced systemic health effects by a group of researchers [2, 24-26, 185, 222, 224-227]. They developed a biokinetic model for cobalt [26, 227], based on a series of novel (human) oral dosing studies [24, 25, 224-226] and existing animal and human toxicology data (see Paustenbach et al. [2]). The model allows an estimation of the blood and tissue Co concentrations associated with various Co-related systemic health effects for MoM implant patients and consumers of inorganic Co supplements during and after exposure [25]. This takes into account the 'background' Co blood concentration of the general population, which was estimated at 0.3 µg/l (range 0.04-0.9 µg/l) as a result of normal dietary Co intake, with 95% of the population having a value lower than 0.6 µg/l [211, 212, 215, 228-230]. According to the model, systemic effects

are unlikely to occur at Co levels below 300 µg/l in healthy individuals, which was proposed as 'point of departure' (POD). Respecting a safety factor of 3 to account for inter-individual variability and long-term Co exposure, it might be useful to start monitoring implant patients from Co levels of 100 µg/l [2]. However, susceptible individuals might exhibit adverse health effects at lower Co concentrations. This susceptibility has been related to the partitioning of Co in the serum: the largest portion (90-95%) binds with albumin and approximately 8% occurs as free ionic Co^{2+} [231-234], which is considered the primary toxic form [38, 235]. Certain disease states (e.g. renal failure, iron deficiency, sepsis, malnutrition, alcoholism) or medication intake may reduce the Co-albumin binding and thus increase the amount of free Co^{2+} ions, ultimately leading to toxic manifestations at lower doses. Consequently, closer follow-up of this subgroup of patients might be necessary [2].

Apart from the dose, the effect of the duration of exposure was also considered in the (refined) biokinetic model [26], based on the complex inter-relationships of renal clearance mechanisms, storage of Co in RBC and abovementioned Co-albumin binding characteristics. These factors taken into account, implant patients with well-functioning MoM devices are not expected to be at risk for adverse health effects after 10 years of exposure with a steady-state blood Co concentration of 10 µg/l [25].

4. Systemic health effects

The toxic reactions to Co exposure primarily depend on its chemical form. In the occupational and environmental setting, people are predominantly exposed to Co metal particles. In the medical setting (e.g. MoM hip implants), exposure to Co (nano)particles as well as Co ions occurs [38, 236].

Particle-responses are immune-mediated and induce local adverse tissue reactions [236]. For example, inhalation of Co dust may cause adverse respiratory effects and the formation of Co nanoparticles in the wear process of MoM hip implants may lead to inflammatory fluid collections or osteolysis. These particle-responses can be subdivided into two categories. 'Metal reactivity' is a normal innate immunity response that manifests as a nonspecific foreign-body reaction to a large amount of metal debris. In contrast, 'metal allergy' is an adaptive immunity response to a small amount of metal debris that occurs in people with a genetic allergic predisposition and is typically associated with contact dermatitis [191]. The exact role of Co in these local reactions is difficult to characterize, since Co particles are often mixed with other substances (e.g. nickel, metallic carbides) [237].

Systemic toxic reactions may arise when Co ions enter the blood and lymphatic circulation and subsequently disseminate to different organs [38]. In vitro experiments demonstrated that ionized cobalt (Co^{2+}) is the primary toxic form for systemic toxicity [38, 235] and more specifically the unbound (free) Co^{2+} ions, which are more bioavailable than their albumin-bound counterparts to interact with various cellular receptors, ion channels and biomolecules [2]. Consequently, a shift in the distribution of free versus bound cobalt towards a larger portion of free Co^{2+} ions is expected to increase the risk for toxic effects. The possible molecular mechanisms of action of free Co^{2+} ions, extensively reviewed by Paustenbach et al. [2], include generation of reactive oxygen species (ROS) and lipid peroxidation, interruption of

the mitochondrial function, alteration of calcium (Ca) and iron (Fe) homeostasis, interactions with body feedback systems triggering erythropoiesis, interruption of thyroid iodine uptake, and induction of genotoxic effects and possible perturbation of DNA repair processes. Involvement of these mechanisms in the toxic response depends on the blood or tissue Co concentrations [2].

Systemic Co toxicity manifests as a clinical syndrome with a variable presentation of neurological, cardiovascular and endocrine symptoms, depending on the systemic Co levels (blood/urine). This interpretation was already proposed in the MoM implant world, where these systemic effects are summarized in the 'arthroprosthetic cobaltism' syndrome [238, 239]. According to a review of the available animal and human dose-response data for adverse health effects [222], supplemented by the abovementioned biokinetic model [227], the lowest blood Co concentrations (around 300 µg/l) are typically associated with reversible hematological and endocrine symptoms. In contrast, more severe effects (e.g. neurologic and cardiac symptoms) were only seen at higher Co levels (> 700 µg/l). Applying these observations on the published cases of 'arthroprosthetic cobaltism', reviewed by Gessner et al. [15], Cheung et al. [240] and Zywiel et al. [16], there are some contradictions. Zywiel et al. [16] concluded that neurological (72%), cardiovascular (55%) and endocrine (50%) effects are most commonly seen in this condition, of which the former two also occurred for Co levels much lower than 700 µg/l and in several cases even below 300 µg/l. However, the anecdotal case reports often lack detailed information to properly estimate the responsibility of Co or other patient-specific factors for the reported symptoms [2, 241, 242]. Consequently, no consensus has been achieved regarding the 'threshold' Co concentration for systemic health effects, which warrants the need for controlled clinical studies in the future.

Below, the effect of Co exposure on different organ systems is further specified. Additionally, a section was dedicated to the occurrence of psychological dysfunction in Co-

exposed individuals and to the concerns regarding the carcinogenic effect of Co, which to date has not been substantiated.

4.1. Cardiovascular system

The toxic potential of Co was first discovered in the 1960s when heavy beer drinkers presented with symptoms of cardiomyopathy, which was attributed to the use of cobalt chloride ($CoCl_2$) or cobalt sulfate ($CoSO_4$) as foam stabilizer in beer [243-246]. However, it is likely that the poor nutritional status of these subjects and the alcoholism itself were contributing factors for the cardiac effects [1, 247] and/or made the person more susceptible for systemic Co toxicity [2]. In addition, several cases of cardiomyopathy were reported in hard metal workers [22, 248-250] and patients with a MoM hip implant [223, 238, 242, 251-259]. In most of these cases, necropsy revealed severely elevated Co levels in the myocardial tissue. Accordingly, research of Horowitz [260] and Linna et al. [261] revealed an association between cumulative Co exposure and an altered diastole by use of Doppler echocardiography measurements, suggesting that Co accumulation in the myocardium may damage the myocardial function. Furthermore, echocardiography has shown a moderately to severely reduced left ventricular systolic function and left ventricular or atrial hypertrophy [223, 238, 242, 257]. Reversible electrocardiographic (ECG) changes, hypertension and a faster heart rate have been described [262, 263]. Two patients presented with paroxysmal atrial fibrillation [242, 252], and three fatal cases of Co-induced cardiomyopathy have been reported to date [253, 255, 257].

4.2. Peripheral & central nervous systems

Cobalt-related neurotoxicity may cause peripheral as well as central deficits. The latter presumably result from the ability of Co to cross the very restrictive blood-brain barrier and deposit in the brain [264, 265].

A variety of symptoms have been described, related to hearing and balance [23, 223, 238, 241, 251, 257, 266-270], vision [23, 238, 252, 266, 269-272], cognitive function [223, 238, 241, 273], and sensory and motor performance [23, 238, 252, 268, 270]. Moreover, these symptoms often coincide with polyneuropathy.

Hearing loss is always sensorineural, but the degree may be variable and is often progressive. Furthermore, the hearing impairment is mostly bilateral and more severe in the high frequencies, but this was not always mentioned properly. In addition, patients may complain about tinnitus and vertigo/dizziness, the latter sometimes accompanied by nausea and vomiting. Visual impairment may include optic nerve atrophy (mostly bilateral), reduced visual acuity, complete blindness, retinal dysfunction, poor color vision, blurred vision, and irregular cortical visual responses. A cognitive decline may be characterized by poor concentration, memory loss (e.g. names and places), impaired attention, disorientation, difficulties with registration of new information, and inefficiency. Regarding the sensory and motor performance, the following problems were mentioned: tremor, incoordination, headaches, motor axonopathy, muscle weakness, slower conduction of sensory stimuli, dyesthesia in the extremities, gait disturbances, numbness and paresthesia. After cessation of the exposure, most of the neurological symptoms gradually improved or resolved. Nevertheless, persistence of the auditory and visual dysfunctions was seen in some cases, despite a substantial decrease in the blood Co concentration.

4.3. Endocrine system

Autopsy of the previously mentioned beer drinkers often revealed thyroid changes, which could be associated with primary myocardial disease [274]. Roy et al. [274] could not find any abnormalities macroscopically, but some microscopical lesions were apparent: follicular distortion, cellular changes and colloid depletion. Furthermore, numerous human studies have reported endocrine effects (e.g. goiter development and reduced iodide uptake) in orally Co-treated subjects, with daily Co doses ranging between 0.5 and 10 mg/kg bw/day and the

treatment duration between 2 weeks and 10 months [275-282]. These effects mostly disappeared after cessation of the exposure [275, 279]. Additionally, chronic thyroiditis, disturbance of the thyroid hormone metabolism (mostly hypothyroidism) and a reduced thyroid volume have been described in Co-exposed individuals [23, 65, 223, 238, 252, 253, 255, 268, 270].

4.4. Hematological system

As cobalt has a known stimulant effect on the RBC production, exposure to Co compounds may increase the RBC count (polycythemia), hematocrit and hemoglobin levels [4]. These effects were reported in a study of Davis et al. [283], in which six healthy men received daily doses of 150 mg $CoCl_2$ up to 22 days. The RBC count normalized approximately two weeks after cessation of the exposure. In contrast, two other oral dosing studies did not find any hematological effects after ingestion of similar or higher doses [276, 284]. Similarly, several authors have investigated the occurrence of hematological effects in occupationally exposed individuals, but could not reveal any abnormalities of this kind [263, 285, 286]. Furthermore, one anecdotal case report of systemic Co toxicity from MoM hip arthroplasty described polycythemia in their patient [254].

4.5. Respiratory system

The association between occupational (hard) metal exposure and dysfunctions of the respiratory system was first made by Jobs et al. [287], based on changes in chest radiographs indicating pneumoconiosis, a term for occupational lung disease. Bech et al. [288] introduced the term ‘hard metal disease’, later adapted to ‘hard metal lung disease’, to describe the respiratory effects due to inhalation of Co-containing dusts. Roto [289] reported cases of asthma in a Finnish cobalt production plant, later referred to as ‘hard metal asthma’ by Kusaka et al. [34]. Information about the clinical and histopathological presentation of this disease is mainly based on case reports and small trials [34, 62, 288-296]. Currently, the scientific community recognizes three entities associated with the inhalation of hard metal dust: (1) occupational asthma, (2) allergic alveolitis

or hypersensitivity pneumonitis, and (3) interstitial pneumonia, presenting in two varieties: the typical giant cell pneumonia or the desquamative type without giant cells [294, 296]. Allergic alveolitis or hypersensitivity pneumonitis usually occurs in the acute stage of the exposure as an early inflammatory phase of fibrosis, but may evolve to a chronic fibrosis after long-term exposure [297-301]. Symptoms of giant cell interstitial pneumonia include weight loss, fatigue, dry cough, dyspnea on exertion, chest pain, wheezing and rales at the end of inhalation [301-303]. Cyanosis, digital clubbing, pulmonary hypertension, signs of right heart failure and cor pulmonale may arise when the disease progresses to fibrosis [301, 304]. Pulmonary dysfunction can be of the restrictive or obstructive type [299, 304], and pneumothorax has been observed in a limited number of cases [293, 296, 305, 306]. Progression of the disease after cessation of the exposure is a frequent finding [307]. Although Co is mostly incorporated in alloys with other components (e.g. tungsten), there is a consensus that cobalt is the main etiological agent for the development of hard metal lung disease [36, 187, 298, 308-310].

4.6. Skin

Occupational contact dermatitis (OCD) is the most common skin disease among all occupational skin diseases [46]. It is mainly caused by contact with metallic Co, Cr and Ni, since these metals are frequently encountered contact allergens in the workplace [1, 311]. Even short and repetitive contact with hard metals may cause harm, according to the findings of Midander et al. [312]. Athavale et al. [45] performed a retrospective analysis on an extended pool of dermatological data, collected over a period of 11 years. Occupational contact dermatitis was found to comprise 77% of all types of occupational skin diseases, with Cr and Co as etiological allergen in 6% and 4% of the cases, respectively. Furthermore, Co-related OCD seems to have an onset early in the work life and may affect a wide range of occupations [45]. The hands involve the greatest risk of cobalt sensitization, for obvious reasons [1, 45, 313-316]. However, Sarma [48] assessed the allergic profile among Indian construction workers and observed that dermatitis

not only affected the exposed body parts (94%), but also the covered parts (62%). Among construction workers, chromate is the most common allergen (60%) followed by Co and Ni (20%), all of which are present in cement. Isolated allergy to Co and Ni without concomitant chromate allergy is highly unlikely in this population, because Co and Ni are present in their insoluble form and therefore have a very low sensitization potential [317]. Consequently, Co and Ni allergies generally occur secondary to an existing chromate allergy that already caused skin damage, which was confirmed by the findings of Sarma [48]. Moreover, Co allergy often coexists with Ni allergy due to their common presence in metal objects. Fischer et al. [313] even concluded that sensitization to Ni may increase the risk of developing Co allergy.

Furthermore, skin effects in the environmental setting seem to be mainly caused by jewelry, cosmetic products and leather. For jewelry and cosmetics, only a few cases of skin problems have been described in literature. Chave et al. [318] reported a case of severe hand eczema in a beauty therapist after using a Co-containing gel for facial massage. The eczema disappeared when she avoided the product. Guarneri et al. [319] described a case of extremely itchy and eczematous lesions on the hands of a woman who undergone a nail-art procedure with Co-containing nail gel. Furthermore, a 45-year-old woman who bought a necklace in Spain developed eczema in the neck. A strong Co release was detected from the necklace using the artificial sweat method [93]. The presence of Co in leather was brought to light by a case report of a patient with chronic allergic contact dermatitis [109]. The patient linked his skin problems to his leather couch, which was later found to contain Co. Moreover, he tested positive for Co but not for Cr on patch testing. This finding led to a more extensive study, in which 183 dermatitis patients who tested positive for Co and not for Cr were identified. A questionnaire revealed that leather was found to be the most likely source of their problems [110].

Finally, dermatological reactions have been associated with (oral) Co therapy. The symptoms mainly consisted of acne, skin rashes and flares of dermatitis, which were temporary and mild in most cases [283, 284, 320, 321].

4.7. Psychological function

The following psychological problems have been reported among patients with MoM hip implants [238, 241]: depression, irritability, extreme fatigue and lack of energy, and anxiety. However, a direct cause-and-effect relationship with Co is uncertain, since this is an extremely versatile problem with a lot of possible underlying factors.

4.8. Carcinogenic effect

The risk of lung cancer related to inhalation of Co-containing dusts has been considered in the occupational exposure setting. However, Co is certainly not the main causative agent in this context; especially the combination with tungsten carbide is considered carcinogenic [5, 322]. The International Agency for Research on Cancer (IARC) classified the mixture Co/WC as 'probably carcinogenic to humans' (group 2A) [5].

Furthermore, there have been some concerns regarding an increased risk for cancer in patients with MoM implants. Numerous epidemiology studies were conducted to evaluate the total and specific cancer rates in implanted patients, but none revealed any indication of an increased cancer risk [323-336].

5. Conclusions

This review aimed to provide a general overview of all historical and contemporary cobalt sources, which were allocated to four categories of exposure. Furthermore, the detection and quantification methods of Co intake were illustrated and recent perspectives on the interpretation of these measures were given. Lastly, the known systemic health effects were described.

In the *occupational* setting, Co exposure is considered to be most prevalent in the hard metal industry, with a wide range of systemic Co levels (urine/blood). This might partially result from the variability in working conditions and protective measures taken in the workplace. *Environmental* Co exposure is extremely versatile and place-dependent, and therefore difficult to quantify in general. Risks for eco- and human toxicity have been estimated, but mainly based on measurements of the Co content and release from these sources, as there is a current lack of physiological biomarker (blood/urine) levels to accurately characterize the amount of human exposure. Moreover, Co often coincides with other metals in environmental sources, and the cumulative toxicity may be hazardous for human health. *Dietary intake* is considered to be the primary exposure route for the general population. Except for vitamin B_{12} and other Co supplements, cobalt is found in ubiquitous nutrients. The background Co levels (blood) are based on a normal dietary Co exposure, which is believed to include no risks for human health. *Medical* exposure to Co is a growing concern, especially in patients implanted with a metal-on-metal hip prosthesis, who are subjected to the most invasive Co exposure route. However, recent human volunteer studies demonstrated that ingestion of over-the-counter Co supplements can lead to considerably higher systemic Co levels than those measured in most MoM hip implant patients [25].

The systemic health effects of excessive cobalt exposure are characterized by a complex clinical syndrome with a varying set of neurological, cardiovascular and endocrine deficits, directly related to the uptake of Co ions in the tissues and blood circulation. However, the often wide range of systemic Co levels in symptomatic patients suggests that other factors might also influence the clinical image. This hampered the establishment of a 'threshold Co concentration' above which toxic effects are known to arise and therapeutic measures should be taken. A recently developed biokinetic model [26, 227] has clarified several issues regarding the dose-response characteristics of Co-related adverse health effects, showing that blood Co concentrations under 300 µg/l (100 µg/l respecting a safety factor of 3, to account for inter-individual variability and long-term Co exposure) are unlikely to result in clinically relevant symptoms for healthy individuals. Furthermore, chronic exposure to acceptable doses (see Unice et al. [26] and Tvermoes et al. [25]) are not expected to pose significant health hazards. Nevertheless, several cases presenting with systemic health effects at much lower doses (mostly from 20 µg/l) have been described in clinical practice, which may be explained by an increased susceptibility of the individual for Co-induced toxicity. This is assumed to originate from a shift towards a higher fraction of free Co^{2+} ions compared to albumin-bound Co in the serum, which may be caused by several underlying disease states that can affect the albumin or reduce the Co^{2+}-binding capacity in human blood. Therefore, monitoring the free Co^{2+} concentration might be more helpful than the total blood Co concentration for risk assessment in the future [2]. In addition, further clinical and longitudinal research is required within the population of MoM hip implant patients to elucidate the current dose-response controversies and contribute to the development of uniform guidelines.

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Table 1: Overview of the systemic Co concentrations reported in different studies about occupational Co exposure.

Study	Occupational source	Number of samples	Whole blood	Urine	Expression of the results
Alexanderson et al. (1980) [262]	Hard metal production	unknown	10.5 µg/l	134 µg/l	mean
Morgan (1983)[337]	Processing cobalt oxide	unknown		340 µg/l	mean
Ichikawa et al. (1985)[338]	Production of hard metal tools	175	3.3–18.7 µg/l	10–235 µg/l	range
Lison et al. (1994)[237]	Hard metal production	132		18.2–32.4 µg/g creatinine	range
Scansetti et al. (1998)[339]	Hard metal production	45		22.28 µg/l	mean
Yokota et al. (2007)[340]	Battery plant	16		28.2 ± 34.0 (1.0–127.8) µg/l	arithmetic mean ± standard deviation (range)
Broding et al. (2009)[31]	Hard metal alloy industry	52		0.81 (0.00–1.46) µg/l	median (interquartile range)
De Palma et al. (2010)[341]	Hard metal alloy industry	36		5.27 (2.95) µg/l	geometric means (geometric standard deviations)
Julander et al. (2014)[55]	E-waste recycling (formal methods)	50 (whole blood) 52 (urine)	0.081 (0.050–0.67) µg/l	0.25 (0.12–1.3) µg/l	median (range)
Nemery et al. (1992)[59]	Diamond polishing	194		0.1 – 137 µg/l	range
Prescott et al. (1992)[65]	Porcelain painting	25		1.17 µg/mmol	mean
Goldoni et al. (2004)[187]	Hard metal alloy industry	23		1.7-366 µmol/mol creatinine	range
	Grinding of hard metal	10		7.2–49.2 µmol/mol creatinine	range
Kraus et al. (2001)[36]	Hard metal production	87		0.19 – 227.8 µg/g creatinine	range
Hutter et al. (2016)[33]	Hard metal production	1166		3.7 (1–159.7) µg/l	median (range)