Overview of Nanoparticle Health and Safety

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Nanomanufacturing Summit 2010

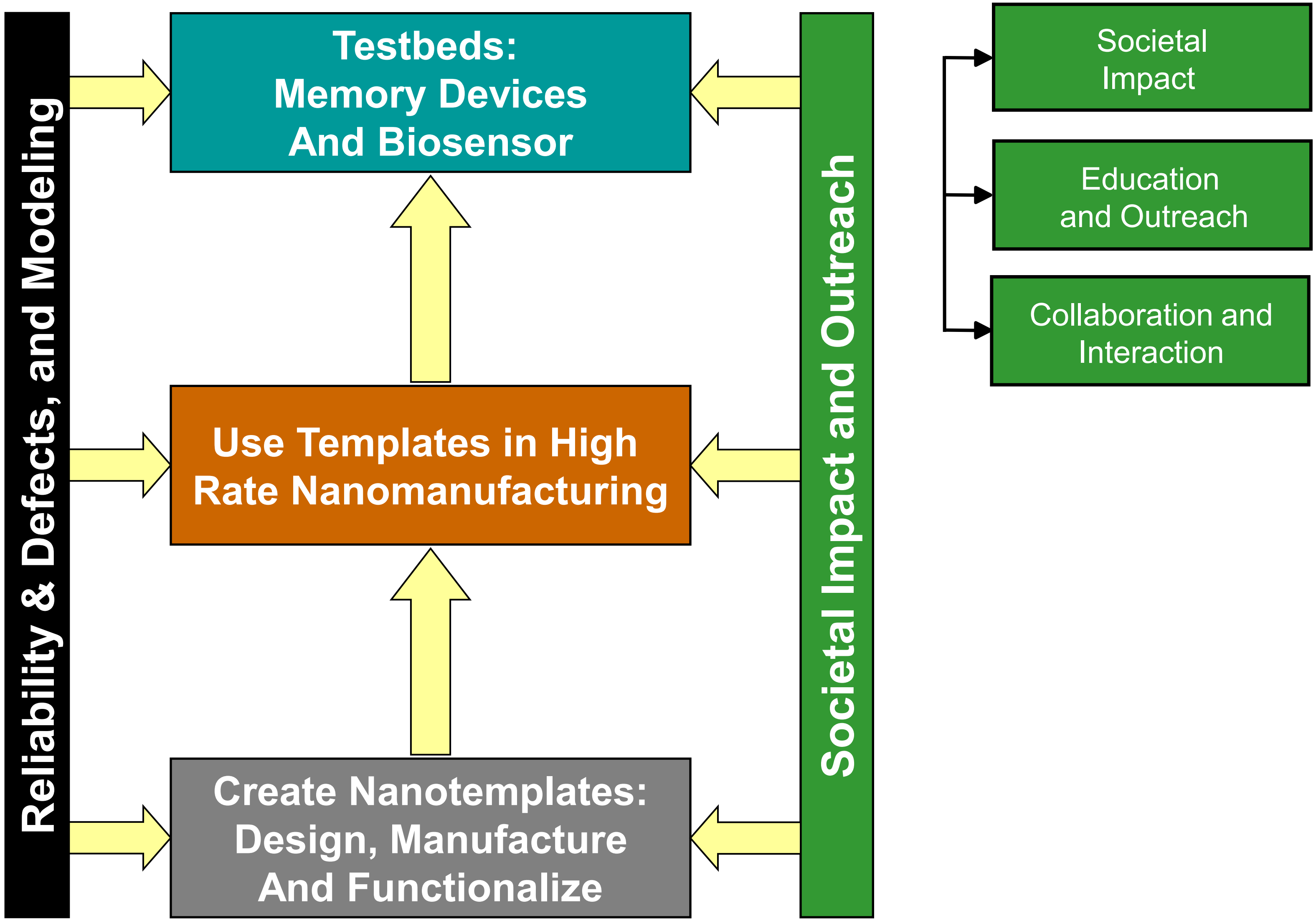
Center for High-Rate Nanomanufacturing

UMASS University of Massachusetts Lowell

UNIVERSITY of NEW HAMPSHIRE

Northeastern UNIVERSITY

CHN Pathway to Nanomanufacturing



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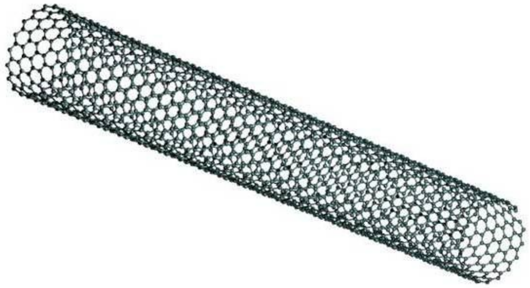
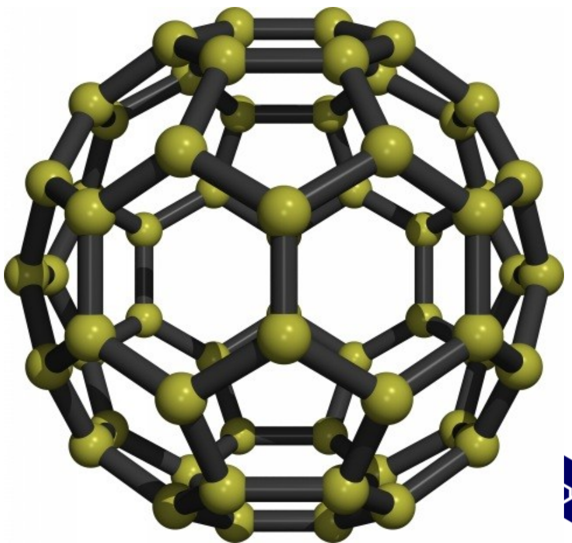
Outline

- Definitions
- Nanoparticle toxicity
- Current regulatory environment
- Worker exposure to nanoparticles
  - Airborne exposure
  - Dermal exposure
- Control of exposures
- Best practices to follow when working with nanoparticles

Categories of Nanoparticles

- Naturally-occurring (*e.g.*, forest fires, volcanoes)
- Industrial (*e.g.*, welding fume, diesel exhaust)
- Engineered (*e.g.*, carbon nanotubes, fullerenes)





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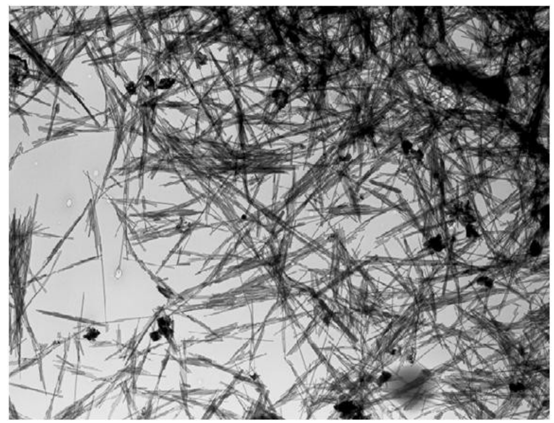
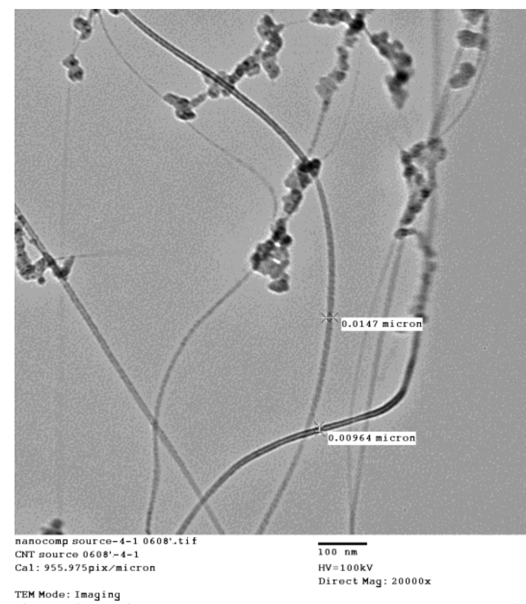
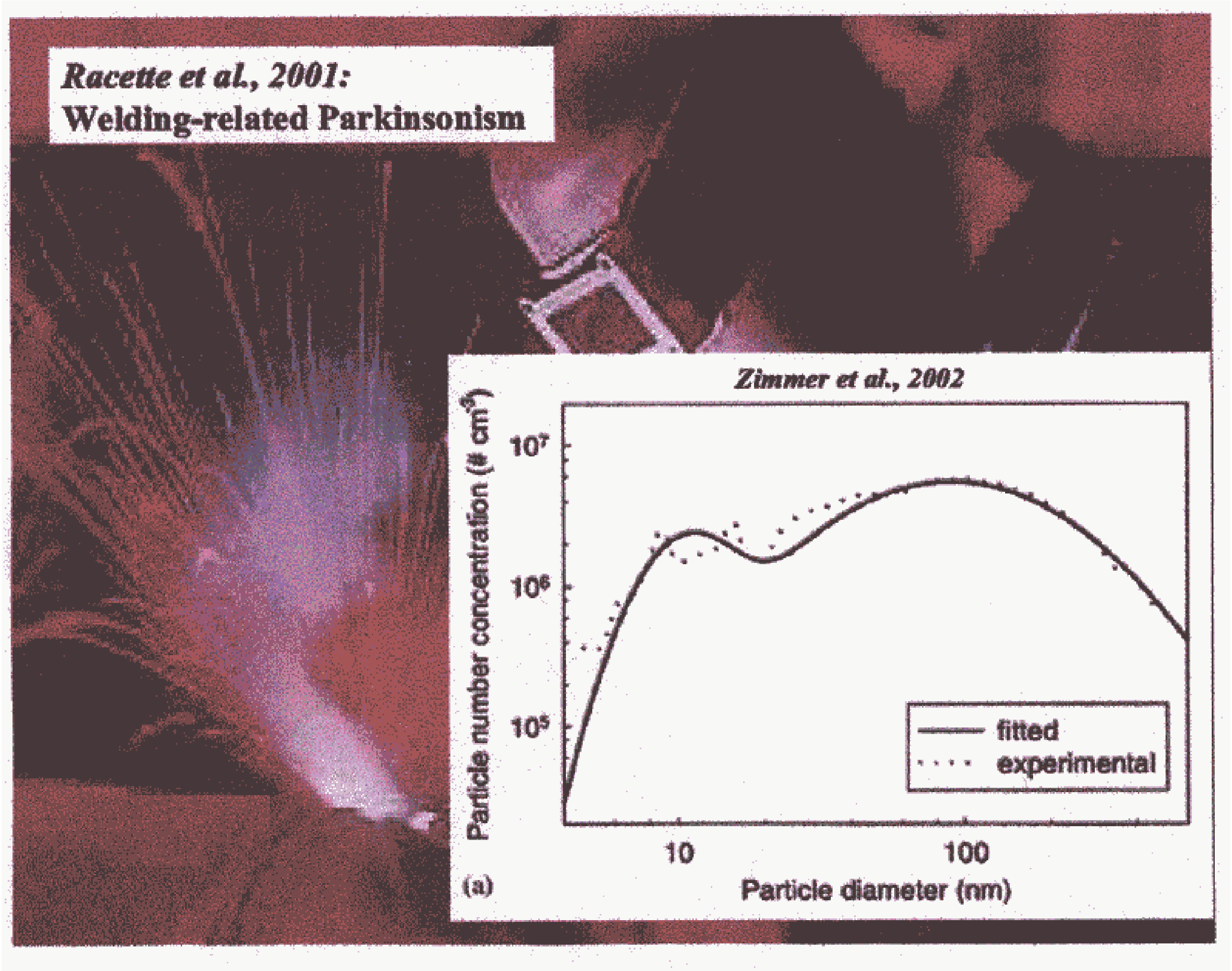
Nanoparticles in the Work Environment

Well-known occupational & environmental exposures



- asbestos
- silica flour
- flour dust
- combustion products
  - **welding fume**
  - **diesel exhaust**
  - **asphalt fume**





Oberdorster, in BIA report 7/2003e

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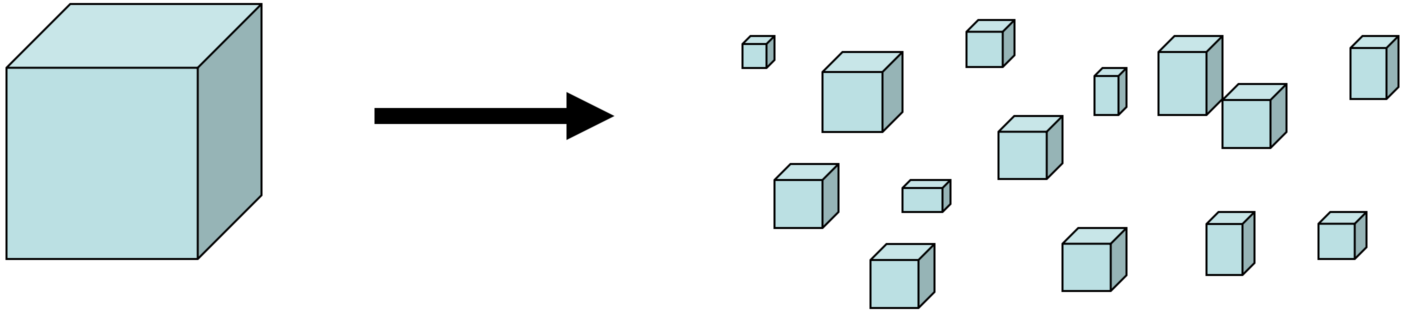
Crucial Factor in Nanoparticle Toxicity

Question:

What makes nanoparticles different from larger particles of the same composition?

Answer:

Particle surface-to-volume ratio increases as the particle diameter decreases



Consider three cases:

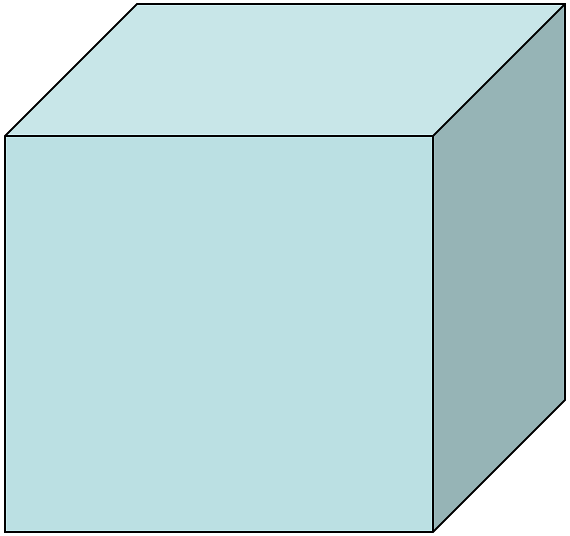
Case 1:

A single cube, 1 m length per side

$n = 1$ particle $L = 1$ m

$SA = 6\ m^2$ $V = 1\ m^3$

$SA/V = 6/1 = 6\ m^{-1}$



Case 2:

Slice the single large cube 1,000,000 times along each axis

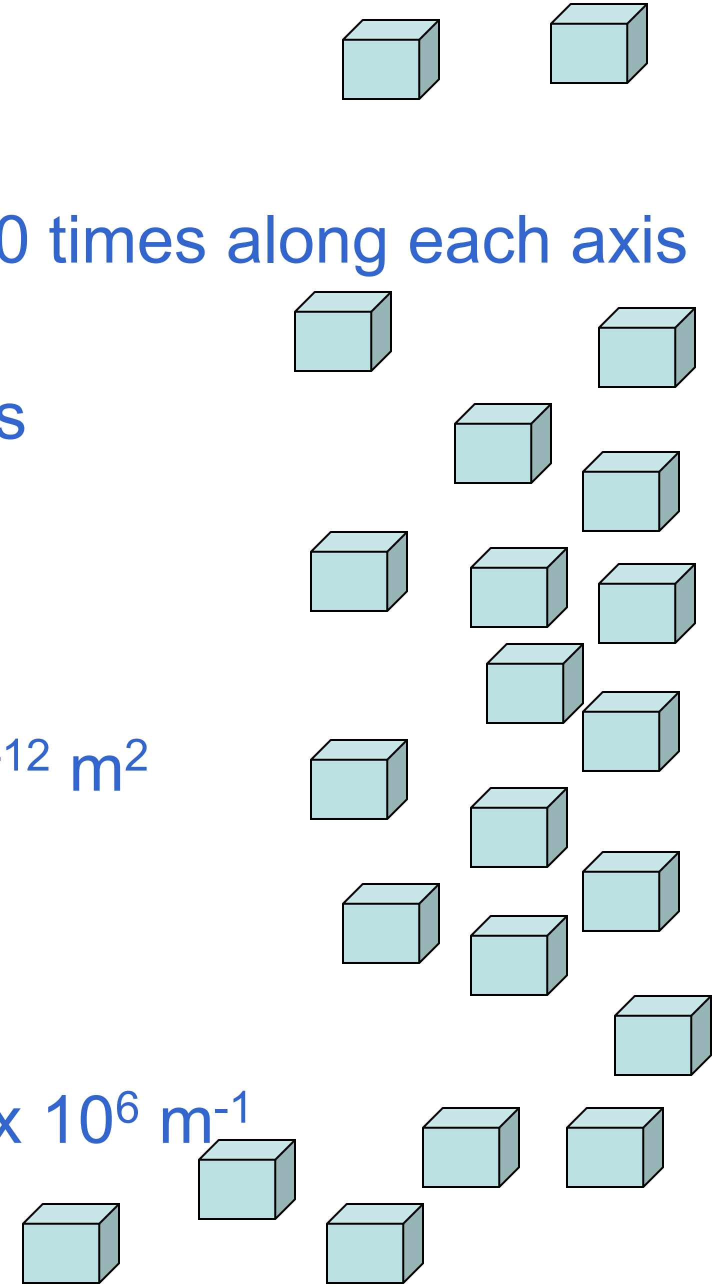
$n = 10^6 \times 10^6 \times 10^6 = 10^{18}$ particles

$L = 1\ \mu m$

$SA = 6 \times 10^{-6}\ m \times 10^{-6}\ m = 6 \times 10^{-12}\ m^2$

$V = 10^{-18}\ m^3$

$SA/V = 6 \times 10^{-12}\ m^2 / 10^{-18}\ m^3 = 6 \times 10^6\ m^{-1}$



Case 3:
Slice each small cube 1,000 times along each axis

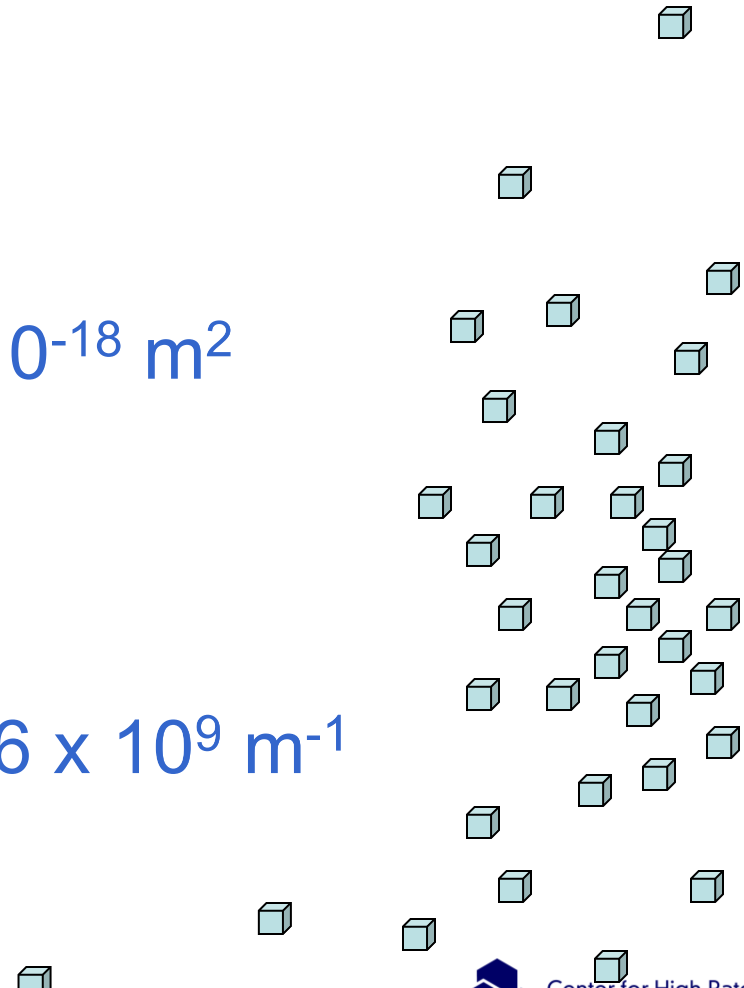
$n = 10^9 \times 10^9 \times 10^9 = 10^{27}$ particles

$L = 1$ nm

$SA = 6 \times 10^{-9}\ m \times 10^{-9}\ m = 6 \times 10^{-18}\ m^2$

$V = 10^{-27}\ m^3$

$SA/V = 6 \times 10^{-18}\ m^2 / 10^{-27}\ m^3 = 6 \times 10^9\ m^{-1}$



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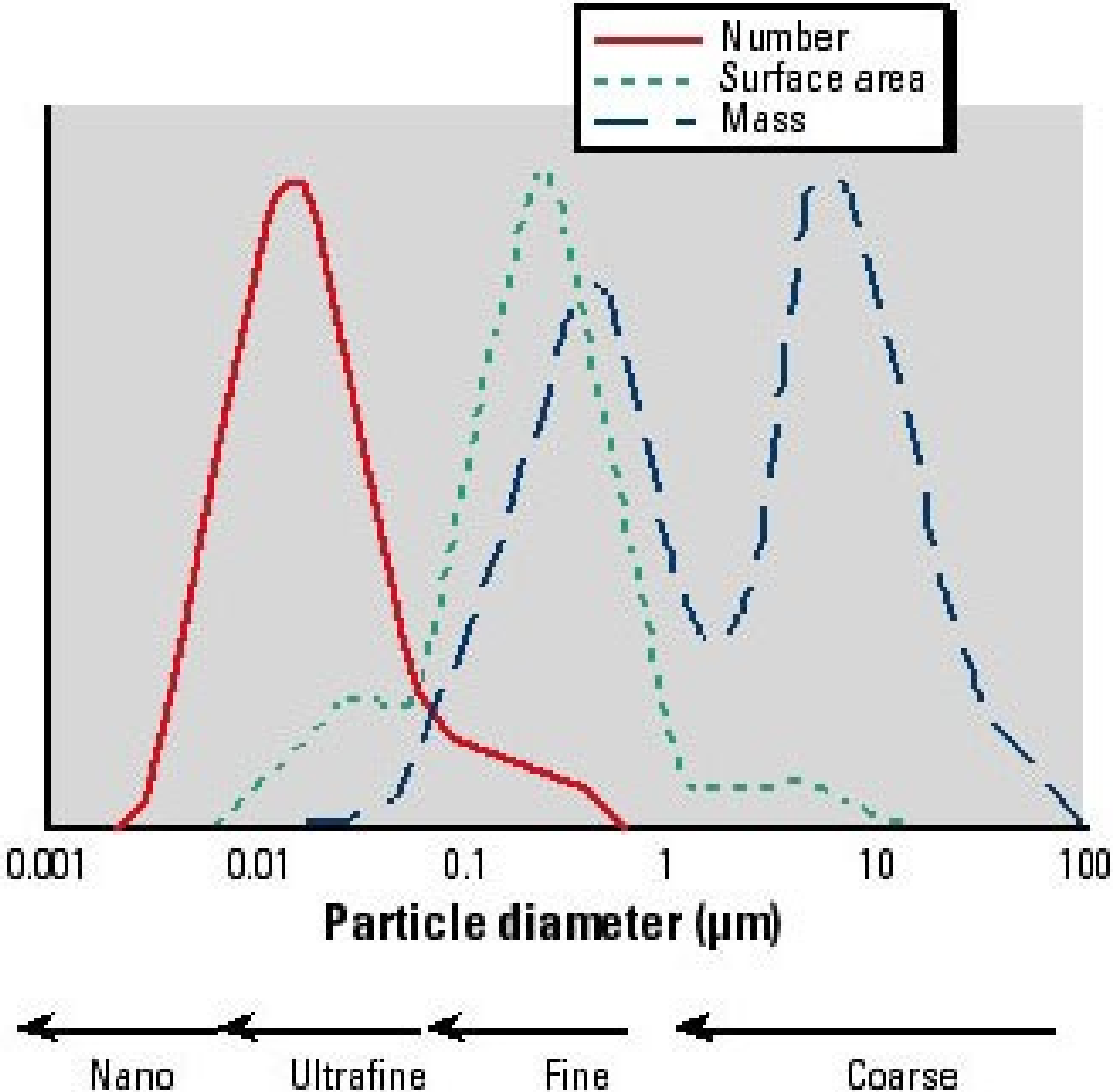

Number
Surface area
Mass
0.001
0.01
0.1
1
10
100
Particle diameter (µm)
Nano
Ultrafine
Fine
Coarse

The Message

- Surface area and particle number become much more important as the particles become smaller, compared to mass

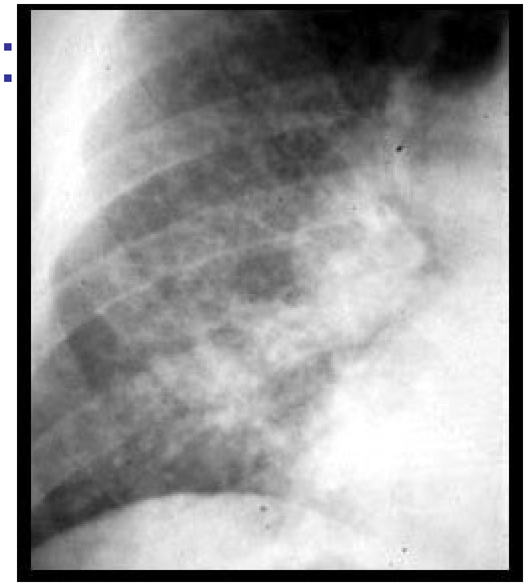
- Toxicological end points that depend on mass may be less important than end points that depend on surface area or number

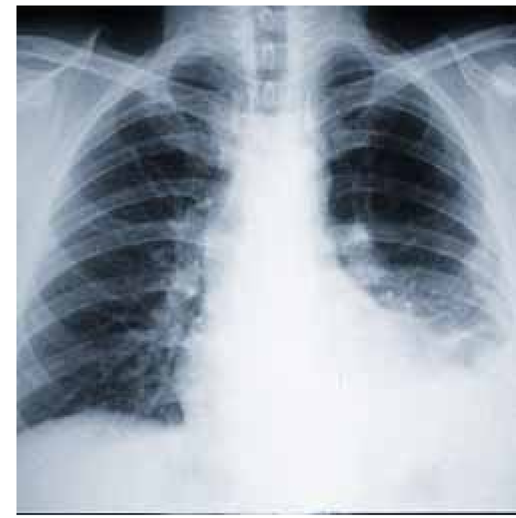
Particle Mobility

- As particles reach the nanometer size range, they may become more biologically mobile
  - Cross cellular boundaries from the alveolar region into the circulatory system
  - Pass through the skin
  - Travel through the olfactory nerve to the brain

Emphasis on CNT Toxicity

- Many studies published in the last 2-3 years
- End point studied:
  - Fibrosis
  - Inflammation
    - Lung tissue
    - Cardiac tissue
- Mesothelioma





- Donaldson: “…there is no experience of a workforce being potentially exposed to a biopersistent fibre of this degree of thinness.”

Donaldson, et al., Carbon nanotubes: a review of their properties in relation to pulmonary toxicology and workplace safety, Toxicol Sci 92: 5-22, 2006

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NIOSH Inhalation Studies

- Purified SWCNT's
- Mice
- Aspiration – 0,10,20,40 µg/mouse
- Ultrafine carbon black and SiO_2 used as control
- Dose equivalent to a worker exposed to the graphite Permissible Exposure Limit (5 mg/m^3) for 20 work days

Effects on Lung

- Both *inflammation* (acute response) and *fibrosis* (chronic response) were found
- Effects were dose-dependent
- No fibrosis and greatly reduced inflammation found with the reference materials

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Is This of Concern?

- Mouse dose equivalent to airborne concentration of 5 mg/m^3 for 8 h/day for 20 days
- 5 mg/m^3 CNT $\rightarrow 10^{17}$ CNT/m^3

  = 10^{11} CNT/cm^3!!

  - Highest concentrations we have measured anywhere in any lab :

    < 10^6 particles/cm^3

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Cardiac Tissue Inflammation

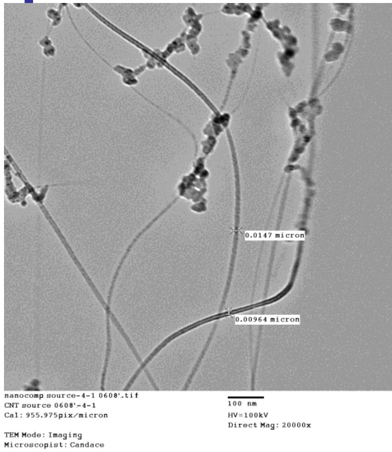
- NIOSH study – same protocol as previous study
- "A single intrapharyngeal instillation of SWCNTs induced activation of heme oxygenase-1 (HO-1), a marker of oxidative insults, in lung, aorta, and heart tissue in HO-1 reporter transgenic mice. Furthermore, we found that C57BL/6 mice, exposed to SWCNT (10 and 40 µg/mouse), developed aortic mtDNA damage at 7, 28, and 60 days after exposure."

Li, et al., Cardiovascular Effects of Pulmonary Exposure to Single-Wall Carbon Nanotubes, Env Health Perspect 115: 377-82, 2007

CNTs cause Mesothelioma?

- Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study.

  •Poland, et al., Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study Nature Nano. 3:423-8, 2008.



- Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube. Takagi, et al., Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube J. Toxicol. Sci 33:105-15, 2008.

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Current Status - Regulations

- Few, if any, regulations exist specifically for engineered nanoparticles
- No exposure limits, no emission limits, no disposal regulations
- In the U.S., EPA, the state of CA and the city of Berkeley are now requiring CNT manufacturers to submit information
- Manufacturers and users must operate in an atmosphere of uncertainty

Recent Regulatory Activity in the United States

- **EPA - Toxic Substances Control Act Inventory Status of Carbon Nanotubes** – 31 Oct 2008

"This document gives notice of the Toxic Substances Control Act (TSCA) requirements potentially applicable to carbon nanotubes (CNTs). EPA generally considers CNTs to be chemical substances distinct from graphite or other allotropes of carbon listed on the TSCA Inventory. Many CNTs may therefore be new chemicals under TSCA section 5. Manufacturers or importers of CNTs not on the TSCA Inventory must submit a premanufacture notice (PMN) (or applicable exemption) under TSCA section 5…"

Recent Regulatory Activity in the United States, Cont.

On January 22, 2009, California's Department of Toxic Substances Control (DTSC) sent a formal request to several California manufacturers and/or importers of carbon nanotubes seeking information regarding analytical test methods, environmental fate and transport, and other relevant environmental, health, and safety information regarding carbon nanotubes.

CA Questions to Manufacturers, Cont.

- Recipients had one year (until Jan 22, 2010) to supply the requested information
- 20 companies/universities/labs responded
- Submitted information available on-line;

http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/nanocallin.cfm

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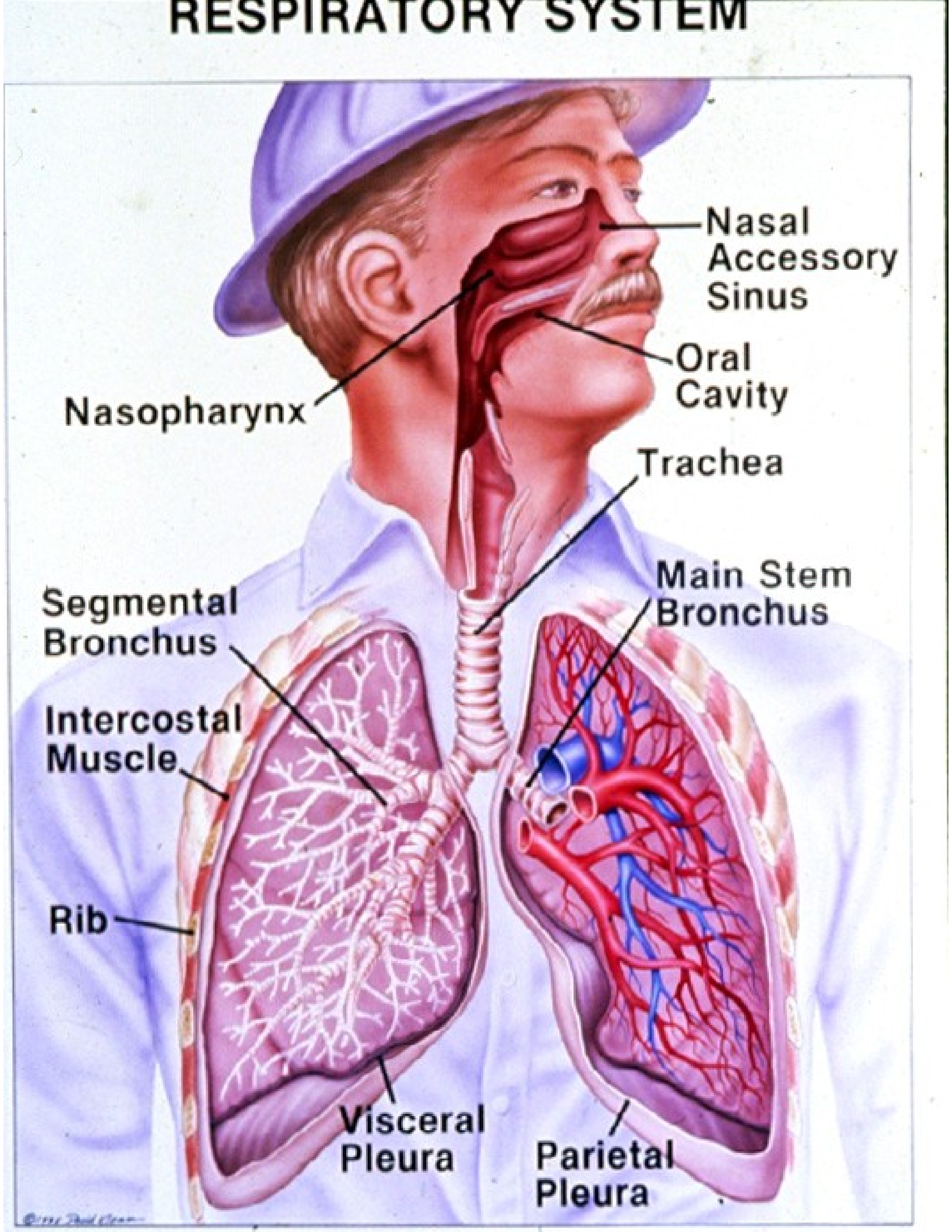

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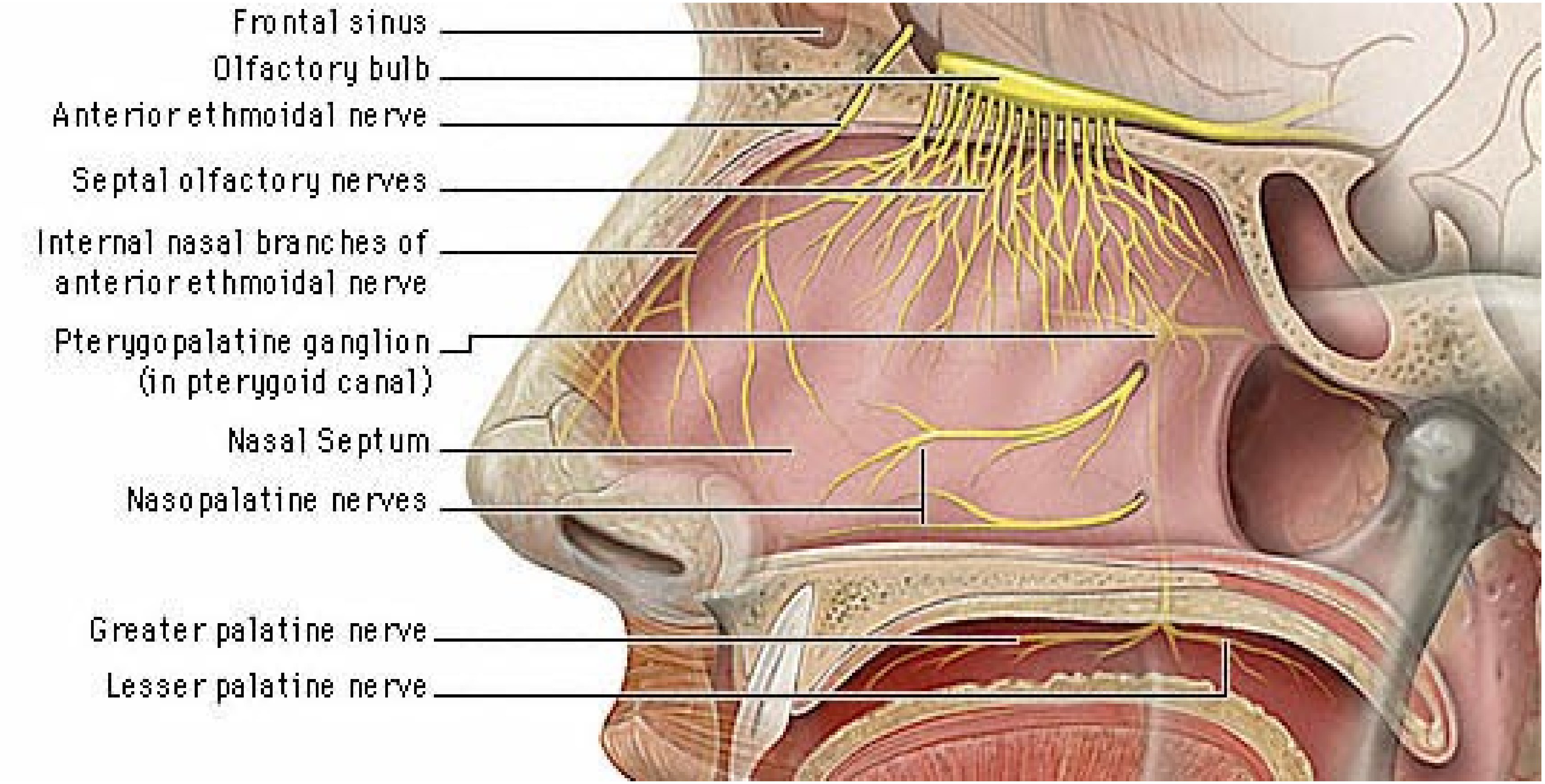
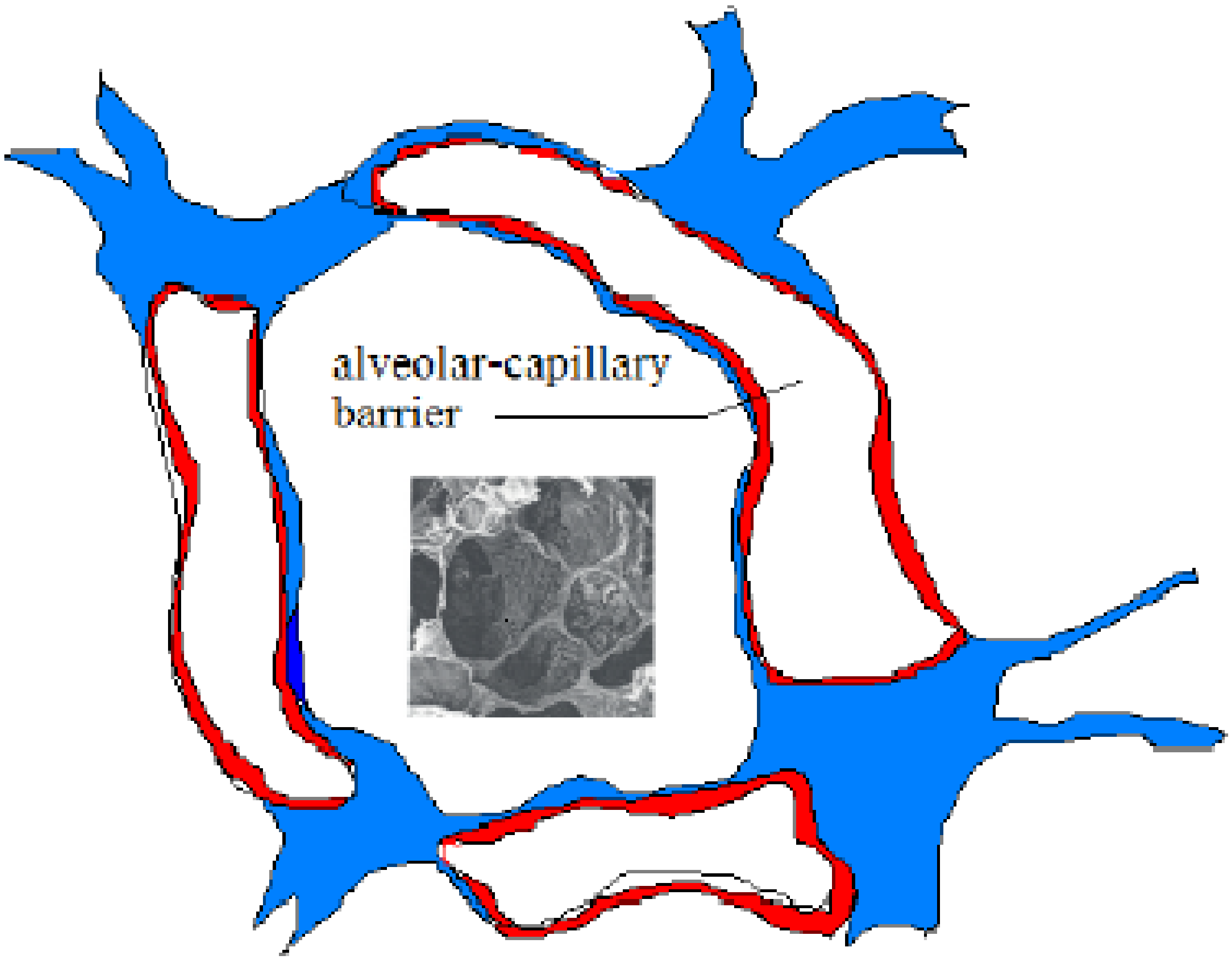
Olfactory Nerve Exposure
and
Central Nervous System Effects

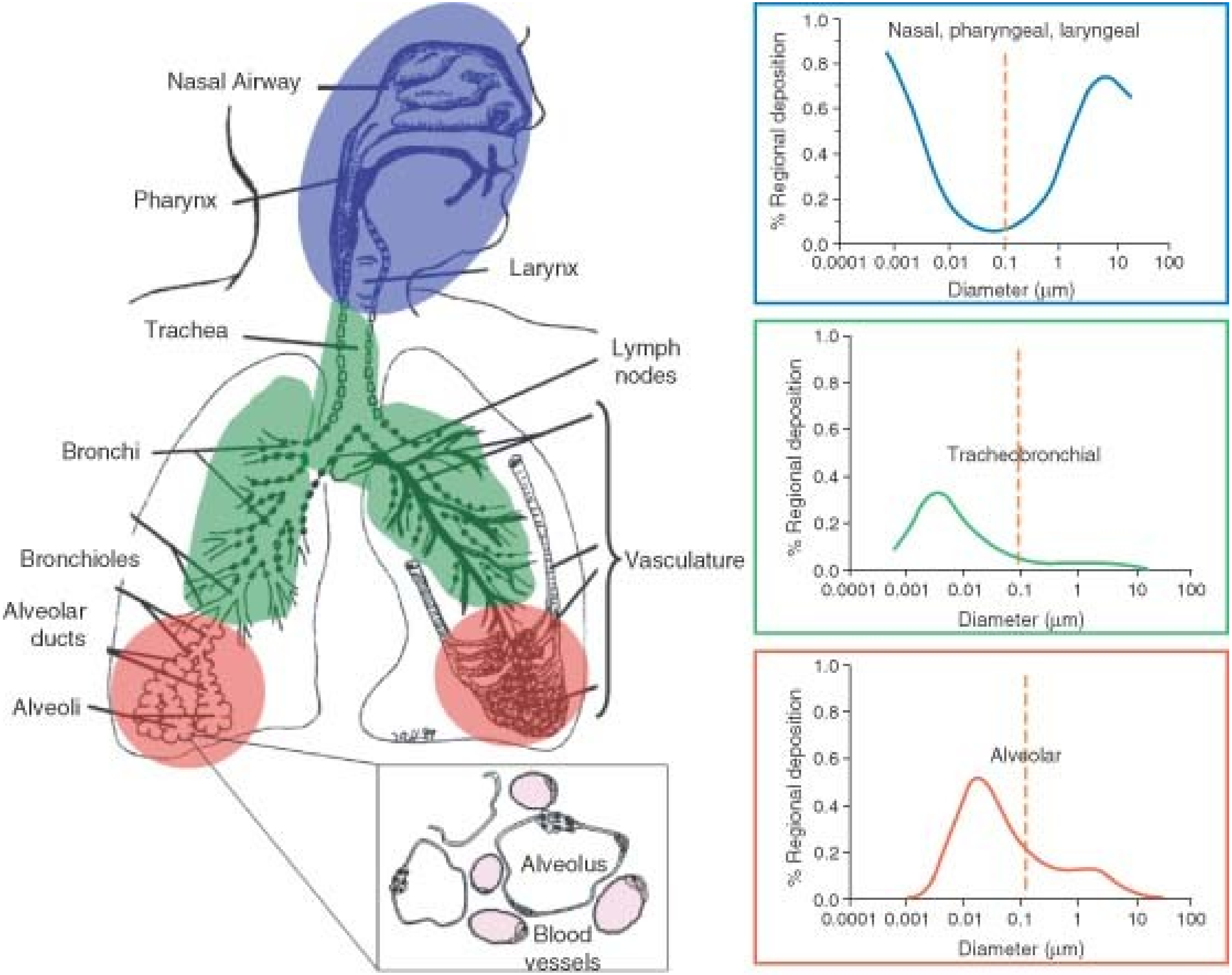


Cross-section of an Alveolus



Shows a very thin (500 nm) separation between blood and air. An SEM image of the alveoli is shown in the inset

Hoet et al. J Nanobiotech 2004.



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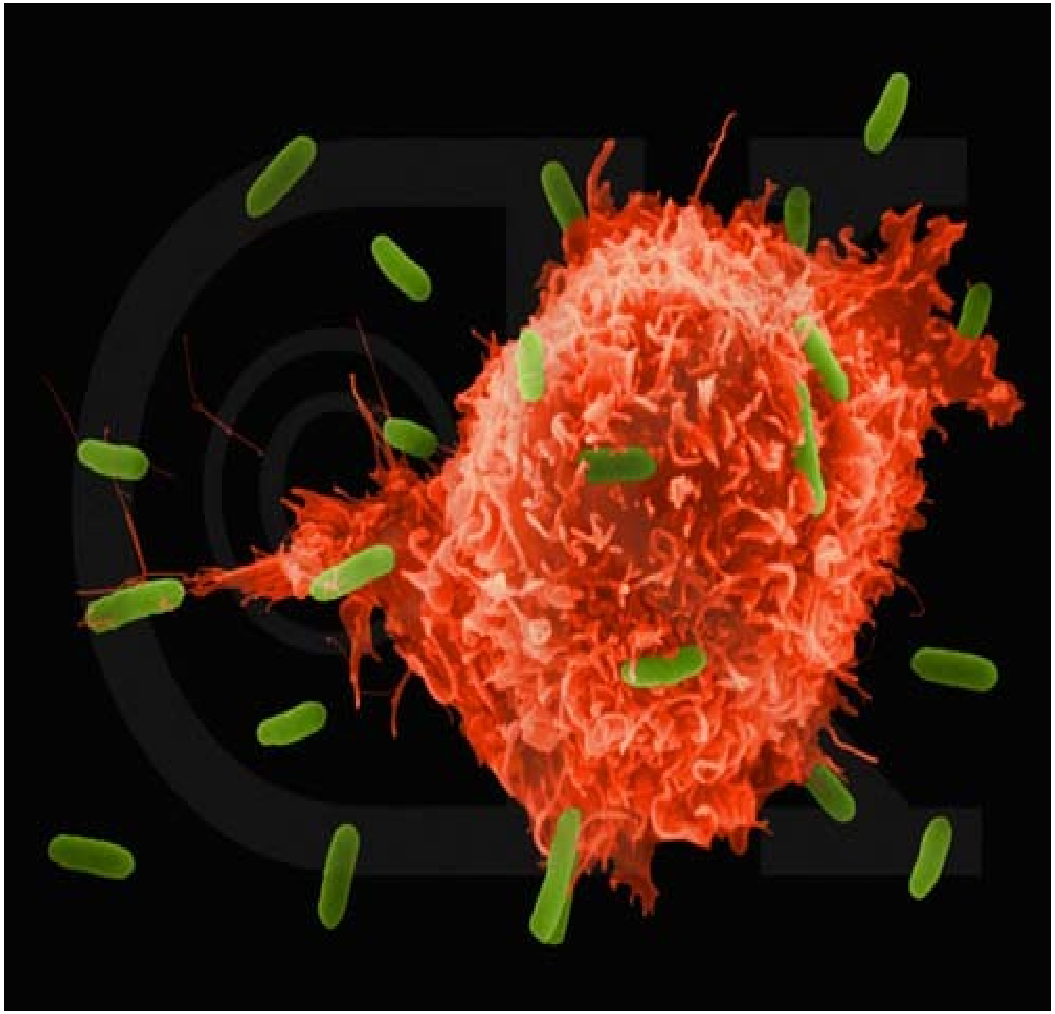
Alveolar Macrophage Attacking *e. coli*



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Alveolar Macrophage Attacking an Asbestos Fiber

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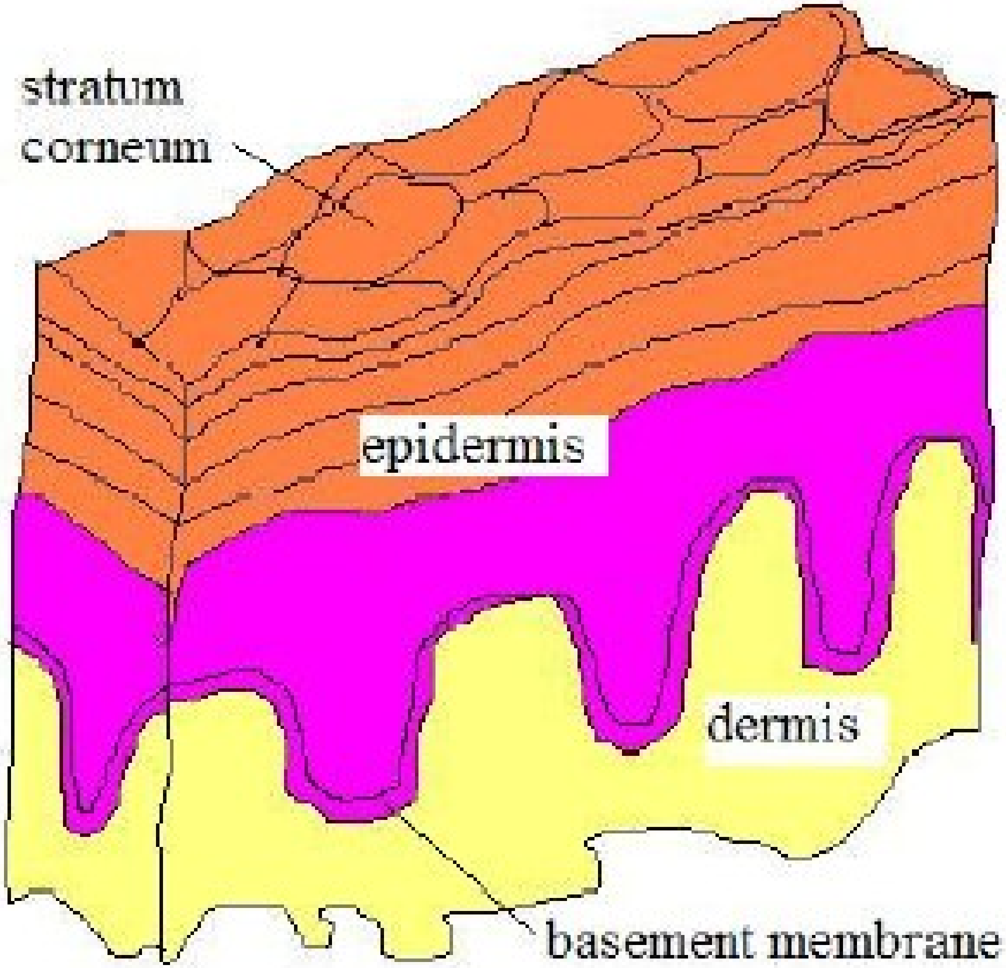
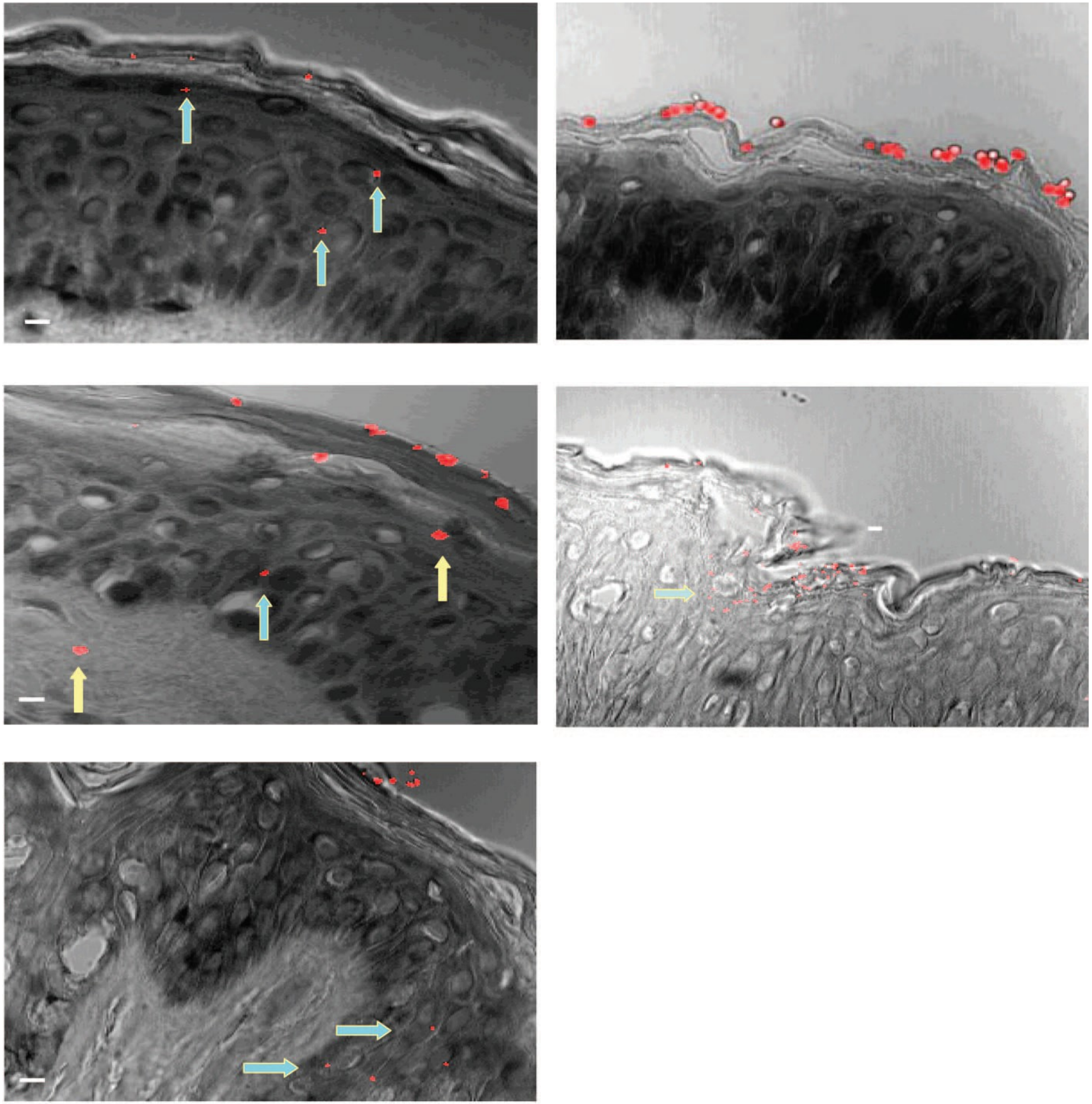
Schematic of Human Skin



Hoet et al. J Nanobiotech 2004.

Stratum corneum, top of the five layers making epidermis, is shed off and replaced every two weeks. Depending on the part of the body its thickness varies from 0.05 mm to 1.5 mm.



Dermal Exposure

Tinkle et al

EHP 2003

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Control of Airborne Exposures

- Airborne nanoparticles behave very much like gas molecules
- Therefore, standard engineering control methods developed for gases should work well to protect workers from exposure to nanoparticles
- One possible exception – respirators
- Less confidence regarding environmental controls

Methods of Control

Hierarchy of controls

- Engineering controls
  - Substitution
  - Isolation
  - Ventilation
    - General exhaust ventilation
    - Local exhaust ventilation
- Administrative controls
  - Worker training
  - Medical monitoring
  - scheduling

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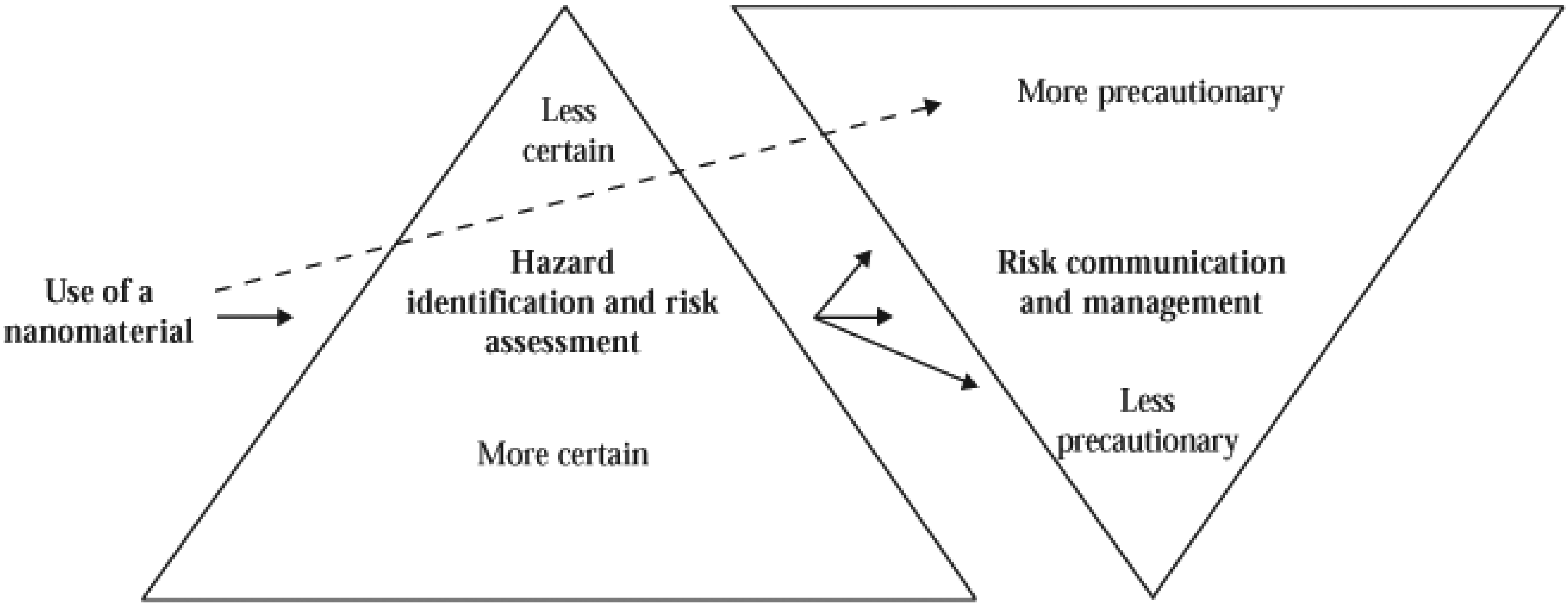
Figure 1. Risk management decisionmaking for nanoparticles in the workplace: what is the appropriate level of controls?



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Control of Airborne Exposures

- See Candace's talk this afternoon, for more information on exposure assessment and control

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Best Practices for Working Safely with Nanoparticles in University Research Laboratories

Michael J. Ellenbecker, Sc.D., CIH

Candace Tsai, Sc.D.

Jacqueline Isaacs, Ph.D.

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Document Outline

1. Introduction
2. Basic Premises
3. Occupational Hygiene Resources Available to CHN Researchers
4. Routine R&D Laboratory Operations
5. Management of Nanomaterials
6. Management of Nanomaterial Spills

NIOSH/CHN Best Practices Document

- **Safe Practices for Working with Engineered Nanomaterials in Research Laboratories**
- Michael Ellenbecker and Su-Jung (Candace) Tsai
- Report submitted to NIOSH – 30 September 09 – 80 pages,~100 references
- Meant to be the most comprehensive guide available
- Published in late 2010
- Watch for it!

Summary

- Toxicity of most engineered nanoparticles is uncertain at this time
  - CNTs in particular look very problematic
  - Many newer particles not studied to date
- Measurements performed by our lab, and others, indicate the potential for significant occupational exposure
- Regulations will be a long time coming

Summary, Continued

- We must take a precautionary, proactive approach to minimize exposures to workers and the general public
- Engineering controls and good work practices are available and must be used to the greatest extent possible
- Engineered nanoparticles have the potential to benefit society greatly; it is the responsibility of the occupational health community to ensure that they are used safely

Acknowledgements

Research Supported by:

NSF Nanoscale Science and Engineering Centers Program

(Award no. NSF-0425826)

THANK YOU!

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