Ann. Occup. Hyg., pp. 1–16
Published by Oxford University Press
on behalf of the British Occupational Hygiene Society
doi:10.1093/annhyg/meq055

Characteristics of Beryllium Exposure to Small Particles at a Beryllium Production Facility

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Received 30 November 2009; in final form 2 June 2010

Epidemiological studies have reported process-specific elevated prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) among workers. However, exposure–response relationships have been inconsistent, possibly due to incomplete characterization of many biologically relevant aspects of exposure, including particle size. In 1999, two surveys were conducted 3–5 months apart at a beryllium metal, oxide, and alloy production facility during which personal impactor samples (n = 198) and personal 37-mm closed-face cassette (CFC) 'total' samples (n = 4026) were collected. Among process areas, median particle mass median aerodynamic diameter ranged from 5 to 14 μm. A large fraction of the beryllium aerosol was in the nonrespirable size range. Respirable beryllium concentrations were among the highest for oxide production [geometric mean (GM) = 2.02 $\mu g\ m^{-3}$, geometric standard deviation (GSD) = 1.3] and pebbles plant (GM = 1.05 $\mu g\ m^{-3}$, GSD = 2.9), areas historically associated with high risk of BeS and CBD. The relationship between GM 'CFC total' and GM respirable beryllium for jobs varied by process areas; the rank order of the jobs showed high overall consistency (Spearman r = 0.84), but the overall correlation was moderate (Pearson r = 0.43). Total beryllium concentrations varied greatly within and between workers among process areas; within-worker variance was larger than between-worker variance for most processes. A review of exposure characteristics among process areas revealed variation in chemical forms and solubility. Process areas with high risk of BeS and CBD had exposure to both soluble and insoluble forms of beryllium. Consideration of biologically relevant aspects of exposure such as beryllium particle size distribution, chemical form, and solubility will likely improve exposure assessment.

Keywords: beryllium; chronic beryllium disease; sensitization; size-selective sampling; solubility; variance components

INTRODUCTION

Beryllium is a lightweight metal used in the aerospace, telecommunications, defense, medical, and automotive industries because of its exceptional physical, mechanical, and nuclear properties (NAS, 2008). The National Institute for Occupational Safety and Health (NIOSH) has estimated that as many as 134 000 workers may be currently exposed to beryllium in the USA (Henneberger *et al.*, 2004); the number of ever-exposed workers is much higher. Exposure to beryllium can lead to beryllium sensitization (BeS), which in some individuals may progress to chronic beryllium disease (CBD), a potentially fatal cell-mediated immunologic granulomatous lung disease (NAS, 2008). Several epidemiological studies have reported elevated prevalences of BeS and

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CBD among employees in specific work processes (Kreiss *et al.*, 2007). These studies used various exposure metrics predicated on airborne beryllium mass concentration to identify process-related risk; however, exposure–response relationships have been inconsistent (Kreiss *et al.*, 2007). The inconsistency in exposure–response relationships for BeS and CBD is possibly due to factors such as exposure misclassification from lack of accurate, precise, and/or biologically relevant exposure metrics; exclusion of skin exposure as a route for sensitization; and lack of consideration of the impact of dose rate and genetic susceptibility. The focus of this paper is on alternative exposure metrics for airborne beryllium that account for the possible role of particle size, chemical form, and solubility in the development of BeS and CBD.

Particle aerodynamic diameter influences the site of aerosol penetration and deposition throughout the respiratory tract. As such, different particle size distributions of the same contaminant will result in differences in deposition among regions of the respiratory tract. Therefore, particle size is an important exposure consideration relevant to development of pulmonary injury or disease (Stuart *et al.*, 1986). Inhalable particles are those with size capable of entering the head airways region and therefore may be relevant to development of BeS (ACGIH, 2009). Thoracic particles are the fraction of aerosol that penetrates the head airways region and enters the tracheobronchial region and are often relevant to development of various lung cancers (Stuart *et al.*, 1986). Finally, respirable particles are the fraction of aerosol that penetrates the tracheobronchial region and enter the nonciliated alveolar region and may be relevant to development of inflammation and CBD (Stuart *et al.*, 1986).

A limited number of studies have reported size-fractionated beryllium exposures for jobs or processes in work places (Cholak *et al.*, 1967; Hoover *et al.*, 1990; Martyny *et al.*, 2000; Kent *et al.*, 2001; McCawley *et al.*, 2001; Thorat *et al.*, 2003; Stefaniak *et al.*, 2004, 2008). A case–control study of workers in a precision machine shop showed that exposure to beryllium particles <6 or <1 μm was associated with BeS or CBD and was higher among BeS or CBD cases than controls, albeit nonsignificant (Kelleher *et al.*, 2001). Kent *et al.* (2001) reported significant associations between CBD and/or BeS and exposure metrics based either on mass or on estimated number of beryllium particles in the size fraction most likely to deposit in the alveolar region of the lung. Similarly, McCawley *et al.* (2001) observed that areas with highest historical risk for CBD (reported in Kreiss *et al.*, 1997) had the highest particle number concentrations but relatively modest beryllium mass concentrations. However, to date, data on inhalable beryllium exposures have not been reported in the literature.

Once beryllium is deposited in a region of the respiratory tract, its chemical form and solubility are hypothesized to be important exposure factors (Stefaniak *et al.*, 2008). Inhalable soluble beryllium mists or particles potentially represent a hazard for development of BeS because deposited beryllium may interact with immune cells in any region of the respiratory tract. In contrast, poorly soluble inhalable beryllium particles will have short residence time and slow dissolution rates (Finch *et al.*, 1988) in the head airway and conducting airway regions, thereby limiting opportunities for interaction with immune competent cells. Additionally, beryllium material deposited in the conducting airways that is cleared to the gastrointestinal tract may have limited interaction with immune cells because $<1\%$ of ingested material is absorbed (US EPA, 1998). Respirable size poorly soluble beryllium particles that deposit in the nonciliated alveolar region of the lung are rapidly engulfed by macrophages where they undergo dissolution in phagolysosomes (Day *et al.*, 2005; Stefaniak *et al.*, 2006). Slow material clearance from the alveolar region of the lung via chemical dissolution may result in prolonged beryllium retention, greater opportunity for interaction with the immune system, and formation of granulomas and chronic inflammation, which is characteristic of CBD (Stefaniak *et al.*, 2003; Sawyer *et al.*, 2005). In general, rates of dissolution between beryllium metal and beryllium oxide (BeO) vary by orders of magnitude in conducting airway fluid (Finch *et al.*, 1988) and alveolar macrophage models (Day *et al.*, 2005; Stefaniak *et al.*, 2006).

This limited evidence from exposure assessment and epidemiological studies, in combination with knowledge of particle lung deposition and solubility, suggests that the ability of particles to penetrate into the respiratory system may be one of several factors relevant to the development of BeS and CBD. The objectives of this paper were to: (i) describe the levels and variability of total and size-fractionated (<6 μm) beryllium exposure in a production facility and (ii) investigate the chemical and physicochemical characteristics of these beryllium exposure aerosols. This information on exposure levels, particle size, chemical form, and solubility in biological fluids is currently being used in conjunction with historical exposure data to reconstruct historical exposures and develop biologically relevant exposure metrics for an epidemiological study of BeS and CBD at this facility.

METHODS

Two separate exposure surveys were conducted at a facility that produces beryllium metal powder, BeO powder, and beryllium alloys. The purpose of the first survey (conducted over a 2-week period in March 1999 by the company and NIOSH) was to collect size-separated personal impactor samples. The purpose of the second survey (conducted from June to August of 1999 by the company) was to collect full-shift personal 37-mm closed-face cassettes (CFCs) 'total' samples. The production processes and characteristics were believed to be similar during the two survey periods.

Process descriptions

The plant is a large and complex manufacturing facility located on a 190 hectare (480 acre) site with 102 buildings totaling 80 400 m^2 (865 000 square feet) under roof. In 1999, the plant employed 808 workers. The three main product lines included beryllium metal, BeO, and beryllium alloys (Fig. 1). The feedstock material for all thee product lines is moist beryllium hydroxide, $Be(OH)_2$, which is produced from bertrandite and beryl ores at another facility.

Production of beryllium metal powder starts in the wet plant by dissolving $Be(OH)_2$, BeO, and/or beryllium scrap in ammonium bifluoride to form an ammonium beryllium fluoride (ABF) solution $[(NH_4)_2BeF_4]$. This solution is then purified, evaporated, and crystallized to form ABF salt. In the pebbles plant, the ABF salt is fed into a fluoride furnace and heated to form glassy beryllium fluoride (BeF_2). The BeF_2 is reduced with magnesium in a reduction furnace resulting in metallic beryllium pebbles within a magnesium fluoride (MgF_2) matrix. Upon cooling, the matrix is wet milled to release and recover the beryllium pebbles. In powder metal products, the metallic beryllium pebbles are cleaned to reduce magnesium contamination and vacuum cast into ingots. The ingots are then chipped on a lathe and ultimately reduced to powder using impact grinding, milling, or atomization. The metal powder is loaded into a die and either cast into a cylindrical billet under heat and pressure in sintering furnaces or compressed into near-net shapes using hot or cold isostatic presses. These products are machined (e.g. lathed, milled, sawed) or rolled and formed into finished products (Stonehouse and Zenczak, 1991; Stonehouse *et al.*, 1992; White and Burke, 1955).

Production of BeO in the oxide department starts by dissolving $Be(OH)_2$ in sulfuric acid and then supersaturating the solution to form beryllium sulfate tetrahydrate salt crystals ($BeSO_4 \bullet 4H_2O$). The salt is then calcined at elevated temperature to convert to crystalline BeO powder and screened to remove large agglomerates from the finished product powder (Stonehouse and Emly, 1992).

Production of alloy materials in primary operations begins with the calcining of $Be(OH)_2$ to BeO, which is then mixed with carbon and fine particles collected in a baghouse and formed into pellets. The BeO pellets, along with furnace dross, additional air cleaning fines, and copper, are fed into an arc furnace to form a nominal 4% by weight beryllium 'master alloy' melt that is subsequently cast into ingots. The master alloy ingots are remelted in induction furnaces and diluted with additional copper and small amounts of other metals to form varying melt compositions ranging from 0.1 to 2% beryllium by weight, which are cast into round or rectangular billets. Round billets are extruded and converted to rod, bar, tube, and wire products; rectangular billets are processed in hot- and cold-rolling mills to form strip and plate products (Stonehouse *et al.*, 1992). A wide range of metal processing is applied to these billets including immersion in pickling solutions (acidic or basic) resulting in formation of soluble beryllium salts.

Data from previously published literature on the physical, chemical, and physicochemical properties of materials used at this facility associated with processes are summarized in Table 1. The table also describes properties of beryllium aerosols collected from inside process-specific local exhaust ventilation ductwork of several process areas in the facility (Stefaniak *et al.*, 2003, 2004, 2006; Day *et al.*, 2005). The feedstock materials used in these process areas and the aerosols generated include different beryllium compounds that confer different physical forms and lung solubilities. Both soluble and poorly soluble beryllium in lung fluid are present in oxide and pebbles plant process areas, which have historically been associated with elevated risk of BeS and CBD. Stefaniak *et al.* (2003, 2004) also reported that regardless of process input materials or product line, beryllium in ventilation ductwork was in the form of crystalline BeO in the respirable size fraction (<4 μm). The exception to this trend was in powder metal products where the aerosol was in the form of crystalline beryllium metal in the thoracic size fraction (<10 μm).

In addition to the processes described above, other production-related jobs include resource recovery, quality assurance and control (QA/QC), and research and development (R&D). Jobs related to production support and administrative functions

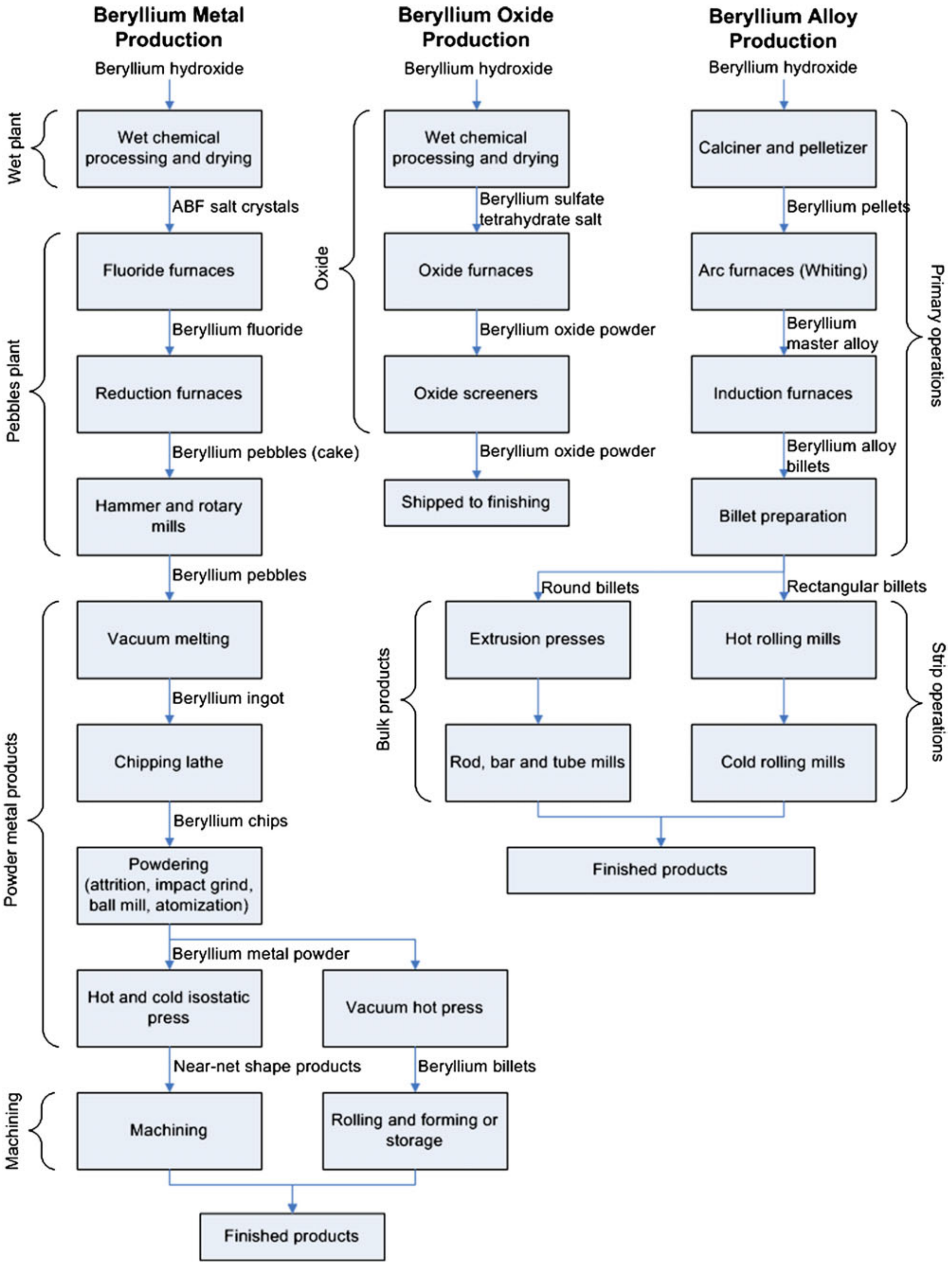

Fig. 1. Simplified schematic diagram of process flow of beryllium production.

include maintenance; facilities including janitorial, decontamination, water treatment, and laundry; medical department and environmental laboratories; process engineering; and administration including secretaries, management and sales, purchasing, human resources, and accounting staff. Some jobs in these functions are exclusively in nonproduction areas of the facility, whereas others are only in production areas or in both production and nonproduction areas.

Impactor sampler survey

The focus of this survey was to evaluate the distribution of small airborne beryllium particles

Table 1. Forms of beryllium materials and characteristics of exposure aerosols by production process area

Production process area	Beryllium process materials[a]		Beryllium aerosol exposures	
	Compound	Physical form	Compound	Lung solubility
Beryllium metal				
Wet plant	$Be(OH)_2$	Moist powder	$Be(OH)_2$	Moderate
	$(NH_4)_2BeF_4$	Salt solution	$(NH_4)_2BeF$	Soluble
Pebbles plant fluoride furnace	$(NH_4)_2BeF_4$	Salt solution	$(NH_4)_2BeF_4$	Soluble
	BeF_2	Solid (glass)	BeF_2[b]	Soluble[c]
			BeO[b]	Poor
Pebbles plant reduction furnace	BeF_2	Solid (glass)	BeF_2[b]	Soluble[c]
	Be	Solid (pebbles)	BeO[b]	Poor
Powder metal product (powder)	Be	Chips/powder	Be[b]	Poor[c]
Metal machining	Be	Solid (parts)	Be	Poor
	Be	Dissolved in MWF	Be^{+2}	Soluble[c]
BeO				
BeO screener	$Be(OH)_2$	Moist powder	$Be(OH)_2$	Moderate
	$BeSO_4 \cdot 4H_2O$	Salt solution	$BeSO_4 \cdot 4H_2O$	Soluble
	BeO	Powder	BeO[b]	Poor[c]
Oxide product (powder)	BeO	Powder	BeO[b]	Poor[c]
Beryllium alloy				
Master alloy arc furnace	$Be(OH)_2$	Moist powder	$Be(OH)_2$	Moderate
	BeO	Powder	BeO	Poor
	CuBe	Molten/solid (ingot)	BeO[b]	Poor[c]
Casting alloy induction furnace	CuBe	Solid (ingot)	BeO[b]	Poor
Bulk product	CuBe	Solid (rod/wire)	Be	Poor
	Be	Dissolved in PS	Be^{+2}	Soluble
Strip products	CuBe	Solid (strip)	Be	Poor
	Be	Dissolved in PS	Be^{+2}	Soluble
Miscellaneous				
Resource recovery	Be	Solid (various)	Be	Poor
	BeO	Solid (various)	BeO	Poor
	CuBe	Solid (various)	Be	Poor
	BeF_2	Salt solution	BeF_2	Soluble
R&D/QA and QC	Be	Solid (various)/powder	Be	Poor
	BeO	Solid (various)/powder	BeO	Poor
	CuBe	Solid (various)/powder	Be	Poor

$Be(OH)_2$ = beryllium hydroxide; $(NH_4)_2BeF_4$ = ammonium beryllium fluoride; BeF_2 = beryllium fluoride; Be = beryllium; $BeSO_4 \cdot 4H_2O$ = beryllium sulfate tetrahydrate; CuBe = copper beryllium; MWF = metal working fluid; PS = pickling solution (acidic or caustic).

[a] White and Burke (1955), Stonehouse *et al.* (1992), Stonehouse and Emly (1992).

[b] Denotes crystalline compound identified using electron or X-ray diffraction (Stefaniak *et al.*, 2003, 2004); all other amorphous and/or crystalline compounds inferred from process chemistry (refs. in footnote a).

[c] Denotes compound solubility determined by Finch *et al.* (1988), Day *et al.* (2005), Stefaniak *et al.* (2006), or Stefaniak *et al.* (unpublished data); all other categories inferred from chemical form of aerosol exposure compound.

for jobs and process areas. Samples were collected using multistage impactors (Series 290 Marple Personal Cascade Impactor; Andersen Instruments Inc., Smyrna, GA, USA) positioned in workers' breathing zones (BZs). The personal impactor samples were collected using Aircheck 52 personal air sampling pumps (SKC Inc., Eighty Four, PA, USA) calibrated to a flow rate of 2.0 l min^{-1} (L.p.m.).

The multistage impactor samplers were configured to use only four of the eight stages of the impactor and provided 50% aerodynamic cutoff diameters (D_{50}) of 6.0 µm (Stage 4), 3.5 µm (Stage 5), 1.55 µm (Stage 6), and 0.93 µm (Stage 7). Particles <0.93 µm aerodynamic diameter entered an experimental trilayer filter assembly placed on Stage 8 of the impactor (described in detail by McCawley *et al.*, 2002), followed by a final filter to retain any particles not collected by the trilayer assembly. Slotted mixed cellulose ester (MCE) filters (0.8-μm pore size) sprayed with Apiezon L grease to minimize particle bounce were used for impactor Stages 4 through 7. Nonslotted polycarbonate filters (5-μm pore size) were used for the trilayer filter assembly on Stage 8; a nonslotted MCE filter was used as the final filter.

One hundred and ninety-eight time-weighted average personal impactor samples were available for data analysis from representative jobs and processes. These samples were collected during the morning and afternoon shifts. In general, a single sample was collected from each worker within any given job; however, multiple samples (two to four repeats) were occasionally collected from some workers (n = 36) on the same or different jobs. For some samples from jobs with low exposures (n = 66), monitoring was conducted over multiple shifts (two to five shifts) to ensure the collection of sufficient masses of beryllium to meet analytical detection requirements. Hence, sampling duration ranged from 188 to 2034 min, with only three samples of <300 min. Multishift samples were collected on different workers (n = 36) or on the same worker (n = 30). The number of samples collected by job ranged from 1 to 12. A total of 76 jobs (57 in production areas and 19 in nonproduction areas) and 155 workers were monitored in the survey, which represented 15 process areas.

37-mm cassette sampler survey

The focus of this second survey was to evaluate total beryllium mass exposures among all jobs and most workers (89% of all workers) at this facility. A total of 4026 full-shift personal time-weighted average CFC samples were available for data analysis. Samples were collected from workers' lapels using MCE filters (0.8-μm pore size) and Aircheck 52 personal air sampling pumps (SKC Inc.) calibrated to a flow rate of 2.0 L.p.m. A majority of the samples (95%) were of duration ≥6 h; only 33 samples had durations of <5 h (most of which were close to 300 min). Exposure monitoring was conducted most frequently not only during the morning shift but also during the afternoon and night shifts for some jobs. In general, a median of 15 samples (range: 2–55 samples) were collected for each job from one or more workers (range: 1–21 workers) within a given job. Samples were collected on consecutive days until the desired sample size ($n \approx 15$) was achieved for a job. A total of 718 workers were monitored in the CFC survey, which likely included most workers from the impactor survey; however, direct comparisons could not be made by individual as personal identifiers were not available. In the CFC survey, a total of 269 jobs (132 in production areas and 137 in nonproduction areas) in 25 process areas were monitored. Repeated measurements (2–17 measurements) were available from 84% (602/718) of the workers. Job codes at this facility were functional jobs identified by the combination of process areas and specific job performed.

Analytical methods

Samples were analyzed by the company laboratory (CFC samples) or a commercial laboratory (impactor samples) for quantification of beryllium. The CFC samples were prepared using NIOSH Analytical Method 7300 modified for microwave digestion and analyzed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (NIOSH, 1994a). The laboratory-reported limit of detection (LOD) for this method was 0.02 μg per filter. Impactor samples were also digested using NIOSH Analytical Method 7300 modified for microwave digestion and analyzed by ICP-AES. Samples below the limit of quantification were reanalyzed using graphite furnace-atomic absorption spectroscopy (GF-AAS) using NIOSH Analytical Method 7102 (NIOSH, 1994b). The laboratory-reported LOD for GF-AAS was 0.003 μg per filter. For data analyses, impactor stages with beryllium mass below the LOD were assigned a value of one-half the LOD value (Hornung and Reed, 1990).

Data analysis

The trilayer filter assembly changed the particle size characteristics of what would normally be collected on Stage 8 (0.93–0.52 μm) and on the final filter (<0.52 μm) of a traditional eight-stage impactor. Hence, for all calculations, including summarizing the impactor stages, calculating the respirable mass concentration, and estimating the mass median aerodynamic diameter (MMAD), the mass of beryllium on the trilayer filter assembly was summed together with the mass of the final filter and the impactor was essentially treated as a four-stage sampler consisting of Stages 4 through 7 followed by the composite final filter. Respirable, thoracic, or inhalable mass concentrations can be estimated from impactor samples (Ramachandran and Vincent, 1997) and is often done for exposure assessment or epidemiological studies (see, for example, Seixas *et al.*, 1995 or Woskie *et al.*, 1994). While the inhalable or thoracic mass concentrations could not be calculated from the impactor samples collected in this study due the configuration of the impactor stages, respirable beryllium concentrations were calculated using the International Organization for Standards respirable convention with a D_{50} of 4 μm (Lippman, 1999). Simpson's rule was used in a tabular–graphical approach to estimate the contribution of each impactor stage to the respirable particle size fraction (Hinds, 1986). Appendix 1 contains the correction factors for inlet efficiency and interstage particle losses (Rubow *et al.*, 1987), particle size ranges and midpoints, and fractions of each stage that were used to estimate respirable mass concentrations. For each impactor sample, the upper limit particle diameter of the stage was plotted versus cumulative mass percent on a log-probability plot (Hinds, 1986). A plot that revealed a straight line was indicative of lognormally distributed data that allowed estimation of the MMAD and geometric standard deviation (GSD) from the plot. In contrast, deviation from a straight line (e.g. an S-shaped pattern) was indicative of non-lognormal particle size distribution for which a single statistic was not sufficient to describe the central tendency of the data. Of the 198 impactor samples, the MMAD and GSD were estimated for 140 samples; the remaining 58 samples displayed characteristics of bimodal or multimodal size distributions.

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). Distributions of the impactor and CFC data were examined graphically via probability plots and were found to be approximately lognormal; hence, they were log transformed and summary statistics including the geometric means (GMs), GSDs, and the minimum variance unbiased estimators (MVUEs) of the arithmetic means (Mulhausen and Damiano, 1998) were calculated for process areas within production departments. For the impactor data, one-way analysis of variance (ANOVA) procedure was used to examine the effects of process areas or jobs on exposure levels. Multiple comparisons of differences between means among process areas and jobs were conducted using the GLM procedure with Tukey's option in SAS. A significance level of $\alpha = 0.05$ was used for all analyses.

For the CFC data, summary statistics (GM, GSD, and MVUE) and the between-worker (S^2_{BW}) and within-worker (S^2_{WW}) variance components were estimated using the maximum likelihood estimate (MLE) method via the NLMIXED procedure in SAS to account for the large fraction of measurements below the LOD for some of the process areas (Theibaut and Jacqmin-Gadda, 2004). Briefly, the procedure uses a log-likelihood function with two components, one for observed data and the other for data below the LOD. The log-likelihood function is then maximized using an algorithm and MLEs of model parameters and variance components are obtained. Summary statistics and variance components were estimated separately for each process area from models with the log-transformed beryllium concentration as the dependent variable, the effect of worker as a random factor and no fixed factors. As a comparison, variance components were also estimated using the traditional one-way random-effects models (random term for worker) via the MIXED procedure in SAS (Rappaport *et al.*, 1999). Maximum likelihood method was used to estimate the model parameters and the between-worker (S^2_{BW}) and within-worker (S^2_{WW}) variance components for different process areas (compound symmetry covariance structure). Two-way nested random-effects models were also run with the additional random terms for job or process area to evaluate the effect of grouping by these variables in epidemiological studies (Kromhout and Heederik, 1995). Variance components from these models were used to calculate contrast (ϵ), defined as the ratio of between-group variance to the sum of between-group and within-group variances, ranging from a value of 0 (indicating no value in grouping) to a value of 1 (indicating unique grouping) (Kromhout and Heederik, 1995). Both Pearson and Spearman correlation coefficients were obtained to evaluate relationships between the GMs of sampler types as they were right skewed and the Pearson correlation is sensitive to non-normally distributed data. The scatter plots of the sampler types were prepared in SigmaPlot 9.01 (Systat Software Inc., San Jose, CA, USA).

RESULTS

Impactor sampler survey

The number of impactor filters below the LOD were $n = 2$ (1%) for Stage 4, $n = 6$ (3%) for Stage 5, $n = 12$ (6%) for Stage 6, $n = 17$ (8.6%) for Stage 7, and $n = 26$ (13.1%) for the combined final filter. For all process areas, the highest beryllium mass concentrations were found on the top impactor stage (>6 μm) (Table 2). Some process area had high concentrations of large particles, e.g. powder metal products, whereas other process areas had bimodal or multimodal distributions (high concentrations of both small and large particles in the distribution), e.g. pebbles plant or oxide process areas.

Table 2. Size-separated beryllium exposure mass concentration (µg m^{-3}) for process areas

Process areas	*n*	Stage 4[a], >6.0 µm, GM (GSD)	Stage 5[a], 6.0–3.5 µm, GM (GSD)	Stage 6[a], 3.5–1.6 µm, GM (GSD)	Stage 7[a], 1.6–0.93 µm, GM (GSD)	Combined final filter[a,b], <0.93 µm, GM (GSD)	All stages combined, GM (GSD)
Beryllium metal production							
Wet plant	3	0.503 (1.1)	0.148 (1.3)	0.081 (1.3)	0.058 (1.3)	0.057 (2.2)	0.857 (1.2)
Pebbles plant	13	1.293 (2.8)	0.438 (3.2)	0.266 (2.8)	0.222 (3.4)	0.337 (3.6)	2.706 (2.8)
Powder metal products	31	1.247 (2.4)	0.276 (2.7)	0.148 (2.8)	0.072 (3.6)	0.068 (3.6)	1.925 (2.4)
Machine shop	6	0.214 (4.5)	0.043 (2.8)	0.024 (2.7)	0.012 (2.3)	0.050 (4.8)	0.437 (2.7)
BeO production							
Oxide	3	3.667 (1.7)	0.767 (1.4)	0.619 (1.8)	0.481 (1.5)	0.564 (1.7)	6.350 (1.4)
Beryllium alloy production							
Primary operations	37	0.732 (3.3)	0.250 (2.7)	0.138 (2.9)	0.100 (2.7)	0.070 (3.3)	1.391 (2.8)
Extrusion	3	0.045 (1.4)	0.019 (1.3)	0.015 (1.7)	0.011 (1.4)	0.011 (1.8)	0.104 (1.3)
Bulk products	16	0.085 (2.8)	0.017 (2.2)	0.011 (2.3)	0.008 (2.7)	0.008 (4.9)	0.146 (2.5)
Strip and plate operations	19	0.033 (4.2)	0.010 (3.7)	0.006 (3.5)	0.008 (4.2)	0.008 (3.7)	0.074 (3.7)
Miscellaneous production							
Resource recovery	8	1.123 (4.6)	0.336 (4.9)	0.217 (3.5)	0.118 (4.8)	0.097 (4.4)	1.965 (4.3)
R&D	1	3.572 (–)	0.844 (–)	0.346 (–)	0.271 (–)	0.058 (–)	5.091 (–)
QA/QC	9	0.057 (2.2)	0.018 (2.8)	0.012 (3.0)	0.007 (3.2)	0.012 (4.2)	0.115 (2.5)
Nonproduction/support							
Administration plant	19	0.030 (4.2)	0.012 (3.7)	0.007 (3.1)	0.006 (2.8)	0.004 (3.2)	0.066 (3.3)
Facilities	13	0.078 (2.1)	0.025 (2.3)	0.015 (2.3)	0.007 (4.1)	0.006 (4.6)	0.138 (2.3)
Maintenance—all	17	0.161 (3.8)	0.060 (3.5)	0.037 (3.4)	0.020 (3.6)	0.015 (5.7)	0.349 (3.4)

[a] The fraction of stage samples below the LOD were Stage 4 ($n = 2$, 1%), Stage 5 ($n = 6$, 3%), Stage 6 ($n = 12$, 6%), Stage 7 ($n = 17$, 8.6%), trilayer assembly (Stage 8) ($n = 26$, 13.1%), and final filter ($n = 110$, 55.6%).

[b] Collection efficiency for the combined final filter was assumed to be 1. The masses on all stages were corrected for the collection efficiency of the stage before calculating the concentration.

Table 3 summarizes the respirable beryllium mass concentrations by process areas. The highest GM respirable mass concentrations (up to 2 µg m^{-3}) were observed among workers in oxide, followed by pebbles plant, resource recovery, powder metal products, and in primary operations. Tukey's multiple comparisons showed that these process areas were significantly different ($P < 0.05$) from the lowest respirable exposure process areas (down to 0.023 µg m^{-3}) measured among workers in administration plant, strip and plate, facilities, bulk products, QA/QC, extrusion, and maintenance. Maintenance workers had higher respirable exposures than some workers in bulk products and strip operations. Results of the ANOVA analyses indicated that GM respirable mass concentrations were significantly different among process areas ($P < 0.05$). However, within most process areas, GM respirable mass concentrations for jobs were not significantly different from one another, except in primary operations (located in separate buildings), QA/QC, facilities, and administration—plant. Overall, a high correlation was observed between the respirable mass concentration and the summed (all stages) mass concentration from the impactor samples (Pearson $r = 0.95$), which varied among process areas and ranged from $r = 0.58$ for oxide to $r = 0.99$ for pebbles plant.

Seventy-four percent (103 out of 140) of the impactor samples had ≥50% of the mass on the top stage (Stage 4), and the MMADs were thus extrapolated by extending the best-fit line in the log-probability plots to the 50th percentile. This assumes that the same trend line continues for the larger particles, which cannot be verified by the current data; thus, only the general ranges of the MMADs are reported here as the MMADs for specific samples cannot be reported with confidence. In general, the impactor samples followed a lognormal size distribution with a wide range of MMADs from 2 to 38 µm indicating the presence of both small and large particles within and among process areas. Median MMADs for process areas ranged from 5 to 14 µm with most process areas having MMADs in the thoracic (<10 µm) size. The smallest median MMADs (ca. 6 µm) were observed in the pebbles plant, primary operations, and the administration areas of the plant. The largest

Table 3. Respirable beryllium exposure mass concentration (μg m^{-3}) for process areas

	n	k	j	GM (μg m^{-3})	GSD	Range (μg m^{-3})	95th percentile
Beryllium metal production							
Wet plant	3	3	3	0.251	1.4	0.173–0.322	0.322
Pebbles plant	13	7	3	1.052	2.9	0.113–5.869	5.869
Powder metal products	31	18	9	0.444	2.6	0.040–2.456	2.326
Machine shop	6	4	4	0.146	2.0	0.064–0.455	0.455
BeO production							
Oxide	3	3	1	2.020	1.3	1.559–2.762	2.762
Beryllium alloy production							
Primary operations	37	30	11	0.425	2.7	0.074–3.685	2.629
Extrusion	3	3	1	0.044	1.4	0.032–0.058	0.058
Bulk products	16	16	13	0.040	2.7	0.008–0.393	0.393
Strip and plate operations	19	16	9	0.029	3.6	0.003–0.489	0.489
Miscellaneous production							
Resource recovery	8	8	3	0.570	4.0	0.065–4.584	4.584
R&D	1	1	1	1.005	—	—	—
QA/QC	9	7	3	0.042	2.9	0.008–0.323	0.323
Nonproduction/support							
Administration plant	19	10	4	0.023	2.9	0.003–0.175	0.175
Facilities—all	13	12	5	0.040	2.6	0.010–0.496	0.496
Maintenance—all	17	17	6	0.109	3.8	0.018–3.549	3.549

n = number of measurements; k = number of workers; j = number of jobs.

median MMADs (11–14 μm) were observed in powder metal products, bulk products, machine shop, and the oxide area of the plant. Bimodal or multimodal particle size distributions were observed in samples from most process areas especially from pebbles plant, machine shop, bulk products, strip and plate operations, and quality control (44–67% of the samples).

37-mm cassette sampler survey

Total airborne beryllium mass concentrations measured using CFC samplers are summarized by process area for production (Table 4) and nonproduction (Table 5) jobs. Overall, 17% (688/4026) of the CFC measurements were below the LOD, mostly in nonproduction areas and production support jobs. For processes with <10% of the measurements below the LOD, results from the MLE method were similar to those obtained from standard approaches (random- or mixed-effects models) and we report only the MLE results. Among production operations (Table 4), GM total aerosol mass concentrations were highest (up to 0.87 μg m^{-3}) in powder metal products, resource recovery, oxide production operations, and pebbles plant. Based on Tukey's multiple comparison, these process areas were significantly higher ($P < 0.05$) than the lowest (down to 0.05 μg m^{-3}) process areas in alloy operations that handled solid material, such as extrusion, bulk products, and strip and plate operations, as well as QA/QC and R&D. Among nonproduction operations (Table 5), GM total aerosol mass concentrations tended to be similar to the lowest levels observed among production operations. The one exception was maintenance-high beryllium where the GM concentration was 0.25 μg m^{-3}. Tukey's multiple comparison showed highest exposures in maintenance-high beryllium and alloy, janitorial, wastewater treatment, and professional support in high beryllium areas were significantly different ($P < 0.05$) from the lowest exposure group that included all administration, environmental labs, and professional support in central areas. Results of the ANOVA models indicated that overall GM total mass concentrations for process areas were significantly different from one another ($P < 0.05$). Within specific process areas, GM concentrations for jobs were generally significantly different from one another ($P < 0.05$) for most process areas except for wet plant, pebbles plant, oxide, facilities—wastewater, and administration—office for which job was not significant in the ANOVA models.

Overall, between-worker variance ($S^2_{\mathrm{BW}} = 1.89$) was larger than within-worker variance ($S^2_{\mathrm{WW}} = 0.84$).

Table 4. Summary of the 'total' beryllium exposure mass concentration (μg m^{-3}) by process areas for production jobs

Production process areas	*n*	<LOD (%)	*k*	*j*	AM (μg m^{-3})	GM (μg m^{-3})	GSD	95th percentile	Range	S^2_{BW}	S^2_{WW}
Beryllium metal production											
Wet plant	35	0	9	3	0.43	0.34	1.96	1.10	0.03–1.29	0.01[a]	0.44
Pebbles plant	62	0	14	5	1.06	0.57	3.11	3.78	0.04–19.91	0.09[a]	1.19
Powder metal products	170	1.2	29	12	3.41	0.87	5.27	16.38	0.02–254.23	0.66	2.10
Machine shop	104	3.8	20	8	0.22	0.13	2.83	0.80	0.02–4.03	0.25	0.83
BeO production											
Oxide	19	5.3	6	2	2.39	0.58	5.95	9.64	0.02–9.64	0.43[a]	2.75
Beryllium alloy production											
Primary operations	310	0.3	89	20	0.92	0.39	3.68	4.16	0.02–48.07	1.10	0.60
Extrusion	110	6.4	18	7	0.09	0.06	2.27	0.21	0.02–0.56	0.20[a]	0.47
Bulk products	268	9.3	56	18	0.11	0.06	2.94	0.38	0.02–2.98	0.18	0.98
Strip and plate operations	335	15.2	65	23	0.11	0.05	3.38	0.39	0.02–19.80	0.51	0.97
Miscellaneous production											
Resource recovery	42	2.4	11	3	1.49	0.59	4.03	5.39	0.02–6.75	0.20[a]	1.75
R&D	118	13.6	12	9	0.10	0.06	2.96	0.37	0.02–2.01	0.42[a]	0.76
QA/QC	343	17.2	49	22	0.08	0.05	2.81	0.24	0.02–13.72	0.43	0.64

Estimates of GM, GSD, AM, S^2_{BW}, and S^2_{WW} are based on maximum likelihood method using NLMIXED procedure. n = number of measurements; k = number of workers; j = number of jobs; AM = MVUE of the arithmetic mean; S^2_{BW} = between-worker variance; S^2_{WW} = within-worker variance.

[a] Estimates not significantly different from 0 at $P \leq 0.05$.

Table 5. Summary of the 'total' beryllium exposure mass concentration (μg m^{-3}) by process areas for nonproduction jobs

Nonproduction/support work areas	*n*	<LOD (%)	*k*	*j*	AM (μg m^{-3})	GM (μg m^{-3})	GSD	95th percentile	Range	S^2_{BW}	S^2_{WW}
Administration—office[a]	91	84.6	37	7	0.02	<0.02	10.46	0.04	0.02–5.15	0[b]	5.51
Administration—plant	548	43.2	89	34	0.04	0.02	2.96	0.11	0.02–1.95	0.41	0.77
Environmental laboratories	65	29.2	8	4	0.05	0.03	2.77	0.09	0.02–1.52	0.36[b]	0.68
Facilities—wastewater	46	2.2	7	3	0.15	0.11	2.31	0.50	0.02–0.99	0.04[b]	0.66
Facilities—janitorial	118	1.7	15	5	0.36	0.15	3.71	0.86	0.02–4.22	1.32	0.40
Facilities—laundry	63	15.9	12	4	0.07	0.05	2.25	0.14	0.02–0.49	0.15[b]	0.51
Facilities—shipping	209	16.7	32	14	0.09	0.05	2.97	0.47	0.02–2.75	0.65	0.54
Maintenance—alloy	207	6.3	55	12	0.29	0.11	3.92	1.31	0.02–22.71	0.95	0.92
Maintenance—central	198	15.7	47	13	0.17	0.07	3.73	0.51	0.02–14.62	0.98	0.76
Maintenance—high beryllium	113	0	34	8	0.58	0.25	3.63	2.82	0.02–11.51	1.04	0.62
Professional support—alloy	187	19.3	24	13	0.07	0.04	2.88	0.21	0.02–0.68	0.73	0.39
Professional support—central	154	37	21	11	0.07	0.02	4.67	0.20	0.02–1.13	1.54	0.84
Professional support—high beryllium	111	2.7	10	9	0.14	0.11	2.24	0.34	0.02–1.98	0.13[b]	0.52

Estimates of GM, GSD, AM, S^2_{BW}, and S^2_{WW} are based on maximum likelihood method using NLMIXED procedure. n = number of measurements; k = number of workers; j = number of jobs; AM = MVUE of the arithmetic mean; S^2_{BW} = between-worker variance; S^2_{WW} = within-worker variance.

[a] Estimates not reliable due to the large fraction of measurements below the LOD.

[b] Estimates not significantly different from 0 at $P \leq 0.05$.

However, in the models stratified by process areas, the within-worker variance component was larger than the between-worker component for all processes except primary operations and several nonproduction jobs including janitorial, all maintenance jobs, and professional support in alloy and central areas. The two-way random-effects model with grouping by process area showed that between-group variance accounted for 49% of the total variance, followed by within-worker (28%) and within-group (between-worker) (23%). Grouping by jobs resulted in between-group variance accounting for 64% of the total

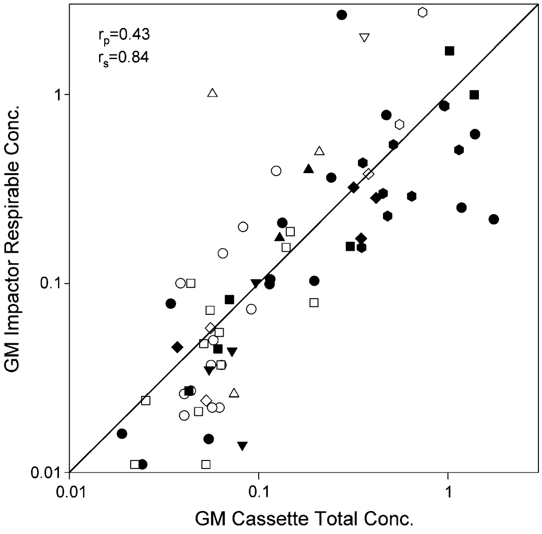

Fig. 2. Relationship of respirable concentrations from impactor samples to the 'total' concentration from 37-mm cassette samples (different symbols indicate different production process areas).

variance, followed by within-worker (28%) and within-group (between-worker) (8%).

GM beryllium mass concentrations measured using CFC samplers were close to the corresponding respirable GM mass concentrations (Fig. 2). For a subset of 76 jobs for which both impactor and CFC samples were available, ratios of the GM of respirable to GM of CFC (respirable ratio) for jobs ranged from 0.6 to 17.7, with most ratios <1.9 except for oxide (5.6) and R&D (17.7). The differences in sampler types by jobs or process areas could not be further evaluated because of the relatively small number of jobs within the process area groupings. The overall correlations between the GM of CFC total and GM respirable from impactor samples were moderate (Pearson $r = 0.43$). However, the rank order of the GMs for jobs showed high consistency between the sampler types (Spearman $r = 0.84$).

DISCUSSION

Historically, mass-based beryllium exposure metrics have been used for epidemiological studies of BeS or CBD, derived from different airborne measurements including short-duration BZ, general area (GA), daily weighted average (DWA—a combination of the BZ and GA with time–motion data), personal 37-mm CFC samplers, personal impactors, and fixed-airhead area samples. In this paper, we characterized beryllium exposures associated with processes at a manufacturing facility and specifically examined the physical characteristics of exposure (particle size distribution), including size-fractionated exposure levels and variation of exposure among processes. Physical exposure factors, in conjunction with chemical (forms of beryllium) and physicochemical (solubility) aerosol properties, may be important in understanding elevated risk for certain processes in previous epidemiological studies (Kreiss *et al.*, 2007), as well as for developing novel exposure metrics that incorporate these biologically relevant factors for use in future epidemiological investigations. Moreover, the information on exposure variability can be used to optimize grouping schemes in epidemiology with the goal of reducing bias due to exposure misclassification.

A large fraction (~60 to 70%) of the aerosol was in the nonrespirable size range, but this is not characterized due to configuration of the impactor sampler used. About 30–40% of aerosol was in the respirable size fraction, which is consistent with findings of Cholak *et al.* (1967) who reported a similar proportion of respirable aerosols in alloy furnace casting areas using a dichotomous sampler. The respirable fraction indicates potential for penetration to the alveolar region of the lung. The highest respirable and particles <1 μm (combined final filter) beryllium concentrations were measured for workers in oxide and pebbles plant process areas, which have historically been associated with elevated risk of BeS and CBD; the same areas were not among the highest total beryllium concentrations obtained from CFC samples. Similarly, McCawley *et al.* (2001) reported the highest particle number concentration in pebbles plant and oxide process areas, which did not correspond to the highest total mass concentration.

The median MMAD values associated with processes were generally in the thoracic size range. While the MMAD provides a summary measure of a particle size distribution, characterizing process area by the shape of the distribution such as bimodal or multimodal provides additional information to better characterize process capability to generate different sized particles. Bimodal or multimodal distributions were observed in a number of processes, which have previously been reported to have bimodal or multimodal distributions, such as the pebbles plant or the oxide process (Kent *et al.*, 2001; McCawley *et al.*, 2001). The ranges of MMADs reported herein cannot be directly compared to those from other studies and should be considered as estimates of capability of process to generate particles of different sizes. The results reported herein suggest the presence of both small and large particles within and among many of the processes. However, exposure to the larger inhalable particles could not be characterized in this study and has not previously been reported in the literature. Thus, the complete characterization of all particle sizes will enable the assessment of inhalable and respirable beryllium exposures, which may be relevant for understanding BeS and CBD.

Comparison of respirable and CFC total exposures

The pattern in the GM total mass concentration measured using CFC samplers for jobs did not follow the pattern observed for the respirable mass concentration from impactor samples. The high Spearman correlations ($r = 0.85$) measured in relation to Pearson correlations ($r = 0.43$) suggests that the pair of metrics are consistently correlated but not in a linear fashion; i.e. an increase in one metric resulted in an increase in the other but not by the same or a constant factor. The relationship between the two sampler types was different among process areas suggesting that the CFC and respirable impactor samples represent different exposure metrics. Similar results are reported by Donaldson and Stringer (1980) who did not observe consistent trends in respirable, total CFC, or DWA beryllium concentrations in their side-by-side sampling of processes at a beryllium manufacturing facility. The GM mass concentrations from CFC samplers in the present study were lower than the corresponding GMs from all stages of the impactors and often closer to the respirable GMs from the impactors. Dufresne *et al.* (2009) observed differences between CFC and impactor samples for beryllium concentrations in a magnesium and aluminum foundry. A number of factors may, in part, explain this difference including, the different inlet characteristics of the two samplers or different particle size distributions in different process areas (O'Shaughnessy *et al.*, 2007) and sampling conditions such as season, sampling strategy, and/or perhaps production-related factors. The impactor survey herein was performed during late winter/early spring when doors were closed, whereas the cassette survey took place in the middle of summer when most doors were often kept open. Stationary area samples collected throughout the year in most process areas for the year 1999 showed consistently higher levels of beryllium exposure during the winter months compared to the summer months (data not shown), but the specific cause for the difference is unknown. Moreover, the impactor survey focused on select jobs and workers, whereas the cassette survey sampled all jobs and most workers within each process area, thus causing exposures to be averaged over a bigger (more diverse and representative) pool of jobs and workers.

Variance components

Overall, there was greater variation in exposure between workers than within workers due to differences in jobs and processes: the largest fraction of the total variance was attributed to jobs and processes. In stratified analysis, within-worker variance was greater than between-worker variance for most process areas, suggesting that exposures varied more from day to day possibly due to differences in jobs and tasks performed from day-to-day or environmental and production conditions (types of materials and products processed, process configuration, production rates, or problems with ventilation or processes) within the process areas. However, within a day, workers in a process area experienced similar exposures. This observation is supported by the fact that most workers operated large well-ventilated pieces of equipment. Information on variance components can be useful in grouping workers and assigning exposures to occupational groups by identifying grouping schemes with small between-worker variance to minimize exposure misclassification (Burdorf, 2003). Grouping by jobs yielded a larger contrast ($\epsilon = 0.89$: a variance ratio) compared to grouping by process area ($\epsilon = 0.68$). Furthermore, grouping by jobs also resulted in very small within-group (between-worker) variance (8%) compared to grouping by process areas (23%). Thus, if adequate exposure data are available to characterize jobs, grouping by jobs would be preferable to grouping by process areas for epidemiological analyses. Many epidemiological studies of BeS and CBD have used process-based groupings and have reported process-specific risk estimates (Kreiss *et al.*, 2007).

Implications for epidemiology

The course of action of particles deposited in the alveolar region depends on chemical form and solubility in biological fluids. Particle deposition in nonciliated lung alveoli can have long-term retention due to slow macrophage-mediated mechanical and chemical dissolution clearance mechanisms. BeO and metal are poorly soluble in airway epithelial lining fluid (Finch *et al.*, 1988) and macrophage phagolysosomal fluid (Day *et al.*, 2005; Stefaniak *et al.*, 2006). The range of chemical dissolution rate constants for these forms of beryllium in these liquids spanned two orders of magnitude, suggesting a varying capacity for aerosols to produce soluble beryllium for interaction with the immune system. The dissolution clearance half times of these materials were on the order of several hundred days. Prolonged particle retention in the lung alveoli provides greater opportunity for interaction with the immune system and may allow buildup of a beryllium lung burden. A persistent beryllium lung burden may be necessary to support inflammation and formation of granulomas that are characteristic of CBD, usually over a period of years. High levels of respirable beryllium are present in process areas historically associated with elevated prevalence of CBD, such as oxide and the pebbles plant. Thus for CBD, a cumulative, respirable exposure-type metric that takes into consideration the physicochemical characteristics and time course of exposure may be the most relevant metric. BeS, which is a necessary precondition for the development of CBD (Newman *et al.*, 2005), is likely associated with inhalable or skin exposure to soluble beryllium aerosols (Curtis, 1951; Day *et al.*, 2006; ACGIH, 2009) and perhaps skin contact with relatively insoluble (Tinkle *et al.*, 2003) forms of beryllium. Peak inhalable soluble exposure is likely to be relevant for BeS if a threshold exposure level is required to elicit an immune response. However, because soluble materials are cleared quickly from the lung, such exposure regimes (skin and peak soluble exposures) may not support development of a lung burden sufficient to cause CBD. Thus, knowledge of physical exposure factors such as particle size, chemical, and physicochemical exposure factors is likely important as these factors relate to current understanding of BeS and CBD development processes and are central to development of biologically relevant exposure metrics (Stefaniak *et al.*, 2008).

The choice of exposure indicator used in an epidemiological study can have significant impact on observed exposure–response relationships. Ideally, the chosen exposure metric is biologically relevant (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. For example, most epidemiological studies of BeS and CBD have used available historical data such as the DWA—which is shown to be poor to moderately correlated with either the respirable ($r = 0.33$) or the total exposure ($r = 0.49$) (Donaldson and Stringer, 1980). In contrast, a metric that accounts for biologically relevant aspects of exposure, including soluble inhalable or insoluble respirable airborne beryllium particles, may inform exposure–response relationships. Lack of knowledge of the etiologic agent(s) and disease mechanism, lack of relevant exposure data, or high variability in measurements of the agent are among the main reasons why biologically relevant measures are not used in epidemiological analysis (Loomis *et al.*, 1999; Burdorf, 2003). Choosing a surrogate exposure metric (e.g. DWA) in place of a more proximal indicator (e.g. respirable or inhalable-sized soluble or insoluble particles) can lead to attenuation of observed exposure–response relationships, even when the exposure metrics are well correlated (Friesen *et al.*, 2007).

Limitations

This study provides detailed information on exposure characteristics associated with processes at a large manufacturing facility; however, as with analysis of any historical data, there are a number of limitations when interpreting the results. Process conditions were believed to be similar during the two surveys. However, each exposure survey was conducted over a relatively short time frame such that seasonal changes that may have a significant impact on exposure estimates were not captured. Details of the sampling strategies, choice of jobs and workers to monitor, or any other assumptions that were made during the two surveys were not explicitly stated or documented. Additional information on process or environmental conditions during exposure monitoring was not available for either survey that might have been useful in understanding exposure variability. The exclusion of the impactor stages that collect larger particle sizes (Stages 1–3) and use of the experimental trilayer filter assembly in Stage 8 to focus the exposure assessment on submicrometer particles likely impacted estimates of MMAD and the respirable mass concentration. Specifically, the exclusion of impactor Stage 3 (cut-point 9.8 μm) resulted in the collection of all particles >6 μm on Stage 4 of the impactor, hence causing an overestimation of the respirable concentration. A sensitivity analysis was conducted to quantify the error in the respirable mass concentration from impactors used without a Stage 3. Impactor data from four jobs at the same facility (reported by Kent *et al.*, 2001) using six-stage impactor samplers (Stages 3–8 and the final filter) were used to estimate the respirable concentration. Stages 3 and 4 and stage 8 and the final filter were then combined to simulate the impactor configuration in the present study and the respirable mass concentration was recalculated. The respirable mass concentration was overestimated in our impactor configuration by a mean of 11% (range 8–16%). This in part explains why in some instances, respirable concentrations were close to or higher than the CFC total concentrations. Furthermore, the exclusion of the upper stages of the impactor prohibited the estimation of the inhalable or thoracic beryllium concentrations, which in turn prevents the evaluation in epidemiological studies of the relevance of large particles in eliciting BeS. Finally, the impactor sampler is not efficient for collecting large particles, and large correction factors are applied to the upper stages of the impactor to account for these losses. Since the upper stages were not used in this impactor configuration, appropriate correction factors could not be applied to account for the losses of larger particles, and hence, the mass concentration for sum of all stages is underestimated. Despite these limitations, an improved understanding is presented in this study on the occurrence of respirable exposures in processes known to confer higher risk of BeS and CBD, including information on the various forms of beryllium and associated solubilities. The use of these data in epidemiological study is an improvement over metrics currently used (i.e. the GA, BZ, or DWA) that are not associated with biologically meaningful fractions.

CONCLUSIONS

This study provides a detailed evaluation of small particle exposure characteristics associated with processes in a beryllium manufacturing facility. The results indicate that exposure aerosol in this primary production facility consists of large particles, respirable, and particles <1 μm. Highest respirable and particle size <1 μm concentrations were observed in oxide production and pebbles plant process areas, which have historically been associated with elevated risk of BeS and CBD; these same areas were not among the highest total beryllium concentrations obtained from CFC samples. Large variation was observed in chemical forms and their associated solubilities in biological fluids among process areas. These results suggest that particle size distribution may be a physical factor to consider in exposure assessment and along with chemical (form of beryllium) and physicochemical (material solubility in biological fluids) exposure factors, may help to improve exposure assessment and reduce exposure misclassification.

FUNDING

The industrial hygiene survey conducted in March 1999 was a joint effort between NIOSH and Brush Wellman Inc.; NIOSH supported staff time for the sample and data collection and analysis. The June to August 1999 industrial hygiene survey was conducted entirely by Brush Wellman Inc. as part of their workplace environmental surveillance.

Acknowledgements—The authors thank Drs Igor Burstyn, Mark Hoover, and Rena Saito for their review of this manuscript, Dr Michael McCawley for conducting the 1999 impactor survey, Nicole Edwards and Brian Tift for data management, and William Miller and Dr James Deddens for their useful discussions on statistical methods for analyzing data below the LOD. Competing interests: M.S.K. is employed by Brush Wellman Inc., the owner of the beryllium manufacturing facility described in this report.

APPENDIX 1

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 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]
4	6.0	21.10[a]	0.89	6	>18[e]	12	0.028
5	3.5	4.75	0.95	3.5	6	4.75	0.360
6	1.55	2.53	0.96	1.55	3.5	2.53	0.819
7	0.93	1.24	0.97	0.93	1.55	1.24	0.962
8+*F*	0	0.52[a]	1	0	0.93	0.47	0.986

[a] PS-D_p is the halfway between the cut-point of Stage i and Stage i−1 ($Dp = ([Dp_i + Dp_{i-1})/2$). The PS-$D_p$ for the first stage and *F* are preselected by convention (Marple, 1980).

[b] The collection efficiency for each stage is obtained from Marple (1980).

[c] MP is the mid point of the LL and UL for each stage (MP = [(UL−LL)/2]).

[d] The respirable factors for each stage are obtained from the International Organization for Standards (ISO) size-selective curves together with Simpson's rule. For example, the respirable factor for each stage is calculated as: Respirable 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 LL, MP, and UL particle size for each stage based on the ISO curve.

[e] The UL particle size diameter for the top stage is surmised from Kent *et al.*, (2001). Neither the MP nor the UL contributes toward respirable mass concentration.

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