


Biological monitoring of dermal and air exposure to cobalt at a Swedish hard metal production plant: does dermal exposure contribute to uptake?

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Summary

Background. Occupational exposure to cobalt is well established in hard metal manufacture. Cobalt is known to cause contact allergy, asthma, hard metal lung disease, and lung cancer. The relationship between skin exposure and uptake determined in blood has not been extensively investigated.

Objective. To examine whether skin and inhalable air exposure to cobalt contributes to uptake, determined as cobalt in blood, in a hard metal manufacturing factory.

Methods. The amount of cobalt on the skin found with an acid wash technique, the air concentrations of inhalable cobalt and cobalt blood concentrations were determined and correlated in exposed workers.

Results. We found a significant rank correlation for cobalt concentrations on the skin, in inhalable air, and in blood (0.376–0.498). Multiple linear regression showed significant regression coefficients for cobalt skin exposure and blood ($B = 0.01$, $p < 0.05$) and for inhalable cobalt in air and blood ($B = 49.1$, $p < 0.001$). According to our model based on data from the regression analyses, a twofold increase in skin exposure levels at different air concentrations caused a 3–14% increase in blood levels.

Conclusions. Our data suggest that skin exposure to cobalt in the hard metal industry could affect the total uptake at the same order of magnitude as air exposure.

Key words: acid wash technique; blood concentration; cobalt; hard metal; skin absorption; skin exposure.

Occupational exposure to cobalt is well established in the hard metal manufacturing industry and from the use of

carbide tools in the manufacture of engineering products. Products made of hard metal are heat-resistant, tough, and extremely durable, which is why they are often used as cutting tools. Hard metal is based on tungsten carbide, for which cobalt constitutes a binder. The hard metal production company in our study is one of the world's leading companies producing hard metal cutting tools, and approximately 1 million carbide inserts are produced each week.

The production of hard metal has been associated with numerous adverse health effects linked with cobalt exposure. Cobalt is a known sensitizer (1, 2), and can induce allergic contact dermatitis (3, 4). Exposure to

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cobalt on the skin can be easily determined with a skin wash technique (5); however, more knowledge is needed for biological monitoring of contact allergens (6).

Exposure to cobalt can also cause other adverse health effects, for example asthma (7, 8), hard metal lung disease (9, 10), and cardiovascular diseases (11, 12). Moreover, the International Agency for Research on Cancer has classified cobalt as a human carcinogen (13). Reported exposure levels for cobalt in air in the hard metal industry vary from 0.001 to 6 mg/m³ (14–16), and are of the same magnitude as in the Swedish manufacturing industry (17). Uptake of cobalt by inhalation has long been known (18); however, extensive skin deposition and absorption from direct contact with materials containing cobalt and through deposited aerosols (19–21) and also by ingestion (22) occurs. A Swedish study on dermal exposure measurements in the production of gas turbines and space propulsion components showed dermal cobalt deposition ranging from 0.0013 to 4.5 µg/cm²/h (21).

In vitro studies on cobalt-containing powder have shown that cobalt ionizes in the presence of sweat and can penetrate the skin (23–25). Correlations between cobalt blood and urine concentrations and cobalt air exposure have been shown (26, 27). In biological monitoring of cobalt exposure, cobalt in urine reflects the exposure as an average of a longer time period of work shifts, whereas cobalt in blood reflects acute exposure.

Currently, there is insufficient knowledge regarding the importance of dermal exposure in relation to absorption via the respiratory tract in cobalt exposure. The aim of this study was to determine the amount of cobalt on the skin, in the air, and in blood, to determine the relationships between skin exposure, inhalable cobalt air concentration, and uptake expressed as cobalt in blood.

Materials and Methods

The study was performed between November 2007 and June 2009 in a hard metal production company in Sweden. The production process consists of several steps, and the departments included were powder production, pressing, periphery grinding (shape and grade), charging/de-charging, physical vapour deposition and chemical vapour deposition furnaces, process laboratory, warehouse, and inspection. Informed oral and written consent was obtained from each participant. Seventy-two employees participated in the study, and measurements of skin exposure were conducted for 62 individuals. Biological monitoring of cobalt concentrations in blood was conducted for all 72 participants. Skin exposure measurements were performed for 2 h during the work shift.

The time during the work day varied, but the exposure period was the same for all participants. Personal air exposure was measured through sampling of inhalable dust in the breathing zone for an 8-h work shift. Biological measurements to determine cobalt concentrations in blood were conducted on four occasions for each person, but it is the difference between before-shift and after-shift samples that is considered to represent the concentration for the test day. Air, skin and biological measurements were conducted on the same day. The study was approved by the ethics committee of the Regional Ethical Review board in Uppsala, Sweden (Dnr 2007/260).

Sampling, measurements, and analysis

Skin exposure was measured with an acid wash technique (5). Participants first washed their hands with soap and water, and the areas of interest for the study were then washed with 1% HNO₃ and rinsed with ultrapure water (Milli-Q Gradient; Merck Millipore, Darmstadt, Germany). Cut-off fabric fingers from both a fabric glove and a plastic glove were carefully fixed with tape in order to avoid exposure of the little finger during the exposure period. For right-handed persons, the little finger on the left hand was covered, and for left-handed persons the little finger on the right hand was covered. The participants then worked as usual for 2 h without washing their hands during this period. After the exposure time had elapsed, areas of 3 × 3 cm were marked on the palm and areas of 1 × 2 cm were marked on the thumb, index finger, middle finger and ring finger on the dominant hand and on the little finger on the non-dominant hand. Each marked surface was washed with three pieces of cellulose paper with 500 µl of 1% HNO₃ each (1.5 ml in total). All three patches from the surface were placed in an acid-washed plastic vial (50 ml), which was filled with 23.5 ml of 1% HNO₃. The flasks were shaken for 30 min, and the liquid was then transferred to a different bottle (50 ml). Three unused scraps were treated in the same manner to serve as a blank. The fluid was analysed for cobalt by the use of inductively coupled plasma mass spectrometry (HP 4500 ICP-MS; Agilent Technologies, Palo Alto, California, USA) (28) at the Department of Occupational and Environmental Medicine, Örebro University Hospital.

Blood samples were collected on four occasions for each participant. The personal exposure measurements of inhalable dust were conducted for 8 h with filters in the breathing zone (29). A standard analytical procedure for metal analysis for blood samples and air sampling filters was performed with inductively coupled plasma mass spectrometry (HP 4500 ICP-MS; Agilent Technologies) for determination of cobalt concentrations (28). As controls, samples of whole blood (Serionorm Trace Elements

Whole Blood, level 1 and 2; SERO, Billingstad, Norway) with known concentrations of cobalt were used. All analyses were performed by the Department of Occupational and Environmental Medicine, Örebro University Hospital.

Statistical methods

Results concerning individual cobalt skin exposure have been converted to the average of 1 h and reported as $\mu\text{g}/\text{cm}^2/\text{h}$. Concentrations for the thumb, index finger, middle finger, ring finger and palm were added up to represent cobalt skin exposure.

Biological monitoring of cobalt concentrations in blood is presented as nmol/l , and all four samples are included for presentation of the descriptive data. The concentration of cobalt in inhalable air is presented as mass (mg/m^3). The blood concentrations used in statistical analyses are based on the difference between before-shift and after-shift samples for each person on the test day, and reflect the uptake of cobalt during a work shift. Cobalt in blood was chosen as a better marker of acute exposure than cobalt in urine, and as more suitable for the investigation of cobalt from inhalation and skin.

For cobalt on skin, and biological monitoring of cobalt in blood and cobalt in air, standard parameters such as arithmetic mean, median, standard deviation and range are presented. Statistical analysis includes only individuals for whom sampling of skin, sampling of blood and personal air exposure measurements were carried out. Rank correlation was quantified by the use of Spearman's rho for the relationships between skin, blood and inhalable air cobalt concentrations. Simple linear regression analysis was further used to study relationships between cobalt concentrations in blood and on the skin and in inhalable air, respectively. In addition, multiple linear regression analysis was used to study the relationships between cobalt in blood, skin exposure and inhalable air exposure together. Cobalt blood concentration was the dependent variable, and skin and inhalable air cobalt concentrations were the independent variables.

Two outliers, representing accidental/extreme process situations, were excluded from the analyses. The concentration data used in our analyses are continuous, and parametric tests were used. The data used in our regression analyses were normally distributed as determined by residual plotting of predicted values and studentized residuals and by kernel density plot. All regression analyses were performed with original values. On the basis of the regression analysis, we also present data on the effect of changes from air and skin exposure concentrations on the uptake presented as cobalt in blood. All statistical analyses were performed with SPSS 17.0 software (PASW Statistics Chicago, Illinois, USA).

Table 1. Background data for the study group ($n = 72$)^a

		n (%)
Sex	Men	47 (65)
	Women	25 (35)
Age (years)	≤29	15 (21)
	30–39	12 (17)
	40–49	22 (30)
	50–59	18 (25)
	≥60	5 (7)
Years at current workplace	≤1	3 (5)
	1–4	23 (34)
	5–9	9 (13)
	≥10	32 (48)
Years with current work tasks	≤1	5 (7)
	1–4	30 (43)
	5–9	12 (17)
	≥10	23 (33)
Smoking habits	Non-smoker	35 (51)
	Ex-smoker	19 (27)
	Smoker	15 (22)

n, number of workers.

^aNot all participants provided information regarding work history and smoking habits.

Results

The study sample comprised all 'working ages' and more men than women (Table 1). Almost 50% of the participants had been employed for >10 years, and one-third have had the same work tasks for >10 years. In previous years, there were cases of contact allergy and eczema in the production plant. However, these persons were relocated and were not working at positions where they might handle cobalt during the study period. As a consequence, none of the workers included in this study has reported eczema.

Skin exposure measurements were performed on 62 persons, and six samples per person were taken, with one blank sample serving as a control. The concentrations on the thumb, index finger, middle finger, ring finger and palm were summed to achieve a measure of the total dermal exposure for the hand (Table 2). Cobalt skin concentrations ranged between 0.046 and 100 $\mu\text{g}/\text{cm}^2/\text{h}$, and the highest concentrations were found in the pressing department (mean: 29 $\mu\text{g}/\text{cm}^2/\text{h}$) and the powder department (mean: 3 $\mu\text{g}/\text{cm}^2/\text{h}$). The concentrations for fingers varied widely among individuals, but, as a tendency, the thumb had a slightly higher value, and values then decreased from the thumb to the ring finger (not shown). Cobalt was found in all types of samples, including the finger considered to be unexposed.

Blood levels for cobalt varied between <3.2 and 110.3 nmol/l (mean: 7.95 nmol/l) (Table 3). Only 1% of the samples exceeded the Biological Exposure Index (BEI)

Table 2. Cobalt skin exposure concentrations from the hand testing areas (thumb, index finger, middle finger, ring finger, and palm) by department ($\mu\text{g}/\text{cm}^2/\text{h}$)

Department	n	Mean	Median	SD	Range
Powder	6	3.0	1.5	3.8	0.9–11
Pressing	25	29.0	23.0	23.0	0.44–100
Periphery grinding (shape)	11	1.9	1.6	0.99	0.33–4.2
Periphery grinding (grade)	1	0.49	0.49	–	–
Charging/decharging	6	0.21	0.21	0.11	0.046–0.33
PVD furnace	3	0.20	0.15	0.084	0.14–0.29
CVD furnace	2	0.10	0.10	0.034	0.075–0.12
Inspection	2	0.55	0.55	0.066	0.088–1.0
Storage	2	0.16	0.16	0.11	0.081–0.23
Process laboratory	4	2.3	1.4	2.1	1.0–5.4
Total	62	12	2.0	20.0	0.046–100

CVD, chemical vapour deposition; n, number of workers; PVD, physical vapour deposition; SD, standard deviation.

Table 3. Concentrations of cobalt in blood (nmol/l), one to four samples per person, and cobalt in the inhalable air (mg/m^3) from personal exposure measurements

	n	Mean	Median	SD	Range
Blood cobalt (nmol/l)	72	7.95	6.39	9.43	<3.2 to 110.3
Inhalable air cobalt (mg/m^3)	72	0.0030	0.00074	0.0083	0.000028–0.056

n, number of workers; SD, standard deviation.

(17 nmol/l) set by the American Conference of Governmental Industrial Hygienists (30), and 4% were below the detection limit (3.2 nmol/l). Personal air exposure measurements of cobalt concentrations in inhalable air were consistently low, ranging between 0.000028 and 0.056 mg/m^3 (mean: 0.0030 mg/m^3), and 6% of the samples exceeded the Swedish Occupational Exposure Level (OEL) (0.02 mg/m^3) set by the Swedish Work Environment Authority (31).

The rank coefficients for blood and skin, blood and inhalable air and skin and inhalable air ranged between 0.376 and 0.498, and all were significant (Table 4). Linear regression analysis was used to investigate whether skin exposure affects the uptake in relation to the established uptake via inhalation. The relationships between skin, air and blood concentrations were examined (Table 5). With simple linear regression analysis, cobalt blood concentrations were regressed on skin concentrations, and a significant regression coefficient was found ($B = 0.009$, $p < 0.05$). When both the skin data and inhalation data were included in a multiple regression analysis, a lower regression coefficient was obtained for cobalt in blood and on skin than for cobalt in blood and in inhalable dust [$B = 0.010$ and $B = 49.1$, respectively, both significant ($p < 0.05$ and $p < 0.001$, respectively)]. In

Table 4. Rank correlation coefficients (Spearman's rho) between cobalt skin, inhalable air and blood concentrations all significant at the 0.01 level (two-tailed)

	Skin cobalt ($\mu\text{g}/\text{cm}^2/\text{h}$)	Blood cobalt (nmol/L)
Skin cobalt ($\mu\text{g}/\text{cm}^2/\text{h}$)	–	0.376 ^a
Inhalable air cobalt (mg/m^3)	0.489 ^b	0.498 ^b

^an = 61.

^bn = 62.

a further attempt to predict how the cobalt blood concentration depends on skin exposure as compared with air exposure, we used a regression formula (Table 6). Furthermore, we present data on how a decrease (increase) in air exposure concentration would affect the uptake in blood as compared with how much a decrease (increase) in skin exposure concentration would influence it. A twofold increase in cobalt skin exposure from 6 to 12 $\mu\text{g}/\text{cm}^2/\text{h}$ at a given air concentration (0.01 mg/m^3) caused an 8% increase in cobalt blood concentration. A fourfold increase in skin exposure concentration caused a 14% increase in blood concentration. For increasing cobalt air concentrations (0.02 and 0.04 mg/m^3), corresponding increases were seen (3–9%).

Discussion

We investigated the relationship between skin exposure to cobalt, cobalt in inhalable air and the uptake expressed as cobalt in blood. Skin exposure levels were in line with those in other studies, and air levels and biological monitoring of cobalt in blood showed that only 1–6% of the samples exceeded the current OEL and BEI. In the present study, measurements of skin exposure and inhalable air

Table 5. Linear regression analysis between cobalt skin exposure, cobalt in inhalable air, and uptake expressed as cobalt in blood

	Uptake	Exposure	r^2	B	95%CI B	p -Value
Simple linear regression	Blood cobalt	Skin cobalt ($\mu\text{g}/\text{cm}^2/\text{h}$)	0.073	0.009	0.001–0.016	<0.05
	Blood cobalt	Inhalable air cobalt (mg/m^3)	0.174	53.0	24.5–81.6	<0.001
Multiple linear regression	Blood cobalt	Skin cobalt ($\mu\text{g}/\text{cm}^2/\text{h}$)	0.317	0.010	0.003–0.016	<0.01
		Inhalable air cobalt (mg/m^3)	–	49.1	26.8–71.4	<0.0001

95%CI (B), 95% confidence interval for B ; B , regression coefficient; r^2 , explained variance.

Table 6. A regression-based model predicting the influence of changes in cobalt air and skin concentrations on cobalt blood levels

Blood (nmol/L)	Air (mg/m^3)	Skin ($\mu\text{g}/\text{m}^2/\text{h}$)
0.77	0.01	6
0.83	0.01	12
0.95	0.01	24
1.26	0.02	6
1.32	0.02	12
1.44	0.02	24
2.24	0.04	6
2.30	0.04	12
2.42	0.04	24

and biological monitoring were all conducted on the same day for each participant, and the data can therefore be used to assess relationships. The results showed a significant correlation between cobalt skin exposure, inhalable air concentrations and cobalt in the blood (Spearman's rho 0.376–0.498). Significant regression coefficients was also seen when multiple linear regression was applied for inhalable cobalt in air and cobalt in blood ($B = 49.1$, $p < 0.001$), and for cobalt skin exposure and cobalt in blood ($B = 0.010$, $p < 0.05$). Using our multiple linear regression data in order to investigate the influence of skin concentrations on the uptake of cobalt in blood, we saw a relationship between cobalt skin and air concentrations. When cobalt skin levels were doubled at a given air level, the blood levels were increased by 3–13%, and a corresponding increase in inhalable air levels caused a 40–80% increase in blood levels. To our knowledge, our study is the first to assess cobalt levels in the hard metal production industry by conducting simultaneous measurements of skin exposure, and biological monitoring of blood and personal air exposure. Exposure was investigated for all departments and workers likely to be exposed to cobalt.

In a Swedish study measuring skin concentrations of cobalt, using acid wiping during the production of gas turbines and space propulsion components, levels ranged from 0.0013 to 4.5 $\mu\text{g}/\text{cm}^2/\text{h}$, the highest concentrations being found on the fingers and palm (21). For the majority of our cobalt skin samples, levels are in line with

those in this Swedish study, ranging between 0.046 and 100 $\mu\text{g}/\text{cm}^2/\text{h}$, but with a few samples showing higher concentrations. Biological monitoring of cobalt in blood at a hard metal alloy factory showed levels of 2.3 $\mu\text{g}/\text{l}$ (geometric mean) (14), which are also in line with our levels ranging between <3.2 and 110.3 nmol/l. Only 1% of our cobalt blood samples exceeded the BEI (17 nmol/l). As compared with other studies reporting cobalt air exposure concentrations of 0.001–6.4 mg/m^3 (15) and 0.0009–0.12 mg/m^3 (32), our cobalt levels (0.00003–0.056 mg/m^3) seem to be very low, which is most likely attributable to the production techniques used. Our statistical analyses showed a significant correlation between cobalt in blood and cobalt air levels, which has also previously been shown (26, 27, 33). A significant correlation was also found for cobalt in blood and skin exposure concentrations. This confirms the significance of cobalt skin exposure in addition to inhalable exposure for the uptake of cobalt in blood. Furthermore, our model reaffirms the results regarding the skin uptake contribution to the total uptake of cobalt in blood. A twofold increase in cobalt skin exposure concentrations caused an increase in blood levels of 3–14%, and a corresponding increase in air concentrations caused an increase in blood levels of 39–83%. The magnitude of the impact on blood levels was greater when the skin exposure was higher. This model shows that exposure via inhalation is of greater importance, but also that exposure via skin plays an essential part as a route of entry.

It is intriguing to investigate the importance of skin uptake, as air levels are consistently low, and the majority of our measurements are below the Swedish OEL of 0.02 mg/m^3 for cobalt in the inhalable air fraction. Despite low measured air concentrations, biological monitoring of cobalt in blood shows relatively high concentrations. It is known that cobalt penetrates the skin (25), and in experimental settings a correlation is seen between dermal exposure to cobalt and the increase over time in urine cobalt concentrations (34). This shows the importance of exposed skin as a route of entry.

Another possible route of entry, which is less studied than inhalation and skin contact, is via ingestion. Unintentional ingestion consists mainly of hand-to-mouth

contact, and is therefore closely related to dermal exposure (22, 35). It may partly explain our finding of low cobalt air levels with relatively high concentrations in our biological monitoring. A study conducted under poor hygiene conditions showed a lack of correlation between urinary cobalt levels and cobalt levels in ambient air, suggesting the contribution of dermal exposure or gastrointestinal absorption as a considerable route of uptake (19).

The methods used in our study are well established, and the acid wash technique for assessment of dermal exposure that we used was developed by Lidén at the Karolinska Institute (5). It is non-invasive, the actual sampling is relatively simple, and it is suitable for measurements in industrial settings involving work with metals. Sampling can be performed in well-defined areas, and the size and number of measurement areas can be adjusted as desired. The technique also has a high recovery (5, 36).

Biological monitoring of cobalt in blood was conducted at the end of an 8-h work shift after 2–4 days off work, and the difference between before-shift and after-shift samples was used as a measure of uptake. The elimination of cobalt shows a rapid phase of a few days, and a second slow phase of several years. The majority is excreted in the rapid phase (37, 38); therefore, in order to measure the current exposure and relate it to dermal exposure and air concentrations, the measurements should be made immediately after exposure. Biological monitoring of cobalt in blood is a well-established technique, and studies have shown that the determination of cobalt concentrations in blood and in urine can be applied as an estimator of exposure (26, 27, 39).

The measurement of cobalt in the inhalable dust fraction was performed according to international standards (29). The technique of measuring skin exposure in our

study involves removal of the contaminant from the body, and small areas on the body where exposure is estimated to be large are measured, and therefore used as a concentration–time value. The area representing skin exposure, the hand, could be considered a limitation, as we do not take into account the total body surface area and the possible differences in exposure there might be owing to, for example, coverage by clothing. There are other methods for skin exposure measurement, such as tape stripping, which also involves direct removal of the contaminant, and recovery from clothing, gloves, or patches. Another option is whole body estimation of concentrations with a fluorescence tracing technique, which also makes it possible to see the pattern of the contaminant on the body (40, 41). None of the techniques takes into account the penetration rate of the substance through skin, and no permeability constant is set.

Conclusion

On the basis of exposure data in the hard metal industry, a significant correlation between cobalt skin and air exposure and uptake, determined as cobalt blood concentrations, has been identified. According to our results, a twofold increase in cobalt skin levels causes a 3–14% increase in blood levels, and the corresponding figure for air exposure was 39–83%. Previously known uptake via inhalation is an important route of entry, but uptake via the skin should not be disregarded.

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References

- 1 Wahlberg JE, Boman A. Sensitization and testing of guinea pigs with cobalt chloride. *Contact Dermatitis* 1978; **4**: 128–132.
- 2 Rystedt I, Fischer T. Relationship between nickel and cobalt sensitization in hard metal workers. *Contact Dermatitis* 1983; **9**: 195–200.
- 3 Giménez Camarasa JM. Cobalt contact dermatitis. *Acta Derm Venereol* 1967; **47**: 287–292.
- 4 Dooms-Goossens A E, Debussche K M, Gevers D M et al. Contact dermatitis caused by airborne agents. A review and case reports. *J Am Acad Dermatol* 1986; **15**: 1–10.
- 5 Lidén C, Skare L, Lind B et al. Assessment of skin exposure to nickel, chromium and cobalt by acid wipe sampling and ICP-MS. *Contact Dermatitis* 2006; **54**: 233–238.
- 6 Thyssen JP, Roeske-Nielsen A, Johansen J D. Contact allergy and human biomonitoring – an overview with a focus on metals. *Contact Dermatitis* 2011; **65**: 125–137.
- 7 Kusaka Y, Nakano Y, Shirakawa T, Morimoto K. Lymphocyte transformation with cobalt in hard metal asthma. *Ind Health* 1989; **27**: 155–163.
- 8 Shirakawa T, Kusaka Y, Fujimura N et al. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. *Chest* 1989; **95**: 29–37.
- 9 Ruokonen EL, Linnainmaa M, Seuri M et al. A fatal case of hard-metal disease. *Scand J Work Environ Health* 1996; **22**: 62–65.
- 10 Nemery B, Nagels J, Verbeke E et al. Rapidly fatal progression of cobalt lung in a diamond polisher. *Am Rev Respir Dis* 1990; **141**(Pt. 1): 1373–1378.
- 11 Barborik M, Dusek J. Cardiomyopathy accompanying industrial cobalt exposure. *Br Heart J* 1972; **34**: 113–116.
- 12 Kennedy A, Dornan JD, King R. Fatal myocardial disease associated with

- industrial exposure to cobalt. *Lancet* 1981; **1**: 412–414.
- 13 IARC. *International Agency for Research on Cancer (IARC): Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 68: Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide*: Lyon, IARC Press, 2006.
 - 14 De Palma G, Manini P, Sarnico M et al. Biological monitoring of tungsten (and cobalt) in workers of a hard metal alloy industry. *Int Arch Occup Environ Health* 2010; **83**: 173–181.
 - 15 Kumagai S, Kusaka Y, Goto S. Cobalt exposure level and variability in the hard metal industry of Japan. *Am Ind Hyg Assoc J* 1996; **57**: 365–369.
 - 16 Kusaka Y, Yokoyama K, Sera Y et al. Respiratory diseases in hard metal workers: an occupational hygiene study in a factory. *Br J Ind Med* 1986; **43**: 474–485.
 - 17 Klasson M, Bryngelsson I L, Pettersson C et al. Occupational exposure to cobalt and tungsten in the Swedish hard metal industry: air concentrations of particle mass, number, and surface area. *Ann Occup Hyg* 2016; **60**: 684–699.
 - 18 Alexandersson R, Lidums V. *Undersökningar över effekter av exposition för kobolt. IV Koboltkoncentrationen i blod och urin som expositionsindikator*: Stockholm, Arbete och Hälsa, 1979.
 - 19 Scansetti G, Botta G C, Spinelli P et al. Absorption and excretion of cobalt in the hard metal industry. *Sci Total Environ* 1994; **150**: 141–144.
 - 20 Midander K, Julander A, Skare L, Lidén C. Cobalt skin dose resulting from short and repetitive contact with hard metals. *Contact Dermatitis* 2014; **70**: 361–368.
 - 21 Julander A, Skare L, Mulder M et al. Skin deposition of nickel, cobalt, and chromium in production of gas turbines and space propulsion components. *Ann Occup Hyg* 2010; **54**: 340–350.
 - 22 Gorman Ng M, Semple S, Cherrie J W et al. The relationship between inadvertent ingestion and dermal exposure pathways: a new integrated conceptual model and a database of dermal and oral transfer efficiencies. *Ann Occup Hyg* 2012; **56**: 1000–1012.
 - 23 Stefaniak A B, Harvey C J, Virji M A, Day G A. Dissolution of cemented carbide powders in artificial sweat: implications for cobalt sensitization and contact dermatitis. *J Environ Monit* 2010; **12**: 1815–1822.
 - 24 Larese F, Gianpietro A, Venier M et al. In vitro percutaneous absorption of metal compounds. *Toxicol Lett* 2007; **170**: 49–56.
 - 25 Larese F, Maina G, Adami G et al. In vitro percutaneous absorption of cobalt. *Int Arch Occup Environ Health* 2004; **77**: 85–89.
 - 26 Ichikawa Y, Kusaka Y, Goto S. Biological monitoring of cobalt exposure, based on cobalt concentrations in blood and urine. *Int Arch Occup Environ Health* 1985; **55**: 269–276.
 - 27 Scansetti G, Lamon S, Talarico S et al. Urinary cobalt as a measure of exposure in the hard metal industry. *Int Arch Occup Environ Health* 1985; **57**: 19–26.
 - 28 NIOSH. *Method 7300: Elements by ICP. NIOSH Manual of Analytical Methods*, 4th edition: Cincinnati, OH, National Institute of Occupational Safety and Health (NIOSH), 2003.
 - 29 HSE. *MDHDS: General Methods for Sampling and Gravimetric Analysis of Inhalable and Respirable Dust*. Report No. 14/3: Suffolk, Health and Safety Executive (HSE), February 2000.
 - 30 ACGIH. Threshold limit values for chemical substances and physical agents and biological exposure indices. In: *American Conference of Governmental Industrial Hygienists*, Cincinnati, OH, 2015. ISBN: 978-1-607260-77-6.
 - 31 SWEA. *Occupational Exposure Limit Values (AFS 2011:18)*: Solna, Swedish Work Environment Authority, 2011 (In Swedish).
 - 32 Kraus T, Schramel P, Schaller K H et al. Exposure assessment in the hard metal manufacturing industry with special regard to tungsten and its compounds. *Occup Environ Med* 2001; **58**: 631–634.
 - 33 Lison D, Buchet J P, Swennen B et al. Biological monitoring of workers exposed to cobalt metal, salt, oxides, and hard metal dust. *Occup Environ Med* 1994; **51**: 447–450.
 - 34 Linnainmaa M, Kiilunen M. Urinary cobalt as a measure of exposure in the wet sharpening of hard metal and stellite blades. *Int Arch Occup Environ Health* 1997; **69**: 193–200.
 - 35 Schneider T, Vermeulen R, Brouwer D H et al. Conceptual model for assessment of dermal exposure. *Occup Environ Med* 1999; **56**: 765–773.
 - 36 Lidén C, Skare L, Nise G, Vahter M. Deposition of nickel, chromium, and cobalt on the skin in some occupations – assessment by acid wipe sampling. *Contact Dermatitis* 2008; **58**: 347–354.
 - 37 Elinder C G, Friberg L. Cobalt. In: *Handbook on the Toxicology of Metals. Vol. II: Specific Metals*, 2nd edition, Friberg L, Nordberg G, Vouk V (eds): Amsterdam, Elsevier Science Publishers, 1986.
 - 38 Davison A G, Haslam P L, Corrin B et al. Interstitial lung disease and asthma in hard-metal workers: bronchoalveolar lavage, ultrastructural, and analytical findings and results of bronchial provocation tests. *Thorax* 1983; **38**: 119–128.
 - 39 Yokota K, Johyama Y, Kunitani Y et al. Urinary elimination of nickel and cobalt in relation to airborne nickel and cobalt exposures in a battery plant. *Int Arch Occup Environ Health* 2007; **80**: 527–531.
 - 40 Cherrie J W, Brouwer D H, Roff M et al. Use of qualitative and quantitative fluorescence techniques to assess dermal exposure. *Ann Occup Hyg* 2000; **44**: 519–522.
 - 41 Wheeler J P, Warren N D. A Dirichlet Tessellation-based sampling scheme for measuring whole-body exposure. *Ann Occup Hyg* 2002; **46**: 209–217.