Journal of Exposure Science and Environmental Epidemiology (2009) 19, 475–491

www.nature.com/jes

Characterization of exposures among cemented tungsten carbide workers. Part I: Size-fractionated exposures to airborne cobalt and tungsten particles

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As many as 30,000 workers in the United States of America are exposed to cemented tungsten carbides (CTC), alloys composed primarily of tungsten carbide and cobalt, which are used in cutting tools. Inhalation of cobalt-containing particles may be sufficient for the development of occupational asthma, whereas tungsten carbide particles in association with cobalt particles are associated with the development of hard metal disease (HMD) and lung cancer. Historical epidemiology and exposure studies of CTC workers often rely only on measures of total airborne cobalt mass concentration. In this study, we characterized cobalt- and tungsten-containing aerosols generated during the production of CTC with emphasis on (1) aerosol ''total'' mass ($n = 252$ closed-face 37 mm cassette samples) and particle size-selective mass concentrations ($n = 108$ eight-stage cascade impactor samples); (2) particle size distributions; and (3) comparison of exposures obtained using personal cassette and impactor samplers. Total cobalt and tungsten exposures were highest in work areas that handled powders (e.g., powder mixing) and lowest in areas that handled finished product (e.g., grinding). Inhalable, thoracic, and respirable cobalt and tungsten exposures were observed in all work areas, indicating potential for co-exposures to particles capable of getting deposited in the upper airways and alveolar region of the lung. Understanding the risk of CTC-induced adverse health effects may require two exposure regimes: one for asthma and the other for HMD and lung cancer. All sizes of cobalt-containing particles that deposit in the lung and airways have potential to cause asthma, thus a thoracic exposure metric is likely biologically appropriate. Cobalt-tungsten mixtures that deposit in the alveolar region of the lung may potentially cause HMD and lung cancer, thus a respirable exposure metric for both metals is likely biologically appropriate. By characterizing size-selective and co-exposures as well as multiple exposure pathways, this series of papers offer an approach for developing biologically meaningful exposure metrics for use in epidemiology.
Journal of Exposure Science and Environmental Epidemiology (2009) **19,** 475–491; doi:10.1038/jes.2008.37; published online 16 July 2008

Keywords: *aerosols, size-selective sampling, asthma, lung disease, lung cancer, exposure assessment*.

Introduction

Cemented tungsten carbides (CTC) refer to a class of carbides composed primarily of tungsten carbide and cobalt (as a binder) that are used as cutting tools for metals and masonry (Schneider, 1989; Kirk-Othmer, 1995). Exposures to CTC occur in hard metal production, sharpening of specialty alloy blades, and machining. In 1977, the National Institute for Occupational Safety and Health (NIOSH) estimated that 30,000 workers were exposed to CTC in the United States of America (NIOSH, 1977); however, the number of workers currently exposed and the impact of these exposures on the total workforce are unknown. Inhalation of dusts generated during the production of CTC is associated with the development of occupational asthma, hard metal lung disease (HMD), and lung cancer. Workplace studies have identified cases of occupational asthma among CTC workers exposed to both cobalt and tungsten (Davison et al., 1983; Sprince et al. 1988; Meyer-Bisch et al., 1989; Shirakawa et al., 1989; Kusaka et al., 1996) and diamond polishers exposed to cobalt alone (Gheysens et al., 1985). Cases of HMD have been reported among workers in all phases of CTC production (Bech et al., 1962; Coates and Watson, 1971; Sjögren et al., 1980; Davison et al., 1983; Sprince et al., 1984, 1988; Meyer-Bisch et al., 1989; Cugell et al., 1990; Figueroa et al., 1992; Fischbein et al., 1992), which may be due to exposures to tungsten carbide particles in association with cobalt particles (Lasfargues et al., 1992, 1995; Lison and Lauwerys, 1990, 1992, 1994, 1995; Lison et al., 1995, 1996). In humans, excess lung cancer has been observed among hard metal workers exposed to CTC dusts (Lasfargues et al., 1994; Moulin et al., 1998; Wild et al., 2000; Lison et al., 2001), but not among cobalt production workers exposed to cobalt alone (Moulin et al., 1993). *In vitro* and *in vivo* studies indicate that the genotoxicty of cobalt in the presence of tungsten carbide is greater than either

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Received 27 February 2008; accepted 16 May 2008; published online 16 July 2008

component alone (Anard et al., 1997; Van Goethem et al., 1997; Lison et al., 2001; De Boeck et al., 2003a, b; Mateuca et al., 2005).

Recent advances in the understanding of the underlying mechanisms of HMD and lung cancer make clear the need for biologically relevant personal exposure data to understand concomitant exposures to cobalt and tungsten. Historically, exposure assessments and epidemiological studies of hard-metal-induced adverse health effects have focused on measurements of total airborne cobalt aerosol mass concentration using 37-mm cassette samplers or other sampling heads without regard to particle size (Fairhall et al., 1947; Bech et al., 1962; Sprince et al., 1984, 1988; Meyer-Bisch et al., 1989; Sesana et al., 1994; Teschke et al., 1995; Kumagai et al., 1996). A few historical studies have investigated combined airborne exposures to cobalt and tungsten among CTC workers (Lichtenstein et al., 1975; Koponen et al., 1981, 1982; Kraus et al., 2001); however, these studies also used total mass concentration exposure estimates. To date, no exposure assessment or epidemiology studies of CTC workers have investigated particle size distribution exposures for both cobalt and tungsten, which are crucial in understanding respiratory heath effects and advancing risk assessment.

Recently, NIOSH responded to a request to perform a health hazard evaluation at a CTC manufacturer. This request presented a unique opportunity to characterize both cobalt and tungsten exposures among workers and the results are presented in a series of two papers. The objectives of this study were to better understand hazard potential by relating mechanisms of CTC-induced adverse health to characteristics of cobalt- and tungsten-containing aerosols generated during the manufacture of hard metal with emphasis on (1) aerosol total and particle size-selective mass concentrations; (2) particle size distributions; and (3) comparison of mass concentration obtained using personal "total" dust and personal size-selective impactor samplers. In the companion paper, we present the results of the assessment of work surfaces contamination and skin exposure to cobalt, chromium, and nickel (Day et al., 2008).

Materials and methods

At the company under study, the CTC-manufacturing process spans three facilities all within a 50 km radius of one another (Stefaniak et al., 2007). The manufacturing process begins in the metal separation facility with the reduction of tungsten oxide powder to yield tungsten metal powder. Tungsten metal powder is blended with carbon black and heated to carburize the powders into tungsten carbide. In the powder-handling facility, tungsten carbide is combined with additives such as nickel, chromium, titanium carbide, and tantalum carbide, to impart performance-specific properties. To provide the necessary strength for end-use applications, cobalt is added to the powder mixture, the mixture wet-milled, and spray dried. At the forming and machining facility, powder is compacted (e.g., pressed or extruded) and, if necessary, pre-sintered and "green" machined. All compacted parts are sintered (heat-treated), and then machined to the final dimension (e.g., grinding). Additional details of these job activities and dustiness of specific jobs are provided in Appendix A. Based on prior knowledge of work processes, similarities in physicochemical properties of airborne particles and bulk powders within work areas (Stefaniak et al., 2007), and practical limitations associated with field sampling, we categorized exposures by work areas.

Personal Air Monitoring

A total of 252 full-shift samples of airborne particles were collected from employees in 21 different work areas using closed-face 37-mm cassette samplers and analyzed for total dust and metals (cobalt, tungsten, chromium, and nickel). In the same 21 work areas, 108 full-shift impactor samples were collected from employees using eight-stage cascade impactor samplers (Marple series 290; MSP Corporation, Shoreview, MN, USA) positioned in the personal breathing zone and analyzed for metals (cobalt, tungsten, chromium, and nickel).

37 mm Cassette Samples In general, two 37-mm cassette samples were collected per participating employee, that is, one sample per day for two consecutive days. Repeated measurements (at least two measurements on consecutive days) were collected from 103 workers, whereas single measurements were collected from the remaining 39 workers. All cassette samples were collected on pre-weighed polyvinyl chloride (PVC) substrate at a flow rate of 2.0 l/min using personal air-sampling pumps (Gillian, Clearwater, FL, USA). Each 37-mm cassette sampler was positioned in the personal breathing zone of employees during the course of their normal work activities. Among the 252 cassette samples collected, one sample was discarded because the air pump faulted during collection, yielding a net of 251 samples. Of these samples, 71 (28%) were collected at the metal separation facility, 65 (26%) at the powder-handling facility, and 115 (46%) at the forming and machining facility.

Eight-Stage Impactor Samples Generally, one impactor sample was collected per employee, usually on the second day that a cassette sample was collected; however, for a subset of the workers (14 of 94), two impactor samples were obtained on consecutive days. As these repeated measurements were so few and not by design, they were assumed to be independent and no special statistical treatment was applied. The aerodynamic diameter cut points for the impactor samplers at a flow rate of 2.0 l/min were $>21.3\,\mu$m (stage 1), 14.8 μm (stage 2), 9.8 μm (stage 3), 6.0 μm (stage 4), 3.5 μm (stage 5), 1.55 μm (stage 6), 0.93 μm (stage 7), 0.52 μm (stage 8), and

$<0.52\,\mu$m (final filter). All impactor samples were collected on PVC substrate that was sprayed with silicone to minimize particle bounce during sampling. Of the 108 samples, 27 (25%) were collected at the metal separation facility, 29 (27%) at the powder-handling facility, and 52 (48%) at the forming and machining facility.

Analytical Methods and Quality Control

All PVC substrates and appropriate field and laboratory blanks were submitted for the determination of total dust in accordance with NIOSH Analytical Method 0500; cobalt, chromium, and nickel content in accordance with NIOSH Analytical Method 7300; and tungsten content in accordance with NIOSH Analytical Method 7074 (NIOSH, 1994). Note that due to a laboratory error, tungsten was not quantified for 37-mm cassette samples collected at the metal separation facility. For quantification of metals, PVC substrates were analyzed in multiple batches. A new instrument calibration curve was established prior to analyzing each batch of samples. Because the analytical limit of detection (LOD) and limit of quantification (LOQ) were unique to a given calibration curve, ranges are provided for these reporting limits: cobalt, LOD = 0.06 to 0.9 μg per filter and LOQ = 0.2 to 3 μg per filter; chromium, LOD = 0.1 to 0.7 μg per filter and LOQ = 0.4 to 2 μg per filter; nickel, LOD = 0.06 to 1 μg per filter and LOQ = 0.2 to 4 μg per filter; and tungsten LOD = 0.4 to 8 μg per filter and LOQ = 1.0 to 30 μg per filter. The analytical LOD for total dust was 0.02 mg (LOQ not reported).

Data Analysis

The concentration of dust and/or metals in air was determined by dividing the mass of analyte collected on a filter (for 37-mm cassette samples) or the sum of analyte masses on all filters in a sample (for impactor samples) by the volume of sampled air. The respirable, thoracic, and inhalable mass concentrations of metals on impactor samples were calculated using the American Conference of Governmental Industrial Hygienists (ACGIH)–International Organization for Standardization (ISO)–Comité Européen de Normalization (CEN) dust criteria (Lippman, 1999). Respirable particles were defined as particles having 50% aerodynamic cutoff (D_{50}) of 4 μm, thoracic particles as having a D_{50} of 10 μm, and inhalable particles as having a D_{50} of 100 μm (Lippman, 1999). Size-selective mass concentrations were calculated using Simpson's rule in a tabular-graphical approach to estimate the contribution of each impactor stage to the overall particle size fraction of interest (Hinds, 1986). Appendix B contains the correction factors for inlet efficiency and inter-stage particle losses (Rubow et al., 1987); particle size range and midpoint; and the fraction of each stage used to estimate the respirable, thoracic, and inhalable particulate mass concentrations.

The size distribution, mass median aerodynamic diameter (MMAD), and geometric standard deviation (GSD) of metal-containing particles in air were estimated for each impactor sample (Hinds, 1986). Estimates of the MMAD were calculated for each sample using the masses of metal collected on all stages of the impactor and for the mass distribution truncated to include only respirable-size (aerodynamic diameter less than 10 μm) (Lippman, 1999) particles, that is, material collected on stages 4 through 8 and the final filter.

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, a value of one-half the appropriate LOD was assigned to the LOD samples (Hornung and Reed, 1990). The distributions of the airborne exposure data were examined graphically via probability plots and found to be approximately lognormal; hence, they were log-transformed and the geometric mean (GM) and GSD were calculated. Summary statistics including various ratios and percent measurements exceeding various fractions of the permissible exposure limit were calculated by process groups (described in Appendix A). For the 37-mm cassette measurements, nested mixed-effects models were used to evaluate the impact of work areas on exposures as well as to estimate variance components between workers (S^2_{BW}) and within worker (S^2_{WW}) (Rappaport et al., 1999). The variance components were assumed to be distinct for the different work areas and were estimated separately for each work area from models with only the random effect of worker identity. To evaluate the impact of work areas or plant on exposures and variance components, nested mixed-effects models were run using all data, with worker identity treated as a random effect and work area or plant as fixed effects. These models were constructed in SAS using Proc Mixed for the log-transformed dust, cobalt, or tungsten concentrations using the restricted maximum likelihood method to estimate parameters and compound symmetry covariance structure. The analysis of variance (ANOVA) procedure was used to conduct multiple comparisons of differences between means of the three facilities and the different work areas within each facility. One-way ANOVAs were used to investigate these differences between means using the GLM procedure. In these procedures, the natural logarithm of exposure was declared as the outcome variable and Tukey's test option was specified for multiple comparisons. ANOVA *F*-statistics was used to note the overall differences between means, whereas Tukey's test was used to identify specific differences between the different means. The Kruskal–Wallis test was performed to examine differences in the medians of the MMADs associated with the different facilities or process areas. The ''npar1way'' procedure was used with the Wilcoxon option. To identify which specific medians were significantly different from one another, multiple pairwise comparisons were conducted *post hoc* using the Mann–Whitney–Wilcoxon test in the npar1way procedure. Pearson correlation coefficients were obtained to

evaluate the relationships among the sampler types and exposure agents using the Proc Corr procedure. The regression equation and plots of the sampler types and exposure agents were prepared in SigmaPlot 9.01 (Systat Software Inc., San Jose, CA, USA).

Results

37-mm Cassette Samples

Table 1 summarizes the total airborne dust, cobalt, and tungsten mass concentrations measured using 37-mm cassette samplers by facility and work area (average sample duration 455 min, range: 43–796 min). The GM dust concentration in the forming/machining facility (236 $\mu g/m^3$) was significantly lower than the powder-handling (607 $\mu g/m^3$) and metal separation (656 $\mu g/m^3$) facilities (Tukey's test: $P<0.05$); there was no difference between dust levels in the powder-handling and metal separation facilities. GM cobalt exposure levels differed among the three facilities: 11 $\mu g/m^3$ (metal separation facility), 45 $\mu g/m^3$ (powder handling facility), and 5 $\mu g/m^3$ (forming/machining facility) ($P<0.0001$). Tukey's multiple comparison test indicated that all paired comparisons of cobalt concentrations among the three facilities were significantly different ($P<0.05$). GM tungsten exposures differed between the powder-handling (156 $\mu g/m^3$) and forming/machining facilities (57 $\mu g/m^3$) ($P<0.0001$).

Within the metal separation facility, GM dust and cobalt concentrations in the powder laboratory were significantly lower than all other work areas. In the powder-handling facility, GM dust, cobalt, and tungsten levels were generally similar among the various work areas. In the machining facility, the pressing, shaping, and product-shipping work areas had the greatest number of significant differences in the multiple paired comparisons for all exposure types (dust, cobalt, and tungsten).

Among all facilities, levels of airborne chromium and nickel were low. GM chromium concentrations ranged from 0.1 $\mu g/m^3$ (product shipping) to 3.1 $\mu g/m^3$ (metal separation); the maximum individual concentration value was 50 $\mu g/m^3$ (metal separation). GM nickel concentrations ranged from 0.05 $\mu g/m^3$ (breakdown) to 17.2 $\mu g/m^3$ (powder mixing), with a maximum individual measurement of 445 $\mu g/m^3$ (powder mixing).

Table 1. Total airborne dust, cobalt, and tungsten mass concentrations by work area measured using 37-mm cassette samplers placed in the breathing zone of workers.

Facility	Work area	Dust			Cobalt			Tungsten		
		n[a]	GM ($\mu g/m^3$)	GSD	n	GM ($\mu g/m^3$)	GSD	n	GM ($\mu g/m^3$)	GSD
Metal separation	Metal separation	30	1704.1	2.5	30	16.4	4.0	0	—[b]	—[b]
	Reclamation A	5	922.0	3.0	5	18.5	4.7	0	—[b]	—[b]
	Reclamation B	9	945.5	3.7	9	47.7	4.3	0	—[b]	—[b]
	Reclamation A and B[c]	9	966.8	2.9	9	31.7	3.0	0	—[b]	—[b]
	Powder laboratory	18	81.1	2.5	18	1.2	5.7	0	—[b]	—[b]
Powder handling	Inventory control	2	97.0	1.3	2	5.7	1.1	2	15.0	1.8
	Powder mixing	20	132.0	4.3	20	126.2	5.7	20	119.9	3.2
	Milling	10	355.9	3.9	10	26.4	7.3	10	150.9	3.6
	Spray drying	18	665.5	2.1	18	44.0	2.1	18	216.1	2.3
	Screening	7	555.9	1.9	7	85.4	1.6	7	431.6	2.8
	Shipping (powder)	2	237.1	1.1	2	18.3	1.2	2	91.7	1.1
	Maintenance (powder)	6	288.8	3.9	6	13.3	2.9	5	139.9	2.3
Forming/machining	Production control	5	146.8	1.8	5	7.2	2.2	3	89.7	2.5
	Pressing	13	403.0	1.5	13	24.2	1.5	9	198.4	1.5
	Extrusion	5	269.9	3.0	5	12.1	4.5	3	86.5	2.4
	Shaping	27	246.3	2.5	27	13.4	3.2	17	113.8	2.1
	Breakdown	1	975.9	—[d]	1	29.0	—[d]	1	21.9	—[d]
	Grinding	15	326.4	2.6	15	4.1	3.9	9	56.3	2.4
	Sandblasting	8	231.4	1.9	8	1.6	3.0	3	10.9	2.1
	Product Testing	15	143.4	1.4	15	2.5	2.4	5	12.2	2.8
	Shipping (product)	16	190.5	1.9	16	1.0	3.4	6	16.0	4.2
	Maintenance (product)	10	251.7	2.0	10	2.4	4.4	6	39.2	3.7

[a] n = number of samples.
[b] Due to a laboratory error, tungsten was not quantified for 37-mm cassette samples collected at the metal separation facility.
[c] Employees who reported working in both reclamation buildings A and B during their work shift.
[d] GSD not calculated for work areas with only one measurement.

Table 2. Variance components for total airborne dust, cobalt, and tungsten mass concentrations by work area measured using 37-mm cassette samplers placed in the breathing zone of workers.

Facility	Work areas	Dust					Cobalt					Tungsten				
		n[a]	k[b]	l[c]	S^2_{BW}	S^2_{WW}	n	k	l	S^2_{BW}	S^2_{WW}	n	k	l	S^2_{BW}	S^2_{WW}
Metal separation	Metal separation	30	18	12	0.42	0.40	30	18	12	1.53	0.44	—	—	—	—	—
	Reclamation A	5	4	1	1.31	0.001	5	4	1	2.31	0.04	—	—	—	—	—
	Reclamation B	9	5	4	0.37	1.35	9	5	4	0.69	1.52	—	—	—	—	—
	Reclamation A and B[d]	9	5	4	1.11	0.15	9	5	4	0.75	0.54	—	—	—	—	—
	Powder laboratory	18	9	7	0.51	0.37	18	9	7	1.76	1.21	—	—	—	—	—
Powder handling	Inventory control	2	1	1	0	0.06	2	1	1	0	0.005	2	1	1	0	0.38
	Powder mixing	20	8	8	1.75	0.44	20	8	8	2.61	0.54	20	8	8	1.51	0.15
	Milling	10	6	4	0.41	1.49	10	6	4	0.36	3.59	10	6	4	0	1.68
	Spray drying	18	9	9	0.42	0.13	18	9	9	0.24	0.35	18	9	9	0.49	0.24
	Screening	7	4	3	0	0.41	7	4	3	0	0.23	7	4	3	0	1.06
	Shipping (powder)	2	1	1	0	0.003	2	1	1	0	0.02	2	1	1	0	0.003
	Maintenance (powder)	6	4	2	1.44	0.85	6	4	2	1.04	0.31	5	3	2	0.20	0.52
Forming/machining	Production control	5	3	2	0.28	0.15	5	3	2	0.85	0.12	3	2	1	1.16	0.06
	Pressing	13	7	6	0.02	0.15	13	7	6	0.001	0.17	9	5	4	0.05	0.14
	Extrusion	5	3	2	0	1.22	5	3	2	0	2.27	3	2	1	0.49	0.46
	Shaping	27	15	12	0.20	0.68	27	15	12	0.67	0.68	17	10	7	0.23	0.33
	Breakdown	1	1	0	0	0	1	1	0	0	0	1	1	0	0	0
	Grinding	15	10	5	0.01	0.93	15	10	5	0.30	1.53	9	7	2	0.61	0.17
	Sandblasting	8	6	2	0.47	0.004	8	6	2	0.71	0.35	3	3	0	0.18	0.34
	Product testing	15	8	7	0.05	0.07	15	8	7	0.66	0.11	5	3	2	0	1.06
	Shipping (product)	16	10	6	0.52	0.02	16	10	6	1.22	0.64	6	5	1	2.56	0.03
	Maintenance (product)	10	6	4	0.23	0.25	10	6	4	0.54	1.72	6	4	2	1.56	0.16
Intercept-only model: random = subject		251	142	103	1.18	0.45	251	142	103	103	0.84	126	74	48	1.20	0.60
Full model: random = subject, fixed = work areas		251	142	103	0.45	0.45	251	142	103	103	0.83	126	74	48	0.42	0.59

[a] n = number of samples.
[b] k = number of subjects.
[c] l = number of subjects with >1 measurements.
[d] Employees who reported working in both reclamation buildings A and B during their work shift.

Table 2 summarizes the variance components for total airborne dust, cobalt, and tungsten mass concentrations measured using 37-mm cassette samplers by work area. These data should be interpreted with caution because some work areas had few workers sampled and/or few workers with repeated measurements. For example, the Reclamation A work area had four workers, but only one worker had repeated measurements; hence, the within worker variance estimate may not be representative of the work area. Likewise, only one worker was sampled from work areas such as inventory control or breakdown, hence the between-worker variance could not be estimated. No consistent pattern was observed for the between- and within-worker variances among all work areas of the plants. Within a work area, the relative ranking of the between- and within-worker variances was generally similar for all exposure agents (dust, cobalt, tungsten). For overall mixed models that assumed common variances among work areas, the between- and within-worker variances were about the same after considering the fixed effect of work areas. The fixed effect of plant was not significant and was not retained in the model.

Table 3 summarizes the percentage of 37-mm cassette samples that exceeded $0.2\times$, $0.5\times$ and $1.0\times$ the US Occupational Safety and Health Administration Permissible Exposure Limit of $100\,\mu g/m^3$ for cobalt. The percentage of samples that exceeded $0.2\times$ the permissible exposure limit was highest in work areas that reclaimed CTC scrap and produced dry powders (metal separation, reclamation), formulated hard metal powders (powder mixing, milling, spray drying, screening), formed dry powders (pressing), and breakdown. In contrast, fewer samples exceeded $0.2\times$ the permissible exposure limit in work areas that handled laboratory-scale quantities of powder (powder laboratory) and in those that handled finished product parts (grinding, sandblasting, product testing, product shipping, and maintenance). Workers in the powder mixing and screening work areas were required to wear half-mask air-purifying respirators with particulate filters; maintenance workers wore respirators during non-routine tasks (e.g., while rebuilding a furnace liner). Workers in the metal separation work area wore half-mask air-purifying respirators with acid/gas filters. There is no permissible exposure limit for tungsten; however,

Table 3. Percentage of 37-mm cassette samples that exceed 0.2, 0.5, and 1.0 × the US Occupational Safety and Health Administration permissible exposure limit for cobalt.

Facility	Work area	n[a]	% Of samples that exceeded		
			0.2 × PEL[b]	0.5 × PEL	1.0 × PEL
Metal separation	Metal separation	30	43.3	26.7	13.3
	Reclamation A	5	60.0	40.0	20.0
	Reclamation B	9	88.9	55.6	33.3
	Reclamation A and B[c]	9	66.7	33.3	11.1
	Powder laboratory	18	0.0	0.0	0.0
Powder handling	Inventory control	2	0.0	0.0	0.0
	Powder mixing	20	55.0	50.0	50.0
	Milling	10	90.0	40.0	20.0
	Spray drying	18	83.3	50.0	16.7
	Screening	7	100.0	85.7	42.9
	Shipping (powder)	2	50.0	0.0	0.0
	Maintenance	6	50.0	16.7	0.0
Forming/machining	Production control	5	20.0	0.0	0.0
	Pressing	13	61.5	7.7	0.0
	Extrusion	5	40.0	20.0	20.0
	Shaping	27	25.9	11.1	7.4
	Breakdown	1	100.0	0.0	0.0
	Grinding	15	13.3	0.0	0.0
	Sandblasting	8	0.0	0.0	0.0
	Product testing	15	0.0	0.0	0.0
	Shipping (product)	16	6.3	0.0	0.0
	Maintenance	10	10.0	0.0	0.0

[a]n = number of personal breathing zone samples.
[b]Permissible exposure limit (PEL) = 100 $\mu g/m^3$.
[c]Employees who reported working in both reclamation buildings A and B during their work shift.

the levels of airborne tungsten on 37-mm cassettes were lower than the NIOSH recommended exposure limit of 5000 $\mu g/m^3$ by at least a factor of three in all facilities. Levels of airborne chromium were at least an order of magnitude below the recommended exposure limit (500 $\mu g/m^3$) and permissible exposure limit (1000 $\mu g/m^3$) in all facilities. For nickel, only one cassette sample (collected in powder mixing) approached the recommended exposure limit (500 $\mu g/m^3$) and none exceeded the permissible exposure limit (1000 $\mu g/m^3$).

Eight-Stage Impactor Samples

Tables 4 and 5 summarize the respirable, thoracic, and inhalable mass concentrations and the concentrations of all sizes of particles determined using impactor samplers for cobalt and tungsten, respectively (average sample duration 441 min, range: 43–786 min). In each work area, respirable cobalt and tungsten exposure components exist, indicating the potential for co-exposures to airborne cobalt- and tungsten-containing particles with sizes that may deposit in the alveolar region of the lung. Additionally, thoracic and inhalable mass concentration exposure components exist, which suggest potential for co-exposure to cobalt- and tungsten-containing particles in the upper airways. Similar to the cassette samplers, mass concentrations for all sizes of cobalt- and tungsten-containing particles collected with the impactor samplers were higher in work areas that prepare and handle dry powders (e.g., reclamation, powder mixing, spray drying, screening), and tended to be lower in the extrusion work area and in work areas that handle finished product (e.g., grinding, sandblasting, product testing, product shipping).

Table 6 summarizes the cobalt- and tungsten-containing particle MMADs by work area. In general, median cobalt- and tungsten-containing particle MMAD values were similar within work areas and confirm the potential for co-exposure to chemically heterogeneous respirable- and thoracic-size particles. Additionally, cobalt MMAD values determined using personal impactor samples were similar to those determined previously using stationary impactor samplers at these facilities (Stefaniak et al., 2007). Median MMADs for cobalt differed among the three facilities: 17.4 μm (metal separation), 13.8 μm (powder handling), and 10.8 μm (forming/machining) ($P < 0.0001$ using the Kruskal–Wallis test). Multiple *post hoc* pairwise comparisons conducted using the Mann–Whitney–Wilcoxon test indicated that all paired comparisons of median cobalt MMADs differed

Table 4. Respirable, thoracic, and inhalable cobalt mass concentrations calculated using the ACGIH/ISO/CEN lung deposition model and cobalt mass concentration for particles of all sizes.

Facility	Work area	n[a]	Cobalt mass concentrations							
			Respirable		Thoracic		Inhalable		All sizes	
			GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD
Metal separation	Metal separation	8	1.1	3.4	5.0	3.7	13.4	4.6	19.2	4.7
	Reclamation A	4	1.7	3.5	9.8	4.2	29.9	4.6	44.0	4.6
	Reclamation B	8	4.6	1.7	29.3	1.6	99.7	1.6	148.3	1.6
	Reclamation A and B[b]	3	7.4	1.2	50.0	1.1	135.6	1.1	195.2	1.1
	Powder laboratory	4	1.2	3.7	5.6	3.8	16.5	4.4	24.2	4.5
Powder handling	Inventory control	1	1.0	—[c]	3.4	—[c]	6.0	—[c]	8.0	—[c]
	Powder Mixing	14	18.2	4.8	77.0	5.1	168.4	5.3	234.5	5.3
	Milling	2	3.3	1.3	18.5	1.5	48.6	1.8	69.5	1.9
	Spray drying	4	3.0	1.5	14.8	1.5	41.7	1.4	60.4	1.5
	Screening	4	6.7	1.7	45.1	1.9	98.4	2.2	136.8	2.3
	Shipping (powder)	1	2.3	—[c]	8.4	—[c]	16.6	—[c]	22.8	—[c]
	Maintenance	3	4.3	2.9	17.4	2.4	39.2	2.2	55.0	2.1
Forming/machining	Production control	2	0.6	1.2	2.4	1.1	4.0	1.0	5.3	1.0
	Pressing	7	1.6	1.9	10.5	1.5	27.3	1.7	38.7	1.8
	Extrusion	2	0.8	3.6	3.0	2.7	5.2	2.5	6.8	2.5
	Shaping	12	2.2	3.8	7.4	3.4	14.0	3.3	18.7	3.3
	Breakdown	1	0.8	—[c]	4.1	—[c]	7.9	—[c]	10.6	—[c]
	Grinding	7	2.6	3.1	8.6	3.2	15.6	3.7	20.4	4.0
	Sandblasting	4	0.5	1.7	1.7	1.8	2.7	1.9	3.5	1.9
	Product testing	5	0.8	2.0	2.7	1.8	4.8	1.9	6.2	1.9
	Shipping (product)	4	0.5	2.0	2.0	3.7	3.8	5.9	5.0	6.4
	Maintenance	5	0.5	1.7	1.7	1.9	2.6	2.0	3.3	2.0

[a]n = number of personal breathing zone samples.
[b]Employees who reported working in both reclamation buildings A and B during their work shift.
[c]GSD not calculated for work areas with only one measurement.

among facilities (all P-values <0.0001). Similarly, median tungsten MMADs differed among the three facilities: 17.9 μm (metal separation), 14.4 μm (powder handling), and 10.5 μm (forming/machining) ($P<0.0001$ using the Kruskal–Wallis test). The multiple pairwise test indicated that all paired comparisons of median tungsten MMADs differed among facilities (all P-values <0.007). Within each facility, the differences in median cobalt and median tungsten MMADs among work areas were not significant (Kruskal–Wallis test).

Table 7 summarizes estimates of the MMAD calculated for the mass distributions truncated to include only respirable-size particles. Median respirable cobalt MMADs differed among the three facilities: 8.0 μm (metal separation), 6.6 μm (powder handling), and 7.4 μm (forming/machining) ($P<0.05$ using the Kruskal–Wallis test). *Post hoc* multiple pairwise comparisons conducted using the Mann–Whitney–Wilcoxon test showed that the respirable cobalt MMAD value for the metal separation facility was higher than the powder handling ($P=0.02$) and forming/machining facilities ($P=0.06$); the respirable cobalt MMADs of these latter facilities were not significantly different from one another. For tungsten, median respirable MMADs were similar among facilities: 7.3 μm (metal separation), 8.1 μm (powder handling), and 6.9 μm (forming/machining) ($P=0.45$ using the Kruskal–Wallis test). Within each facility, differences in median respirable cobalt and tungsten MMADs for the different work areas within plants were not significant (Kruskal–Wallis test).

Comparison of Sample Types

Scatter plots were constructed of airborne cobalt (Figure 1a) and tungsten (Figure 1b) concentrations measured using 37-mm cassette samplers (total) relative to the thoracic concentrations measured using impactor samplers. For cobalt, concentrations measured on the two sampler types were significantly correlated ($r=0.81$, $P<0.0001$) and the relationship is described by the regression equation $\ln \text{total} = 0.462 + 0.998 \ln \text{thoracic}$. When a term for facility was included in this regression analysis, it was not significant and the regression parameters did not change appreciably; hence, the relationship between total and thoracic cobalt concentrations did not vary among facilities. There was a small but significant intercept in the model and the slope is not significantly different from 1.0. One possible explanation for this observation is that the cassette sampler consistently

Table 5. Respirable, thoracic, and inhalable tungsten mass concentrations calculated using the ACGIH/ISO/CEN lung deposition model and tungsten mass concentration for all sizes of particles.

Facility	Work area	n[a]	Tungsten mass concentrations							
			Respirable		Thoracic		Inhalable		All sizes	
			GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD	GM ($\mu g/m^3$)	GSD
Metal separation	Metal separation	8	27.0	2.3	124.5	2.5	370.6	2.7	540.1	2.8
	Reclamation A	4	21.2	2.8	122.1	4.2	364.5	4.9	533.8	5.0
	Reclamation B	8	61.2	1.9	326.1	1.5	963.1	1.4	1411.7	1.4
	Reclamation A and B[b]	3	120.5	2.1	620.3	1.9	1499.4	1.6	2129.0	1.5
	Powder laboratory	4	8.3	2.0	34.8	2.5	98.8	3.4	143.1	3.6
Powder handling	Inventory control	1	3.6	—[c]	12.3	—[c]	23.9	—[c]	32.7	—[c]
	Powder mixing	14	46.3	3.3	238.3	3.5	597.5	3.7	849.6	3.8
	Milling	2	20.7	1.2	137.2	1.5	391.7	1.9	566.1	2.0
	Spray drying	4	22.1	1.8	117.8	1.5	334.1	1.4	480.9	1.4
	Screening	4	64.2	1.8	425.6	1.9	941.5	2.2	1314.4	2.3
	Shipping (powder)	1	9.2	—[c]	40.7	—[c]	85.8	—[c]	118.9	—[c]
	Maintenance	3	24.3	2.7	108.7	2.6	253.4	2.3	358.1	2.3
Forming/machining	Production control	2	3.1	1.1	14.2	1.2	24.1	1.3	31.5	1.3
	Pressing	7	12.1	2.0	76.9	1.6	197.8	1.7	280.4	1.8
	Extrusion	2	4.4	3.3	18.8	2.6	31.9	2.3	41.7	2.2
	Shaping	13	15.8	4.2	53.2	3.6	94.5	3.7	124.4	3.7
	Breakdown	1	2.0	—[c]	7.5	—[c]	12.5	—[c]	16.3	—[c]
	Grinding	7	15.0	4.7	54.7	4.3	105.1	4.7	139.6	4.9
	Sandblasting	4	2.3	1.8	9.0	1.7	15.0	1.7	19.4	1.7
	Product testing	5	2.8	1.8	9.8	1.4	15.7	1.3	20.1	1.3
	Shipping (product)	3	4.2	1.4	19.6	3.8	44.6	6.6	59.7	7.4
	Maintenance	5	3.2	1.7	11.3	1.8	17.3	2.0	22.0	2.0

[a]n = number of personal breathing zone samples.
[b]Employees who reported working in both reclamation buildings A and B during their work shift.
[c]GSD not calculated for work areas with only one measurement.

collected more of the larger particles. This observation is consistent with Davies et al. (1999) who reported that the cassette sampler has collection efficiency consistent with the thoracic convention for particles $<10\,\mu$m, a high collection efficiency for extra-thoracic particles ($>15\,\mu$m up to $30\,\mu$m), and low collection efficiency for particles $>30\,\mu$m. The overall mean ratio of thoracic to total concentration was 0.68, suggesting that the thoracic fraction is substantially smaller than the total mass. For tungsten, concentrations measured by the two sampler types were also significantly correlated ($r=0.56$, $P<0.0001$) and described by the relationship $\ln \text{total} = 2.317 + 0.520 \ln \text{thoracic}$. Similar to the results for cobalt, the regression equation for tungsten did not vary by facility.

Figure 2 summarizes the relationships among total cobalt, tungsten, and dust mass concentrations measured using 37-mm cassette samplers. Airborne cobalt and dust concentrations were significantly correlated ($r=0.75$, $P<0.0001$), as was the relationship between tungsten and dust concentrations ($r=0.51$, $P<0.0001$), and cobalt and tungsten concentrations ($r=0.67$, $P<0.0001$). This mass correlation between cobalt and tungsten measured with 37-mm cassette samplers suggests widespread opportunities for co-exposure to these metals throughout the facilities. However, understanding the differences in health effects between exposures to cobalt alone and to tungsten-cobalt associated particles may also require information on particle physical exposure characteristics such as size distributions (see Discussion), which are not captured by total aerosol samplers.

Discussion

Data reported in Tables 1 and 3 demonstrate high exposures to total cobalt in most work areas in the powder handling facility; exposures were elevated in fewer work areas in the metal separation and forming/machining facilities. In occupational exposure assessment, fractions of exposure limits are often used as concentration levels that prompt actions to reduce exposures. Thus, the percentage of measurements that exceeded $0.2\times$ and $0.5\times$ the permissible exposure limit (Table 3) is a further indication of the potential for noncompliance in the following work areas: metal separation, reclamation, powder mixing, milling, spray drying, screening, shipping, maintenance (powder handling), pressing, extrusion, and breakdown. Efforts to reduce exposures in these

Table 6. Mass median aerodynamic diameter (MMAD) of airborne cobalt- and tungsten-containing particles by work area.

Facility	Work area	n[a]	Cobalt				n	Tungsten			
			MMAD		GSD			MMAD		GSD	
			Median (μm)	Range (μm)	Median (μm)	Range (μm)		Median (μm)	Range (μm)	Median (μm)	Range (μm)
Metal separation	Metal separation	8	16.8	9.4–21.5	2.0	1.6–2.7	8	18.0	9.8–21.3	2.0	1.9–2.9
	Reclamation A	4	18.1	16.8–19.2	2.0	1.9–2.3	4	18.2	15.2–18.7	2.0	1.7–2.5
	Reclamation B	8	18.4	16.3–23.3	1.9	1.7–2.2	8	17.9	16.0–19.7	2.1	1.7–2.4
	Reclamation A and B[b]	3	15.1	14.8–17.2	1.9	1.8–1.9	3	13.6	12.7–18.9	2.0	1.9–2.0
	Powder laboratory	4	17.9	14.8–23.3	2.2	2.0–2.7	4	18.1	11.5–24.1	2.2	2.1–2.8
Powder handling	Inventory control	1	10.6	—[c]	—[c]	—[c]	1	12.5	—[c]	—[c]	—[c]
	Powder mixing	14	13.7	11.3–16.9	2.2	1.7–2.8	14	15.2	9.7–21.4	2.0	1.6–2.7
	Milling	2	15.5	13.9–17.1	1.9	1.8–2.0	2	16.0	14.3–17.8	1.8	1.7–1.8
	Spray drying	4	17.3	12.5–20.7	2.0	1.9–2.3	4	15.8	11.8–20.5	1.9	1.7–2.0
	Screening	4	12.9	11.8–16.2	1.8	1.7–1.9	4	13.2	12.0–16.2	1.8	1.7–1.9
	Shipping (powder)	1	12.4	—[c]	—[c]	—[c]	1	13.1	—[c]	—[c]	—[c]
	Maintenance	3	12.8	12.0–18.2	2.1	2.1–2.1	3	13.1	12.6–19.9	2.0	2.0–2.3
Forming/machining	Production control	2	10.5	9.9–11.1	1.9	1.9–1.9	2	10.5	9.7–11.2	1.8	1.8–1.8
	Pressing	7	15.9	9.4–17.2	1.8	1.3–2.1	7	15.9	8.8–18.1	1.9	1.4–2.3
	Extrusion	2	10.4	9.7–11.0	2.0	1.9–2.1	2	10.3	9.1–11.4	2.0	1.8–2.2
	Shaping	11	10.7	8.2–13.7	2.0	1.8–2.3	13	10.5	8.2–26.3	2.1	1.8–5.6
	Breakdown	1	12.5	—[c]	—[c]	—[c]	1	10.2	—[c]	—[c]	—[c]
	Grinding	7	12.0	2.5–16.5	2.0	1.7–7.3	7	11.9	6.5–16.5	2.0	1.6–2.6
	Sandblasting	4	10.6	8.6–22.0	2.4	2.1–3.6	3	9.2	8.9–11.7	2.2	2.0–2.3
	Product testing	5	9.4	8.6–11.6	1.9	1.5–2.1	5	9.3	8.8–10.5	2.0	1.3–2.4
	Shipping (product)	4	12.1	3.0–17.8	2.2	1.4–9.9	3	12.1	2.8–17.8	1.7	1.4–12.5
	Maintenance	5	8.6	8.3–10.6	2.0	1.7–2.3	5	8.9	6.0–10.7	1.8	1.7–2.1

[a] n = number of personal breathing zone samples.
[b] Employees who reported working in both reclamation buildings A and B during their work shift.
[c] GSD not calculated for work areas with only one measurement.

work areas are being evaluated and/or have been implemented by the company under study. For example, in the metal separation and reclamation work areas, designs for local exhaust ventilation systems and process automation (engineering controls) are being considered, whereas in the powder-mixing work area, access has been restricted (administrative control) and workers wear respiratory and dermal protection.

A large portion of the overall exposure variability could be attributed to work areas as shown by the large reduction in between-worker variance in models with the fixed effect of work area compared with the random intercept model (Table 2). The effect of the work area was almost entirely on the between-worker variance component for all exposure agents. Within-worker variance is likely impacted by factors that may vary daily, such as production levels, nature of production activities (intermittent *versus* continuous), changes in ventilation (e.g., open or closed windows and doors), and so on. Exposures were highly variable within many work areas, particularly in the powder-handling and metal separation facilities and less variable in the machining facility for all exposure agents (Tables 1 and 2). In general, no consistent pattern was observed for the variance components within or among facilities, that is, in some work areas, the between-worker variance was larger than the within-worker variance (powder mixing, and so on), but the converse was true in other work areas (reclamation B, and so on). These exposure measurements were collected on consecutive days; a higher correlation was expected between the repeated measurements, and hence a smaller within-worker variance component. However, we observed larger within-worker variance for a number of work areas, which was not always consistent for cobalt and tungsten. In general, there are many competing factors that would influence within- and between-worker variance components. For example, the production levels and relative fractions of cobalt and tungsten in hard metal formulations vary among batches in a day and/or between days (Stefaniak et al., 2007); therefore, it is difficult to elucidate the potential contribution of different factors to the variance components. Despite our inability to collect additional information on exposure determinants during sampling, which limits our ability to further investigate the causes of exposure variation and their impact on between- or within-worker variances, these data have practical implications for exposure mitigation efforts. For example, in work areas where the between-worker

Table 7. Mass median aerodynamic diameter (MMAD) of respirable cobalt- and tungsten-containing particles by work area

Facility	Work area	n[a]	Cobalt				n	Tungsten			
			MMAD		GSD			MMAD		GSD	
			Median (μm)	Range (μm)	Median (μm)	Range (μm)		Median (μm)	Range (μm)	Median (μm)	Range (μm)
Metal separation	Metal separation	6	7.0	5.2–9.7	2.8	2.2–9.6	8	7.4	4.4–9.9	2.5	2.2–4.4
	Reclamation A	4	7.8	7.3–8.5	2.1	2.0–2.6	4	7.5	6.0–9.8	2.0	2.0–2.3
	Reclamation B	8	8.5	7.2–9.9	2.3	2.0–2.5	8	7.3	6.3–9.9	2.1	1.9–2.5
	Reclamation A and B[b]	3	8.8	8.0–9.8	1.9	1.9–2.2	2	6.9	5.6–8.1	1.8	1.7–1.9
	Powder laboratory	4	7.8	4.9–9.2	2.3	2.1–4.2	4	7.1	4.9–8.6	2.5	2.2–2.7
Powder handling	Inventory control	1	6.2	—[c]	—[c]	—[c]	1	6.5	—[c]	—[c]	—[c]
	Powder mixing	13	6.2	4.8–8.3	2.0	1.9–2.6	11	7.9	3.8–9.2	2.1	1.8–3.0
	Milling	2	8.7	7.3–10.2	2.5	1.8–3.3	2	9.6	9.0–10.2	2.6	2.1–3.1
	Spray drying	4	8.3	6.2–9.1	2.6	2.2–3.0	4	8.1	7.3–9.2	2.9	2.2–3.2
	Screening	0	—[c]	—[c]	—[c]	—[c]	0	—[c]	—[c]	—[c]	—[c]
	Shipping (powder)	1	6.2	—[c]	—[c]	—[c]	1	6.7	—[c]	—[c]	—[c]
	Maintenance	3	6.8	6.5–8.6	2.5	2.0–3.0	3	8.2	7.8–9.2	2.6	2.2–3.0
Forming/machining	Production control	2	7.6	6.8–8.5	2.5	2.3–2.8	0	—[c]	—[c]	—[c]	—[c]
	Pressing	5	9.1	6.1–9.5	2.6	2.1–3.9	5	9.5	5.6–10.1	2.3	2.0–3.0
	Extrusion	2	7.3	6.1–8.5	3.2	3.0–3.4	1	6.7	—[c]	—[c]	—[c]
	Shaping	10	6.8	2.4–9.0	2.2	1.8–4.2	12	6.8	2.7–9.0	2.3	1.7–3.7
	Breakdown	1	7.9	—[c]	—[c]	—[c]	1	10.2	—[c]	—[c]	—[c]
	Grinding	5	6.7	4.4–8.2	2.2	1.9–2.8	5	6.6	3.9–9.9	2.2	1.9–4.6
	Sandblasting	4	6.5	6.1–7.7	3.6	2.2–4.3	3	6.0	5.6–8.9	3.5	2.5–4.8
	Product testing	4	6.2	5.0–7.9	2.3	2.0–4.9	3	6.4	4.4–7.9	3.7	2.1–3.9
	Shipping (product)	3	5.6	4.8–7.7	3.0	2.2–3.8	2	6.9	5.1–8.6	2.7	2.2–3.3
	Maintenance	4	9.1	7.8–10.3	3.8	3.4–4.7	3	9.3	8.1–9.9	4.1	2.2–4.5

[a]n = number of personal breathing zone samples.
[b]Employees who reported working in both reclamation buildings A and B during their work shift.
[c]GSD not calculated for work areas with zero or one measurement.

variance component was higher than the within-worker component, efforts could be refocused to ensure correct usage of control technologies by individual workers, such as correct donning and fit of respiratory protection. For work areas where the within-worker variance component was higher than the between-worker component, because exposures differ by day, efforts could be focused on more universal approaches to exposure control, such as installation of local exhaust ventilation at a process or selection of a more protective type of respirator for all workers in a work area.

Going beyond the total mass, results of air monitoring presented as Tables 4–7 demonstrate worker exposures to a range of cobalt mass concentrations and cobalt-containing particle sizes among the surveyed facilities. Based on existing *in vitro* and *in vivo* toxicology data and human epidemiology studies and our air-monitoring results, we hypothesize that understanding the risk of CTC-induced adverse health effects may require consideration of two different exposure regimes, one for occupational asthma and the other for HMD and lung cancer. These exposure regimes consist of a physical exposure material component (particle size distribution) and a chemical exposure material component (chemical heterogeneity), but differ in the relative contribution of these components to the development of specific adverse health outcomes.

Occupational Asthma

If occupational asthma is caused by exposure to particles with aerodynamic sizes capable of depositing in the tracheobronchial, bronchial, and alveolar regions of the lung and with chemical composition that contains cobalt (alone or in the presence of tungsten carbide), then our air-monitoring results in conjunction with *in vitro* dissolution test results may help to explain why cases of occupational asthma are observed among workers who handle pre-sintered hard metal powders and grind and manipulate sintered CTC parts (Davison et al., 1983; Sprince et al. 1988; Meyer-Bisch et al., 1989; Shirakawa et al., 1989; Kusaka et al., 1996) and among diamond polishers whose only exposure is to cobalt (Gheysens et al., 1985). Consistent with these studies, we observed exposures to cobalt in all work areas spanning powder production to handling finished product parts. Of the

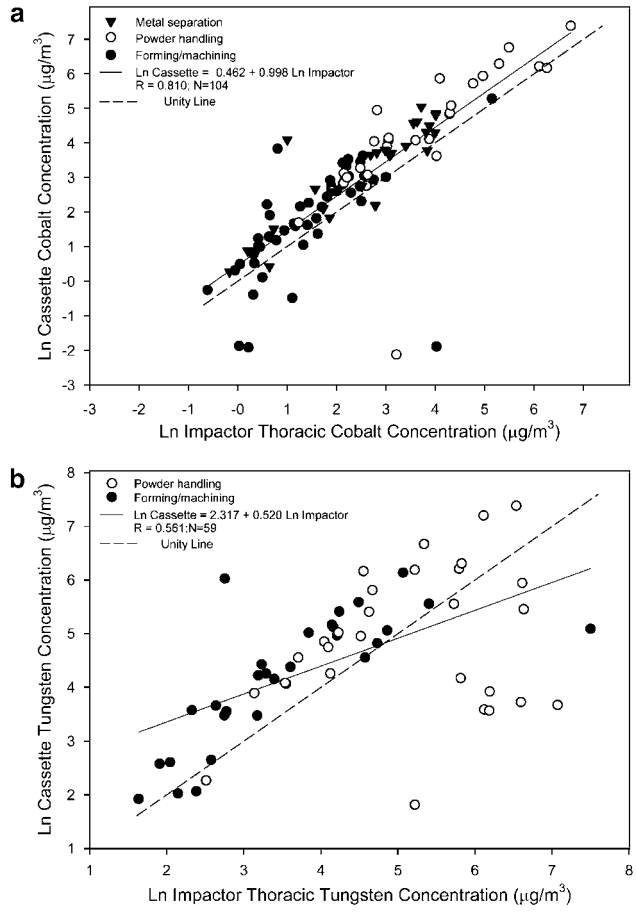

Figure 1. Airborne (a) cobalt and (b) tungsten concentrations measured using 37-mm cassette samplers relative to the thoracic fraction estimated using impactor samplers.

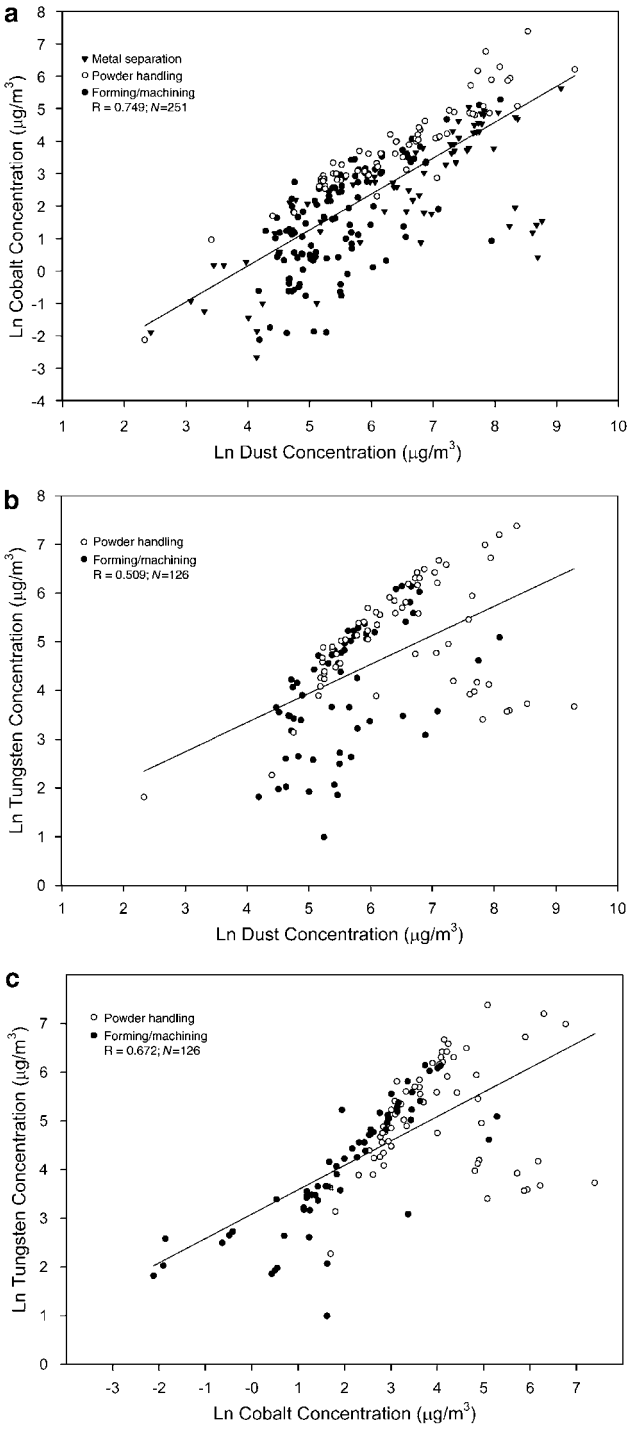

Figure 2. Ratios of airborne (a) cobalt and dust, (b) tungsten and dust, and (c) cobalt and tungsten concentrations measured using 37-mm cassette samplers.

three biologically relevant particle size fractions, inhalable cobalt mass concentration exposures were the highest, especially in the reclamation work areas (metal separation facility); powder mixing, milling, spray drying, screening, and maintenance work areas (powder handling facility); and pressing work area (machining facility). The MMADs of cobalt-containing particles tended to be in the thoracic and inhalable range (Tables 6 and 7), though measurable mass concentrations of respirable particle fractions existed in all work areas (Table 4). Previous elemental analysis of aerosols generated among these three facilities revealed that regardless of the work area, all particles contained cobalt, either as discrete cobalt particles or in association (agglomerated/aggregated) with tungsten (Stefaniak et al., 2007). *In vitro* tests revealed that cobalt dissolves from both pure cobalt powder and from pre- and post-sintered tungsten carbide powders in artificial lung fluids (Stopford et al., 2003). Cobalt was more soluble in artificial lung alveolar macrophage phagolysosomal fluid than in artificial extracellular lung fluid (Johansson et al., 1980; Collier et al., 1992). Collectively, these data suggest that all cobalt-containing particles (cobalt either alone or in the presence of tungsten carbide) that deposit in the lung and conducting airways have the potential to produce dissolved cobalt. Although a clear toxicological mechanism for cobalt-induced asthma is lacking

(Cirla, 1994), this dissolved cobalt is hypothesized to form a hapten and elicit an immune response (Shirakawa et al., 1988, 1989). Thus, a thoracic exposure metric is likely the appropriate exposure measure for investigating occupational asthma and other lower respiratory symptoms among cobalt-exposed workers. Estimates of thoracic exposures to cobalt for evaluation of occupational asthma may be obtained using personal impactor samplers or 37-mm cassette sampler and applying a ratio of 0.7 for converting exposure estimates from total to thoracic concentration. An analogous situation exists for the evaluation of the respiratory effects of metalworking fluids, for which NIOSH recommends a thoracic exposure limit (NIOSH, 1998) and using a ratio of 0.8 for converting exposure estimates from total to thoracic concentration, representing a more biologically relevant exposure metric for respiratory effects. Similar ratios of thoracic to total exposure in the range of 0.6 to 0.7 have been reported in a number of studies of metalworking fluid exposures (Reh et al., 2005; Verma et al., 2006).

Hard Metal Disease and Lung Cancer

If HMD and lung cancer are caused by alveolar deposition of respirable-size particles that contain cobalt associated with tungsten, then our air monitoring exposure data may help to understand lung cancer and explain why HMD is observed among workers exposed to pre-sintered material alone (Meyer-Bisch et al., 1989), post-sintered CTC material alone (Sprince et al., 1988), and both pre- and post-sintered materials (Bech et al., 1962; Coates and Watson, 1971; Sjögren et al., 1980; Davison et al., 1983; Sprince et al., 1984; Cugell et al., 1990; Figueroa et al., 1992; Fischbein et al., 1992). Consistent with these studies, we observed that workers were co-exposed to respirable cobalt- and tungsten-containing particles in all work areas (see Tables 4 and 5) spanning powder production (pre-sintered materials) through handling final product parts (post-sintered materials). In these facilities, the lower ends of the ranges of MMADs were often less than 10 μm, especially in the forming/machining facility (see Table 6). Despite the importance of particle size in lung deposition, historical studies of CTC workers used measurements of total airborne cobalt aerosol mass concentration using 37-mm cassette samplers or other sampling heads without regard to particle size. In a previous study at these three facilities, Stefaniak et al. (2007) determined the MMAD of cobalt-containing particles from impactor samples of general work room air; values were similar to those reported for personal impactor samples in the current study (Table 6). Kusaka et al. (1992) reported that the MMAD of dust particles in a CTC-grinding facility was 2.8 μm, which is similar to the lower end of the range of cobalt-containing particle MMADs we observed in the grinding work area. Generally, respirable cobalt and tungsten mass concentration exposure levels varied among facilities, reflecting differences in the types of work activities. For example, the reclamation work areas (metal separation plant) and powder mixing and screening work areas (powder handling facility) had some of the highest GM levels of combined respirable cobalt and tungsten exposures. Note that the rank order of work areas with respect to respirable cobalt exposures (Table 4) was not always the same as that for respirable tungsten exposures (Table 5), despite a significant, but modest, correlation between total cobalt and total tungsten exposures (Figure 2c). Some work areas are ranked higher for respirable exposure to one element than the other, for example, the metal separation work area (metal separation facility). The chemical composition of airborne particles generated at these facilities becomes increasingly heterogeneous with processing: mostly discrete cobalt- or tungsten-containing particles prior to spray drying, and then heterogeneous cobalt- and tungsten-containing particles in subsequent work areas. Variability in CTC powder formulations (relative masses and sizes of feedstock tungsten carbide, cobalt, and additive metal powders) and work activities may explain variability in relative airborne cobalt and tungsten mass concentrations and size distributions (Stefaniak et al., 2007).

Using *in vitro* and *in vivo* models, researchers investigating the mechanistic basis of HMD (Lasfargues et al., 1992; Lison and Lauwerys, 1990, 1992, 1994, 1995; Lison et al., 1995, 1996; Zanetti and Fubini, 1997; Keane et al., 2002; Mutti and Corradi, 2006; Moriyama et al., 2007) observed that a mechanical mixture of pure cobalt and tungsten carbide powders prepared in the laboratory and pre-sintered hard metal powder (mixture of cobalt, tungsten, and carbon) were more toxic than pure tungsten carbide or pure cobalt powder alone; the increased toxicity of the powder mixtures was attributed to the generation of free radicals via a localized reaction, that is, on a particle surface or between particle surfaces in contact, and not from the reaction of a solubilized component at the solid surface. Using powder concentrations of 22.5 mg/ml (which is high relative to observed mass concentrations in Table 1) and an electron spin resonance technique, Lison et al. (1995, 1996) proposed the following precise mechanism for HMD: when both cobalt metal (which is thermodynamically able to reduce ambient oxygen) particles and tungsten carbide (a good electron conductor) particles are associated, electrons provided by the cobalt metal are easily transferred to the surface of the carbide particles, where reduction of oxygen can occur at an increased rate, resulting in the generation of free radicals. Analogous results have been reported for genotoxicity studies (Anard et al., 1997; Van Goethem et al., 1997; Lison et al., 2001; De Boeck et al., 2003a, b; Mateuca et al., 2005): cobalt associated with tungsten carbide particles (mechanical mixture or pre-sintered hard metal powder) produce more free radicals and DNA strand breaks than pure cobalt or tungsten carbide powder alone. Additionally, *in vitro* cobalt ions (75 μM) can inhibit DNA repair as measured by the

alkaline unwinding method (Lison et al., 2001). Thus, for HMD and lung cancer, understanding the differences in total cobalt mass concentration exposure levels among work areas may not be sufficient for exposure assessment, rather considerations must be given to particle size and potential differences in toxicity of cobalt-tungsten mixtures. Estimates of respirable exposures to cobalt- and tungsten-containing particles for evaluation of HMD and lung cancer should be obtained using a personal size-selective sampler such as an impactor rather than 37-mm cassette samplers. Relying on measures of total cobalt exposure alone could result in exposure misclassification with regard to combined respirable cobalt and tungsten exposures. A respirable exposure metric for cobalt- and tungsten-associated particles is likely the biologically appropriate exposure measure for investigating HMD and lung cancer among exposed workers.

Considerations for Epidemiology

The choice of exposure indicator used in an epidemiologic study can have significant impact on observed exposure–response relationships. Ideally, the chosen exposure metric is a biologically relevant agent (Loomis et al., 1999; Kriebel et al., 2007); however, in practice, the exposure metric is often selected based on the type of exposure data available (Aherns and Stewart, 2003). For example, in the case of HMD and lung cancer, rather than measuring the total dust or total cobalt concentration alone, a more biologically relevant agent would be the mass of respirable-size cobalt and tungsten particles. Lack of knowledge of the etiologic agent(s) and disease mechanism and high variability in measurements of the agent are just some reasons why biologically relevant measures are not always used in epidemiologic analysis (Loomis et al., 1999; Burdof, 2003). Choosing a surrogate exposure metric (e.g., total dust) in place of a more proximal indicator (e.g., respirable-size cobalt and tungsten particles) may lead to the attenuation of observed exposure–response relationships, even in the presence of moderately high correlation ($r = 0.68$ to 0.88) between the exposure metrics (Friesen et al., 2007). If the biologically relevant exposure is a mixture whose composition varies between work areas, as is observed for CTC dusts (Stefaniak et al., 2007), then selection of a less-specific surrogate exposure metric (e.g., cobalt alone) may bias exposure–response relationships for HMD due to exposure misclassification, despite moderately high correlation between the respirable-size cobalt and tungsten exposure constituents (Blair et al., 2007; Friesen et al., 2007). For example, Blair et al. (2007) demonstrated that even moderately high correlation ($r \approx 0.7$) between a surrogate and proximal exposure index may cause misclassification of up to 60% of subjects into exposure quintiles, which in turn may cause an appreciable bias in estimates of relative risk. Thus, it is important to develop an exposure metric that represents the specific agent(s) that is related to the disease process in order to detect small risks, or risk related to mixed exposures. In the case of occupational asthma among CTC workers, a ratio (conversion factor) of 0.6 to 0.8, as observed in this and other (NIOSH, 1998; Reh et al., 2005; Verma et al., 2006) studies, may be used to convert total cobalt exposure concentrations measured via 37-mm cassette to thoracic equivalent exposures, which represent a biologically more valid metric.

Summary

By characterizing size-selective and co-exposures, as well as describing the varying solubilities and multiple exposure pathways including dermal exposures, this series of papers offer an approach for future epidemiologic studies to consider biologically meaningful exposure metrics. We are not aware of any previous epidemiological studies of CTC-related health outcomes that have used biologically relevant exposure metrics such as those described here. Our model for adverse health effects associated with airborne exposure to dusts generated during production and manipulation of CTC consists of two different exposure regimes, one for occupational asthma and the other for HMD and lung cancer. These exposure regimes were developed through consideration of information from multiple research disciplines, including toxicology, genotoxicology, epidemiology, and industrial hygiene in order to achieve a biologically relevant exposure metric. Further, these exposure regimes present opportunities for the development of biologically relevant exposure metrics for epidemiological studies.

Acknowledgements

We thank K Teschke of the University of British Columbia and M Waters of NIOSH for critical review of this paper. We also thank B Tift and N Edwards at NIOSH for data management and graphics development, and W Miller at NIOSH for useful discussion of this work.

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. The authors declare that they have no competing interests, financial or otherwise.

References

Aherns W., and Stewart P. Retrospective exposure assessment. In: Nieuwenhuijsen M.J. (Ed.). *Exposure Assessment in Occupational and Environmental Epidemiology*. Oxford University Press Inc., New York, 2003, pp 103–118.

Anard D., Kirsch-Volders M., Elhajouji A., Belpaeme K., and Lison D. *In vitro* genotoxic effects of hard metal particles assessed by alkaline single gel and elution assays. *Carcinogenesis* 1997: 18: 177–184.

Bech A.O., Kipling M.D., and Heather J.C. Hard metal disease. *Br J Ind Med* 1962: 19: 239–252.

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.

Burdof A. Analysis and modeling of personal exposure. In: Nieuwenhuijsen M.J. (Ed.). *Exposure Assessment in Occupational and Environmental Epidemiology*. Oxford University Press Inc., New York, 2003, pp 85–102.

Cirla A.M. Cobalt-related asthma: clinical and immunological aspects. *Sci Total Environ* 1994: 150: 85–94.

Coates E.O., and Watson J.L. Diffuse interstitial lung disease in tungsten carbide workers. *Ann Int Med* 1971: 75: 709–716.

Collier C.G., Pearce M.J., Hodgson A., and Ball A. Factors affecting the *in vitro* dissolution of cobalt oxide. *Environ Health Perspect* 1992: 97: 109–113.

Cugell D.W., Morgan W.K.C., Perkins D.G., and Rubin A. The respiratory effects of cobalt. *Arch Intern Med* 1990: 150: 177–183.

Davies H.W., Tesche K., and Demers P.A. A field comparison of inhalable and thoracic size selective sampling techniques. *Ann Occup Hyg* 1999: 6: 381–392.

Davison A.G., 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.

Day G.A., Virji M.A., and Stefaniak A.B. Characterization of exposures among cemented tungsten carbide workers. Part II: assessment of surface contamination and skin exposures to cobalt, chromium and nickel. *J Expos Anal Environ Epidemiol* 2008; doi:10.1038/jes200833.

De Boeck M., Hoet P., Lombaert N., Nemery B., Kirsch-Volders M., and Lison D. *In vivo* genotoxicity of hard metal dusts: induction of micronuclei in rat type II epithelial lung cells. *Carcinogenesis* 2003a: 24: 1793–1800.

De Boeck M., Lombaert N., De Backer S., Finsy R., Lison D., and Kirsch-Volders M. *In vitro* genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis* 2003b: 18: 177–186.

Fairhall L.T., Castber H.T., Carrozzo N.J., and Brinton H.P. Industrial hygiene aspects of the cemented tungsten carbide industry. *Occup Med* 1947: 4: 371–379.

Figueroa S., Gerstenhaber B., Welch L., Klimstra D., Walker Smith G.J., and Beckett W. Hard metal interstitial pulmonary disease associated with a form of welding in a metal parts coating plant. *Am J Ind Med* 1992: 21: 363–373.

Fischbein A., Luo J.-C.J., Solomon S.J., Horowitz S., Hailoo W., and Miller A. Clinical findings among hard metal workers. *Br J Ind Med* 1992: 49: 17–24.

Friesen M.C., Davies H.W., Teschke K., Ostry A.S., Hertzman C., and Demers P.A. Impact of the specificity of the exposure metric on exposure–response relationships. *Epidemiology* 2007: 18: 88–94.

Gheysens B., Auwerx J., Van den Eeckhout A., and Demedts M. Cobalt-induced bronchial asthma in diamond polishers. *Chest* 1985: 88: 740–744.

Hinds W.C. Data analysis. In: Lodge J.P., and Chan T.L. (Eds.). *Cascade Impactor Sampling and Data Analysis*. American Industrial Hygiene Association, Akron, Ohio, 1986, pp 45–77.

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.

Johansson A., et al. Effect of iron, cobalt, and chromium dust on rabbit alveolar macrophages: a comparison with the effects of nickel dust. *Environ Res* 1980: 21: 165–176.

Keane M.J., Hornsby-Myers J.L., Stephens J.W., Harrison J.C., Myers J.R., and Wallace W.E. Characterization of hard metal dusts from sintering and detonation coating processes and comparative hydroxyl radical production. *Chem Res Toxicol* 2002: 15: 1010–1016.

Kirk-Othmer. Encyclopedia of Chemical Technology. In: Howe-Grant M. (Ed.). *Mass Transfer to Neuroregulators*, 4th edn. John Wiley & Sons Inc., New York, 1995, Vol. 16, pp 386–387.

Koponen M., Gustaffson T., Kalliomäki P.-L., Kalliomäki K, and Moilanen M. Grinding dusts of alloyed steel and hard metal. *Ann Occup Hyg* 1981: 24: 191–204.

Koponen M., Gustaffson T., and Kalliomäki P.-L. Cobalt in hard metal manufacturing dusts. *Am Ind Hyg Assoc J* 1982: 43: 645–651.

Kraus T., Schramel P., Schaller K.H., Zöbelein P., Weber A., and Angerer J. Exposure assessment in the hard metal manufacturing industry with special regard to tungsten and its compounds. *Occup Environ Med* 2001: 58: 631–634.

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

Kumagai S., Kusaka Y., and Goto S. Cobalt exposure level and variability in the hard metal industry of Japan. *Am Ind Hyg Assoc J* 1996: 57: 365–369.

Kusaka Y., Iki M., Kumagai S., and Goto S. Epidemiological study of hard metal asthma. *Occup Environ Med* 1996: 53: 188–193.

Kusaka Y., Kumagai S., Kyono H., Kohyama N., and Shirakawa T. Determination of exposure to cobalt and nickel in the atmosphere in the hard metal industry. *Ann Occup Hyg* 1992: 36: 497–507.

Lasfargues G., et al. Lung cancer mortality in a French cohort of hard-metal workers. *Am J Ind Med* 1994: 26: 585–596.

Lasfargues G., Lardot C., Delos M., Lauwerys R., and Lison D. The delayed lung responses to single and repeated intratracheal administration of pure cobalt and hard metal powder in the rat. *Environ Res* 1995: 69: 108–121.

Lasfargues G., Lison D., Maldague P., and Lauwerys R. Comparative study of the acute lung toxicity of pure cobalt powder and cobalt-tungsten carbide mixture in rat. *Toxicol Appl Pharmacol* 1992: 112: 41–50.

Lichtenstein M.E., Bartl F., and Pierce R.T. Control of cobalt exposures during wet process tungsten carbide grinding. *Am Ind Hyg Assoc J* 1975: 36: 879–885.

Lippman M. Rationale for particle size-selective aerosol sampling. In: Vincent J.H. (Ed.). *Particle Size-Selective Sampling for Particulate Air Contaminants*. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1999, pp 18.

Lison D., Carbonnelle P., Mollo L., Lauwerys R., and Fubini B. Physicochemical mechanism of the interaction between cobalt metal and carbide particles to generate toxic activated oxygen species. *Chem Res Toxicol* 1995: 8: 600–606.

Lison D., De Boeck M., Verougstraete V., and Kirsch-Volders M. Update on the genotoxicity and carcinogenicity of cobalt compounds. *Occup Environ Med* 2001: 58: 619–625.

Lison D., Lauwery R., Demedts M., and Nemery B. Experimental research into the pathogenesis of cobalt/hard metal lung disease. *Eur Respir J* 1996: 9: 1024–1028.

Lison D., and Lauwerys R. Cobalt bioavailability from hard metal particles: further evidence that cobalt alone is not responsible for the toxicity of hard metal particles. *Arch Toxicol* 1994: 68: 528–531.

Lison D., and Lauwerys R. *In vitro* cytotoxic effects of cobalt-containing dusts on mouse peritoneal and rat alveolar macrophages. *Environ Res* 1990: 52: 187–198.

Lison D., and Lauwerys R. Study of the mechanism responsible for the elective toxicity of tungsten carbide-cobalt powder toward macrophages. *Toxicol Lett* 1992: 60: 203–210.

Lison D., and Lauwerys R. The interaction of cobalt metal with different carbides and other mineral particles on mouse peritoneal macrophages. *Toxicol In Vitro* 1995: 9: 341–347.

Loomis D., Salvan A., Kromhout H., and Kriebel D. Selecting indices of occupational exposure for epidemiologic studies. *Occup Hyg* 1999: 5: 73–91.

Marple V.A. Series 290 marple personal cascade impactors instruction manual. Bulletin No. 290I.M.-3-82 1980.

Mateuca R., Aka P.V., De Boeck M., Hauspie R., Kirsch-Volders M., and Lison D. Influence of *hOGG1*, *XRCC1* and *XRCC3* genotypes on biomarkers of genotoxicity in workers exposed to cobalt or hard metal dusts. *Toxicol Lett* 2005: 156: 277–288.

Meyer-Bisch C., et al. Respiratory hazards in hard metal workers: a cross sectional study. *Br J Ind Med* 1989: 46: 302–309.

Moriyama H., et al. Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. *Am J Resp Crit Care Med* 2007: 176: 70–77.

Moulin J.J., et al. Lung cancer risk in hard-metal workers. *Am J Epi* 1998: 148: 241–248.

Moulin J.J., Wild P., Mur J.M., Fournier-Betz M., and Mercier-Gallay M. A mortality study of cobalt production workers: an extension to the follow-up. *Am J Ind Med* 1993: 23: 281–288.

Mutti A., and Corradi M. Recent developments in human biomonitoring: non-invasive assessment of target tissue dose and effects of pneumotoxic metals. *Med Lav* 2006: 97: 199–206.

National Institute for Occupational Safety and Health. Criteria for a recommended standard – occupational exposure to tungsten and cemented tungsten carbide. *DHEW (NIOSH)* 1977 Pub. No. 77-227.

National Institute for Occupational Safety and Health In: Schlecht P.C., and O'Connor P.F. (Eds.). *NIOSH Manual of Analytical Methods (NMAM®)*, 4th edn. DHHS (NIOSH) Publication 94-113 (August, 1994), 1st Supplement

Publication 96-135, 2nd Supplement Publication 98-119, 3rd Supplement 2003-154 1994.
National Institute for Occupational Safety and Health. *Criteria for a Recommended Standard – Occupational Exposure to Metalworking Fluids*. DHHS (NIOSH) Pub. No. 98-102 1998.
Rappaport S.M., Weaver M., Taylor D., Kepper L., and Susi P. Application of mixed models to assess exposures monitored by construction workers during hot processes. *Ann Occup Hyg* 1999: 43: 457–469.
Reh B.D., Harney J.M., McCleery R.E., and Mueller C.A. Evaluation of the NIOSH MWF total particulate matter: thoracic particulate matter conversion factor in a machining environment. *J Occup Environ Hyg* 2005: 2: 239–243.
Rubow K.L., Marple V.A., Olin J., and McCawley M.A. A personal cascade impactor: design, evaluation and calibration. *Am Ind Hyg Assoc J* 1987: 48: 532–538.
Schneider G. *Principles of Tungsten Carbide Engineering*, 2nd edn. ASM International, Materials Park, Ohio, 1989, pp 1–15.
Seixas N.S., Hewett P., Robins T.G., and Haney R. Variability of particle size-specific fractions of personal coal mine dust exposures. *Am Ind Hyg Assoc J* 1995: 56: 243–250.
Sesana G., Cortona G., Baj A., Quaianni T., and Colombo E. Cobalt exposure in wet grinding of hard metal tools for wood manufacture. *Sci Total Environ* 1994: 150: 117–119.
Shirakawa T., et al. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. *Chest* 1989: 95: 29–37.
Shirakawa T., Kusaka Y., Fujimura N., Goto S., and Morimoto M. The existence of specific antibodies to cobalt in hard metal asthma. *Clin Allergy* 1988: 18: 451–460.
Sjögren I., Hillerdal G., Andersson A., and Zetterström O. Hard metal lung disease: importance of cobalt in coolants. *Thorax* 1980: 35: 653–659.
Sprince N.L., Chamberlin R.I., Hales C.A., Weber A.L., and Kazemi H. Respiratory disease in tungsten carbide production workers. *Chest* 1984: 86: 549–557.
Sprince N.L., Oliver L.C., Eisen E.A., Greene R.E., and Chamberlin R.I. Cobalt exposure and lung disease in tungsten carbide production. A cross-sectional study of current workers. *Am Rev Respir Dis* 1988: 138: 1220–1226.
Stefaniak A.B., et al. Characteristics of dusts encountered during the production of cemented tungsten carbides. *Ind Health* 2007: 45: 793–803.
Stopford W., Turner J., Cappellini D., and Brock T. Bioaccessibility testing of cobalt compounds. *J Environ Monit* 2003: 5: 675–680.
Teschke K., Marion S.A., van Zuylen M.J.A., and Kennedy S.M. Maintenance of Stellite and tungsten carbide saw tips: determinants of exposure to cobalt and chromium. *Am Ind Hyg Assoc J* 1995: 56: 661–669.
Van Goethem F., Lison D., and Kirsch-Volders M. Comparative evaluation of the *in vitro* micronucleus test and the alkaline single cell gel electrophoresis assay for the detection of DNA damaging agents: genotoxic effects of cobalt powder, tungsten carbide and cobalt-tungsten carbide. *Mut Res* 1997: 392: 31–43.
Verma D.K., Shaw D.S., Shaw M.L., Julian J.A., McCollin S.-A., and des Tombe K. An evaluation of analytical methods, air sampling techniques, and airborne occupational exposure to metalworking fluids. *J Occup Environ Hyg* 2006: 3: 53–66.
Wild P., Perdrix A., Romazini S., Moulin J.-J., and Pellet F. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 2000: 57: 568–573.
Zanetti G., and Fubini B. Surface interactions between metallic cobalt and tungsten carbide particles as a primary cause of hard metal disease. *J Mater Chem* 1997: 7: 1647–1654.

Appendix A

The manufacturing process and the metallurgical characteristics of CTC are described in detail by Schneider (1989) and Kirk-Othmer (1995). The purpose of this appendix is to describe the work activities and potential sources of exposure variability encountered during manufacture of CTC at the time of the airborne (this study) and dermal and surface contaminations (see companion paper) surveys.

Metal separation facility

At the metal separation facility, tungsten, cobalt, and other metals (molybdenum, and so on) are recovered from machining fluid sludge (metal separation), hard metal powder is reclaimed from off-specification sintered material and/or worn and used product (reclamation), and resultant powders tested for conformance to quality control specifications (powder laboratory).

Metal Separation The CTC manufacturing process begins in the metal separation plant with a worker loading tungsten-containing metalworking fluid sludge into an oxygen–atmosphere furnace and heating the material to oxidize the tungsten. The resulting tungsten oxide cake is crushed and passed through a rotary furnace to yield tungsten oxide powder, which is placed in a tank with caustic and heated to form sodium tungstenate solution. The solution is purified, converted into ammonium tungstenate, and heated to form ammonium paratungstate (APT) crystals. APT crystals are manually loaded into feed bins, then placed in a calciner (heat-treater) to form tungsten oxide powder, which is reduced (manually or using an automated process) in hydrogen atmosphere furnaces to form tungsten metal powder, and then placed in a blender to homogenize. In manual reduction, a worker scoops tungsten oxide powder into oblong heating containers referred to as ''boats,'' places the powder boats in the furnace, and then unloads the resultant tungsten metal. In contrast, during automated reduction, the tungsten oxide powder is augered into the boats, and a machine loads the boats into the furnace and unloads the boats.

Carburization Tungsten metal powder and carbon black powder are ball-milled to homogenize constituents and the resulting powder is manually loaded onto powder boats by a worker, heated (carburization) to form aggregated tungsten carbide (WC) ''bricks,'' which are automatically dumped into a coarse crusher and then further processed by ball milling and/or jet milling to break the material into discrete WC particles. The WC powder is either packaged and sold to external customers or sent to the powder handling facility.

Reclamation The reclamation process is housed in two buildings (A and B). CTC scrap is recycled into powder with a composition that matches the parent material. Beginning in building A, a worker dumps several hundred kilograms of sintered scrap (e.g., worn drill bits) into furnace trays using a hydraulic lift to assist with picking up and dumping the scrap-laden buckets; this tray-loading operation generates visible dust plumes. The trays are placed in a furnace using an overhead chain hoist, heated using a proprietary process, and the resultant cake mechanically crushed and screened (these jobs are visibly dusty). The screened powder material is moved to building B, manually placed in trays, the trays

inserted in a furnace and heated, and the resultant cake mechanically crushed (a dusty job) and milled to form hard metal powder. This hard metal powder is placed in bins and loaded on top of a screener, sized, and the final product powder blended to homogenize, if necessary, and then placed in storage containers for sale to external customers or shipment to the powder-handling facility.

Powder Laboratory In the powder laboratory, small (in grams) quantities of powders are tested to ensure that the formulations meet customer and manufacturer quality control specifications. Powders include raw materials, in-process materials, and finished powder for use in production.

Maintenance Maintenance workers at this facility work throughout the work areas and also maintain a maintenance crib (separate building from main production facility), where contaminated equipment may be brought for repair.

Administration Administrative workers at this facility are mainly accountants and other white-collar professionals. Administrative offices are located in a building that is physically separated from the production buildings; however, employees occasionally walk through the production areas.

Powder-handling facility

In the powder-handling facility, powders from the metal separation facility are received (inventory control) and processed (powder mixing, wet milling, spray drying, screening) into hard metal powders that are sent (shipping) to the forming and machining facility.

Inventory Control Tungsten carbide and reclaimed hard metal powders received from the metal separation facility and feedstock powders (cobalt, chromium, nickel, tantalum carbide, etc.) purchased from external suppliers are inventoried by a receiving clerk and then distributed for processing. Inventory control clerks may open and seal several containers during a work shift that contain WC, reclaimed hard metal, and feedstock powders. Each container may weigh tens to hundreds of kilograms. From the inventory control, powders are sent to the powder-mixing work area, which is collocated with a soft (unsintered) scrap-reprocessing operation.

Powder Mixing In powder mixing, powders are formulated by manually scooping several hundred kilograms of cobalt feedstock powder and lesser quantities of additives (including chromium, nickel, titanium carbide, tantalum carbide, and vanadium) and pouring the powders into large hoppers that contain WC and reclaimed hard metal powders. Adjacent to the powder-mixing area, pre-sintered compacts of hard metal that fail quality control specifications are reprocessed by crushing, screening, and blending in batches containing several hundred kilograms, which generates visible airborne dust. The powder-mixing and reprocessing work areas are among the most dusty work areas in this facility and are physically isolated from the remainder of the facility; workers wear protective disposable coveralls and respirators.

Milling (Wet) Each hopper containing hard metal powder is connected to a ball mill, filled with an organic solvent and other liquids, and then wet-milled into a slurry; each charge consists of several hundred kilograms of hard metal powder.

Spray Drying After milling, the slurry is transferred to a pumping container and dispersed in a spray dryer to evaporate the liquids to form homogenized hard metal powder, which is discharged onto a conveyor belt, and, depending on the grade of powder, either dropped into a storage container or passed across a coarse screen and dropped into a drum for further processing. In spray drying, workers may fill several containers each with tens of kilograms of hard metal powder per work shift, which requires the worker to be in close proximity to the spray dryer powder discharge and the powder conveyor belt.

Screening If necessary, powder from the spray dryer is sent for screening to attain a customer-specified size; at the time of this survey, the cowls on each screener used to contain discharged powder as it dropped into the storage containers were in poor repair or were not used properly. Prior to shipment, gram quantities of each powder were sent to the powder laboratory at the metal separation facility for quality control testing.

Shipping The final product hard metal powders are shipped to the forming and machining facility for compacting or to external customers.

Maintenance Maintenance workers at this facility work throughout the work areas and also maintain a maintenance crib work area, where cobalt-contaminated equipment may be brought for repair.

Forming and machining facility

At the forming and machining facility, hard metal powders are received (production control) and distributed throughout the facility for compacting, sintering, machining to final dimensional specification, and then packaged and shipped to customers.

Production Control Hard metal powder is received from the powder-handling facility and distributed by an inventory control clerk for compaction via pneumatic pressing or extrusion; clerks may open and reseal several containers of hard metal during a work shift.

Pressing At this facility, 95% of the hard metal powder received is pressed mechanically or pneumatically into "green" (i.e., unsintered forms) customer-specified compact shapes; at each press, the hard metal powder is manually scooped into a hopper and gravity fed into the die.

Extrusion The remaining 5% of hard metal powder received from the powder-handling facility is augmented with a plasticizer to form a clay-like material and extruded to form "green" compacts.

Shaping Some green compacts may first be rough shaped (machined), for example, using high-pressure water to cut pieces. All compacts are sintered (heat-treated in vacuum furnaces) on graphite-coated trays to form CTC.

Breakdown Sintered compacts are removed from their sintering trays by manually flipping the trays over and dumping the parts on a table (i.e., breakdown); at the time of this survey, a ventilated table had been purchased, but not yet installed, by the company to replace the current unventilated table used for breakdown.

Grinding During sintering, the compacts shrink, necessitating grinding to precise final dimension; most sintered compacts are wet-ground, although dry grinding is performed as necessary.

Sandblasting After grinding, about one-third of sintered compacts are sandblasted in an enclosed glove box to remove burrs.

Product testing All finished products are sent for product testing (quality control) to ensure that the parts meet customer specifications.

Shipping All products that pass quality control inspection are packaged manually and sent (shipping) to customers. During packaging, finished product parts are stacked and organized, which may generate dust.

Maintenance Maintenance workers at this facility repair machinery throughout work areas and, if necessary, take cobalt-contaminated equipment from work areas to their maintenance crib for repair.

Administration Administrative workers at this facility include clerical staff responsible for filing production records, photocopying, and record keeping. At the forming and machining facility, administrative offices are located within the same building as the production work areas and separated only by a short hallway. "Shop packets" (tracking sheets that accompany all orders from the metal separation plant through to shipment of final product to customer) are filed and maintained by the clerical staff at this facility.

Appendix B

The table below presents the correction factors for inlet efficiency and interstage particle losses (Rubow et al., 1987); particle size range and midpoint; and factors applied to each impactor stage to estimate the respirable, thoracic, and inhalable particulate mass concentrations.

Stage	Cut point (D_p)	Particle size (PS-D_p)[a]	Collection efficiency[b]	Lower limit (LL)	Upper limit (UL)	Midpoint (MP)[c]	Respirable factor[d]	Thoracic factor[d]	Inhalable factor[d]
1	21.3	21.10[a]	0.52	21.1	42[e]	31.55	0.000	0.010	0.580
2	14.8	17.95	0.61	14.8	21.1	17.95	0.000	0.104	0.671
3	9.8	12.30	0.78	9.8	14.8	12.30	0.005	0.338	0.740
4	6.0	7.90	0.89	6	9.8	7.90	0.065	0.669	0.812
5	3.5	4.75	0.95	3.5	6	4.75	0.360	0.861	0.876
6	1.55	2.53	0.96	1.55	3.5	2.53	0.819	0.930	0.930
7	0.93	1.24	0.97	0.93	1.55	1.24	0.962	0.964	0.964
8	0.52	0.73	0.99	0.52	0.93	0.73	0.979	0.979	0.979
F	0	0.52[a]	1	0	0.52	0.26	0.992	0.992	0.992

[a]PS-D_p is the halfway between the cut-point of stage i and stage i−1 ($D_p = (D_{p_i} + D_{p_{i-1}})/2$). The PS-$D_p$ for stage 1 and F are preselected by convention (Marple, 1980).
[b]The collection efficiency for each stage is obtained from Marple (1980).
[c]MP is the midpoint of the lower and upper limits for each stage (MP = [(UL−LL)/2] + LL).
[d]The respirable, thoracic, and inhalable factors for each stage are obtained from the ACGIH/ISO/CEN size-selective curves along with using Simpson's rule. For example, the respirable factor for each stage is calculated as: Respirable $\text{Factor}_{\text{stage}}$ = (RF LL + 4(RF MP) + RF UL)/6, where RF LL, RF MP, and RF UL are the respirable fractions associated with the lower limit, midpoint, and upper limit particle size for each stage based on the ACGIH/ISO/CEN curve.
[e]The upper limit particle size diameter for stage 1 is obtained from Seixas et al. (1995).