Final Progress Report

Dose of Beryllium Causing Beryllium Sensitization and Disease

April 15, 2005

National Institutes of Occupational Safety and Health: 5 R01/CCR815751
Occupational Radiation and Energy-related Health Research Grants
Non-cancer Morbidity and Mortality Outcomes.

Division of Environmental and Occupational Health Sciences
National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206

Lee S. Newman, MD, MA,
Principal Investigator, Division of Environmental and Occupational Health Sciences,
National Jewish Medical and Research Center, Denver, Colorado
Department of Medicine and Department of Preventive Medicine and Biometrics,
University of Colorado School of Medicine, Denver, Colorado

This research was supported by the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health,
Grant Number: R01/CCR815751

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BeS - Beryllium Sensitization

CBD - Chronic Beryllium Disease

BeLPT - Beryllium Lymphocyte Proliferation Test

LTW- Lifetime Weighted Average

DAM - Daily air monitoring

UTL - 95% upper tolerance limit

ABSTRACT

Chronic beryllium disease (CBD) and beryllium sensitization (BeS) continue to occur in the modern beryllium industry, despite efforts to reduce exposure. This disease is the consequence of a cell-mediated hypersensitivity immune response to beryllium, and may preferentially affect those exposed individuals with genetic susceptibility to beryllium. There appears to be an atypical dose-response relationship between beryllium exposure and disease with both genetics and features of exposure contributing independently to the risk of BeS and CBD. Studies suggest that features of exposure, such as particle size, may be important in determining risk for CBD. We set out to determine the personal beryllium dose that produces BeS and CBD in a beryllium machining plant and examined the relationship of particle size to the development of BeS and CBD.

Methods. We examined the personal daily beryllium exposures for new employees in a precision beryllium machining plant. New workers wore a personal sampling pump each day for the first three months of employment. We also examined exposure to beryllium and the presence of BeS and CBD in a cohort of workers in at this facility. Twenty cases of BeS or CBD were compared to 206 worker controls in a case-control study. Exposure for each job title was measured using cascade impactors placed in the workers breathing zone to measure total beryllium exposure and exposure to particles < 6 μm and < 1 μm in aerodynamic diameter. Cumulative exposure was calculated as Σ (Job Title Exposure Estimate x Years in Job Title). Individual lifetime-weighted (LTW) exposure was calculated as Σ [(Job Title Exposure x Years in Job Title)/Total Years Employment)]. We also assessed the agreement of individual personal sampling to the routine air sampling collected by the plant.

Results. Personal daily exposures for new employees were below the plant action level of 0.2 μg/m^3 for 90% of workers participating. Cases of BeS and CBD in this plant were more likely to have worked as a machinist (odds ratio [OR], 4.4; 95% confidence interval [CI], 1.1 to 17.5) than controls. The median cumulative exposure was consistently greater in cases compared to controls for all exposure estimates and particle size fractions, although not statistically significant. Median cumulative exposure was 2.9 μg/m^3-yrs in cases vs. 1.2 μg/m^3-yrs in controls for total exposure and 1.7 μg/m^3-yrs in cases vs. 0.5 μg/m^3-yrs in

controls for exposure to particles less than 6 μm in diameter. The median LTW exposure was 0.25 $\mu g/m^3$ in both cases and controls. The median LTW exposure to particles less than 6 μm was 0.20 $\mu g/m^3$ in cases compared to 0.14 $\mu g/m^3$ in controls. The differences in cumulative and lifetime-weighted exposure were not statistically significant. None of the 22 workers with LTW exposure less than 0.02 $\mu g/m^3$ had BeS or CBD. Twelve (60%) of the cases had LTW exposures greater than 0.20. Mean and median exposures for daily air monitoring (DAM) were significantly lower than median exposures for the systematic sampling approach with exposures from the systematic sampling approach ranging from 0.06 $\mu g/m^3$ to 0.13 $\mu g/m^3$ and the median exposures for daily monitoring ranging from 0.02 $\mu g/m^3$ to 0.08 $\mu g/m^3$. The 95% upper tolerance limit (UTL) calculated from the systematic sampling approach data was effective in predicting that fewer than 5% of the exposures reported in the daily air monitoring data would exceed the UTL for six of the seven operations.

Conclusions: In conclusion, increased cumulative and lifetime weighted exposure to total and respirable beryllium was observed in cases of CBD and BeS compared to the controls. Despite the lack of statistical significance, these results support efforts to control beryllium exposure in the workplace. In addition routine air monitoring performed by the plants for target level compliance may overestimate median beryllium exposures. However, the use of the Upper Tolerance Limit (UTL) appears to be relatively effective in controlling exposures below a given target level. This study suggests that exposures causing BeS may be lower than those reported using data from systematic exposures assessments.

HIGHLIGHTS/SIGNIFICANT FINDINGS

Daily air monitoring of employees shows that plant-wide exposures are generally low and significantly below the 2.0 $\mu g/m^3$ standard for beryllium. Daily average exposures for the majority of workers sampled were below 0.08 $\mu g/m^3$ and 89% of detectable samples were below the plant exposure target level of 0.2 $\mu g/m^3$.

Increased cumulative and lifetime weighted exposure to total and respirable beryllium was observed in cases of CBD and BeS compared to the controls. Despite the lack of statistical significance, these results support efforts to control beryllium exposure in the workplace. Although 60% of workers with BeS or CBD had lifetime weighted average exposures over the plant's 0.2 $\mu g/m^3$ target level, there were no cases of BeS or CBD among the 22 workers with LTW exposure less than 0.02 $\mu g/m^3$. These findings suggest that maintaining exposures below this level may be protective in preventing BeS.

Routine air monitoring performed by the plant for target level compliance may overestimate median personal beryllium exposures. The use of the Upper Tolerance Limit (UTL) appears to be relatively effective in controlling exposures below a given target level. These analyses suggest that exposures causing BeS may be lower than those reported using data from systematic exposures assessments.

TRANSLATION OF FINDINGS

Exposure levels below 0.02 $\mu g/m^3$ may protect the majority of workers from developing BeS and CBD. However, personal daily monitoring suggests that although overall beryllium levels in this precision machining plant are generally low, sporadic excursions over the plant target level and the OSHA standard continue to occur. Given these occurrences, efforts should be made to continue personal sampling of all employees and determine exposure circumstances that result in excursions.

Analysis of routine air monitoring performed by the plant for target level compliance may overestimate median personal beryllium exposures as measured by daily personal sampling. Managing exposures in the plant using the Upper Tolerance Limit (UTL) appears to be relatively effective in controlling exposures below a given target level.

OUTCOMES/RELEVANCE/IMPACT

Although BeS and CBD continue to occur even when plant-wide exposures are targeted well below the OSHA, these results suggest that maintaining exposures below 0.02 $\mu g/m^3$ may be protective in preventing BeS and CBD. Despite efforts to control exposures, excursions still occur especially in specialty operations. The use of the Upper Tolerance Limit (UTL) appears to be relatively effective in controlling exposures below a given target level.

SCIENTIFIC REPORT

Background

Exposure to beryllium results in the granulomatous disorder called chronic beryllium disease (CBD) in 2-16% of exposed individuals (1-7) . Cases continue to occur in the modern beryllium industry, despite efforts to reduce exposure. There appears to be an atypical dose-response relationship between beryllium exposure and disease, as both beryllium sensitization (BeS) and CBD have occurred in persons with minimal and casual exposure (8-12) and in family members of beryllium workers (13) . Although the OSHA standard for daily weighted average beryllium exposure is set at 2 $\mu g/m^3$ (14) , BeS and CBD have been reported in plants with average exposures below that standard (6, 12) . These findings are consistent with our current understanding of the mechanism underlying BeS and CBD. This disease is the consequence of a cell-mediated hypersensitivity immune response to beryllium (15-18) , and may preferentially affect those exposed individuals with genetic susceptibility to beryllium (17, 19-21) . Both genetics and features of exposure--such as working as a machinist--contribute independently to the risk of BeS and CBD (4-6, 22) . Our most recent work demonstrates that certain processes, such as machining of beryllium, produce a high proportion of highly respirable, submicron (<1 µm in aerodynamic diameter) beryllium particulate with high rates of lung deposition (23-25) . These data suggest that features of exposure, such as particle size, may be important in determining risk for CBD (6) .

Specific Aims

At a time when federal agencies – U.S. Department of Energy, Environmental Protection Agency, and Occupational and Safety and Health Administration – and the American Conference of Governmental Industrial Hygienists (ACGIH) are re-examining the merits of lowering the existing standard, it is still not known how low an exposure is sufficient to produce BeS and CBD. The mounting evidence suggests that adherence to the current standard is not sufficiently protective (6, 9, 11, 12) , but the dose and characteristics of beryllium exposure that must be avoided remain to be determined. Such information will prove valuable in preventing CBD, and would help advance our understanding of dose-response relationships for this and other occupational, immune hypersensitivity disorders. Our central hypothesis is that there is a definable level of exposure below which BeS and CBD will not occur, and that this level is well below the current 2$\mu g/m^3$ standard. Thus, we proposed the following Specific Aims:

Specific Aim 1. To determine the personal beryllium dose that produces beryllium sensitization (BeS) and chronic beryllium disease (CBD) in beryllium machining plant workers. To do this we planned to test the following hypotheses:

A) The 2 $\mu g/m^3$ standard does not protect against BeS and CBD.

B) Cases of BeS and CBD have higher measured average total beryllium exposures than do noncases within the same workforce.

C) Individuals develop BeS and CBD with no daily measurable excursions above the 2 μg/m^3 standard for an 8 hour time weight average (TWA).

Specific Aim 2. To characterize the beryllium aerosol and lung deposition that produce BeS and CBD in beryllium machining plant workers. To do this we planned to test the following hypotheses:

A) Individuals who develop BeS and CBD work in processes or work areas where higher percentages of submicron (<1 μM mass median aerodynamic diameter) are found, as compared to processes and work areas where BeS and CBD do not occur.

B) BeS and CBD cases have higher estimated lung deposition of beryllium than do noncases.

Progress Towards Achievement Of Specific Aims

Specific Aim 1. To determine the personal beryllium dose that produces BeS and CBD in beryllium machining plant workers.

We anticipated that we would hang pumps each day for three months on a total of 75 new employees, over the course of three years. Due to a decrease in business at the Axsys plant, fewer new employees were hired than anticipated. In addition, the plant had rehired a number of employees who had been previously laid-off and thus had a previous exposure history making them ineligible for the study protocol. With this limitation we addressed our question of whether workers with higher exposures were at increased risk for BeS and CBD by expanding the personal sampling that had been previously conducted by our group at the plant in order to complete the characterization of beryllium exposure. Using these data we generated a job exposure matrix for Axsys workers using estimates of total exposure and exposure differentiated by particle size. Using this altered methodology we were able to address two of the three hypotheses of the aim: a) the 2 μg/m^3 standard does not protect against BeS and CBD; and b) cases of BeS and CBD have higher measured average total beryllium exposures than do noncases within the same workforce. Since none of the employees we evaluated with daily sampling developed BeS or CBD we were unable to address the third hypothesis under this aim; c) individuals develop BeS and CBD with no daily measurable excursions above the 2 μg/m^3 standard for an 8 hour time weight average (TWA).

Specific Aim 2. To characterize the beryllium aerosol and lung deposition that produce BeS and CBD in beryllium machining plant workers.

Using the alternative protocol and were able to address the hypothesis that a) individuals who develop BeS and CBD work in processes or work areas where higher percentages of submicron (<1 μM mass median aerodynamic diameter) are found, as compared to processes and work areas where BeS and CBD do not occur and b) BeS and CBD cases have higher estimated lung deposition of beryllium than do noncases.

Although we were unable to perform sampling on 75 individuals as anticipated, we are planning to continue this protocol with the plant to collect daily sampling on additional new employees within the next year.

Methods

Daily Personal Sampling: We performed personal sampling on new employees at the Axsys plant in Cullman, AL. New employees were interviewed by our industrial hygiene assistant regarding their previous opportunities for beryllium exposure. If it was determined that they had no previous exposure, then they underwent venipuncture to determine their baseline blood BeLPT status (Clinical Immunology Laboratory, National Jewish Medical and Research Center, Denver, CO). Only those individuals with negative industrial hygiene histories for beryllium and with negative baseline blood BeLPT completed the three-month protocol. All workers entering the study completed a brief questionnaire that collected demographic and smoking status information

On their first day working in the plant, participants were trained on how to use the personal monitors. A personal total beryllium-sampling pump was hung on their lapel in their breathing zone. The total beryllium sampler consisted of a pre-loaded 37-µm cassette with a 0.8 µm pore-sized multiple cellulose ester filter utilized in a closed-face configuration. This sampling method is the personal sampling method currently used for beryllium in accordance with current NIOSH guidelines. Our industrial hygiene assistant provided study subjects with pumps charged and calibrated at the beginning of each of their work shifts. They wore the pump throughout the workday. At the end of each shift that they work in the plant, they completed a brief checklist of (a) machines on which they worked that day, (b) material used and (c) other areas of the plant visited. This was attached to the pump and collected by the industrial hygiene assistant who gathered all pumps, prepared filters for analysis, logged data, and calibrated and recharged pumps for the next work day. The assistant sent filters to DataChem (Salt Lake City, UT) for analysis. The method of analysis was NIOSH Method 7300 using a Fisons Accuris Radial ICP Spectrometer.

At the end of a study subject's three months, the worker had a second blood BeLPT performed. We anticipated that we would hang pumps each day for three months on a total of 75 new employees, over the course of three years. Due to a decrease in business at the Axsys plant fewer new employees were hired than anticipated. In addition, the plant had rehired a number of employees who had been previously laid-off and thus had a previous exposure history making them ineligible for the study protocol.

With this limitation we addressed our question of whether workers with higher exposures were at increased risk for BeS and CBD by expanding the personal sampling that had been previously conducted by our group at the plant in order to complete the characterization of beryllium exposure. Using these data we generated a job exposure matrix for Axsys workers using estimates of exposure.

Cumulative and Lifetime-weighted average exposure estimates:
Personal sampling for beryllium exposure of machining jobs within the plant was conducted previously from June 1996 to February 1997 and included only the machining processes of lap, lathe, mill, grind, and deburr. In September 1999 we returned to the plant to complete sampling of the major non-machinist job titles including assembly, inspection, chemical finishing, shipping and receiving, maintenance, engineering, specialty cell, electron-discharge machining (EDM), management and administration.

Personal impactor samples were taken in the workers' breathing zone with Series 290 Marple Personal Cascade Impactors (Graesby-Anderson, Atlanta, GA) attached to the lapel of the workers. The five stages utilized were designed to give particle size cut points of 0.6 μm, 1.0 μm, 6.0 μm, and 10 μm. Samples were collected over two shifts to ensure an adequate collection of beryllium on the impactor filters.

To ensure comparability with other studies, we chose to generate exposure estimates using three measures of central tendency (mean, median and geometric mean). The cumulative exposure was calculated using the estimate from the three measures of central tendency. We computed a lifetime-weighted average beryllium exposure by dividing cumulative median exposure, expressed in $\mu g/m^3$-years, by the total number of years employed at the plant (Σ[Median Estimate of Job Title Exposure*(Years in Job Title/Total Years Employment)]).

Using the methods detailed above we also collected particle-sized samples using Series 290 Marple Personal Cascade Impactors (Graesby-Anderson, Atlanta, GA). The impactors collected samples with particle size cut-points of 0.6 μm, 1.0 μm, 6.0 μm, and 10 μm. We chose to analyze exposure by particle size less than 6μm and particle size less than 1 μm. For exposure to particle sizes less than 6 μm and particle size less than 1 μm, the masses from the appropriate stages were summed and divided by the cubic meters of air supplied during the sampling period to obtain a TWA exposure for the respective particle size fraction. The theoretical number of particles per stage of the cascade impactors was calculated using methods previously published.

By the end of 1999, 235 workers had the opportunity to participate in two phases of the medical surveillance program and 226 participated in the study. Twenty of the workers were identified with either BeS (n=7) or CBD (n=13). We then calculated and compared both cumulative and lifetime-weighted average exposures for BeS cases and for noncases.

Comparison of Systematic Exposure Assessment to Daily Air Monitoring:
Due to fewer new employees than anticipated in the study, we also used the data we collected on new employees to compare this daily air monitoring data (DAM) to routine air monitoring (RAM) data performed at the plant. RAM samples for comparison were selected to include six months prior to the new employee starting, the months corresponding to the dates in the personal sampling dataset, and an additional six months after the daily air monitoring stopped. Sampling results from the DAM dataset were adjusted upward to account for the differences in the reporting limits. This adjustment involved setting all sampling results less than 0.02 $\mu g/m^3$ equal to 0.02 $\mu g/m^3$. Ninety-five percent upper tolerance limits were calculated for processes in the RAM dataset using LogNorm Software (InTech Software Corp.) assuming

data follow a lognormal distribution. Dataset by process comparisons were made using the Wilcoxon Rank Sum test.

Results

<u>Daily Personal Sampling</u>. Ten new employees at the precision machining plant enrolled in the study. There were a total of 568 personal monitoring samples were performed. Of those samples, we found that less than half (41%) of the samples were detectable. Of detectable samples, 89% were below the Axsys target level of 0.2 $\mu g/m^3$. Peak exposures for the participants had a wide range from 0.1 $\mu g/m^3$ to 3.8 $\mu g/m^3$, with 3 daily samples (0.5%) greater than the OSHA standard of 2.0 $\mu g/m^3$. Data on the ten participants are presented in Table 1. Three of the 10 worked in non-routine jobs in production areas as a maintenance worker, engineer and shop manager. Two others worked on a gas bearing project that only occasionally involved work with pure beryllium metal. Those working in the beryllium production areas (EDM, Lapper/Polisher, Machinist) had a higher percentage of detectable beryllium samples with the highest peak exposure reaching 3.2 $\mu g/m^3$ in the lapping and polishing area. No participants have developed BeS, thus far

Table 1. Daily Personal Monitoring for New Employees in a Beryllium Machining Plant.

Job Title	% Samples with Detectable Beryllium	Maximum Exposure $\mu g/m^3$	Average Exposure $\mu g/m^3$	% Samples over Axsys Target Level
EDM Operator	100%	0.2	0.08	0%
EDM Operator	81%	0.3	0.05	5%
Lapper/Polisher	56%	3.2	0.42	32%
Machinist	44%	0.6	0.04	2%
Engineer	20%	0.1	0.01	0%
Gas Bearings	5%	0.1	0.003	0%
Gas Bearings	11%	0.1	0.005	0%
Inspector, Calibrator	16%	0.1	0.005	0%
Maintenance	52%	0.3	0.03	2%
Shop Manager	73%	0.2	0.03	0%

Demographic and Employment Variables

Twenty of the workers in our case-control study were identified with either BeS (n=7) or CBD (n=13). Of the 20 cases, 18 reported experience as a machinist in the plant. Cases were more likely to have worked as a machinist (odds ratio [OR], 4.4; 95% confidence interval [CI], 1.1 to 17.6) compared to the 206 control workers. No statistically significant differences were observed for age, employment duration or smoking status (ever/never).

Beryllium Personal Impactor Sampling

For the 100 PI beryllium samples, the median total beryllium exposure was 0.13 $\mu g/m^3$ (range 0.006 to 22.62) with the following distribution: 9 samples > 2 $\mu g/m^3$, 4 samples < 2 $\mu g/m^3$ and > 1 $\mu g/m^3$; 37 samples < 1.0 $\mu g/m^3$ and > 0.2 $\mu g/m^3$ and 50 samples < 0.2 $\mu g/m^3$. Samples exceeding 2 $\mu g/m^3$ were measured in the following job titles: deburrer (6 samples) and lathe operator, lapper, and grinder (1 sample each).

The arithmetic mean, median and geometric mean of the PI samples for each job title and particle size fraction are shown in Table 2. The highest samples were observed in the lathe operator, deburrer and grinder job titles. With the exception of deburrer and grinder job titles, the values for the median and geometric mean of the total beryllium samples were similar in magnitude. The values for the arithmetic mean of total beryllium samples were consistently larger than the median or geometric mean for the machinist job titles, reflecting the skewed distribution of the samples. In contrast, the values for the arithmetic mean of the samples for the non-machinist job titles were similar in magnitude to the median and geometric mean. This was evident even in non-machinist job titles with higher sample values such as chemical finisher and maintenance worker.

The particle size distribution was determined for all job titles. With the exception of EDM, the machinists had consistently higher exposure to particles less than 1 μm. The particle size distributions for the non-machinists with comparatively high exposure ("chemical finisher" and "maintenance worker") were composed predominantly of particles greater than 1 μm.

Cumulative and Lifetime-Weighted Exposure

Table 3 compares exposures of cases and controls, including cumulative occupational exposure for total beryllium, cumulative exposure to particles < 6 μm and to particles < 1 μm, with exposure based on arithmetic mean or median of the PI samples. Results based on the geometric mean exposure estimate (data not shown) were comparable to those based on the median exposure estimate. No significant differences were observed in any cumulative exposure regardless of the measure of central tendency used for the exposure estimate. The medians of the cumulative exposures, however, were consistently larger for the cases compared to controls. This trend was greatest with cumulative exposure measured by particle size < 6 and < 1 μm where the medians of the cumulative exposure for cases were three times greater than for controls. Similarly, median cumulative particle number was greater for cases than for controls, but the difference did not achieve statistical significance (Table 3).

As shown in Table 4, the LTW total exposure was the same in cases compared to controls. However, the LTW exposure for particles < 6 μm and < 1 μm were greater for the cases than the controls, although the differences were not statistically significant.

Table 2. Comparison of Time-Weighted Average Exposure Concentrations in $\mu g/m^3$ for each Job Title Based on Results from Sampling with Personal Impactors

		TOTAL EXPOSURE				
Job Title	N	Mean	SD	Median	Geometric Mean	(σSD)
Lathe	7	0.89	0.98	0.60	0.43	4.39
Lap	12	0.44	0.74	0.13	0.19	3.39
Deburr	15	3.72	6.54	0.74	1.33	3.98
Grind	11	1.47	3.06	0.35	0.46	4.43
Mill	14	0.39	0.34	0.25	0.26	2.93
Tooling	4	0.03	0.01	0.03	0.03	1.91
Assembly	1	0.08	.	0.08	0.08	.
Inspector	4	0.07	0.04	0.06	0.06	1.85
EDM	4	0.05	0.03	0.04	0.04	1.62
Chemical Finishing	4	0.49	0.13	0.47	0.48	1.29
Shipping/Receiving	4	0.03	0.01	0.02	0.03	1.55
Maintenance	4	0.19	0.11	0.18	0.16	2.05
Engineering	4	0.01	0.00	0.01	0.01	1.16
Shop Management	4	0.06	0.07	0.04	0.03	4.50
Front Administration	4	0.01	0.01	0.01	0.01	1.95
Specialty Cell	4	0.01	0.00	0.01	0.01	1.37

Note: For values < 0.005 a value of 0.00 is listed.

Table 3. Cumulative Beryllium Exposure for Cases Compared to Controls (Particle Size < 6 μm and < 1 μm), Based on Geometric Mean, Arithmetic Mean or Median of Personal Cascade Impactor Samples.

Cumulative Exposure[a], Median μg/m^3-yrs or Median particle #/m3-yrs (Range, 1st to 3rd Quartile)			
	Employment Duration		
	Cases (n=20)	Controls (n=206)	P value[b]
Geometric Mean			
Particles < 6 μm	1.69 (0.31, 3.09)	0.50 (0.05, 2.93)	0.36
Particles < 1 μm	1.03 (0.18, 1.69)	0.32 (0.03, 1.47)	0.29
Arithmetic Mean			
Particles < 6 μm	3.26 (0.35, 5.98)	0.87 (0.07, 6.09)	0.32
Particles < 1 μm	1.69 (0.22, 3.30)	0.35 (0.05, 2.68)	0.30
Median Exposure			
Particles < 6 μm	1.33 (0.33, 3.50)	0.46 (0.05, 2.98)	0.27
Particles < 1 μm	0.77 (0.22, 2.21)	0.33 (0.04, 1.94)	0.22
Particle Number (x10^8)	1.35 (0.21, 4.11)	0.51 (0.05, 3.24)	0.19

[a] Cumulative exposure = Σ(Job Title Exposure*Years in Job Title).
[b] Wilcoxon Rank Sum Test.

Table 4. Lifetime-Weighted Beryllium Exposure for Cases Compared To Controls, Precision Beryllium Machining Plant

Variable	Median Lifetime-Weighted Exposure[a], μg/m3 (Range, 1st to 3rd quartile)		
	Cases (n=20)	Controls (n=206)	P value[b]
Total Exposure	0.25 (0.11, 0.34)	0.25 (0.06, 0.34)	0.72
Particles < 6 μm	0.20 (0.06, 0.21)	0.14 (0.02, 0.22)	0.62
Particles < 1 μm	0.13 (0.04, 0.16)	0.11 (0.01, 0.14)	0.31

[a] Lifetime-Weighted Exposure = Σ [Median Estimate of Job Title Exposure*(Years in Job Title/Total
Years Employment)] with years in machinist job titles multiplied by 1.25 to adjust for longer workdays.
[b] Wilcoxon rank sum test.

Of the cases, 17 (85%) had LTW exposures greater than 0.10 μm. Table 5 shows the distribution of LTW exposure for cases and controls. We observed no BeS or CBD among the 22 workers with LTW exposure less than 0.02 $\mu g/m^3$. Of the 33 workers with LTW exposure less than 0.035 $\mu g/m^3$, only one had CBD. Twelve (60%) of the cases had a LTW exposure greater than 0.20 $\mu g/m^3$.

Table 5. Distribution of Lifetime-Weighted Exposures [a]
for Cases and Controls, Precision Beryllium Machining Plant

Lifetime-Weighted Exposure ($\mu g/m^3$)	Cases (N)	Controls (N)
< 0.02	0	22
0.02 to 0.10	4	46
0.10 to 0.20	4	29
0.20 to 0.50	10	72
0.50 to 1.00	2	37
Total	20	206

[a] Lifetime-Weighted Exposure = Σ [Median Estimate of
Job Title Exposure*(Years in Job Title/Total Years Employment)].

<u>Comparison of Systematic Exposure Assessment to Daily Air Monitoring</u>:

We compared daily air monitoring (DAM) to routine air monitoring (RAM) and found that RAM may overestimate median beryllium exposure concentrations and may miss significant peak exposures for processes with high exposure variability (Table 6). Mean and median exposures for DAM data were significantly lower than median exposures for the RAM sampling approach for six of seven operations ($p < 0.05$). Median exposures from the RAM approach ranged from 0.06 $\mu g/m^3$ to 0.13 $\mu g/m^3$ while the median exposures for DAM data ranged from 0.02 $\mu g/m^3$ to 0.08 $\mu g/m^3$ The ratio of the median for the RAM approach to the median for the DAM data for these operations ranged from 1.35 to 3.35 $\mu g/m^3$. The mean exposure for beryllium lapping was significantly higher ($p < 0.05$) for daily sampling than for the systematic sampling approach (0.35 $\mu g/m^3$ vs. 0.14 $\mu g/m^3$).

The 95% upper tolerance limit (UTL) calculated from the RAM approach data was effective in predicting that fewer than 5% of the exposures reported in the DAM data would exceed the UTL for six of the seven operations. Exposures for beryllium lapping reported in daily air monitoring exceeded the UTL from the systematic sampling approach 24% of the time. The use of the 95% Upper Tolerance Limit from RAM data appears to be relatively effective in controlling exposures below a given target level.

Table 6: DAM and RAM sampling results by process.

	Samples		%≤ 0.02 μg/m³		%≤ 0.05 μg/m³		%≤ 0.10 μg/m³		%≤ 0.20μg/m³	
	RAM	DAM	RAM	DAM	RAM	DAM	RAM	DAM	RAM	DAM
EDM	17	62	0	26	100	31	94	14	0	3
Lapping	19	63	0	43	89	43	58	35	5	32
Non-Be machining	26	122	0	0	100	2	15	0	0	0
Maintenance	29	64	3	2	96	20	72	6	21	2
Engineering	44	58	0	9	93	10	2	0	0	0
Inspection	33	61	0	18	73	3	0	0	0	0
Administration	20	64	0	50	100	15	4	15	0	0

Discussion and Conclusions

This case-control analysis of workers in a precision beryllium machining plant is the first to use personal sampling with total and particle size fractions to investigate the relationship between beryllium exposure and health effects. The study confirmed the increased risk of beryllium sensitization and disease in workers performing certain processes, specifically machining beryllium. Nine of the 100 samples were above the 2 μg/m³ standard and all nine were in machining processes. This suggests that daily excursions in machining may contribute to the increased risk of BeS and CBD for machinists.

The exposure levels at which workers developed CBD and BeS were predominantly below the U.S. Occupational Safety and Health Administration's current permissible exposure limit (PEL) of 2 μg/m³ suggesting that the current PEL does not protect workers completely from beryllium related health effects. Although not statistically significant, the median cumulative exposures were consistently higher in the cases than in the controls.

Cumulative occupational beryllium exposure did not differ significantly in cases and controls. However, the median cumulative exposure was higher in cases than in controls for all categories of exposure estimates (arithmetic mean, geometric mean, median) and all particle size fractions (total exposure, < 6 μm, < 1 μm). While the differences we observed were not significant, the power of our tests to detect a difference between cases and controls was limited. For example, the power was only 0.15 for total cumulative exposure and 0.23 for cumulative exposure to particles less than 6 μm using the median exposure estimate based on our current sample size. Consequently, we little chance of finding statistically significant differences if, in fact, they exist.

The inability to detect a significant difference in cumulative or lifetime-weighted exposure between cases and controls may also reflect the role of other factors in determining sensitization to beryllium. For example, genetic susceptibility markers have been associated with CBD risk. Richeldi et al. reported a relationship between CBD and the allelic substitution of a Glu69 in the HLA-DPB1 gene. This increased risk is related to specific Glu69- containing alleles and their copy number (homozygous or heterozygous) and may be independent of process related risks. Other factors may play a role in defining exposure-related risk such as the form of beryllium (metal, oxide, or alloy, the use of coolant, peak exposure to beryllium, or hygiene and handling practices that might allow beryllium to be carried outside of plants and, thus, result in both work and non-workplace exposures.

Analysis of the RAM and DAM data sets suggests that systematic sampling approaches that lack statistical rigor may overestimate median beryllium exposures. However, the use of the Upper Tolerance Limit (UTL), even in systematic approaches lacking statistical rigor, appears to be relatively effective in controlling exposures below a given target level. This study also suggests that exposures causing beryllium sensitization may be lower than those reported using data from systematic exposures assessments.

In summary, our data support the process related risks associated with exposure to beryllium particularly for machinists. These risks occur despite exposure within the current OSHA permissible exposure limit of 2 $\mu g/m^3$. The observation that few of the cases occur in job titles with the lowest exposures suggests that control of exposure can reduce the prevalence of beryllium sensitization and chronic beryllium disease. Although cases and controls did not differ significantly in cumulative and lifetime-weighted beryllium exposure, the magnitude of the median exposure was consistently greater in the cases than the controls. Particle size may play a role in beryllium disease. However, in our study cumulative and lifetime-weighted exposure to smaller particle size fractions, as in total exposure, did not differ between cases and controls. Further investigation is warranted in larger cohorts to clarify the relationship between respirable beryllium exposure and development of beryllium sensitization and chronic beryllium disease.

PUBLICATIONS

Kelleher PC, Martyny JW, Mroz MM, Maier LA, Ruttenber AJ, Young DA, Newman LS: [2001] Beryllium Particulate Exposure and Disease Relations in a Beryllium Machining Plant. J Occup Environ Med 2001; 43:238-249.

INCLUSION OF GENDER AND MINORITY STUDY SUBJECTS

The 'gender and minority inclusion table' is attached. The gender and ethnic distribution in this study reflects the hiring practices of this precision machining workforce and matches the demographics of the town in which the plant is located.

INCLUSION OF CHILDREN

Children were not involved in this study. Since this was an industry-based occupational study, all participants were adults.

MATERIALS AVAILABLE FOR OTHER INVESTIGATORS

No blood or cellular materials were retained from this study. Industrial hygiene sampling data from this project are still being analyzed by the study group.

LITERATURE CITED

1. Kriebel, D., N. L. Sprince, E. A. Eisen, I. A. Greaves, H. A. Feldman, and R. E. Greene. 1988. Beryllium exposure and pulmonary functions: A cross-sectional study of beryllium workers. *Br. J. Industr. Med.* 45:167-173.

2. Kriebel, D., J. D. Brain, N. L. Sprince, and H. Kazemi. 1988. The pulmonary toxicity of beryllium. *Am. Rev. Respir. Dis.* 137:464-473.

3. Kreiss, K., L. S. Newman, M. M. Mroz, and P. A. Campbell. 1989. Screening blood test identifies subclinical beryllium disease. *J. Occup. Med.* 31:603-608.

4. Kreiss, K., M. M. Mroz, B. Zhen, J. Martyny, and L. S. Newman. 1993. Epidemiology of beryllium sensitization and disease in nuclear workers. *Am Rev Respir Dis* 148:985-991.

5. Kreiss, K., S. Wasserman, M. M. Mroz, and L. S. Newman. 1993. Beryllium disease screening in the ceramics industry: Blood test performance and exposure-disease relations. *J. Occup. Med.* 35:267-274.

6. Kreiss, K., M. M. Mroz, L. S. Newman, J. Martyny, and B. Zhen. 1996. Machining risk of beryllium disease and sensitization with median exposures below 2 $\mu g/m^3$. *Am. J. Industr. Med.* 30:16-25.

7. Eisenbud, M., and J. Lisson. 1983. Epidemiological aspects of beryllium-induced non-malignant lung disease: A 30-year update. *J Occup Med* 25:196-202.

8. Eisenbud, M., R. C. Wanta, C. Dustan, L. T. Steadman, W. B. Harris, and B. S. Wolf. 1949. Non-occupational berylliosis. *J. Industr. Hyg. Toxicol.* 31:281-294.

9. Sterner, J. H., and M. Eisenbud. 1951. Epidemiology of beryllium intoxication. *Arch Industr Hyg Occup Med* 4:123-151.

10. Lieben, J., and F. Metzner. 1959. Epidemiological findings assciated with beryllium extraction. *Am Ind Hyg Assoc J* 20:494-499.

11. Shima, S. 1971. Hygienic control of beryllium (translation from Japanese). *Rodo no Kagaku* 26:36-46.

12. Cullen, M. R., J. R. Kominsky, M. D. Rossman, M. G. Cherniack, J. A. Rankin, J. R. Balmes, J. Kern, R. P. Daniele, L. Palmer, G. P. Naegel, K. McManus, and R. Cruz. 1987. Chronic beryllium disease in a precious metal refinery: Clinical, epidemiologic, and immunologic evidence for continuing risk from exposure to low level beryllium fume. *Am. Rev. Respir. Dis.* 135:201-208.

13. Newman, L. S., and K. Kreiss. 1992. Non-occupational chronic beryllium disease masquerading as sarcoidosis: Identification by blood lymphocyte proliferative response to beryllium. *Am Rev Respir Dis* 145:1212-1214.

14. Eisenbud, M. 1982. Origins of the standard for control of beryllium disease (1947-1949). *Environ. Res.* 27:79-88.

15. Newman, L. S. 1994. Beryllium lung disease: The role of cell-mediated immunity in pathogenesis. In: Immunotoxicology and Immunopharmacology. Dean, J. H., M. I. Luster, A. E. Munson, and I. Kimber ed. New York: Raven Press, Ltd., 377-393.

16. Kreiss, K., F. Miller, L. S. Newman, E. A. Ojo-Amaize, M. D. Rossman, and C. Saltini. 1994. Chronic beryllium disease: From the workplace to cellular immunology, molecular immunogenetics, and back. *Clin. Immunol. Immunopathol.* 71:123-129.

17. Newman, L. S. 1996. Immunology, genetics, and epidemiology of beryllium disease. *Chest* 109:40S-43S.

18. Newman, L. S. 1998. Immunotoxicology of Environmental and Occupational Metals. In: Zelikoff, J. T., and P. T. Thomas ed. London: Taylor and Francis, 27-39.

19. Newman, L. S. 1993. To Be^{2+} or not to Be^{2+}: Relating immunogenetics to occupational exposure. *Science* 262:197-198.

20. Richeldi, L., R. Sorrentino, and C. Saltini. 1993. HLA-DPβ1 glutamate 69: A genetic marker of beryllium disease. *Science* 262:242-244.

21. Stubbs, J., E. Argyris, C. W. Lee, D. Monos, and M. D. Rossmann. 1996. Genetic markers in beryllium hypersensitivity. *Chest* 109:45S.

22. Richeldi, L., K. Kreiss, M. M. Mroz, B. Zhen, P. Tartoni, and C. Saltini. 1997. Interaction of genetic and exposure factors in the prevalence of berylliosis. *Am. J. Indus. Med.* 32:337-340.

23. Mroz, M., J. Martyny, M. Hoover, R. Balkissoon, K. Kreiss, K. Ellis, and L. Newman. 1997. Exposure-response relationships for beryllium sensitization and disease. *Am. J. Respir. Crit. Care Med.* 155:A812.

24. Ellis, K., J. Martyny, R. Buchan, B. Bartleson, M. Hoover, and L. newman. 1998. A comparison of the particle size distributions for aerosols generated during wet grinding and dry deburring of beryllium. Atlanta, Georgia:

25. Martyny, J., M. Hoover, K. Ellis, B. Bartelson, M. Mroz, and L. Newman. 1998. Characterization of beryllium aerosols associated with machining operations. Atlanta, Georgia:

Principal Investigator/Program Director (Last, First, Middle):

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Dose of Beryllium Causing Beryllium Sensitization and Disease

Total Enrollment: 236 **Protocol Number:**

Grant Number: R01/CCR815751

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	0	1	0	1 **
Not Hispanic or Latino	24	211	0	235
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	24	212	0	236 *
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	0	0	1
White	23	212	0	235
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of All Subjects*	24	212	0	236 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	0	1	0	1
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	0	1	0	1 **

* These totals must agree.
** These totals must agree.