Investigation of silica dust toxicity based on particle characteristics and exposure dose

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Objectives

✓ To investigate the respirable silica dust (RCS) true dose of exposure
✓ To understand the RCS level of toxicity

- RCD total mass monitoring
- RCD Characterization studies
- RCS external dose
- Lung deposition studies
- RCS internal dose
- RCS toxicity studies
- RCS level of toxicity
- Molecular epidemiological study
- Degree of lung injury
RCS monitoring methods
(crystalline silica on filters)

<table>
<thead>
<tr>
<th>Method</th>
<th>Application</th>
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</thead>
<tbody>
<tr>
<td>P7 method (FTIR)</td>
<td>Coal mines</td>
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<tr>
<td>P2 method (XRD)</td>
<td>Metal/nonmetal mines</td>
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<tr>
<td>NIOSH 7500</td>
<td>XRD</td>
</tr>
<tr>
<td>NIOSH 7602</td>
<td>IR-KBr pellet</td>
</tr>
<tr>
<td>NIOSH 7603</td>
<td>IR-redeposition</td>
</tr>
<tr>
<td>OSHA ID#142</td>
<td>XRD</td>
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Filters with the maximum collection efficiency (e.g., PVC filters)

The total mass of the RCS collected on a filter is assumed to all become the miner’s exposure dose
Respirable dust inhalation vs deposition

- Not all the inhaled particles will be deposited in the respiratory system
- ~20% of 5 μm dust particles will be exhaled (AMEC, 2013)

**Mucociliary clearance** is the physical unidirectional movement and removal of deposited particles and gases dissolved in the mucus from the respiratory tract.

- Dust particle respiratory deposition depends on the particle size and particle shape
- The level of toxicity depends on the true dose of exposure
- The number-concentration-based RCS samples could be an alternative index for RCS true dose estimations

Dust particle respiratory deposition depends on the particle size and shape:
- Smaller particles tend to be more easily exhaled due to their lighter weight and lower inertia.
- Larger particles, on the other hand, may settle more quickly due to gravity.

The level of toxicity depends on the true dose of exposure:
- Higher concentrations of particles can lead to increased biological effects.
- The true dose is often quantified by the concentration of particles inhaled.

The number-concentration-based RCS samples could be an alternative index for RCS true dose estimations:
- RCS (Respirable Carcinogen Survey) samples are collected to assess the potential risk of respiratory exposure to carcinogenic substances.
- Number-concentration-based samples can provide a more direct measure of the number of particles inhaled, which can be used to estimate the true dose.

Lesser degree reenter into the interstitium and enter the lymphatics:
- Once deposited, particles can be transported through the body via the lymphatic system, which is an important route for the absorption and subsequent elimination of substances.
- This process can be influenced by factors such as particle size, shape, and surface properties.
Respirable dust particle deposition experiment

This study is funded by the National Institute for Occupational Safety and Health (NIOSH) [75D30119C06390]. Mobile Aerosol Lung Deposition Apparatus (MALDA) was designed and fabricated by Dr. Wei-Chung Su at the UTHealth.
**Previous Studies**

**Aspirations**
(100µg/50µL Claim 28 or St. Anthony Mine)

**Euthanize Mice**

- Cellular infiltration into the lung
- Lung gene expression
- Autoantibodies in serum

**Study design.** Mice were subjected to PM exposures via pharyngeal aspiration (100µg/50µL). Three groups of mice (n=8) were exposed to either dispersion media (DM), Claim 28 dust, or St. Anthony mine dust, repeatedly, once per week (wks. 8-11)
Previous Studies

Claim 28 and St. Anthony mine dust exposure led to an increase in neutrophil infiltration into the lung.

**Bronchoalveolar lavage (BAL) fluid parameters.** Following euthanasia of each mouse, BAL was collected via tracheal puncture and assessed for number of inflammatory cells for A) total cell counts (cells x 10^5) B) macrophage cells (cells x 10^5) C) neutrophilic cells (cells x 10^5) and D) total protein.
Previous Studies

- Early-life exposure to St. Anthony mine dust resulted in long-term lung inflammation in a mouse model.
- Claim 28 dust exposure did not result in the same long-term lung inflammation in a mouse model.
- Follow-up studies involving exposure to dusts with silica and other metals is warranted.

**Lung gene expression and neutrophil elastase** Statistics were executed using a one-way ANOVA followed by a Kruskal-Wallis post hoc test and considered significant at p<0.05.
Silica Dust Toxicity Level

- Collection of PM from mine-sites
- Characterization of PM
- Expose rodents to aerosolized dusts in the chamber (controlled exposures)
- Measure biological endpoints

"Bench-scale" biomass exposure system in the University of New Mexico Inhalation Toxicology Laboratory allows for control of fuel type, air supply, dilution and filtration, with real-time monitoring of PM1, PM2.5 and PM10 mass concentration and PM size distribution.
A Molecular Epidemiological Study of Lung Injury in Miners

**Study subjects**
- Miners with PMF
- Miners with silicosis
- Miners with healthy lungs
- Non-miners controls

**Environmental exposure**
- Number concentration
- Mass concentration
- Size distribution
- Surface area
- Elemental content

**Induction sputum**
- Particle characterization in macrophages
- Inflammatory cell count and differential
- Cytokines and chemokines
- Fibroblast chemoattractant and growth and collagen production factors

**Outcome**
- Group identification (Differences between exposures or injuries)
- Lung function
- Airway dimensions
- Lung injury biomarker

**External exposure**

**Internal Exposure**

**Lung inflammation**

**Lung tissue injury and remodeling**
Conceptual Framework

Phagocytosis
silica content in airway

Lung inflammation
Cytokines and chemokines

Lung injury (\(\downarrow\)CC16 - Clara cell injury; \(\uparrow\)SPA - airway membrane leakage, and \(\downarrow\)spirometry – unknown mechanism)

Airway remodeling

Genomic instability

Endothelial cell activation

Pulmonary toxicity

Extra-Pulmonary toxicity
Previous Studies

Carbon content in airway macrophage as an internal bio-effective dose of nano-scale carbon black exposure

- 10-50 nm diameter for primary carbon sphere
- Aggregate as smallest inseparable unit of nano-scale size (<1000 nm)
- Inhalation as major exposure path in humans during manufacture
Quantitative Computerized Tomography Assessment of Small Airway Dimensions

Karayama, et al. Scientific Reports 2017
Carbon content in airway macrophages was associated with airway wall thickening at 6th and 9th generations of airways in a monotonically increasing dose-response manner.
Higher airway wall thickening at 6th and 9th generations of airways was associated with lower lung function (FEV1 and FVC) and worse airway obstruction (FEV1/FVC).
Long-term Goal

- Prediction of lung diseases
- True dose of exposure
- Dust control improvement
Thank You!

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Tracheobronchial Tree

- No cartilage
- No goblet cells
- ↓Ciliated cells
- ↑Smooth muscle
- ↑Clara cells
- SPA

Small airway
Intraclass Correlation Coefficient

How strongly the pattern of first measures as a group resembles the second measures

Quantitative CT and advanced analytical informatics allow a precise and reliable assessment of small airway dimensions

Cao X, ..., Leng S. Toxicol Sci, 2020