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

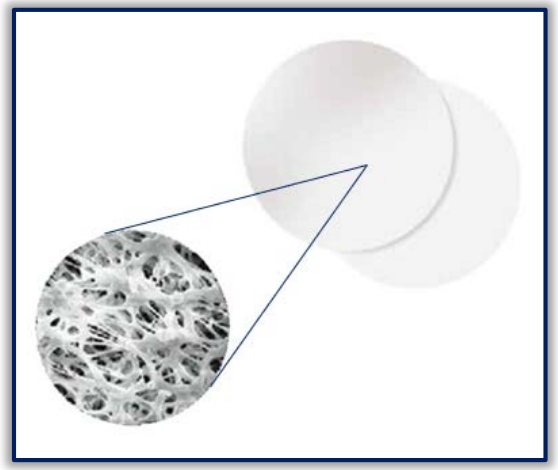
Degree of lung injury

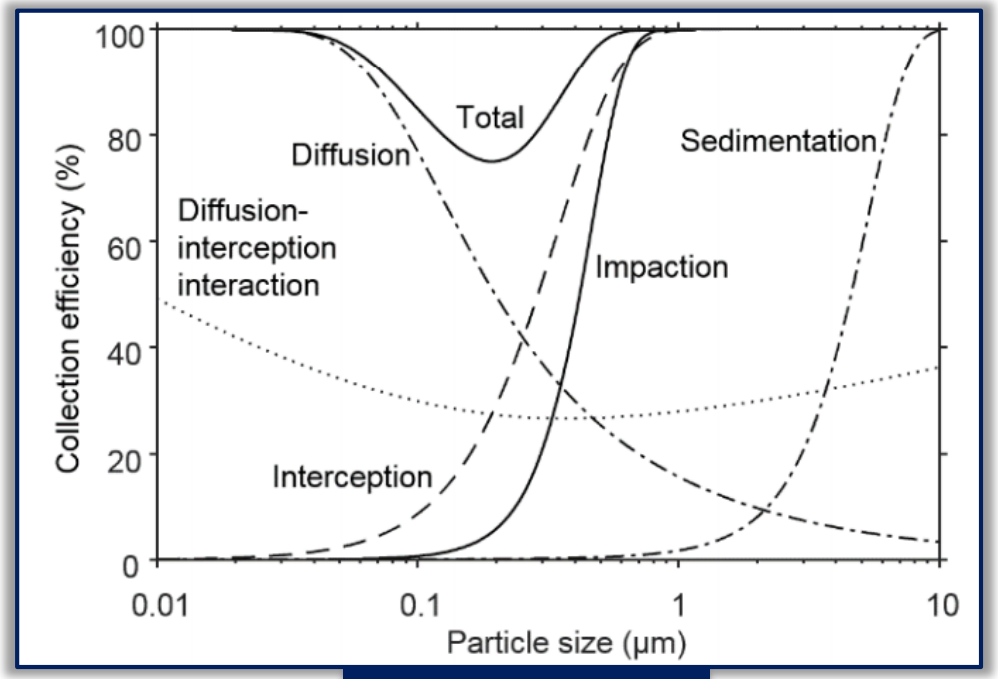
RCS monitoring methods (crystalline silica on filters)

P7 method (FTIR)	Coal mines
P2 method (XRD)	Metal/nonmetal mines
NIOSH	7500 (XRD)
NIOSH	7602 (IR-KBr pellet)
NIOSH	7603 (IR-redeposition)
OSHA	ID#142 (XRD)

Filters with the maximum collection efficiency (e.g., PVC filters)

The total mass of the RCS collected on a filter is assumed to <u>all become the miner's exposure dose</u>

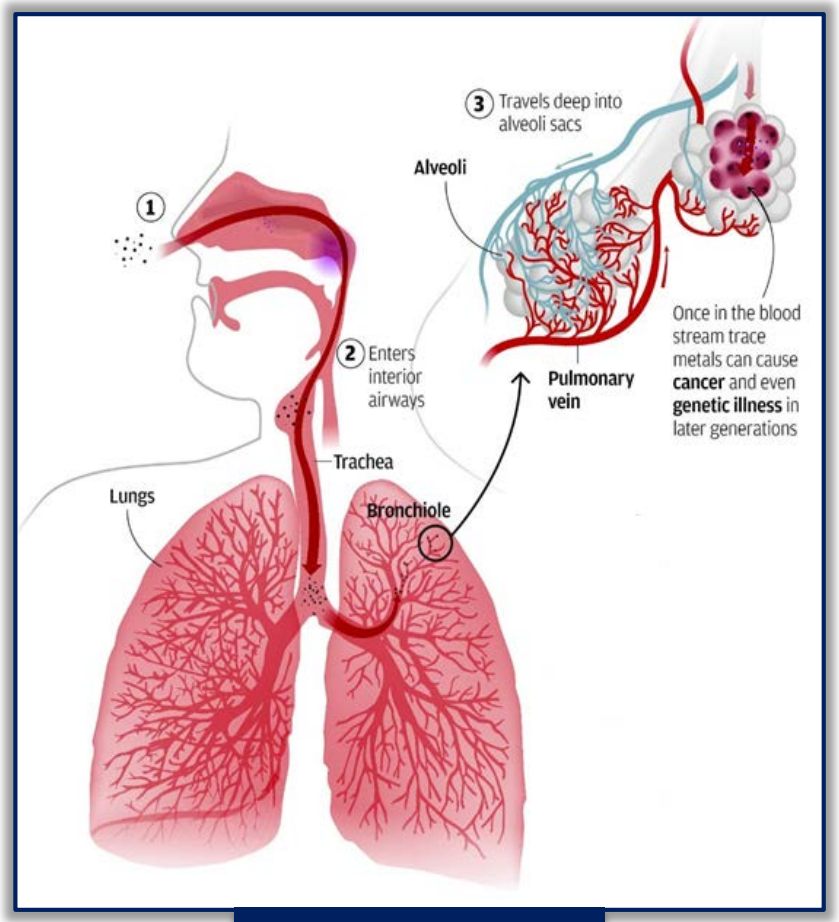




Graph from NIOSH manual of Analytical Methods

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)

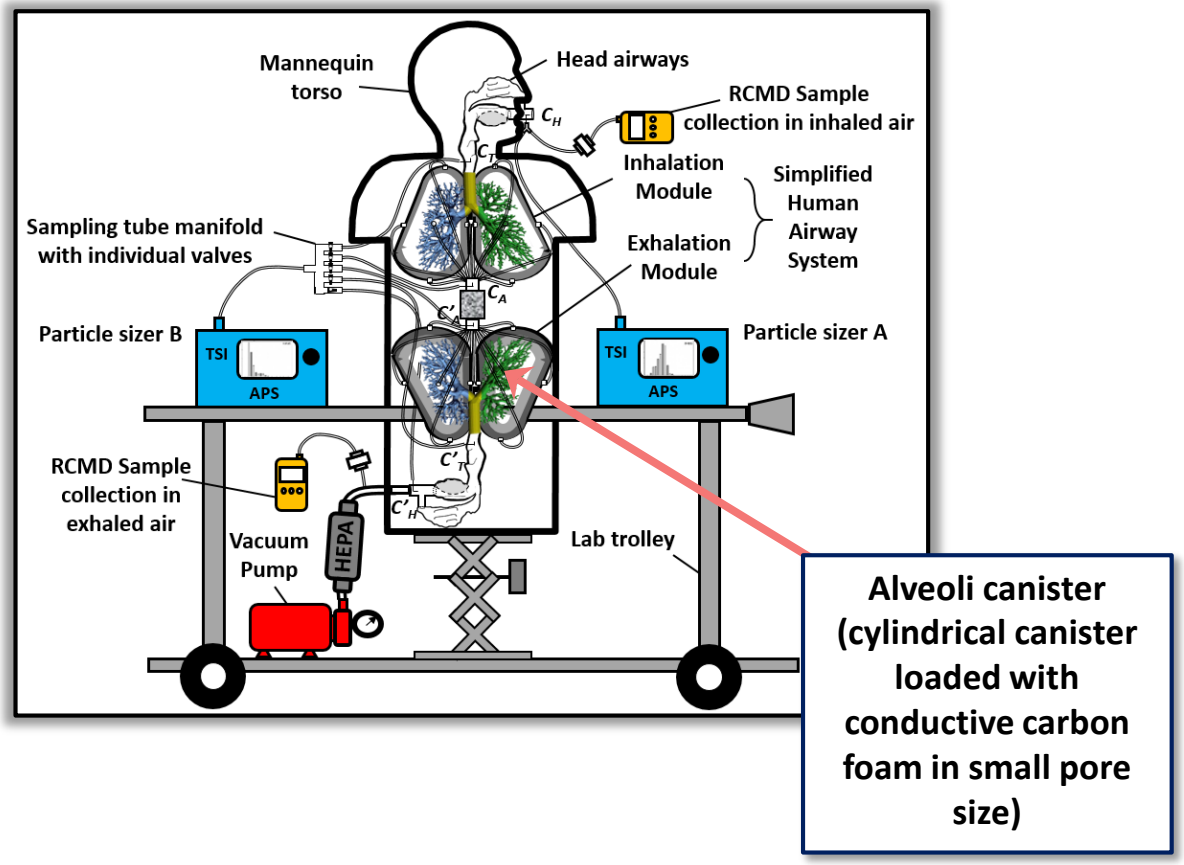


(Photo from epa.gov)

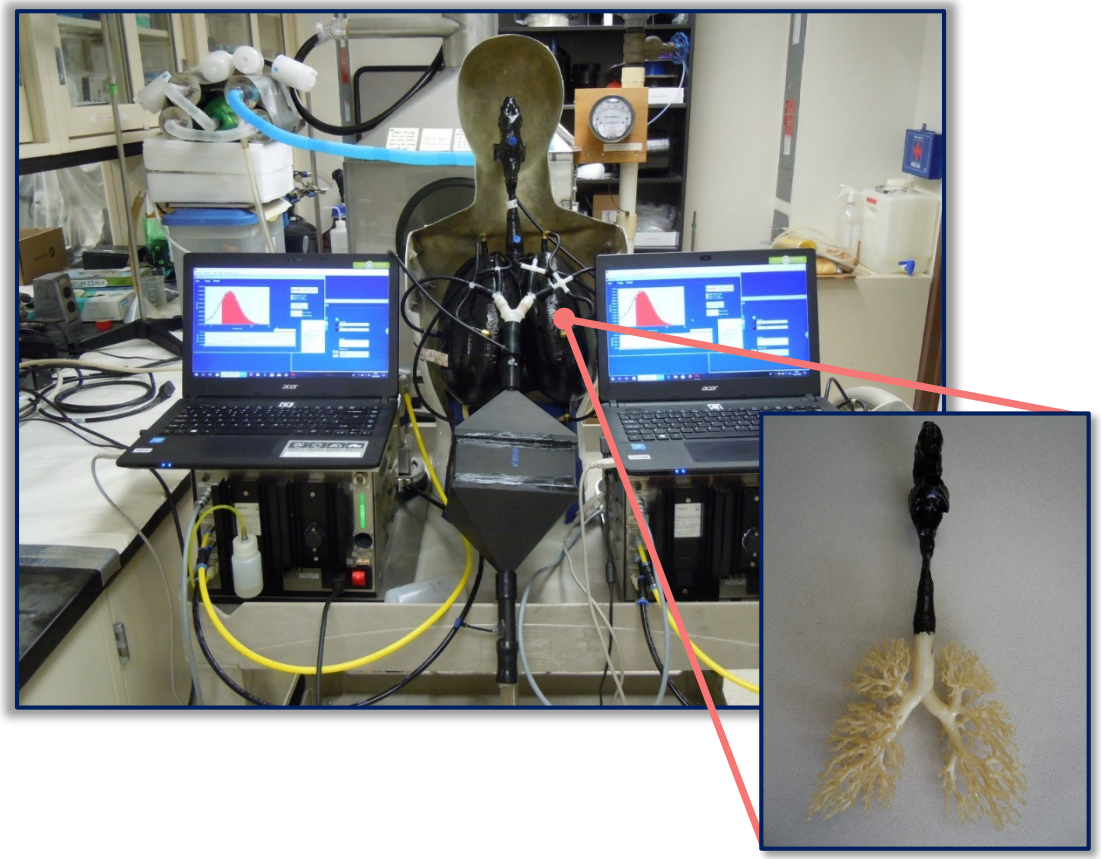
- **Mucociliary clearance** is the
- Dust particle respiratory deposition depends on the particle size and particle shape
- The level of toxicity depends on the true dose of exposure
- The number-concentration-based RCS samples could be an alternative index for RCS true dose estimations

lesser degree reenter into the interstitium and enter the lymphatics

Respirable dust particle deposition experiment



Alveoli canister (cylindrical canister loaded with conductive carbon foam in small pore size)



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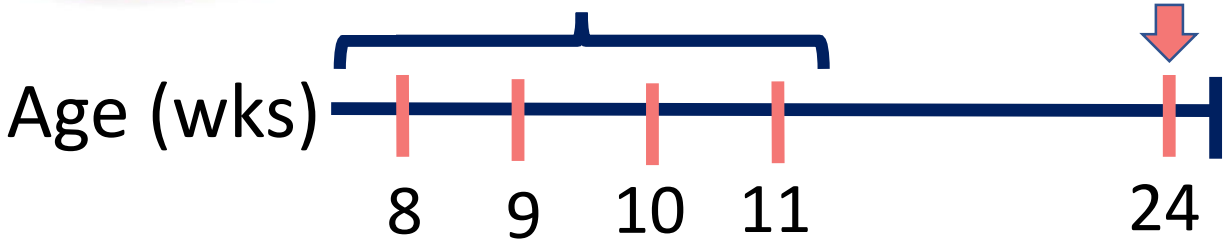
Previous Studies

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

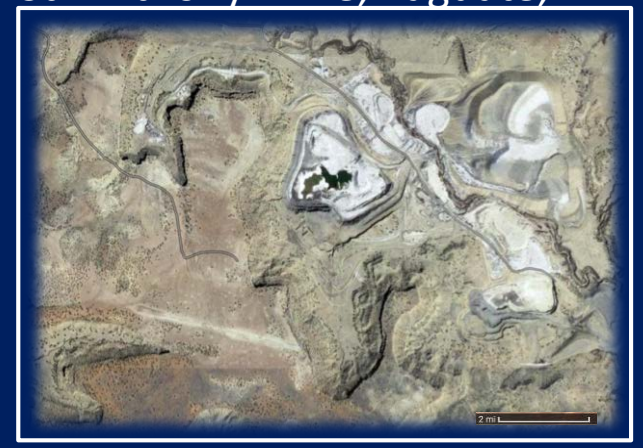
Euthanize
Mice



- 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)

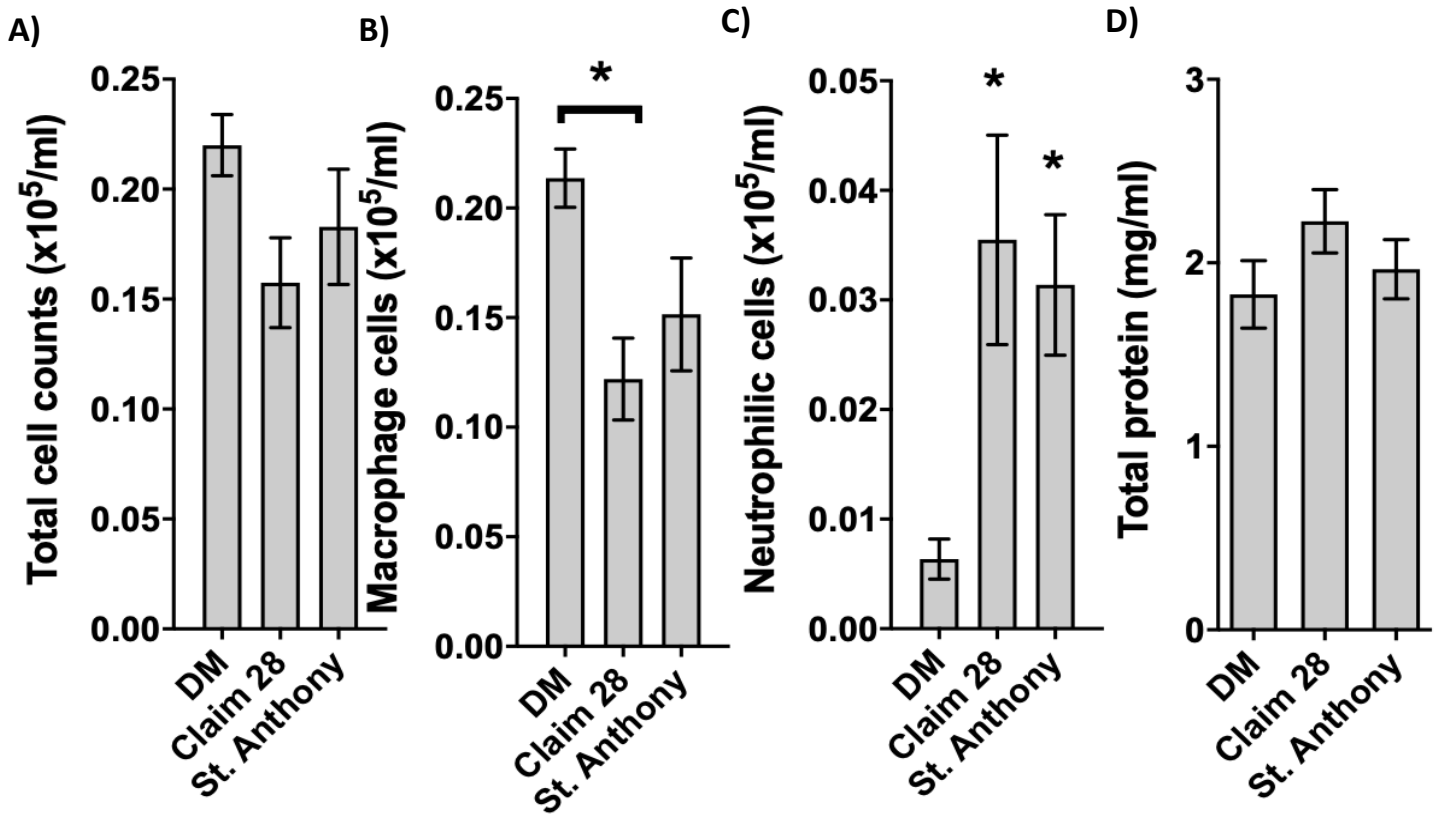
St. Anthony Mine, Paguate, NM



Claim 28, Blue Gap Tachee, AZ

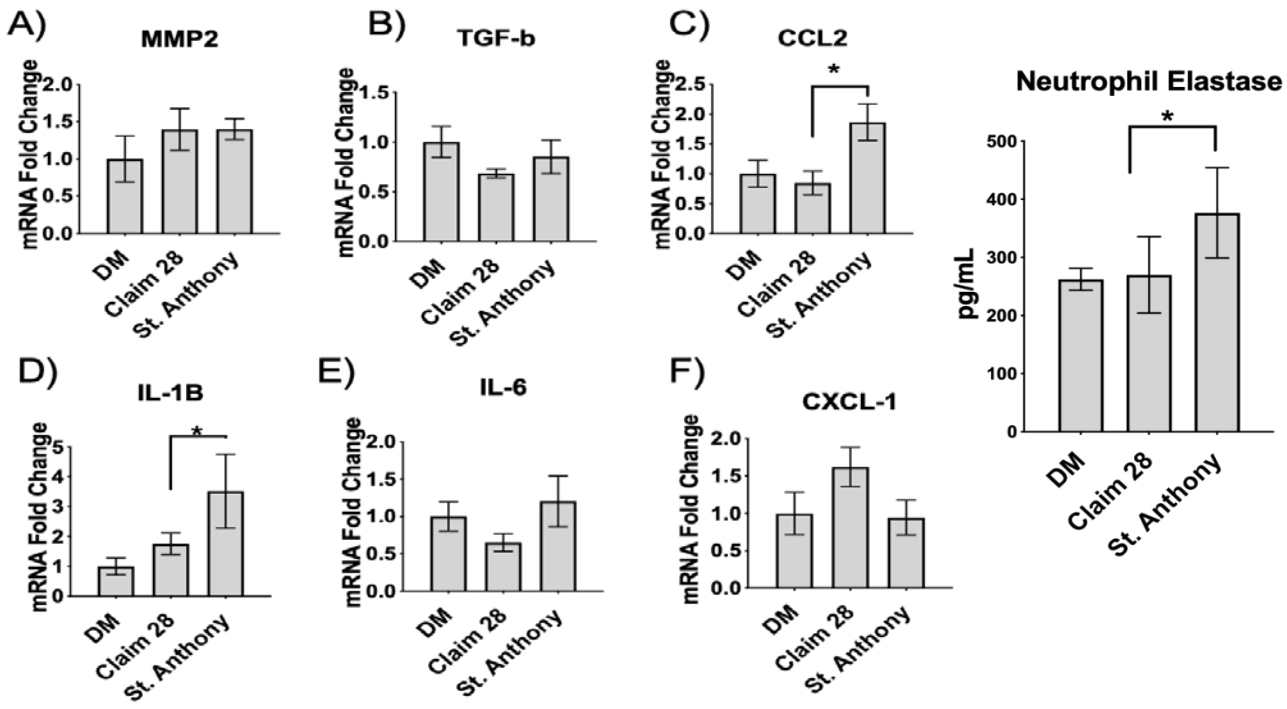
Previous Studies

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 x10^5) B) macrophage cells (cells x10^5) C) neutrophilic cells (cells x10^5) and D) total protein

Previous Studies

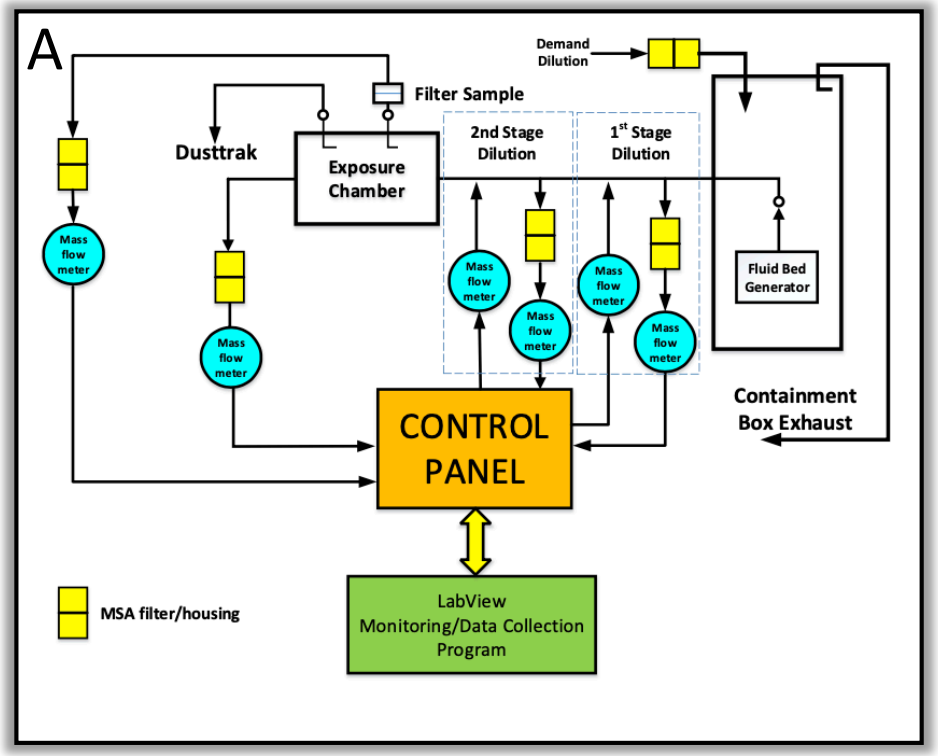


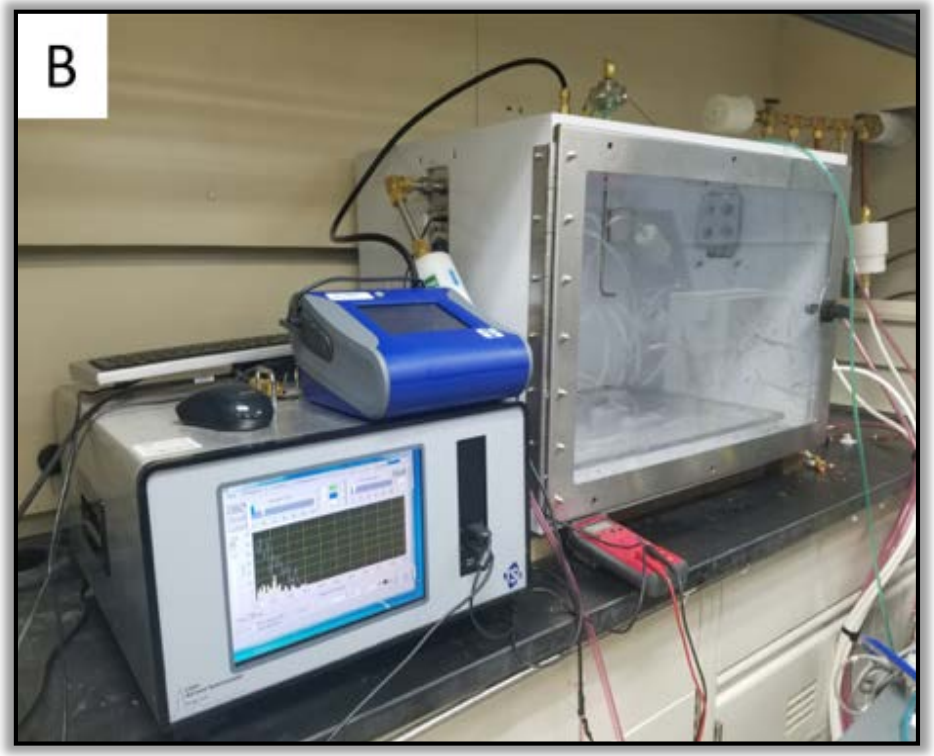
Lung gene expression and neutrophil elastase Statistics were executed using a one-way ANOVA followed by a Kruskal-Wallis post hoc test and considered significant at $p<0.05$.

- 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

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

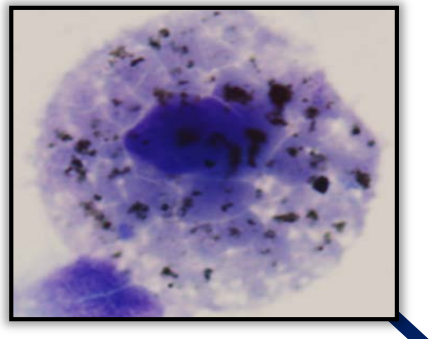
A Molecular Epidemiological Study of Lung Injury in Miners

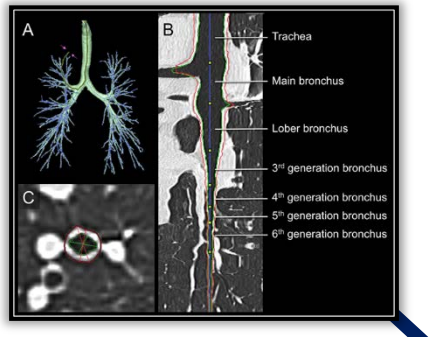
Study subjects
- Miners with PMF
- Miners with silicosis
- Miners with healthy lungs
- Non-miners controls

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

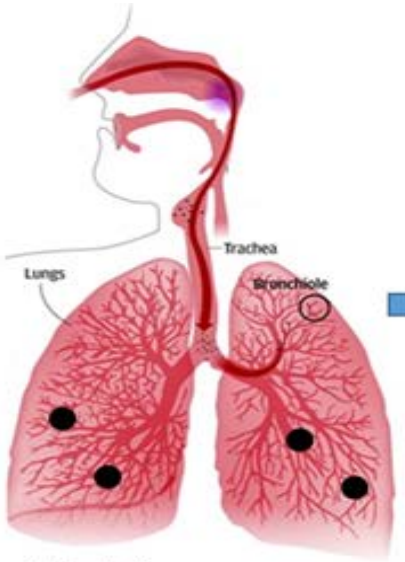
Outcome
- Group identification (Differences between exposures or injuries)
- Lung function
- Airway dimensions
- Lung injury biomarker



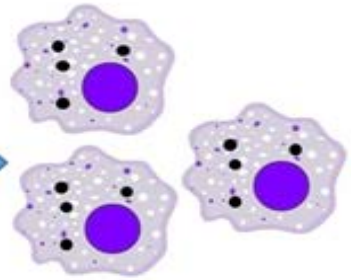


External exposure → **Internal Exposure** → **Lung inflammation** → **Lung tissue injury and remodeling**

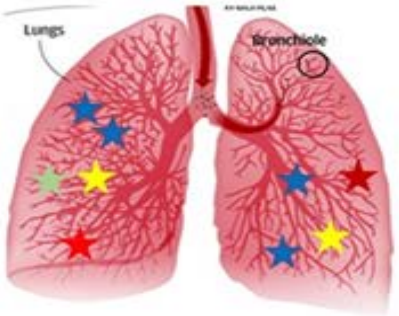
Conceptual Framework



Inhalation exposure



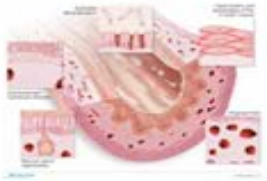
Phagocytosis silica content in airway



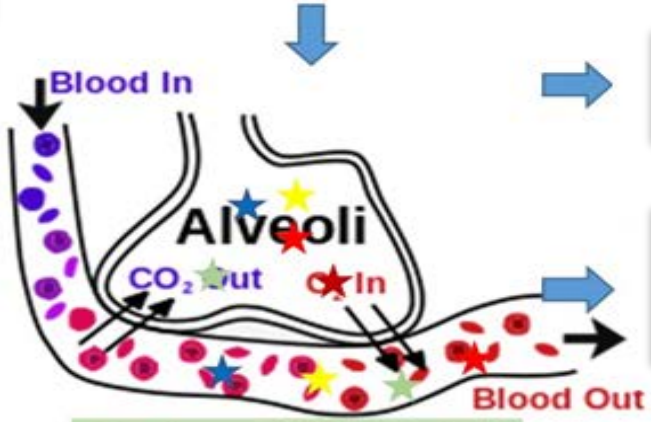
Lung inflammation
Cytokines and chemokines

Lung injury (↓CC16 - Clara cell injury; ↑SPA - airway membrane leakage, and ↓spirometry – unknown mechanism)

Airway remodeling



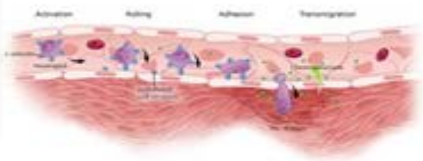
Pulmonary toxicity



Circulatory inflammation

Genomic instability

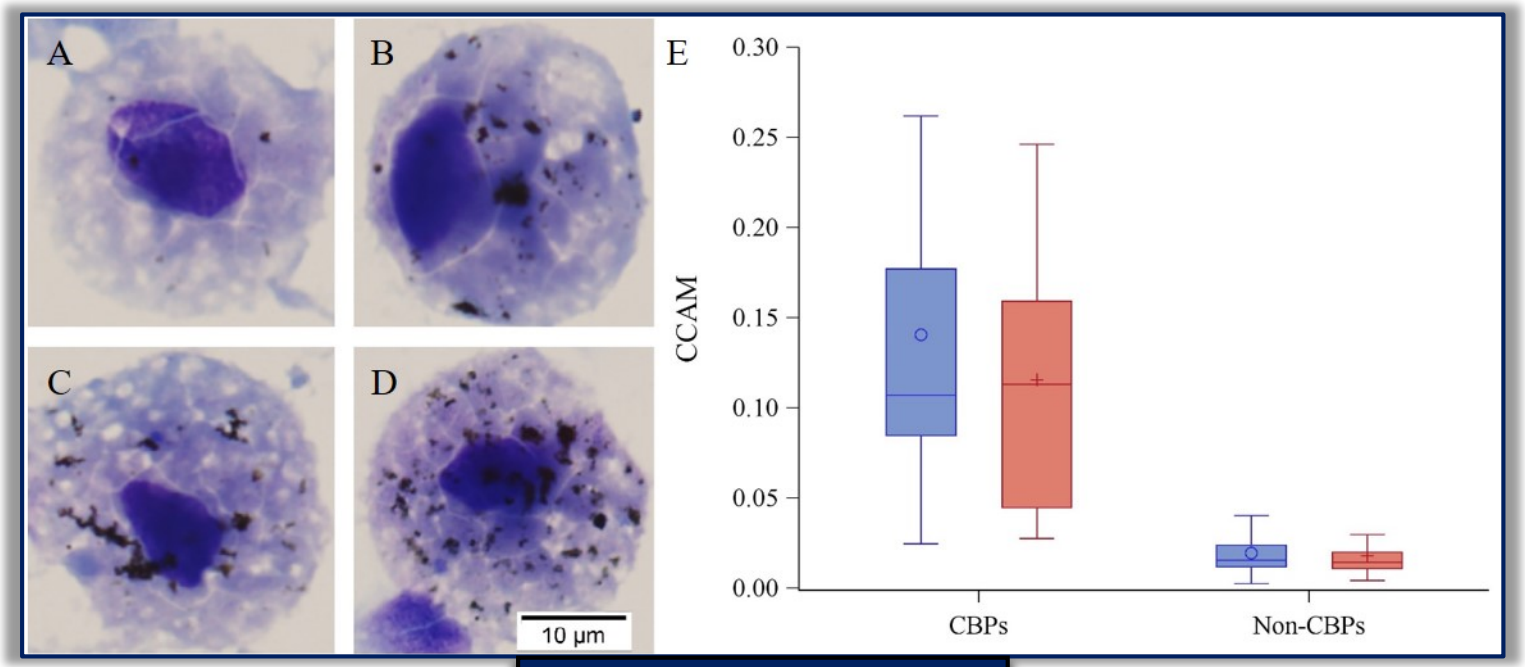
Endothelial cell activation



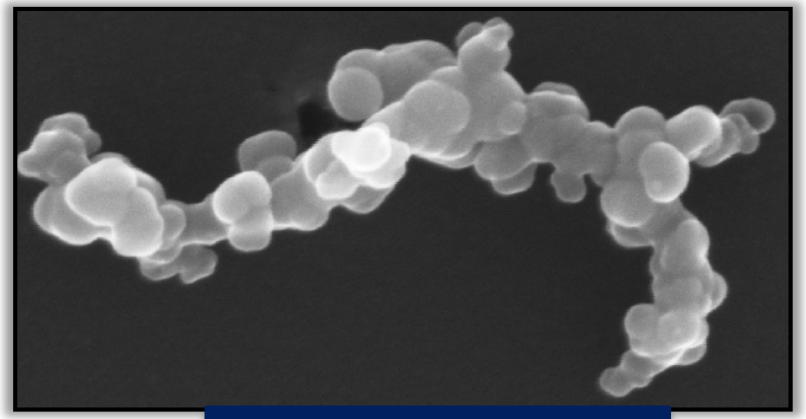
Extra-Pulmonary toxicity

Previous Studies

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



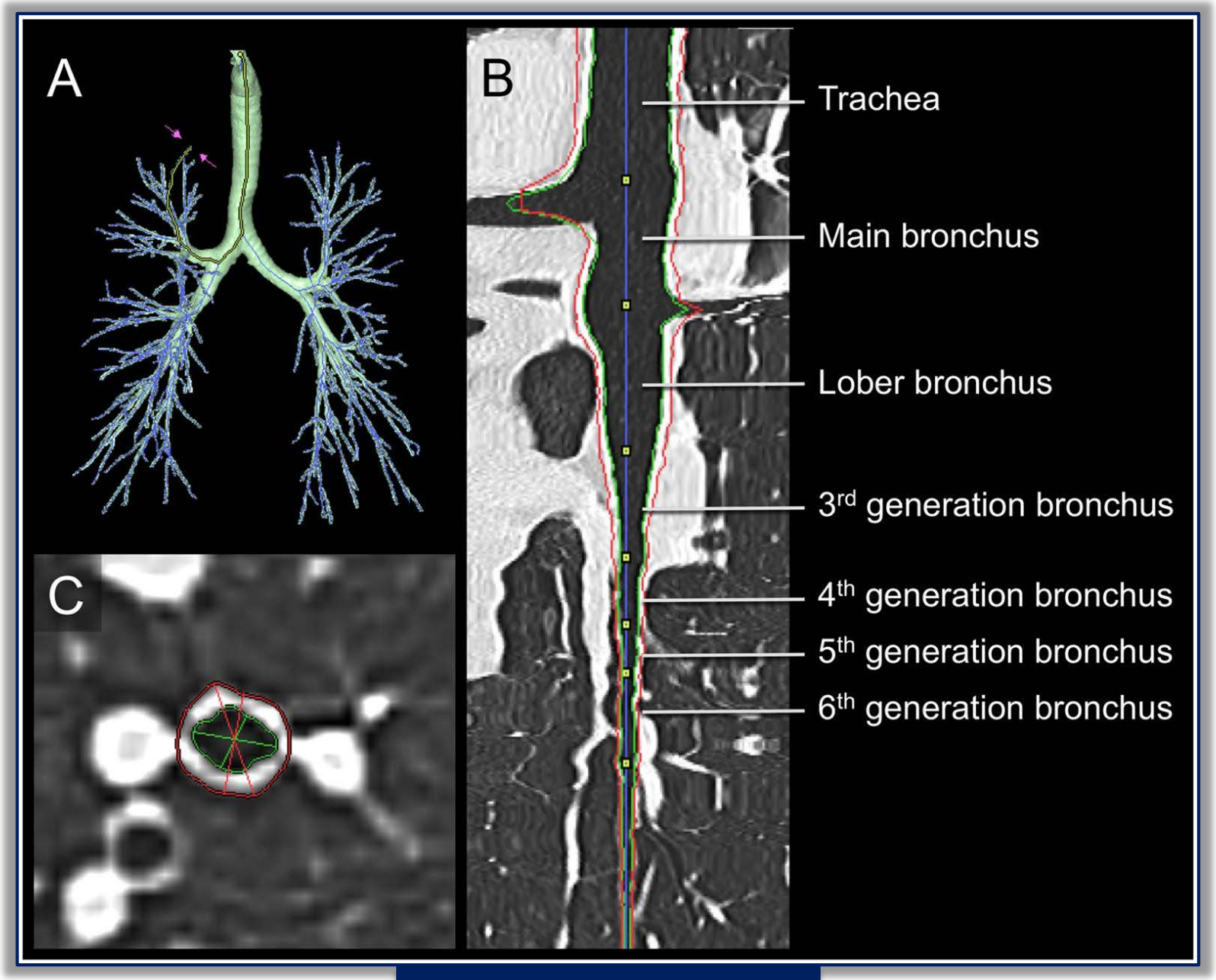
Cao X, …, Leng S. Toxicol Sci, 2020



Carbon black aggregate under Scanning Electron Microscope

- 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

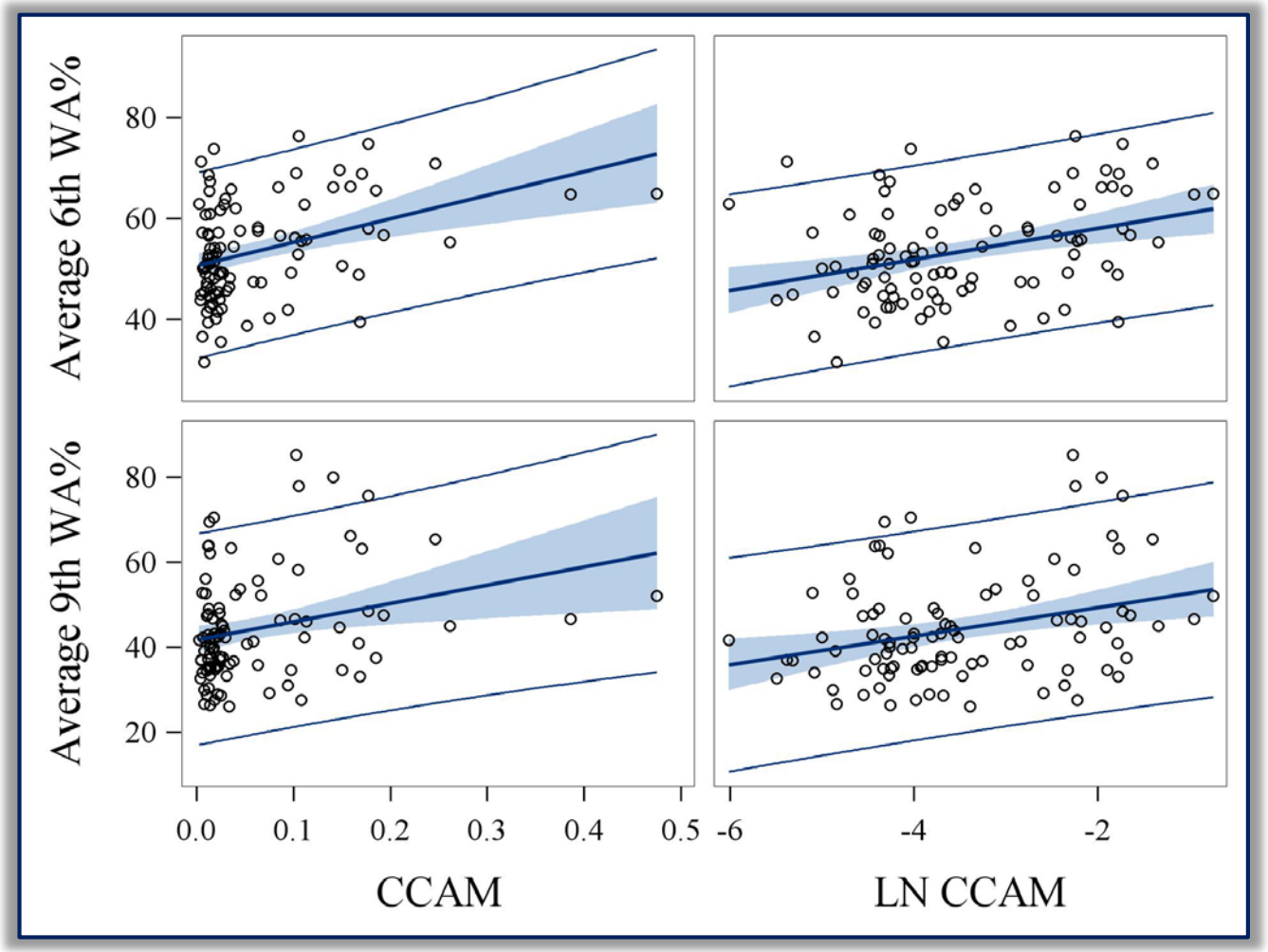
Quantitative Computerized Tomography Assessment of Small Airway Dimensions



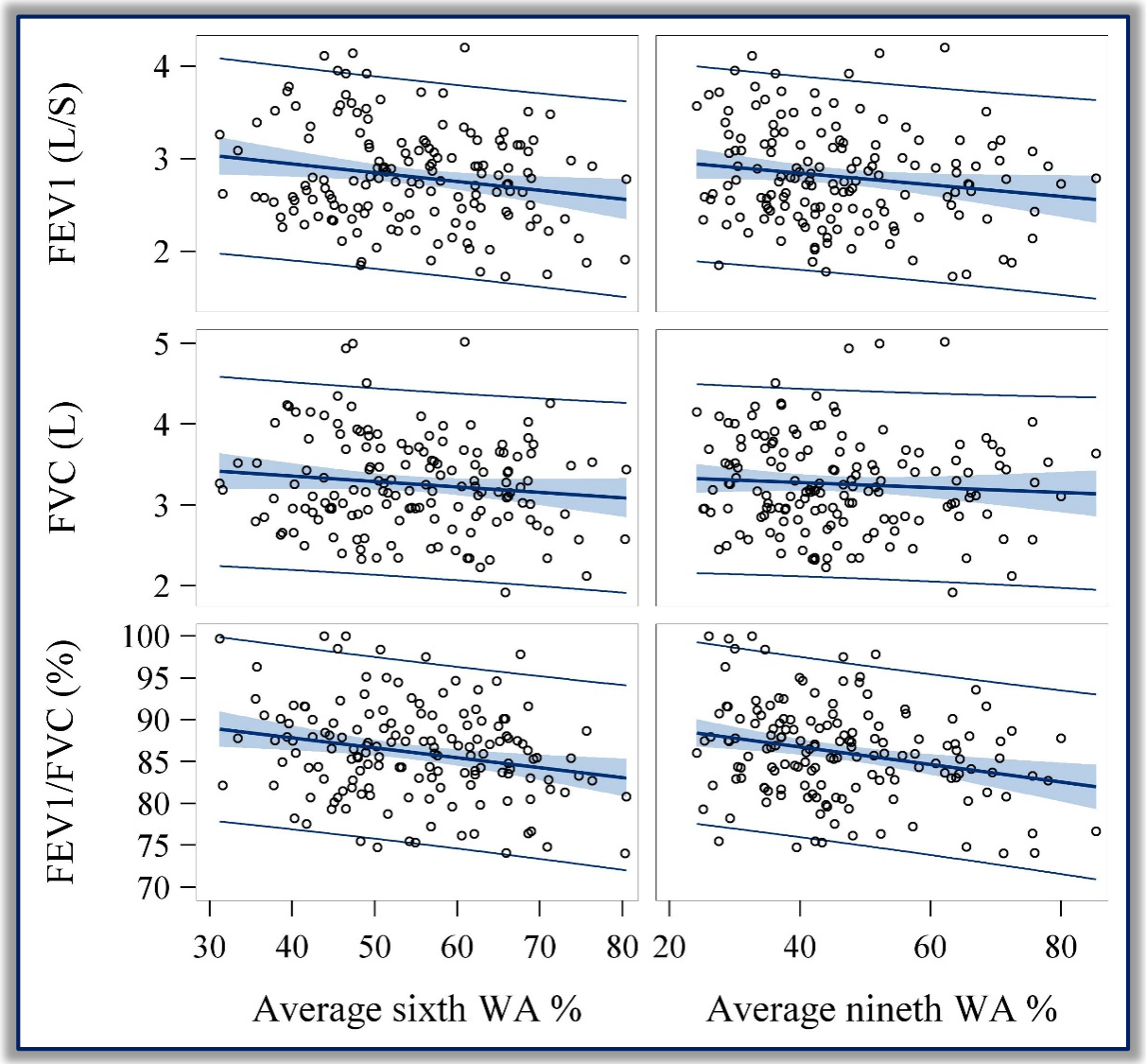
Karayama, et al. Scientific Reports 2017

Scatter Plots and Correlation Between CCAM and Average Wall Area %

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.

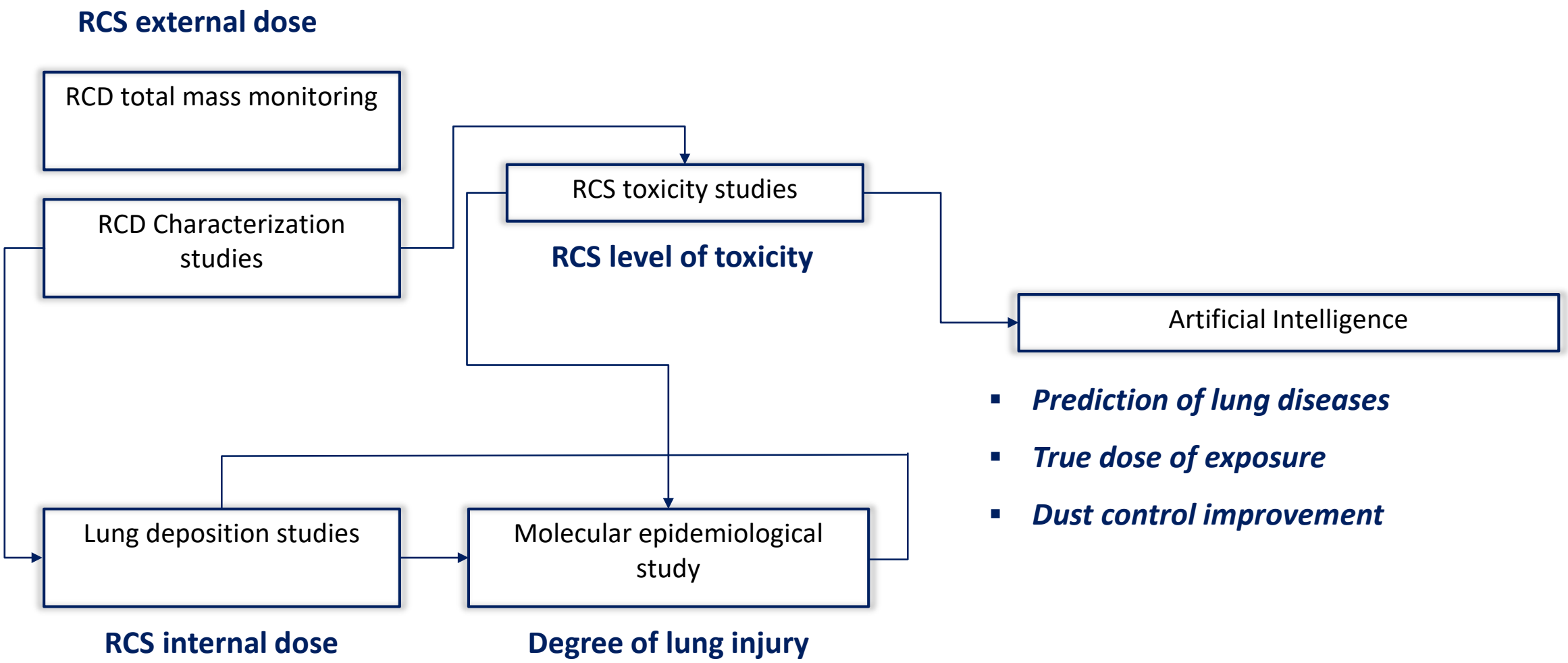


Scatter Plots and Correlation Between Small Airway Measurements and Lung Function



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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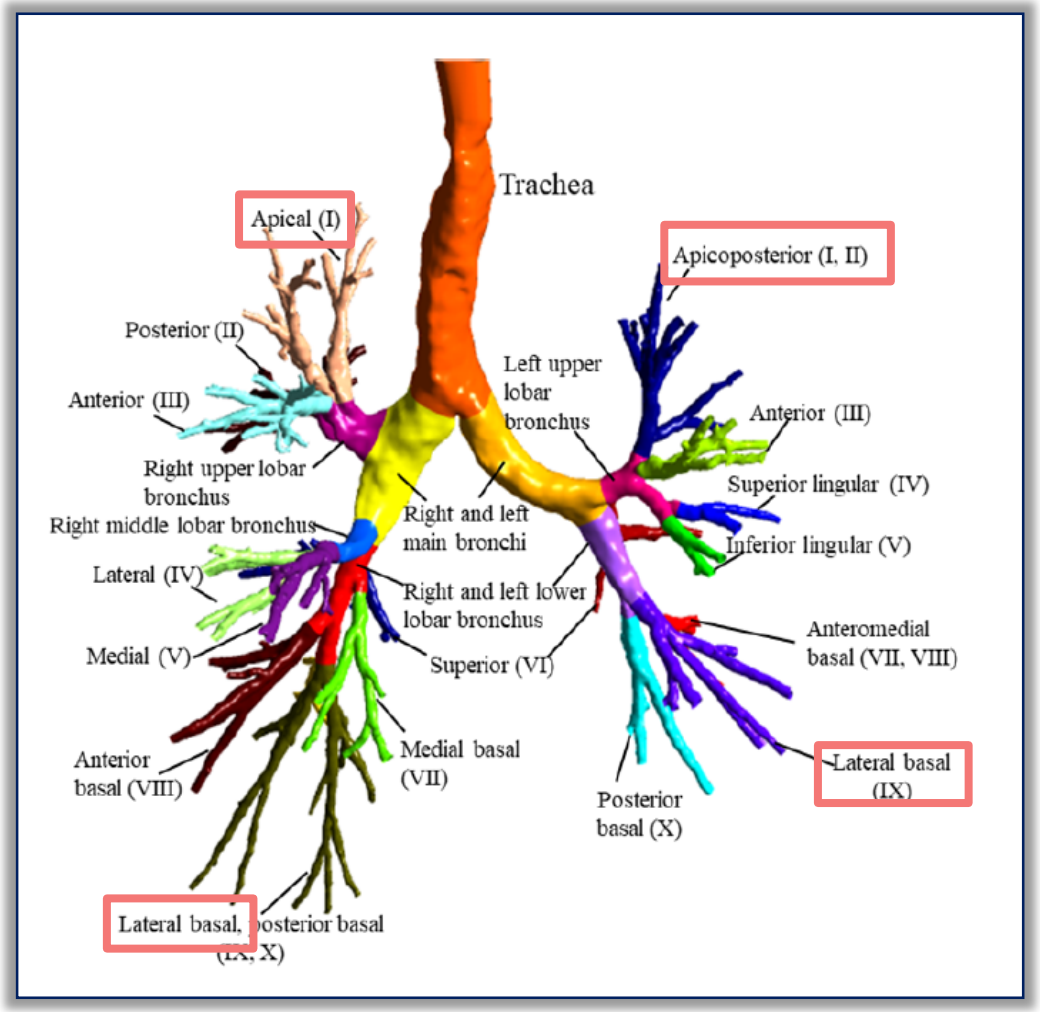
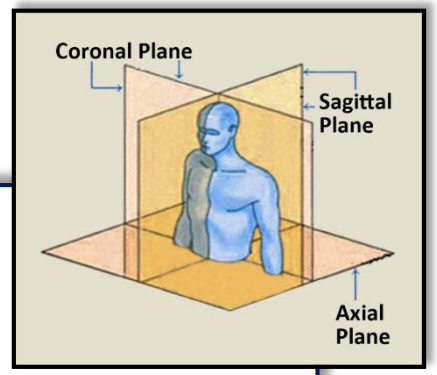
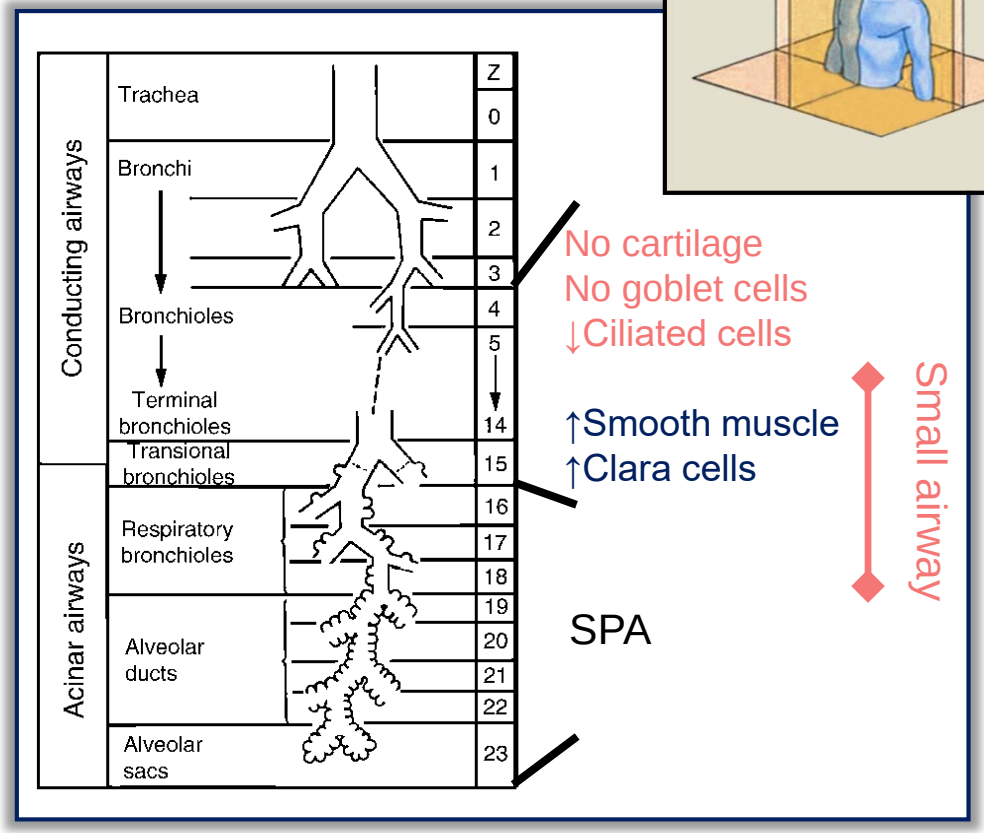
Tracheobronchial Tree

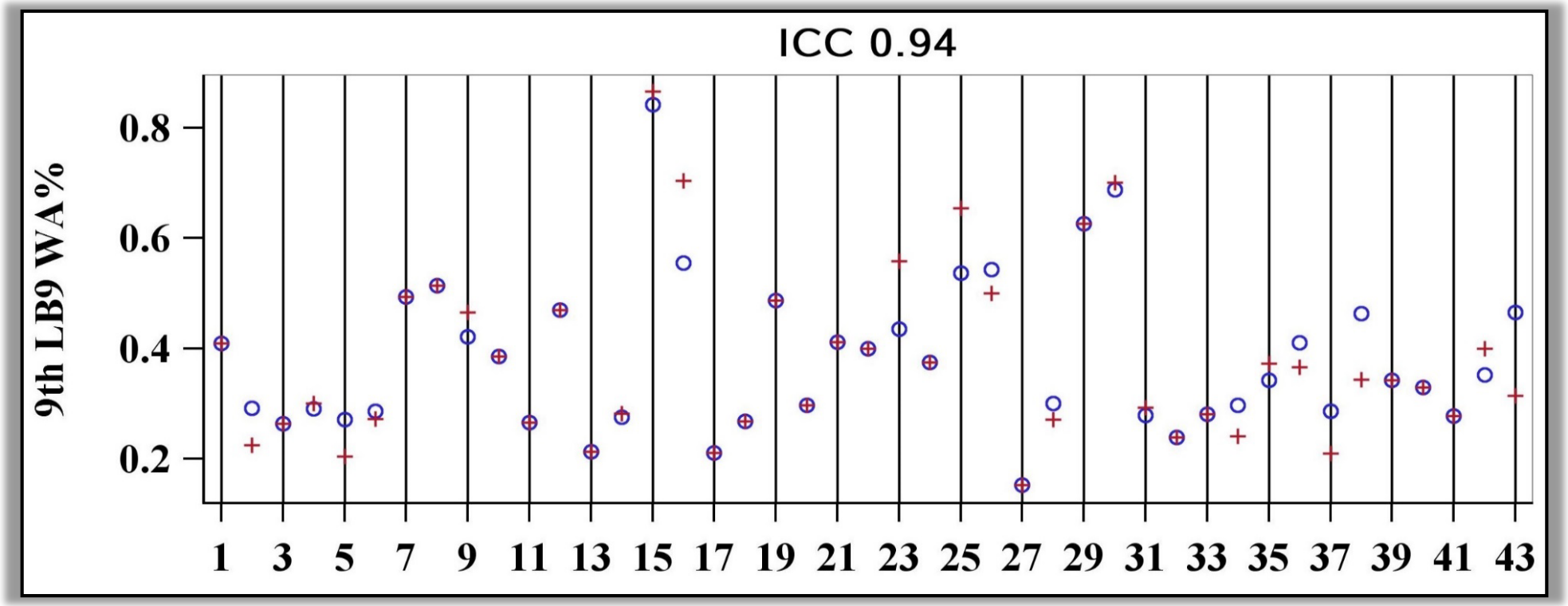






Intraclass Correlation Coefficient

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