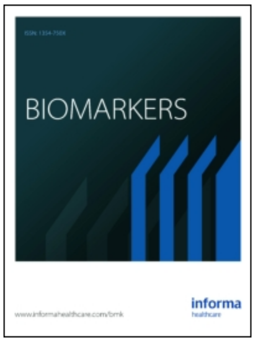

Taylor & Francis
Taylor & Francis Group

Biomarkers

ISSN: 1354-750X (Print) 1366-5804 (Online) Journal homepage: https://www.tandfonline.com/loi/ibmk20

Occupational low-level exposure to hard metals: cobalt and tungsten biomonitoring as an effective tool to evaluate the effectiveness of industrial hygiene interventions for risk management

M. Paganelli, J. Fostinelli, S. Renzetti, M. Sarnico, C. Tomasi, P. Lovreglio, I. Pilia, L. I. Lecca & G. De Palma

BIOMARKERS
https://doi.org/10.1080/1354750X.2020.1724195

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

Occupational low-level exposure to hard metals: cobalt and tungsten biomonitoring as an effective tool to evaluate the effectiveness of industrial hygiene interventions for risk management

M. Paganelli[a], J. Fostinelli[a], S. Renzetti[a], M. Sarnico[b], C. Tomasi[a#], P. Lovreglio[c], I. Pilia[d], L. I. Lecca[d] and G. De Palma[a]

[a]Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Section of Public Health and Human Sciences, University of Brescia, Brescia, Italy; [b]Unit of Prevention and Safety in Workplaces, Health Protection Agency of Brescia, Italy; [c]Interdisciplinary Department of Medicine, Section of Occupational Medicine "E.C. Vigliani", University of Bari Aldo Moro, Bari, Italy; [d]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

ABSTRACT

Purpose: The aim of the study was to assess the exposure to Cobalt (Co) and Tungsten (W) in a group of hard metal tool sharpeners through a combined approach of air and biological monitoring, and to evaluate the effectiveness of a control and improvement intervention carried out in collaboration with the medical officers of the local Health Protection Agency, by biomonitoring.

Methods: We enrolled 132 workers from 17 companies of the province of Brescia, northern Italy. The study was performed in two phases: (1) an environmental and biomonitoring survey to assess the workers' exposure to Co and W at their usual working conditions; (2) a further biomonitoring survey 3 months after the enforcement of a control and improvement intervention, to assess its effectiveness.

Results: Workers were found to be exposed to low concentration of airborne dust containing Co and W but after the intervention we recorded a significant decrease of the urinary concentrations of both Co and W. The extent of the decrease was correlated to the number of preventive industrial hygiene interventions that were carried out.

Conclusions: Biological monitoring of Co and W in the hard metal tools manufacturing industry is a sensitive and effective method to evaluate the effectiveness of prevention practices.

ARTICLE HISTORY
Received 4 September 2019
Accepted 12 December 2019

KEYWORDS
Hard metal; cobalt; industrial hygiene; biological monitoring; evidence-based prevention

Introduction

Cobalt (Co) and tungsten carbide (W-C) are the main components of the sintered hard metal alloys (HMA), mostly used for the manufacturing of cutting tools. Co is a transition element occurring in four valences (0, +2, +3 and +4), the divalent oxidation state being the most common whereas W is a metal that can occur in the natural state only in the form of chemical compounds with other elements (Goldoni *et al*. 2004). HMA are made of more than 80% W-C, small percentages of other carbides and about 5–10% Co (Lauwerys and Lison 1994).

Occupational exposure to Co can lead to diseases mainly affecting the respiratory system such as interstitial pneumonitis, fibrosis and asthma (IARC 1991, Cirla 1994, Nordberg 1994, Lison 1996, ATSDR 2000). On the other hand, no toxic effects have been clearly demonstrated for W-C alone.

The toxic properties of HMA significantly differ from those of Co metal alone. Hard metal lung disease (HMLD) is a giant cell interstitial pneumonia, resembling a foreign body reaction, and following inhalation and deposition of hard metal particles containing both Co and W-C in the lung and cannot be attributed to Co alone (Adams *et al*. 2017, Leyssens 2017). The exposure-response relationship is unpredictable, as in hypersensitivity pneumonia (individual susceptibility plays a main role). Co sulphate is classified by IARC as possibly carcinogen to humans (group 2B) whereas Co in HMA is classified as a group 2 A (probable) human carcinogen (Swennen *et al*. 1993, IARC 2003). The pathogenic effects of Co metal are due to its ability to reduce ambient oxygen giving rise to reactive oxygen species (ROS) but, due to the surface characteristics of Co particles, the rate of this reaction is very low (Lison 1996). W-C is an inert material but it is a good electron conductor with unique surface properties: when particles of Co and W-C are associated, electrons are easily transferred from Co through W-C and the reduction of oxygen, that is present at high concentrations in lung tissue, can occur at a greatly increased rate, therefore magnifying the effects (Lison 1996).

Risk characterization and risk reduction in HMA manufacturing plants relies on exposure assessment of Co and W, that can be achieved through both workplace air analysis and biological monitoring, as a good exposure-dose

CONTACT G. De Palma giuseppe.depalma@unibs.it Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Section of Public Health and Human Sciences, University of Brescia, Brescia, Italy
[#]C. Tomasi is responsible for statistical design and analysis. cesare.tomasi@live.com

Supplemental data for this article can be accessed here.

relationship for both elements, in particular for cobalturia (urinary concentration of Co, Co–U), has been demonstrated (Scansetti *et al*. 1985, Linnainmaa and Kiilunen 1997, ACGIH 2003, De Palma *et al*. 2010, Princivalle *et al*. 2017, SIVR 2017).

Some studies report the biomonitoring of exposure to HMA through exhaled breath condensate analysis; the measurement of Co and W in this biological matrix allows indeed the assessment of dose at the target organ (lung) but has not yet been validated; urinary concentration of both elements still remains the most reliable method for internal dose assessment by biomonitoring (Goldoni *et al*. 2004, Broding *et al*. 2009).

The present study was performed in order to asses, through a combined approach of environmental and prospective biological monitoring:(i) the current exposure levels to Co and W of HMA tool sharpeners in the province of Brescia, Northern Italy and (ii) the effectiveness of a control and improvement intervention carried out by our Unit in collaboration with the medical officers of the local Health Agency.

Clinical significance

- Periodical biological monitoring of both cobalt and tungsten in hard metal alloy workers can contribute to a more effective risk management and prevention of new cases of hard metal lung disease and, possibly, lung cancer.

Methods

Study design

We planned a two-phase interventional study, including a basal (T_0) sampling to assess the exposure to Co and W through a combined approach of environmental and biological monitoring and a nested (T_1) biomonitoring survey to assess the effectiveness of a control and improvement intervention plan carried out by the medical officers of the Unit of Prevention and Safety in Workplaces (PSW) of the local Health Protection Agency. In any case, the T_1 phase was performed within a 3-month period from the intervention plan.

Subjects

We enrolled 132 HMA tool sharpeners from 17 companies in the province of Brescia, whose main characteristics are resumed in Table 1. For all the workers, the source of exposure consisted of metal dust and fumes coming from the sharpening process made through automatic or manual machines, all equipped with an aspiration hood. Depending on the use of cutting fluid in the process, workers were classified as wet (no = 94) or dry (no = 38) grinders.

Potential confounders were investigated by a structured questionnaire developed and administered by skilled medical personnel to all participants. Apart from socio-demographic information, the questionnaire included questions regarding smoking habit, alcohol consumption, eating habits (meat and fish consumption), medical history (orthopedic or dental metal prosthesis; vitamin B12 therapy). All workers denied being under treatment with vitamin B_{12} medications or having ever undergone a metal prosthesis implant; no kidney disease was recorded.

Table 1. Main characteristics of the study sample.

Variables	Values
Gender (Males/Females), no.	129/3
Age (years), mean–range (Min-Max)	39 (18–67)
Work seniority (years)	14 (1–38)
Ethnic group, Caucasian/non Caucasian, no.	123/9
Smokers (NS; ES; CS), no.	59; 27; 48
Wet/dry grinding, no.	94/38

ES: ex smokers; CS: current smokers; NS: not smokers.

The study followed the ethical standards laid down in the 1964 Declaration of Helsinki. All enrolled subjects provided a written informed consent to the procedures prior to their inclusion in the study that was performed in the context of a control programme of the local PSW Unit.

Control and improvement intervention

The intervention was carried out in all the companies and consisted in verifying and enforcing in the field the correct application of the best industrial preventive and hygiene practices including: the availability and the correct use of adjustable aspiration devices and respirators; not smoking, eating or drinking during work; the appropriateness of work-clothes, the use of gloves to prevent skin absorption, the presence of clean toilets and showers and changing rooms with double compartment lockers (Table 2). When these requirements were not satisfied, specific and compelling prescriptions were enforced and verified. According to the Italian law regarding workers' health and safety, fines and sanctions were directly imposed by the Health Protection Agency officers. Employers as well as workers were provided with detailed information about HMA and the risks for health deriving from the exposure/inhalation of their dusts.

Air sampling and analysis

We determined airborne Co (Air-Co) and W (Air-W) concentrations in four companies, representative of the sector, on the same day of biomonitoring by stationary dust sampling over 6 to 7 h. The inhalable particulate matter (aerodynamic diameter $\leq$100 μm) was collected on nitrocellulose membranes (0.8 μm porosity; 25 mm diameter) mounted on IOM samplers (SKC Limited, Dorset, UK), according to the CEN 481 standard on size fraction for measurement of airborne particles (CEN EN 481: 1993). Pumps were set up at constant flows of 2.0 L/min. Membranes conditioned before and after dust sampling were weighed in a thermo-hygrometrically conditioned cabinet using a precision microbalance reading up to 0.00001 g. The Laboratory of Occupational Hygiene, Toxicology and Prevention of the University of Brescia, has been participating for 20 years to external quality assessment schemes organized by the German Society of Occupational

Table 2. Details of type and number of improvement interventions carried out in each plant. ✓: prevention measures already adopted; X: enforced practices.

Plant	Workers (No.)	Aspiration hoods	PPE Enforcement Airways	PPE Enforcement Gloves	Removal of food and coffee vending machines from the work environment	Renewal of the changing rooms
1	3	✓	✓	X	✓	✓
2	4	X	X	X	X	✓
3	4	X	X	X	X	X
4	5	✓	X	X	✓	✓
5	3	X	X	X	✓	X
6	4	✓	X	X	✓	✓
7	7	✓	✓	X	✓	✓
8	4	X	✓	X	✓	✓
9	3	✓	✓	X	✓	✓
10	2	X	X	X	X	X
11	18	✓	✓	X	✓	✓
12	4	X	X	X	X	X
13	15	✓	✓	X	✓	✓
14	36	✓	X	X	✓	✓
15	5	X	X	X	✓	X
16	12	X	X	X	X	✓
17	3	X	X	X	✓	✓

PPE: personal protective equipment.

and Environmental Medicine (Erlangen, Germany), showing a high degree of proficiency in metal analysis. Membranes were dissolved in concentrated hyper pure nitric acid (ACS Reagent; Sigma-Aldrich, Milan, Italy) and the solution diluted with Tracepure® water for inorganic analysis (Merck & Co., Inc., NJ, USA). The analytical blank was obtained from virgin membranes, treated in the same way with nitric acid and Tracepure® water. Air-Co and Air-W were determined by inductively coupled plasma mass spectrometry (ICP-MS) on an ELAN DRC II (PerkinElmer SCIEX, Shelton, CT, USA) instrument using the analytical technique total quant with external calibration. We applied the following analytical conditions: plasma source, 99.998% Argon; auxiliary gas Xow, 1.2 l/min; plasma gas Xow, 15 ml/min; nebuliser gas Xow, 0.94 ml/min; radiofrequency power, 1.2 kW; lens voltage, 6.00 V, adjusted by Be, Co, In, Pb (DAC value 5.6; 6.3; 7.8; 8.8); vacuum, 10– 7 mbar; mass range (*m/z*): 6–15, 19–39, 42–210, 230–240; dwell time, 100 *ms*; sweep reading, 1; number of replicates, 2; scanning mode, peak hopping; sample uptake, 0.9 ml/min; material of the cones, nickel; autolens, on; nebuliser, Meinhard nebuliser. The instrument was calibrated using a 10 μg/l multi-element standard solution (Multi-element ICP-MS Calibration Standard 3, Matrix per Volume: 5% HNO_3 per 100 mL, Perkin Elmer Plus). For Co, the accuracy and precision (as coefficient of variation, CV) of the method were determined using the NIST 1643e Trace Elements in Water solution and were 98 and 6.5%, respectively. For Air-W, accuracy could not be evaluated, given the unavailability of certified material, and a precision of 8.5% was found. The limits of detection (LODs), determined on the basis of three standard deviations (SD) of the background signal, were 0.0003 and 0.0001 μg/m^3 for Co and W, respectively. Results of environmental monitoring are shown in Table 3.

Table 3. Descriptive results of air monitoring in three representative workshops.

Parameters	No. of samples	Geometric mean	Median	Minimum	Maximum
Inhalable dust	19	0.09	0.06	0.025	1.15
Co (μg/m^3)	19	0.30	0.27	0.005	4.5
W (μg/m^3)	19	0.40	0.10	0.003	80.2

Biomonitoring

Biomarkers of internal dose were determined on urine samples collected at the end of the shift (ES), end of the workweek (on Friday). In order to avoid sample contamination, workers were instructed to strip off their work clothes before the collection of the urine and to carefully wash their hands and wear nitrile gloves. Urine samples were transferred refrigerated to the lab and stored frozen (−20 °C) until analysis that was performed within 30 days from collection. Urine were diluted 1:10 with bi-distilled water before the analysis. Urinary Co (Co-U) and W (W_U) concentrations were determined by the same ICP-MS instrument as above described, by quantitative analysis with addition calibration, using standard solutions of Co (1,000 ppm) and W (1,000 ppm) in nitric acid 2%. Standard additions brought to final solutions of 1.0, 5.0, 10.0 and 20.0 g/l for Co and 0.5, 1.0, 2.0 and 5.0 g/l for W. The analytical conditions were similar as for *total-quant* analyses, with the following differences: Co mass, 59; W mass, 184, with correction for Os 189; dwell time, 1,500 *ms*; sweep reading 3; no. of replicates, 3. Accuracy was assessed using specific certified materials for different matrices2A/B (for urine), all from the German Society of Occupational and Environmental Medicine (Erlangen, Germany). The accuracy of methods was 95%. For both elements, method precision was 4.3% for Co–U and 6.2% for W–U. For each matrix, the LODs were determined as three SD of the background signal. The LOD was 0.02 g/l for W–U. The corresponding figures for Co were 0.06 g/l for Co–U. Creatininuria was determined by the method of Jaffè (Kroll *et al*. 1986). Two urine samples at T_0 and 16 samples at T_1 were excluded from data analysis because creatinine concentrations were out from the recommended concentration range of 0.3–3 g/l (ACGIH 2017).

Statistical analysis

Statistical analysis was performed using the statistical software package IBM SPSS® Statistics V25.0. Owing to the non-normal data distribution as assessed by the one-sample Kolmogorov–Smirnov test, the non-parametric Wilcoxon's test was applied to test paired sample (T_0 vs T_1) differences of biomarker concentrations. A linear mixed model analysis was then performed using the statistical software package R, version 3.5.2 for Windows®, in order to test the differences of T_1 *vs* T_0 U-Co and U-W log-transformed concentrations both at subject and company level, taking into account the no. of prescriptions imposed to companies. To this end, workers or companies were grouped according to the number of prescriptions. Workers were grouped into Group 1 (1 prescription), Group 2 (2–3 prescriptions) and Group 3 (more than 3 prescriptions), and companies into Group 1 (1–2 prescriptions) and Group 2 (more than 2 prescriptions). In the analyses on companies, the geometric means of U-Co and U-W concentrations by company were included in the model. A random intercept model was fitted in all cases to consider the structure of the data where each worker or company (depending on the analysis) has a repeated measure of metal concentration. When looking at worker level, a first model was run taking into account the phase (T_1, T_0) and the no. prescriptions whereas a second regression was fitted adjusting for covariates such as company, age, wet *vs* dry grinding, years of exposure and the smoking status.

Results

Airborne concentrations of Co and W (Table 1) were consistently below the threshold limit value – 8 h time weighed average (TLV-TWA®) as proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) in 2017 for Co (20 μg/m^3) and W (3 mg/m^3) in all the investigated plants.

Both U-Co and U-W could be determined in every biological sample, at T_0 as well as at T_1 phase. The biomonitoring results were compared to the existing reference values for the unexposed healthy subjects living in Italy, as assessed by the Italian Society for Reference Values (SIVR 2017) and, limitedly to Co-U, the biological exposure index (BEI®) of ACGIH (ACGIH 2017). The 95th percentile of *SIVR* values is 2.2 μg/l and 0.37 μg/l for Co-U and W-U, respectively. At T_0, 26% and 92% workers exceeded the 95th percentile of *SIVR* values for Co-U and W-U, respectively, whereas at T_1 the proportions dropped to 16% and 84%, respectively. No statistically significant differences were recorded (at T_0 and T_1) between the groups of dry and wet grinders(data not shown). The Wilcoxon paired sample analysis showed a statistically significant decrease of both Co-U and W-U concentrations at T_1 as compared to T_0 ($p = 0.002$ and 0.003, respectively) (Table 4). In particular, we could appreciate an average reduction of 0.3 μg/l for U-CO and 0.5 μg/l for U-W, from T0 to T1. The linear mixed model analysis, looking at the interaction term between the time variable and the no. of prescriptions allowed us to test the impact of the latter on biomarker values over time. Table 5 shows the results on workers classified by the no. of prescriptions imposed to their company. In the first linear mixed model, both Co-U and W-U concentrations showed a not significant negative trend from T_0 to T_1 for Group 1 subjects. As expected, baseline values of Co-U and W-U in Group 2 and Group 3 were significantly lower than in Group 1 workers, but both groups 2 and 3 showed a decreasing not statistically significant concentration trend over time as compared to group 1. By setting one by one the 2nd and the 3rd group as reference, we could test for the difference between T_1 and T_0 for each intervention group. W-U shows a nearly significant and a significant negative trend for groups 2 and 3, respectively ($\beta = -0.372$, p-value = 0.068; $\beta = -0.598$, p-value = 0.012), whereas Co-U presents a significant decreased urine concentration over time only for group 3 ($\beta = -0.573$, p-value = 0.009). Figure 1(A,B) confirm these trends showing a steeper slope as the number of interventions increases. When adjusting for covariates we can still see an average decrease of U-Co and U-W concentration from T_0 to T_1, but no further significant difference could be appreciated anymore (data not shown). As biological monitoring provides information regarding the working environment, it is mandatory to study the available data also at a company level: to do so we performed the same analysis using the geometric means of Co and W urine concentration by companies (Table 6). Again, we obtained a higher decrease from T_0 to T_1 of Co-U and W-U concentration as the no. of adopted measures increased (not statistically significant). In the companies where only 1 or 2 interventions were enforced, no appreciable difference between the two time points was detectable especially for Co. Also in this case, setting group 2 as reference, we could test for the T_0 to T1 difference and we saw a negative difference of Co–U and W-U concentrations, statistically significant only for W-U ($\beta = -0.417$, *p*-

Table 4. Distributions of urinary concentrations of Cobalt (Co-U) and Tungsten (W-U) in the sample group before and after the intervention.

	T_0		T_1		T_1-T_0	
Biomarkers	N°	Median (Min-max)	N°	Median (Min-max)	N°	Median (Min-max)
U-Co (μg/L)	132	1.3 (1.0–92.5)	101	0.95 (0.1–23.7)	101	−0.3** (−92.1, 14.5)
U-W (μg/L)	132	2.2 (1.0–151)	101	1.4 (0.1–123.2)	101	−0.5** (−83.7, 40.1)

**$p < 0.005$.

Table 5. Results of linear mixed models (β coefficients and 95% CI) to test the impact of the number of interventions on Co and W urine concentrations in workers grouped by the no. of interventions enforced in the companies.

	U-Co β (95% CI)	U-W β (95% CI)
Constant	−0.218 (−0.521, 0.085)	0.036 (−0.332, 0.405)
Group 1, T1 vs T0	−0.218 (−0.567, 0.131)	−0.309 (−0.685, 0.067)
Group 2 vs Group 1 at T0	0.562** (0.136, 0.988)	0.741** (0.223, 1.260)
Group 3 vs Group 1 at T0	1.062*** (0.615, 1.509)	1.786*** (1.242, 2.330)
Group 2 vs Group 1, at T1 *vs* T0	−0.010 (−0.518, 0.497)	−0.062 (−0.611, 0.486)
Group 3 vs Group 1, at T1 *vs* T0	−0.355 (−0.908, 0.198)	−0.289 (−0.888, 0.310)

**$p < 0.01$, ***$p < 0.001$.
Group 1, 1 intervention; Group 2, 2–3 interventions; Group 3, 4–5 interventions.

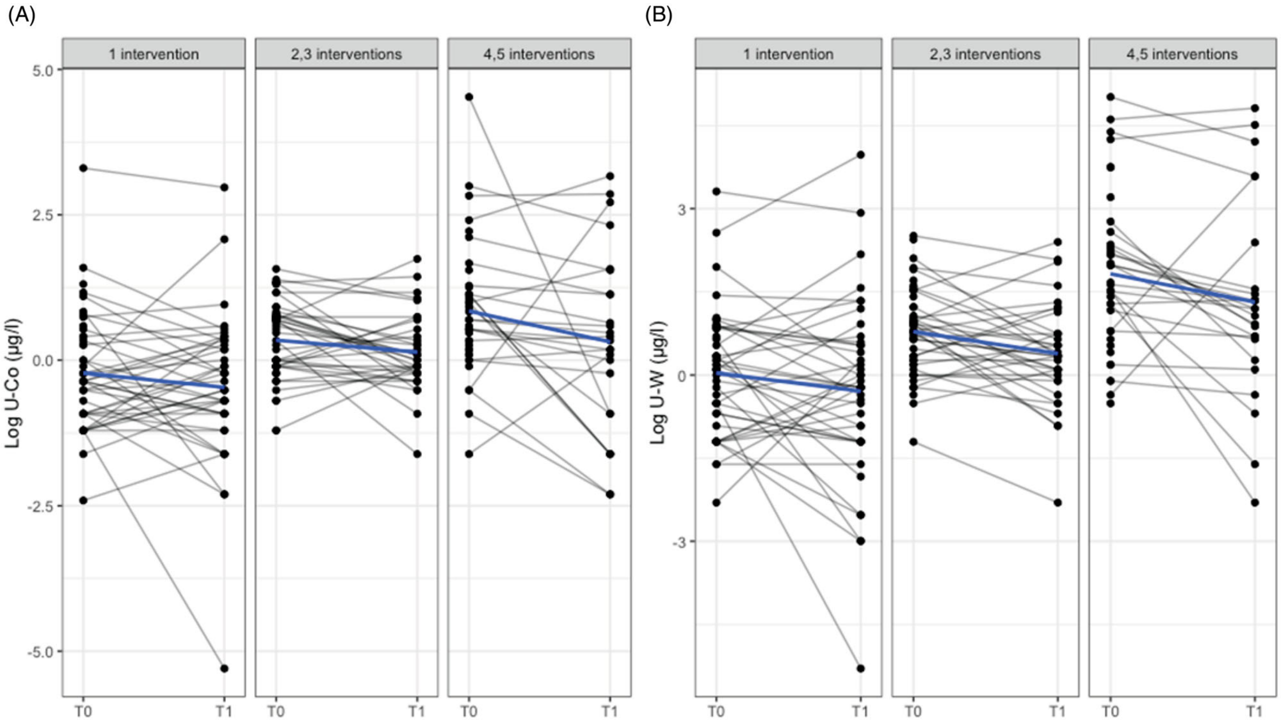

Figure 1. (A and B) Longitudinal trend of U-Co and U-W concentrations in the worker sample stratified by the no. of interventions in the respective companies.

Table 6. Results of linear mixed models (β coefficients and 95% CI) to test the impact of the no. of interventions on geometric means of Co and W urine concentrations (U-Co and U-W)in companies grouped by the no. of interventions (Group 1, 1–2 intervention; Group 2, more than 2 interventions).

	U-Co *β* (95% CI)	U-W *β* (95% CI)
Constant	0.233 (–0.364,0.830)	0.450 (–0.459, 1.359)
1 or 2 Interventions at T1 vs T0	0.001 (–0.426, 0.429)	–0.357 (–0.989, 0.275)
3,4 or 5 Interventions vs 1 or 2 at T0	0.506 (–0.295, 1.308)	1.322* (0.102, 2.541)
3,4 or 5 Interventions vs 1 or 2 at T1 vs T0	–0.419 (–1.062, 0.225)	–0.388 (–1.339, 0.564)

*$p < 0.05$.

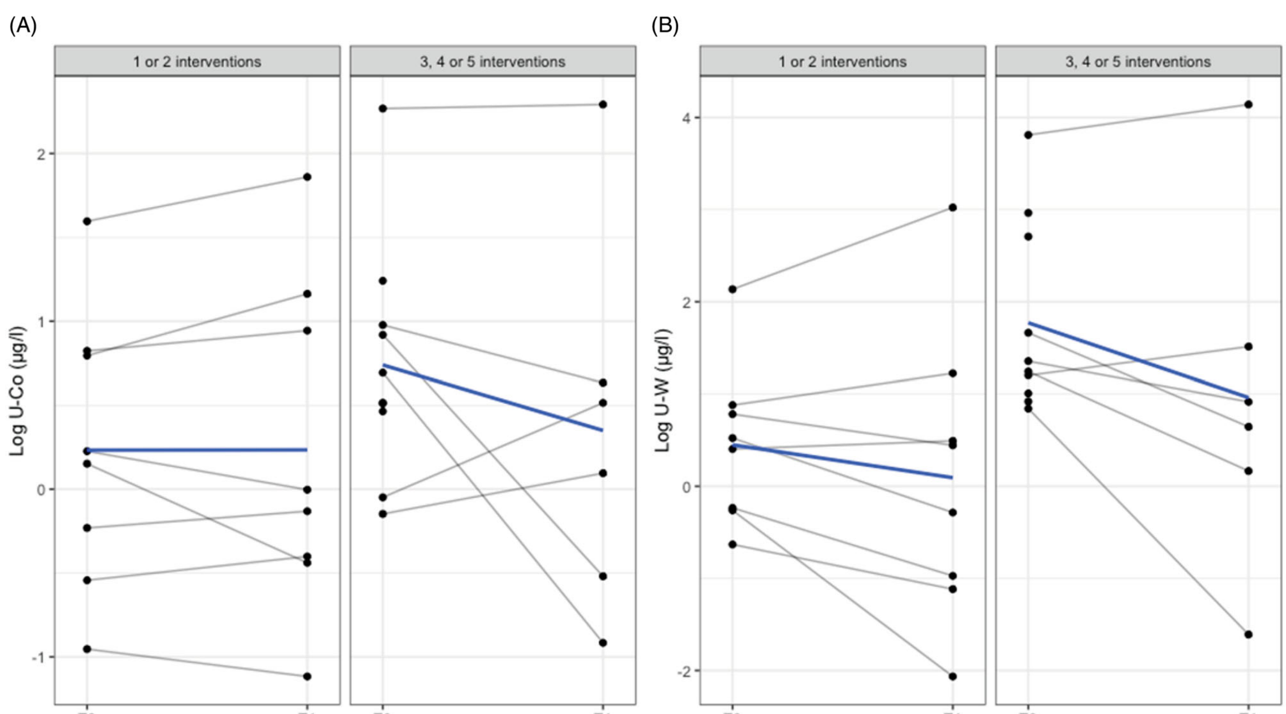

Figure 2. (A and B) Longitudinal trend of geometric means of U-Co and U-W concentrations in the company sample stratified by the no. of interventions.

value = 0.089; $\beta = -0.745$, p-value = 0.040 for Co-U and W-U, respectively) (Figure 2(A,B) show steeper negative slopes between T_0 and T_1, as the no. of interventions increased both for Co-U and W-U concentrations). Further information can be found as supplementary material (Table S1).

Discussion and conclusion

Occupational exposure to Co and W has been mainly investigated in sintering plants where the alloy is produced out of Co and W-C powders. Few studies are available so far on HMA tool grinders and sharpeners (Leyssens *et al*. 2017, Princivalle *et al*. 2017). HMA tool sharpening plants are often small factories employing less than 10 workers each; new data collection from such companies is therefore precious in order to assess the health risks in this specific sector.

Results of air monitoring carried out in our sample displayed very low airborne concentration of HMA dust, as compared to available literature data (Mosconi *et al*. 1994), anyway confirming airborne Co levels far lower than measured in HMA sintering plants. The 8 h-TWA threshold limit value proposed by ACGIH in 2018 for HMA airborne dust containing Co and W-C (5 $\mu g/m^3$) is specific for the thoracic fraction. In this study, we measured inhalable dust and obtained results, although possibly leading to an overestimate when compared to thoracic dust, that showed a well-controlled exposure in the sector of HMA tool sharpening. Nevertheless, the intervention plan was decided by the Health Care Agency officers after we posed a diagnosis of HMLD in a HMA tool sharpener. According to literature data (Nemery and Abraham 2007), HMLD is a sort of hypersensitivity disease for which a threshold exposure level is not known. Thus, apart from controlling occupational exposure levels below limit values, risk assessment and management in this sector would require a careful control of industrial and hygienic preventive measures whose application could be effectively checked by biomonitoring. As compared to air monitoring, in fact, such activity can allow a more sensitive detection of the overall daily HMA dust intake through all absorption routes, i.e. inhalatory, cutaneous and gastrointestinal. Both the latter in particular are relevant for the inobservance of hygienic preventive measures.

Consistent with air monitoring results, biomonitoring at T_0-showed that most HMA tool sharpeners excreted Co-U concentrations comparable to the general non-exposed population while most workers exceeded the 95° percentile of the reference values for W-U. This different behaviour of both elements is probably related due to the higher amount of W-C (more than 90%) as compared to Co in the alloy. Thus, in agreement with another our previous study (De Palma *et al*. 2010), W-U seems to be a biomarker more specific and more sensitive than Co-U to characterize HMA dust exposure. A previous survey on 16 different HMA blade sharpening plants (Linnainmaa and Kiilunen 1997) reported a median Co-U value of 14.2 µg/l (range 0.47–159.9 µg/l)]. In another large survey carried out more than twenty years ago in Northern Italy (Imbrogno and Alborghetti 1994) in 12 HMA tool sharpening factories, the median values of Co-U varied from 1 to 26.5 µg/l, with half of the plants displaying median values higher than 9 µg/l. The aforementioned study was part of a bigger survey involving 250 factories (diamond tools; HMA tool grinding; dental and skeletal prosthesis) in which more than 600 urine samples were collected. U-Co concentrations ranged from the highest median value of 320 µg/l (diamond tool production) to the lowest of 5 µg/l in HMA filling (Mosconi *et al*. 1994). Compared to such studies, Co-U levels in our cohort resulted lower, probably owing to the improvement of the industrial hygiene practices related to the significant changes of the safety standards and knowledge regarding such exposure. This is supported by literature (Simonsen *et al*. 2012, Hutter *et al*. 2016, Klasson *et al*. 2016), showing a significant decrease of Co-air levels mostly well below the available occupational exposure limits. As to W-U, the only study available for result comparison was another by our group on workers producing HMA (De Palma *et al*. 2010). Again, and as expected, our current results were lower.

The second aim of our study was to assess the effectiveness of industrial hygiene measures adopted and enforced in our sample. The demonstration of the effectiveness is a key point in medicine for both therapy and prevention and is the basis of the so called evidence-based approach (Chokshi and Farley 2012). The challenge for evidence-based prevention is often harder than that for evidence-based therapy as the choice of the outcomes to be assessed in order to demonstrate the effectiveness of preventive measures, policies or practices are often not so straightforward (Verbeek *et al*. 2002, Trzcinka-Ochocka *et al*. 2006). Prevention literally means to avoid something from happening, therefore as it's pretty intuitive that it's impossible to measure and very difficult to estimate events that do not take place, proxy variables have to be assessed.

As stated above, biomonitoring can be a valid tool for the evaluation of the effectiveness of a prevention intervention aimed to control the exposure levels and the daily intake of occupational xenobiotics. The significant decrease of Co-U and W-U concentrations at T_1 as compared to T_0 in the paired sample analysis, was further supported by the linear mixed model analysis that allowed us to show the direct positive relationship between the magnitude of the decreases and the no. of preventive interventions enforced in each plant. As it often happens in the field of occupational health and safety, no revolutionary ideas or new devices are required to significantly improve the working conditions: the careful application of simple industrial hygiene measures can be enough to significantly improve the workers' safety and health. In the scientific literature, few studies have demonstrated the effectiveness of preventive interventions (in particular introduction and enforcement of personal and collective protection devices) in the field of workplace exposure to airborne metals (Dyosi 2007). To the best of our knowledge, so far this is the first study assessing the effectiveness of prevention practices through biological monitoring in the sector of HMA tool manufacturing, in presence of low levels of airborne HMA dusts.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

P. Lovreglio http://orcid.org/0000-0002-1609-9397
I. Pilia http://orcid.org/0000-0003-2834-5652

References

Adams, T.N., *et al.*, 2017. Cobalt related interstitial lung disease. *Respiratory medicine*, 129, 91–97.

American Conference of Governmental Industrial Hygienists (ACGIH), 2003. *Threshold limit values for chemical substances and physical agents and biological exposure indices*. Ohio, USA: American Conference of Governmental Industrial Hygienists.

American Conference of Governmental Industrial Hygienists (ACGIH), 2017. *Threshold limit values for chemical substances and physical agents and biological exposure indices*. Ohio, USA: American Conference of Governmental Industrial Hygienists.

ATSDR, 2000. ATSDR (Agency for toxic substances and disease registry). *Prepared by clement international corp., under contract*, 205, 88–0608.

Broding, H.C., *et al.*, 2009. Comparison between exhaled breath condensate analysis as a marker for cobalt and tungsten exposure and biomonitoring in workers of a hard metal alloy processing plant. *International archives of occupational and environmental health*, 82 (5), 565–573.

Chokshi, D.A., and Farley, T.A., 2012. The cost-effectiveness of environmental approaches to disease prevention. *New England journal of medicine*, 367 (4), 295–297.

Cirla, A.M., 1994. Cobalt-related asthma: clinical and immunological aspects. *Science of the total environment*, 150 (1–3), 85–94.

De Palma, G., *et al.*, 2010. Biological monitoring of tungsten (and cobalt) in workers of a hard metal alloy industry. *International archives of occupational and environmental health*, 83 (2), 173–181.

Dyosi, S., 2007. Evaluation of preventive and control measures for lead exposure in a South African lead-acid battery recycling smelter. *Journal of occupational and environmental hygiene*, 4 (10), 762–769.

Goldoni, M., *et al.*, 2004. Exhaled breath condensate as a suitable matrix to assess lung dose and effects in workers exposed to cobalt and tungsten. *Environmental health perspectives*, 112 (13), 1293–1298.

Hutter, H.P., *et al.*, 2016. Dust and cobalt levels in the Austrian tungsten industry: workplace and human biomonitoring data. *International journal of environmental research and public health*, 13 (9), 931.

Imbrogno, P., and Alborghetti, F., 1994. Evaluation and comparison of the levels of occupational exposure to cobalt during dry and/or wet hard metal sharpening. Environmental and biological monitoring. *Science of the total environment*, 150 (1–3), 259–262.

International Agency for Research on Cancer (IARC), 1991. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Cobalt and cobalt compounds. *IARC monographs on the evaluation of carcinogenic risks to humans*, 52, 363–472.

International Agency for Research on Cancer (IARC), 2003. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. *IARC monographs on the evaluation of carcinogenic risks to humans*, 86, 1–294.

Klasson, M., *et al.*, 2016. Occupational exposure to cobalt and tungsten in the Swedish hard metal industry: air concentrations of particle mass, number, and surface area. *Annals of occupational hygiene*, 60 (6), 684–699.

Kroll, M.H., *et al.*, 1986. Automated determination of urinary creatinine without sample dilution: theory and practice. *Clinical chemistry*, 32 (3), 446–452.

Lauwerys, R., and Lison, D., 1994. Health risks associated with cobalt exposure—an overview. *Science of the total environment*, 150 (1–3), 1–6.

Leyssens, L., *et al.*, 2017. Cobalt toxicity in humans—A review of the potential sources and systemic health effects. *Toxicology*, 387, 43–56.

Linnainmaa, M., and Kiilunen, M., 1997. Urinary cobalt as a measure of exposure in the wet sharpening of hard metal and stellite blades. *International archives of occupational and environmental health*, 69 (3), 193–200.

Lison, D., 1996. Human toxicity of cobalt-containing dust and experimental studies on the mechanism of interstitial lung disease (hard metal disease). *Critical reviews in toxicology*, 26 (6), 585–616.

Lison, D., *et al.*, 1994. Biological monitoring of workers exposed to cobalt metal, salt, oxides, and hard metal dust. *Occupational and environmental medicine*, 51 (7), 447–450.

Mosconi, G., *et al.*, 1994. Occupational exposure to metallic cobalt in the Province of Bergamo. Results of a 1991 survey. *Science of the total environment*, 150 (1–3), 121–128.

Nemery, B., and Abraham, J.L., 2007. Hard metal lung disease: still hard to understand. *American journal of respiratory and critical care medicine*, 176 (1), 2–3.

Nordberg, G., 1994. Assessment of risks in occupational cobalt exposures. *Science of the total environment*, 150 (1–3), 201–207.

Princivalle, A., *et al.*, 2017. Biological monitoring of cobalt in hard metal factory workers. *International archives of occupational and environmental health*, 90 (2), 243–254.

Scansetti, G., *et al.*, 1985. Urinary cobalt as a measure of exposure in the hard metal industry. *International archives of occupational and environmental health*, 57 (1), 19–26.

Simonsen, L.O., Harbak, H., and Bennekou, P., 2012. Cobalt metabolism and toxicology—a brief update. *Science of the total environment*, 432, 210–215.

Società Italiana Valori di Riferimento (SIVR), 2017. Fourth list of reference values for elements, organic compounds and their metabolites [online]. Available from: http://fad.saepe.it/approfondimenti/Valori_di_riferimento_LISTA_SIVR_2017.0.pdf [Accessed 2 April 2019].

Swennen, B., *et al.*, 1993. Epidemiological survey of workers exposed to cobalt oxides, cobalt salts, and cobalt metal. *Occupational and environmental medicine*, 50 (9), 835–842.

Trzcinka-Ochocka, M., Jakubowski, M., and Nowak, U., 2006. Effectiveness of preventive actions for lead exposed workers: an assessment based on biological monitoring. *Medycyna pracy*, 57 (6), 537–542.

Verbeek, J.H., *et al.*, 2002. Evidence-based medicine for occupational health. *Scandinavian journal of work, environment and health*, 28 (3), 197–204.