Principles of Nanomaterials Toxicology

Nanoscale Science Research Centers Symposium:

Safe Handling of Engineered Nanoscale Materials

Argonne National Laboratory

July 7-9, 2008

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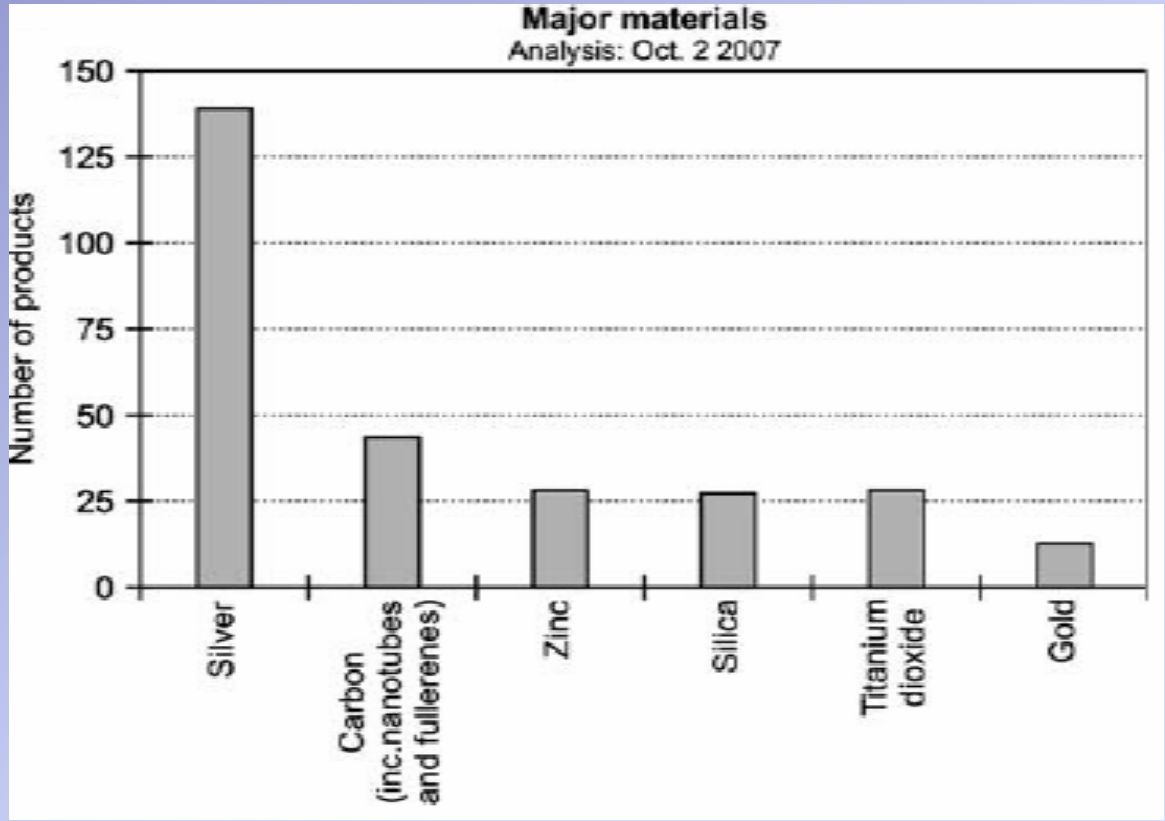
University of Rochester

Nanomaterials in Consumer Products



From Hansen et al., 2008

Wilson Center Project on Emerging Nanotechnologies (PEN):

580 consumer products

4 therapeutic products (FDA-approved)

Exposures to Nanomaterials

Cotton sheets

Socks

Stain-resistant fabric coatings

16 Gb flash drives

Organic LEDs

Automotive exteriors

Self-cleaning glass

Sunscreen

Cigarette filters

Cosmetics, e.g. fullerene C_{60} eye cream

Humidifiers, air filters

Wound dressings

Floor cleaner

Scent-eliminating spray (hunting)

From: Woodrow Wilson Center for Scholars, Project on Emerging Nanotechnologies

Rochester MURI

Correlating Physico-Chemical and Toxicological Properties of Nanoparticles

Synthesis

↓

Physico-chemical
Characterization

Methods Development

Collaborations:

- *NIOSH*
- *Owens Corning*
- *Health Canada*
- *ManTech (AFRL)*
- *Michigan State Univ.*
- *GSF-Germany*

Testing

cell-free ↔ **cellular/subcellular**

Correlations?

in vivo

? ? ?

Benchmark NP
low toxicity

T o x i c i t y | R a n k i n g

Benchmark NP
high toxicity

↓

Bioinformatics

Predicting nanostructure-induced responses

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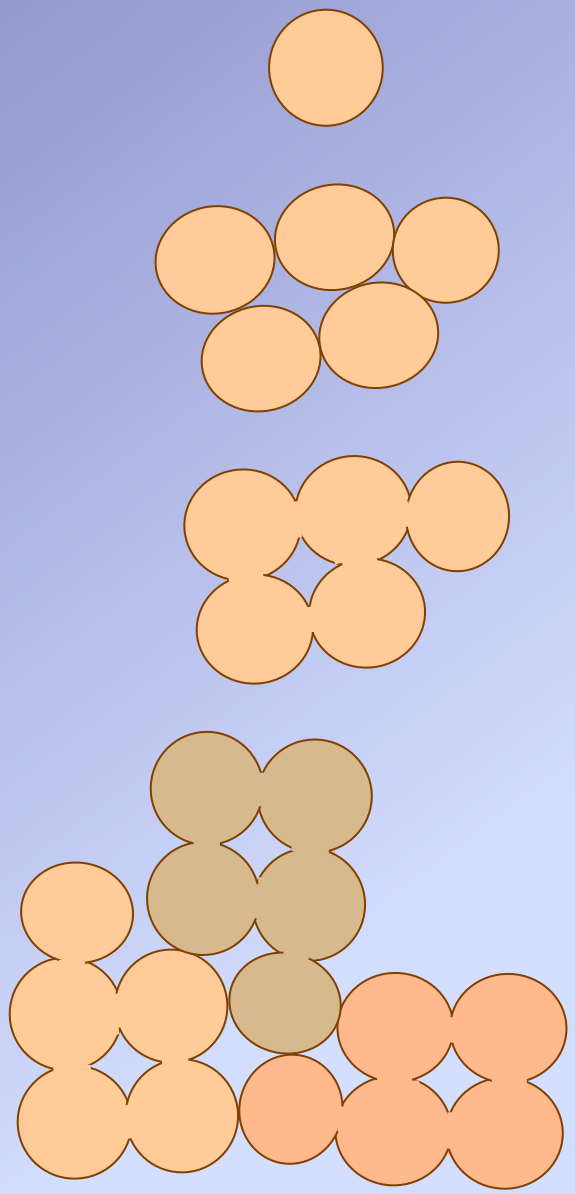
Nanoparticle Physicochemical Properties: What is Important?

Primary *vs*. Agglomerated *vs*. Aggregated Nanoparticles



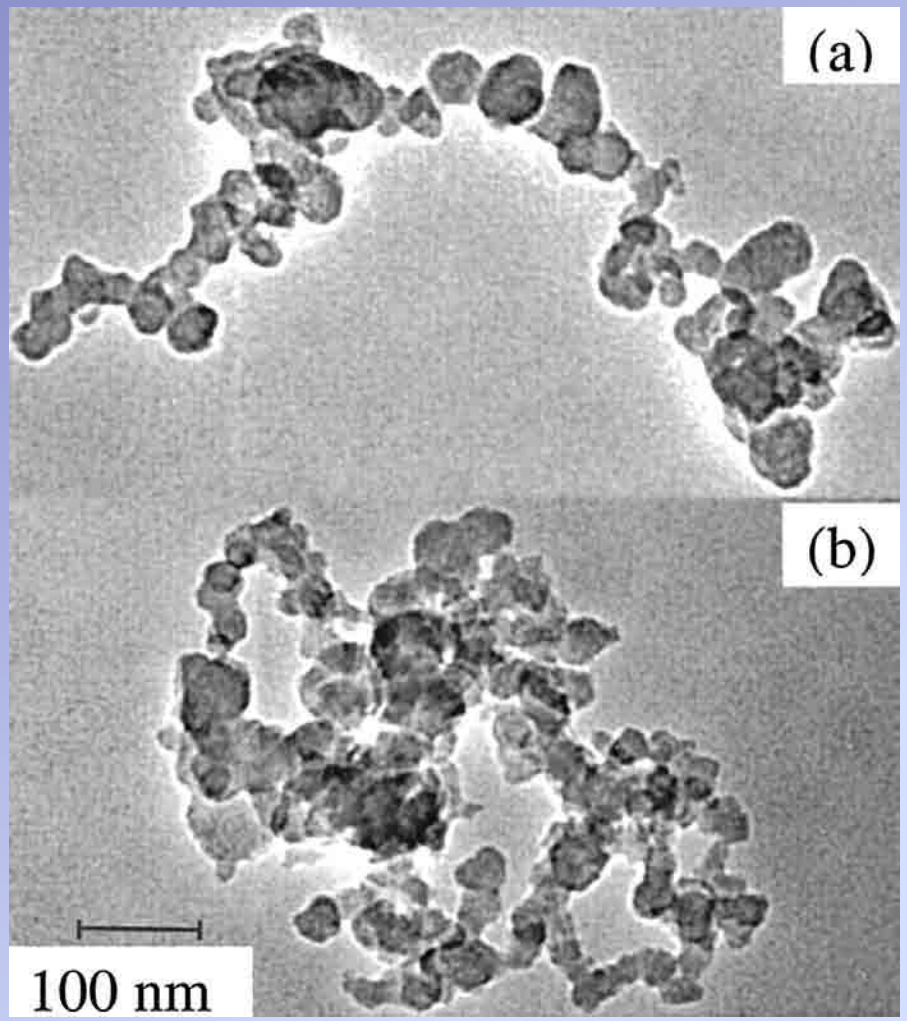
Primary Particle
e.g. quantum dot

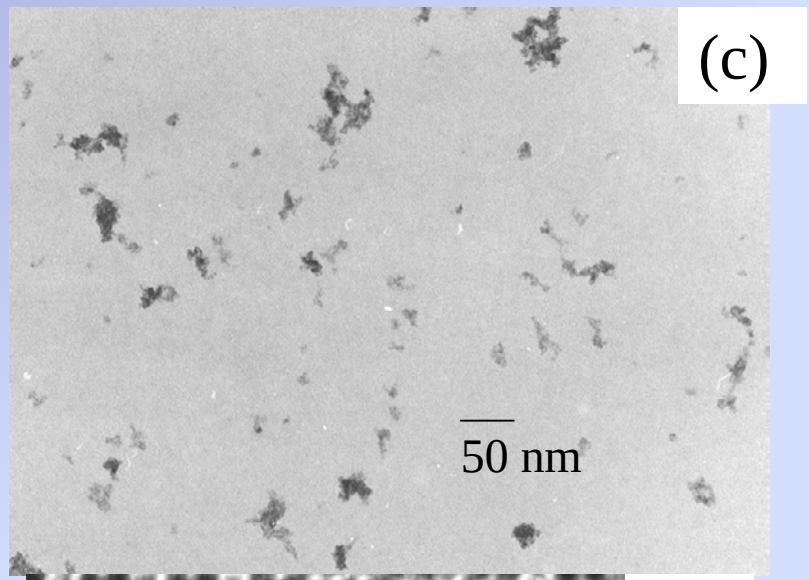
Agglomerated Primary Particles (Agglomerates)
e.g. nC_{60} fullerenes

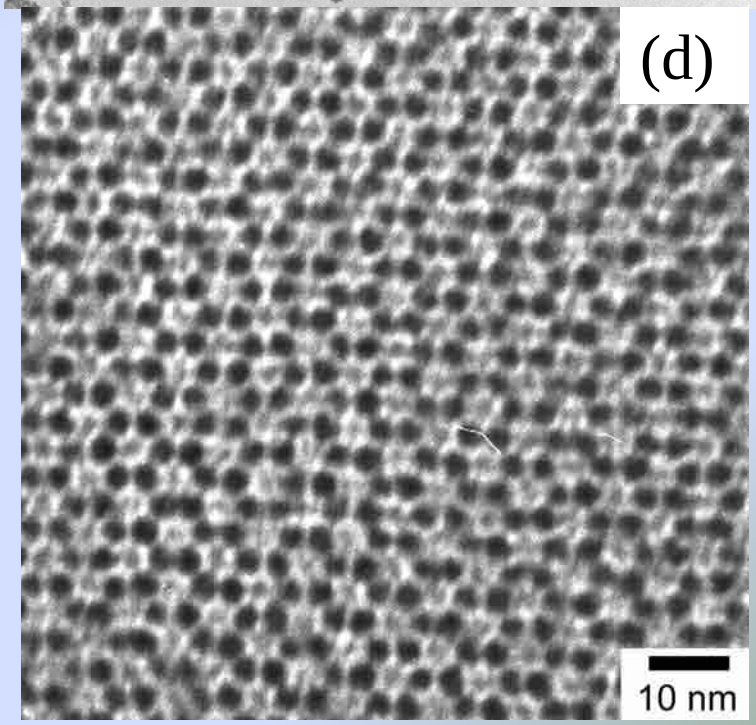
Aggregated Primary Particles (Aggregates)
e.g. carbon black

Agglomerated Aggregates
e.g. ambient air PM

Nano-sized Ambient and Engineered Particles

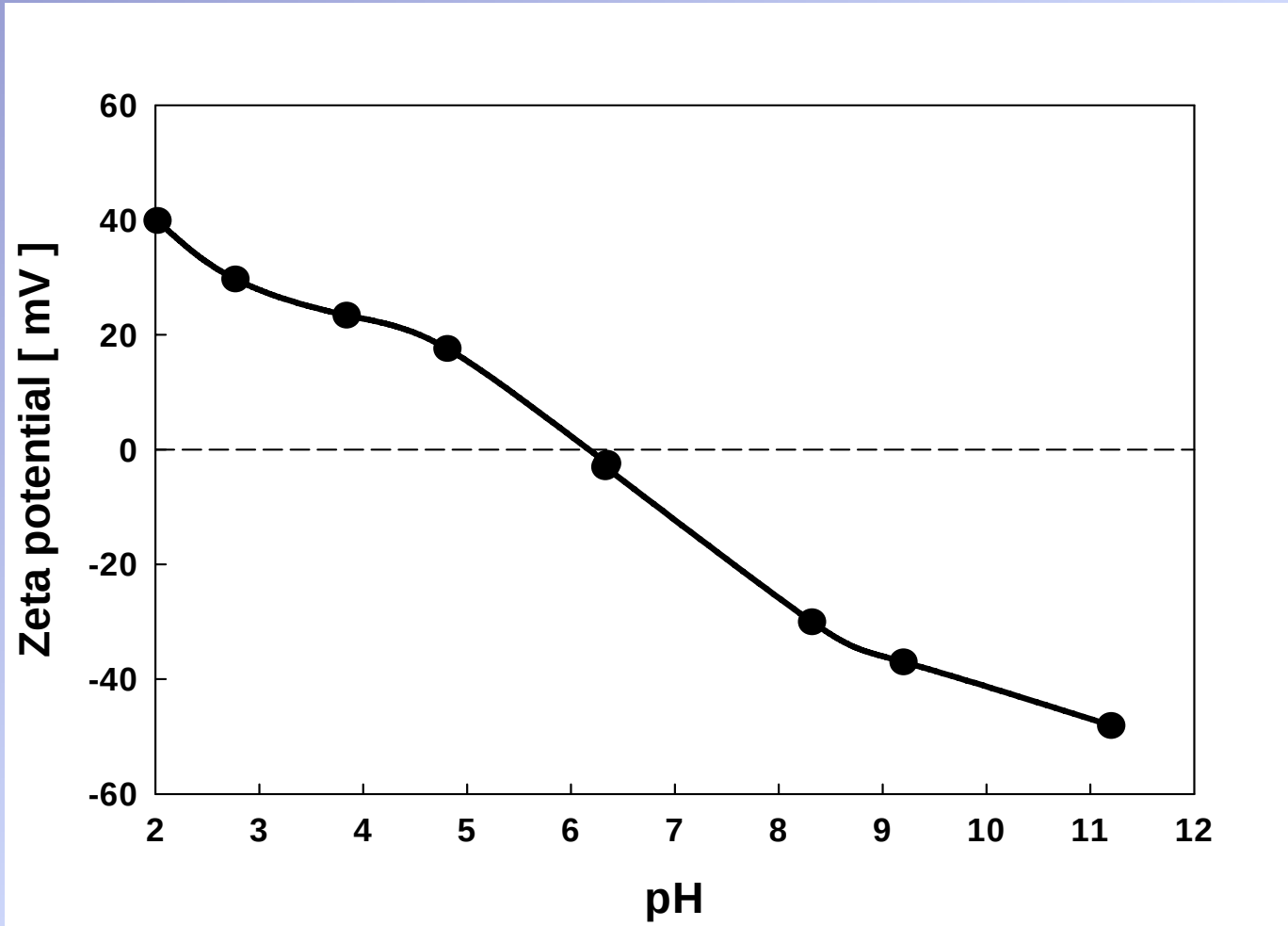






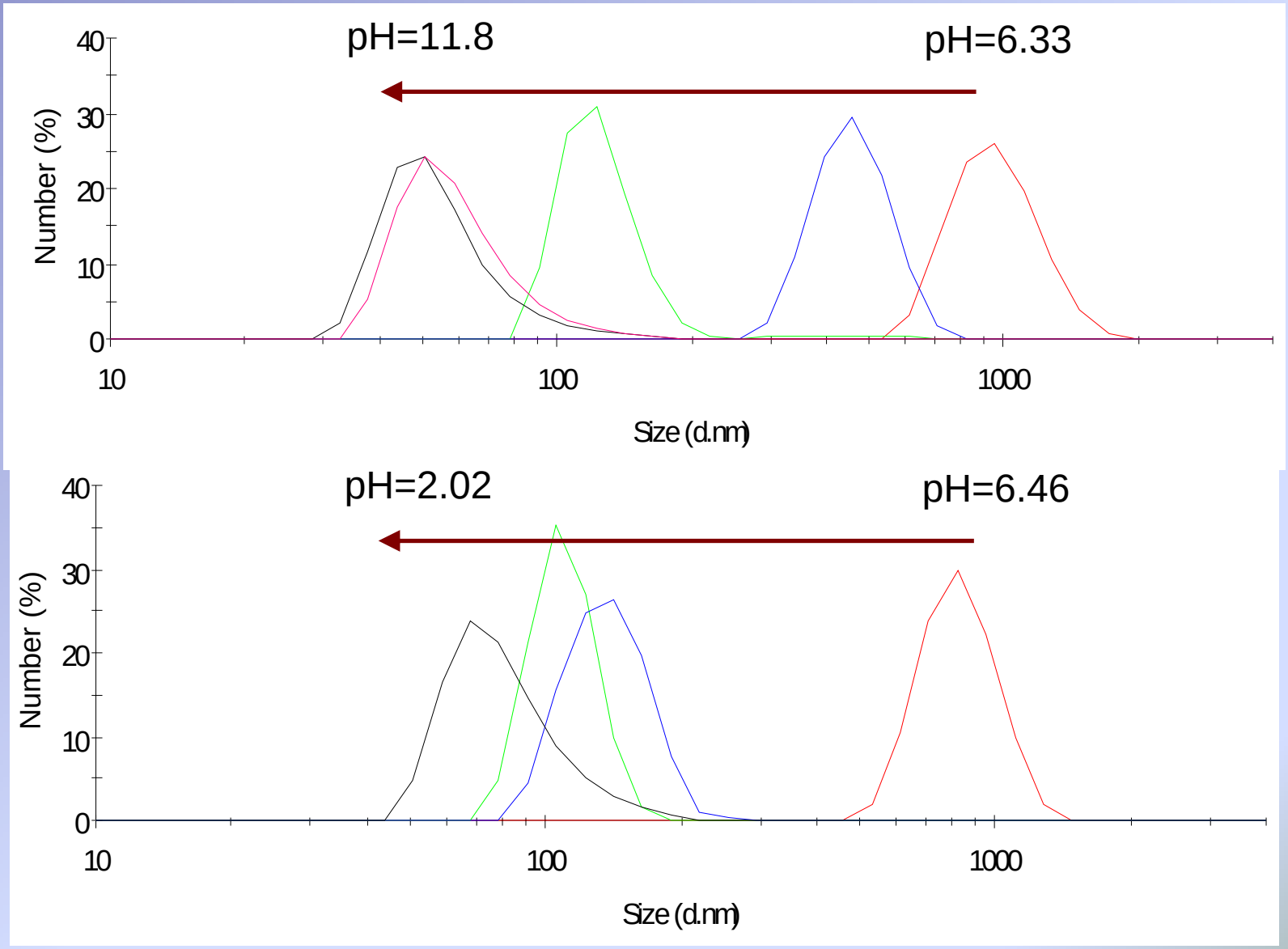
from: Xiong & Friedlander, 2001; Roth et al., 2004; Teng et al., 2003

Zeta Potential vs. pH (Degussa P-25 TiO_2)



from: Jiang et al., 2008

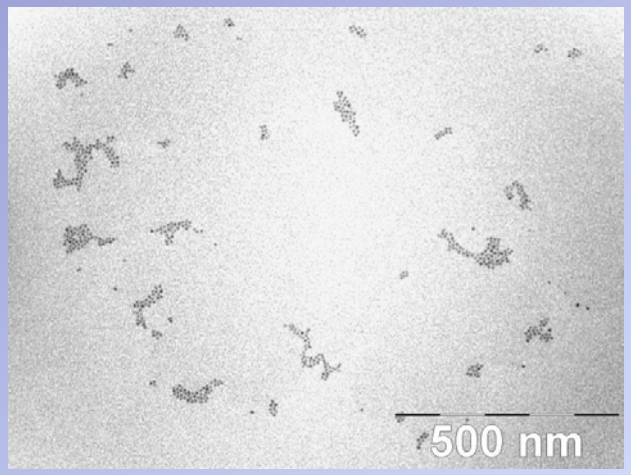
Size Distribution vs. pH (Degussa P-25 TiO_2, by number)



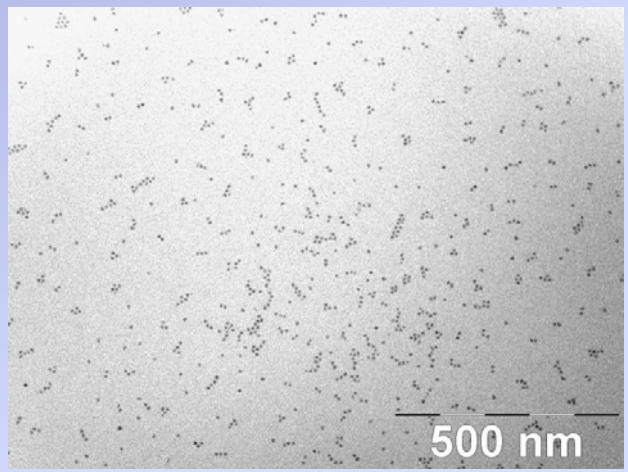
from: Jiang et al., 2008

Physicochemical Characteristics of Semiconductor Nanocrystals (Quantum Dots)

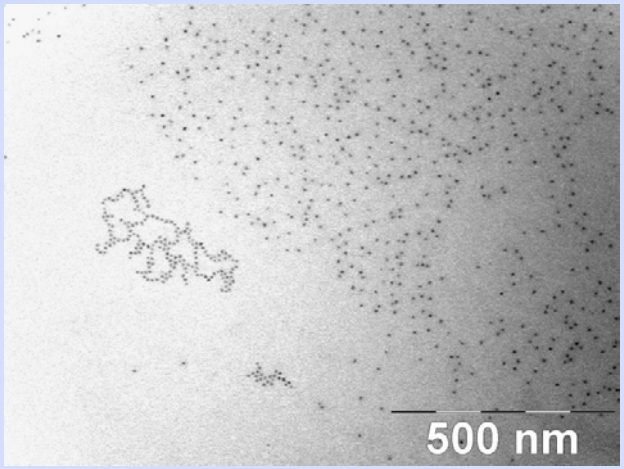
CdSe-ZnS Quantum Dots in 0.9% Saline



PEG



PEGamine



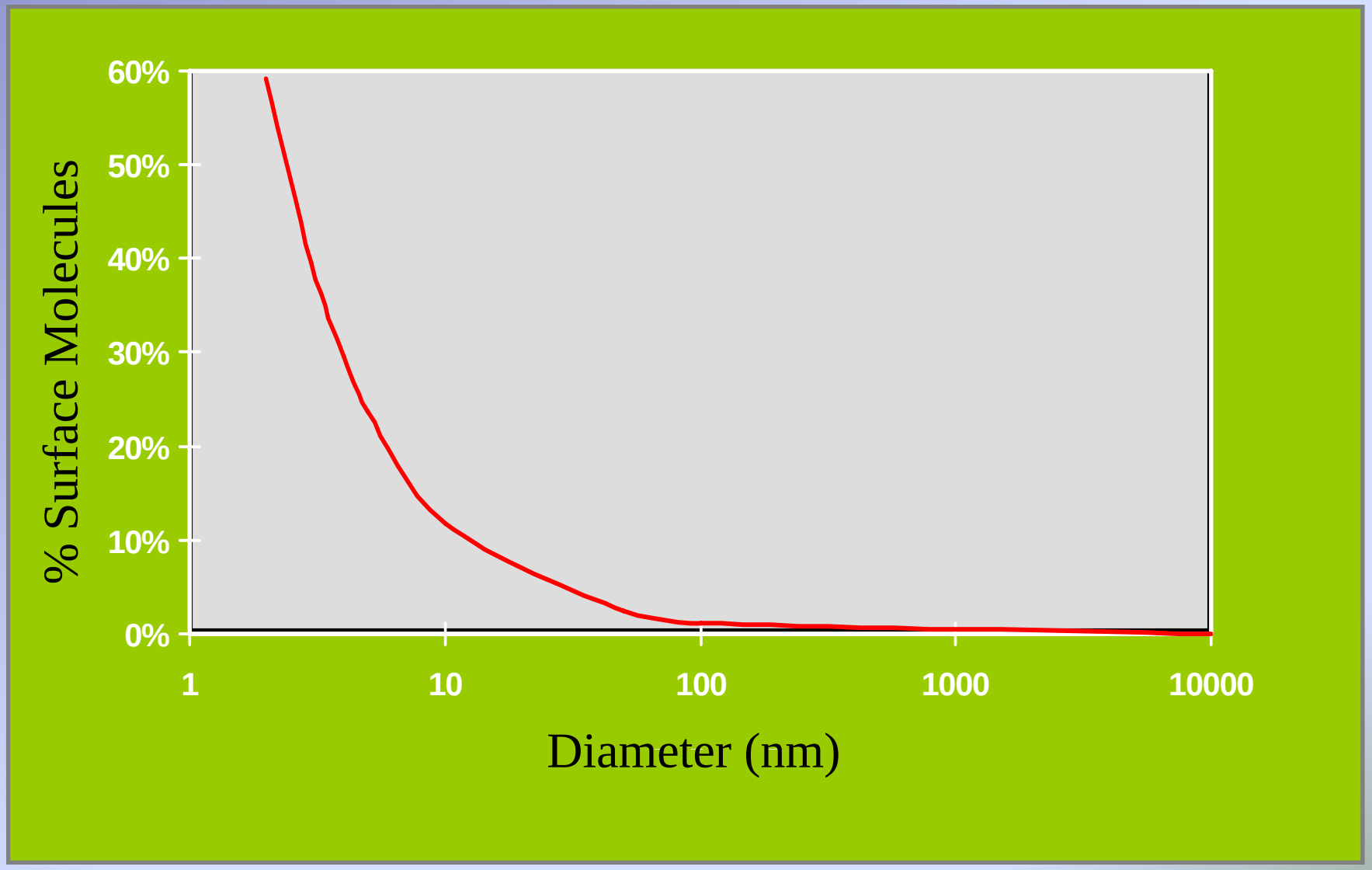
Carboxyl

<u>Hydrodynamic diameter:</u>

23 nm	17 nm	14 nm

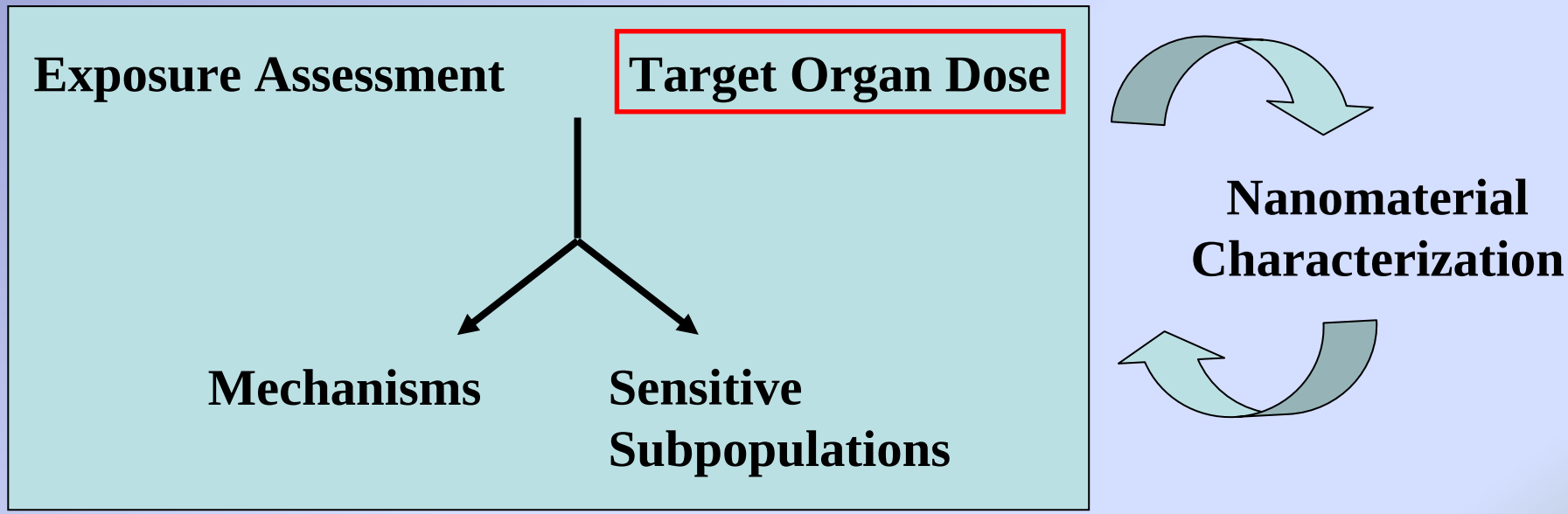
What Nanoparticle Properties Are Important?

Surface Molecules as Function of Particle Size

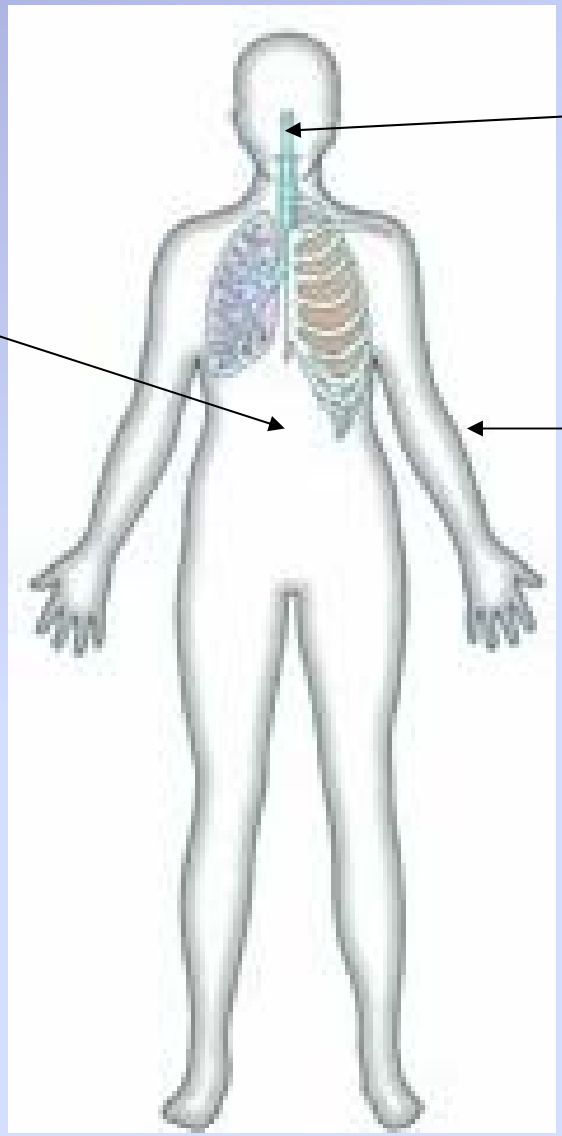


from: Fissan, 2003

Framework for Defining Human Health Risks and Benefits of Nanomaterials



Exposures to Nanomaterials: Most Likely Routes



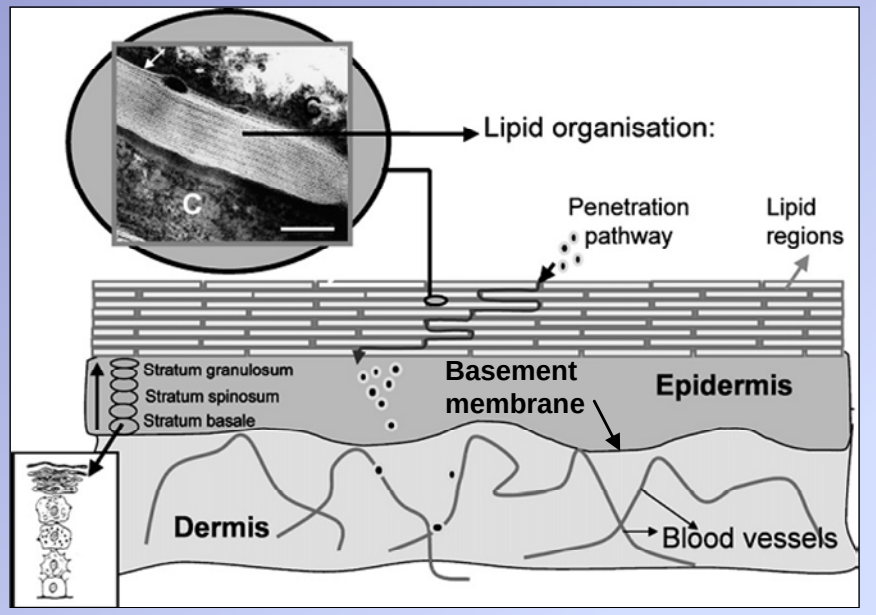
From: Borm et al., 2006

Gastrointestinal Tract

- Data suggests that persorption of particles can occur.
  - Persorption of micron-sized “insoluble” PVC particles (Volkheimer, 1975).
  - About 0.0001% Pu dioxide GI tract absorption in humans (Stather et al., 1979).
  - Very little absorption of orally-administered poorly-soluble 15 nm ^{192}Ir particles from GI tract (Kreyling et al., 2002; Semmler-Behnke et al., 2008).
- Tissue distribution of colloidal Au nanoparticles is size-dependent following exposures in drinking water for 7 days (Hillyer and Albrecht, 2001).

Do particle density and surface charge play a role?

Skin Architecture



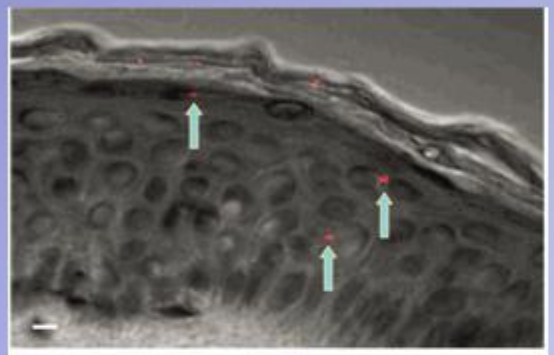
From: Bouwstra et al., 2006

Key Considerations for Studies of Nanomaterials Interactions with Skin

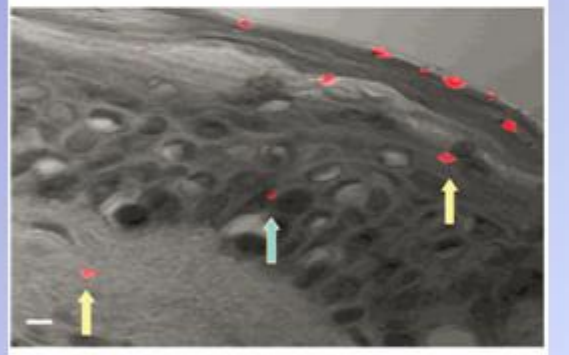
- Surface pH of ~5.0
- Lipid lamellae of stratum corneum

Main question: Can nanoparticles breach the stratum corneum and under what conditions?

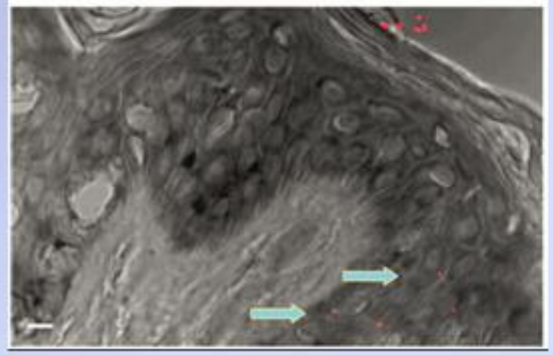
Considerations Regarding Nanomaterials Absorption through Skin: *Particle Size*



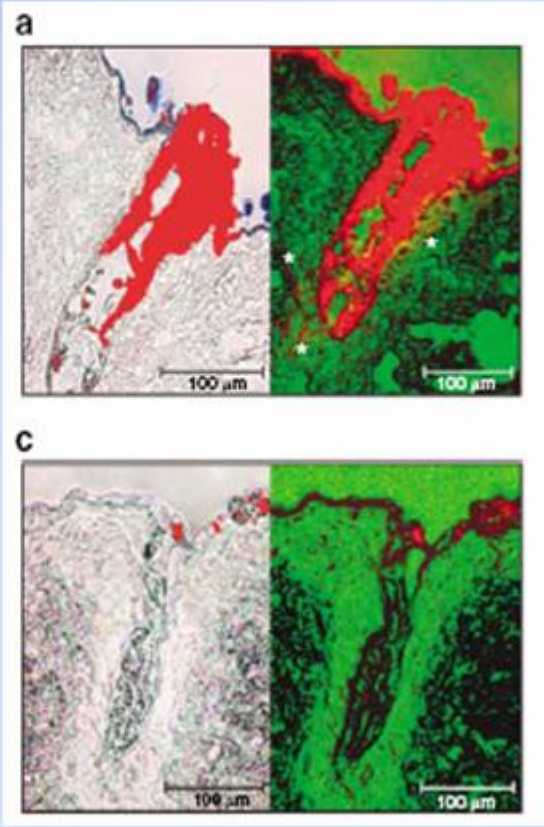
1 μm beads,
30 mins



1 μm beads,
60 mins



0.5 μm beads,
30 mins

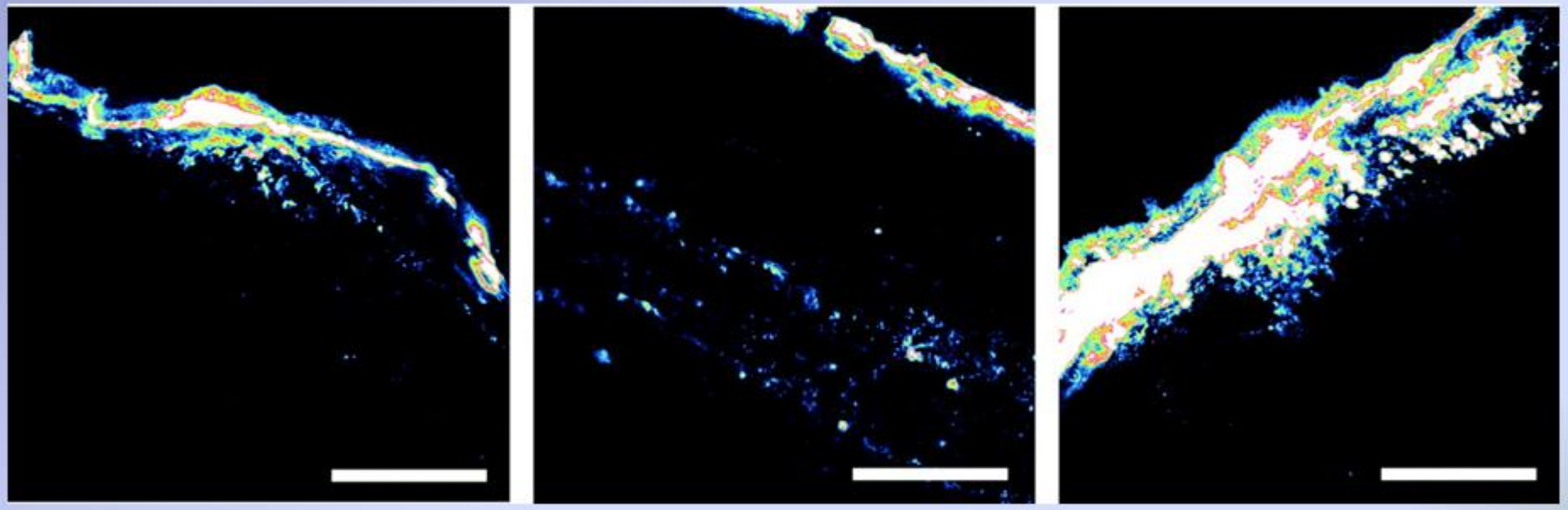


40 nm beads,
~16 hrs

750 nm beads,
~16 hrs

From: Tinkle et al., 2003; Vogt et al., 2006

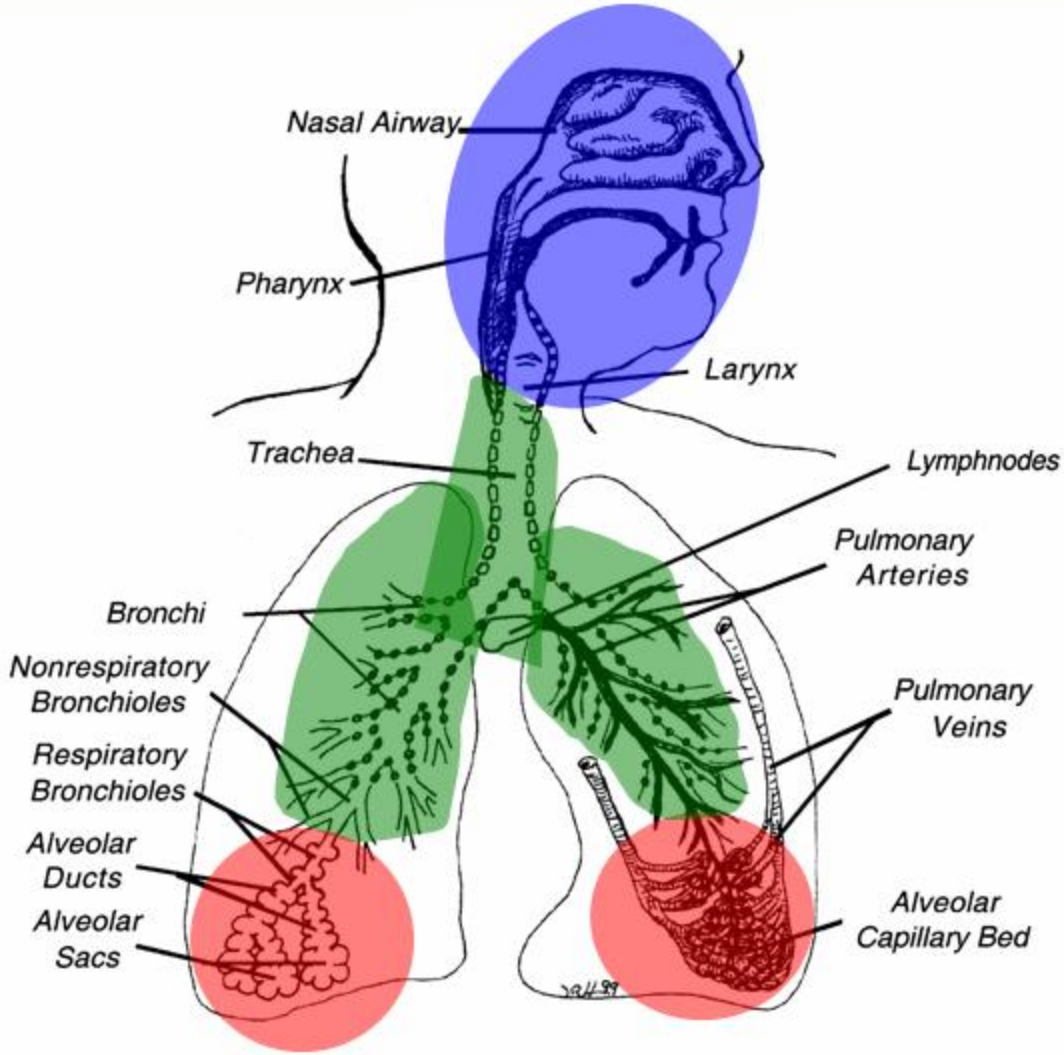
Considerations Regarding Nanomaterials Absorption through Skin: *Surface Charge*

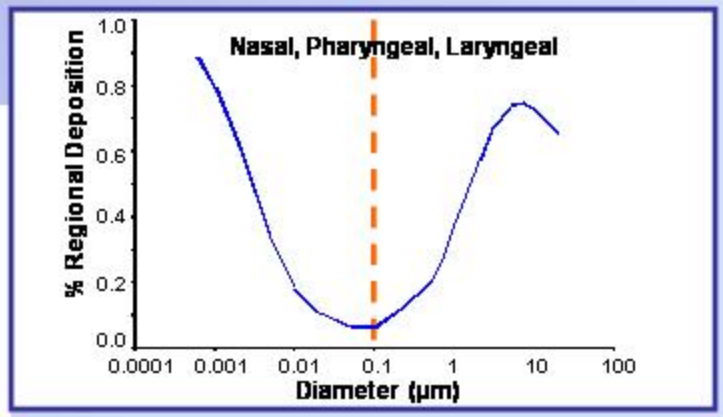


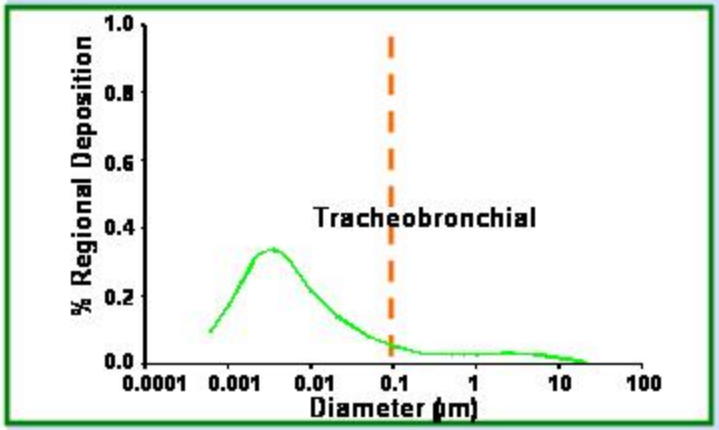
Scale bar, 50 μm

From: Ryman-Rasmussen et al., 2006

Respiratory Tract







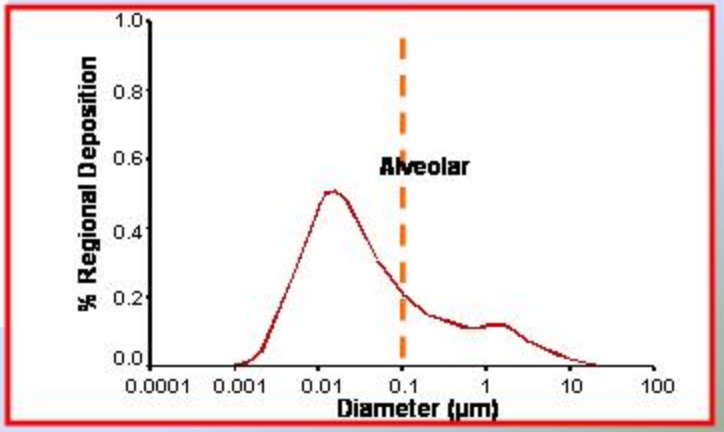
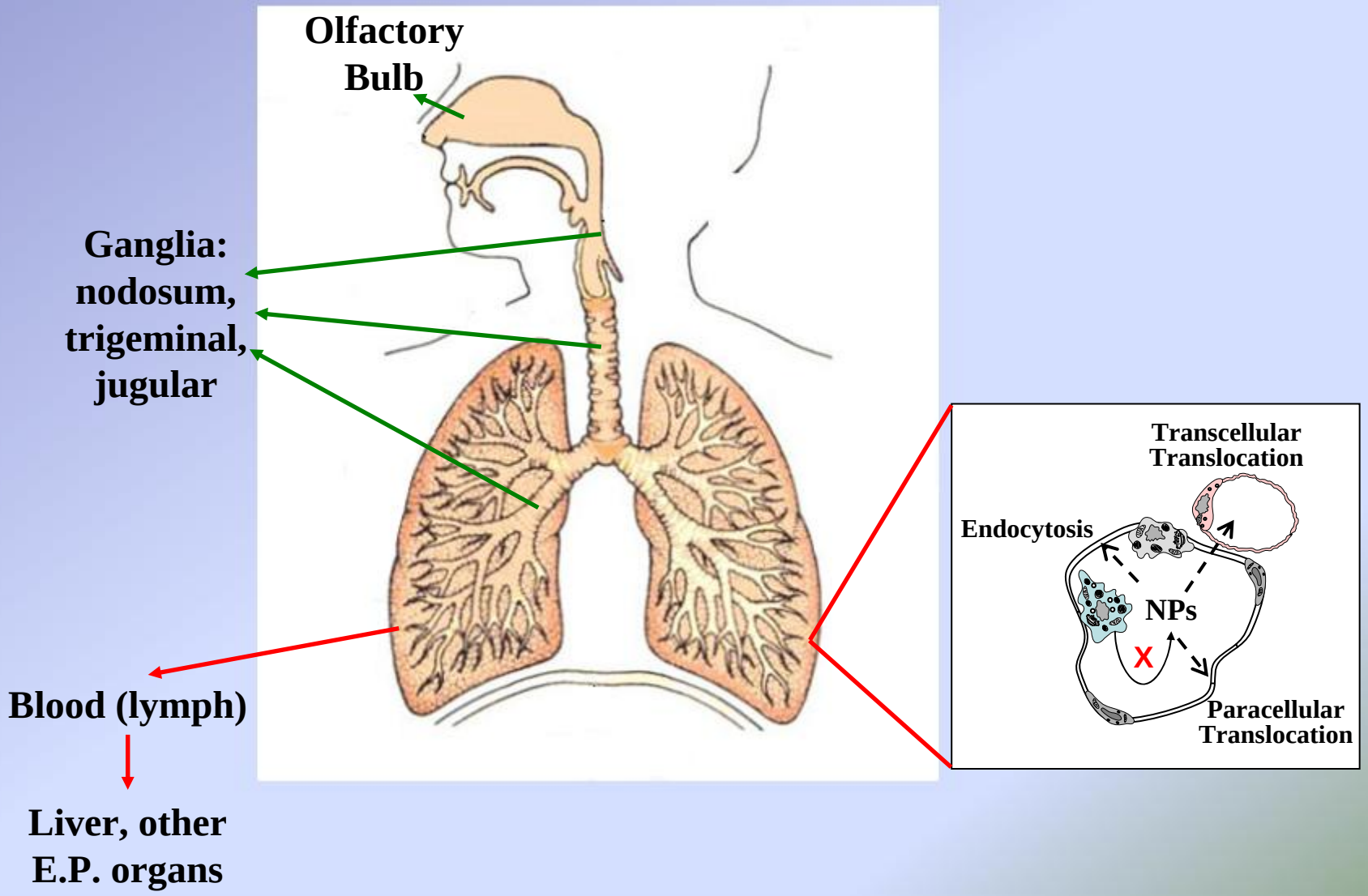


Figure courtesy of J. Harkema; adapted from ICRP, 1994

Potential Transport Pathways for Nanosized Particles



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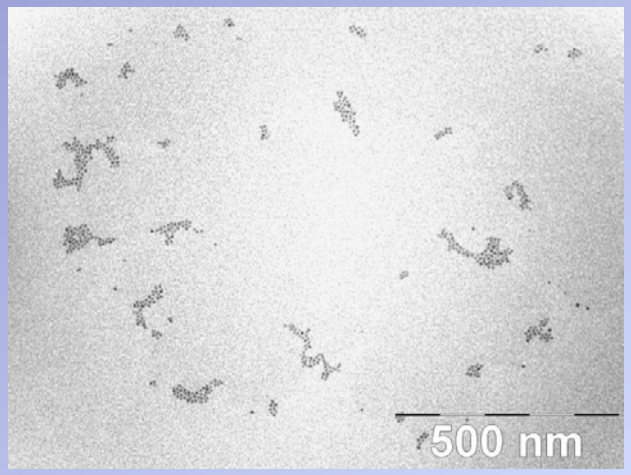
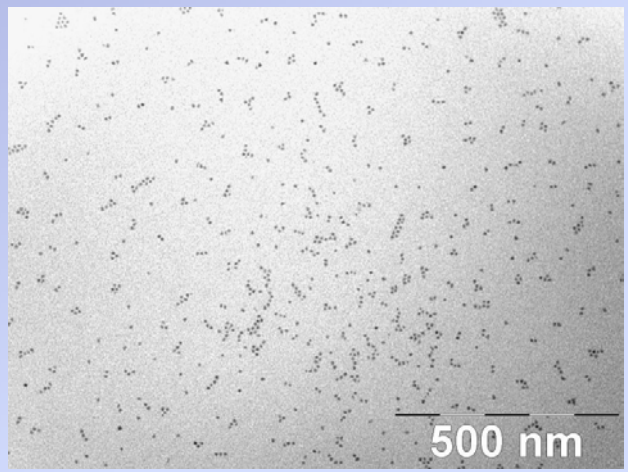
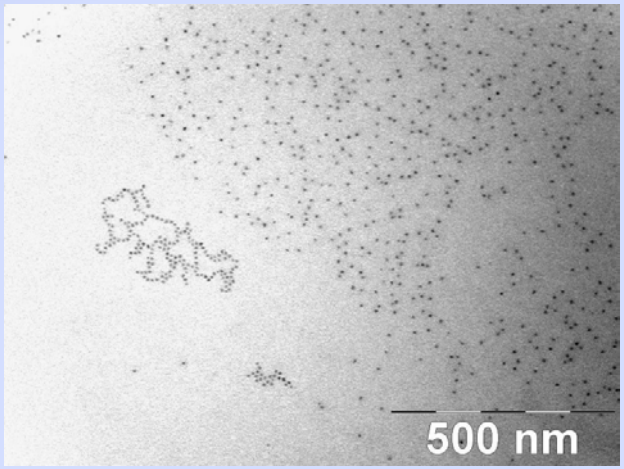
CdSe-ZnS Quantum Dots in 0.9% Saline



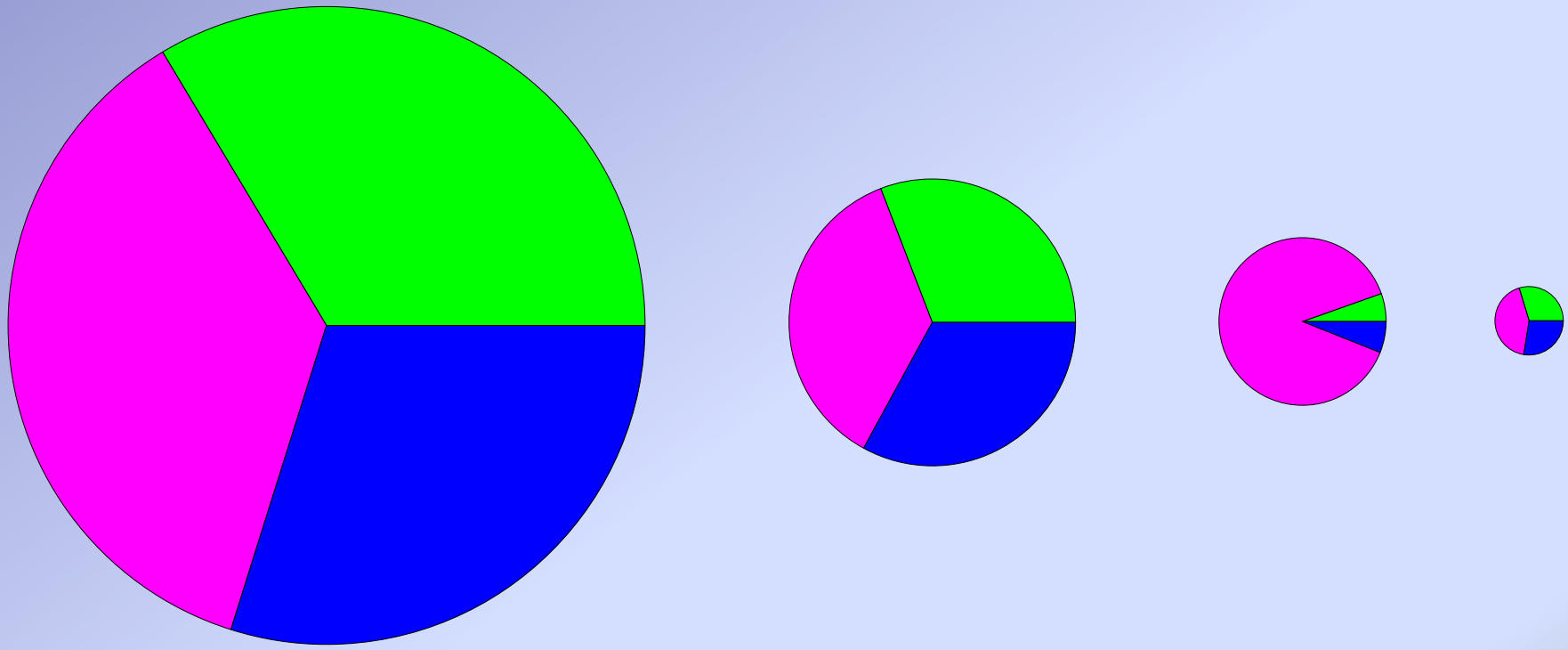




PEG	PEGamine	Carboxyl
Hydrodynamic diameter:		
23 nm	17 nm	14 nm
Zeta potential:		
-1.5 mV	**-0.3 mV**	**-40.0 mV**

in part from: Jiang et al., 2008

Tissue Retention of QDots One Week after Intratracheal Exposure



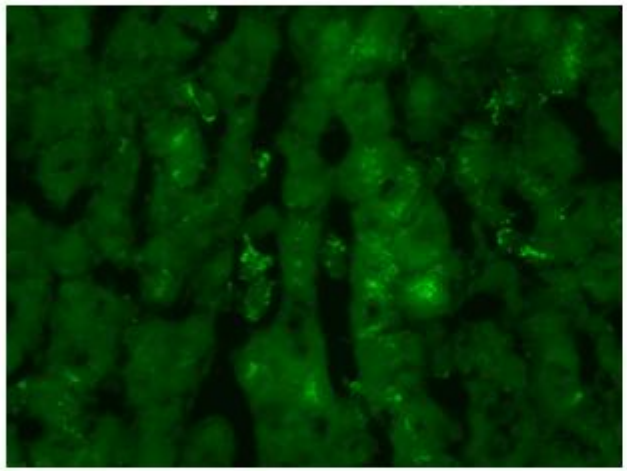
Lung Kidney Liver Spleen

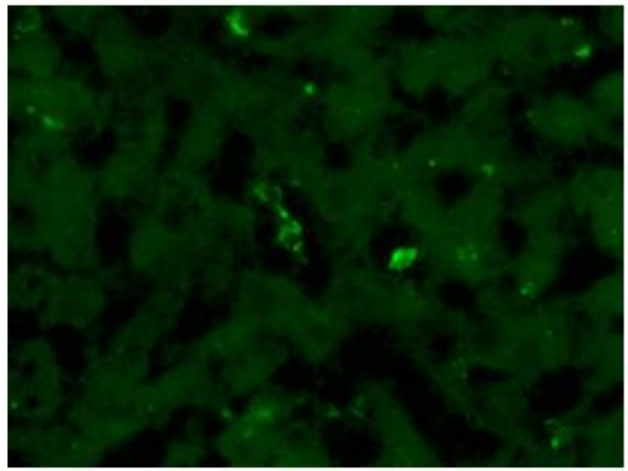
Retention of Quantum Dots in Liver Tissue after IV injection

PEGamine-coated QDs

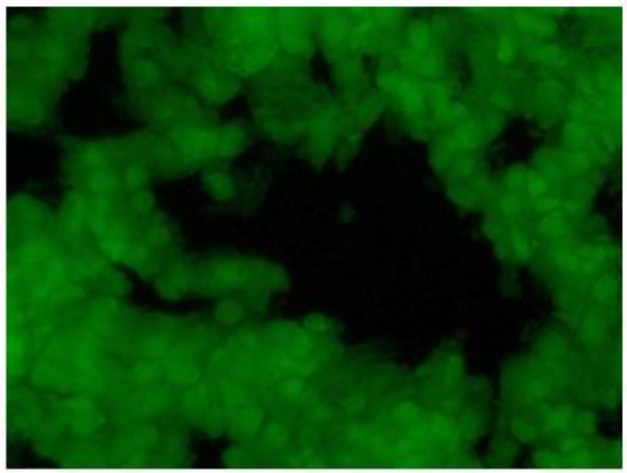
Carboxyl-coated QDs

1 Day



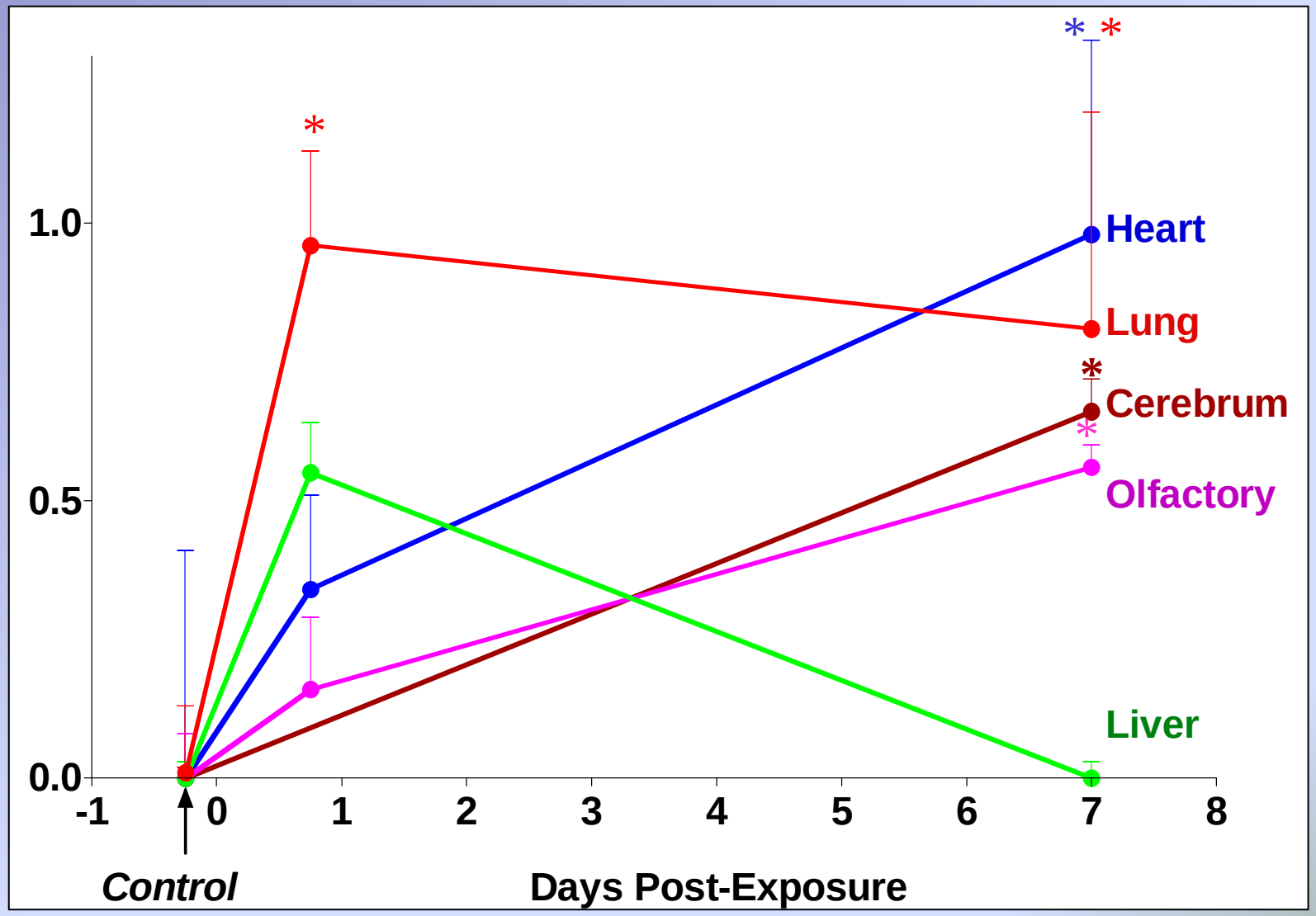


7 Days



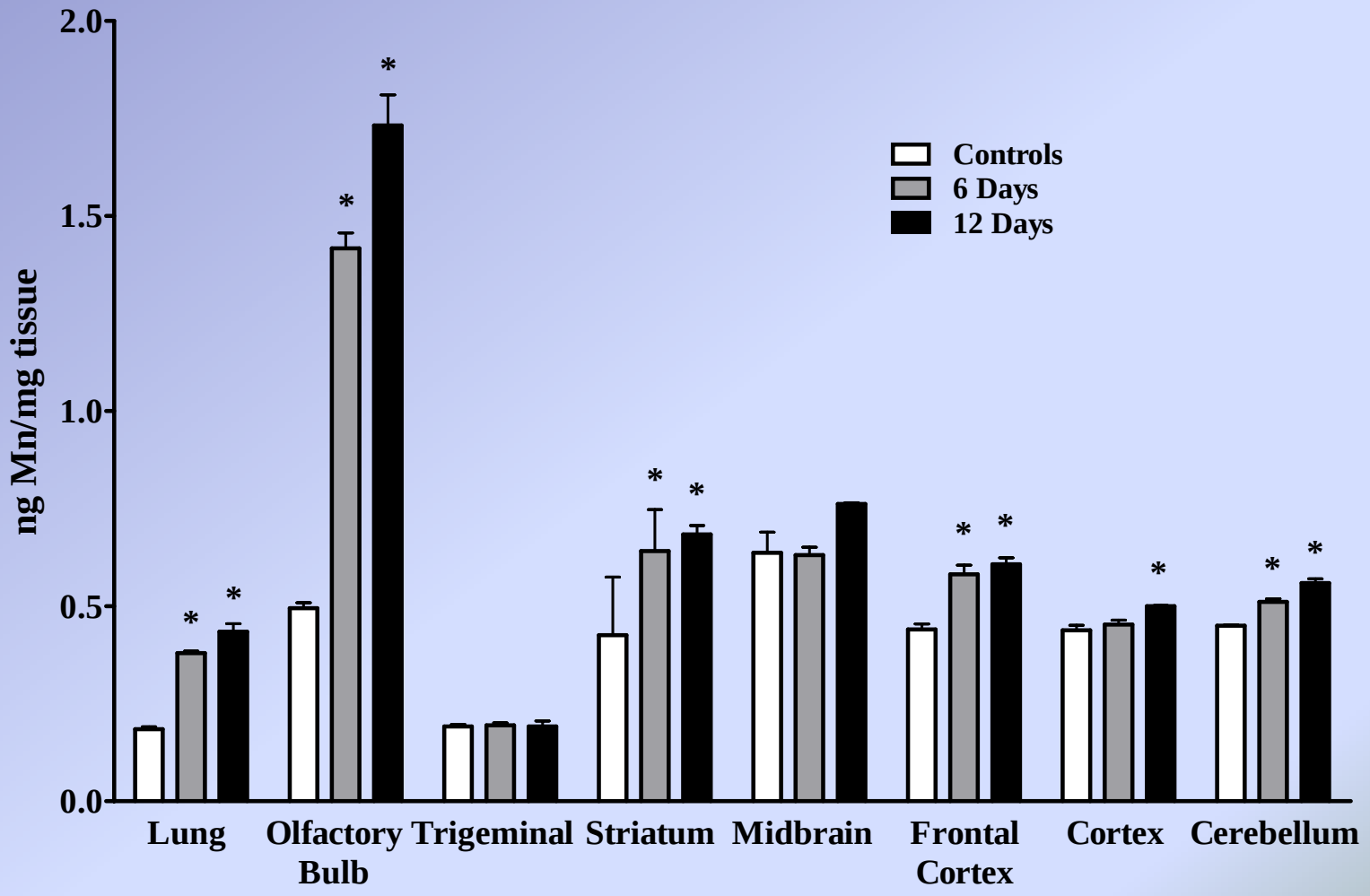
10 µm frozen sections
Magnification, 60x

Transport of Ultrafine (36 nm) ^{13}C Particles to Extrapulmonary Tissues



from: Oberdörster et al., 2002

Translocation in Rats of Inhaled Ultrafine Manganese Oxide to the Brain

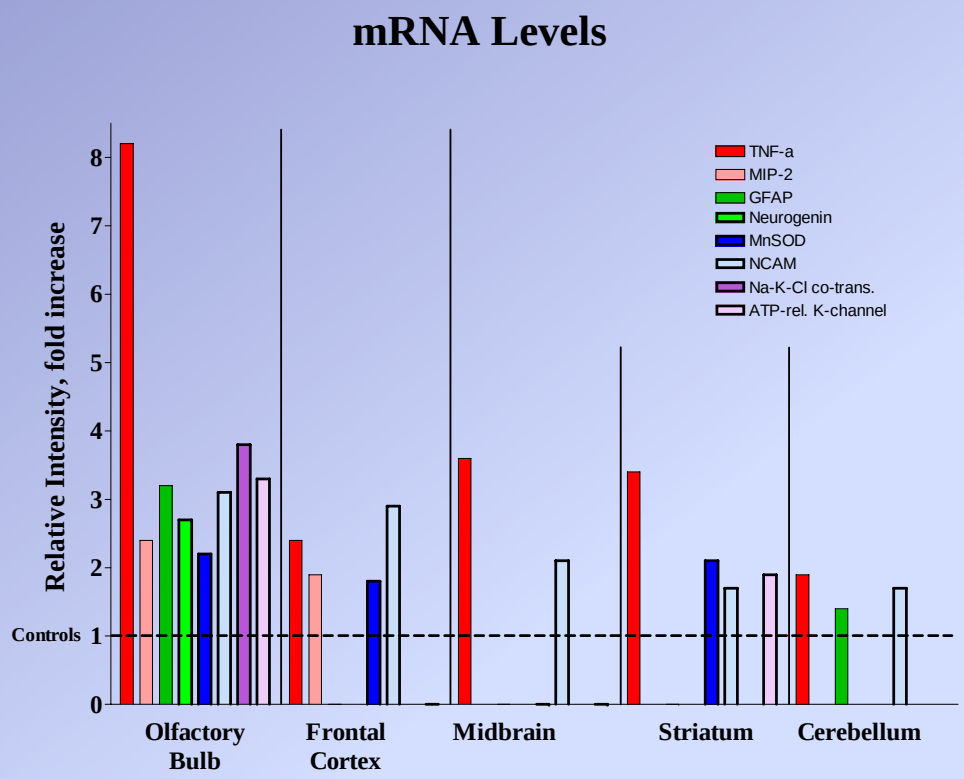


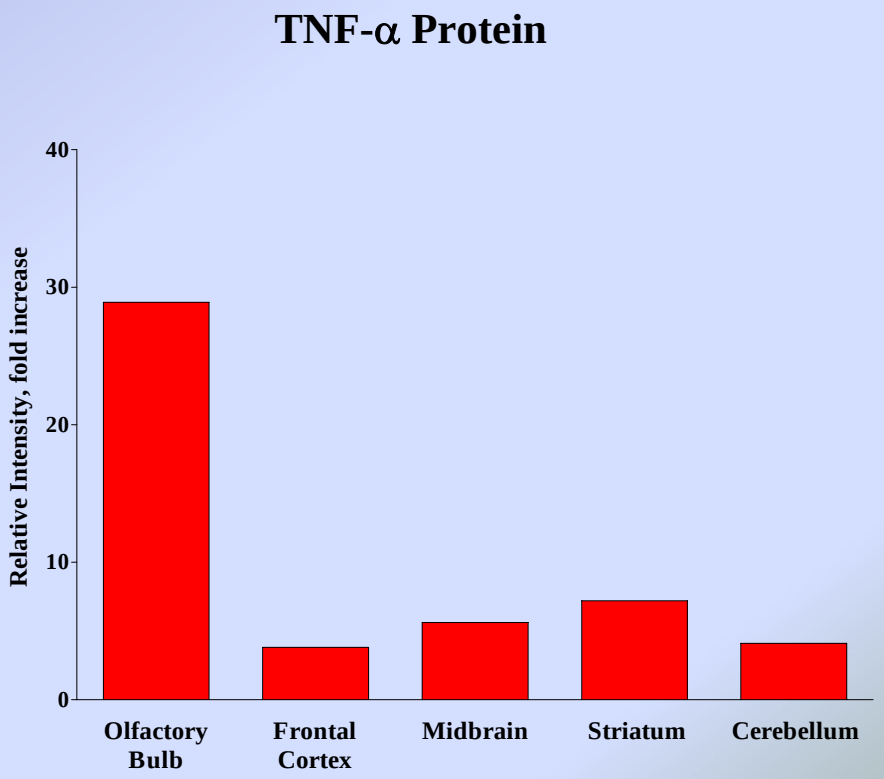
From: Elder et al., 2006

Consequences of Translocation?

- Nanosized particles to **brain** ⟶ increased expression of inflammatory/oxidative stress markers

Inflammation in the Brain Regions where Mn Signal was Found



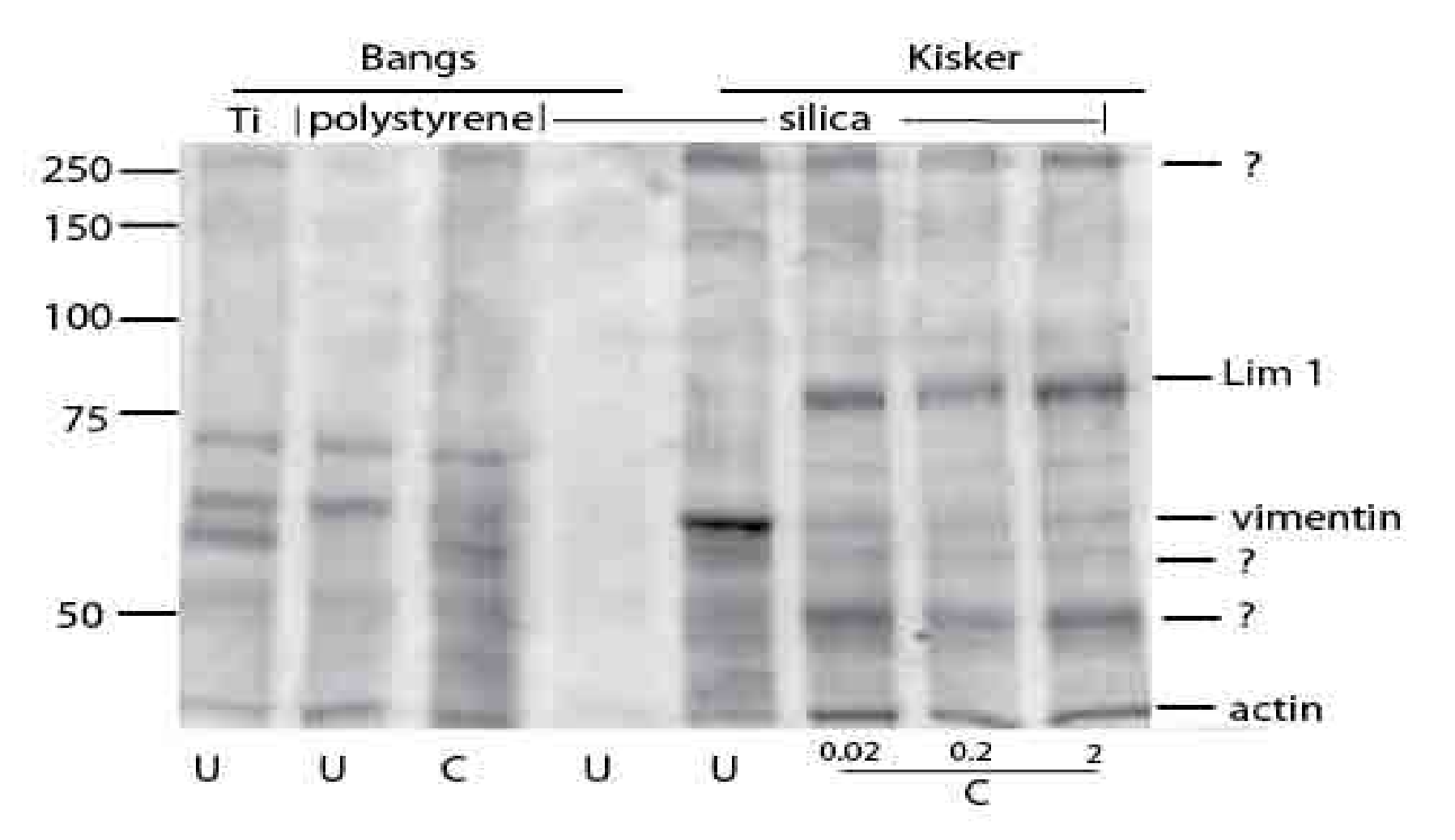


from: Elder et al., 2006

Consequences of Translocation?

- Nanosized particles to **brain** ⟶ increased expression of inflammatory/oxidative stress markers
- Nanosized particles into **blood** ⟶ thrombosis, cellular activation, adhesive property changes
- Nanoparticles to **blood/heart/sensory neurons** ⟶ heart rate/heart rate variability changes, arrhythmia

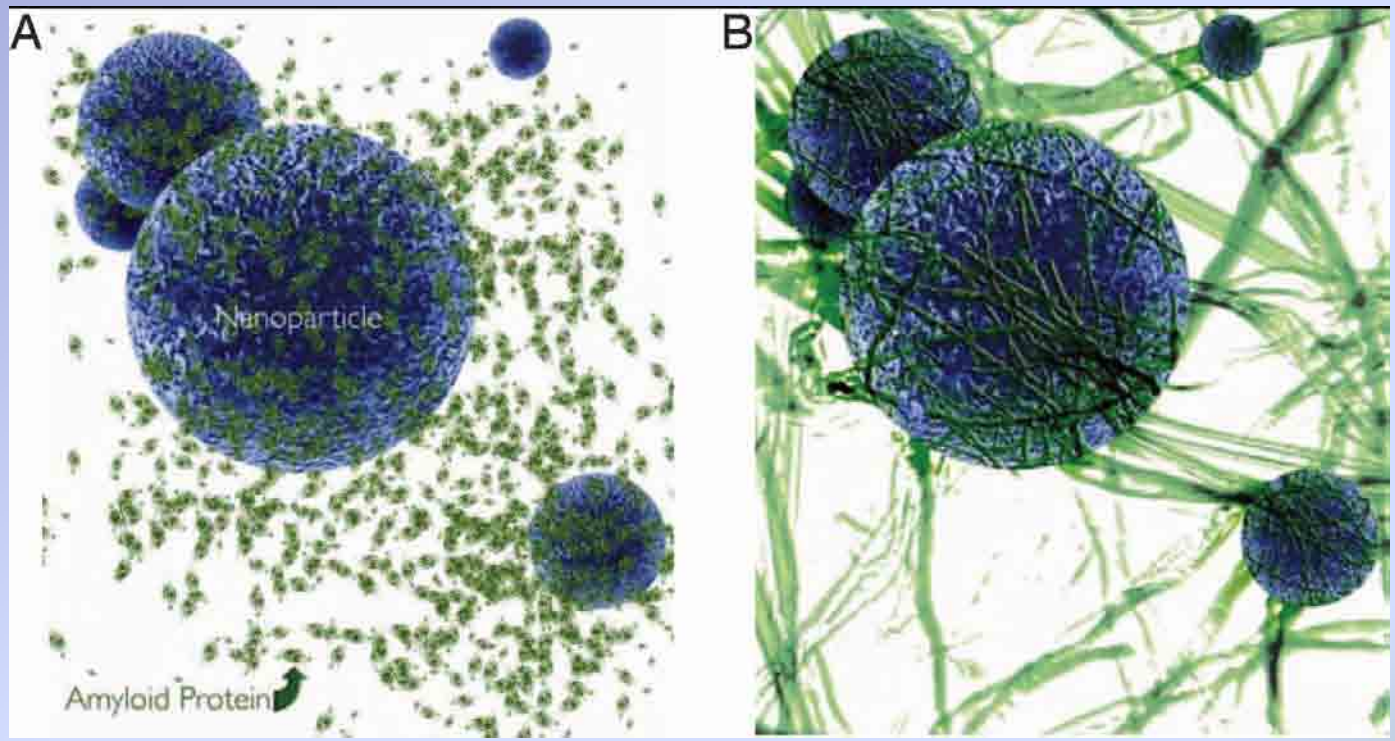
Binding of Proteins from Bovine Brain Extracts to NP Surfaces



from: Ehrenberg and McGrath, 2005

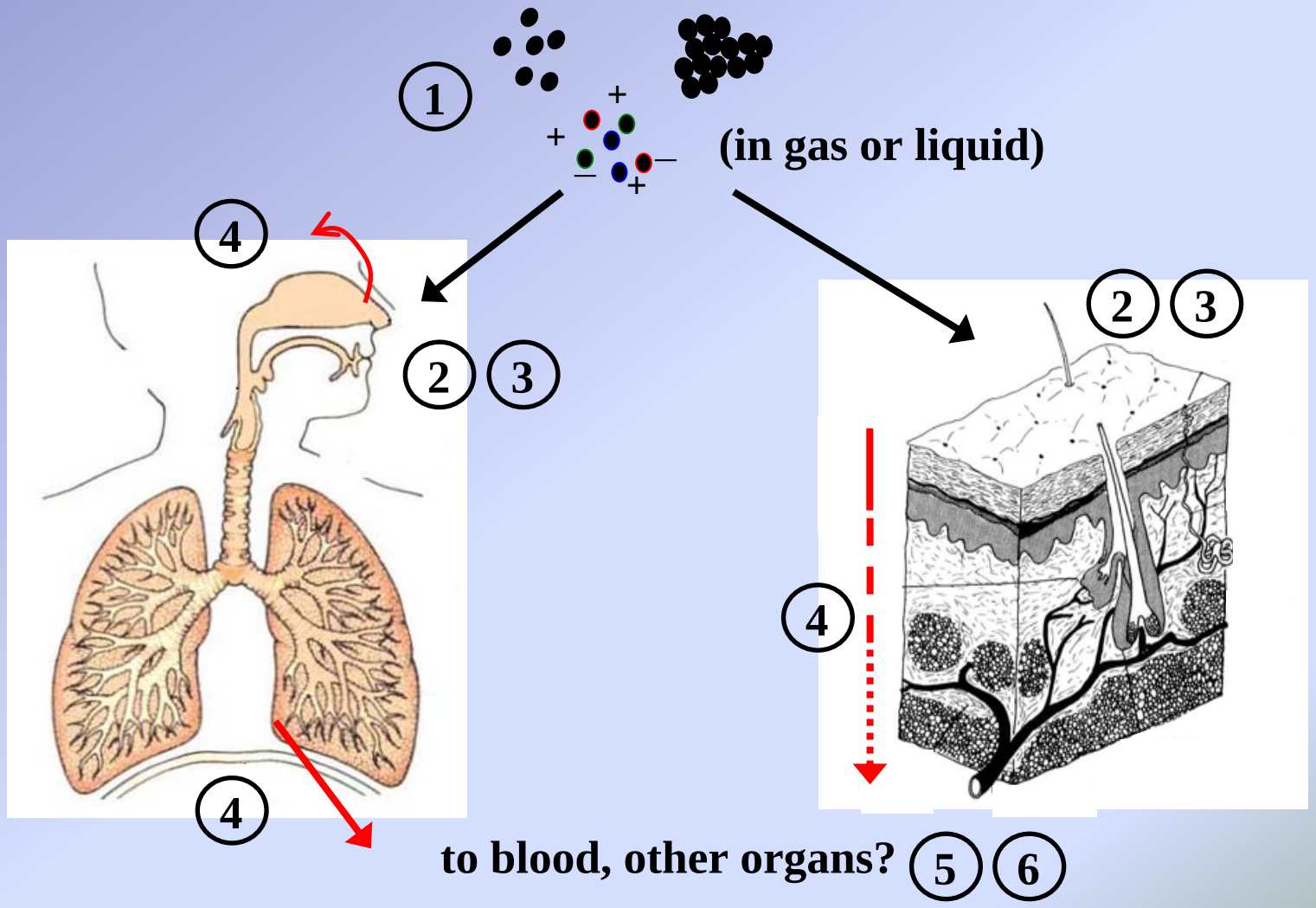
Emerging Issues

Are the fate and effects of nanoparticles determined by their interactions with biomolecules?



(from Linse et al., 2007; image from Colvin and Kulinowski, 2007)

Key Questions in Assessing Human Health Risk from Nanomaterials Exposure



Critical Issues in Assessing the Risk of Engineered Nanomaterials

- Deposited dose (airborne concentration, duration of exposure)
- Deposition site (underlying disease?)
- Biodistribution (integrity of barrier, responses caused by nanoparticle-cell interactions)
- Physicochemical properties (surface area, surface reactivity, agglomeration state, solubility, protein corona)
- Susceptibility of exposed individual