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Addendum to Cobalt and Cobalt Compounds

Assessment Values in Biological Material – Translation of the German version from 2018

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Keywords: cobalt; cobalt compounds; biological guidance value; BLW; biological reference value; BAR; background exposure; exposure equivalents for carcinogenic substances; EKA

Citation Note: Schmitz-Spanke S, Drexler H, Hartwig A, MAK Commission. Addendum to Cobalt and Cobalt Compounds. Assessment Values in Biological Material – Translation of the German version from 2018. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2019 Jul;4(3):1604–1627]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/bb744048vere2319_w

Republished (online): 30 Apr 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.bb744048vere2319

Addendum completed: 18 Jan 2017

Published (online): 25 Jul 2019

The commission established rules and measures to avoid conflicts of interest.

1604

Addendum to Cobalt and Cobalt compounds

BAT value documentation

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DOI: 10.1002/3527600418.bb744048vere2319

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has derived a biological guidance value at the workplace ("Biologischer Leitwert", BLW) and a biological reference value ("Biologischer Arbeitsstoff-Referenzwert", BAR) and has re-evaluated the exposure equivalents for carcinogenic substances (EKA) for cobalt and cobalt compounds [CAS No. 7440-48-4] in 2017. Available publications are described in detail.

The evaluation of the BLW was based on the association between urinary concentration of cobalt to characterize the internal exposure and cardiotoxicity as critical effect. Moderate restrictive lung dysfunctions and slight interferences with thyroid metabolism (hypothyroidism) were observed at urinary cobalt concentrations of 79 µg/L urine and 84 µg/L urine, respectively. At urinary concentrations of 38 µg cobalt/L urine and 36 µg cobalt/L urine no adverse effects of restrictive lung dysfunction and cardiotoxicity were observed. Therefore, a BLW of 35 µg/L urine was derived. The sampling time is for long-term exposures at the end of the shift after several shifts.

In some biomonitoring studies, the excretion of cobalt in urine of persons occupationally not exposed to cobalt was examined. Due to geogenic differences, a German study was considered for the evaluation, where urine samples of 87 adults were analyzed and a 95th percentile of 1.53 µg cobalt/L urine was recorded. These results are in good accordance with other international studies. Therefore, a BAR of 1.5 µg cobalt/L urine was evaluated.

The relationships between the concentration of cobalt in ambient air and that in urine derived from the more recent studies are in good accordance with the present EKA. The Commission therefore retains the EKA already derived in 1986 and extended in 2006 in the lower range between the concentration of cobalt in the air and in urine.

Keywords

cobalt; BAT value; biological guidance value; EKA; BAR; occupational exposure; toxicity

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Addendum to Cobalt and Cobalt Compounds

BLW (2017)

35 µg cobalt/L urine
Sampling time: for long-term exposure: at the end of the shift after several shifts

EKA (2017)

The correlation between external and internal exposure is as follows:

Air Cobalt [mg/m³]	Urine Cobalt [µg/L]
0.005	3
0.010	6
0.025	15
0.050	30
0.100	60
0.500	300

Sampling time: for long-term exposure: at the end of the shift after several shifts

BAR (2017)

1.5 µg cobalt/L urine
Sampling time: for long-term exposure: at the end of the shift after several shifts

MAK value	–
Absorption through the skin (2008)	H
Carcinogenicity (1971)	Category 2

16 Re-evaluation

In 2001, the 1971 classification of cobalt and its compounds (in the form of respirable dusts or aerosols) as Category 2 carcinogens was confirmed. The basis for this was the substances' carcinogenicity demonstrated in inhalation tests on rats and mice (Greim 2001).

In 1986, an EKA correlation was derived between the concentration of cobalt in air and that in whole blood or urine (see Angerer 1989, translated). In 2006, the EKA

correlation between airborne cobalt levels and urinary cobalt levels was suspended (see Angerer 2007, translated). This was justified by the fact that the concentrations of cobalt in urine are about 10 times higher than those in blood, and that cobalt in urine can be more reliably determined both diagnostically and analytically. Besides, urine collection is non-invasive.

In this addendum, a BLW (biological guidance value at the workplace) and a BAR (biological reference value for workplace substances) are derived. As a part of this derivation, the EKA correlation was also revised on the basis of data from more recent studies.

16.1 Relationship between External and Internal Exposure

Table 1 summarizes the results of studies in which biological effects were attributed to the internal exposure to cobalt.

16.1.1 Occupational Health Studies

Prescott et al. carried out a cross-sectional study of female plate painters at two Danish porcelain factories (Prescott et al. 1992). The mean urinary cobalt concentrations were 0.2 µg/mmol creatinine (~ 2.12 µg/L) in painters working with insoluble cobalt dyes and 1.17 µg/mmol creatinine (~ 12.4 µg/L) in those working with semisoluble cobalt dyes. Compared to a control group, workers with increased cobalt excretion had significantly elevated levels of thyroxine (T_4) and free T4 (fT_4). As the observed hormone level fluctuations were still within the normal range, the TSH level was unaffected and a postulated cobalt effect is more likely to lead to hypothyroidism, the effects are not considered as a response to exposure to cobalt.

At the factory, in which semisoluble cobalt dyes were used, a previous cross-sectional study had been carried out of the 46 porcelain painters and of 51 painters not exposed to cobalt as a reference group (Raffn et al. 1988). Prior to the introduction of technical improvements, the plate painters were heavily exposed to cobalt in the past. They were examined twice – right after an approximately six-week holiday and after resuming work for four weeks. In the first series of measurements, urinary cobalt excretion was 81.6 nmol/L (~ 4.8 µg/L), while it was 1308 nmol/L (~ 77 µg/L) in the second series about four weeks after resumption of work. Further examinations included ECG recording, lung function tests and the determination of blood parameters. Apart from an insignificant increase in heart rate, no cardiac effects were observed. Obstruction and a slight, albeit significant decrease in haematocrit and mean corpuscular volume were observed in exposed painters. None of these changes were associated with cobalt exposure. The obstructive changes were attributed to the high cobalt exposure in the past and the dust effect.

Sensitizing effects on the respiratory tract were described in the studies by Kusaka et al. (1986) and Roto (1980).

Workers at a Belgian cobalt refinery and control groups were examined at different times for possible effects of cobalt exposure on the heart, lungs, thyroid gland and blood count. The first examinations were carried out in 1993 (Swennen et al. 1993). At that time, the 82 workers excreted on average 69.8 µg cobalt/g creatinine (geometric mean, GM), which corresponds to approximately 84 µg cobalt/L urine.

Thyroid hormone concentrations were decreased without any clinical relevance. Haematocrit, haemoglobin level and RBC count decreased. No significant changes were found in creatine kinase of the MB type (CK-MB) and in type III procollagen peptide. For the dyspnoea reported by the workers, no abnormalities were detected in the lung function tests or on chest radiographs.

The working group headed by Lantin examined 249 workers in the same facility from February 2008 to August 2009 (Lantin et al. 2011, 2013). The median cobalt excretion was 3.9 µg/g creatinine (~ 4,68 µg cobalt/L urine). Blood count, thyroid hormones, ECG and echocardiogram showed no changes caused by cobalt exposure.

146 workers at a Swedish hard metal factory were examined for cardiac (ECG) and pulmonary effects (lung function tests, chest radiography) (Alexandersson and Atterhög 1980). The workers exposed to an indoor air concentration of 0.01 mg cobalt/m^3 (corresponding to ~ 6 µg cobalt/L urine according to the EKA correlation) showed ECG changes, which, however, were attributed to exposure to cutting oil. Another argument for a non-cobalt-associated change is that in the group exposed to 0.06 mg cobalt/m^3 (corresponding to ~ 36 µg/L urine according to the EKA correlation) there were no ECG abnormalities. In this group, however, obstructive pulmonary changes were observed.

Linna et al. (2003, 2004) investigated the cardiac and pulmonary functions in workers at a Finnish cobalt factory. Cobalt exposure in the highly exposed group averaged 0.1 mg/m^3 from 1977 to 1986 and 0.06 mg/m^3 from 1987 to 2000 (data read off a graphical representation of the average exposure). For this group, the authors indicate a prolonged isovolumic relaxation time (IVRT) in echocardiographic analyses. According to the current guidelines (Nagueh et al. 2009), the standard values for the age group examined (median 45 years) are 74 ± 7 ms. In the examined collective, they were 49.7 ± 10 ms in the control group and 53.3 ± 7.9 ms in the higher exposed group. There seems to be a systematic error. In general, IVRT is considered to be a weak criterion for diastolic dysfunction and to be susceptible to measurement errors. No deviations from normal clinical findings were observed for the deceleration time. However, discrete changes within the normal range were observed.

Gennart and Lauwerys (1990) subjected 48 workers at a Belgian plant producing diamond cobalt circular saws and 23 control subjects to lung function tests. During manufacturing diamond cobalt circular saws, exposure to cobalt without additional exposure to tungsten is assumed. Exposed subjects considerably more often reported symptoms such as cough, sputum and dyspnoea and had significantly lower FVC and FEV1 values in lung function tests than the control subjects. However, their overall results were still within the normal range. In contrast to workers with less than five years of employment and an internal exposure of 31.6 µg/g creatinine (~ 38 µg/L), restrictive lung function was prevalent in workers with a longer period of employment and an excretion of 66.1 µg cobalt/g creatinine (~ 79 µg/L).

No haematological or cardiac changes were observed in cobalt foundry workers at a blood cobalt concentration of 26 µg/L (Paustenbach et al. 2013), which corresponds to approximately 312 µg cobalt/L urine (Angerer et al. 1985).

Workers involved in the manufacture of cobalt salts were examined for haematological and pulmonary effects (Morgan 1983). Neither the blood count, the chest X-ray, the lung function test nor the ECG showed any pathological changes at a mean internal exposure of 340 µg cobalt/L urine.

Workers at a Swedish hard metal producing plant underwent spirometry (Rehfisch et al. 2012). The workers were grouped into four categories (0–3) depending on the level of exposure. The authors described a dose-dependent, insignificant decline in FEV1 (forced expiratory volume in the first second), although this decline was still within the range of the age-related decline of this parameter.

16.1.2 Studies not Related to Occupational Medicine

Cobalt salt used to be added to beer to stabilize the foam, which led to fatal cardiomyopathy in malnourished alcohol-addicted beer drinkers (Kesteloot et al. 1968). This effect was possibly caused by a decrease in serum albumin induced by malnutrition. This probably increased the concentration of free, unbound cobalt, which in turn increased the adverse effects. Kesteloot et al. (1968) therefore examined beer drinkers eating an adequate diet, in whom neither ECG, echocardiographic, chest radiographic nor blood abnormalities were observed as a result of cobalt consumption. Based on the kinetic model of Finley et al. (2012) and Paustenbach et al. (2013), the internal exposure of this collective was 34 µg cobalt/L blood (~ 408 µg/L urine).

In a study by Tvermoes et al. (2014), healthy subjects voluntarily ingested 1 mg cobalt per day for 90 days. The subjects were extensively examined and checked for effects of the cobalt exposure on cardiac, thyroid, haematological and neurological functions. A clinically significant change in the analysed parameters was not observed. At the same oral dosage, the blood cobalt concentration in the female subjects was significantly higher than in the male subjects. One possible explanation given was women's increased iron demand, as iron and cobalt share a common intestinal uptake mechanism.

Cobalt(II) ions seem to stimulate the erythropoietin-dependent erythrocyte regeneration via HIF-1α (hypoxia-inducible factor). In healthy adults, cobalt has an erythropoietic effect (Davis and Fields 1958) from a concentration of 320 µg/L in blood, which corresponds to a concentration of 3840 µg/L in urine. In anaemic patients undergoing dialysis (Bowie and Hurley 1975), cobalt stimulates erythropoiesis from a concentration of 600 µg/L blood (corresponds to approx. 7200 µg/L urine) (Paustenbach et al. 2013).

As already mentioned, cobalt inhibits the iodine uptake by the thyroid gland. In 12 healthy adults, iodine-131 uptake decreased considerably during and after a two-week ingestion of 150 mg cobalt per day (Roche and Larysse 1956). According to Paustenbach et al. (2013), this dosage corresponds to a concentration of 300 µg/L blood (~ 3600 µg cobalt/L urine).

16.1.3 Case Reports for Patients with Endoprosthetic Replacements

Non-occupational cobalt exposure is described for patients with endoprosthetic replacements. The reported cobalt concentrations in these patients were between 168 and 78 252 µg/L urine (see Figure 1). Table 2 summarizes cases of systemic toxicity of cobalt released from metal implants. The lowest concentration at which cardiomyopathy was diagnosed was 163 µg cobalt/L urine (Machado et al. 2012). Other risk factors identified for this patient were overweight and non-insulin-dependent diabetes mellitus, while cardiac symptoms improved after revision of the

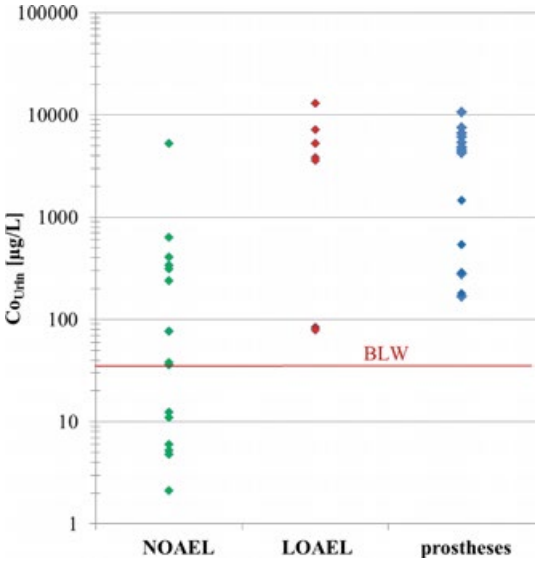

Figure 1 NOAEL and LOAEL exposure levels for urinary cobalt concentrations (studies see Table 1) as well as cobalt concentrations in the urine of symptomatic patients after prosthesis implantation (studies see Table 2)

hip replacement. From 276 µg cobalt/L urine, auditory perception was impaired; sometimes retinopathy and optic nerve atrophy were described. Such effects have not been reported yet in connection with occupational exposure. At concentrations greater than 4700 µg/L, impaired thyroid function was reported.

16.2 Evaluation of the BLW Value

The sensitizing effect of cobalt on the respiratory tract is not an endpoint for the evaluation of the Biological Guidance Value as it does not result from systemic internal exposure. Pulmonary fibrosis is to be assessed more critically. Especially in the hard metal industry, co-exposure to tungsten plays a major role in the pathogenesis of this disease (Lison 1996). The findings of hard metal workers are therefore not taken into account.

At a concentration of 84 µg/L urine, altered laboratory parameters indicating hypothyroidism were found in workers at a cobalt refinery (Swennen et al. 1993). At a concentration of 79 µg/L urine, restrictive ventilatory defects were observed in workers at a plant producing diamond circular saws. Workers with a concentration of 38 µg cobalt/L urine showed no abnormalities in spirometric parameters (Gennart and Lauwerys 1990).

The cardiotoxic effect of cobalt and cobalt compounds is considered as a critical endpoint for the derivation of a systemic toxicity limit. At a concentration of approx. 36 µg cobalt/L urine (calculated from airborne concentrations taking into account the EKA correlation), echocardiographic findings were obtained in workers at a Finnish cobalt plant, which showed no clear cardiotoxic effects: clinical symptoms were absent, the findings were within normal limits of the current recommendations for echocardiography and there were minor deviations in two parameters only (Linna et al. 2003, 2004).

A BLW of 35 µg cobalt/L urine is therefore derived.

In the case of long-term exposure, sampling should be performed at the end of shift after several preceding shifts.

16.3 Evaluation of the EKA Correlation

Since the last re-evaluation, several studies have been published investigating the relationship between external and internal exposure (see Table 3).

In Spain, a group of 20 hard metal industry workers exposed for seven years on average was examined (Torra et al. 2005). Both stationary and personal air samplings were performed to determine the cobalt concentration in air. At a mean cobalt concentration of 100 µg/m³ in ambient air, the mean urinary excretion was 46 µg/g creatinine.

Yokota et al. (2007) collected personal air samples from workers manufacturing nickel-hydrogen batteries on two consecutive days. The nickel and cobalt concentrations in urine were determined at the beginning and end of shift. The 16 workers had been employed at the factory for 0.5 to 7 (mean 3.5) years and were exposed to a mixture of metallic cobalt, cobalt oxyhydroxide and nickel hydroxide, wearing dust masks as a personal protective measure. The correlation between cobalt concentrations in post-shift urine and in air (averaged over the length of the shift) was given by the equation Co (µg/L) = 15.8 + 243.8 · Co air (mg/m³). The relatively low coefficient of determination of 0.491 ($p < 0.01$) was attributed to the wearing of dust masks.

Personal ambient air samples were collected from 16 workers who were exposed to cobalt oxide at a factory manufacturing digital video cassettes and correlated with the cobalt concentration in post-shift urine (Fujio et al. 2009). Workers wearing dust respirators were excluded from the study. In total, the concentrations were determined in 60 samples on three days. Except for one sample, all ambient air concentrations were below 50 µg/m³. For ambient air concentrations below 3 µg/m³, there was a significant correlation with a correlation coefficient of 0.76 ($p < 0.01$) and the regression equation Co (µg/g creatinine) = 3.02 + 1050 · Co air (mg/m³).

The working group headed by Martin used data collected in 1988 and 1993 to verify a toxicokinetic model (Martin et al. 2010). During one working week, personal ambient air and urine samples were collected to measure cobalt concentrations in 16 workers from two factories producing tungsten carbide cutting tools. Air concentrations were between 4.9 and 144.2 µg/m³, while urinary concentrations were between 1.6 and 16.4 µg/g creatinine and 2.3 and 15.5 µg/L, respectively. The stated cobalt concentra-

tions in air and urine, giving only the geometric mean of a person's collected samples, yield the following correlation: Co (µg/g creatinine) = 3.63 + 103.1 · Co air (mg/m³) with a coefficient of determination of $R^2 = 0.75$. If excretion is not related to creatinine, the correlation Co (µg/L) = 5.06 + 91 · Co air (mg/m³) ($R^2 = 0.49$) is obtained.

Cobalt concentrations in blood, plasma and spot urine were determined for 55 workers employed for 11 years on average in the production of carbide cutting tools. Air monitoring was performed by stationary sampling in the different areas (De Palma et al. 2010). The authors described a positive correlation between the cobalt concentrations in air and in blood (0.58), plasma (0.53) and urine (0.50).

Table 4 shows the regression equations of various studies and the corresponding EKA correlations. The wearing of dust masks affected the correlation in the study by Yokota et al. (2007). Data from workers with dust respirators were therefore excluded in the second study carried out by the same working group (Fujio et al. 2009). Furthermore, in this study workers were exposed only to cobalt oxide and not to mixtures of cobalt and tungsten as in the studies by Martin et al. (2010), De Palma et al. (2010) and Torra et al. (2005). It is noticeable that the regression curve for mixed exposure to hard metals appears to be significantly flatter than for exposure to cobalt alone. In the study by Fujio et al. (2009), a relationship between external and internal exposure comparable to the EKA correlation is derived. In the study by Torra et al. (2005), a mean concentration of 100 µg cobalt/m³ in ambient air corresponded to an excretion of 55.2 µg cobalt/L urine (assuming a creatinine excretion of 1.2 g/24 h). This value also closely approximates the EKA correlation.

The EKA correlation for cobalt and cobalt compounds is thus confirmed and extrapolated to the low-dose range.

The correlation between external and internal exposure yields the following data:

Air Cobalt [mg/m³]	Urine Cobalt [µg/L]
0.005	3
0.010	6
0.025	15
0.050	30
0.100	60
0.500	300

Sampling time: in the case of long-term exposure: at the end of shift after several preceding shifts

16.4 Evaluation of a BAR Value

Since 2006, various studies have been published investigating the background exposure of the general population (see Table 5). The mean and median urinary cobalt concentrations range from 0.34 to 1.5 µg/L.

In the study by De Palma et al. (2010), the 95th percentile in 34 persons of the general population in Italy was 1.16 µg cobalt/L urine (0.08–1.21 µg/L urine). The U. S. environmental study for 2013–2014 indicates a 95th percentile of 1.23 µg cobalt/L urine (1.17–1.34 µg/L urine) for the population aged 20 and over (CDC 2017). The concentration was measured in 1811 subjects. From 1999 to 2019, the 95th percentile varied between 1.06 and 1.35 µg/L urine in this population group. Overall, the cobalt concentration is higher in women and 12–19-year-olds.

Heitland and Köster (2006) determined a background exposure to cobalt of 1.53 µg/L urine in 87 adults in Germany.

International studies on background exposure to cobalt yield a background level of 1.2 µg cobalt/L urine. The BAR is derived from the data collected in Germany by Heitland and Köster (2006) in order to take relevant regional/geogenic influencing factors into account.

Based on these considerations, a

BAR of 1.5 µg cobalt/L urine

has been set.

In the case of long-term exposure, sampling should be performed at the end of shift after several preceding shifts.

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Table 1 Studies on internal exposure and effects on the human body

Authors	Workplace, n	NOAEL [µg Co/L urine]	LOAEL [µg Co/L urine]	Biological effects
Porcelain plate painting				
Prescott et al. 1992	36 ♀ Cobalt aluminate	2.12[1),3)]		
	25 ♀ Cobalt zinc silicate	12.4[1),3)]		Thyroid: T_4 ↑, fT_4 ↑ (but still within the normal range)
Raffn et al. 1988	46 ♀ Cobalt blue			
	After 6 weeks off work	4.8[1)]		Heart: heart rate ↑[9)] Lung: RV ↑, PEF ↓, FEV1 ↓[9)] Blood count: no effects:
	After 4 weeks of work	77[1)]		Heart: heart rate ↑[9)] Lung: PEF ↑, FEV1 ↑, MEF50 + 25 ↓[9)] Blood count: Hct ↓, MCV ↓[9)]
Cobalt refinery				
Lantin et al. 2011, 2013 (same collective)	249/248 ♂	4.68[4),10)]		Thyroid: no effects Blood count: no effects Heart: no effects (ECG, echo)
Swennen et al. 1993 (same plant as in Lantin studies)	82 ♂	84.0[2),4)]		Heart: no effect on creatine kinase (MB type)
			84.0[2),4)]	Thyroid: T_3 ↓, T_4 ↓, TSH ↑ Blood count: Hct ↓, RBC ↓, Hb ↓
		84.0[2),4)]		Lung: dyspnoea, spirometry: NAD

Table 1 (continued)

Authors	Workplace, n	NOAEL [µg Co/L urine]	LOAEL [µg Co/L urine]	Biological effects
Cobalt production				
Roto 1980	147		18–90[5)]	occupational asthma; no pulmonary fibrosis, no chronic bronchitis
Linna et al. 2003, 2004	110 ♂	36[6)]		Heart: prolonged DT when comparing the highly exposed subjects to the control group, but still within the normal range shortened IVRT (control group > highly exposed subjects; but systematic deviation) Lung: MEF25 + 50 ↓ only for exposed smokers[9)]; 1 case of cobalt-induced asthma
Hard metal industry				
Kusaka et al. 1986	319 (ill 18 ♂)		11[5)]	occupational asthma
Alexandersson and Atterhög 1980	146 ♂	36[1),5)]		Heart: no effect (ECG)
			36[1),5)]	Lung: obstruction

Table 1 (continued)

Authors	Workplace, n	NOAEL [µg Co/L urine]	LOAEL [µg Co/L urine]	Biological effects
Production of diamond circular saws				
Gennart and Lauwerys 1990	48 ♂ + ♀			
	Smokers (n = 19)	30.8[4)]		FVC and FEV1 ratios were significantly lower in exposed subjects than in control subjects, but still within the normal range
	Non-smokers (n = 29)	48.8[4)]		
	29 ♂ + ♀ (non-smokers)			
	Exposure < 5 years (n = 19)	38[1),4)]		Lung: restrictive ventilation disorder with increasing duration of employment
	Exposure > 5 years (n = 10)		79[1),4)]	
Foundry workers				
Angerer et al. 1985	40 ♂	312[7)]		Heart: no cardiomyopathy no effect on erythropoiesis
Workers involved in the manufacture of cobalt salt				
Morgan 1983	49 ♂	340[1)]		Blood count: NAD Lung: X-ray, spirometry: NAD Heart: no cardiomyopathy
Kesteloot et al. 1968	12 beer drinkers without calorie restriction	408[7)]		Heart: X-ray, ECG NAD Blood count: Hb, Hct NAD

Table 1 (continued)

Authors	Workplace, n	NOAEL [µg Co/L urine]	LOAEL [µg Co/L urine]	Biological effects
Tvermoes et al. 2014	Adults (5 ♂, 5 ♀) 90-day trial, 1 mg Cobalt/d p. o.	♀ 636[1),8)] ♂ 240		Heart: laboratory findings, ECG, echo: NAD neurological effects: hearing, vision, sensory function, etc.: NAD Thyroid: laboratory findings: NAD Blood count: laboratory findings: NAD
Bowie and Hurley 1975	11 dialysis patients Therapy with cobalt chloride p. o. (25 mg/d for 4 weeks, then 50 mg/d for 4 weeks)	7200[7)] 5280[7)]	7200[7)] 13044[7)]	Thyroid: NAD Blood count: Hct ↑ Hearing loss
Davis and Fields 1958	6 adults Therapy with cobalt chloride p. o. (150 mg/d)		3840[7)]	Blood count: polycythaemia
Roche and Larysse 1956	12 adults Cobalt chloride p. o. (3 x 50 mg/d for 2 weeks)		3600	Thyroid: Iodine-131 uptake ↓

HF = heart rate; RV = residual volume; PEF = peak expiratory flow; FEV1 = forced expiratory volume in one second; BB = blood count; Hct = haematocrit; NAD = no abnormality detected; DT = deceleration time; p. o. = per os; MCV = mean corpuscular volume

[1)] Arithmetic mean (AM)

[2)] Geometric mean (GM)

[3)] Conversion: µg/mmol Crea · 8.84 = µg/g Crea · 1.2 = µg/L

[4)] Conversion: µg/g Crea · 1.2 = µg/L

[5)] derived from cobalt concentration in air

[6)] lowest exposure of the highly exposed group (0.06 mg/m^3)

[7)] Cobalt concentration in blood · 12, based on 1986 EKA correlation; according to Finley et al. (2012) and Paustenbach et al. (2013)

[8)] Cobalt concentration in blood · 12

[9)] Authors see no relationship between exposure to cobalt and observed effects

[10)] Median

Table 2 Internal exposure and biological effects on patients with endoprosthetic replacements

Authors	Patient [Age]	Co Urine [µg/L]	Effects					
			Cardiac	Thyroid	Auditory	Visual	Neurological	Other
Machado et al. 2012	♂ (75 y)	163[1)]	Cardiomyopathy					Overweight, non-insulin-dependent diabetes mellitus
Mao et al. 2011	♂ (60 y)	182[1)]	Hypertension				Muscular fatigue, cognitive problems, impaired memory, concentration disorders	Hand and foot spasms
Tower 2010		276[1)]			Hearing loss		Vertigo, cognitive problems	Dyspnoea, exanthema,
Mao et al. 2011	♀ (73 y)	290[1)]					Neurological symptoms, cognitive problems, impaired memory	Anorexia, apoplexy, metallic taste,
Ng et al. 2013	♀ (39 y)	535[1)]	NAD	NAD		Retinopathy (chorioretinal degeneration)	Nausea	Metallic taste
Tower 2010	♂ (49 y)	1464[1)]	Diastolic dysfunction		Tinnitus, hearing loss	Optic nerve atrophy	Cognitive problems, depression, hand tremor	Fatigue, headache
Allen et al. 2014	♀ (59 y)	4783[1)]	Cardiomyopathy	Hypothyroidism				Dyspnoea, fatigue, oedema
Steens et al. 2006	♂ (53 y)	4776[1)]			Hearing loss	Retinopathy, optic nerve atrophy, dysfunction of the macula densa	Paraesthesia	Dermatitis

Table 2 (continued)

Authors	Patient [Age]	Co Urine [µg/L]	Effects					
			Cardiac	Thyroid	Auditory	Visual	Neurological	Other
Ikeda et al. 2010	♀ (56 y)	> 4800[2)]		Hypothyroidism	Hearing loss		Distal sensory neuropathy	
Apel et al. 2013	♂ (65 y)	5357[1)]	Cardiomyopathy	Hypothyroidism		Retinal dysfunction (reduced vision)	Bulbar paralysis, motor axonopathy	Pulmonary embolism
Pelclova et al. 2012	♂ (56 y)	6072[1)]	Cardiomyopathy	Hypothyroidism	Hearing loss		Distal paraesthesia	Weight loss
Rizzetti et al. 2009	♀ (58 y)	6588[2)]		Hypothyroidism	Hearing loss	Vision loss	Central and peripheral neuropathies	
Oldenburg et al. 2009	♂ (55 y)	7500[2)]	Cardiomyopathy	Hypothyroidism	Hearing loss		Peripheral neuropathy, fatigue	Eczema
Dahms et al. 2014	♂ (55 y)	10607[2)]	Cardiomyopathy	Hypothyroidism	Hearing loss	Vision loss		Fever, oesophagitis
Zywiel et al. 2013	♂ (52 y)	78252[2)]	Cardiomyopathy	Hypothyroidism	Tinnitus		Fatigue	Anorexia, death

y = years
[1)] calculated from the maximum concentrations of cobalt in serum reported in the literature · 12
[2)] calculated from the maximum concentrations of cobalt in blood reported in the literature · 12

Table 3 Studies on internal and external exposure at the workplace

Authors	Workplace, workers	Cobalt in air	Cobalt in blood	Cobalt in urine	
		[µg/m³]	[µg/L]	[µg/L]	[µg/g creatinine]
Hard metal production					
Torra et al. 2005	n = 19 ♂; Age: 41 years (20–56 y)	100 ± 25 (79–130) [AM ± SD (range)]			46 ± 17 (11–110) [AM ± SD (range)]
Manufacture of tungsten carbide cutting tools					
Martin et al. 2010	n = 16 ♂	4.9–144.2 (GM range) 108 samples		2.3–15.5 (GM range) 507 samples	1.6–16.4 (GM range) 507 samples
De Palma et al. 2010	n = 55 (37 ♂, 18 ♀) Age: 38.5 ± 10.4 years (21–61) [AM ± SD (range)]				
	Pre-sintering: Pouder weighing Pouder pressing	 1.7 2.5	 3.27 ± 1.4 n = 17	 10.28 ± 2.09 n = 13	
	Sintering:	0.45	1.15 ± 2.5 n = 5	3.38 ± 2.24 n = 6	
	Wet grinding:	1.50	2.22 ± 1.68 n = 14 (GM ± GSD)	4.47 ± 3.44 n = 13 (GM ± GSD)	
Manufacture of nickel-hydrogen accumulators; Co-metal, CoO(OH), $Ni(OH)_2$					
Yokota et al. 2007	n = 16 ♂; Mean age: 39 years dust masks	67 (4–330) [AM (range)] TWA		38.6 ± 47.4 (1.0–176.8)[1)] 28.2 ± 34.0 (1.0–127.8)[1)] [AM ± SD (range)]	

Table 3 (continued)

Authors	Workplace, workers	Cobalt in air	Cobalt in blood	Cobalt in urine	
		[µg/m³]	[µg/L]	[µg/L]	[µg/g creatinine]
Manufacture of digital video cassettes (cobalt oxide)					
Fujio et al. 2009	n = 16 ♂ Age: 46.3 ± 4.8 years (AM ± SD) no dust respirators	<50 60 samples		(diagram)	

AM = arithmetic mean; GM = geometric mean; GSD = geometric standard deviation; SD = standard deviation; TWA = time-weighted average
[1)] results from two consecutive days

Table 4 Correlations between cobalt concentrations in workplace air and urine; information on exposure and collective Table 3

Authors	n	Regression equation $Co_{Urine} = a \cdot Co_{Air} + b$ Co_{Urine} [µg/L], Co_{Air} [mg/m³]	Correlation coefficient r Coefficient of determination R^2	Correlations Air [mg/m³]	 Urine [µg/L]	Remarks
Yokota et al. 2007	30	$Co_{Urine} = 243.8 \cdot Co_{Air} + 15.8$[1)]	r = 0.491	0.01	18	Wearing dust masks
				0.025	22	
				0.05	28	
				0.1	40	
				0.5	138	
Fujio et al. 2009	20	$Co_{Urine} = (1050 \cdot Co_{Air} + 3.02) : 1.2$[1),2)]	r = 0.76	0.01	11	No personal protective measures
				0.025	24	
				0.05	46	
				0.1	90	
				0.5	440	
Martin et al. 2010	16	$Co_{Urine} = 91 \cdot Co_{Air} + 5.06$	$R^2 = 0.49$	0.01	6	
				0.025	7	
				0.05	10	
				0.1	14	
				0.5	51	

[1)] regression was calculated by authors of the study
[2)] 1.2 g/L creatinine was used for conversion to µg/L

Table 5 Urinary cobalt concentrations in the general population

Country, collective	Cobalt in urine		Authors
	[µg/L]	[µg/g creatinine]	
Germany			
n = 87 Age: 18–65 years	95th percentile: 1.53 Range (0.02–3.3)		Heitland and Köster 2006
Italy			
n = 34 (14 ♂, 20 ♀) Age: 61.4 ± 12.4 (28–80) years	95th percentile: 1.16 Range (0.08–1.21)		De Palma et al. 2010
Spain			
n = 50 Age: 21–83 years		1.2 ± 0.4 (1.1–1.5) [AM ± SD (range)] 95th percentile < 1.3	Torra et al. 2005
Pakistan			
n = 75 ♂ Age: 25–55 years	1.5 ± 0.4 (1.05–1.96) [AM ± SD (range)] 95% KI: 1.35–1.57		Afridi et al. 2009

Table 5 (continued)

Country, collective	Cobalt in urine		Authors
	[µg/L]	[µg/g creatinine]	
Japan			
n = 13,000 urine samples from 1000 ♀ Age: 47.5 ± 10.4 years (20–81) [AM ± SD (range)]	0.68 ± 3.04 (< 0.1 (LOD)–281) [GM ± SD (range)]	0.6 ± 2.75 (< 0.1 (LOD)–77) [GM ± SD (range)]	Ohashi et al. 2006
n = 25 ♂ Age: 45.0 ± 2.9 years [AM ± SD]		0.5 ± 0.4 (AM ± SD)	Fujio et al. 2009
United States[1)]			
n = 1811 > 20 years	95th percentile: 1.23 (95% KI: 1.17–1.34)		CDC 2017

LOD = limit of detection; CI = confidence interval; GM = geometric mean; AM = arithmetic mean; SD = standard deviation

[1)] The data specified are from the 2013–2014 survey

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Approved by the Working Group: 18.01.2017