Biomonitoring for Beryllium: Experience With a U.S. Work Force

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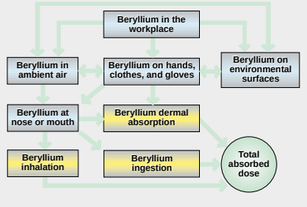
ABSTRACT

Experiments in animals indicate that beryllium (Be) has a very low bioavailability, a moderate to long half-life, and that urine is the primary route of excretion for absorbed Be. Studies conducted in the 1960s indicated that Be workers had elevated levels of urinary Be, but a correlation between levels of Be in urine or blood and airborne concentrations of Be in work areas could not be established. There have been suggestions that exposure in the Be industry may occur by other routes in addition to inhalation. Therefore, the purpose of this study was to determine whether a biomarker approach (using urine or blood) could be applicable to evaluating the extent and route of exposure using more modern analytical techniques. If so, the method would also be useful in assessing whether workplace behaviors or exposure interventions are effective in limiting human exposures to beryllium in the workplace. The population evaluated consisted of individuals working with beryllium metal, beryllium oxide, and alloys. A control population of administrative personnel from buildings that are separate from the manufacturing facility were included in the survey. Of the 193 urine samples collected, only 18 had detectable levels of Be (detection limit of 0.2 ug/L). Based on a comparison to nationwide data collected as part of the National Health and Nutrition Examination Survey (NHANES III), the data indicated that workers exposed to different forms of beryllium in the workplace had urinary levels that were indistinguishable from background levels in the United States. These preliminary results suggest that a more sensitive method for detecting beryllium in biological media is needed. Therefore, use of Be concentration in blood or urine as a biomonitoring tool for evidence of Be exposure will only be appropriate when the quantitative technique is sensitive enough to distinguish Be concentrations in exposed and unexposed populations.

INTRODUCTION

Chronic beryllium disease (CBD) is a hypersensitive immunological response to beryllium, resulting in granulomas in the lungs of affected individuals, which may progress with a mild to severe reduction in lung function. The possible mechanisms that lead to beryllium sensitization are currently being studied. It is not clear whether CBD is related only to direct pulmonary exposure to beryllium, or whether sensitization or disease outcome is related to systemic burdens of beryllium. To date, research has failed to establish a clear relation between inhalation exposure to beryllium and disease outcome. Therefore, a hypothesis is that total beryllium exposures (i.e., oral, dermal, and inhalation) may result in a systemic dose of beryllium that causes immunological sensitization. Subsequent inhalation exposures to small amounts of beryllium may then elicit the development of CBD.



If total exposure to beryllium is important in disease outcome, then absorption of beryllium from all exposure pathways (e.g., ingestion and dermal absorption as well as inhalation) is important.

The research reported here constitutes a "pre-pilot study," undertaken to determine whether a biomonitoring approach could be used to assess:

- Whether a biomarker exists for assessing human exposures to beryllium
- The appropriate biological matrix to measure (blood or urine)
- Whether spot urine samples or 24-hour samples are more informative
- Whether a biomarker might distinguish among different occupational exposure groups.

Using this biomonitoring approach, if total exposures exceed the amount that might be contributed from inhalation, then it would be possible to assess contributions from other pathways.

This poster is a visual representation of our journey with the analytical results from this pre-pilot biomonitoring effort of this U.S. workforce.

AVAILABLE LITERATURE

The available literature suggests that beryllium is detectable in the blood and urine of the general population in the U.S. and Europe. Additionally, workers inadvertently exposed to some forms of beryllium in the workplace demonstrate increased concentrations of beryllium in biological matrices. This suggests that current analytical methodologies are available to assess levels of beryllium in biological samples, and that occupational exposures should result in measurable increases of beryllium. Based on this information, a preliminary study was undertaken to assess beryllium concentrations in the blood and urine of individuals currently working in the beryllium industry.

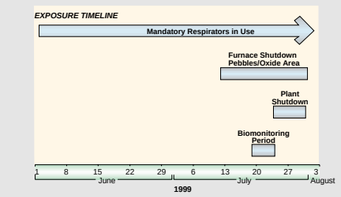
STUDY POPULATION

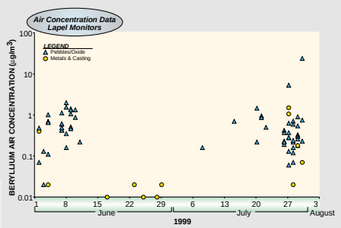
- Workers from several operations at the Brush Wellman beryllium production facility in Elmore, Ohio.
- Two different production areas of the facility, and a control group of administrative staff
  - Pebbles Plant: exposures to beryllium oxide and soluble salts
  - Metals and Casting: exposures to metal and alloys (e.g., BeCu, AlBe)
  - Administrative workers with negligible exposures.

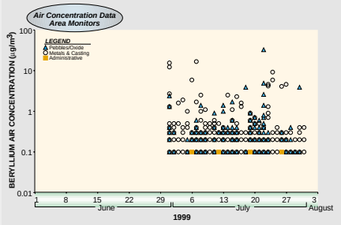
APPROACH

- Pilot Study Design
  - Collect urine and blood for several days
  - Discrete urine samples; each void over 3 days
  - Blood samples before and after work shift on day #1 and #3
  - Collect creatinine data on urine to adjust for hydration level
- Develop analytical methods to quantify beryllium
- Determine if spot, composites, or individual urinary voids are best to assess exposures
- Determine if levels of beryllium are different for different exposure groups
- Determine if urinary/blood beryllium correlates with inhalation exposures.

EXPOSURE ASSESSMENT







UNANTICIPATED RESULTS

URINE

	Percent Detected ∞0.2 µg/L	Percent Tentatively Identified < D.L. (0.1 µg/L)	Percent Undetected at (0.2 µg/L)	Range of Detected Be Conc. (creat. adj.) (µg/g creat.)
Population				
Pebbles/Oxide (n = 92)	20%	13%	67%	0.07–6.21
Metals & Casting (n = 40)	0%	0%	100%	--
Administrative (n = 61)	0%	2%	98%	--

BLOOD

	Percent Detected ∞0.2 µg/L	Percent Tentatively Identified < D.L. (0.1 µg/L)	Percent Undetected at (0.2 µg/L)
Population			
Pebbles/Oxide (n = 27)	0%	11%	89%
Metals & Casting (n = 22)	0%	5%	95%
Administrative (n = 17)	0%	0%	100%

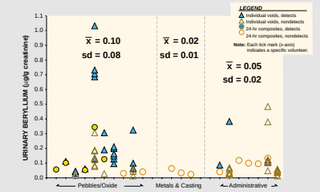
METHOD DEVELOPMENT

The initial data received was surprising because of the high level of non-detect data. Based on the available literature, we expected 25% of samples of an unexposed population to be above the analytical detection limit. Therefore we undertook a research effort to determine whether a more sensitive method of analysis could be used. The method development sequence, and the most recent data are presented below.

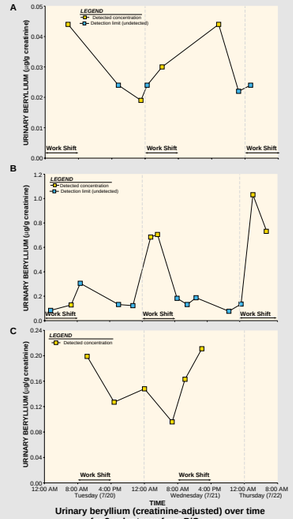
Summary of Analytical Techniques Used for Analysis of Beryllium in Urine

D.L. 0.001 µg/L in seawater 0.05 µg/L in urine	**Sample Preparation:**	Fe/Pd preconcentration method developed for seawater
	Analysis:	ICP–MS
	Issues:	Mixed results. Results not consistently reproducible. Apparent matrix problems.
D.L. Not determined	**Sample Preparation:**	Acid digestion preconcentration
	Analysis:	GFAA
	Issues:	Extensive interference from salts in urine
D.L. Not determined	**Sample Preparation:**	None
	Analysis:	GFAA using external calibration curve.
	Issues:	Significant noise in signal and matrix interference.
D.L. 0.06 µg/L	**Sample Preparation:**	Urine diluted 1:1 with 4% nitric acid matrix modifier added to samples
	Analysis:	GFAA
	Issues:	Good signal from samples; initial spike recoveries acceptable, subsequent spike recoveries consistently biased high (approximatley 200%)
D.L. 0.03 µg/L MSA 0.06 µg/L external calibration curve	**Sample Preparation:**	Urine diluted 1:1 with 4% nitric acid matrix modifier added to samples
	Analysis:	GFAA: Concentrations quantitated using external calibration curve for results previously reported as undetected; Concentrations quantitated by MSA
	Issues:	Matrix effects decreased with dilution of sample and quantitation by MSA

MOST RECENT DATA



Urinary beryllium (creatinine-adjusted) for workers in three different areas of a beryllium plant.



Urinary beryllium (creatinine-adjusted) over time for 3 volunteers from P/O group.

INTERPRETATION

- Levels of beryllium in urine and blood of our study population are lower than expected from literature available at initiation of study
- A limitation of literature values is that they are not adjusted for hydration level (e.g. creatinine-adjusted)
- Spot samples are not sufficient to characterize exposures due to variability
- Workers in some production areas appear to experience higher doses than in other production or administrative areas
- Daily trends suggest a form of beryllium with a short biological half-life and/or contamination during sample collection

FUTURE EFFORTS

- Refine analytical methodology for blood
- Focus on 24-hour urine samples
- Assess pharmacodynamics: collect individual voids before and for 2 weeks following a substantial change in exposures (i.e., vacation)

CONCLUSIONS

- Urinary beryllium levels among the work force fall within the range of expected values for the general population
- Published data from pre-2000 may have been constrained due to inadequate detection limits
- Some production activities are distinguishable from administrative jobs on the basis of urinary beryllium data, demonstrating the value of thes data in detecting differences in exposure among different job classifications
- More work needs to be done to fully understand the time-varying trends in urinary excretion and the relation between exposure control measures and urinary beryllium
- Additional development of analytical methods for analysis of beryllium in biological samples is critical to ensure the reliability of data at sub-ppb concentration levels.

Urinary beryllium concentrations reported in literature

Authors	Year	Number of Subjects	Occupation	Mean	Standard Deviation	Detection Limit	Units
General Populations							
Grewal and Kearns	1977	120	--	0.9	0.4	--	µg/L
Stiefel et al.	1980	NR	--	0.9	0.5	0.05	ng/g
Minoia et al.	1985	56	--	0.6	0.2	0.02	µg/L
Paschal and Bailey	1986	NR	--	0.13	NR	--	µg/L
Reeves	1986	NR	--	Undetected	NR	--	µg/L
Apostoli et al.	1989	163	--	0.24	0.16	0.03	µg/L
Minoia et al.	1990	579	--	0.4	0.18	0.02	µg/L
Paschal et al.	1998	496	--	0.28	0.79[a]	0.1	µg/L
Populations with Occupational Exposure to Beryllium							
Apostoli et al.	1989	35	Dental Technicians (Melting/Finishing)	0.37	0.31	0.03	µg/L
Apostoli et al.	1989	11	Dental Technicians (Modeling)	0.24	0.17	0.03	µg/L
Wegner et al.	2000	27	Gemstone Cutters	0.13	0.12	0.06	µg/L

Note: NR - not reported

[a]Upper 95th percentile