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

Lee S. Newman, MD, MA
Professor, Environmental and Occupational Health, Colorado School of Public Health and Professor of Medicine, Division of Allergy and Clinical Immunology University of Colorado, Anschutz Medical Campus

Acknowledgements

- NIEHS
- NHLBI
- NIAID
- CDC/NIOSH
- US Department of Energy
- US Environmental Protection Agency
- United Steelworkers of America
- Patients participating in our research
- Andrew Fontenot
- Lisa Maier
- Peggy Muir
- Richard Sawyer
- John Martyny
- Mike Van Dyke
- Sally Tinkle
- Yoshikazu Inoue
- Priscilla Campbell
- Kay Kreiss
- Elizabeth Fireman

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

Scope of the Problem

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

Department of Energy Statistics
Former Workers (2005)

Data reported by ORISE as of January 2005; data does not reflect some former worker studies.
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)

Exposure

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.

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
- Children’s 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
- 1990s: continued “carry-out” exposures occurring
- Reading, PA, “revisited”
  - “Community acquired CBD”
  - Residents living in vicinity of beryllium production facility

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

<table>
<thead>
<tr>
<th>LWE* (µg/m3)</th>
<th>CBD Cases</th>
<th>Exposed Controls</th>
<th>Percent CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50-1.00</td>
<td>2</td>
<td>37</td>
<td>5.4%</td>
</tr>
<tr>
<td>0.20-0.50</td>
<td>10</td>
<td>72</td>
<td>13.9%</td>
</tr>
<tr>
<td>0.10-0.20</td>
<td>4</td>
<td>29</td>
<td>13.8%</td>
</tr>
<tr>
<td>0.02-0.10</td>
<td>4</td>
<td>46</td>
<td>8.7%</td>
</tr>
<tr>
<td>&lt;0.02</td>
<td>0</td>
<td>22</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
<td><strong>206</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Lifetime Weighted Exposure (JOEM 2001; 43:238)
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/m³ Permissible Exposure Limit not protective
- Materion Brush and United Steelworkers recommending a 10 fold reduction in Permissible Exposure Limit (0.2 ug/m³)

Sensitization to CBD

- Early disease
- Beryllium Sensitized
- Beryllium Exposed

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

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 (µg/m³)

<table>
<thead>
<tr>
<th>Exposure Quartile (µg/m³)</th>
<th>BeS</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.001</td>
<td>24 (34.3%)</td>
<td>10 (18.4%)</td>
</tr>
<tr>
<td>0.001 to &lt;0.03</td>
<td>21 (30.0%)</td>
<td>14 (22.9%)</td>
</tr>
<tr>
<td>0.03 to &lt;0.17</td>
<td>10 (14.3%)</td>
<td>12 (19.7%)</td>
</tr>
<tr>
<td>≥0.17</td>
<td>15 (24.4%)</td>
<td>25 (41.0%)</td>
</tr>
</tbody>
</table>

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