

Impact on human health: Effects by inhaled particles

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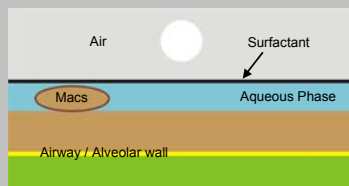


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Health effects from environmental particles (PM 10, PM 2.5)

- Most lung diseases originate from inhaled particles
- Carcinogenic – Lung cancer
- Respiratory and cardiovascular effects, especially in children, elderly and those with pre-existing disease
- Increases in heart beat frequency and blood viscosity, triggering of myocardial infarction

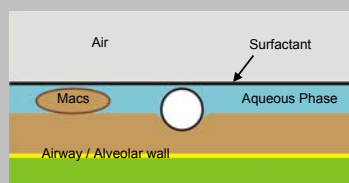
Components of the inner surface of the lung



In vivo inhalation study: Rodent model

- Aerosol Inhalation via intratracheal cannula
 - ◆ Short inhalation times
- Continuous negative-pressure ventilation
 - ◆ Controlled breathing pattern
- Lung fixation by vascular triple perfusion
 - ◆ Inner surface of the lungs undisturbed
- Light and electron microscopy
 - ◆ Analysis of deposited particles at the ultrastructural level

Particle displacement by surfactant



Summary I: Inhaled particles of 1-10 μm in diameter

- Regardless of the anatomical site and of particles nature, all particles with aerodynamic diameters between 1 and 10 μm are submersed in the aqueous lining layer
- The displacement of particles is promoted by the surfactant film at the air-liquid interface
- Complete immersion of particles occurred at film surface tensions of 15 mJ/m² or less

Summary II: Inhaled particles of 1-10 μm in diameter

- Submersed particles are found adjacent to the epithelial cells
- The displacement of particles allows further interaction with lung cells (phagocytosis)
- Within less than 1 hour after the inhalation 15-43% of particles deposited in airways were phagocytosed. The phagocytosis of particles not cleared by other means was essentially complete within 24 h

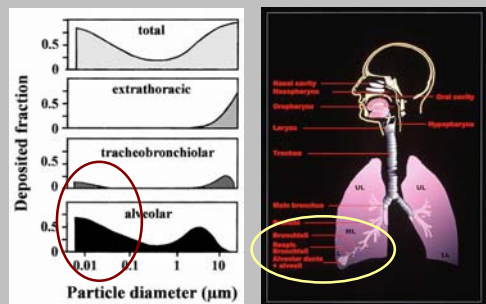
Definition, specialty of ultrafine particles

- Diameter < 100 nm
- Negligible mass
- High number concentrations in the ambient air
- Large specific surface area for adsorption and interaction

Deposition of ultrafine particles

- By diffusion
- With high efficiency
- In the peripheral lungs
- Distribution over a large surface area, in humans about 140 m^2
- Air-blood barrier thickness $2 \mu\text{m}$ or less

Deposition of ultrafine particles



From Holger Schulz et al., Lenfant Series, 2000

Ultrastructure of the lung parenchyma



Air-blood barrier = $2 \mu\text{m}$
1/50 Air mail paper

Evidence for different fate of inhaled ultrafine particles

- Ultrafine particles are more toxic than larger ones of the same material (Ferin *et al.*, 1992)
- Ultrafine particles are taken up by epithelial cells (Churg, 1996)
- Passage of inhaled $^{99\text{m}}\text{Tc}$ -carbon particles into the blood circulation in humans (Nemmar *et al.*, 2002)
- Substantial translocation of inhaled ^{13}C -carbon particles into the liver following whole body inhalation exposure of rats (Oberdörster *et al.*, 2002)
- Minute translocation of inhaled insoluble ^{192}Ir particles from lung epithelium to extrapulmonary organs (Kreyling *et al.*, 2002)

In vivo inhalation study with ultrafine particles I: Rodent model

- Titanium dioxide (TiO₂), CMD = 22 nm
- Aerosol generation: spark generator (Palas), pure titanium electrodes, argon, oxygen
- Aerosol inhalation via intratracheal cannula for 1h
- Continuous negative-pressure ventilation

In vivo inhalation study with ultrafine particles II: Rodent model

- Lung fixation: vascular triple perfusion 1 h and 24 h after inhalation
- Systematic sampling of lung tissue for TEM analysis
- Analytical TEM: Energy filtering TEM (EFTEM), electron energy-loss spectroscopy (EELS)
- Localization of individual particles within lung tissue and elemental microanalysis

Summary: Inhaled ultrafine TiO₂ particles

- Penetrate through the lining layer and the epithelial barrier
- Distribute rapidly and evenly in all lung tissues and cells
- Are not membrane bound within cells
- Overwhelm the biological membranes by a yet unknown mechanism

Particles within cells: Possible effects

- Cytoplasm
 - ◆ Intracellular transport
 - ◆ Oxidative burst
 - ◆ RBC: reduced life span
- Cell organelles
 - ◆ E.g. mitochondrial damage
- Nucleus
 - ◆ Change of gene expression pattern

Local / systemic effects

- Local
 - ◆ Inflammation at the deposition site
 - ◆ Fibrosis
 - ◆ Mutagenesis – lung cancer
- Systemic
 - ◆ Cardiovascular effects
 - ◆ Effects in other organs (liver, kidney, brain)

Factors influencing the effects

- Solubility – chemical composition
- Surface area – surface molecules
- Concentration in ambient air – singlets/agglomerates
- Other particles – reaction with these particles
- Overall reactivity of particles

Future experiments

- In vivo: Rodent models
 - ◆ Application by inhalation of particles
 - ◆ Well defined aerosol
 - ◆ Dose not too high
- In vitro: 3-d multicell cultures
 - ◆ All components of the inner surface of the lungs
 - ◆ Application of aerosols

Collaborators

- P. Gehr, V. Im Hof, I. Maye, U. Waber
- M. Baumann, P. Gerber, N. Kapp, N. Leupin, M. Matter
- S. Frank, B. Kupferschmid

- W. Kreyling, H. Schulz, M. Semmler (GSF-Neuherberg, Munich, FRG)
- S. Schürch (Calgary, CDN)
- L.M. Cruz-Orive (Santander, E)

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