20th ETH Conference on Combustion Generated Nanoparticles

June 13th – 16th, 2016
ETH Zurich, Switzerland

Section 6B: Health Session

Dosimetry, Dose-metrics, Bioprocessing and Human Risk Extrapolation

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and
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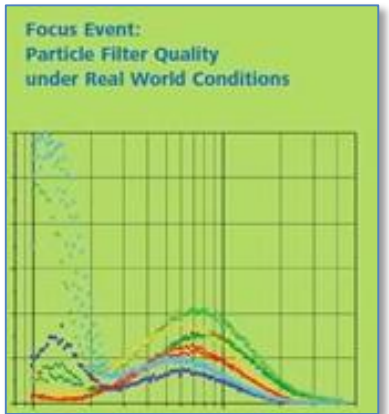
University of Kentucky

15 June 2016



UNIVERSITY of ROCHESTER MEDICAL CENTER

REACTIVITY OF ULTRAFINE PARTICLES

High specific surface area: m^2/g

Surface Reactivity as Dose-Metric,

***e.g.*, ROS inducing potential to determine response per unit particle surface area**

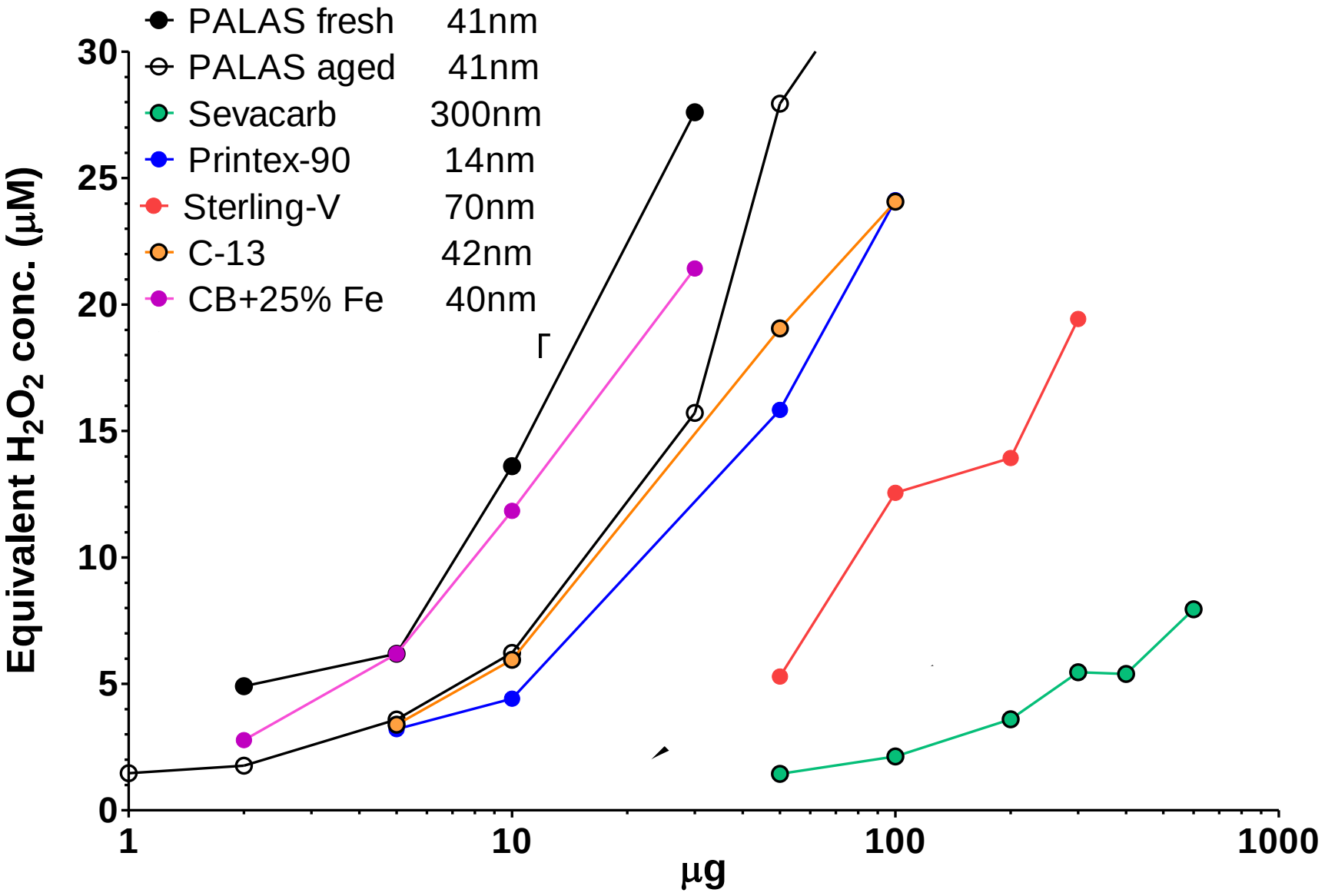
DTT *(dithiothreitol)* assay
DCFH-DA *(2'-7' dichlorofluorescin-diacetate)* assay
FRAS *(ferric reducing ability of serum)* assay
Vit C assay
ESR
others…

as screening tool for categorization of UFPs based on reactivity in cellular or cell free assays for Hazard Ranking

[Bello et al., 2009; Rushton et al., 2010]

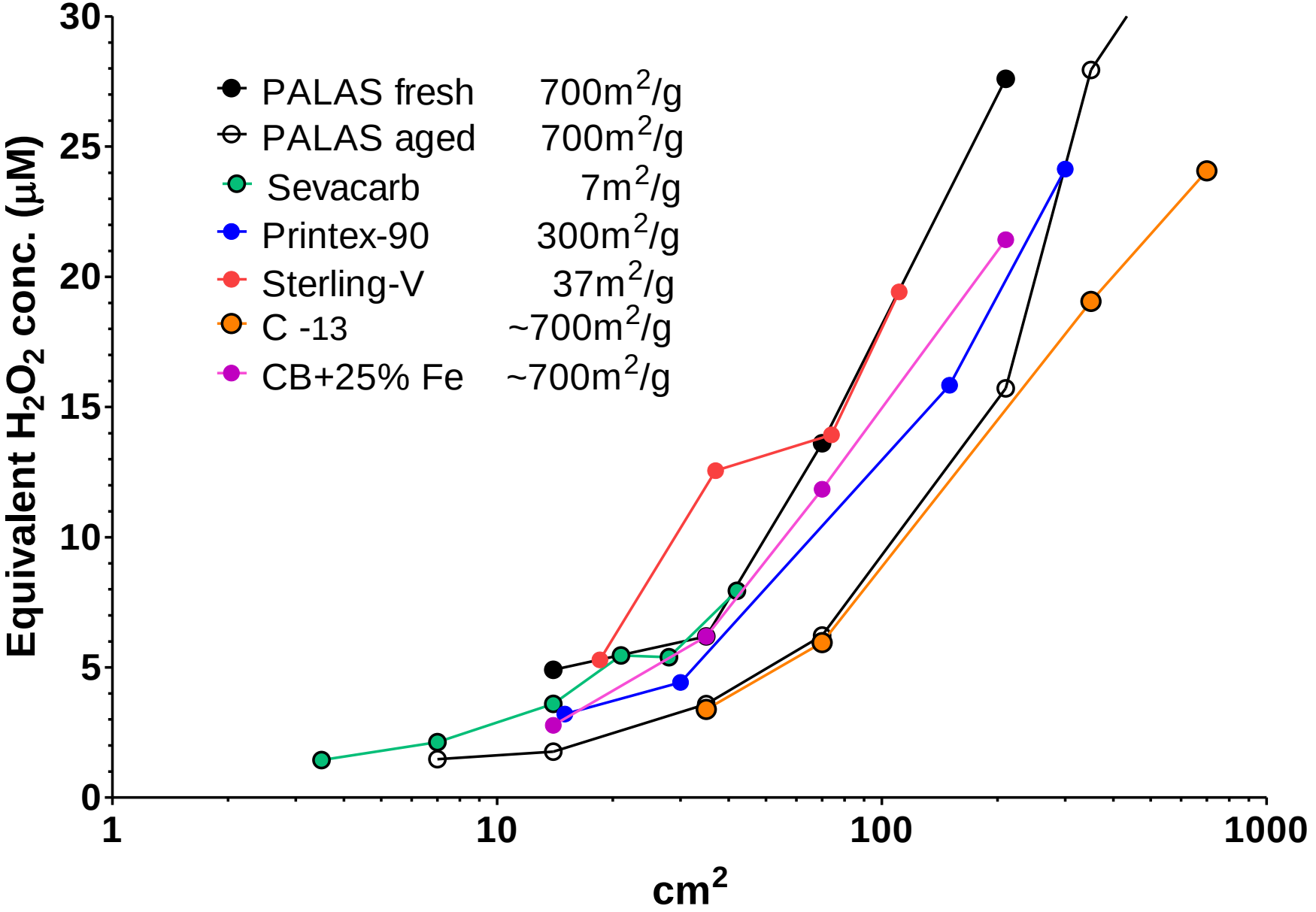
Noncellular Nanoparticle ROS Summary *(Carbon Particles)*

Particle Mass Correlation

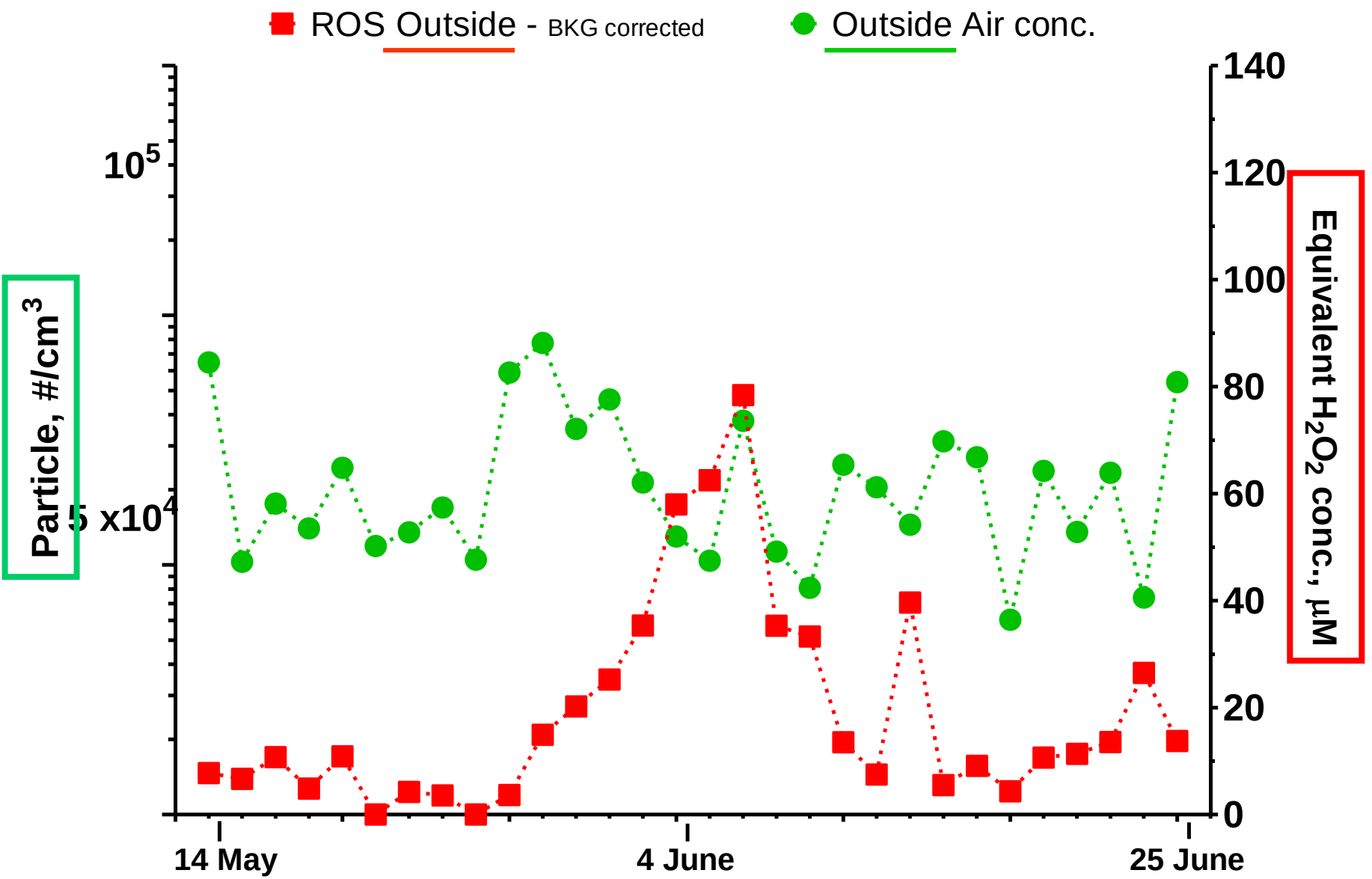


Noncellular ROS Summary *(Carbon Particles)*

Particle Surface Area Correlation



Animal Studies: May 14 - June 25, 2008



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CONCLUSIONS, UF PARTICLE BOUND ROS (oxidative potential)

- **ROS activity/m^3 of ambient UFP can vary widely**
- **ROS activity of lab-generated nanoparticles seems to reasonably well predict acute in vivo responses**
- **ROS activity of ambient UFP does not necessarily parallel their number or mass concentration**
- **Do results of epidemiological studies indicate association between UFP reactivity and effects at organ of entry or secondary organs?**

Challenges re UFP Standard:

Physico-chemical properties of UFP are different from different sources:

Elemental carbon
Organic carbon compounds
Inorganics (metals)
Agglomeration/aggregtion
Surface properties
Solubility
Volatility

} **influence Toxicity**

UFP source A ≠ UFP source B ⟹ different biol./toxicol. effects

Proposed Concept for Standard

- **UFP standard should best be source-specific**
- **Based on number concentration of emitted UFP**
- **Need to identify sources that emit most reactive UFP**
- **Regulate these sources *(rather than all UFP)* by introducing a number emission standard, based on UFP risk assessment**

What is surface reactivity of Coal/Biomass Combustion Generated Nanoparticles?

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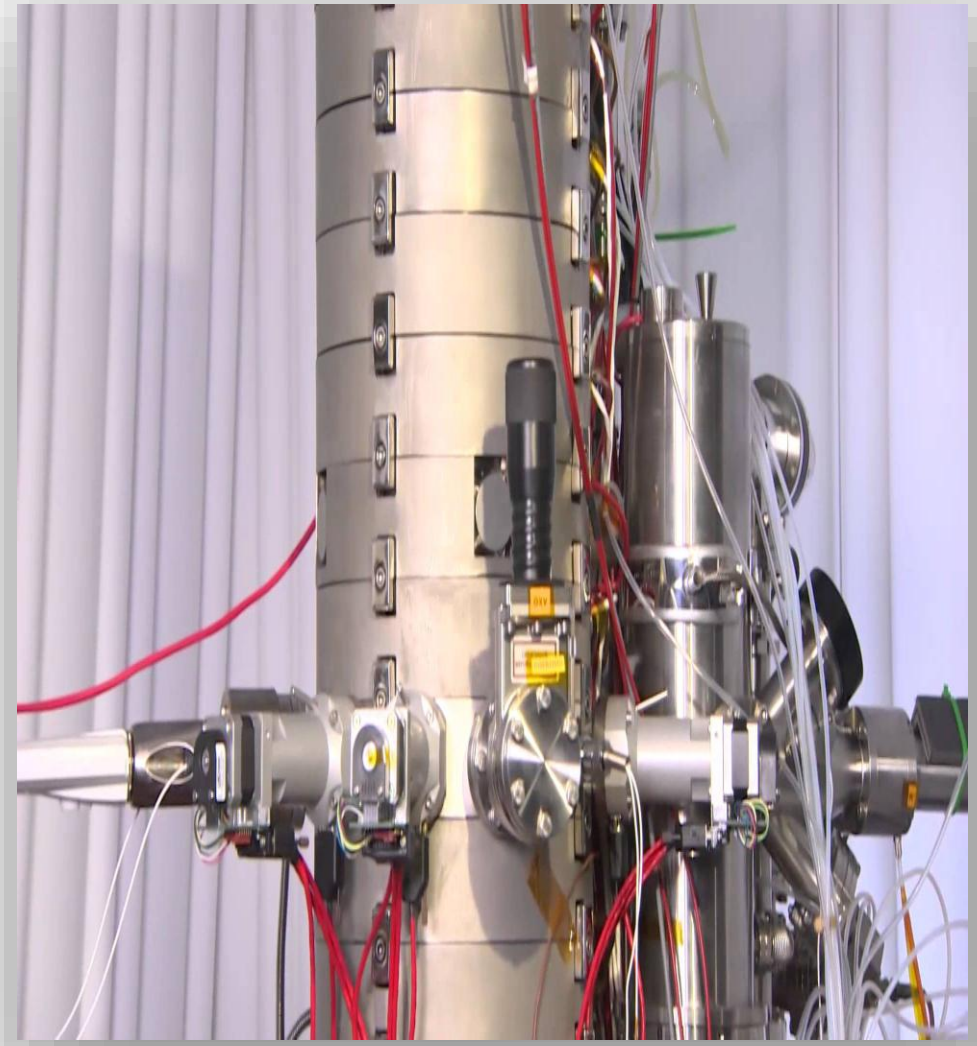
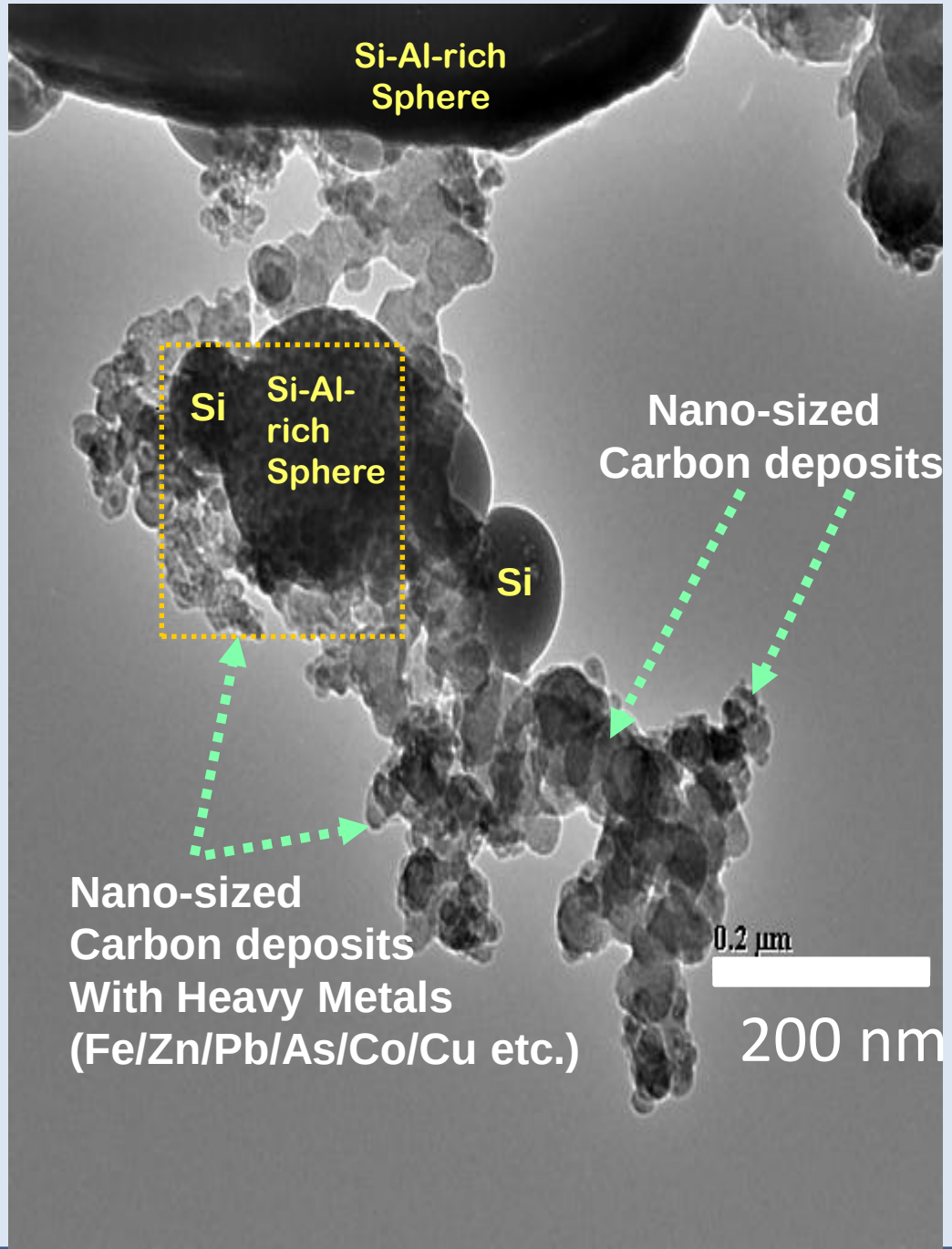
Chem. Characterization by HR-TEM/STEM/EELS



Coal Combustion Ash



Case study with inhaled Nano SiO_2NPs:

Exposure-Dose-Response Inhalation Study in Rats to determine No Effect Level

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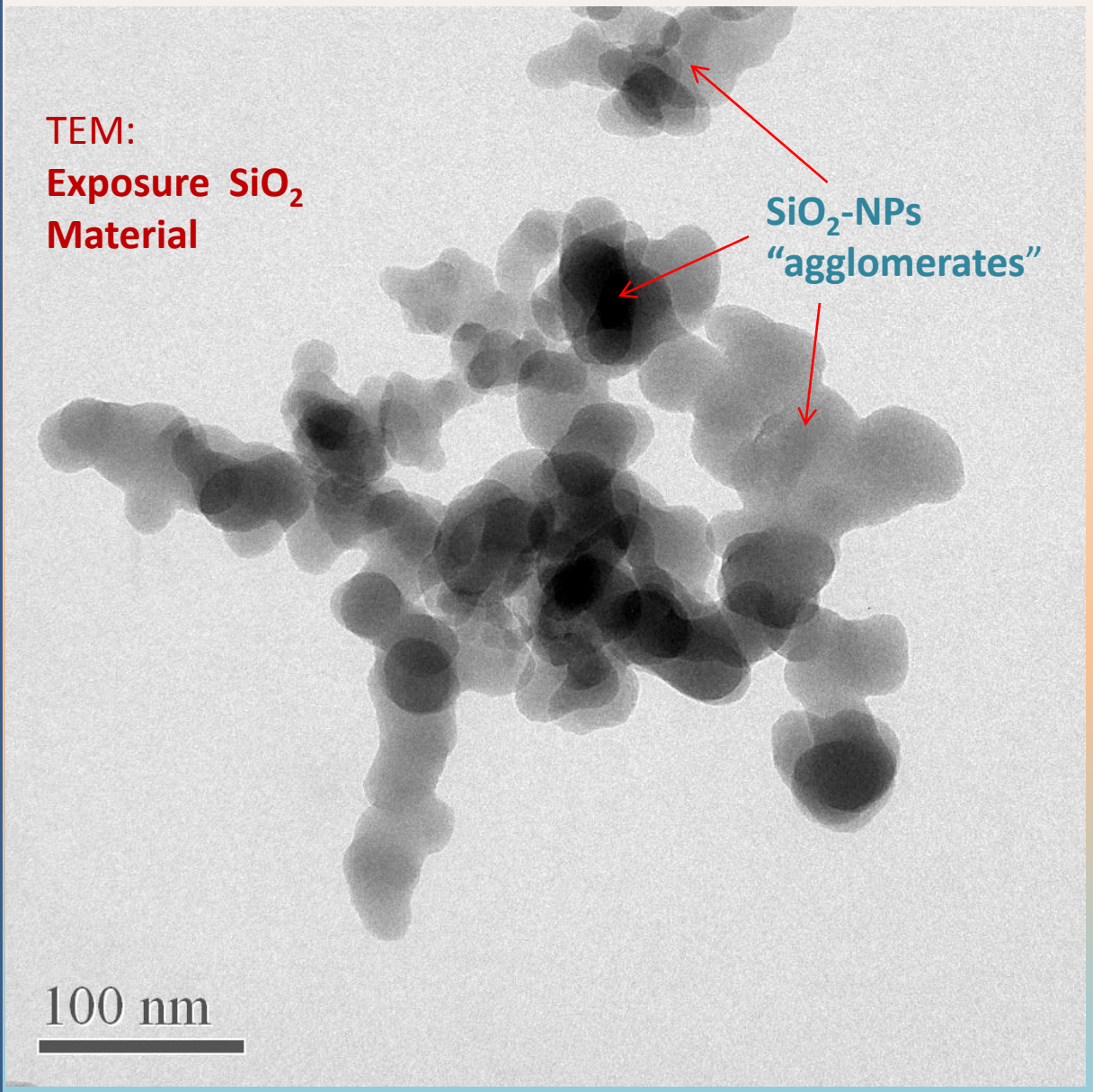
Exposure-Dose-Response Inhalation Study in Rats to determine No Effect Level

Dosimetric extrapolation modeling to assess human risk

Silica/SiO_2 Starting Materials

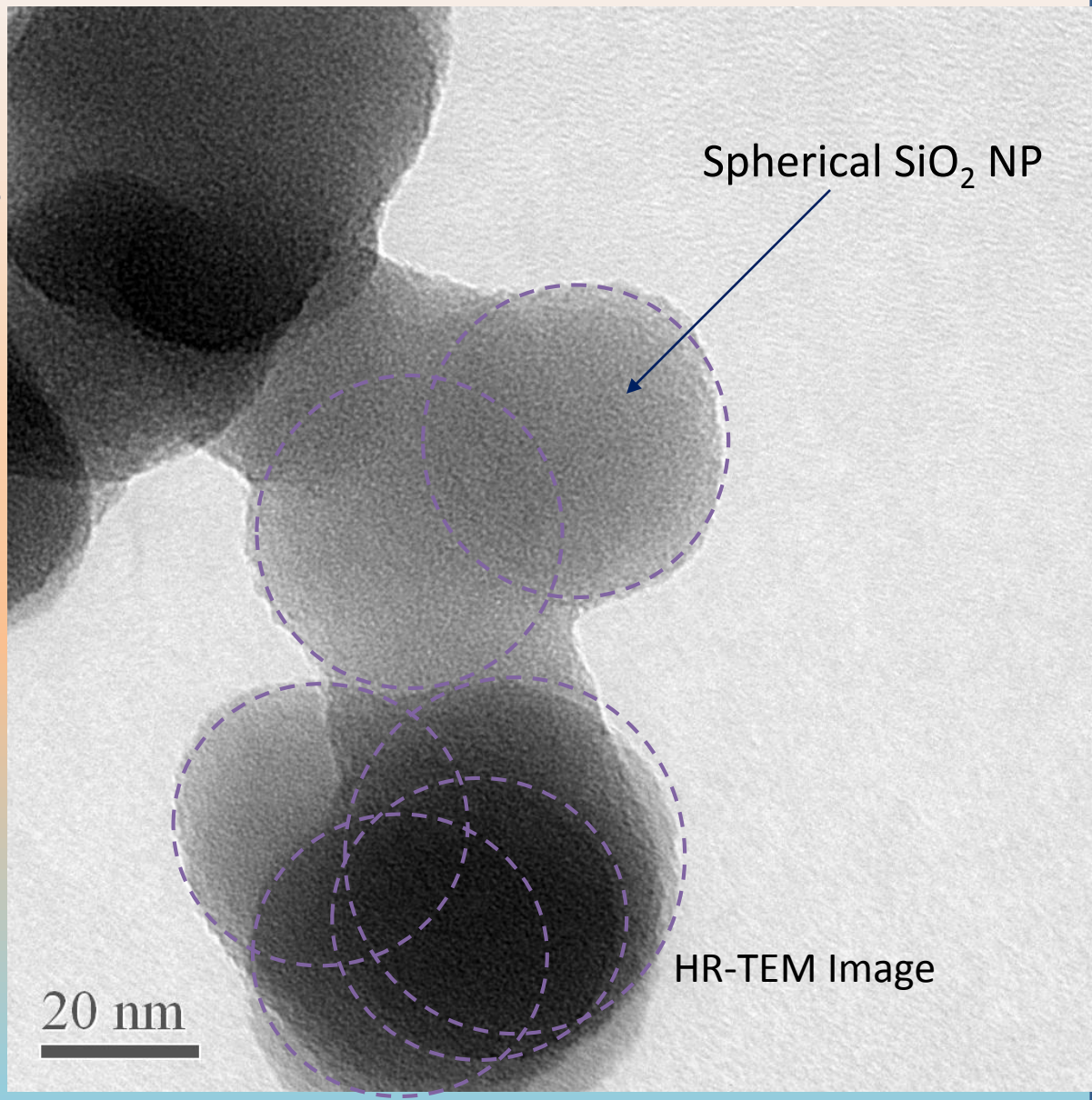


- Majority of the NPs are spherical or semi-spherical and ~ 20-40 nm in size.
- Nanoparticles tend to form dense agglomerated aggregates.
- Nanoparticles have smooth surfaces without etching or dissolution patterns.
- Particles are not zoned or show different densities (core to surface).
- Particles are amorphous

SiO_2 Starting Nanoparticles

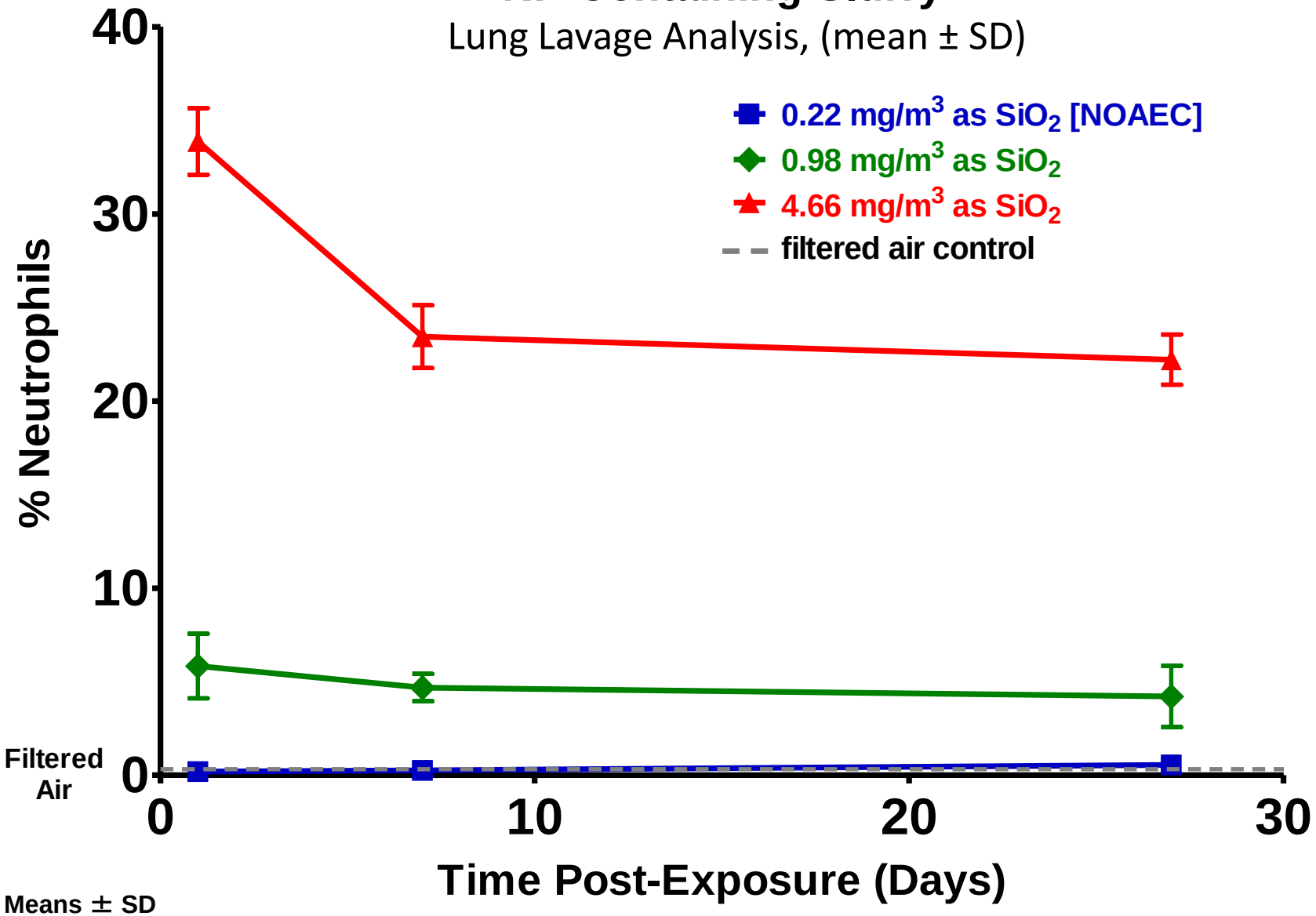
This HR-TEM shows the amorphous nature of the supplied SiO_2 NPs.

Aggregation and Agglomeration is part of NPs Formation.



Pulmonary Inflammation in Rats After 4 Weeks of Exposure to Silica NP-Containing Slurry

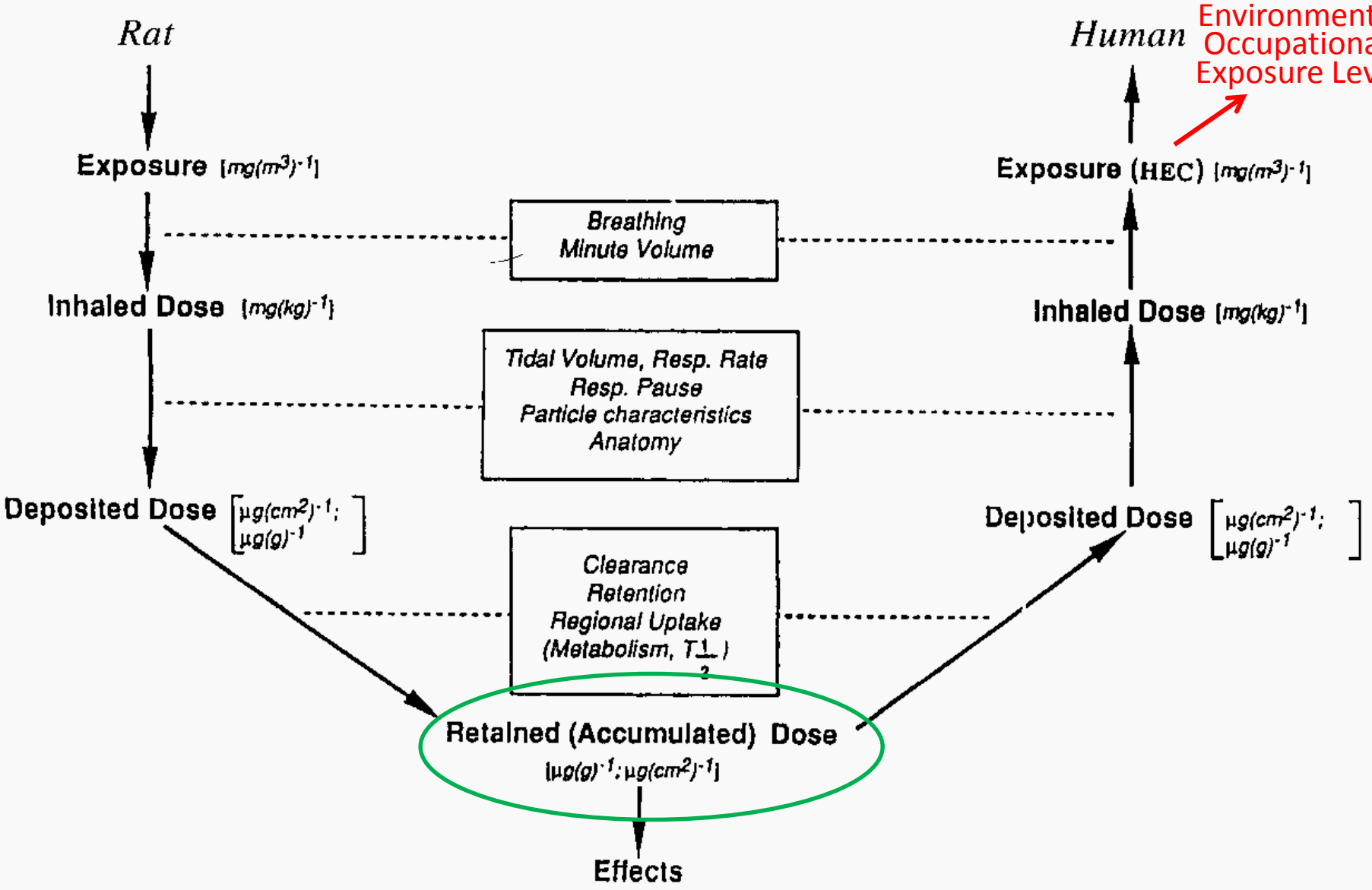
Lung Lavage Analysis, (mean ± SD)



Means ± SD

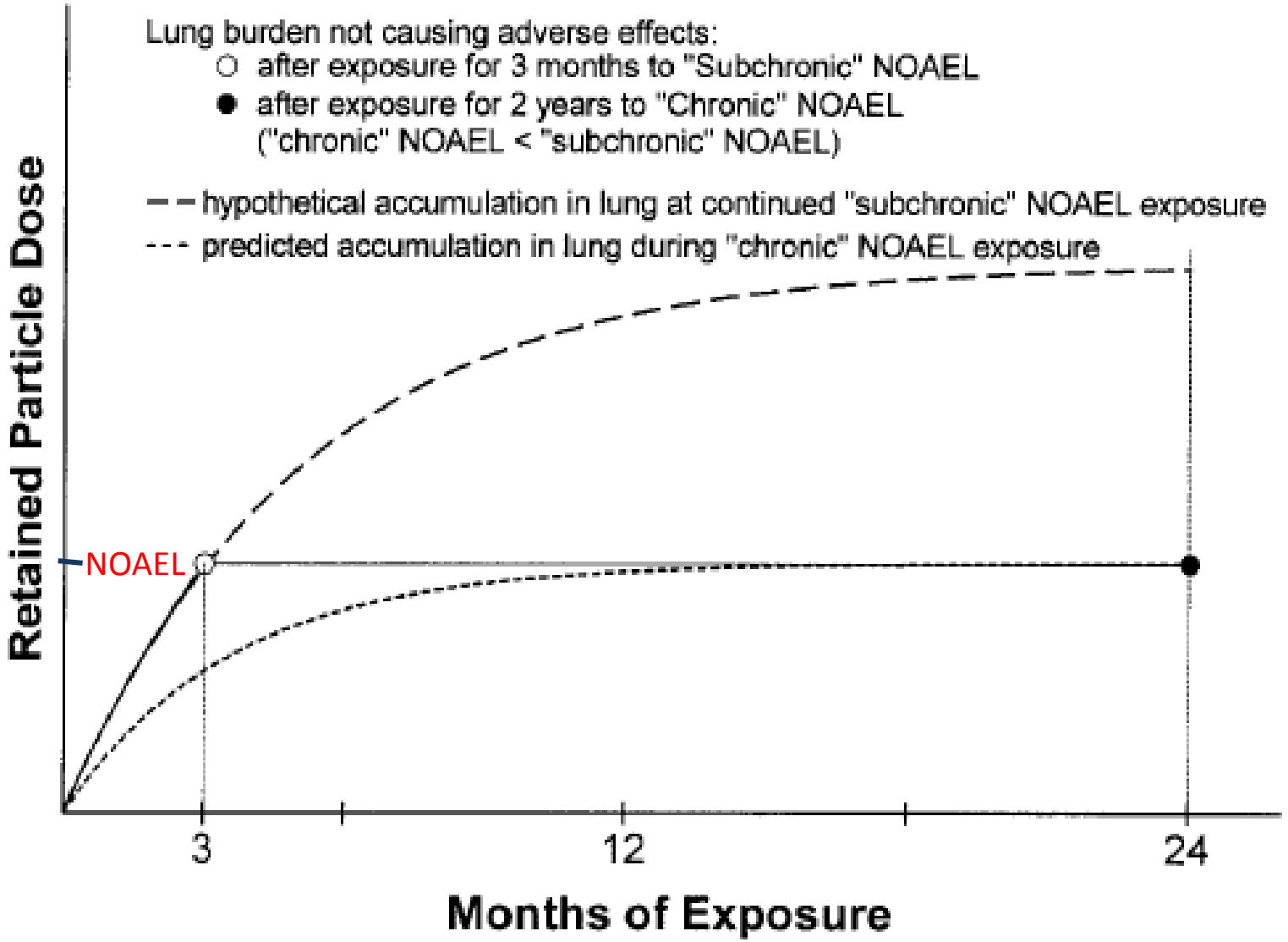
Dosimetric Extrapolation of Inhaled Particles from Rats to Humans

HEC, Human Equivalent Concentration



Assumption: If retained dose is the same in rats and humans, then effects will be the same

Estimation of Chronic NOAEL from Subchronic Rodent Study using MPPD Model



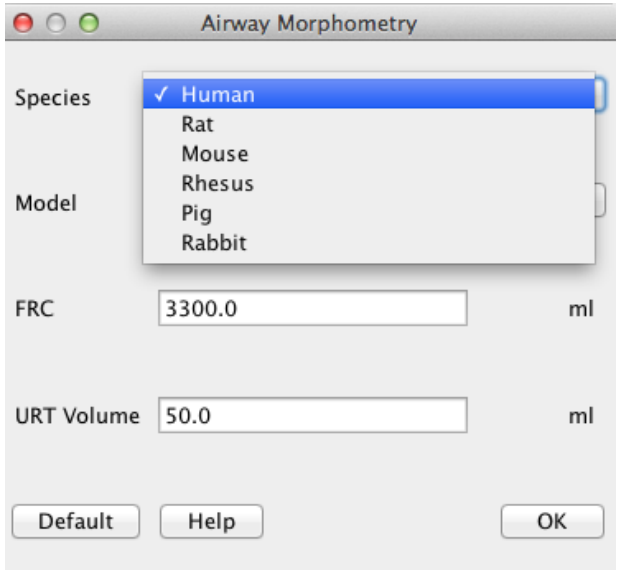
From: Oberdörster, 2002

MPPD v3.04

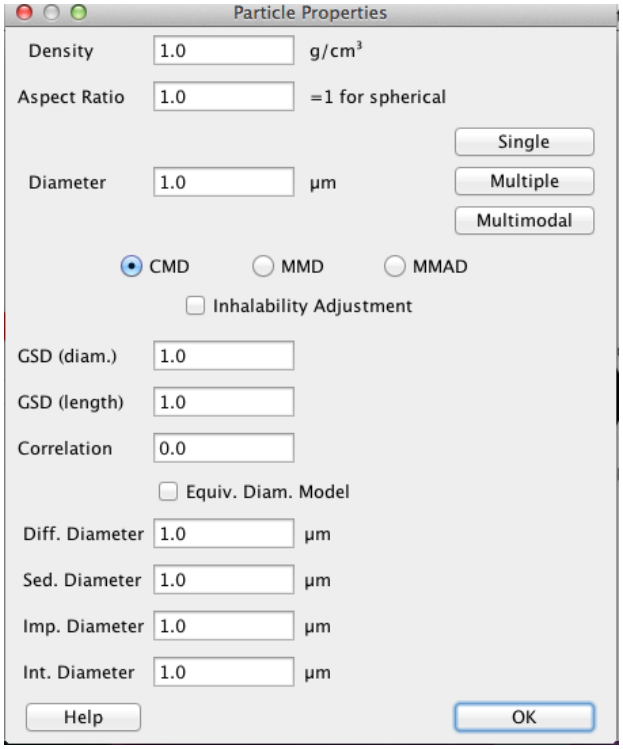
File Input Data Calculations Report Results Plot Results Help Get Started

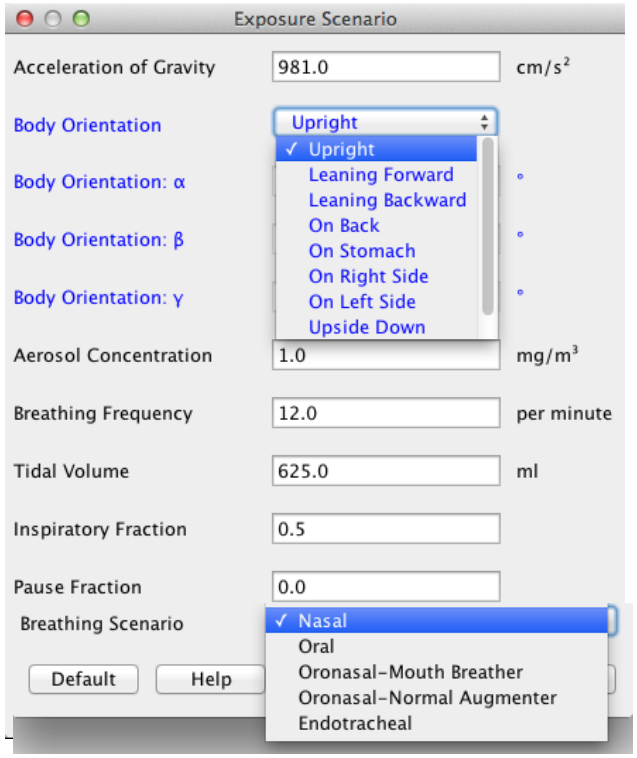
MPPD©

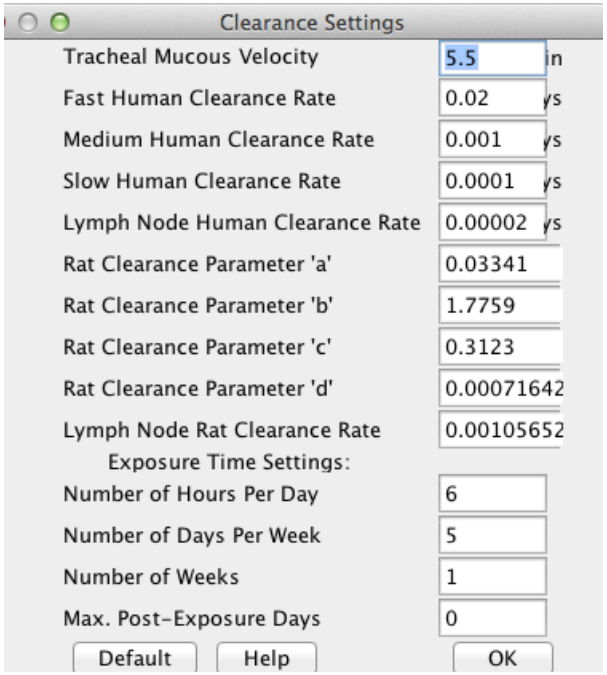
MULTIPLE-PATH PARTICLE DOSIMETRY MODEL



MPPD Model Input Choices



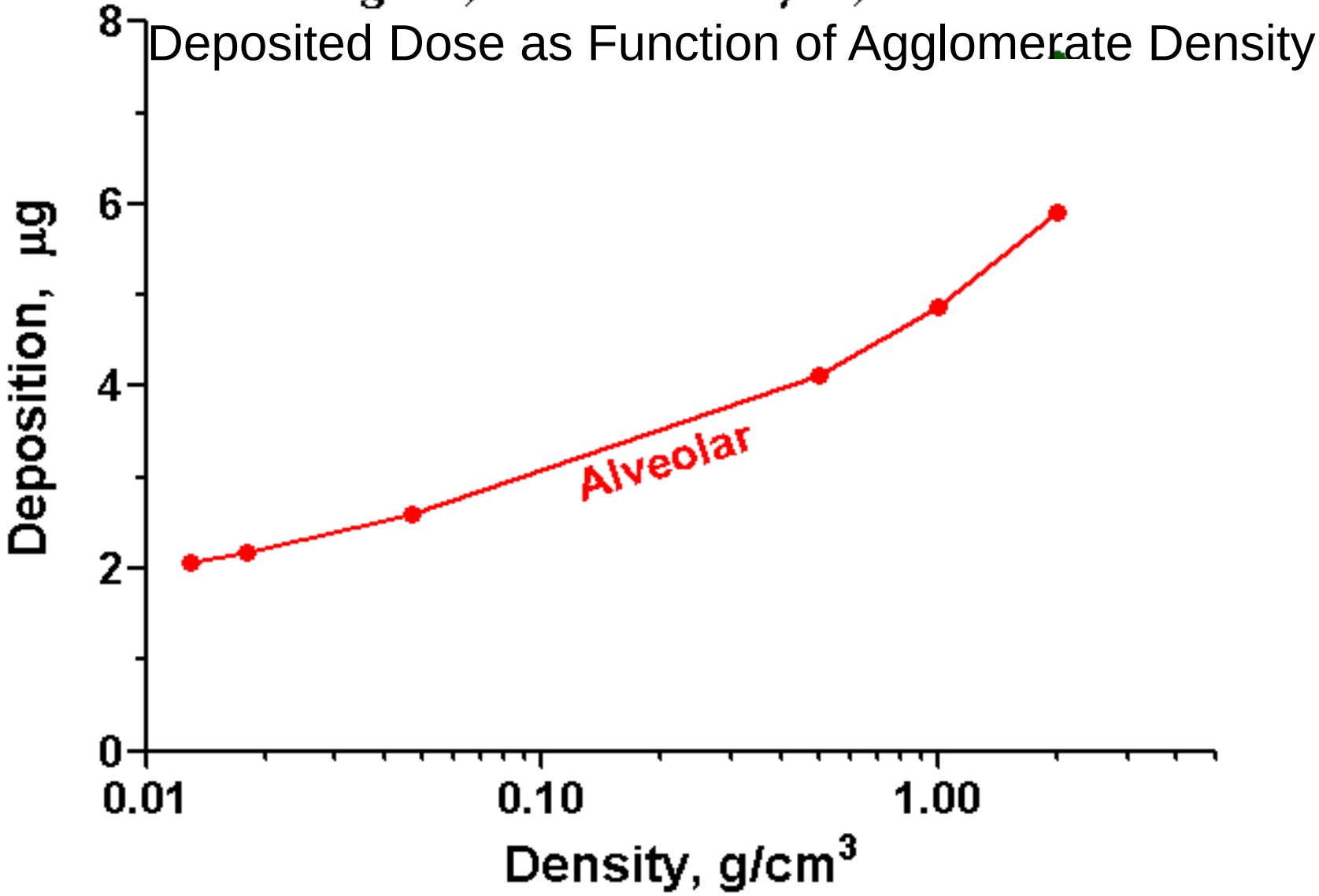




Impact of Aerosol Density on Lung Deposition of Inhaled Agglomerated Particles: MPPD Prediction, Rat, 4 hour Inhalation

$2.5 mg/m^3$; $MMAD = 1.4 \mu m$; $GSD = 2.9$

Deposited Dose as Function of Agglomerate Density



Determining Aerosol Density for Input into MPPD Model

Several terms and meanings for density (ρ = mass/volume):
specific; material; packing, effective, relative ….

Deposition of airborne particles in the respiratory tract is affected by effective or actual density of aerosols

A number of suggested methods to determine aerosol density:

Charvet et al., 2014, 2015; Maricq et al., 2004, Spencer et al., 2007

Miller et al., 2013; Park et al., 2003; Hering and Stolzenburg, 1995; Wang et al., 2015

Result of MPPD derived ρ_{eff} for SiO_2 slurry aerosols using data of 4-hr. rat inhalation study:

$$\rho_{eff} = 0.165\ g/cm^3$$

Compare to SiO_2 material density of ***2.65 g/cm^3 !***

Determining in vivo SiO_2 dissolution

b_{tot} of biosoluble particles in the lung is the sum of mechanical (AM-mediated) removal and of dissolution:

$$b_{tot} = b_{mech} + b_{diss}$$

$$b_{diss} = b_{tot} - b_{mech}$$

Note:

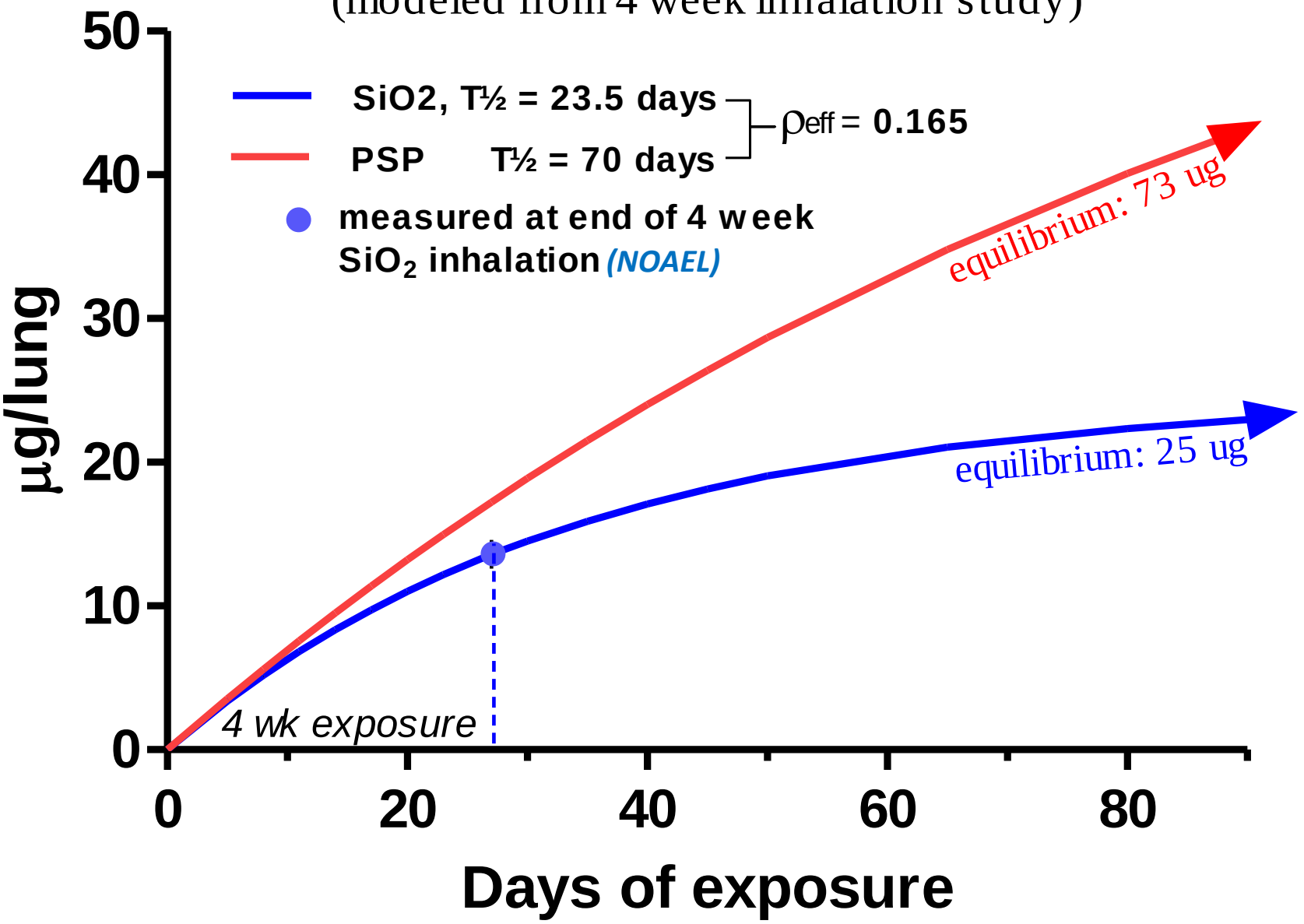
Species differences of particle clearance rates in rat and human lung:

mechanical clearance rate: very different (T½ rat ~ 70 days, human ~400-700 days)

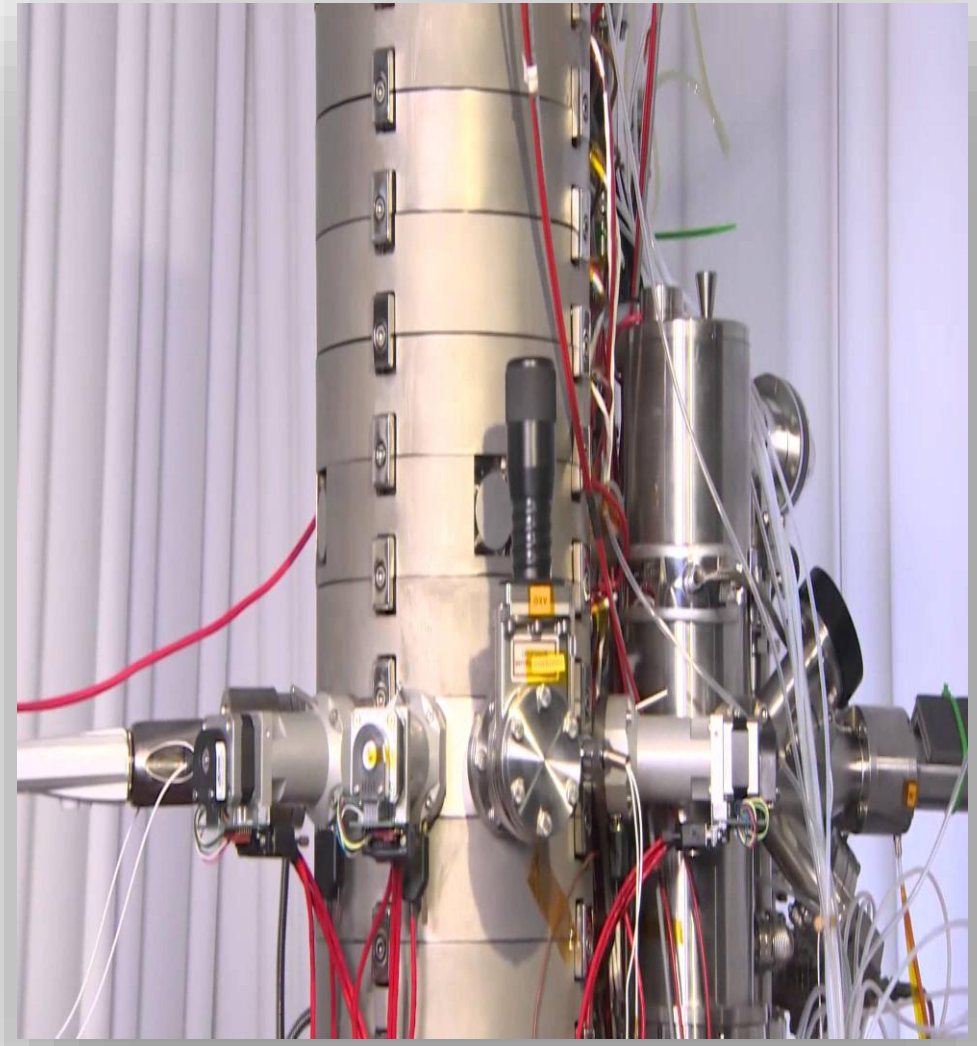
dissolution clearance rate: assumed to be the same in mammalian lungs

Accumulation in rat lungs of inhaled SiO_2 NPs vs PSPs

(modeled from 4 week inhalation study)



Verifying in vivo dissolution of SiO_2 NPs by HR-TEM/STEM/EELS analysis



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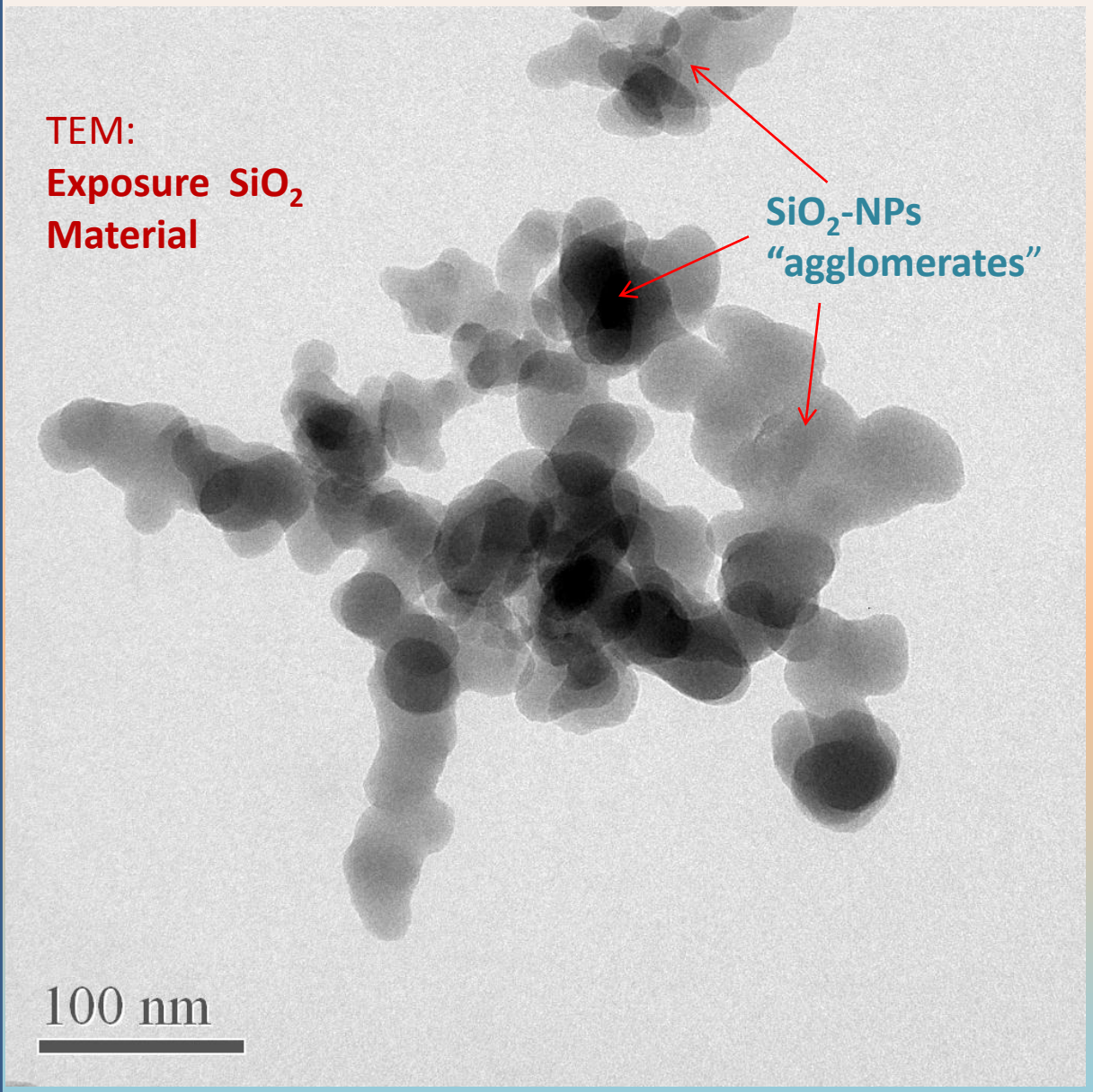

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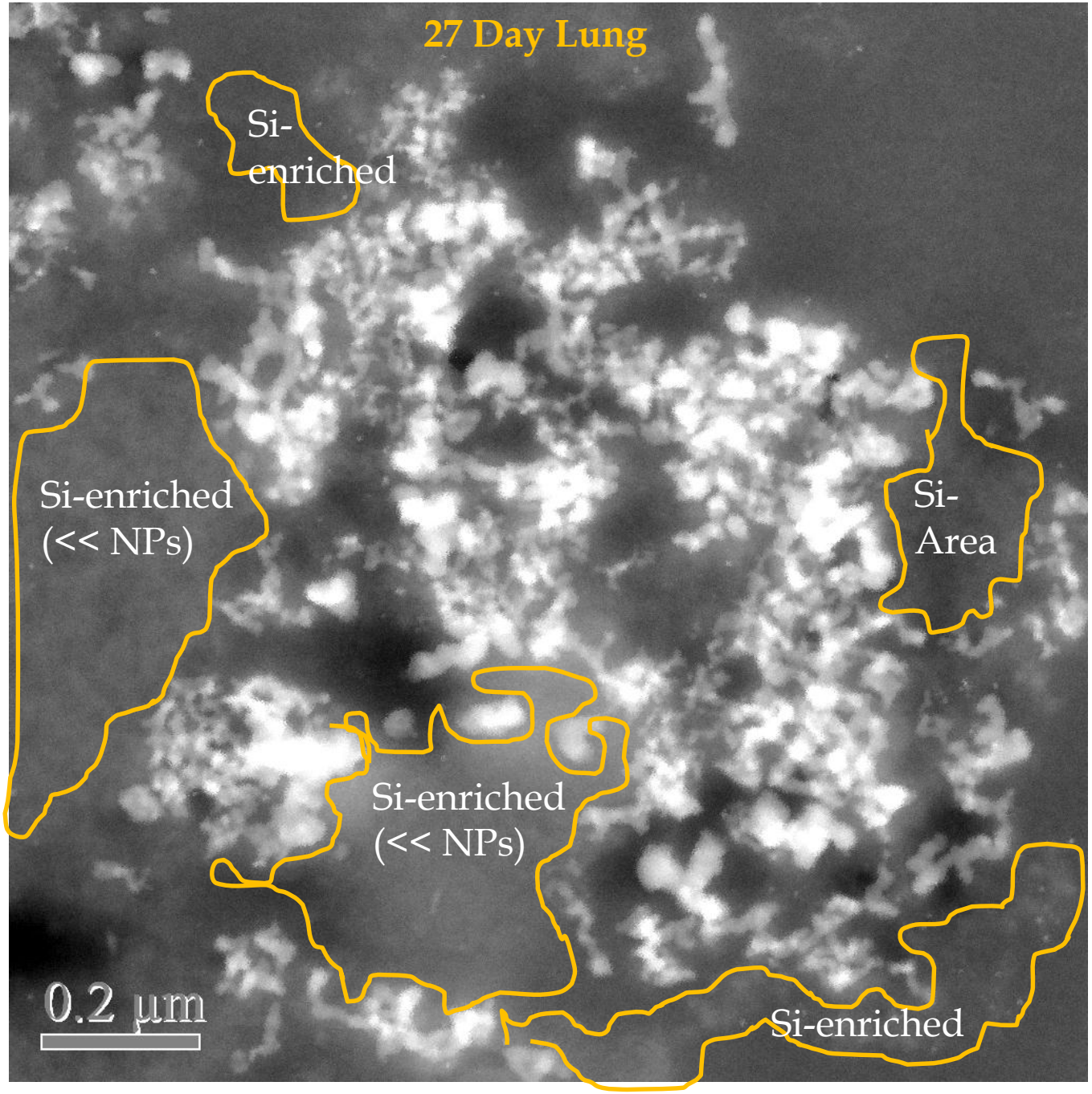


After 27 days p.E., STEM shows many areas that are enriched in Si, but the nanoparticle size is so small that at the depicted Magnification, the particles appear like clouds (outlined with the yellow lines).

The Si-enriched zones have very small nanoparticles that could be Identified to have Si, but it is not Determined whether they are SiO_2, or Si-phosphates (see next slide).

The formation of the Si-enriched areas is a clear indication, that after 27 days, the original SiO_2 NPs have undergone at least partial in vivo processing. We observe dissolution patterns (rough surfaces, pore formation in the starting materials, edge pits with areas of high solubility) In addition we see formation of precipitates that are << 2 nm and are part of what appears as Si-clouds. The Si-nanoparticles inside clouds are well dispersed suggesting, t hat there is some in-situ mechanism that prevents particle agglomeration. More work needed to identify coronas.

HEC Calculation from 4 week rat inhalation study with SiO_2 slurry aerosol:

Environmental Exposure

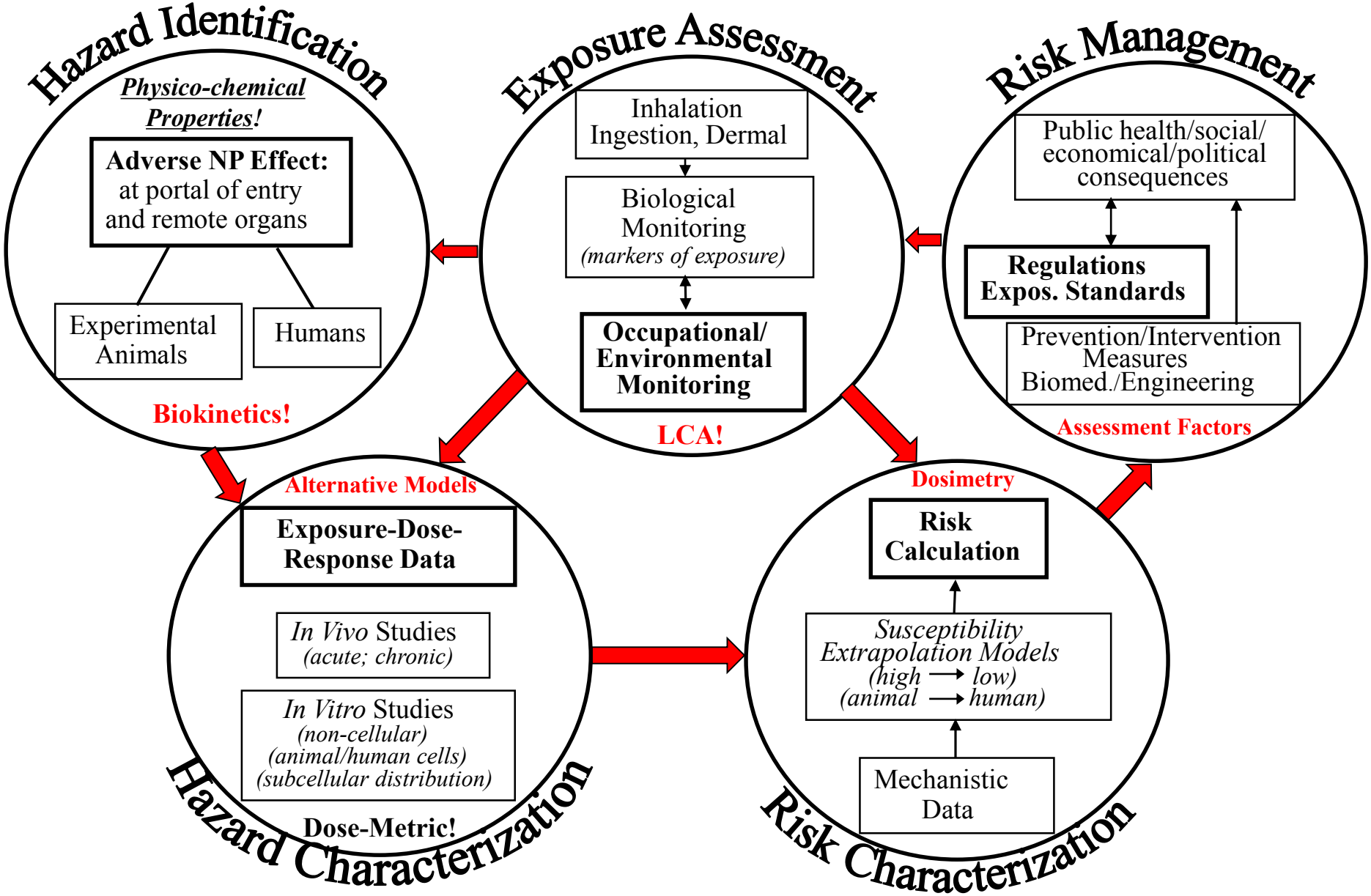
Deposition in **human lung** of inhaled SiO_2 aerosol of same particle size as in rat study, predicted by MPPD model with MMAD = 0.38 µm, GSD = 2.0, ρ = 0.165:
6.3 % deposition in alveolar region, **3.75 %** in tracheo-bronchial region
environmental setting: TV 625 ml; BF 12 min^{-1} *(resting breathing)*

Alveolar Surface Area Basis

NOAEL rat: 13.6 µg (retained lung dose at end of 4 week exposure in rats)
Normalized by alveolar surface area: **5.97 ng/cm²** surface area
Equivalent total retained dose in humans' lungs to be reached after continuous exposure:
3,787 µg

HEC to reach this lung burden over total life at
24 hours/day, 7 days/ week, resting breathing, 365 days/year:
304 µg/m³
Daily deposited dose in humans: 208 µg/day
(additional safety/assessment factors to define Reference value?)

Risk Assessment and Risk Management Paradigm For Engineered Nanoparticles (NPs)



Modified from Oberdörster et al., 2005

Risk = f (hazard; exposure)