Global Recognition of Chronic Beryllium Disease: A Challenge for Medical Surveillance and Disease Prevention

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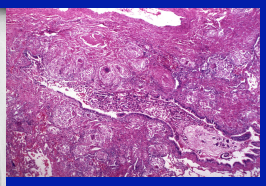
Outline

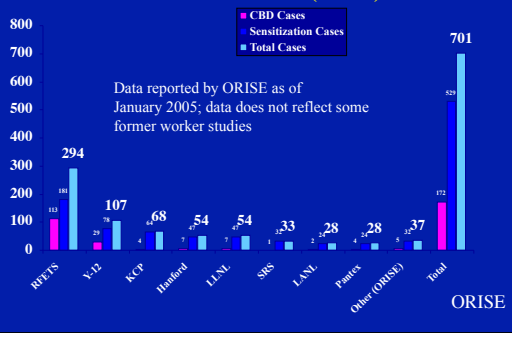
1. Sources of exposure to beryllium
2. Extent of global problem
3. Exposure levels
4. Beryllium health effects
   Medical surveillance results
5. Implications, needs

Index Case of Chronic Beryllium Disease in US Nuclear Weapons Industry 1985



"cause unknown"…
…Nuclear Weapons Machinist
First of > 600 Cases

Department of Energy Statistics Former Workers (2005)



Scope of the Problem

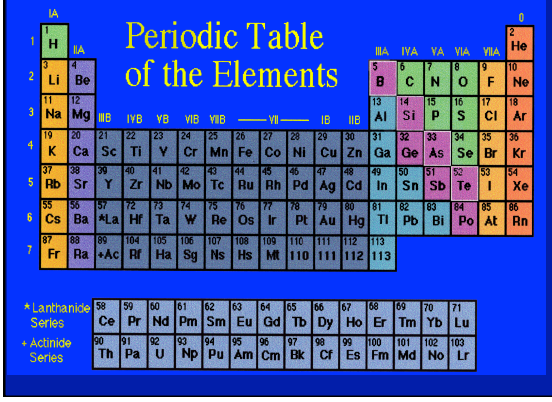
- Primary and "Downstream" Industries
  - companies and their subcontractors
  - Workers: direct and bystander
  - Former Workers
- Communities
- Countries

At Risk Industries

- Defense industries
- Aerospace, Airline Industry
- Alloy manufacture
- Alloy machine shops
- Automotive
- Electronics, Telecommunications
- Computer
- Mining and manufacture of beryllium
- Dental
- Foundries
- Recycling

(Infante and Newman *Lancet* 2004)

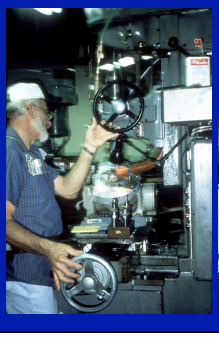
Periodic Table of the Elements



Exposure

Brush Wellman, Inc.

Beryllium Machining Risks



Countries with Published Cases

- North America: U.S. and Canada
- Europe: Britain, France, Germany, Belgium, Sweden (others?)
- Middle East: Israel
- Asia: Kazakhstan, Russia, India, Japan, South Korea
- Others where disease is likely occurring but not yet recognized: China, Australia, NZ, Americas
- 3,800 of 7,000 direct customers of the primary beryllium industry are *outside* the U.S.

(Lancet 2004; 363:415; J Occup Environ Hyg 2004; 1:648)

Recycling, Quebec, CA

- 47 sensitized, 2.2%
- 30 Chronic beryllium disease

ULBA Metallurgical, Ust-Kamenogorsk, KZ

Health Consequences for Ust-Kamenogorsk ULBA Beryllium Plant (1951-1995)

- Acute berylliosis 252
  - 34% toxic bronchitis
  - 6% CBD
- CBD 459
  - Rate 3.2% over all; 76% in high exposure jobs
- Dermatitis 602
- Conjunctivitis 455
- Lung cancer in 60% of CBD or bronchitis cases
- Mortality 157
  - life expectancy after CBD diagnosis: 9.2 y

Community: Explosion 9/12/1990

- Childrens' hair, breast milk, urine, liver, hilar nodes, lungs, bones, elevated Beryllium levels
- No known clinical evaluations of general population

Recent Studies of Community Exposure and Health Risk

- 1940s – now Family cases
  - (Am Rev Respir Dis 1992; 145:1212)
- 1990s: continued "carry-out" exposures occurring
  (Am J Industr Med 1999; 1:72)
- Reading, PA, "revisited"
  - "Community acquired CBD"
  - Residents living in vicinity of beryllium production facility
  (Am J Respir Crit Care Med 2008)

Lifetime Weighted Exposures for Cases and Controls, Precision Beryllium Machining Plant

LWE* (µg/m3)	CBD Cases	Exposed Controls	Percent CBD
• 0.50-1.00	2	37	5.4%
• 0.20-0.50	10	72	13.9%
• 0.10-0.20	4	29	13.8%
• 0.02-0.10	4	46	8.7%
• <0.02	0	22	0%⇐
Total	20	206	

*Lifetime Weighted Exposure

(JOEM 2001; 43:238)

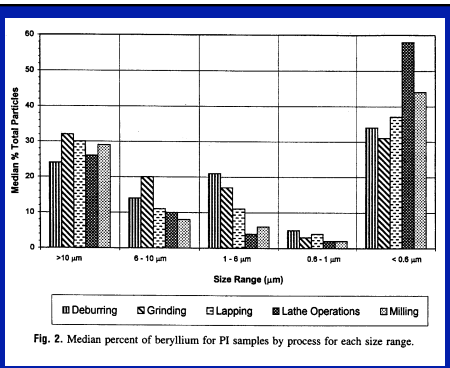


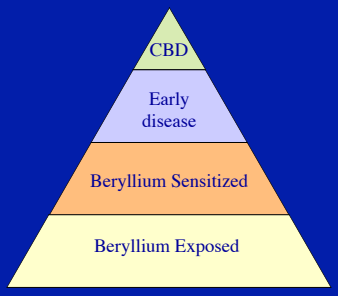
Fig. 2. Median percent of beryllium for PI samples by process for each size range.

Martyny J, et al. Aerosol generated during beryllium machining. *J Occup Environ Med*. 2000;42:14.

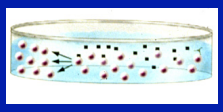
Overview of CBD and Exposure Field Studies

- CBD risk is associated with:
  - Job Task
  - Job Title
- CBD also seen among people with low exposures
- Due to genetic risk (HLA DPB1 E69)
- OSHA 2.0 ug/m^3 Permissible Exposure Limit not protective
- Materion Brush and United Steelworkers recommending a 10 fold reduction in Permissible Exposure Limit (0.2 ug/m^3)

Sensitization to CBD



Testing for Immune Response to Be, 1970's- Present Beryllium Lymphocyte Proliferation Test (BeLPT)

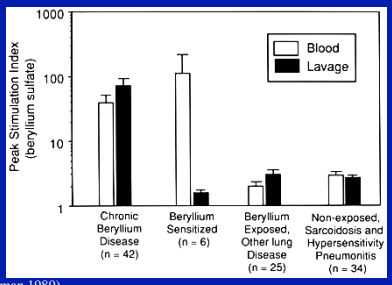


- Immunoassay
- Measures T lymphocyte proliferation when exposed to beryllium salts
- Detects sensitized to beryllium, but cannot separate sensitization from chronic beryllium disease (CBD)

Medical Surveillance

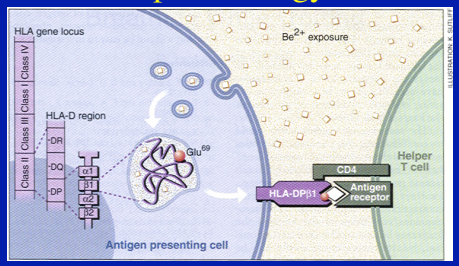
- Blood BeLPT
  - Highest predictive value of available tests
    - Sensitivity 66-86%
    - Specificity >99%
  - 25 years of use in field
  - Recommended for surveillance by
    - US Institute of Medicine Panel (2011)
    - Materion Brush and United Steelworkers (2012)

Beryllium lymphocyte proliferation: Lavage and Blood



(Newman 1989)

Genetic Epidemiology of CBD



(Richeldi 1993; Newman, *Science* 1993)

Gene x Environment

- Van Dyke et al. Risk of Chronic beryllium disease by HLA-DPB1 E69 Genotype and Beryllium Exposure in Nuclear Workers Am J Respir Crit Care Med (2011)
- Van Dyke et al. Exposure and genetics increase risk of beryllium sensitisation and chronic beryllium disease in the nuclear weapons industry. Occ Environ Med (2011)

Exposure Reconstruction

- CBD higher *lifetime weighted average* exposure ($\mu g/m^3$)

	Total	Control	BeS	CBD
n	386	255	70	61
Cumulative Be Exposure (Median)	0.03	0.03	0.01	0.07
(Mean)	0.24	0.15	0.25	0.64

Lifetime Weighted Average Exposure Quartiles

Exposure Quartile ($\mu g/m^3$)	BeS	CBD
<0.001	24 (34.3%)	10 (16.4%)
>0.001 to <0.03	21 (30.0%)	14 (22.9%)
>0.03 to <0.17	10 (14.3%)	12 (19.7%)
>0.17	15 (24.4%)	25 (41.0%)

Conclusions Van Dyke Papers

- Exposure response seen for CBD
- No exposure response for BeS (low exposures produce the allergy)
- Risk associated with E69, as in prior research
- No significant gene x environment interaction
- Emphasis on exposure reduction to serve public health

Summary and Conclusions

- We continue to expose workers to beryllium at levels that cause chronic, incurable lung disease in 2-15%.
- Beryllium triggers over-reaction by the immune system leading to 'sensitization' and granuloma formation
- Beryllium exposure and genetics contribute to disease risk…but the key is to *control exposure*

Conclusions

- There is an international epidemic of beryllium-related disease
- Multiple factors contribute to the underrecognition of the beryllium epidemic
- Where beryllium goes, disease follows
- A systematic, multifaceted, public health response is required to reduce the risk

Directions for Prevention

- Medical monitoring for early detection needed in more countries
- Reduction of exposure for all workers
  - Limit beryllium use to essential use only
  - Lower the permissible exposure limit
  - Multi-prong approach to exposure reduction
- Education of downstream users, workforce