CBD and Current Research on Solubility of Exposure Materials

Beryllium Health and Safety Committee Meeting
Edgewood, Maryland
April 7, 2011

Mark D. Hoover, PhD, CHP, CIH
304-285-6374
mark.hoover@cdc.hhs.gov

Aleksandr B. Stefaniak, PhD, CIH
304-285-6302
aleksandr.stefaniak@cdc.hhs.gov

National Institute for Occupational Safety and Health
Morgantown, West Virginia

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of company names or products does not constitute endorsement by NIOSH.

NIOSH has been partnering to develop a *comprehensive* risk management scheme to:

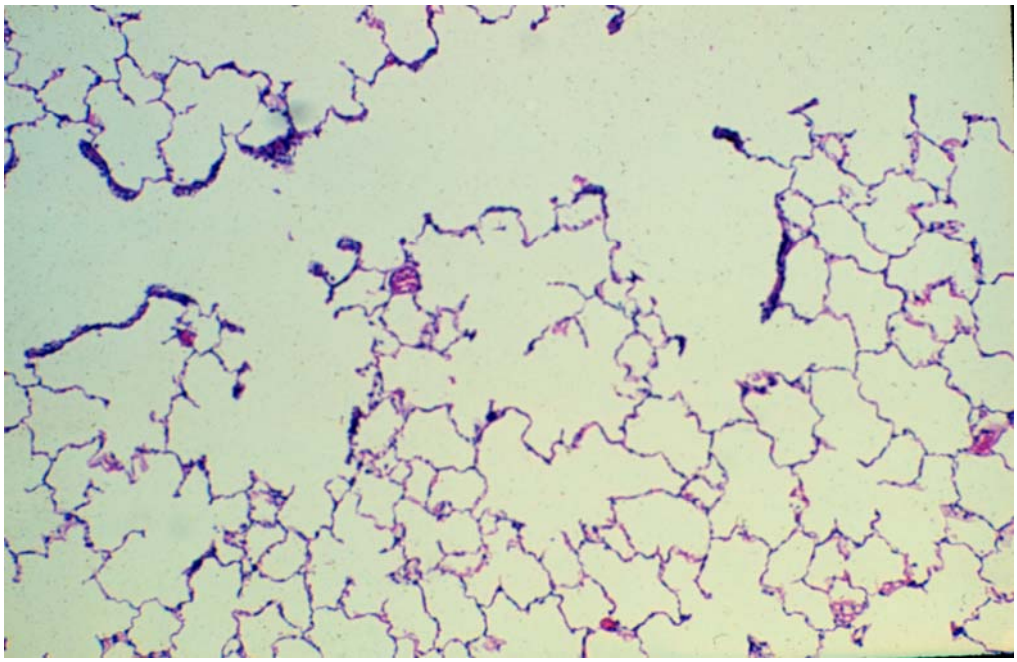
- **Anticipate,**
- **Recognize,**
- **Evaluate,**
- **Control, and**
- ***Confirm***

Hoover et al., Synergist, 22(1): 10, 2011

appropriate control of potential health risks for beryllium sensitization and CBD

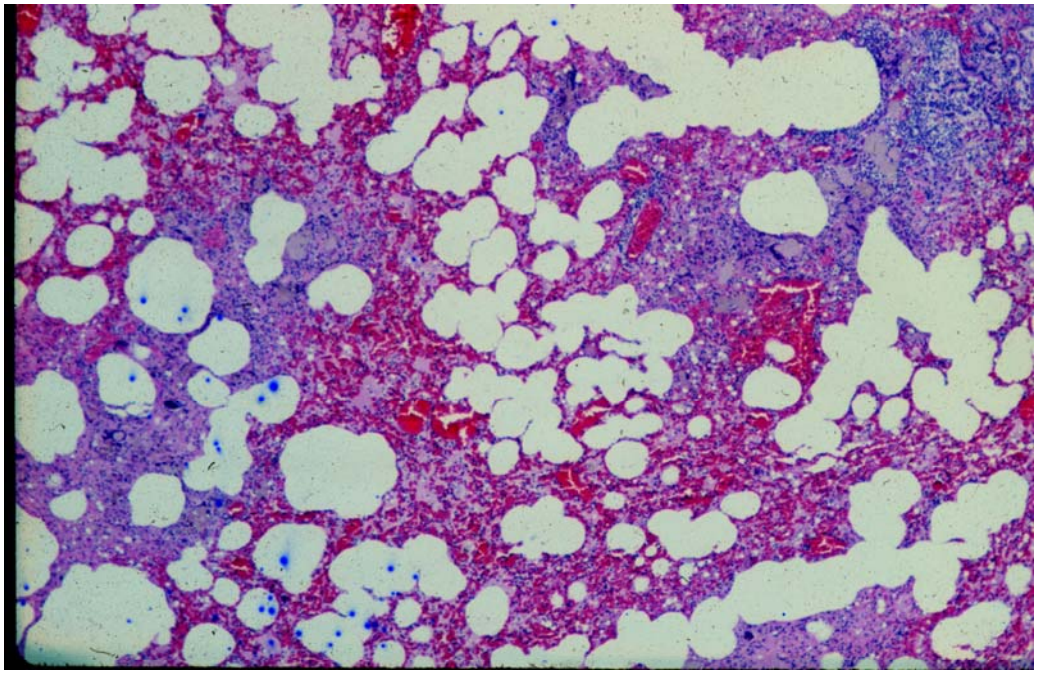
by applying a science-based approach to understanding and managing the ***critical elements*** over which we have control.

What combination of particle concentration, size, and chemical form will turn this ...



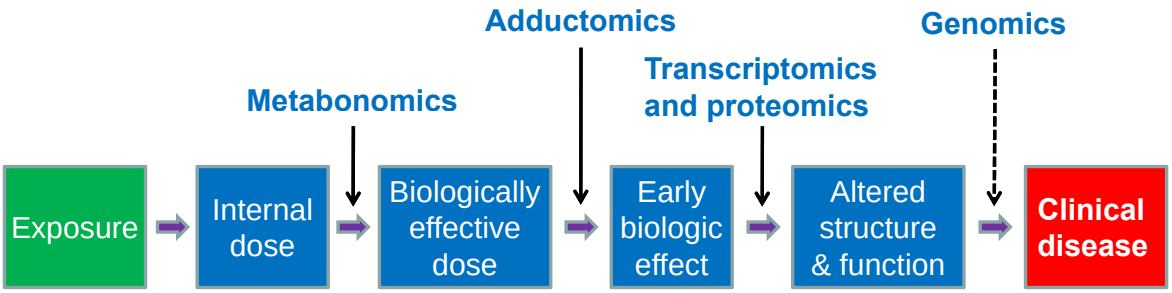
NORMAL LUNG TISSUE

…into this ?



GRANULOMATOUS LUNG TISSUE

Progression from Exposure to Disease



As presented in Decker et al., Synergist, 21(6): 32-33, 2010

Hypotheses

- Beryllium sensitization may occur by the dermal route as well as by the inhalation route.
- CBD requires the persistent availability of Be in lung
  - From repeated exposures to a soluble material or
  - From discrete exposure(s) to less soluble materials.
- Understanding bioavailability is key to understanding both sensitization and CBD
- Bioavailability depends on the timing, concentration, and physico-chemical properties of particles:
  - Aerodynamic size (dispersion and deposition in the respiratory tract),
  - Physical size (composition, particle number, and number of affected cells),
  - Intrinsic solubility (response to surfactant and phagocytic solvents)
  - Surface area (contact of the beryllium material with the solvents)

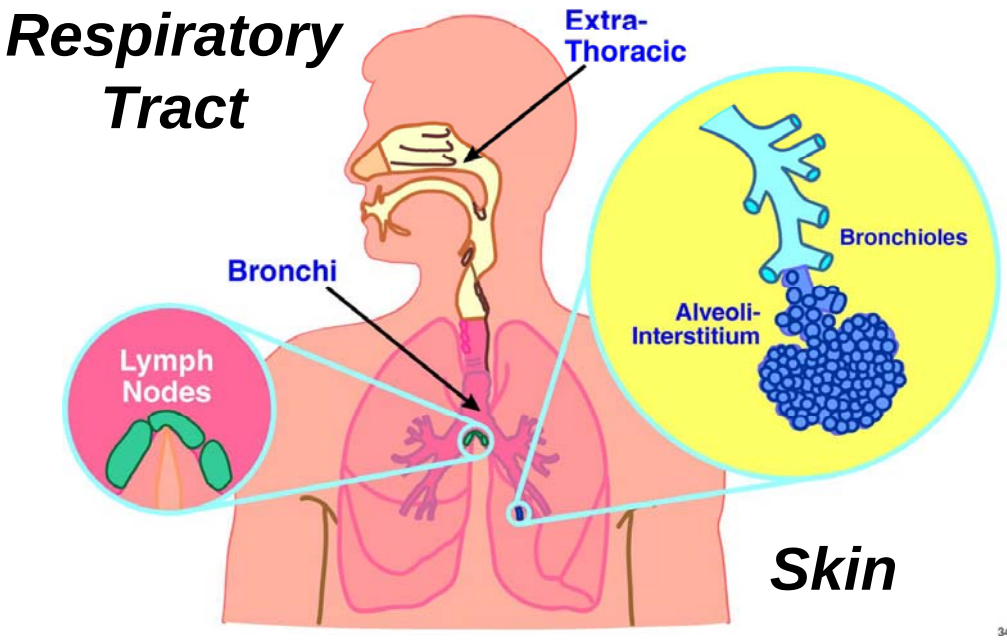
A conceptual model for development of CBD

- Beryllium enters the skin or lung and sensitization occurs
  - ***The beryllium is recognized as foreign by the immune system***
- The body's defense cells "patrol" the body, including the lung
- ***If beryllium is recognized in the lung,*** the body's defense cells release messengers that cause general effects – night sweats, fever, fatigue
- The defense cells continue to enter and divide in the lung and result in scarring of the lung – The patient may be short of breath and fatigued. More serious impairment may arise.

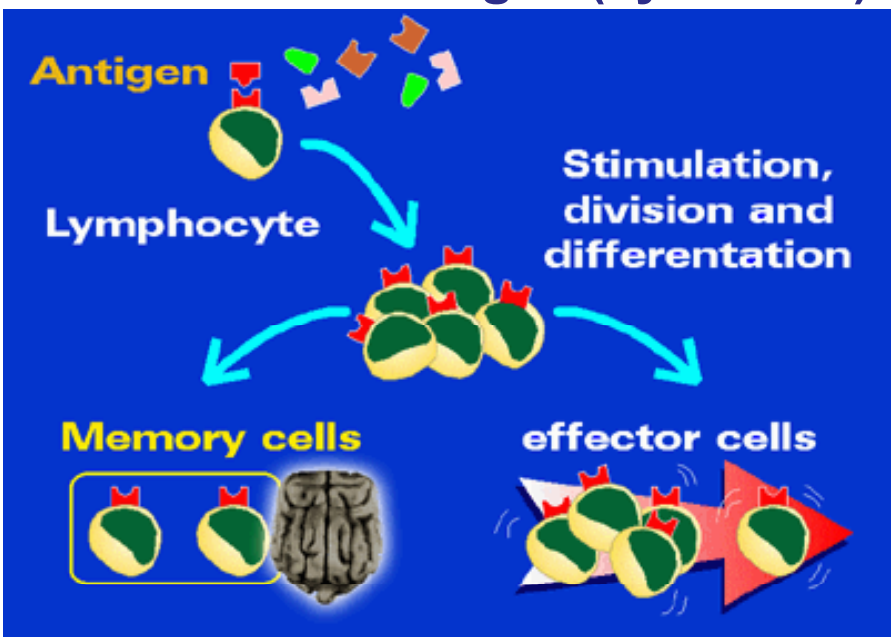
Factors affecting hazard, exposure, and risk

- Airborne beryllium mass concentration
  - Average ($\mu g/m^3$)
  - Peak ($\mu g/m^3$)
  - Cumulative ($\mu g/m^3$•days)
- Inhaled or skin-deposited beryllium
  - Inhalable, thoracic, or respirable
  - Mass, number, surface area
- Biologically available beryllium
  - Dissolved Be (ions / gram lung / day)
  - Peak, average, cumulative, instantaneous

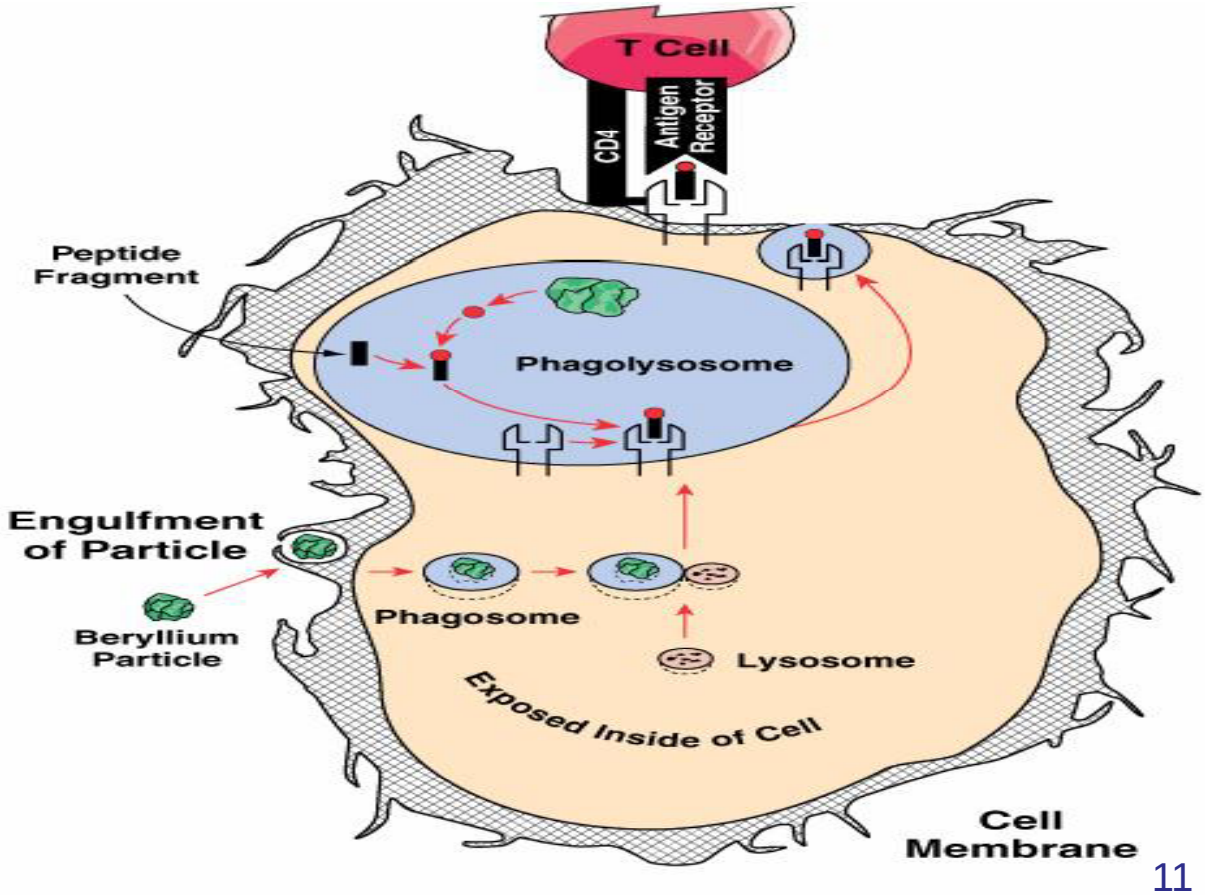
NIOSH studies address Be material bioavailability (how it contacts the body) and bioaccessibility (how Be can be taken up)



Lymphocytes have memory and communicate through receptors and secreted messages (cytokines)



From Jose Manuel Sanchez-Vizcaino Rodriguez
http://www.sanidadanimal.info/inmun/welcome1.htm



Initial characterization of exposure materials was described in:

Surface Area and Morphology of Respirable Beryllium Metal, Oxide, and Copper Alloy Aerosols

Aleksandr B. Stefaniak[a,b], Mark D. Hoover[c], Robert M. Dickerson[a], Eric J. Peterson[a], Gregory A. Day[a,c,d], Patrick N. Breysse[b], Michael S. Kent[e], and Ronald C. Scripsick[a]

AIHA Journal, 64: 297-305 (2003)

[a] Los Alamos National Laboratory, Los Alamos, NM

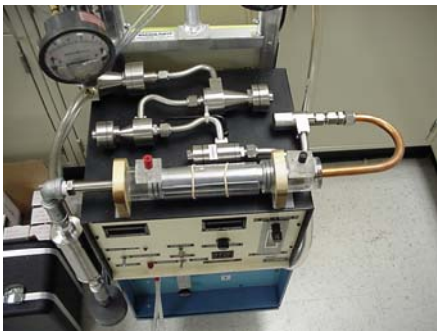
[b] Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

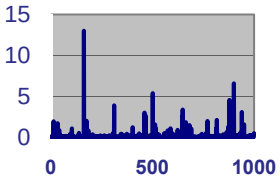
[c] Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV

[d] University of Oklahoma Health Sciences Center, Oklahoma City, OK

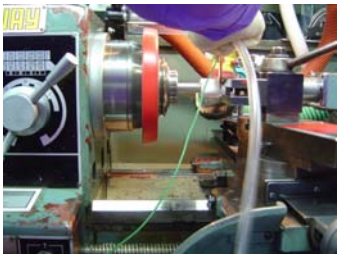
[e] Brush Wellman Inc., Elmore, OH

Work has involved field studies, laboratory evaluations, and modeling





Exposure assessment locations



Beryllium Materials

- Size-separated powders
  - Be metal (I-400, Brush Wellman, Inc., Elmore, OH)
  - BeO (UOX-125, Brush Wellman, Inc.)

- Process-sampled particles
  - Be Metal: Fluoride furnace and Reduction furnace
  - BeO: Screener
  - Copper-Be Alloys: Master alloy and Casting alloy

Characterization Methods

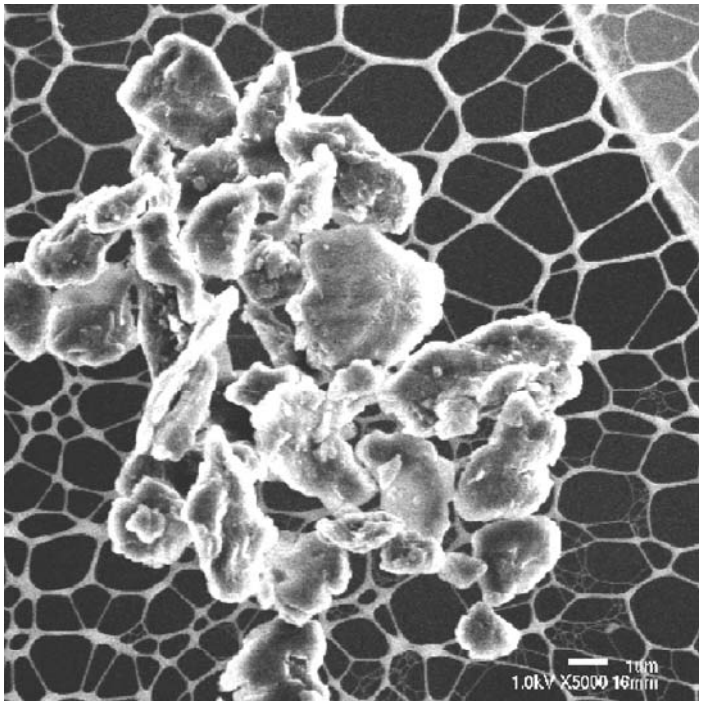
- Aerodynamic Size
  - Aerosol cyclone and cascade impaction
- Morphology
  - Transmission or Scanning electron microscopy
- Chemical composition
  - X-ray diffraction (XRD) and other techniques
- Particle surface area
  - Brunauer, Emmett, and Teller (BET) method
  - Surface area (m^2) normalized by sample mass to obtain SSA (m^2/g)
- In vitro dissolution in various biological media

In Vitro dissolution methods

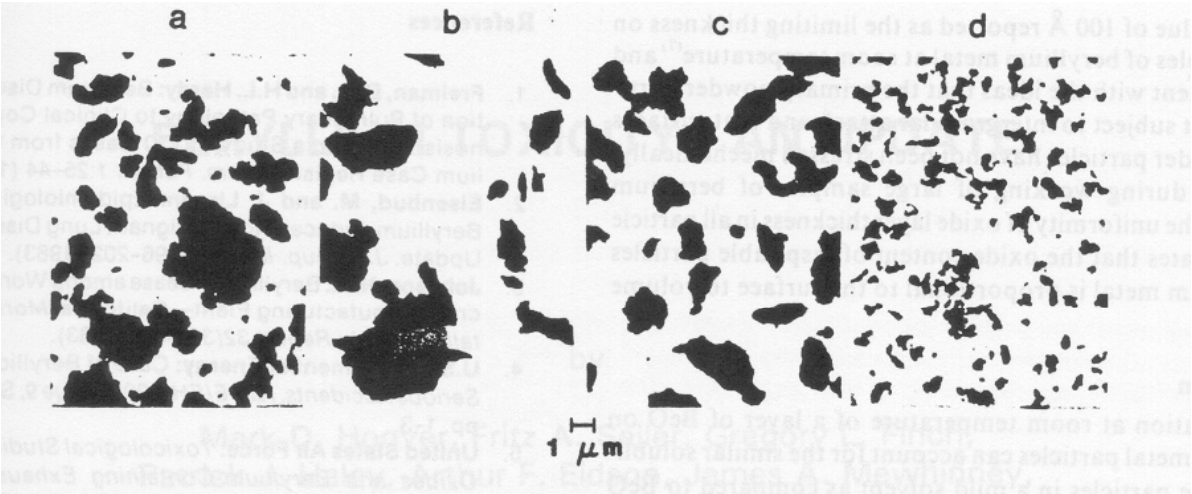
- Aim
  - Evaluate the solubility and absorption potential of beryllium
- Four compartments were modeled
  - Upper airways, pH 7.4
  - Alveolar macrophages, pH 4.5
  - Gastric juice, pH 1.2
  - Skin surface liquids, pH 5.3

Be Metal Powder

- Morphology
  - Compact
  - Surface roughness
  - Small particles adhered
- Composition
  - High purity metal



Beryllium metal particles separated by aerosol cyclone

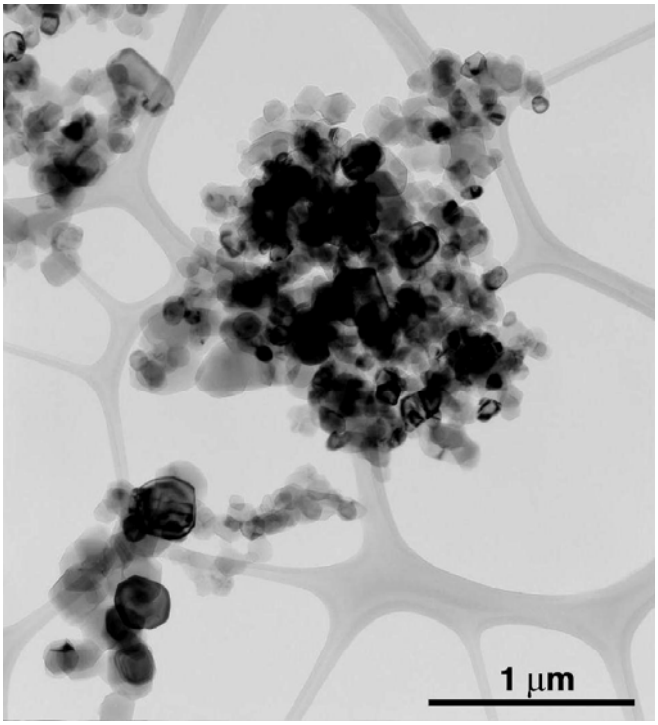


Particle morphology is similar for all sizes.

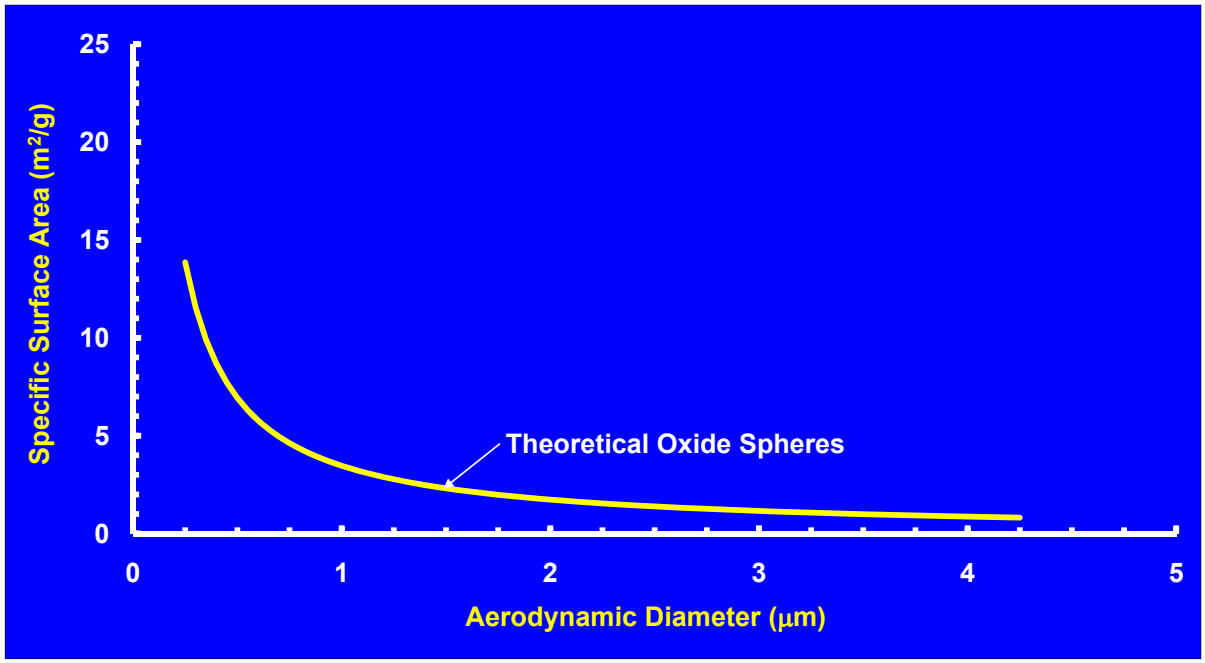
Hoover, M. D., B. T. Castorina, G. L. Finch and S. J. Rothenberg: Determination of the Oxide Layer Thickness on Beryllium Metal Particles. Am. Ind. Hyg. Assoc. J. 50:550-553, 1989.

BeO Powder and Screener BeO

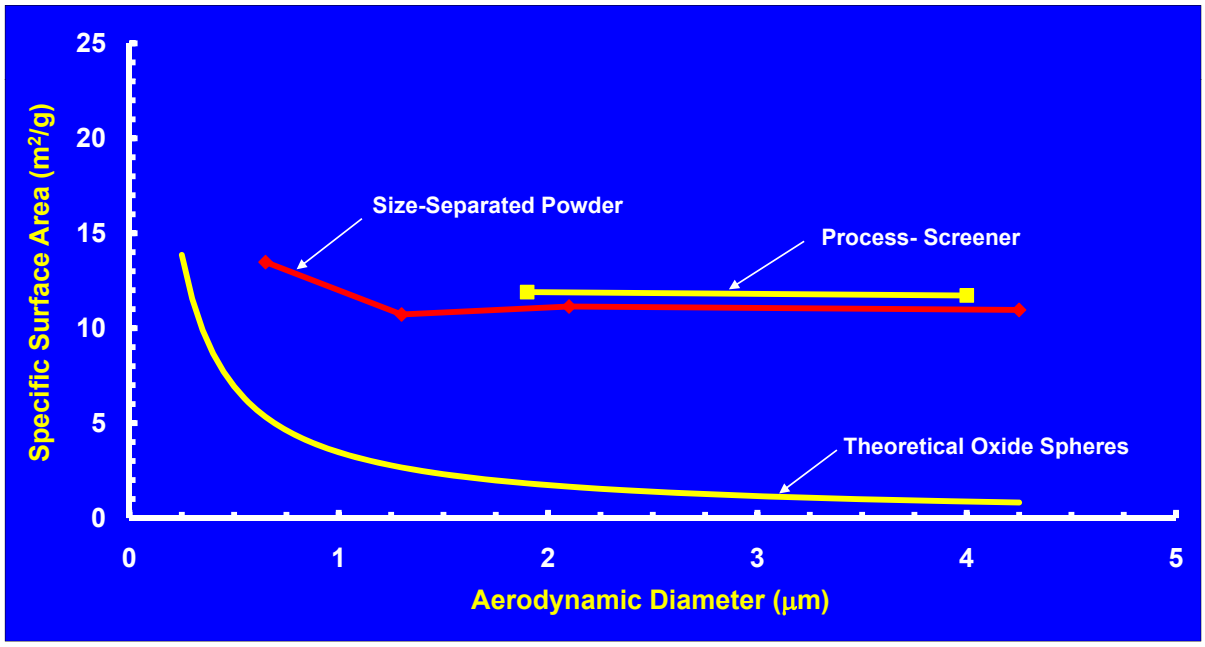
- Morphology
  - Clusters of primary particles
- Composition
  - High purity BeO
  - Primary particle diameters
    - Powder: 0.19 um
    - Particles: 0.22 um



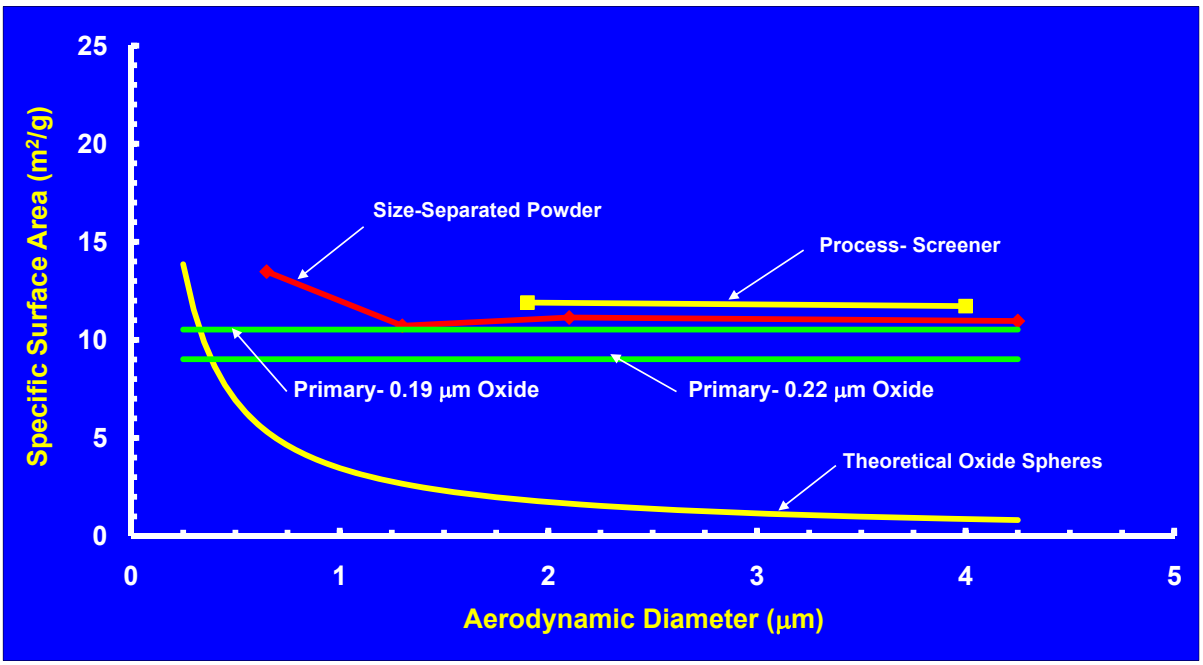
Theoretical - Beryllium Oxide



Measured - BeO Powder and Screener BeO

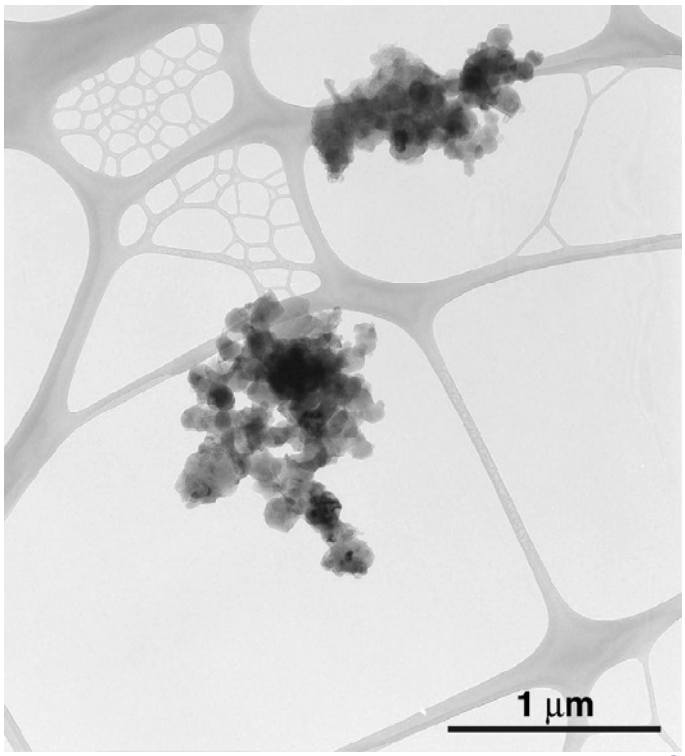


Measured - BeO Powder and Screener BeO compared to predicted SSA for small spheres

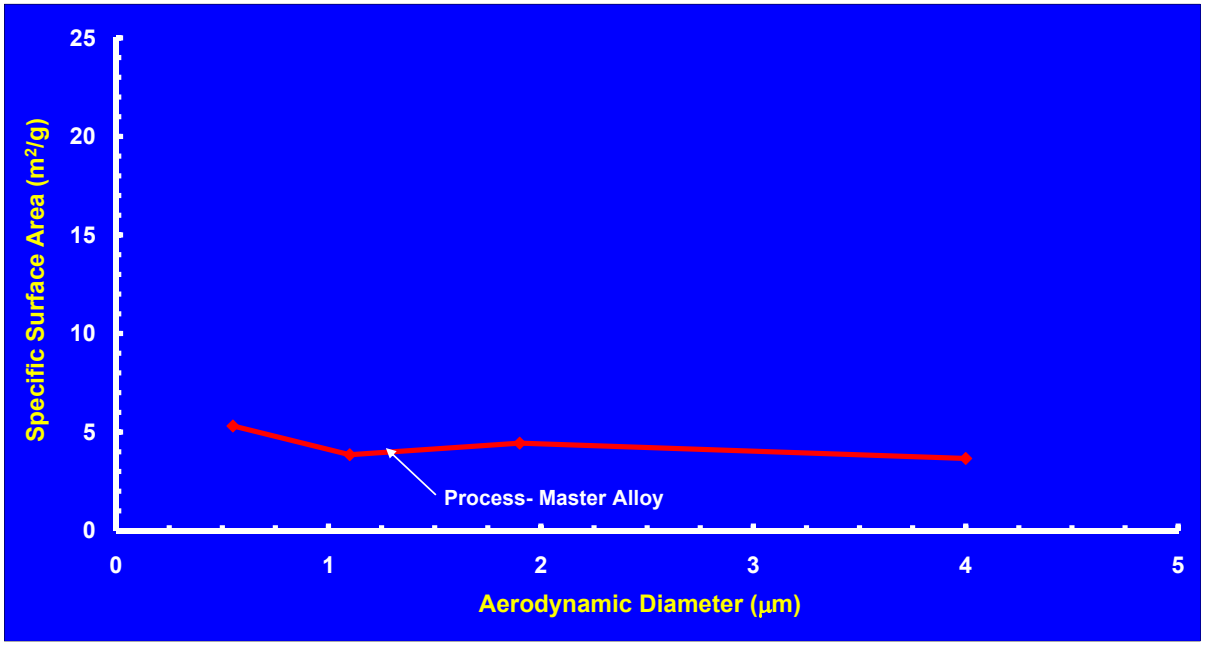


Cu-Be master and casting alloys

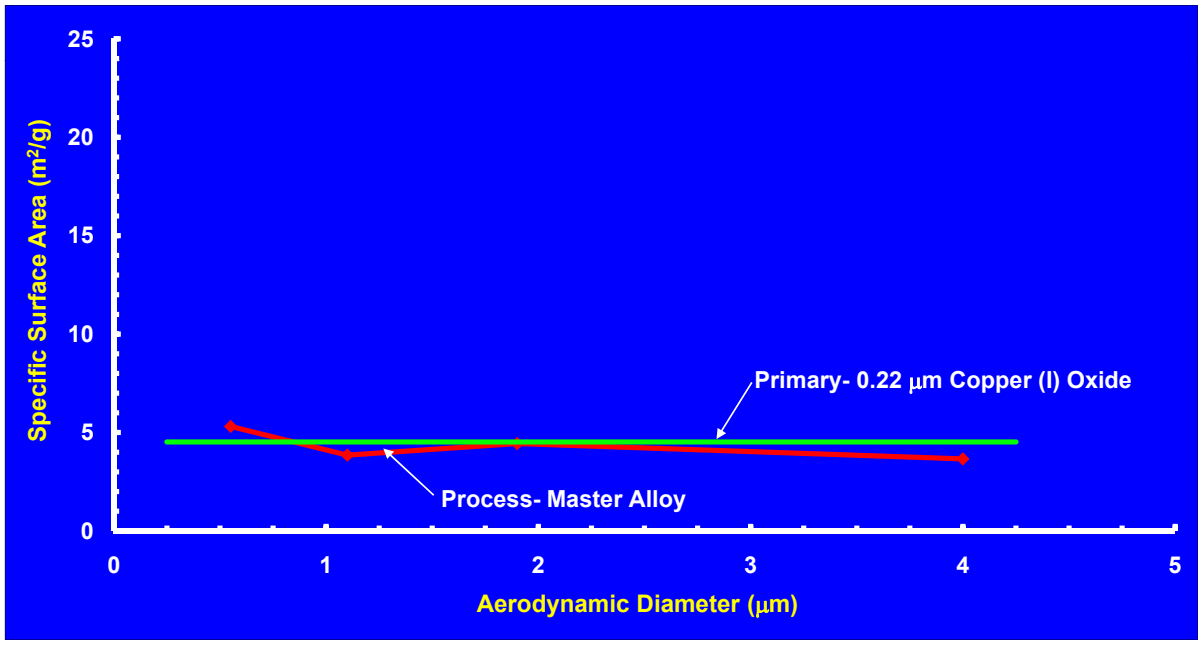
- Morphology
  - Clusters of primary particles
- Composition
  - Cu oxides, BeO



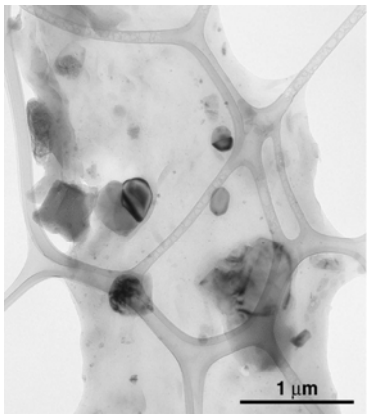
Measured Cu-Be Master Alloy



Measured Cu-Be master alloy compared to predicted SSA for small spheres

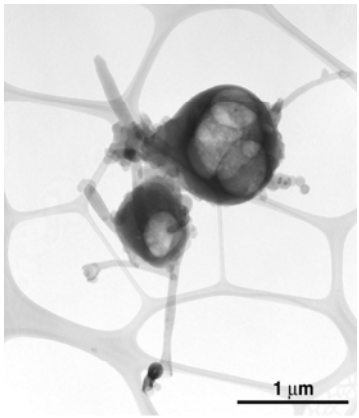


Fluoride Furnace



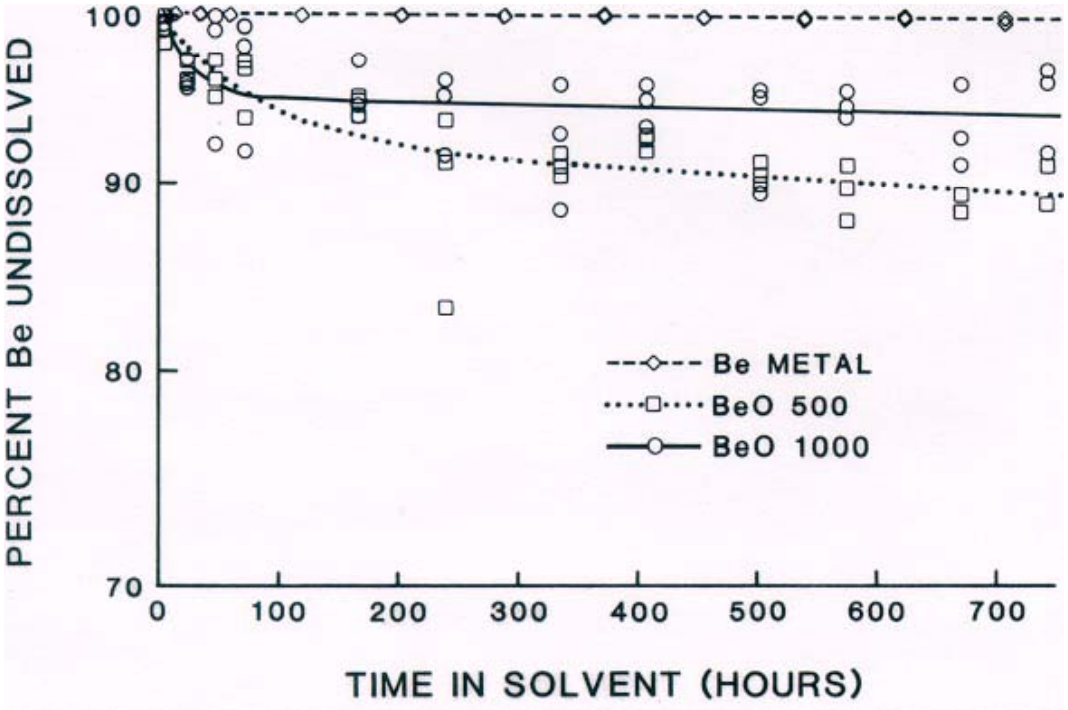
- Reactivity precluded SSA determination
  - Fluoride etched glass samples cells
  - Particles transformed into agglomerated solids

Reduction Furnace



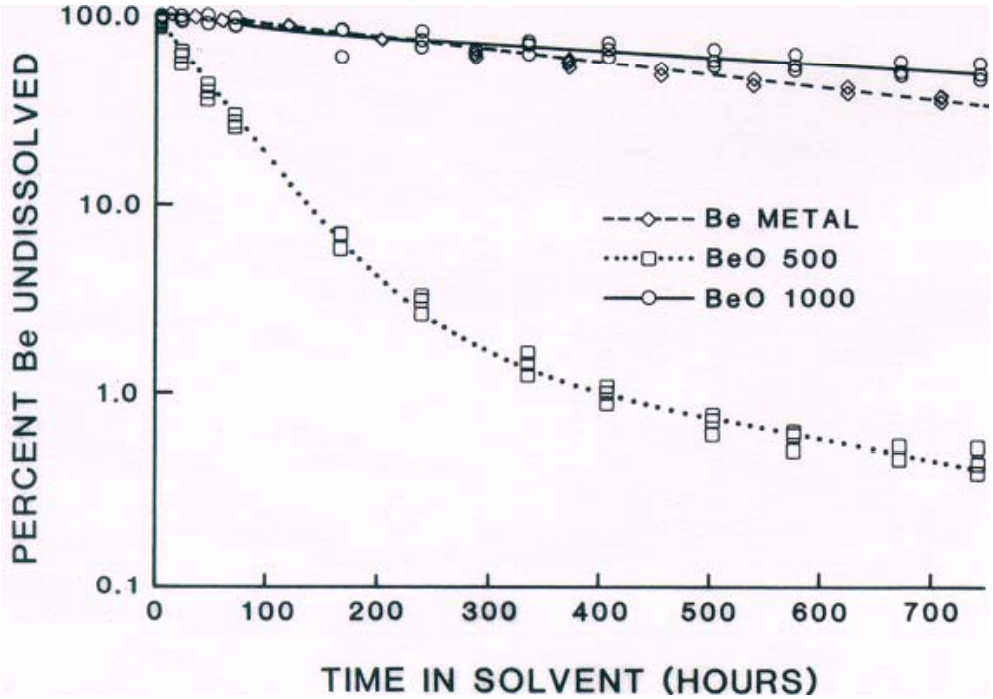
- Reactivity precluded reliable SSA determination
  - Particles transformed into agglomerated solids

SOLUBILITY IN LUNG SERUM



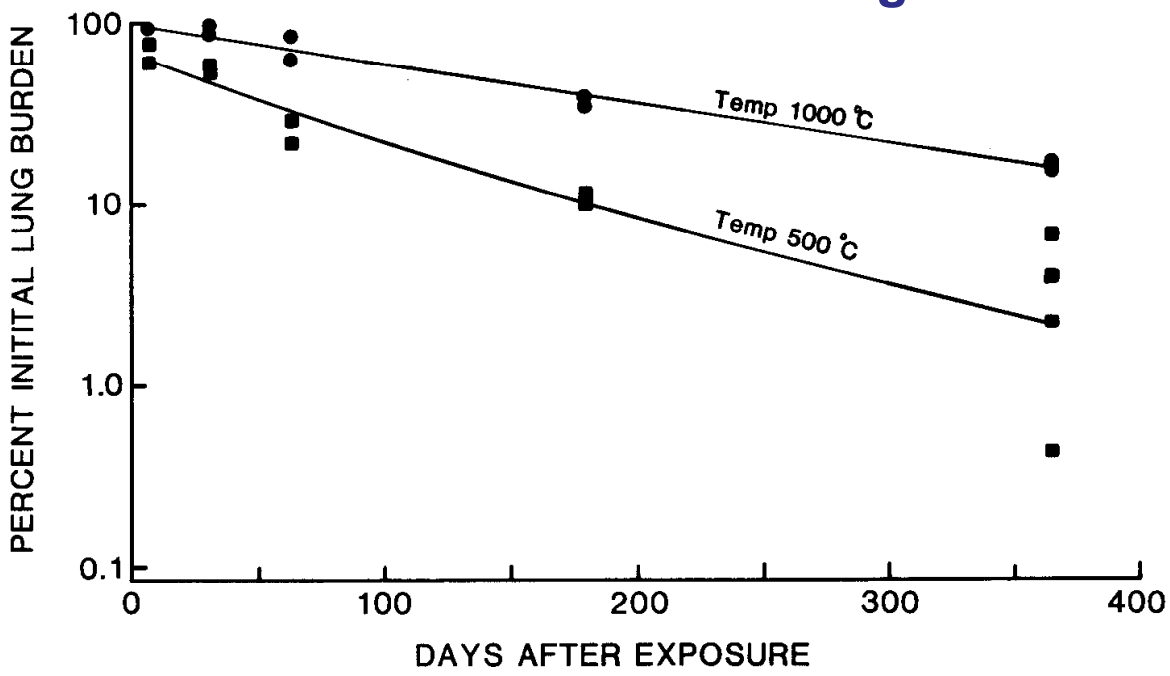
The BeO materials are more soluble than Be in the lung surface media.

Solubility in phagolysosomal media



Solubility of low-fired BeO in macrophages is high and may allow bioavailability of Be

BeO Clearance from lung



BeO calcined at lower temperature clears more rapidly from lung

Be dissolution in dermally relevant media

- Artificial sweat
  - Aqueous component of skin film
- Artificial sebum
  - Oily phase component of skin film
- Solution buffered to pH 5.3 or pH 6.5
  - Maintained at 36°C (skin temperature)
  - Changed at 1, 4, 8, 12, 24, 48, 72, 168 hrs
  - Dissolved beryllium quantified using ICP-AES

Be exposure materials

- 18 beryllium-containing materials
  - Beryllium hydroxide (1)
  - Beryllium metal (2)
  - Beryllium oxide (7)
  - Copper-beryllium alloy (4)
  - Copper-beryllium alloy tools (4)

Dissolution results in artificial sweat and sebum

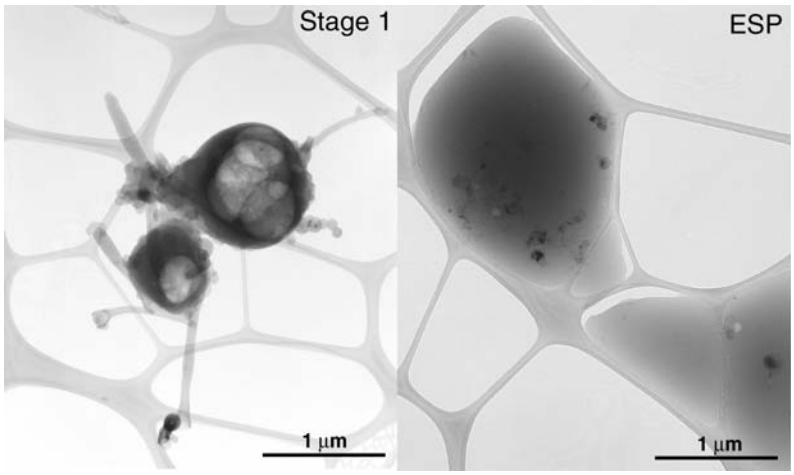
- Dissolved beryllium quantified in all samples
- Fractions of beryllium dissolved (pH 5.3)
  - 48.9±5.0% (reduction fume) to 0.05±0.00% (oxide)
- Fractions of beryllium dissolved (pH 6.5)
  - 10 to 140 times lower

Results – Homogeneous Materials

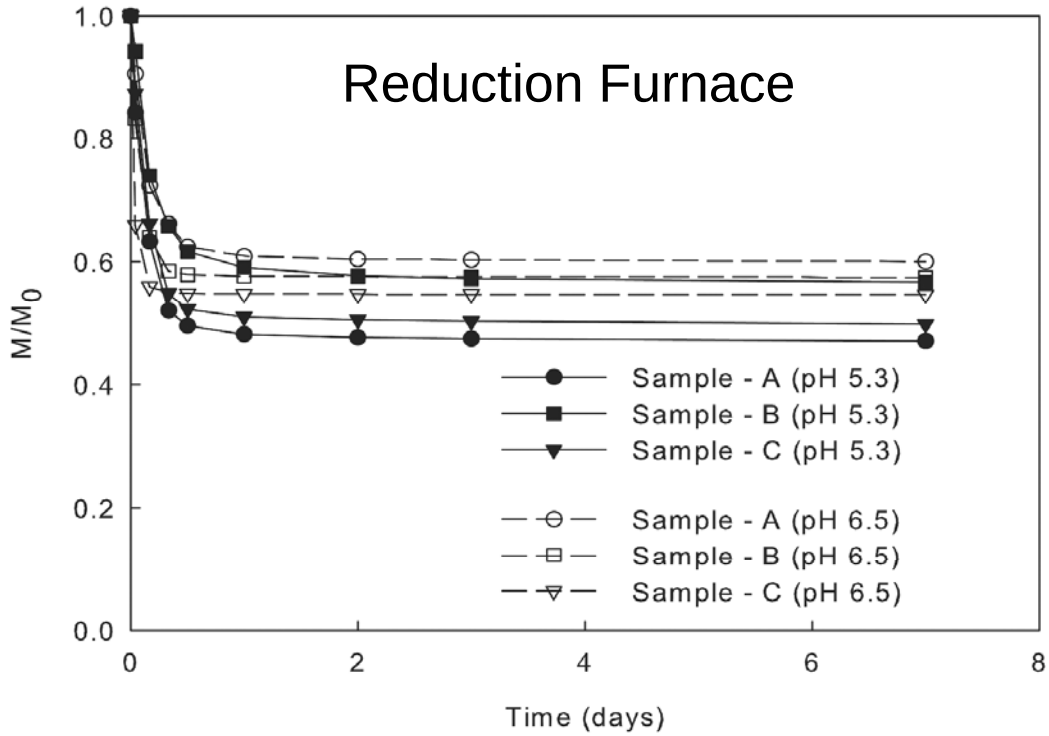
- Beryllium hydroxide
  - Most soluble, $k_{pH5.3} = 1.7 \pm 0.0 \times 10^{-7}$ g/(cm^2·d)
- Beryllium metal
  - Medium soluble, $k_{pH5.3} = 1.7 \pm 0.6 \times 10^{-8}$ g/(cm^2·d)
- Beryllium oxides
  - Least soluble, $k_{pH5.3} = 1.0 \pm 0.5 \times 10^{-9}$ g/(cm^2·d)

Results – Heterogeneous Materials

- Reduction furnace (metal production)
  - 42% Be (10 mg) dissolved in 8 hours (pH 5.3)



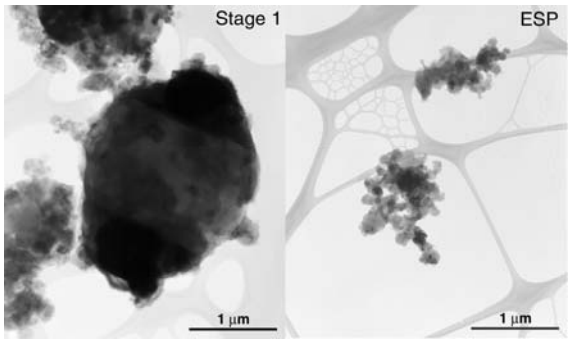
Dissolution kinetics



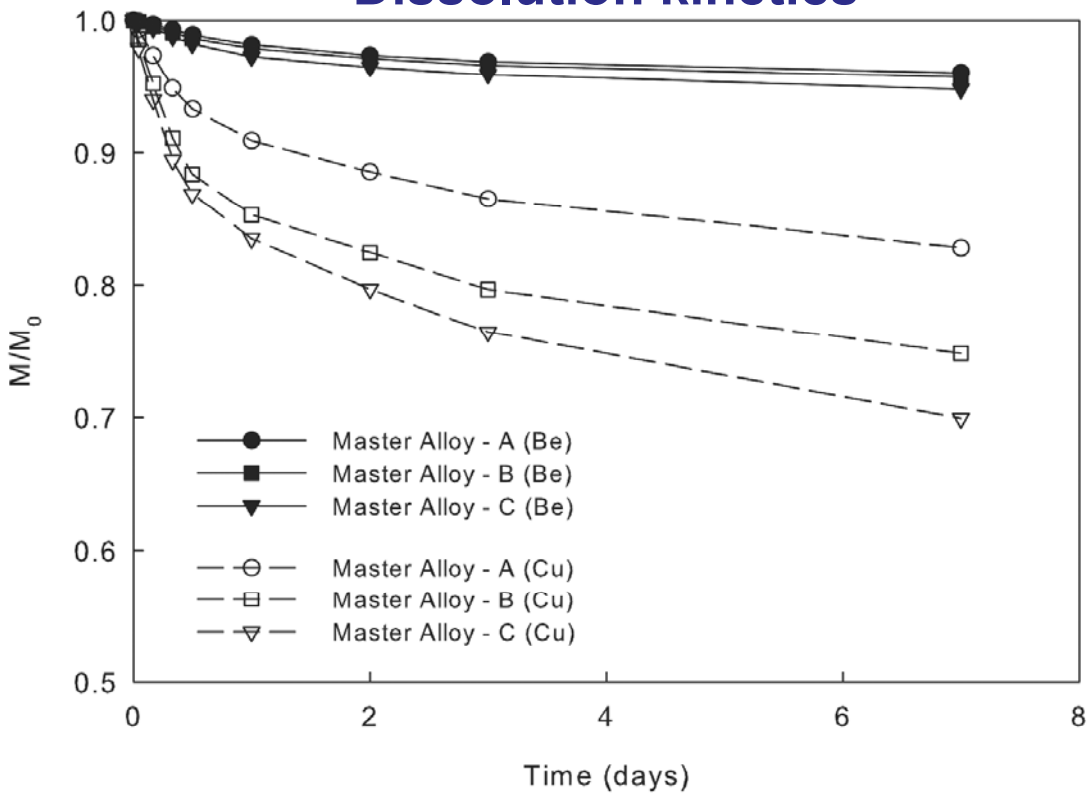
Results – Heterogeneous Materials

Be (10 mg) dissolved in 8 hours (pH 5.3)

- Master alloy fume (alloy production)
  - 0.9% Be (107 µg) dissolved in 8 hours (pH 5.3)



Dissolution kinetics



Results – Heterogeneous Materials

- Reduction furnace (metal production)
  - 42% Be (10 mg) dissolved in 8 hours (pH 5.3)
- Master alloy fume (alloy production)
  - 0.9% Be (107 µg) dissolved in 8 hours (pH 5.3)
- Tools
  - Tens to thousands of micrograms Be dissolved

Example dissolution study configuration for solid items

Dissolution results from solid items

	Dissolved Be (µg)		
	1 hour	8 hours	7 days
Pliers	15	56	610
Pipe Wrench	24	61	668
Hammer A	15	50	1600
Hammer B	30	150	2660

Dose Estimation

– *Ex.* Reduction furnace aerosol
– Hands evenly contaminated with 50 µg beryllium
– One-hour exposure

Skin Condition	Absorption (% hr^{-1})	Be penetrated (pg)	Be^{+2} (#)
Intact	0.001	30	~10^{12}
Abraded	0.150	4350	~10^{14}

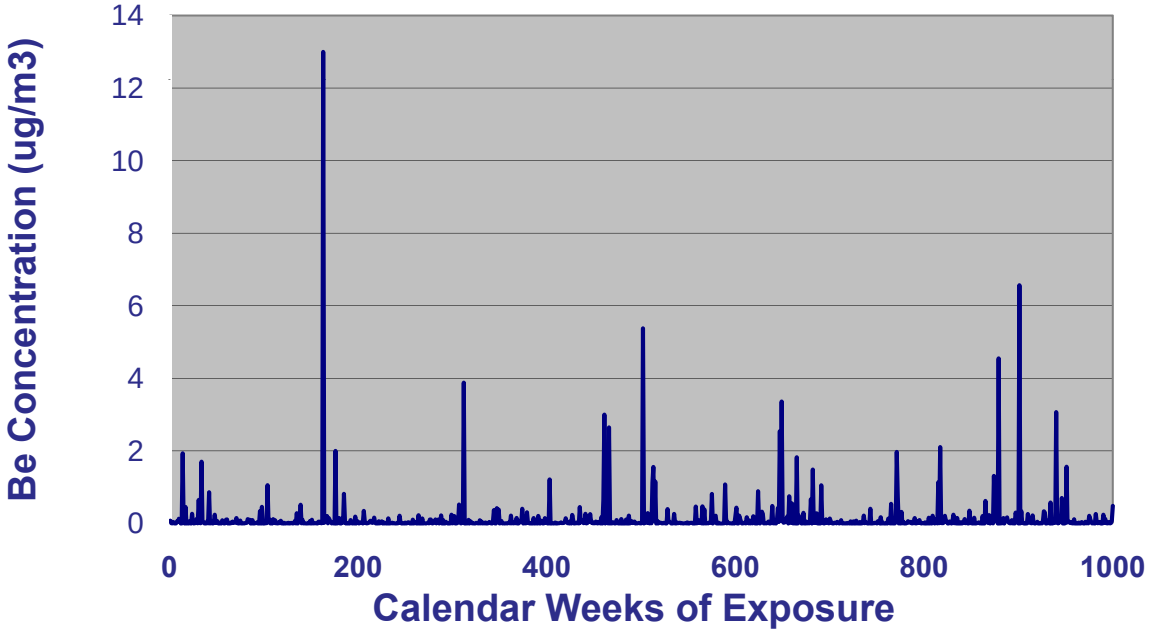
Dermal study results summary

- Beryllium dissolved from poorly soluble materials in artificial sweat
  – Skin is an exposure pathway for BeS
- Artificial sweat pH important for dissolution
- Prudent to protect skin

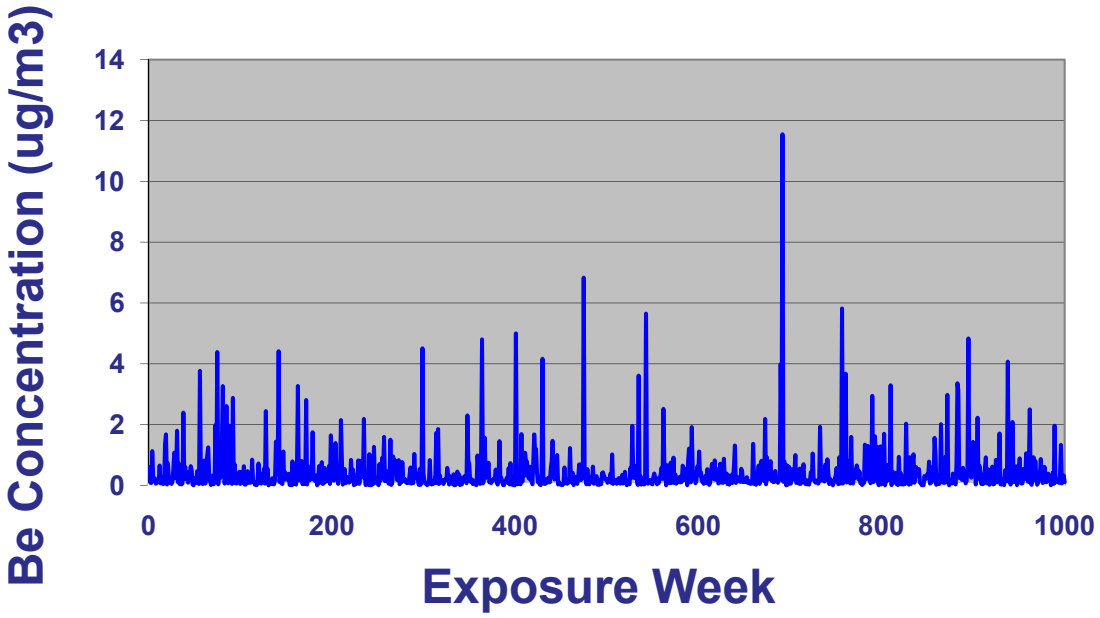
Example of a modeling strategy

- 20 years of work experience
- Weekly personal sampling for average airborne concentration of beryllium
- "Typical" lognormal concentration distribution
  - Median concentration: 0.2 ug/m³
  - Geometric standard deviation: 3.5
- Data from Monte Carlo Simulation
  - Crystal Ball (Decisioneering, Inc.)

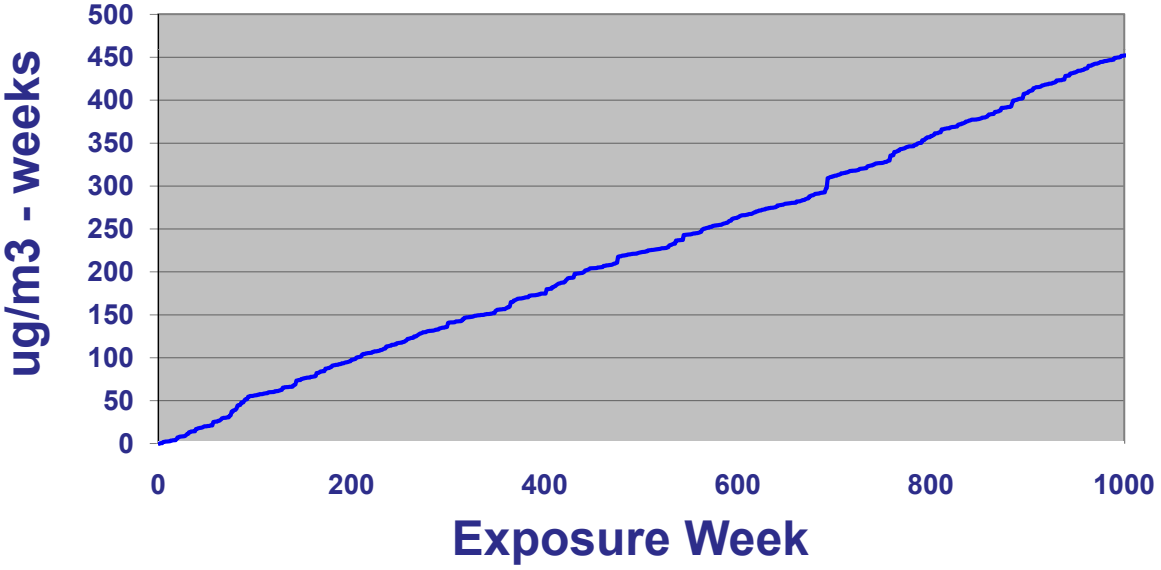
Be Aerosol Concentration



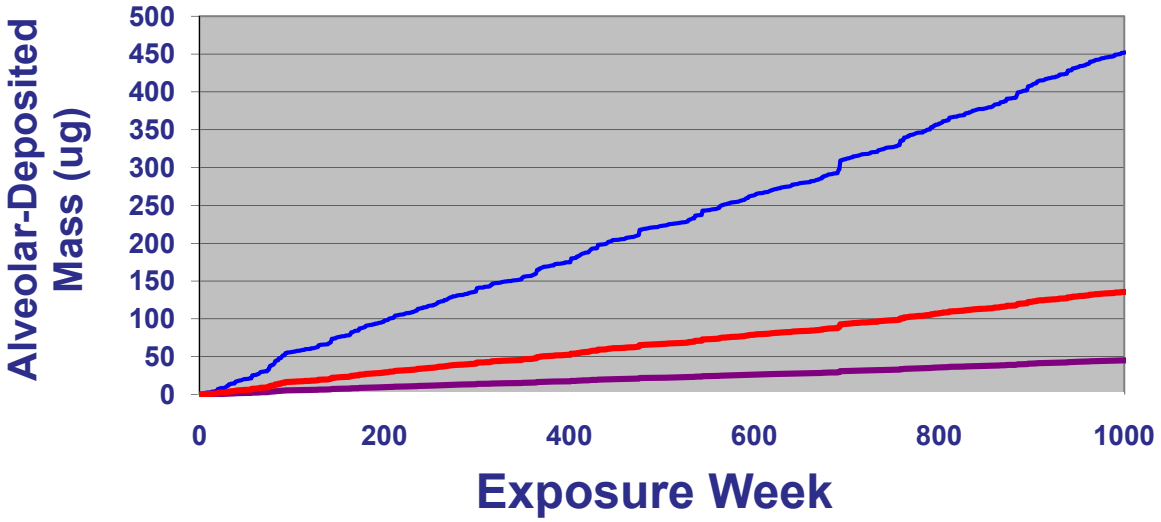
Exposure History - Worker 1



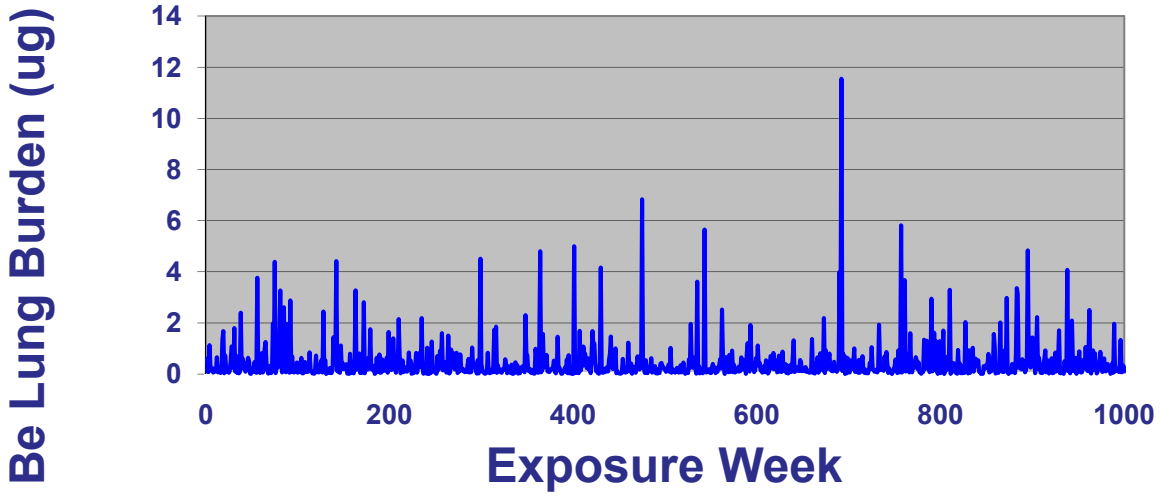
Cumulative Exposure - Worker 1



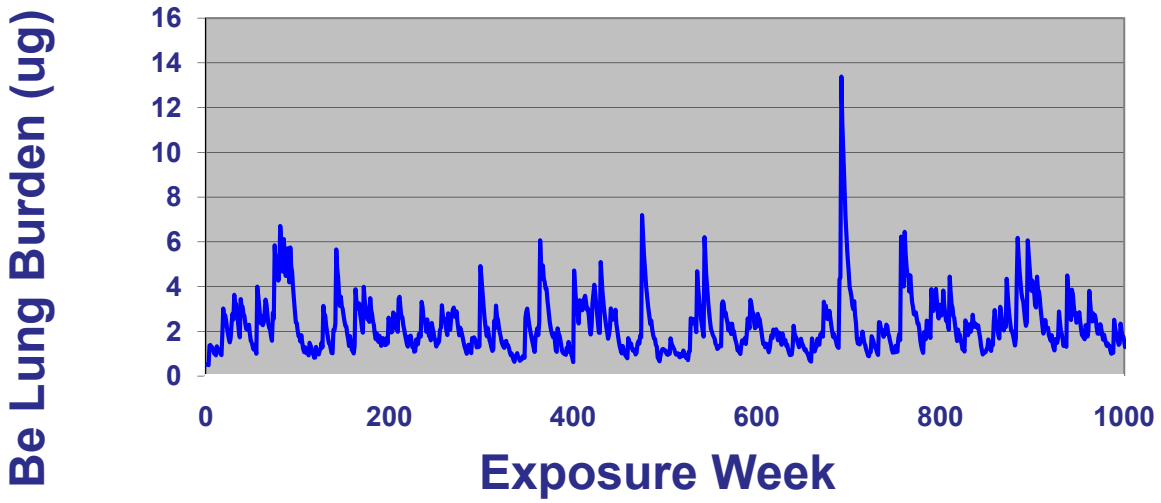
Cumulative Exposure - Worker 1
(blue-inhaled, red-0.005 um, purple 1 um)



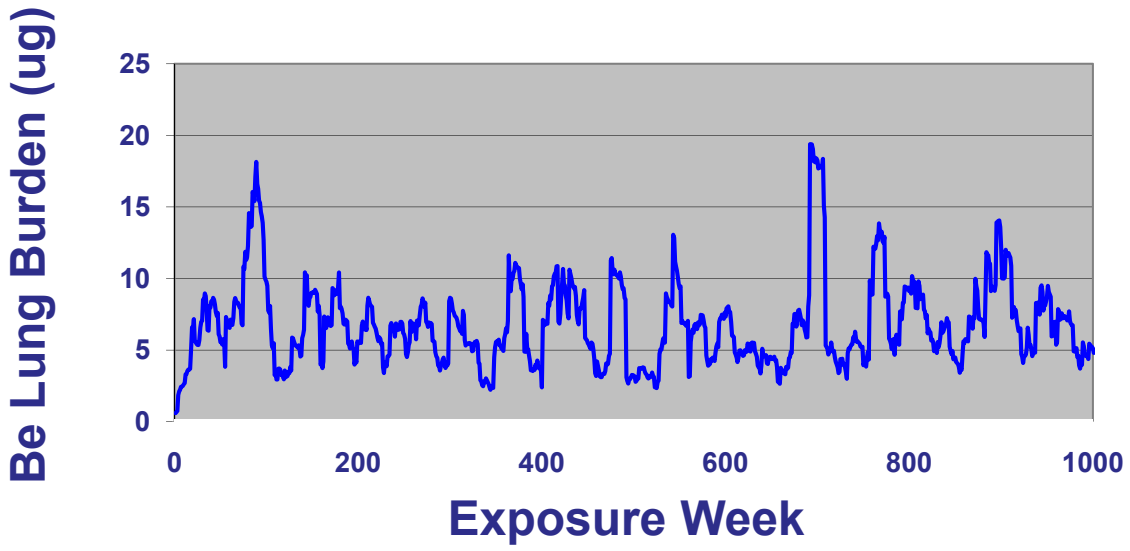
Lung Burden History - Worker 1
(1 d clearance halftime)



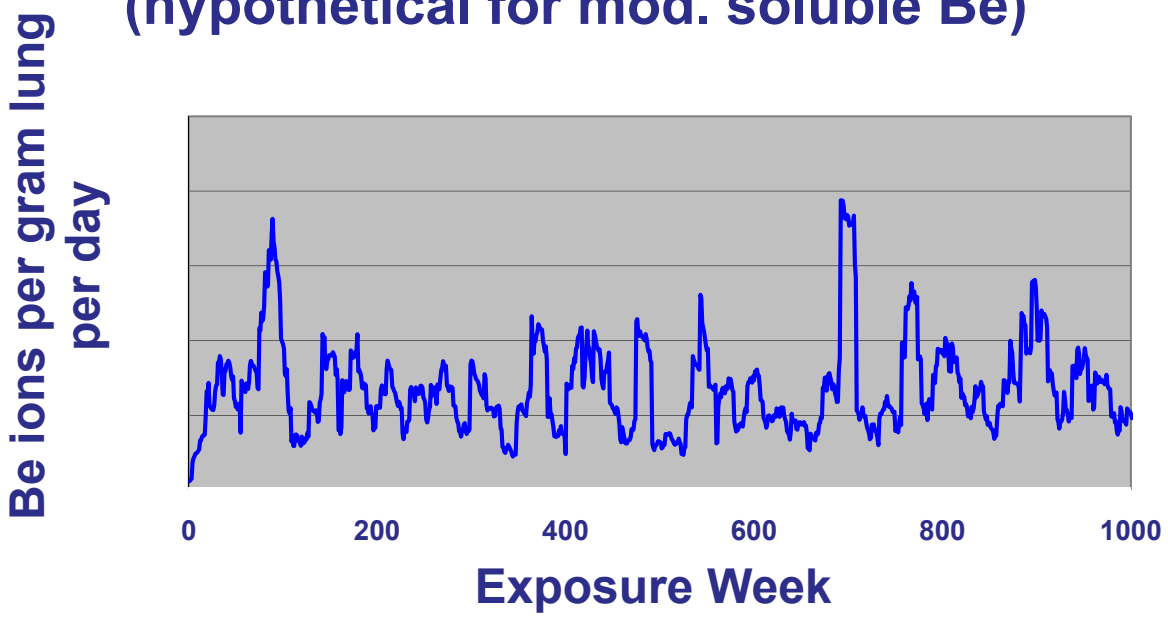
Lung Burden History - Worker 1 (28 d clearance halftime)



Lung Burden History - Worker 1 (350 d clearance halftime)



Lung Dose History - Worker 1 (hypothetical for mod. soluble Be)



Beryllium health and safety informatics (a working definition)

- The ***science and practice*** of determining ***which information is relevant*** to the beryllium health and safety community,
- and then developing and implementing effective mechanisms
- for *collecting, validating, storing, sharing, analyzing, modeling, and applying* that information.

The studies of CBD and dissolution behavior of exposure materials contributes to the Be health and safety knowledgebase.

Conclusion and recommendations

- Understanding the interrelationships of particle size, surface area, bioavailability of Be, and associated risks for CBD may lead to more protective exposure limits
- Particle morphology influences the size-dependent specific surface area
- Direct measurements of particle surface area are needed parts of a comprehensive sampling program
- Both inhalation and dermal routes must be addressed.
- Epidemiology studies, in vitro studies, and studies in genetically-engineered mice must work together

Acknowledgments

- NIOSH
  - Greg Day
  - Matt Duling
  - Mark Hoover
  - Kay Kreiss
  - Brent Lawrence
  - Mark Millson
  - Deborah Sbarra
  - Christine Schuler
  - Marcia Stanton
  - Aleks Stefaniak
  - Abbas Virji
- Los Alamos National Lab
  - Steve Chipera
  - Robert Dickerson
  - Ron Scripsick
- Brush Wellman Inc.
  - Al Bielli
  - Mark Corbett
  - David Deubner
  - Mike Kent
  - Dan Perry
  - Phil Sabey

Questions?