Update on Toxicology and Health Effects associated with Engineered Nanoparticles

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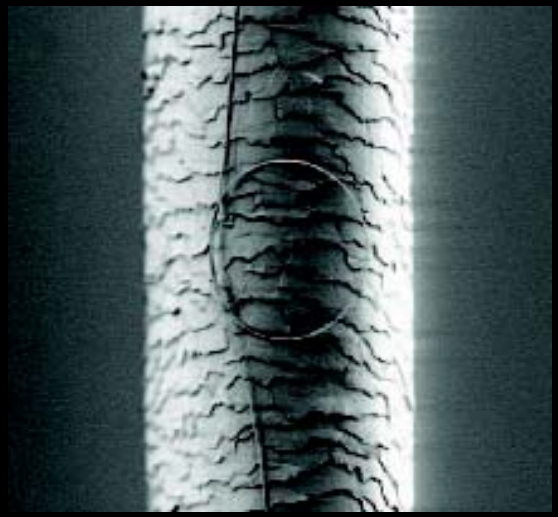
TURI CE Workshop

Center for High-rate Nanomanufacturing

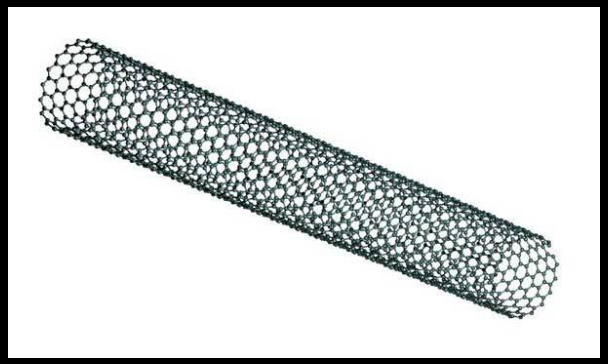
What is Nanotechnology?

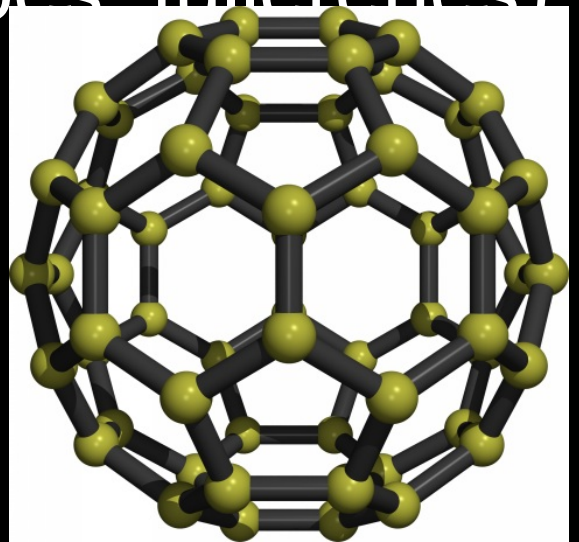
- "Nano-" = 10^{-9} unit
- Refers to particles or structures with at least 1 diameter in 1-100 nm Size range
- Compare to:
  - Human Hair = 60 – 120 micrometers
  - DNA = 2 – 12 micrometers
  - Red Blood Cell = 7,000 nm
  - Water molecule = 0.3 nm



Categories of Nanoparticles

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

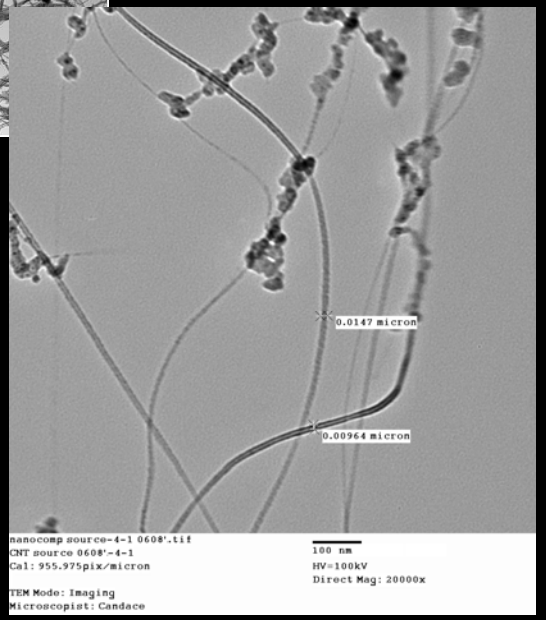


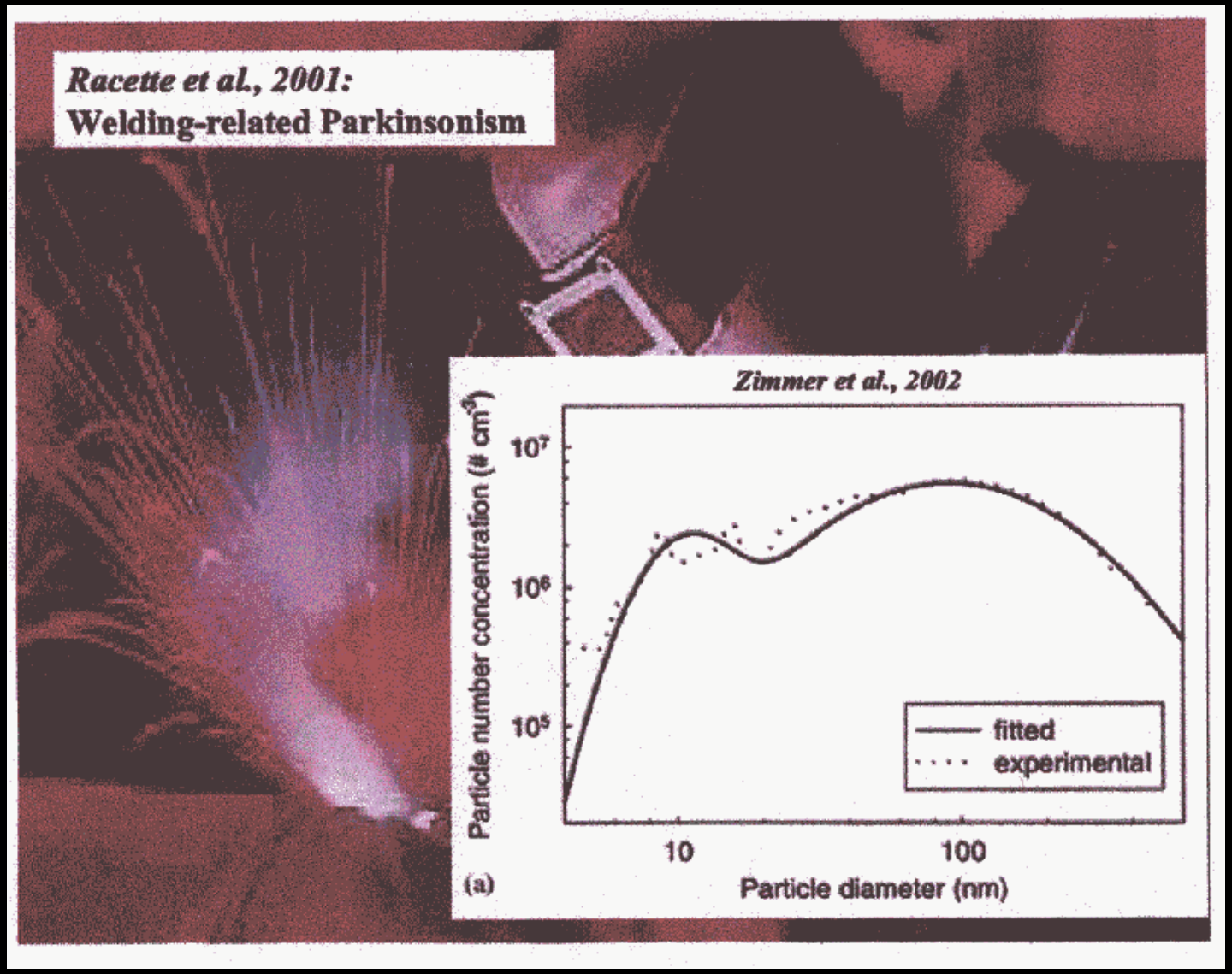


Nanoparticles in the Work Environment

Well-known occupational & environmental exposures

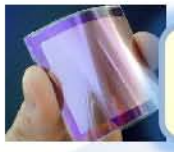
- asbestos
- silica flour
- flour dust
- combustion products
  - **welding fume**
  - **diesel exhaust**
  - **asphalt fume**





Oberdorster, in BIA report 7/2003e

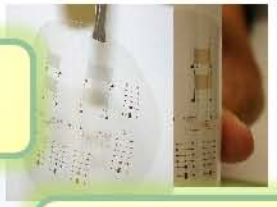
NSF Nanoscale Science and Engineering Center for High-rate Nanomanufacturings and Applications Roadmap



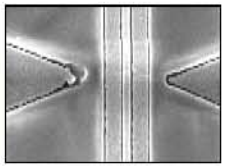
Photovoltaic

Batteries

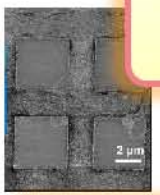
Flexible Electronics



Memory Devices



Structural



Biosensors

EMI-shielding

Drug Delivery

Energy

Electronics

Materials

Bio/Med

Technology Platform

Nanoscale Science

Center for High-rate Nanomanufacturing

Crucial Factor in Nanoparticle Toxicity

Question:

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

Answers:

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

Number of particles increases

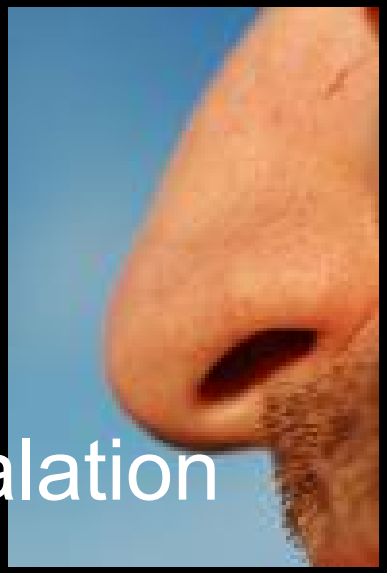
Key Points

- 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

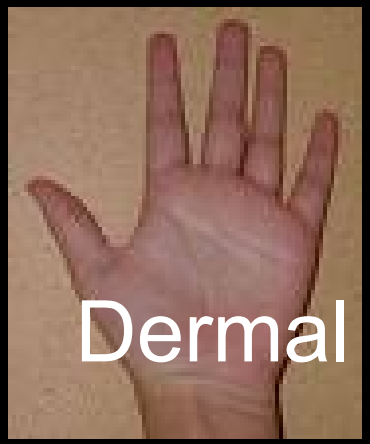
Particle Mobility

- 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

Routes of Exposure



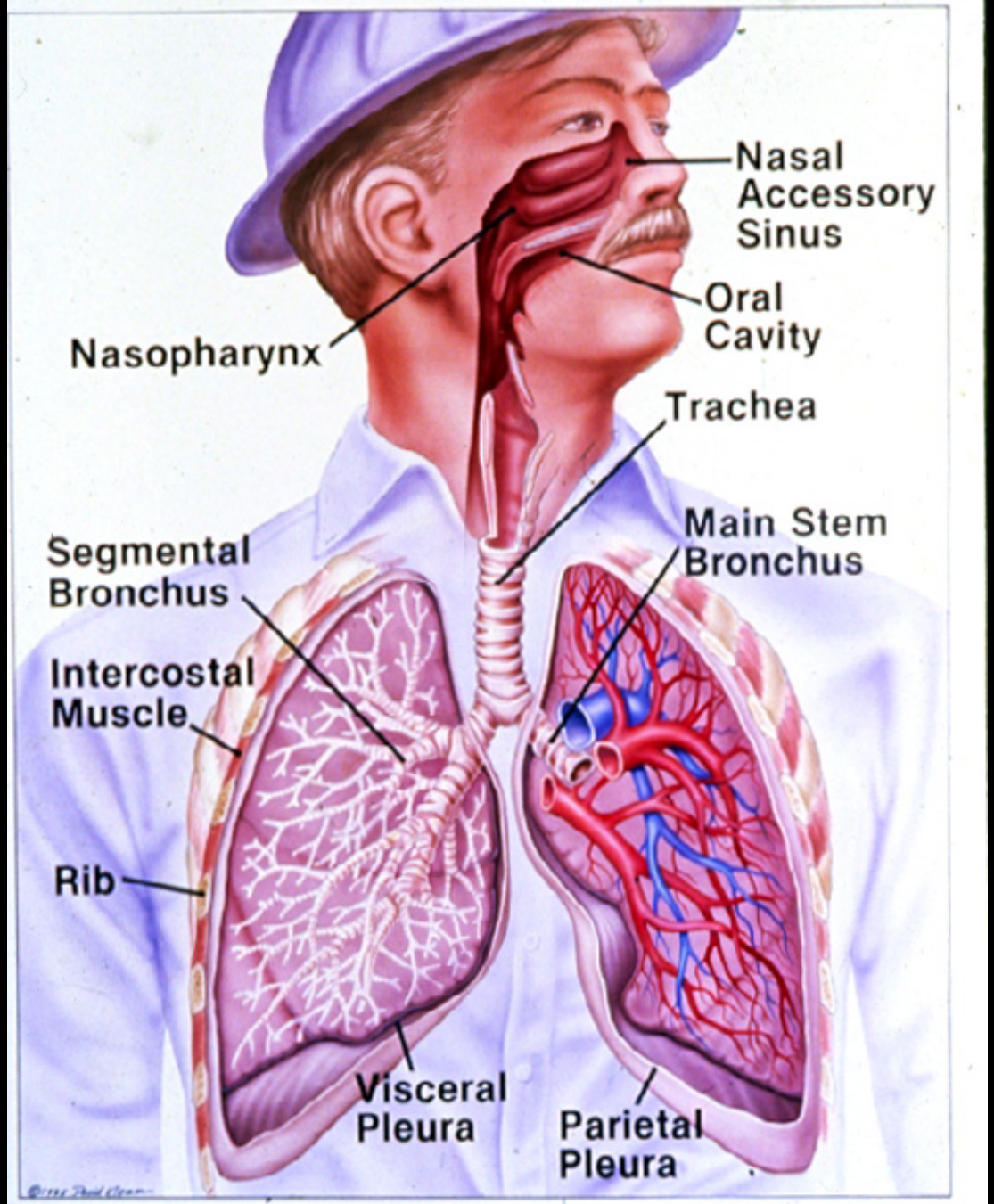
Inhalation



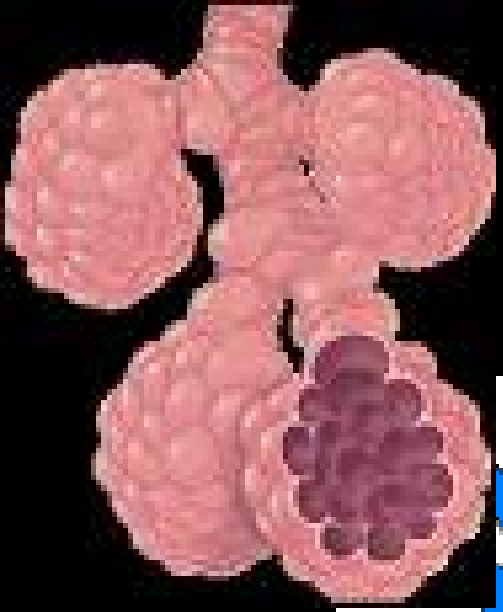
Dermal penetration

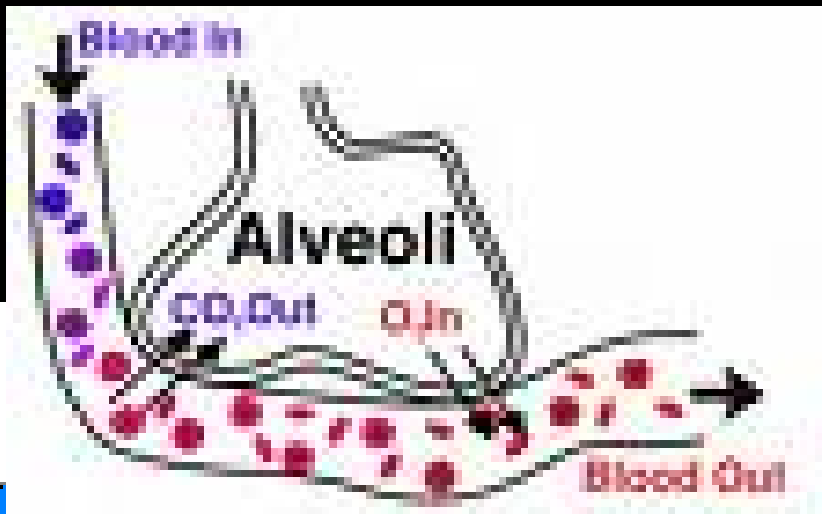
Ingestion

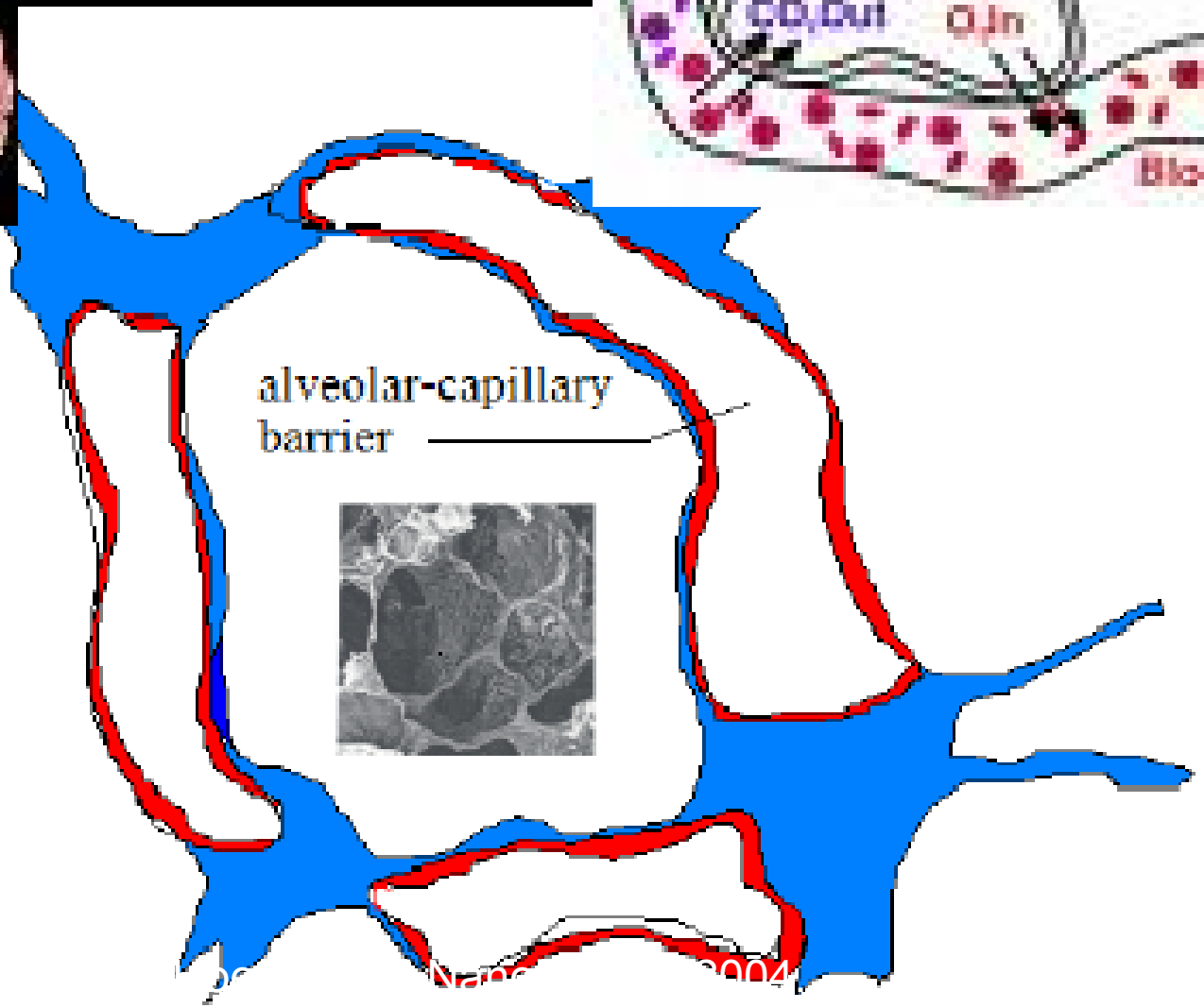
RESPIRATORY SYSTEM



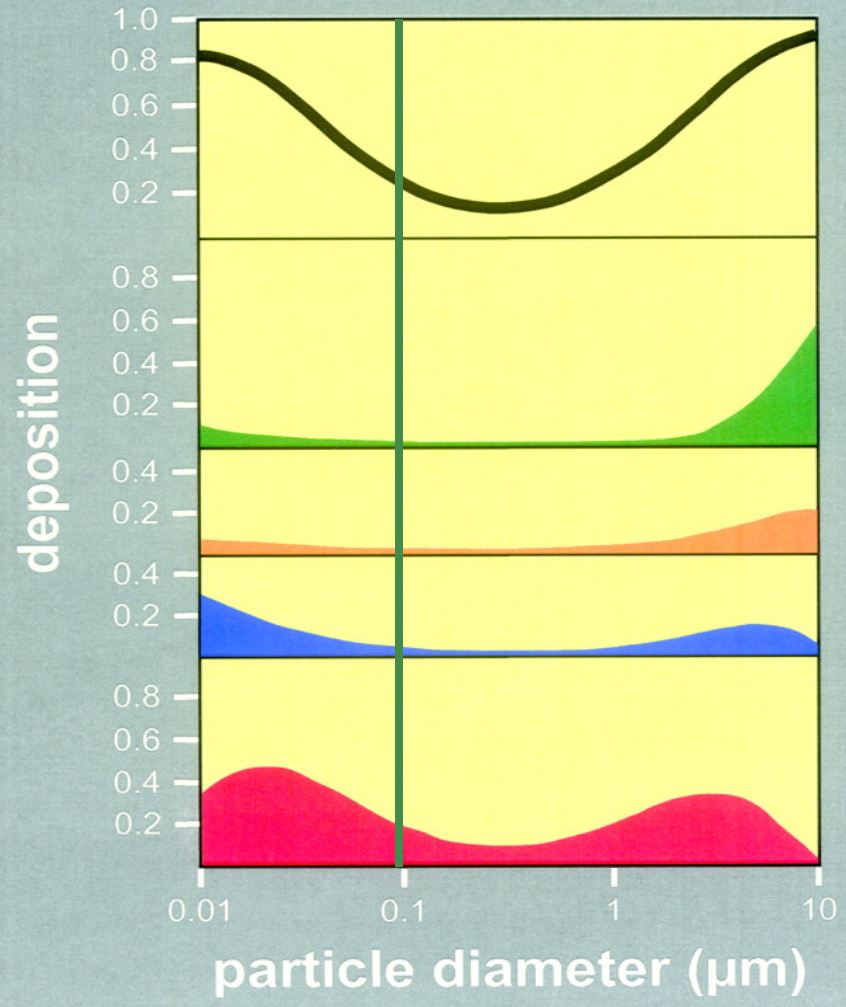
Alveoli



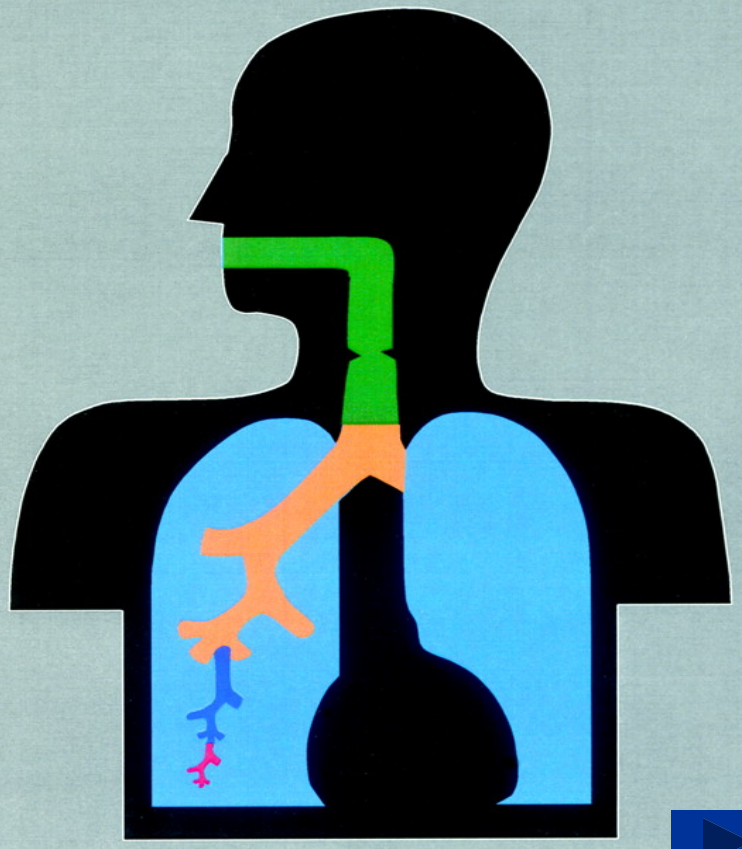

Blood In
Alveoli
CO2Out
O2In
Blood Out


alveolar-capillary
barrier

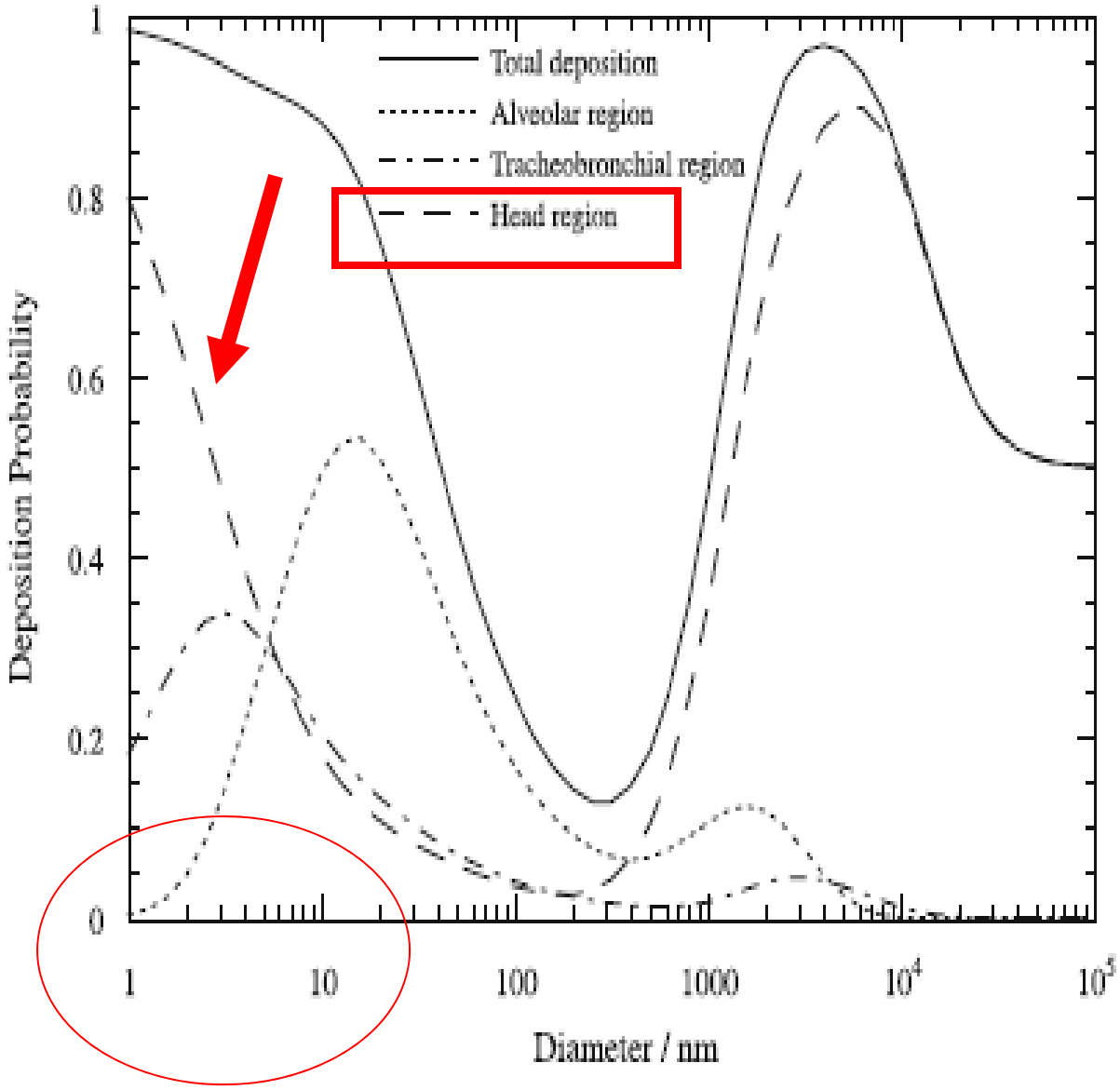
Regional Lung Deposition



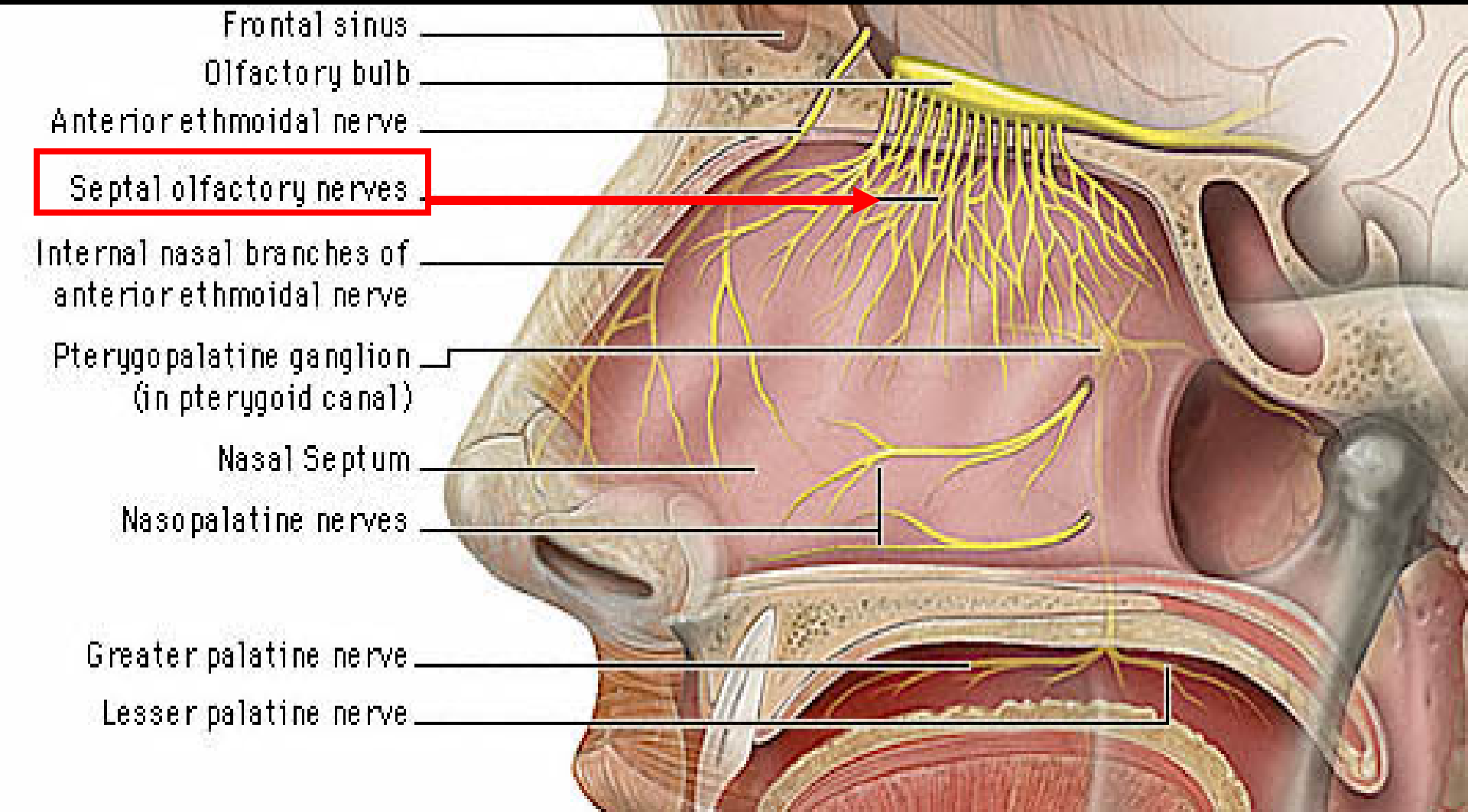
particle density: 1 g cm^{-3}
respiratory flow rate: 300 $cm^3 s^{-1}$
respiratory cycle period : 5 s

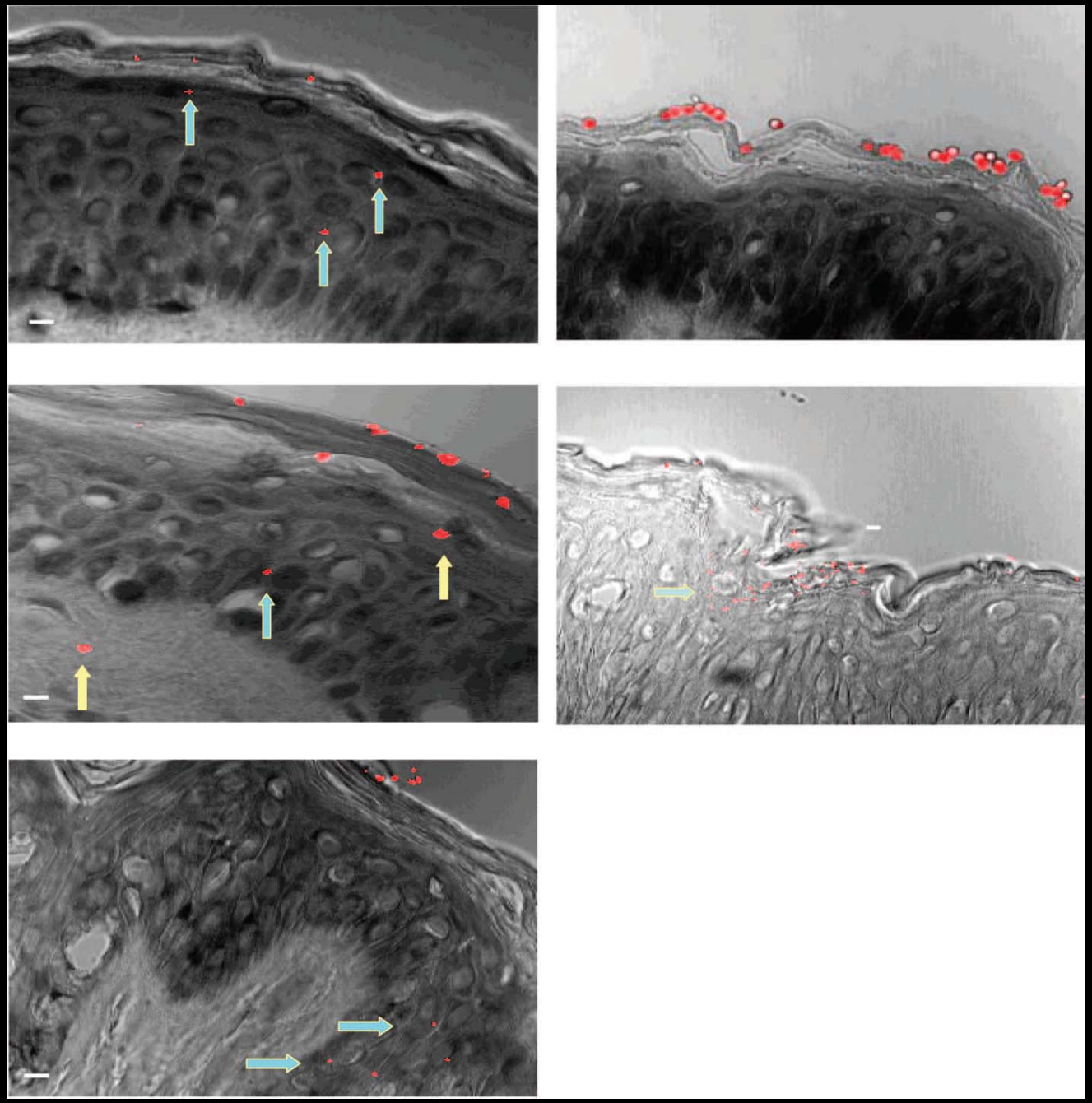


Modeled Total Particle Deposition Probability



Olfactory nerve exposure and central nervous system effects





Dermal Exposure

Tinkle et al

EHP 2003

Exposure

- Occupational setting
  - Exposed to nanomaterials?
  - Airborne nanoparticle?
  - Magnitude?
  - Permissible exposure limit?

- Daily life
  - Commercial products?
  - Unknown ingredients?
  - Product testing?
- End of product life?

Toxicology Studies

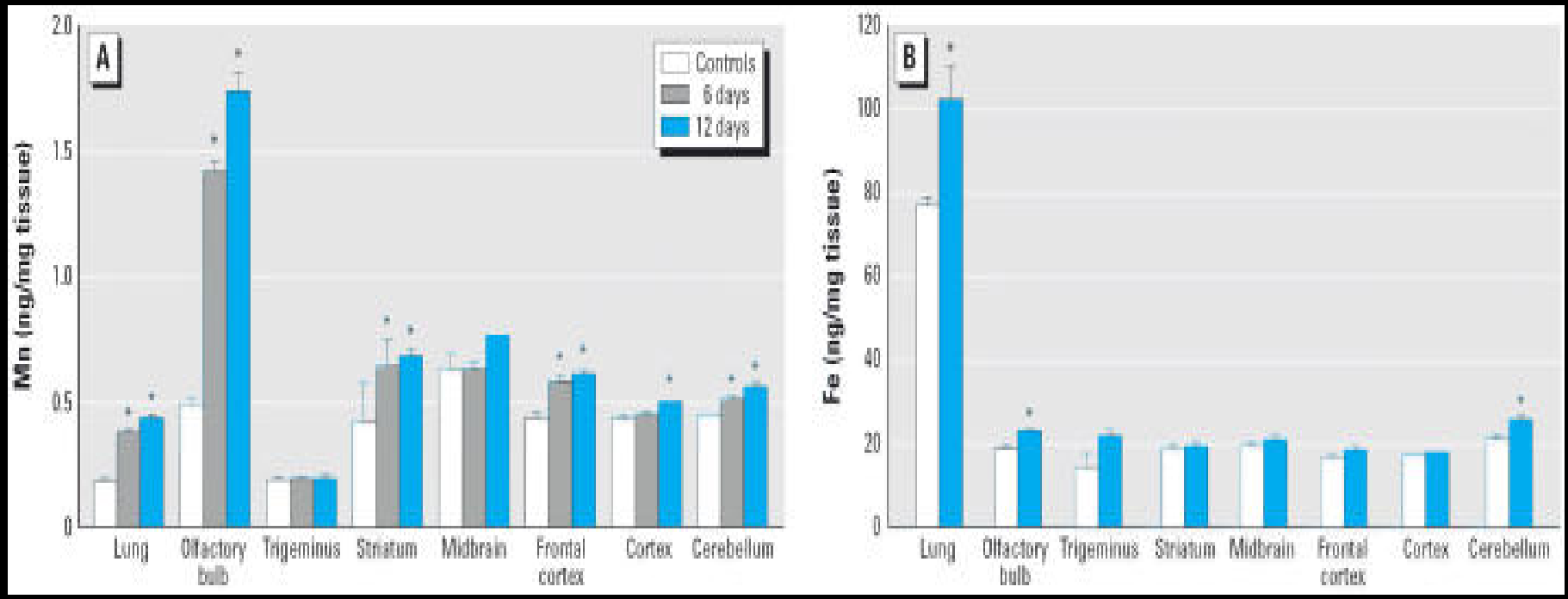
- Cardiovascular Effects of Pulmonary Exposure to Single-Wall Carbon Nanotubes, Env. Health. Perspect., 2007.

- Instillation of six different ultrafine carbon particles indicates a surface area threshold dose for acute lung inflammation in mice, Env. Health. Perspect., 2006.

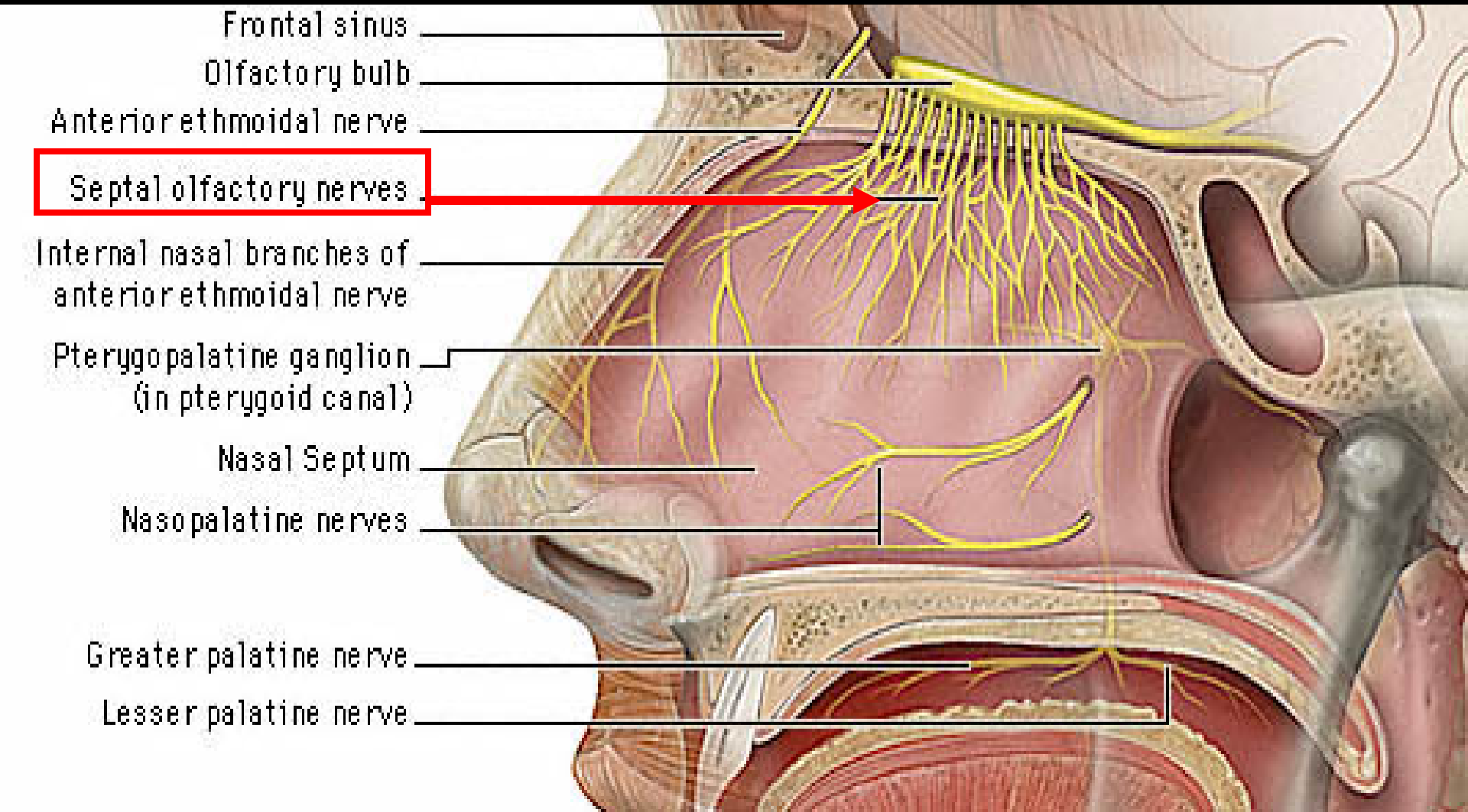
Toxicology Studies, Cont.

- Translocation of inhaled ultrafine manganese oxide particles to the central nervous system, Env. Health. Perspect., 2006.
- Translocation of Inhaled Ultrafine Particles to the Brain, Inhal. Toxicol., 2004.
- Effect of gold nanoparticles on spermatozoa: the first world report, ASRM, 2007.

Translocation of inhaled ultrafine manganese oxide particles to the central nervous system



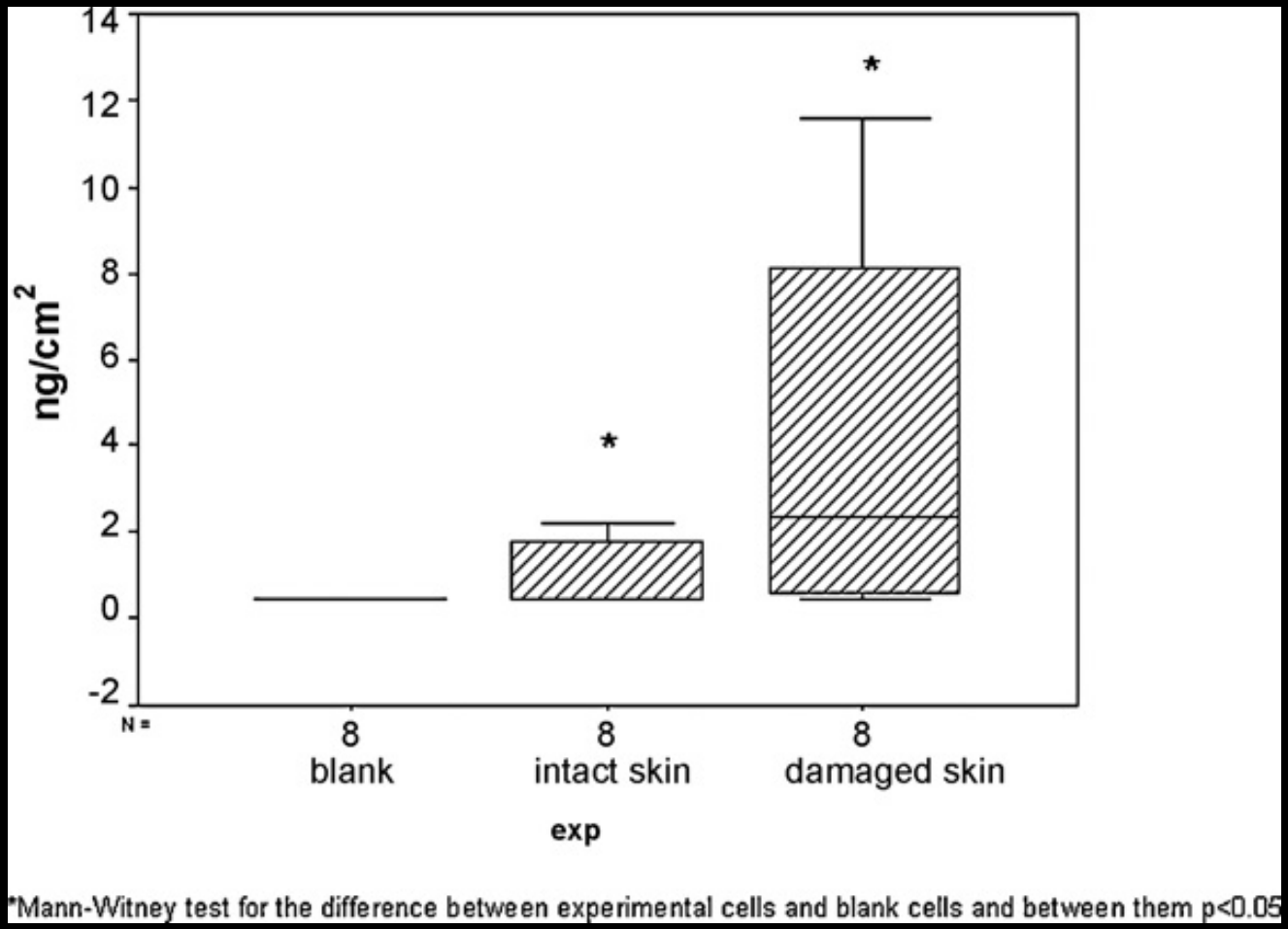
Olfactory nerve exposure and central nervous system effects



Toxicology Studies, Cont.

- Human skin penetration of silver nanoparticles through intact and damaged skin, Toxicol., 2009.
- Adverse effects of citrate/gold nanoparticles on human dermal fibroblasts, Small, 2006.
- Penetration of intact skin by quantum dots with diverse physicochemical properties, Toxicol Sci, 2006.

Human skin penetration of silver nanoparticles through intact and damaged skin



Emphasis on CNT Toxicity

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

CNT Inhalation – Reported Health Effects

Warheit-DuPont – intratracheal instillation

- Nonprogressive multifocal granulomas
- Transient inflammation
- Typical foreign body response
- No dose-response noted

Warheit et al. Comparative Pulmonary Toxicity Assessment of Single-Wall Carbon nanotubes in Rats. Tox Sci 77: 117-25, 2004.

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

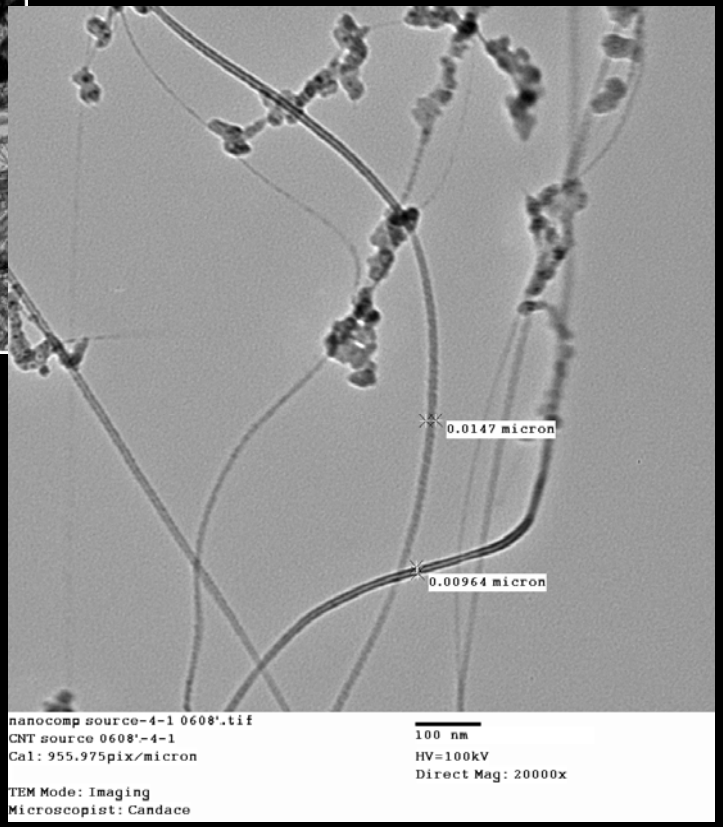
- Both *inflammation* (acute response) and *fibrosis* (chronic response) were found
- Effects were dose-dependent
- No fibrosis and greatly reduced inflammation found with the reference materials

Shvedova, et al. Unusual Inflammatory and Fibrogenic Pulmonary Responses to Single-walled Carbon nanotubes in Mice. Am J Physiol Lun Cell Mol Physiol 289: L698-708, 2005

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

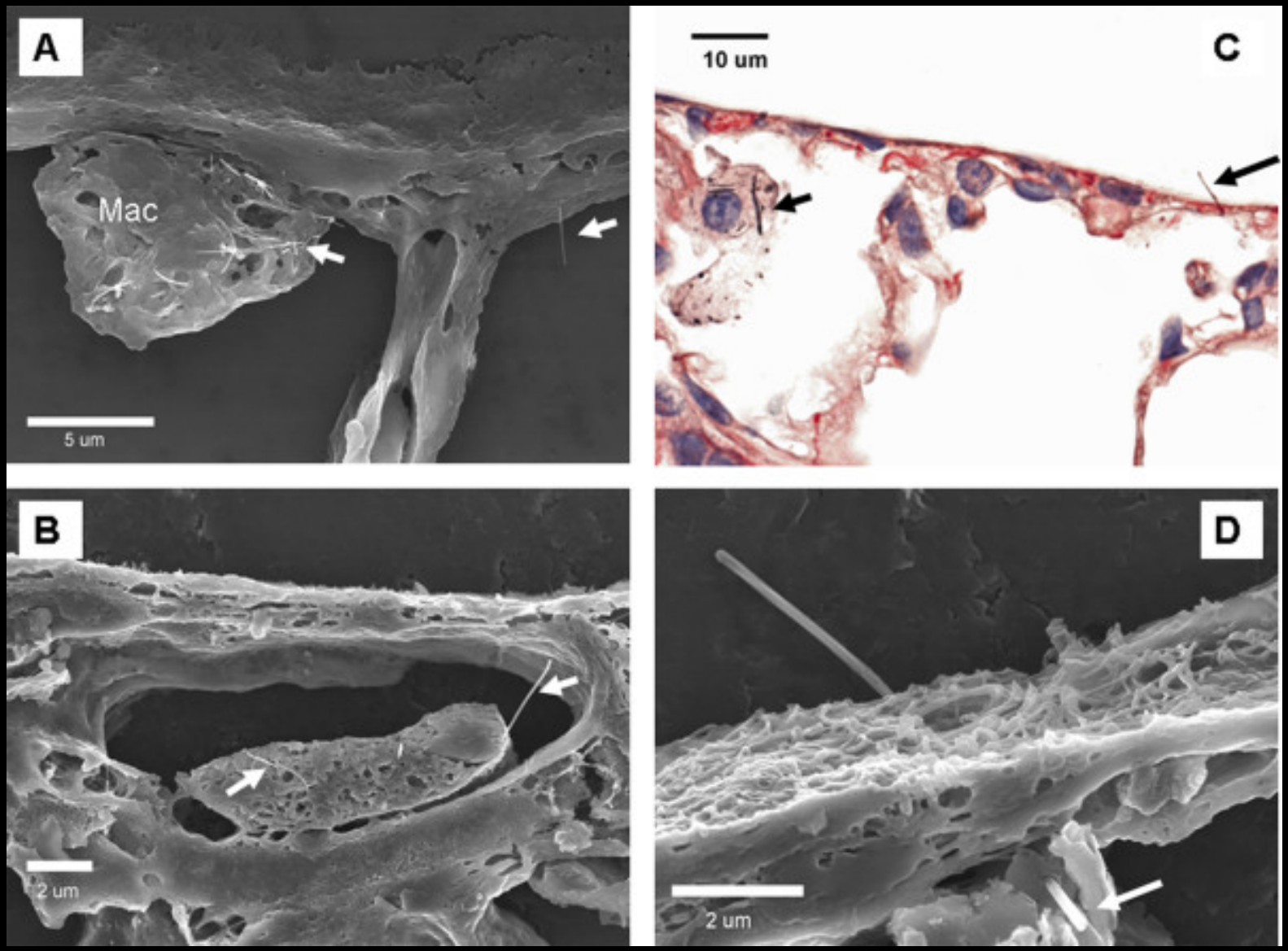

0.0147 micron
0.00964 micron
nanocomp source-4-1 0608'.tif
CNT source 0608'-4-1
Cal: 955.975pix/micron
TEM Mode: Imaging
Microscopist: Candace
100 nm
HV=100kV
Direct Mag: 20000x

CNTs cause Mesothelioma?

- Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study, Poland, et al., Nature Nano., 2008.
- Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube, Takagi, et al., J. Toxicol. Sci, 2008.

New Work Reported – 5th International Symposium on Nanotechnology, Occupational and Environmental Health

- "Durability and inflammogenicity of carbon nanotubes compared with asbestos fibres"
- "Alteration of long carbon nanotube mesothelial response using surface modification"
- "The retention of long, but not short, carbon nanotubes leads to inflammation and progressive fibrosis in the pleural space of mice"
- "Circulating fibrocytes contribute to single-walled carbon nanotube induced pulmonary fibrosis"



Mercer, et al., Part. Fib. Tox., 7:28, 2010

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

- What is the value chain for your company? For example, in what products are your carbon nanotubes used by others?
- What sampling, detection and measurement methods are you using to monitor (detect and measure) the presence of your chemical in the workplace and the environment?

CA Questions to Manufacturers, Cont.

- What is your knowledge about the current and projected presence of your chemical in the environment that results from manufacturing, distribution, use, and end-of-life disposal?
- What is your knowledge about the safety of your chemical in terms of occupational safety, public health and the environment?

CA Questions to Manufacturers, Cont.

- What methods are you using to protect workers in the research, development and manufacturing environment?
- When released, does your material constitute a hazardous waste under California Health &Safety Code provisions? Are discarded off-spec materials a hazardous waste? Once discarded are the carbon nanotubes you produce a hazardous waste? What are your waste handling practices for 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

CA 2nd Call-In:

FORMAL REQUEST FOR CHEMICAL INFORMATION AND ANALYTICAL TEST METHODS
FOR SPECIFIED NANOMATERIALS

Dear Sir or Madam:

The Department of Toxic Substances Control (DTSC) formally requests information regarding the chemical and physical properties, including analytical test methods and other relevant information, about six specified chemicals. DTSC has identified your company or institution as a manufacturer who produces or imports one or more of the following nanomaterial chemicals:

- Nano Silver
- Nano Zero Valent Iron
- Nano Cerium Oxide
- Nano Titanium Dioxide
- Nano Zinc Oxide
- Quantum Dots

…required to provide the information in writing to DTSC no later than Wednesday, December 21, 2011

Highlights – Policy/Regulatory Issues

- No OELs exist for ENPs
- NIOSH has a TiO_2 REL and a draft document with a proposed CNT REL – mass based, widely debated
- EU leading the U.S. in progress towards OELs
- Nano-specific PELs will be issued in ????

NIOSH RELs for NPs

- Only two Recommended Exposure Limits issued to date:
  - "Occupational Exposure to Titanium Dioxide," CIB No. 63, DHHS (NIOSH) Publication No. 2011–160, April 2011: http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf
  - "Occupational Exposure to Carbon Nanotubes and Nanofibers," draft document, November 2010: http://www.cdc.gov/niosh/docket/review/docket161A/pdfs/carbonNanotubeCIB_PublicReviewOfDraft.pdf

TiO_2 REL

- Fine grade TiO_2 (d > 100 nm): 2.4 mg/m^3
- Ultra-fine (including engineered nanoscale) TiO_2 (d < 100 nm) : 0.3 mg/m^3
- Both are 10-hour TWA values
- “Exposure to ultrafine TiO2 should be considered a potential occupational carcinogen”
- Comments received re: mass vs. SA vs. number concentration, etc.: http://www.cdc.gov/niosh/docket/archive/pdfs/NIOSH-033/0033-040111-NIOSH_Response.pdf

NIOSH CNT Current Intelligence Bulletin

"Occupational Exposure to Carbon Nanotubes and Nanofibers"

- Reviews animal studies
- REL based on "pulmonary inflammation and fibrosis" – NOT cancer risk
- REL: 7 μg/m^3 elemental carbon (EC) as an 8-hr TWA respirable mass airborne concentration

NIOSH CIB, cont.

- “Occupational exposures to all types of CNT can be quantified by NIOSH Method 5040 as airborne EC”
- “The LOQ for NIOSH Method 5040 is 7 µg/m^3”
- “Although the REL is set at the lowest airborne CNT and CNF concentration that can be accurately measured by NIOSH 5040 (i.e., LOQ of Method 5040), an excess risk of adverse lung effects is predicted below this level.”

CNT Number Comparison

- Assume a CNT – 10 nm in diameter, 50 μm long, density = 2000 kg/m^3
- Mass of one fiber = 8 x 10^{-9} μg
- Number concentration at 7 μg/m^3:

$$n = (7\ \mu g/m^3)/(8 \times 10^{-9}\ \mu g/CNT)$$

$$= 9 \times 10^8\ CNT/m^3 = 900\ CNT/cm^3$$

- Asbestos PEL = 0.1 f/cm^3

Even Worse News

- Method measures ALL elemental carbon – our measurements have found lots of “soot”
- Can have an actual exposure of 100’s of CNTs/cm^3 and if you sample using the NIOSH 5040 method the sample result will come back “none detectable” and the exposure will be assumed to be “zero” and/or “safe” by unsophisticated people
- My opinion – a mass-based OEL cannot work for ANY ENP

NIOSH Recommendation

"Until results from research studies can fully elucidate the physicochemical properties of CNT and CNF that define their inhalation toxicity, steps should be taken to minimize CNT and CNF exposures of all workers and to implement an occupational health surveillance program that includes elements of hazard and medical surveillance."

Policy, Cont.

- Beginning discussions of medical monitoring and possible epi studies
  - First study now being conducted in Taiwan
  - P. Schulte, NIOSH, has proposed coordinated international approach
  - Need consensus on exposure assessment methods and biologic end points to measure
- In the meantime – consensus on precautionary approach to limit exposures while toxicology is uncertain