Journal of Exposure Science and Environmental Epidemiology **(2009) 19, 423–434**
 1559-0631/09/$32.00

www.nature.com/jes

Characterization of exposures among cemented tungsten carbide workers. Part II: Assessment of surface contamination and skin exposures to cobalt, chromium and nickel

GREGORY A. DAY, M. ABBAS VIRJI AND ALEKSANDR B. STEFANIAK

Division of Respiratory Disease Studies, Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), Morgantown, West Virginia, USA

Cobalt, chromium and nickel are among the most commonly encountered contact allergens in the workplace, all used in the production of cemented tungsten carbides (CTC). Exposures to these metal-containing dusts are frequently associated with skin sensitization and/or development of occupational asthma. The objectives of this study were to assess the levels of cobalt, chromium and nickel on work surfaces and on workers' skin in three CTC production facilities. At least one worker in each of 26 work areas (among all facilities) provided hand and neck wipe samples. Wipe samples were also collected from work surfaces frequently contacted by the 41 participating workers. Results indicated that all surfaces in all work areas were contaminated with cobalt and nickel, with geometric means (GMs) ranging from 4.1 to 3057 μg/100 cm^2 and 1.1–185 μg/100 cm^2, respectively; most surfaces were contaminated with chromium (GM = 0.36–67 μg/100 cm^2). The highest GM levels of all metals were found on control panels, containers and hand tools, whereas lowest levels were on office and telecommunication equipment. The highest GM levels of cobalt and nickel on skin were observed among workers in the powder-handling facility (hands: 388 and 24 μg; necks: 55 and 6 μg, respectively). Levels of chromium on workers' skin were generally low among all facilities. Geometric standard deviations associated with surface and skin wipe measurements among work areas were highly variable. Exposure assessment indicated widespread contamination of multiple sensitizing metals in these three facilities, suggesting potential transfer of contaminants from surfaces to skin. Specific action, including improved housekeeping and training workers on appropriate use and care of personal protective equipment, should be implemented to reduce pathways of skin exposure. Epidemiologic studies of associated adverse health effects will likely require more biologically relevant exposure metrics to improve the ability to detect exposure–response relationships.
Journal of Exposure Science and Environmental Epidemiology (2009) **19,** 423–434; doi:10.1038/jes.2008.33; published online 4 June 2008

Keywords: *dermal exposure, particle migration pathways, exposure methods, occupational asthma.*

Introduction

Cemented tungsten carbides (CTCs) are a class of wear-resistant alloys that contain carbides of tungsten, titanium and/or tantalum with many additives, including chromium and nickel, all commonly bound in a cobalt matrix. CTC manufacturing processes and production activities generate aerosols with varying physicochemical properties (Stefaniak et al., 2007), and size and concentration distributions (Stefaniak et al., 2008). We previously adapted a total-body exposure model (Schneider et al., 1999) to describe various pathways of particulate exposure (Day et al., 2007), including inhalation and dermal routes as well as consideration of contaminated work surfaces, which provides a framework for the present analyses. This model was developed to assess exposure to beryllium-containing particles at a copper–beryllium alloy strip and wire finishing facility, where we examined correlations among various exposure pathways including air to surface, air to skin and surface to skin. With regard to CTC exposures, control measures such as local exhaust and general ventilation systems may remove a fraction of process-generated aerosols, whereas the remainder (i.e. fugitive aerosols) may be inhaled by workers or may settle onto work surfaces and skin. Equipment, tools, floors and stairs, work clothing or areas of uncovered skin may become contaminated via direct contact with particles, as may occur during routine work activities or a material spill. Particles on contaminated clothing or hands may also be redistributed to other areas of the skin.

Cobalt, chromium and nickel are among the most frequent and commonly encountered contact allergens in the workplace (Walberg, 2000); simultaneous exposure may augment distinct sensitization to the individual metals (Guy et al., 1999). Workers engaged in the manufacture of CTCs are potentially co-exposed to cobalt, chromium and nickel. Exposure to cobalt-containing dust is frequently associated with skin sensitization (Walberg, 2000) and the development of occupational asthma (OA) (Bernstein and Merget, 2006).

1. Address all correspondence to: Dr. Gregory A. Day, CDC/NIOSH, 1095 Willowdale Road, MS H-2703, Morgantown, West Virginia 26505-2888, USA. Tel.: +1 304 285 6387. Fax: +1 304 285 6321.
E-mail: GDay@cdc.gov
Received 27 February 2008; accepted 8 April 2008; published online 4 June 2008

Chromium and nickel compounds are also skin sensitizers commonly associated with dermatitis (see for example, Halbert et al., 1992; Lidén and Carter, 2001) and less commonly with OA (Bernstein and Merget, 2006; Fernández-Nieto et al., 2006). Skin exposure to tungsten also likely occurs, yet to our knowledge such exposures have not been associated with skin disorders.

Upon contact with skin, cobalt (Scansetti et al., 1994; Linnainmaa and Kiilunen, 1997) and nickel (Hemingway and Molokhia, 1987; Randin, 1988; Morgan and Flint, 1989; Haudrechy et al., 1993; Chiba et al., 1997) may become solubilized in sweat and subsequently pass into and through the skin (Linnainmaa and Kiilunen, 1997; Filon et al., 2004; Larese et al., 2007). Both cobalt and nickel ions may interact with immunologically active layers of the skin and upregulate endothelial adhesion molecules; such upregulation may represent a mechanism that promotes sensitization and elicitation of contact hypersensitivity involving antigen-specific Langerhans- and T-cell-dependent events (Goebeler et al., 1993, 1995). The role, if any, of dissolved cobalt and nickel that permeates the skin in development of OA is unclear. Similarly, upon contact with sweat on the skin surface, many chromium-containing materials (e.g. soluble salts) release ions (Chiba et al., 1997; Hansen et al., 2003) that can pass into and through the skin (Van Lierde et al., 2006). In contrast, skin contact with metallic chromium does not appear to release ions that pass through the skin (Larese et al., 2007). Chromium sensitization is thought to occur through a cell-mediated immunologic response; however, the exact toxicological mechanism is not well understood (Barceloux, 1999; Cohen and Costa, 2000).

Among CTC workers, understanding occupational skin exposure to metals has historically focused on cobalt (Scansetti et al., 1994; Linnainmaa and Kiilunen, 1997), with little concern for co-exposures to known sensitizers such as chromium and nickel. Evaluation of resulting health effects from skin exposure to these and other sensitizing agents has largely focused on allergic dermatitis; however, emerging evidence suggests that the skin is an important route of exposure that leads to respiratory disease upon subsequent inhalation exposures (Day et al., 2006; Bello et al., 2007; Redlich and Herrick, 2008). Thus, the understanding of occupational skin exposures to multiple metal sensitizers remains poor and there is little methodological guidance in terms of the assessment of such exposures, the combined toxicological mechanisms or risk to health.

The National Institute for Occupational Safety and Health (NIOSH) recently responded to a request to perform a health hazard evaluation at a company that produces CTC blanks from feedstock powders. In a companion paper (Stefaniak et al., 2008), we describe size-fractionated exposures among CTC workers to airborne cobalt and tungsten particles. The objectives of this exposure assessment study were to: (1) measure mass concentrations of cobalt, chromium and nickel on work surfaces; (2) estimate masses of cobalt, chromium and nickel on workers' hands and necks and (3) evaluate relationships among measured levels of these metals in air, on work surfaces, and on hands and necks.

Methods

This study was performed at three different facilities located in the southern United States, each specializing in a specific aspect of CTC production. A variety of processes were used to convert input materials into semifinished and finished products. The three main types of production work involved (1) metal separation and reclamation, and calcining, reduction and carburization of tungsten carbide powder (metal separation facility); (2) mixing, milling, spray drying and screening of CTC powders (powder-handling facility) and (3) forming, shaping, sintering, grinding and sandblasting of final CTC product (forming/machining facility). Input materials consisted of both high-purity metal powders and metals recovered from sintered and unsintered scrap. Work at each facility included production, production support and administrative functions. Production support work at all three facilities included maintenance mechanics with frequent entry into production areas; administrative work required less frequent entry into production areas. These and other production processes are further described in the companion paper (Stefaniak et al., 2008).

Exposure control strategies at the facilities included engineering and administrative controls as well as use of personal protective equipment, such as gloves and respirators during the performance of designated tasks. At the time of our survey, none of these facilities had a formal skin protection program in place.

Industrial Hygiene Sampling

Two types of samples were collected to estimate levels of surface contamination and worker skin exposure: (1) wipes from work surfaces handled or touched during routine work activities and (2) wipes from the skin of workers' hands and necks. We chose workers' necks rather than another area of exposed skin, such as the forearm, as the neck represented a consistently uncovered area of skin; some workers wore long-sleeved shirts, whereas others did not. All samples were collected over a period of six working days, two successive days at each of the three facilities. In total, 41 workers across the three facilities from each of 26 work areas volunteered to participate by providing skin wipe samples on one or both days. Written informed consent was obtained from each study participant. Note that personal lapel air samples were collected 2 weeks earlier, the results of which are reported in the companion paper (Stefaniak et al., 2008).

Surface Wipe Samples Six surfaces likely to be contacted by workers on a daily basis were selected for wipe sampling within each of the 26 separate work areas across the three facilities ($n = 157$). Specific examples of wiped surfaces included process equipment, tools, bench tops and control panels. Samples were collected in accordance with NIOSH Method 9102 (NIOSH, 2003a). Briefly, donning a pair of clean, nitrile gloves, a single surveyor used a disposable template to delineate an area equal to 100 cm^2 and wiped the delineated surface with one Wash 'n Dri® wipe (First Brands Corporation, Danbury, CT, USA) by applying firm pressure. Each surface was wiped three times, first in a horizontal, then a vertical and finally a diagonal direction. The exposed side of the wipe was folded inward after each wiping direction. When sampling from irregular-shaped surfaces, dimensions of the wiped surface were measured and recorded to allow accurate calculation of area for subsequent normalization to 100 cm^2. Each wipe sample was placed into an individually labeled, sealed plastic bag and sent for analysis to a commercial laboratory.

Skin Wipe Samples On the same 2 days that surface wipe samples were collected at each facility, skin wipe samples were also collected from the hands ($n = 114$) and necks ($n = 114$) of participating employees; 16 of the 41 participants provided samples on both days. All participants provided baseline (before starting work) and mid-shift (before lunchtime) hand and neck wipe samples, for a total of four samples per person per day. At mid-shift, participants also provided information regarding the use of protective gloves during the performance of their work, including the frequency of glove changes. This report emphasizes the results of mid-shift skin wipe samples, as adequate detail regarding pre-shift activities was not obtainable during sample collection. Upon the instruction and observation of investigators, each person wiped both of their hands (palm and back) from the top of the wrist to the tip of the fingers for no more than one minute and placed the sample into an individually labeled and sealed plastic bag. Each person then put on a clean pair of nitrile gloves and wiped his or her neck from ear to ear and under the chin down to the top of the Adam's apple for no more than 1 min and placed that sample into another separate plastic bag; all samples were sent for analysis to a commercial laboratory.

Analytical Methods and Quality Assurance
All wipe samples and blanks were analyzed for cobalt, chromium and nickel using NIOSH Analytical Method 7300 (NIOSH, 2003b). Field and laboratory blanks were each submitted at a proportion of approximately one per every 15–20 samples for each sample type. Analytical results from all blank samples were less than the limits of detection (LOD). For all sample types (i.e. surfaces, hands and necks), analytical LODs were 0.7 μg per wipe for cobalt, 0.6 μg per wipe for chromium and 0.3 μg per wipe for nickel.

Statistical Analysis
All statistical analyses were performed using PC-SAS version 9.1. (SAS Institute, Cary, NC, USA). To permit the use of data below the LOD for statistical analyses, values equal to one-half of the appropriate LOD were assigned to samples $\leq$LOD (Hornung and Reed, 1990). The distributions of all sample types were examined and found to be approximately lognormal, hence each was log-transformed, and geometric means (GMs) and geometric standard deviations (GSDs) were calculated. Summary statistics, including percent mass on different types of surfaces, were calculated by work area. The analysis of variance (ANOVA) procedure was used to conduct multiple comparisons of differences between GMs of the three facilities, different work areas within each facility and different types of work surfaces. One-way ANOVAs were used to investigate differences among GMs using the Proc GLM in SAS in which the natural logarithm of exposure was declared as the outcome variable. Tukey's test option was specified for pairwise multiple comparisons, which is useful for grouping together similar work areas. ANOVA F-statistics were used to note the overall differences among GMs, whereas Tukey's test was used to identify specific differences between the different GMs. Two-way ANOVAs with interaction terms for work surfaces and work areas or work surfaces and facilities were used to evaluate whether the work surfaces wiped within work areas or facilities were significantly different. Pearson correlation coefficients were obtained to evaluate relationships among sample types and exposure agents using the Proc Corr in SAS. Scatter plots of sample types and exposure agents were prepared in SigmaPlot 9.01 (Systat Software Inc., San Jose, CA, USA).

Results and discussion

Surface Wipe Samples
All surface wipe samples in all work areas had measurable levels of cobalt and nickel, whereas only 5% (7/157) were less than the LOD for chromium. Results of surface wipes by work area among the three facilities are summarized in Table 1. Measurable concentrations of all three metals were observed on surfaces in non-production areas at all facilities, including inventory control and administration. Generally, lower variability of measurements (i.e. GSDs) was associated with these non-production work areas, whereas the highest variability was associated with production work areas at the metal separation facility. The range of variability in levels of surface contamination is consistent with ranges of variability observed for airborne exposures in this occupational environment (Stefaniak et al., 2008).

Table 1. Cobalt, chromium and nickel concentrations (μg/100 cm^2) on surfaces by facility and work area

Facility	Work area	n^a	Cobalt			Chromium			Nickel		
			GM[b]	GSD[c]	Range[d]	GM	GSD	Range	GM	GSD	Range
Metal separation	Metal separation	6	986	7.4	93–17,000	67	7.7	5.9–960	185	8.5	19–4000
	Reclamation A	6	227	7.1	32–7000	8.2	6.8	0.92–240	15	4.2	1.7–100
	Reclamation B	6	946	3.0	220–3004	17	2.3	5.1–43	47	2.6	11–150
	Carbide	6	71	5.5	9.7–580	11	7.9	1.0–140	10	10	1.1–200
	Maintenance	6	43	4.0	9.4–400	5.8	2.9	1.3–28	34	4.4	5.3–310
	Administration	6	4.1	1.7	2.3–8.0	0.36	1.4	0.30–0.70	1.5	2.4	0.60–6.6
Powder handling	Inventory control	6	70	2.7	16–275	1.8	2.5	0.80–9.5	10	3.3	1.9–60
	Powder mixing	12	1710	4.0	340–22,000	9.6	4.2	0.82–70	104	5.5	5.4–2000
	Milling	6	1349	2.1	550–3200	17	2.3	7.1–47	115	4.2	20–520
	Spray drying	6	1051	4.7	75–4900	6.8	4.2	0.96–33	48	6.1	4.5–390
	Screening	6	3057	3.2	670–14,000	47.4	2.9	12–160	81	2.2	27–240
	Shipping (powder)	6	129	1.9	46–330	2.7	2.2	1.0–8.8	19	2.4	5.0–63
	Maintenance (powder)	6	447	2.2	120–1300	11	1.7	4.8–19	44	1.9	13–78
Forming/machining	Production control	6	118	3.0	17–400	2.7	2.4	0.70–8.6	5.9	2.9	1.1–25
	Pressing	6	497	3.1	140–2900	10	2.8	2.9–46	26	4.9	7.6–530
	Extrusion	7	976	2.5	430–5426	29.4	2.6	11–181	10	4.2	1.9–155
	Shaping	6	981	3.4	100–2800	22	4.0	2.0–94	22	2.1	8.7–73
	Breakdown	6	356	2.2	130–630	9.0	2.2	3.2–20	15	2.2	5.6–34
	Grinding	12	468	2.7	160–3600	17	2.6	6.3–120	29	2.7	7.3–200
	Sandblasting	6	52	4.4	6.2–500	2.8	2.3	0.90–11	3.6	2.6	0.90–18
	Shipping (product)	6	40	2.2	10–97	1.7	1.6	0.80–2.6	3.1	2.2	0.80–8.9
	Maintenance	6	211	1.9	71–470	18	3.1	5.2–120	16	2.4	7.7–68
	Tray preparation	6	624	2.3	219–1656	15	2.3	4.8–37	27	2.6	8.5–74
	Administration	6	11	3.3	2.6–59	0.70	1.9	0.30–1.3	1.1	2.2	0.40–3.6

[a] n = number of samples; 0/157 < LOD for cobalt, 7/157 < LOD for chromium and 0/157 < LOD for nickel.
[b] GM = geometric mean.
[c] GSD = geometric standard deviation.
[d] Range = minimum to maximum values.

GM concentrations of cobalt, chromium and nickel on all surfaces combined in each of the three facilities are illustrated in Figure 1a. Cobalt and nickel concentrations were significantly greater in the powder-handling facility (690 μg/100 cm^2 and 51 μg/100 cm^2, respectively) than in either the metal separation facility (118 μg/100 cm^2 and 20 μg/100 cm^2) or forming/machining facility (225 μg/100 cm^2 and 11 μg/100 cm^2). GM concentrations of chromium on surfaces were not significantly different among the three facilities (metal separation = 7.7 μg/100 cm^2; powder handling = 8.5 μg/100 cm^2; forming/machining = 7.8 μg/100 cm^2). The higher concentrations of metals observed in the powder-handling facility were not unexpected owing to the characteristics of the material handled at this facility (powder) and the high-energy nature of the processes (Stefaniak et al., 2008).

Within the metal separation facility, overall GM concentrations of cobalt, chromium and nickel were significantly different among work areas ($P \leq 0.0006$). Concentrations of the three metals were significantly lower ($P < 0.05$) in administration than in production work areas. Within production, concentrations were significantly different only between a few work areas. Within the powder-handling facility, overall GM concentrations of cobalt, chromium and nickel were significantly different among work areas ($P \leq 0.02$); however, there were few statistically significant pairwise differences between the work areas. Within the forming/machining facility, GM concentrations of the three metals had the greatest number of significant pairwise differences between work areas.

Table 2 summarizes results of surface wipes from all three facilities by category. Concentrations of cobalt, chromium and nickel on control panels ($n = 22$), hand tools ($n = 27$), containers ($n = 18$) and ventilation equipment ($n = 2$) were consistently higher than concentrations on other surfaces. Excluding ventilation equipment, these same categories ($n = 67$) contributed 49%, 60% and 52% of the total masses of cobalt, chromium and nickel, respectively on all surfaces. All three elements were also detected on bench and desktops, as well as on furniture, office equipment and to a lesser extent on telecommunication equipment. These results suggest that practically all surfaces frequently handled by workers at the three facilities were contaminated with measurable levels of cobalt, chromium and nickel. Overall, ANOVA results indicated that the GM concentrations of cobalt, chromium and nickel on work surfaces were significantly different from one another ($P < 0.0001$). As expected, pairwise comparisons

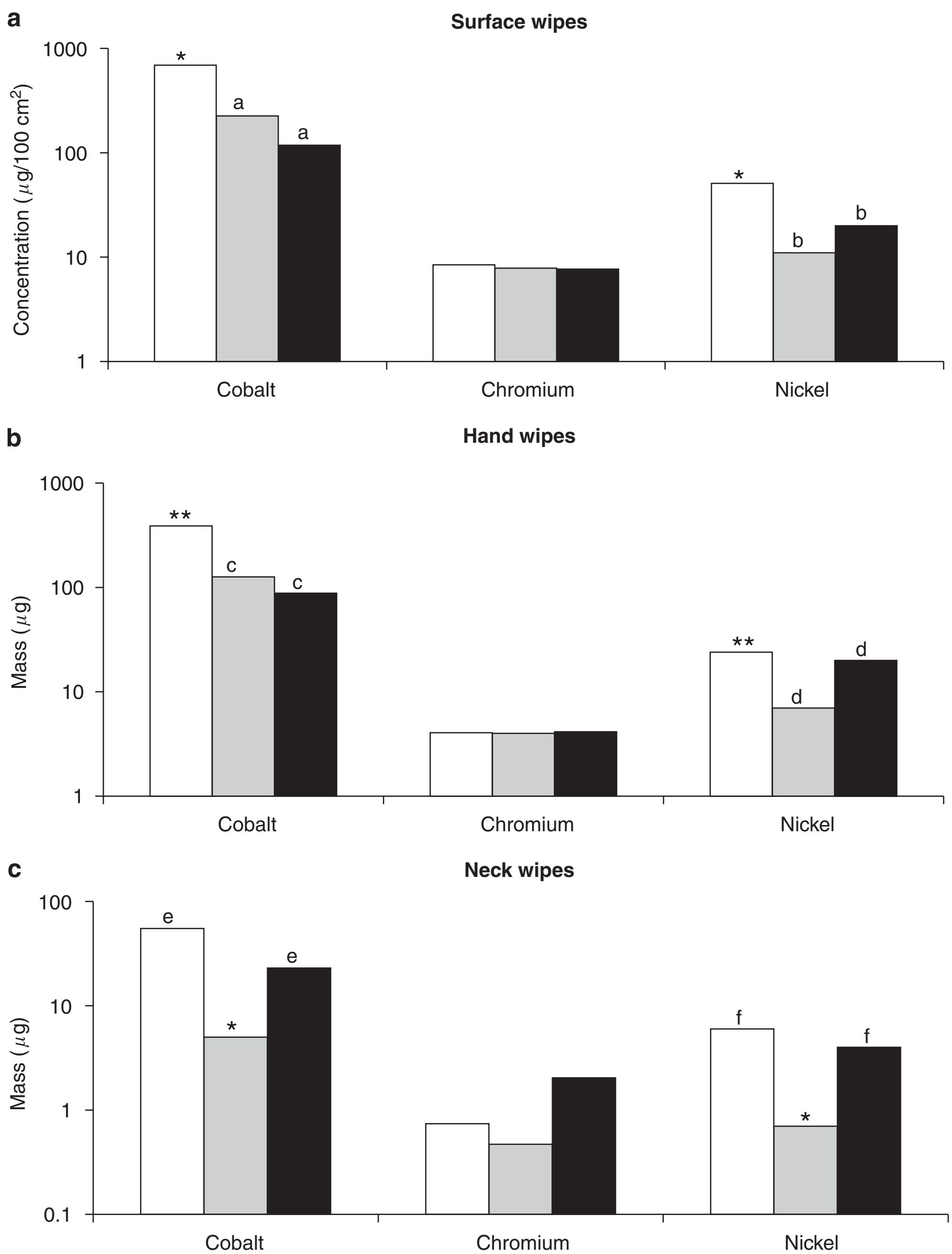

Figure 1. Comparison bar graphs (log scale) illustrating levels of cobalt, chromium and nickel among surface wipe measurements (a), hand wipe measurements (b) and neck wipe measurements (c) in three different CTC facilities. □ powder-handling facility; ▒ forming/machining facility; ■ metal separation facility; * significantly different from the remaining two facilities ($P<0.05$); ** significantly different from only one facility ($P<0.05$); a, b, c, d, e and f, not significantly different from one another.

generally indicated that GM concentrations of the three metals associated with the highest contaminated surfaces (i.e. control panels, hand tools and containers) were significantly different from the lowest contaminated surfaces (i.e. telecommunication, mobile and office equipment). These data are useful for prioritizing work surfaces for decontamination efforts and for developing elements of facility-specific housekeeping programs. Exposure and migration control strategies may include engineering controls (e.g. isolation of processes, increased ventilation and tacky floor mats); administrative controls (e.g. restricted access areas, minimizing the number of employees in the area, and specific protocols for entering and exiting the area) and proper use of personal protective equipment (e.g. gloves and coveralls).

Table 2. Cobalt, chromium and nickel concentrations (μg/100 cm^2) on surfaces by category

Category	Descriptions/examples	n^a	Cobalt			Chromium			Nickel		
			GM[b]	GSD[c]	Percent[d]	GM	GSD	Percent	GM	GSD	Percent
Bench or desktops	Benches, desks	15	205	14	9.1	6.9	7.5	8.9	21	10	9.7
Containers	Bins, bottles, boxes	18	526	2.6	12.8	18	2.5	16.1	40	3.1	14.1
Control panels	Buttons, switches, keypads	22	1231	4.3	17.8	27	4.8	22.2	64	6.8	19.5
Fixed equipment	Handrails, rungs, latches	15	190	7.9	8.9	5.9	3.9	8.1	15	6.7	8.6
Furniture	Lockers, filing cabinets	11	119	4.9	6.0	5.0	3.6	5.4	19	2.4	6.9
Hand tools	Mallets, wrenches	27	445	3.9	18.7	14	3.0	21.7	25	3.7	18.5
Mobile equipment	Handcart, forklift handles	19	154	3.5	10.9	3.5	2.6	7.3	9.8	2.7	9.2
Office equipment	Fax machines, printers	19	93	14	9.8	3.1	7.5	6.6	7.1	6.7	7.9
Shop packets	Plastic sleeves for orders	4	109	1.8	2.1	3.3	1.6	1.5	5.8	1.6	1.5
Telecommunication	Telephone keypads, receivers	5	40	4.9	2.1	1.8	5.9	0.9	4.8	4.0	1.7
Ventilation equipment	Dust control hoods	2	4034	11	1.9	8.4	5.2	1.3	253	19	2.4

[a] n = number of samples.
[b] GM = geometric mean.
[c] GSD = geometric standard deviation.
[d] Percent = fraction of total mass among all categories.

The two-way ANOVA model indicated a significant interaction term between work surface and facility, suggesting that the GM concentrations of metals on work surfaces were different between facilities. Similar results were obtained when the interaction term was between work surfaces and work areas, again suggesting that the GM concentrations of metals on work surfaces were different between work areas. The practical implication of this finding is that the results of a wipe sample taken from a particular type of surface in one facility or work area may be significantly different from the results of a wipe sample collected from the same type of surface in another facility or work area. Hence, efforts to control the migration of surface contamination should not only be limited to good control and work practices within individual work areas but should also mitigate the contribution of migration from the transfer of tools and equipment between work areas within facilities.

Skin Wipe Samples

Similar to surface wipes, all hand wipe samples had measurable levels of cobalt and nickel, whereas only 4% (2/57) were less than LOD for chromium. In contrast, 5% (3/57) of neck wipe samples were less than LOD for cobalt, 14% (8/57) for nickel and 49% (28/57) for chromium. Even though a larger proportion of neck wipe sample results were below the LOD for chromium, we were unable to use special statistics to estimate means (e.g. maximum likelihood) because there were often only two samples in each work area.

Hands Table 3 summarizes the levels of cobalt, chromium and nickel removed from workers' hands by facility and work area. In general, levels of contamination on hands were highest among workers in most work areas of the powder-handling facility and in selected work areas at the metal separation and forming/machining facilities. Low to moderate levels of cobalt, chromium and nickel were measured on workers' hands in administration. GM levels of cobalt, chromium and nickel on the hands of all workers in each of the three facilities are illustrated in Figure 1b. Levels of cobalt on the hands of powder-handling workers (388 μg) were significantly greater than metal separation workers (88 μg), but not different from forming/machining workers (126 μg). In contrast, levels of nickel on the hands of powder-handling workers (24 μg) were significantly greater than forming/machining workers (7 μg), but not different from metal separation workers' hands (20 μg). The GM chromium levels on workers' hands were low ($\sim$4 μg), and were not significantly different among facilities.

Within the metal separation facility, GM levels of cobalt and chromium measured on workers' hands did not differ significantly among work areas. The GM level of nickel on workers' hands in administration was significantly lower than in other work areas ($P<0.05$) at this facility. Within the powder-handling facility, GM levels of all three metals on workers' hands were not significantly different among work areas. Conversely, at the forming/machining facility GM levels of all three metals on workers' hands differed significantly among work areas ($P\leq0.01$). GM levels of cobalt and nickel on hands of workers in production control were significantly higher than in all other areas, whereas GM chromium levels were significantly different among many work areas.

We evaluated the relationship of glove use and frequency of glove changes on the GM levels of cobalt, chromium and nickel measured on workers' hands. Workers who reported wearing gloves generally worked in production areas associated with the highest concentrations of metals on surfaces. Likewise, workers who reported not wearing gloves

Table 3. Cobalt, chromium and nickel masses (μg) on hands by facility and work area

Facility	Work area	n[a]	Cobalt		Chromium		Nickel	
			GM[b]	GSD[c]	GM	GSD	GM	GSD
Metal separation	Metal separation	2	443	5.1	30	7.1	98	4.6
	Reclamation A	2	161	5.5	6.6	4.8	14	2.3
	Reclamation B	2	67	3.8	1.5	1.8	11	4.2
	Carbide	2	57	2.6	0.8	4.2	5.2	4.9
	Maintenance	2[d]	425	1.1	38.5	2.7	488	4.4
	Administration	2[d]	4.1	2.7	0.5	2.2	1.7	1.3
Powder handling	Inventory control	2	156	2.1	3.0	1.8	13	1.2
	Powder mixing	3	1328	26	3.3	2.4	21	3.9
	Milling	2	601	5.1	7.3	2.3	64	3.4
	Spray drying	2	498	2.0	4.3	1.1	29	1.5
	Screening	2	442	4.6	7.7	6.8	29	4.6
	Shipping (powder)	2	170	1.1	3.0	1.0	17	1.3
	Maintenance (powder)	2	154	8.5	2.7	4.2	17	4.6
Forming/machining	Production control	2[d]	4285	1.9	101	1.9	141	1.4
	Pressing	4[e]	69	1.5	1.7	1.4	2.4	1.4
	Extrusion	2[d]	170	1.1	4.1	1.2	2.2	1.3
	Shaping	4[e]	76	4.1	2.2	2.1	6.6	9.8
	Breakdown	2[d]	123	1.3	3.1	1.0	5.6	1.1
	Grinding	6[e]	121	2.0	5.0	1.6	7.6	1.8
	Sandblasting	2[d]	23	1.3	1.0	1.0	1.6	1.4
	Shipping (product)	2[d]	358	1.2	6.8	1.1	31	1.1
	Maintenance	2[d]	84	3.4	8.3	1.5	11	3.0
	Tray preparation	2[d]	105	1.1	3.0	1.1	4.9	1.0
	Administration	2[d]	108	1.2	2.8	1.3	6.0	1.4

[a]n = number of samples; 0/57 <LOD for cobalt, 2/57 <LOD for chromium and 0/57 <LOD for nickel.
[b]GM = geometric mean.
[c]GSD = geometric standard deviation.
[d]Samples collected from one subject.
[e]Samples collected as repeated measurements from multiple subjects.

generally worked in non-production areas, such as administration, which were associated with the lowest concentrations of metals on surfaces. Interestingly, workers who reported wearing gloves during the performance of their work had higher levels of metals detected on their hands than did those who did not report wearing gloves. A similar trend was observed with the frequency of glove changes, with those reporting the greatest number of glove changes having the highest levels of metals on their hands. It is plausible that participants who worked in areas with the highest levels of contamination changed their gloves more frequently in an attempt to keep their hands clean. These results clearly demonstrate the importance of a skin protection program that includes training workers on proper glove use. Note that the protective glove barrier may be bypassed by placing already-contaminated hands into a clean pair of gloves, which may occur when putting on and tying the laces of contaminated shoes before gloving.

Necks Table 4 summarizes levels of cobalt, chromium and nickel on workers' necks by facility and work area. High levels of cobalt and nickel were measured on workers' necks in the metal separation and powder-handling facilities with less on workers' necks in the forming/machining facility. GM levels of cobalt, chromium and nickel on the necks of all workers in each of the three facilities are illustrated in Figure 1c. Levels of cobalt and nickel on workers' necks were significantly lower in forming/machining (5 and 0.7 μg, respectively) than either powder handling (55 and 6 μg) or metal separation (23 and 4 μg). Levels of chromium on workers' necks were generally low for all facilities.

Within the metal separation facility, GM levels of cobalt, chromium and nickel on the necks of workers significantly differed among work areas; a number of pairwise differences were observed, with the metal separation and administration work areas at either extreme. Within the powder-handling facility, GM levels of all three metals on workers' necks did not significantly differ among the work areas. Within the forming/machining facility, there were no significant differences in the GM levels of cobalt and nickel on workers' necks among work areas, but the GM levels of chromium on necks differed significantly among work areas; maintenance had the highest GM level of chromium on necks compared to all other work areas.

Table 4. Cobalt, chromium and nickel masses (μg) on necks by facility and work area

Facility	Work area	n^a	Cobalt		Chromium		Nickel	
			GM[b]	GSD[c]	GM	GSD	GM	GSD
Metal separation	Metal separation	2	693	3.3	39	3.6	137	3.5
	Reclamation A	2	117	3.6	3.3	5.4	7.4	1.2
	Reclamation B	2	21	2.0	0.8	1.4	2.6	1.7
	Carbide	2	4.3	1.3	0.5	2.2	0.4	4.1
	Maintenance	2[d]	35	1.8	4.6	1.9	37	2.7
	Administration	2[d]	0.5	1.8	0.3	1.0	0.2	1.0
Powder handling	Inventory control	2	7.8	2.1	0.5	1.8	1.4	1.5
	Powder mixing	3	342	2.5	0.8	2.6	7.2	3.7
	Milling	2	64	1.1	0.8	3.8	6.3	1.1
	Spray drying	2	135	3.2	0.8	3.8	16	4.7
	Screening	2	81	7.3	2.0	2.6	4.4	7.2
	Shipping (powder)	2	19	1.5	0.3	1.0	8.4	1.5
	Maintenance (powder)	2	18	5.4	0.9	1.1	3.7	3.6
Forming/machining	Production control	2[d]	19	1.2	0.3	1.0	1.1	1.5
	Pressing	4[e]	2.7	5.2	0.4	1.4	0.4	2.8
	Extrusion	2[d]	3.6	1.3	0.3	1.0	0.3	2.3
	Shaping	4[e]	5.5	2.3	0.4	1.5	0.6	3.6
	Breakdown	2[d]	17	1.2	0.7	1.1	1.3	1.9
	Grinding	6[e]	4.3	2.4	0.5	1.8	0.5	1.8
	Sandblasting	2[d]	2.5	1.1	0.3	1.0	0.4	1.2
	Shipping (product)	2[d]	4.0	1.0	0.6	1.0	0.6	1.3
	Maintenance	2[d]	5.7	4.4	4.3	3.0	2.7	1.9
	Tray preparation	2[d]	12	1.4	0.3	1.0	0.9	1.0
	Administration	2[d]	0.6	2.1	0.3	1.0	1.2	2.8

[a]n = number of samples; 3/57 < LOD for cobalt, 28/57 < LOD for chromium and 8/57 < LOD for nickel.
[b]GM = geometric mean.
[c]GSD = geometric standard deviation.
[d]Samples collected from one subject.
[e]Samples collected as repeated measurements from multiple subjects.

Baseline Measurements Of interest are results of baseline skin wipe samples that showed moderate levels of skin contamination at the start of the work shift (data not shown). Hand wipe levels ranged from 0.8 to 410 μg for cobalt, 0.3 to 18 μg for chromium and 0.3 to 80 μg for nickel. Neck wipe levels ranged from 0.4 to 130 μg for cobalt, 0.3 to 2 μg for chromium and 0.2 to 49 μg for nickel. Baseline measurements (hands and necks) for all three metals were significantly lower than mid-shift measurements. Although details of workers' pre-shift activities were not systematically collected, it is plausible that some individual worker's hands became contaminated when handling already-contaminated clothing, shoes or equipment prior to providing baseline samples. It is also plausible that some workers had started to work earlier to providing baseline samples. Alternatively, some level of hand contamination may have remained from the previous shift, suggesting the occurrence of take-home exposures. This alternative possibility is further corroborated by the levels of the metals measured on workers' necks at baseline. Re-distribution from contaminated hands or surfaces to necks is less probable over the short period of time before starting work.

Table 5. Summary of correlations among cobalt, chromium and nickel by sample type

	Chromium	Nickel
Cobalt		
Surfaces	0.77	0.78
Hands	0.60	0.81
Necks	0.86	0.85
Chromium		
Surfaces	1	0.82
Hands	1	0.73
Necks	1	0.81

All P-values < 0.0001.

Relationships among Surface, Hand and Neck Wipe Samples

Table 5 is a summary of correlations among metals for all sample types. Generally, high correlations were observed among all metals and sample types, suggesting that when high concentrations of cobalt were sampled from work

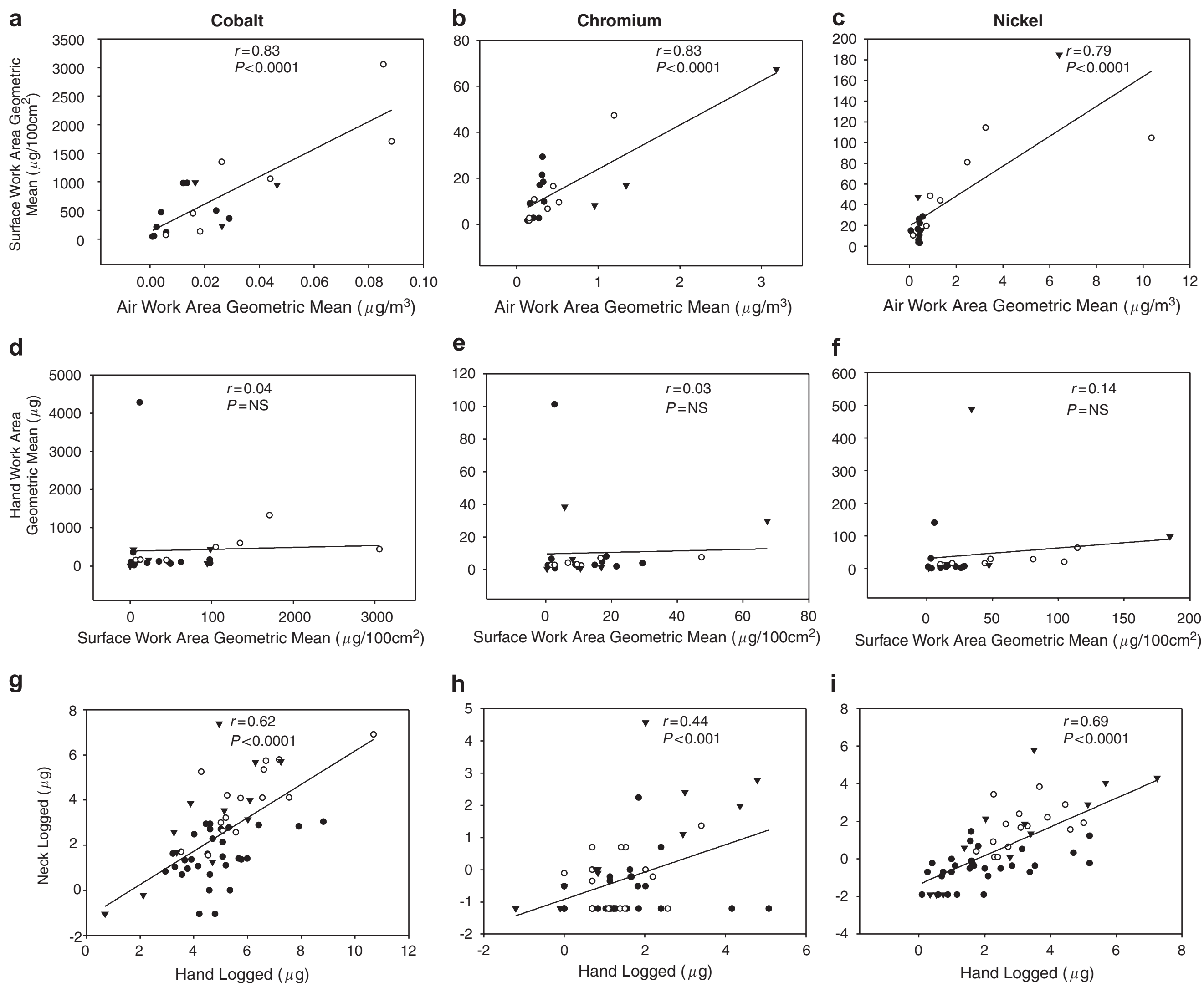

Figure 2. Comparison plots illustrating the relationships of levels of cobalt, chromium and nickel among surface wipe and air measurements (a–c), hand and surface wipe measurements (d–f) and neck and hand wipe measurements (g–i). ▼ metal separation; ○ powder handling; ● forming/machining; trend line, least-squares regression; NS, not significant.

surfaces or from the skin, high levels of chromium and nickel were also present. Figure 2 illustrates relationships (i.e. Pearson correlations) among various sample types for cobalt, chromium and nickel, corresponding to an exposure model that includes potential pathways among air, work surfaces and body segments (Day et al., 2007). As expected, high correlations were observed between GM concentrations (by work area) of cobalt, chromium and nickel in air and on work surfaces (Figure 2a–c); however, no correlation was observed between GM levels (by work area) of metals on surfaces and on workers' hands (Figure 2d–f). Absence of an association between surface contamination and exposure to workers' hands may be due, in part, to inconsistent use of gloves or differences in hand washing practices by workers. Likewise, no correlations were observed between GM levels (by work area) of metals in air (Stefaniak et al., 2008) and on workers' hands and necks (data not shown). There is less likelihood of a direct association between airborne concentrations and skin exposures, except during the performance of high dust-generating tasks, when particles may settle onto the skin (Vermeulen et al., 2000). Likewise, there is less likelihood of a direct association between contaminated work surfaces and exposure to the skin of workers' necks or other body segments that may not come into direct contact with work surfaces. Moderate correlations were observed between levels of metals on hands and necks of workers (Figure 2g–i). Hand-to-neck contact may be the primary exposure pathway, but the association is likely confounded by glove use.

Skin Exposure Assessment

Available methods for assessing skin contamination include removal and interception techniques; however, an internationally accepted method has not yet been agreed upon. We assessed potential skin exposures through removal techniques (i.e. wiping potentially contaminated work surfaces and workers' hands and necks). The major assumption of all removal techniques is that the majority of contamination is captured by the collection medium. Que Hee et al. (1985) observed experimentally that serial wipe sampling is insufficient to remove all lead-containing dust from the hands of study subjects. Other issues to consider with regard to removal techniques in general is that they only remove the contaminant present on the skin surface at a given point in time and do not account for (1) the fraction that may have brushed off, (2) material washed off by sweating or hygienic practices or (3) dissolved contaminant that permeated the skin prior to sample collection. Thus, results from our wipe samples probably underestimate the masses of metals that contacted workers' skin during the shift. Cherrie and Robertson (1995) suggest that in addition to the level of contamination and duration of exposure, consideration should also be given to the area of exposed skin. If a permeability coefficient is available for the contaminant of interest, then it may be possible to estimate total mass uptake through the skin, a factor closely related to solubility of the contaminant in sweat. Constituents of CTC dusts, cobalt, nickel and chromium are thought to be mostly of the metallic form. Research indicates that metallic cobalt and nickel but not chromium can dissolve in sweat and may permeate the skin (Filon et al., 2004; Larese et al., 2007). Hence, permeation through the skin of cobalt and nickel is likely, suggesting that the fraction of the total skin-deposited mass that dissolves in sweat may provide a more biologically appropriate estimate of exposure for these metals; however, such an exposure assessment tool is currently lacking. Additionally, dissolution of metal particles on the skin surface with subsequent permeation of dissolved metal ions through skin may have important implications for the assessment of total-body exposure and for interpreting biomonitoring results.

Health Implications of Exposure Pathways

Simultaneous exposure to cobalt, chromium and nickel may augment distinct sensitization to the individual metals (Guy et al., 1999). Hence, from a medical perspective, documenting exposure to multiple agents may be useful in diagnosing and managing adverse health effects. From an epidemiological perspective, even moderately high correlation ($r \sim 0.7$) between surrogate and "true" indices of exposure may cause misclassification of up to 60% of subjects into exposure quintiles, which in turn may cause a significant bias in the relative risk estimate (Blair et al., 2007). Additionally, high correlation among the metals in terms of exposure may not necessarily correspond to high correlation with dose, as dose is very likely dependent upon the physicochemical properties and toxicokinetics of the individual metals. Hence, it is important to develop exposure metrics that represent the specific agent(s) related to the disease process to observe small risks, or risk related to mixed exposures.

In addition to airborne exposure, high levels of surface contamination and exposures to hands and necks were observed among employees in these three CTC facilities. These multiple pathways and routes of exposure necessitate comprehensive evaluation and deeper understanding of disease mechanisms. For systemic effects, indices of total exposure may be obtained by combining estimates of exposure by each applicable route, taking into consideration the kinetics of the substance for each route. Note that combining estimates of exposure for multiple routes may be inappropriate when mechanisms of disease are specific to a particular exposure route. For OA, inhalation exposure to cobalt, chromium and/or nickel compounds may play a role in the development of sensitization and/or disease. Upon contact with sweat on the skin surface, many of these compounds may release ions that can pass into and through the skin, but the role of skin exposure in development of respiratory sensitization and/or OA is less well understood. Because sensitization via inhalation exposure may occur by a different mechanism than skin exposure, simply combining estimates of exposure for these routes may yield an exposure metric that is not biologically relevant. Comprehensive characterization of exposures by multiple routes is a first step toward developing biologically relevant exposure indices, which will permit the examination of different hypotheses regarding the importance of exposure routes and the interactions between exposure routes and health outcomes in epidemiologic investigations. Estimates of inhalation and skin exposure by work area can be used in conjunction with additional information on work history, pattern of movement between work areas among the different jobs among other factors to create appropriate exposure metrics for epidemiological investigations.

These disease mechanisms and exposure pathways suggest the need for a total exposure assessment approach, including assessment of multiple constituents and exposure pathways. Although moderately high correlations exist among constituents and pathways of exposure, the toxicokinetics and pharmacodynamics of such an exposure scenario may require more sophisticated exposure metrics. Such biologically relevant metrics may reduce exposure misclassification in epidemiologic studies and improve our ability to detect exposure–response relationships for CTC dust-induced adverse health effects (Kriebel et al., 2007).

Exposure Control

Guidance is currently lacking for establishing acceptable cleanliness levels on work surfaces, either for individual chemicals or mixtures of chemicals. Establishing criteria for surface (and skin) cleanliness can be useful for reducing not only the potential for skin exposure but also the occurrence of sensitization. In these facilities, virtually all sampled surfaces were contaminated with three known sensitizers: cobalt, chromium and nickel. The high correlation among the three metals suggests that improved housekeeping for certain categories of surfaces would go a long way toward reducing overall contamination and potential for metal-induced sensitization in each facility. Cummings et al. (2007) reported that an enhanced industrial hygiene preventive program, incorporating novel interventions to minimize particle migration and both respiratory and dermal exposures, reduced beryllium sensitization among newly hired workers in the first years of employment. Another example related to cleanliness criteria is the nickel release limit established by the European Union to prevent nickel sensitization and contact dermatitis in the general public (where release rate is determined by immersion of nickel-containing consumer products in artificial sweat) (Lidén et al., 1996).

Limitations

We have noted some considerations regarding the skin sampling method (removal) used in this study, which generally reflect the inherent uncertainty associated with exposure assessment. In addition, the small number of participants who provided skin wipe samples limited more accurate estimation and comparison of dermal exposures within and among facilities. Specific information on exposure determinants (such as task-based factors and engineering controls, etc.) associated with each sample collected could not be obtained for a variety of reasons. Hence, we provide a detailed appendix in the companion paper (Stefaniak et al., 2008) to describe the processes from which the samples were collected to facilitate additional interpretation of the data.

Acknowledgements

We acknowledge the following NIOSH staff: Drs. C. Coffey, J. Cox-Ganser, and K. Kreiss for their support and helpful discussions of this work; N. Edwards and S. White for data management and graphics development. We also acknowledge Drs. L. Geer and T. Buckley for their useful reviews of the paper.

Disclaimer

Mention of a specific product or company does not constitute endorsement by the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

References

Barceloux D.G. Chromium. *J Toxicol Clin Toxicol* 1999: 37(2): 173–194.

Bello D., Herrick C.A., Smith T.J., Woskie S.R., Streicher R.P., Cullen M.R., et al. Skin exposure to isocyanates: reasons for concern. *Environ Health Perspect* 2007: 115(3): 328–335.

Bernstein I.L., and Merget R. Metals. In: Bernstein I.L., Chan-Yeung M., Malo J.-L., and Bernstein D.I. (Eds.). *Asthma in the Workplace and Related Conditions*, 3rd edn. Taylor and Francis, New York, 2006, pp 525–554.

Blair A., Stewart P., Lubin J.H., and Forastiere F. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. *Am J Ind Med* 2007: 50(3): 199–207.

Cherrie J.W., and Robertson A. Biologically relevant assessment of dermal exposure. *Ann Occup Hyg* 1995: 39: 387–392.

Chiba A., Sakakura S., Kobayashi K., and Kusayanagi K. Dissolution amounts of nickel, chromium and iron from SUS 304, 316 and 444 stainless steels in sodium chloride solutions. *J Mater Sci* 1997: 32(8): 1995–2000.

Cohen M.D., and Costa M. Chromium. In: Lippman M.I. (Ed.). *Environmental Toxicants. Human Exposures and their Health Effects*, 2nd edn. John Wiley and Sons, New York, 2000, pp 180–182.

Cummings K.J., Deubner D.C., Day G.A., Henneberger P.K., Kitt M.M., Kent M.S., et al. Enhanced preventive programme at a beryllium ceramics plant reduces beryllium sensitisation among new workers. *Occup Environ Med* 2007: 64(2): 134–140.

Day G.A., Dufresne A., Stefaniak A.B., Schuler C.R., Stanton M.L., Miller W.E., et al. Exposure pathway assessment at a copper–beryllium alloy facility. *Ann Occup Hyg* 2007: 51: 67–80.

Day G.A., Stefaniak A.B., Weston A., and Tinkle S.S. Beryllium exposure: dermal and immunological considerations. *Int Arch Occup Environ Health* 2006: 79(2): 161–164.

Fernández-Nieto M., Quirce S., Carnés J., and Sastré J. Occupational asthma due to chromium and nickel salts. *Int Arch Occup Environ Health* 2006: 79: 483–486.

Filon F.L., Maina G., Adami G., Venier M., Coceani N., Bussani R., et al. *In vitro* percutaneous absorption of cobalt. *Int Arch Occup Environ Health* 2004: 77: 85–89.

Goebeler M., Meinardus-Hager G., Roth J., Goerdt S., and Sorg C. Nickel chloride and cobalt chloride, two common contact sensitizers, directly induce expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule (ELAM-1) by endothelial cells. *J Invest Dermatol* 1993: 100(6): 759–765.

Goebeler M., Roth J., Bröcker E.B., Sorg C., and Schulze-Osthoff K. Activation of nuclear factor-kappa B and gene expression in human endothelial cells by the common haptens nickel and cobalt. *J Immunol* 1995: 155(5): 2459–2467.

Guy R.H., Hostỳnek J.J., Hinz R.S., and Lorence C.R. *Metals and the Skin. Topical Effects and Systemic Absorption*. Marcel Dekker, New York, 1999 pp 127–128.

Halbert A.R., Gebauer K.A., and Wall L.M. Prognosis of occupational chromate dermatitis. *Contact Dermatitis* 1992: 27: 214–219.

Hansen M.B., Johansen J.D., and Menné T. Chromium allergy: significance of both Cr(III) and Cr(VI). *Contact Dermatitis* 2003: 49: 206–212.

Haudrechy P., Foussereau J., Mantout B., and Baroux B. Nickel release from 304 and 316 stainless steels in synthetic sweat. Comparison with nickel and nickel-plated metals. Consequences on allergic contact dermatitis. *Contact Dermatitis* 1993: 35(1–4): 329–336.

Hemingway J.D., and Molokhia M.M. The dissolution of metallic nickel in artificial sweat. *Contact Dermatitis* 1987: 16: 99–105.

Hornung R.W., and Reed L.D. Estimation of average concentration in the presence of nondetectable values. *Appl Occup Environ Hyg* 1990: 5: 46–51.

Kriebel D., Checkoway H., and Pearce N. Exposure and dose modelling in occupational epidemiology. *Occup Environ Med* 2007: 64(7): 492–498.

Larese F., Gianpietro A., Venier M., Maina G., and Renzi N. *In vitro* percutaneous absorption of metal compounds. *Toxicol Lett* 2007: 170: 49–56.

Lidén C., and Carter S. Nickel release from coins. *Contact Dermatitis* 2001: 44(3): 160–165.

Lidén C., Menné T., and Burrows D. Nickel-containing alloys and platings and their ability to cause dermatitis. *Br J Dermatol* 1996: 134(2): 193–198.

Linnainmaa M., and 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.

Morgan L.G., and Flint G.N. Nickel alloys and coatings: release of nickel. In: Maibach H.I., and Menné T. (Eds.). *Nickel and the Skin: Immunology and Toxicology*. CRC Press, Boca Raton, FL, 1989, pp 45–54.

NIOSH. Elements on Wipes: Method 9102. *NIOSH Manual of Analytical Methods (NMAM)* 2003a 4th ed., 3rd suppl. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati.

NIOSH. Elements by ICP: Method 7300. *NIOSH Manual of Analytical Methods (NMAM)* 2003b 4th ed., 3rd suppl. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati.

Que Hee S.S., Peace B., Clark C.S., Boyle J.R., Bornschein R.L., and Hammond P.B. Evolution of efficient methods to sample lead sources, such as house dust and hand dust, in the homes of children. *Environ Res* 1985: 38: 77–95.

Randin J.P. Corrosion behavior of nickel-containing alloys in artificial sweat. *J Biomed Mater Res* 1988: 22: 649–666.

Redlich C.A., and Herrick C.A. Lung/skin connections in occupational lung diseases. *Curr Opin Allergy Clin Immunol* 2008: 8: 115–119.

Scansetti G., Botta G.C., Spinelli P., Reviglione L., and Ponzetti C. Absorption and excretion of cobalt in the hard metal industry. *Sci Total Environ* 1994: 150: 141–144.

Schneider T., Vermeulen R., Brouwer D.H., Cherrie J.W., Kromhout H., and Fogh C.L. Conceptual model for assessment of dermal exposure. *Occup Environ Med* 1999: 56: 765–773.

Stefaniak A.B., Day G.A., Harvey C.J., Leonard S.S., Schwegler-Berry D.E., Chipera S.J., et al. Characteristics of process-generated tungsten carbide dusts associated with hard metal disease and asthma. *Ind Health* 2007: 45: 793–803.

Stefaniak A.B., Virji M.A., and Day G.A. Characterization of exposures among cemented tungsten carbide workers. Part I: Size-fractionated exposures to airborne cobalt and tungsten particles. *J Expos Anal Environ Epidemiol* 2008 (this issue).

Van Lierde V., Chéry C.C., Roche M., Monstrey S., and Vanhaecke F. *In vitro* permeation of chromium species through porcine and human skin as determined by capillary electrophoresis-inductively coupled plasma-sector field mass spectrometry. *Anal Bioanal Chem* 2006: 384: 378–384.

Vermeulen R., Heideman J., Bos R.P., and Kromhout H. Identification of dermal exposure pathways in the rubber manufacturing industry. *Ann Occup Hyg* 2000: 44: 533–541.

Walberg J.E. Other metals. In: Kanerva L., Elsner P., Wahlberg J.E., and Maibach H.I. (Eds.). *Handbook of Occupational Dermatology*. Springer-Verlag, Berlin, 2000, pp 551.