Update on Nanotechnology EHS Issues: Focus on Carbon Nanotubes

Michael Ellenbecker, Sc.D., CIH
Director, TURI
Professor Emeritus
University of Massachusetts Lowell

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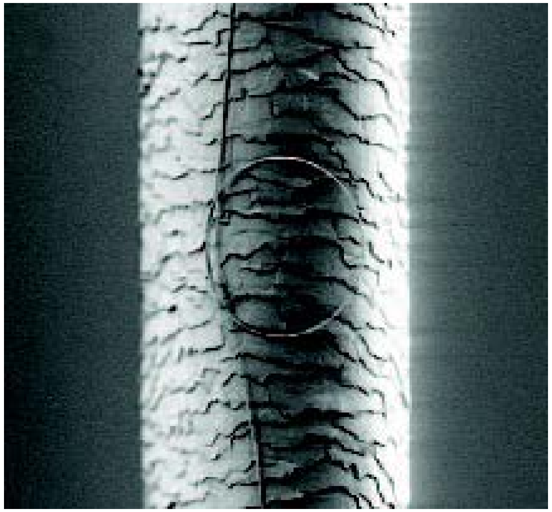
What is Nanotechnology?

- "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



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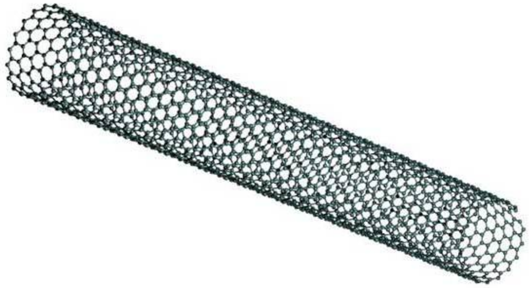
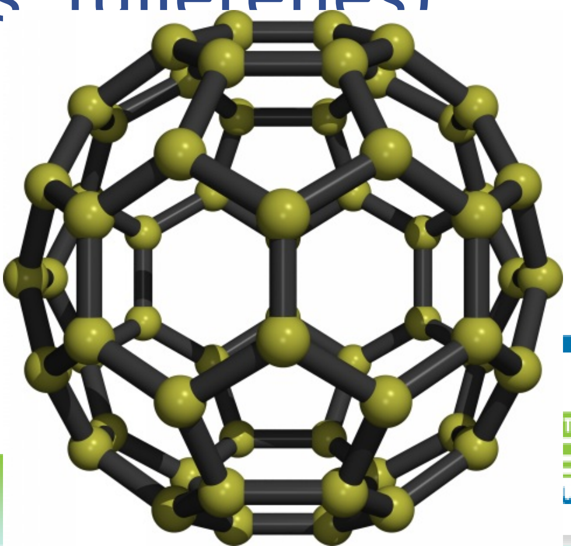
What is a Nanoparticle?

- US Federal Office of Science and Technology Policy: nanotechnology is “R&D…in the length scale of approximately 1 – 100 nanometer range…”
- Some consensus that a nanoparticle is any particle with at least one dimension less than 100 nm

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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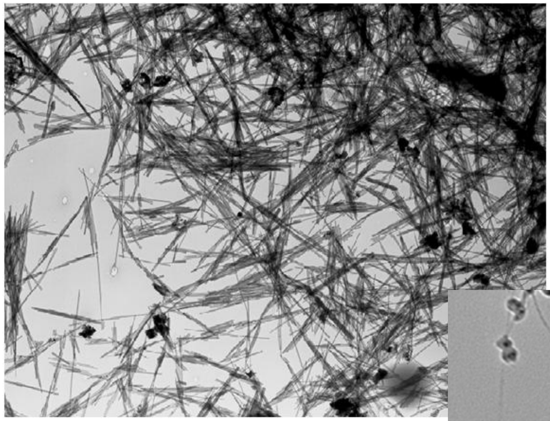
Nanoparticle Exposures are not New

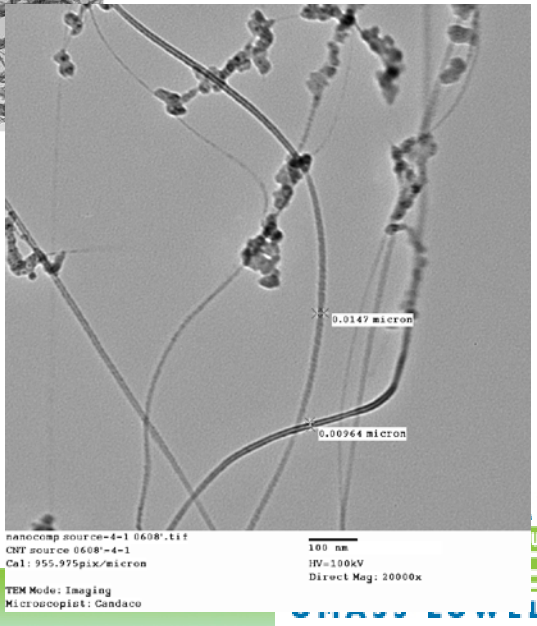
Icelandic volcano Eyjafjallajökull, two days after eruption

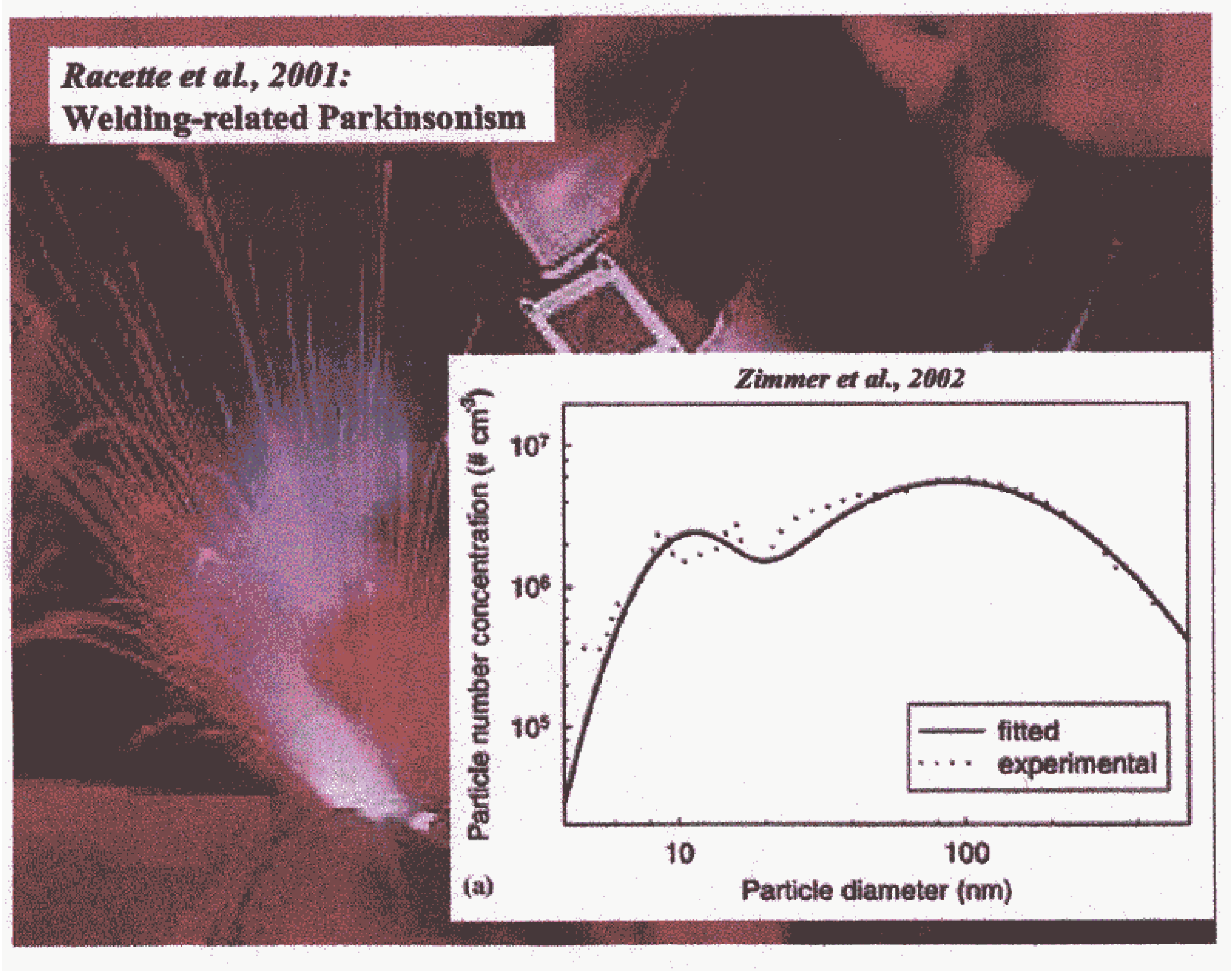
Nanoparticles in the Work Environment

Well-known occupational & environmental exposures

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







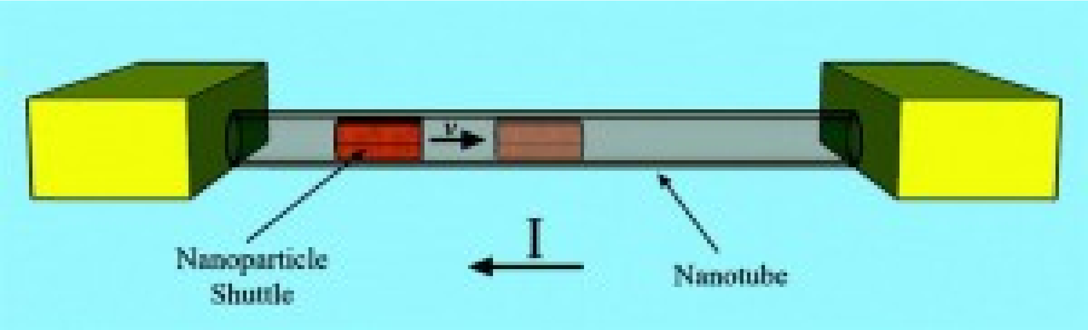
Oberdorster, in BIA report 7/2003e

Applications of ENPs in Industry

- Consumer products
- Advances in technology
  - Electronics
  - Energy production and storage
  - Sensors
  - Medicine
    - Drug delivery
    - Diagnostics


The New York Times
Tennis Racket
Carbon nanotubes help stiffen the frame.
Foot warmers
With nanoscale air pockets.
ECO-FABRIC SHORT SOCKS
NANOWAX
The New York Times
ECO-FABRIC KNEE GUARD
BEHR PREMIUM PLUS
KITCHEN & BATH
NanoMask
LANCÔME
CLARITY
Moist+
Spray Vitamins
"Nanodroplets" for better absorption.
Skin Cream
Contains "nano-encapsulated" compounds.
Kitchen Paint
Nanoscale additives for durability.

CNT Digital Memory Storage Device



- This illustration shows the configuration of a new digital memory storage device consisting of an iron nanoparticle shuttle that moves through a carbon nanotube when a voltage is applied. This memory device can pack a trillion bits of data into one square inch of medium and retain that data for a billion years. (Image from the American Chemical Society)

Fundamentals of Aerosols as Applied to Engineered Nanoparticles (ENPs)

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Factor that determines if a particle is an aerosol is Settling Velocity

- Isaac Newton first studied this for large spheres
- Newton's Drag Law
- Stokes developed general equations of motion

Navier-Stokes Equations

3 - dimensional - unsteady

Glenn Research Center

Coordinates: (x,y,z)

Velocity Components: (u,v,w)

Time : t

Density: ρ

Total Energy: Et

Pressure: p

Stress: τ

Heat Flux: q

Reynolds Number: Re

Prandtl Number: Pr

Continuity:

$$\frac{\partial \rho}{\partial t} + \frac{\partial(\rho u)}{\partial x} + \frac{\partial(\rho v)}{\partial y} + \frac{\partial(\rho w)}{\partial z} = 0$$

X – Momentum:

$$\frac{\partial(\rho u)}{\partial t} + \frac{\partial(\rho u^2)}{\partial x} + \frac{\partial(\rho uv)}{\partial y} + \frac{\partial(\rho uw)}{\partial z} = -\frac{\partial p}{\partial x} + \frac{1}{Re_r}\left[\frac{\partial \tau_{xx}}{\partial x} + \frac{\partial \tau_{xy}}{\partial y} + \frac{\partial \tau_{xz}}{\partial z}\right]$$

Y – Momentum:

$$\frac{\partial(\rho v)}{\partial t} + \frac{\partial(\rho uv)}{\partial x} + \frac{\partial(\rho v^2)}{\partial y} + \frac{\partial(\rho vw)}{\partial z} = -\frac{\partial p}{\partial y} + \frac{1}{Re_r}\left[\frac{\partial \tau_{xy}}{\partial x} + \frac{\partial \tau_{yy}}{\partial y} + \frac{\partial \tau_{yz}}{\partial z}\right]$$

Z – Momentum

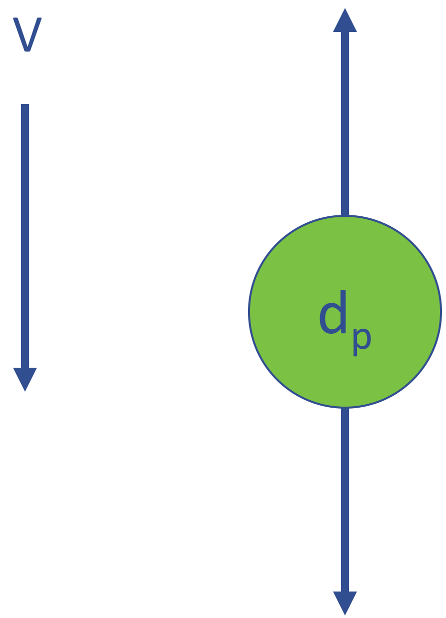
$$\frac{\partial(\rho w)}{\partial t} + \frac{\partial(\rho uw)}{\partial x} + \frac{\partial(\rho vw)}{\partial y} + \frac{\partial(\rho w^2)}{\partial z} = -\frac{\partial p}{\partial z} + \frac{1}{Re_r}\left[\frac{\partial \tau_{xz}}{\partial x} + \frac{\partial \tau_{yz}}{\partial y} + \frac{\partial \tau_{zz}}{\partial z}\right]$$

Energy:

$$\frac{\partial(E_T)}{\partial t} + \frac{\partial(uE_T)}{\partial x} + \frac{\partial(vE_T)}{\partial y} + \frac{\partial(wE_T)}{\partial z} = -\frac{\partial(up)}{\partial x} - \frac{\partial(vp)}{\partial y} - \frac{\partial(wp)}{\partial z} - \frac{1}{Re_r Pr_r}\left[\frac{\partial q_x}{\partial x} + \frac{\partial q_y}{\partial y} + \frac{\partial q_z}{\partial z}\right]$$

$$+ \frac{1}{Re_r}\left[\frac{\partial}{\partial x}(u\,\tau_{xx} + v\,\tau_{xy} + w\,\tau_{xz}) + \frac{\partial}{\partial y}(u\,\tau_{xy} + v\,\tau_{yy} + w\,\tau_{yz}) + \frac{\partial}{\partial z}(u\,\tau_{xz} + v\,\tau_{yz} + w\,\tau_{zz})\right]$$

By making simplifying assumptions that apply to small spherical particles, Stokes developed a second drag force equation



$$F_D = 3\pi \eta V d$$

$$F_G = mg = \rho_p V_p = \rho_p \frac{\pi d_p^3}{6} g$$

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At equilibrium, $F_D = F_G$

$$3\pi\eta V d = \frac{\rho_p \pi d^3 g}{6}$$

$$V_{TS} = \frac{\rho_p d_p^2 g}{18\eta}$$

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Theoretical Settling Velocities

Particle Diameter, μm	Settling Velocity, cm/s
100	30
10	0.3
1	0.003
0.1	0.00003
0.01	0.0000003

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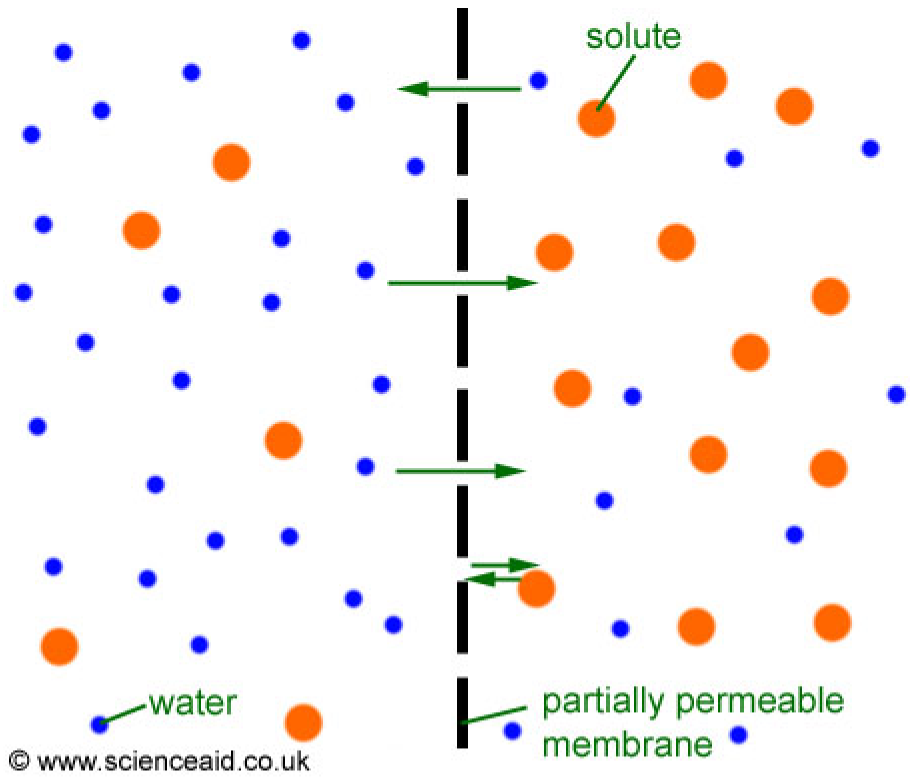
Brownian Motion and Diffusion

- Small particles are bombarded unequally on different sides by air molecules
- This causes random movement – Brownian motion
- Fick's Law – due to random motion, particles move from regions of high concentration to regions of low concentration - diffusion

Osmotic Pressure



Einstein's Contribution to Aerosol Science

Starting from the concept of osmotic pressure, he calculated the average distance an aerosol particle would travel in time t:

$$x_{rms} = \sqrt{2Dt}$$

D is the diffusion coefficient, given by the Stokes-Einstein Equation:

$$D = \frac{kTC_c}{3\pi\eta d_p}$$

Net Displacement in 1 s

d (μm)	x_{BM} (μm)	X_{grav} (μm)	Ratio
0.01	330	0.007	4800
0.1	37	0.088	42
1.0	7.4	3.5	2.1
10	2.2	3,100	0.0007

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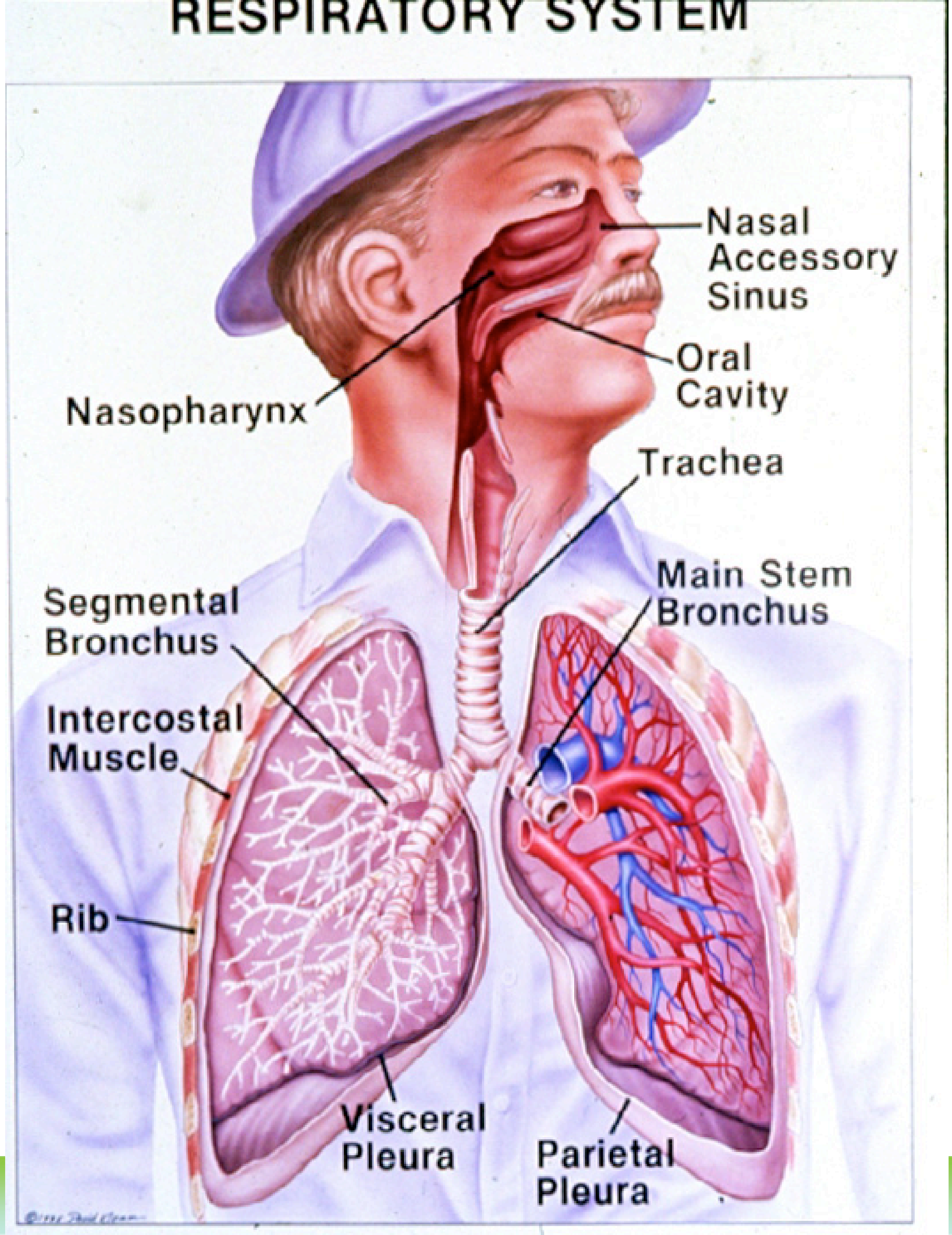

RESPIRATORY SYSTEM
Nasal
Accessory
Sinus
Oral
Cavity
Nasopharynx
Trachea
Main Stem
Bronchus
Segmental
Bronchus
Intercostal
Muscle
Rib
Visceral
Pleura
Parietal
Pleura

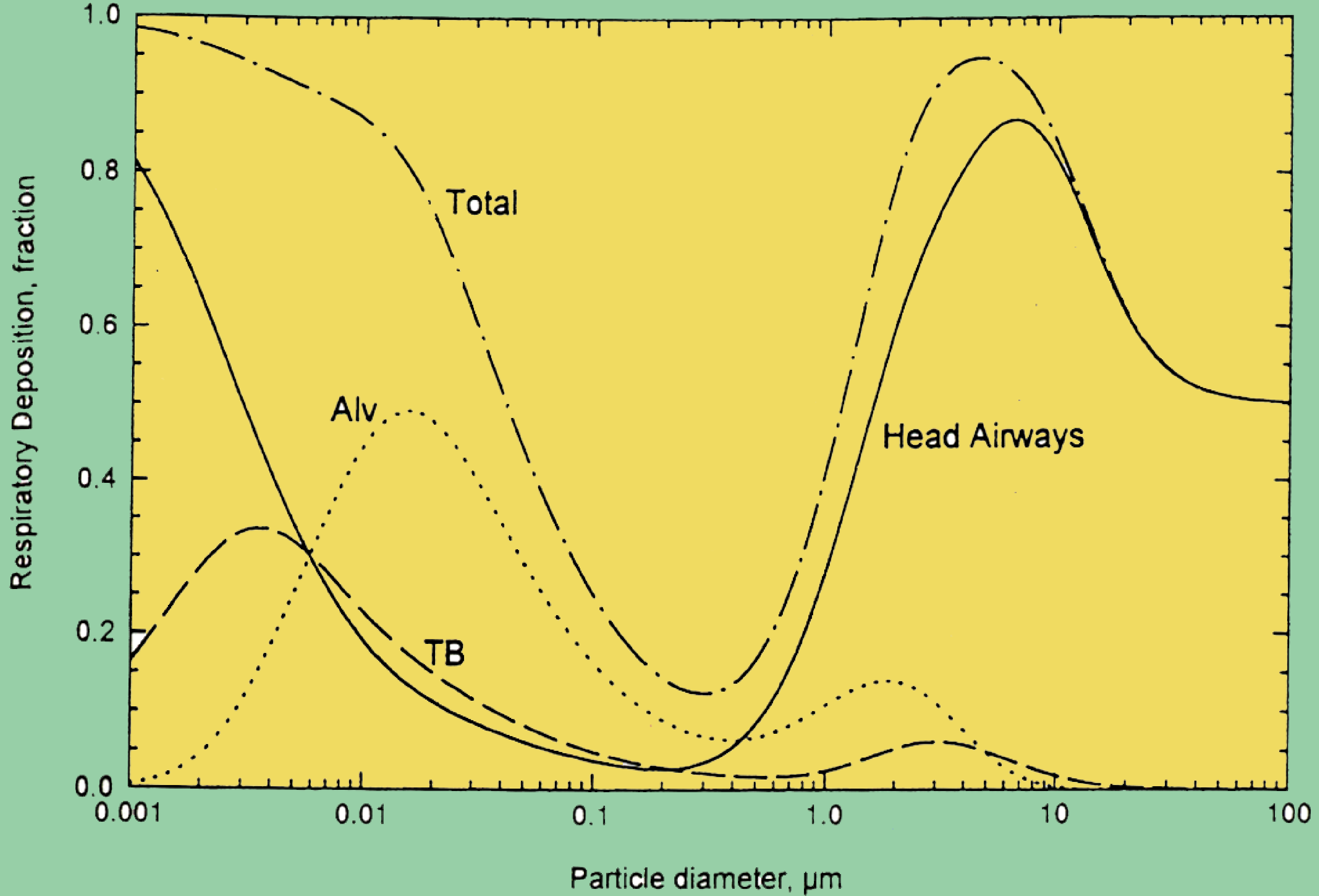
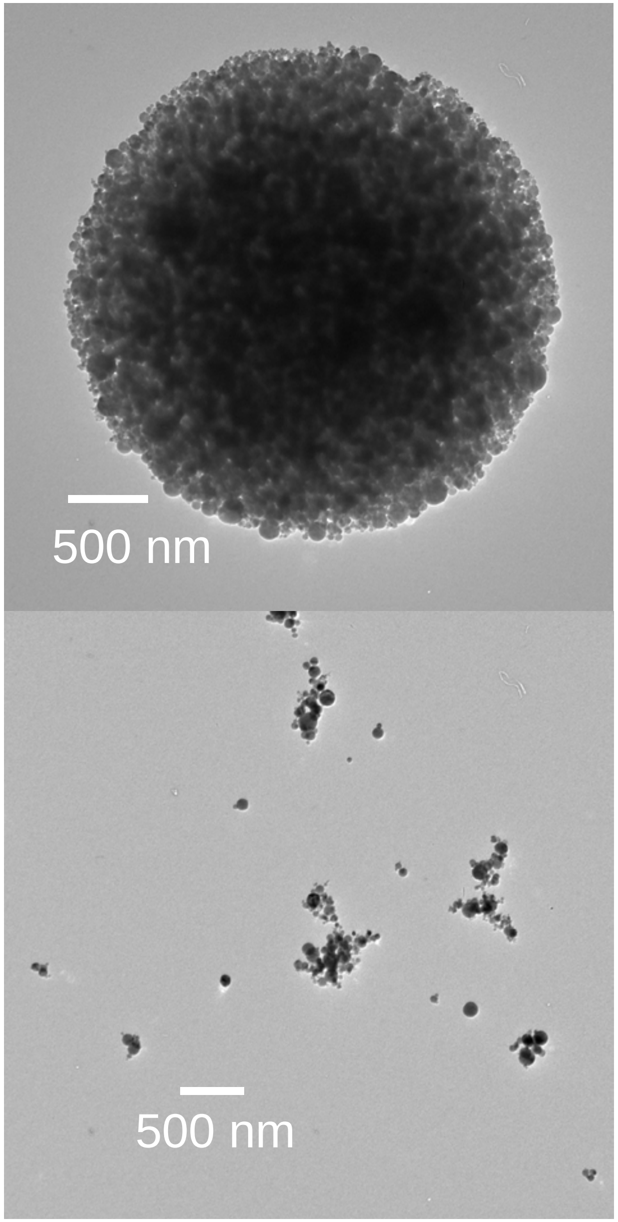


FIGURE 11.3 Predicted total and regional deposition for light exercise (nose breathing) based on ICRP deposition model. Average data for males and females.

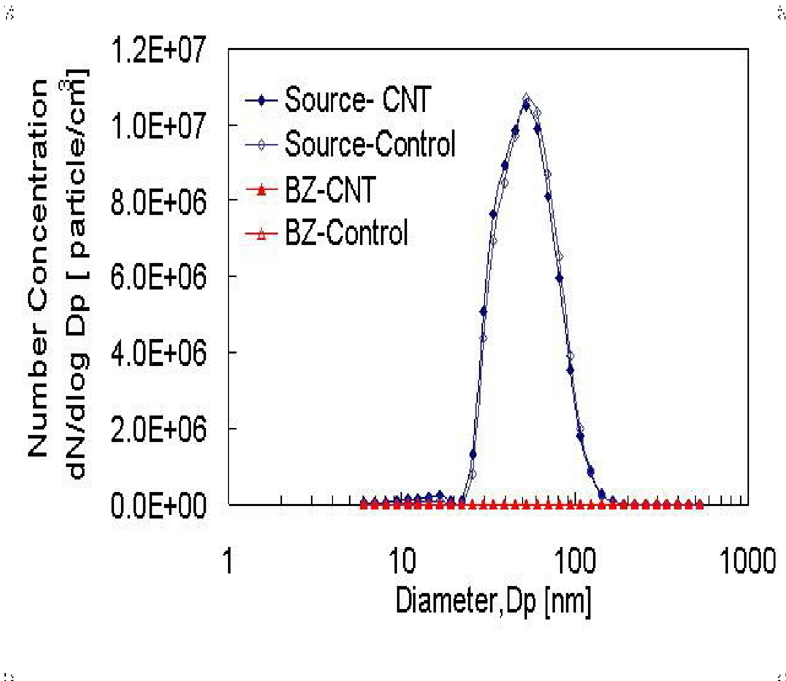
Methods used to evaluate ENP exposure

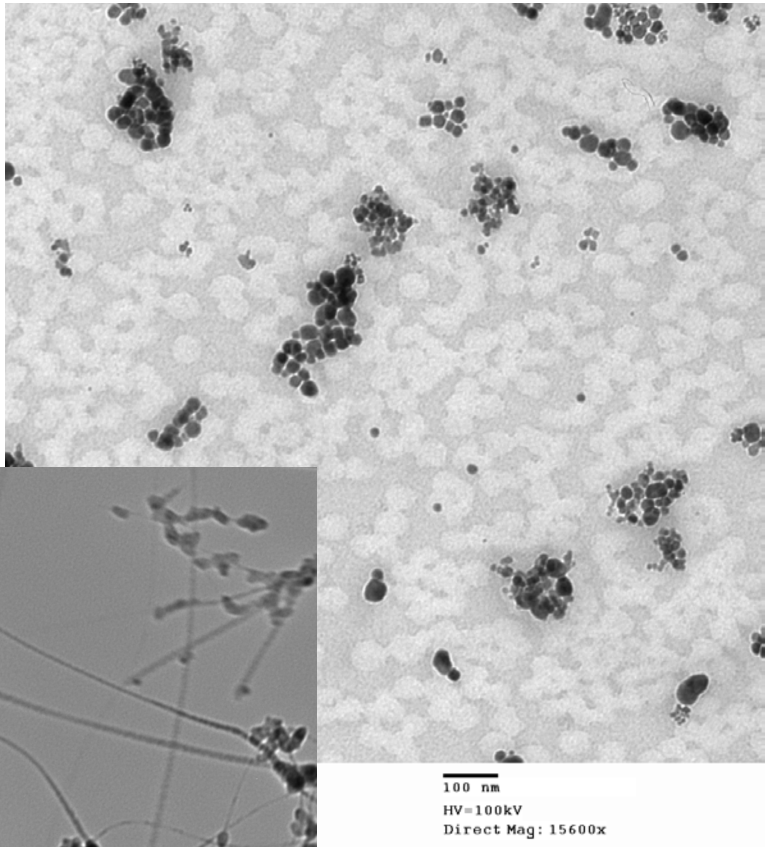
24

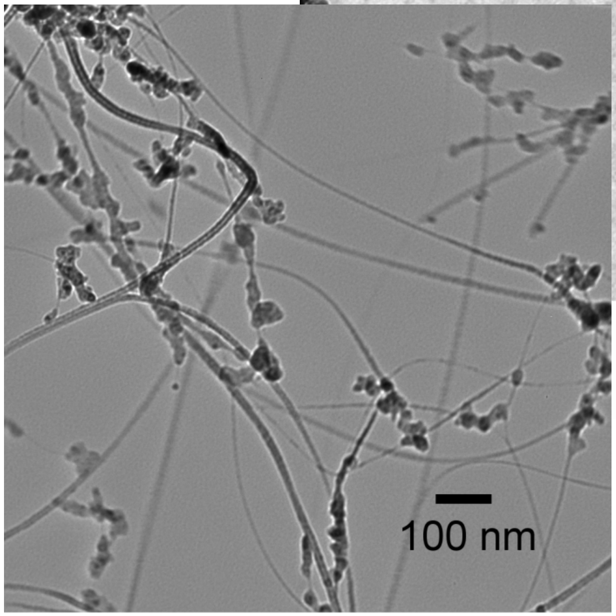


- Mass concentration
- Surface area concentration
- Number concentration
- Particle size distribution
- Total particle number concentration
- Morphology
- Elemental composition

Released from CNT furnace



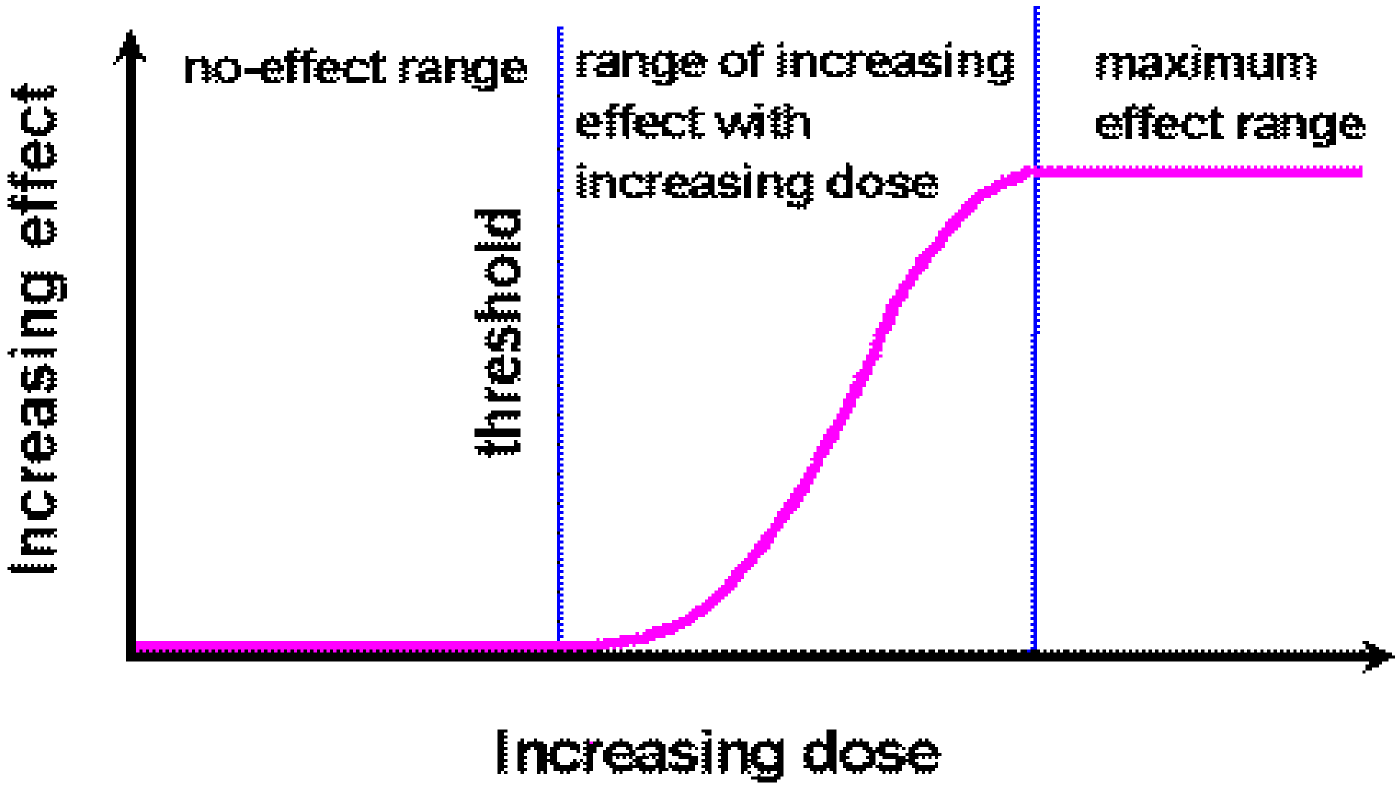




26

Review of the Current State of ENP Toxicology

Dose-Response Curve, I



Toxicity of Nanoparticles

- Key issue – **material** vs. **size**
- Example: carbon
  - Large particles – e.g., carbon black – relatively nontoxic
  - Nanoscale size particle (e.g., carbon nanotubes, fullerenes) – toxicity is **unknown**
  - Even more so for **functionalized** nanoparticles

Key Question Today

- Nanoparticles are so new that we don't know
  - What toxic end-points might be involved
  - The shape of the dose-response curve

Consider three cases:

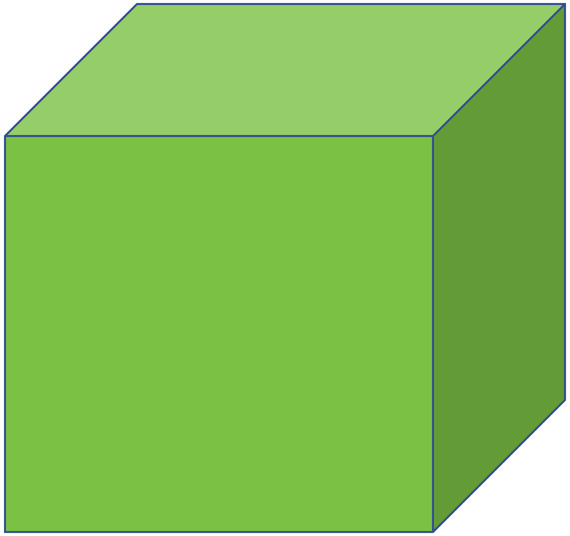
<u>Case 1:</u>

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

$L = 1\ \mu m$

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

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

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

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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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What happens if you stack them up?

10^{27} particles x 10^{-9} m/particle = 10^{18} m

Distance to the sun = 1.5×10^{11} m

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

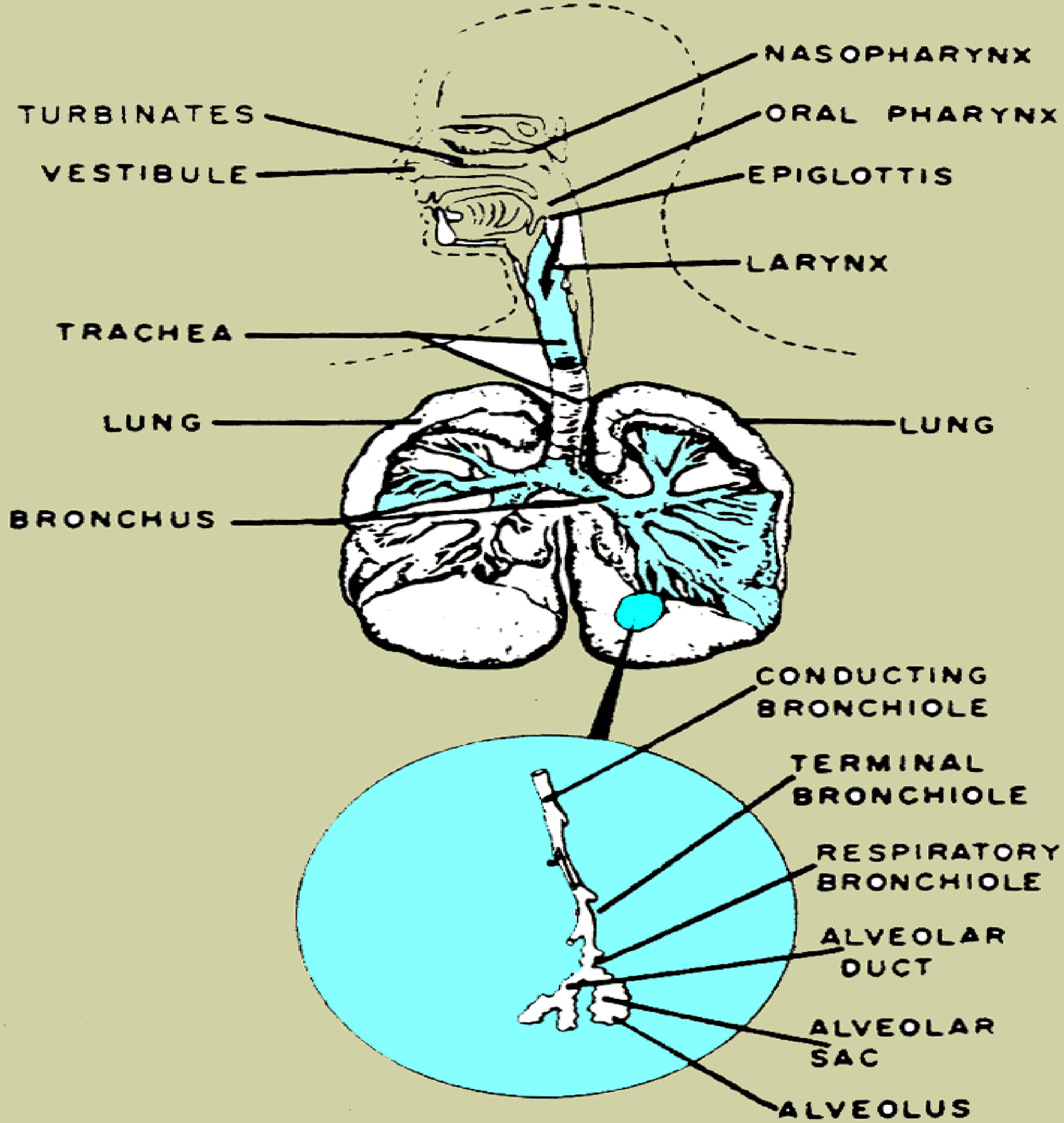
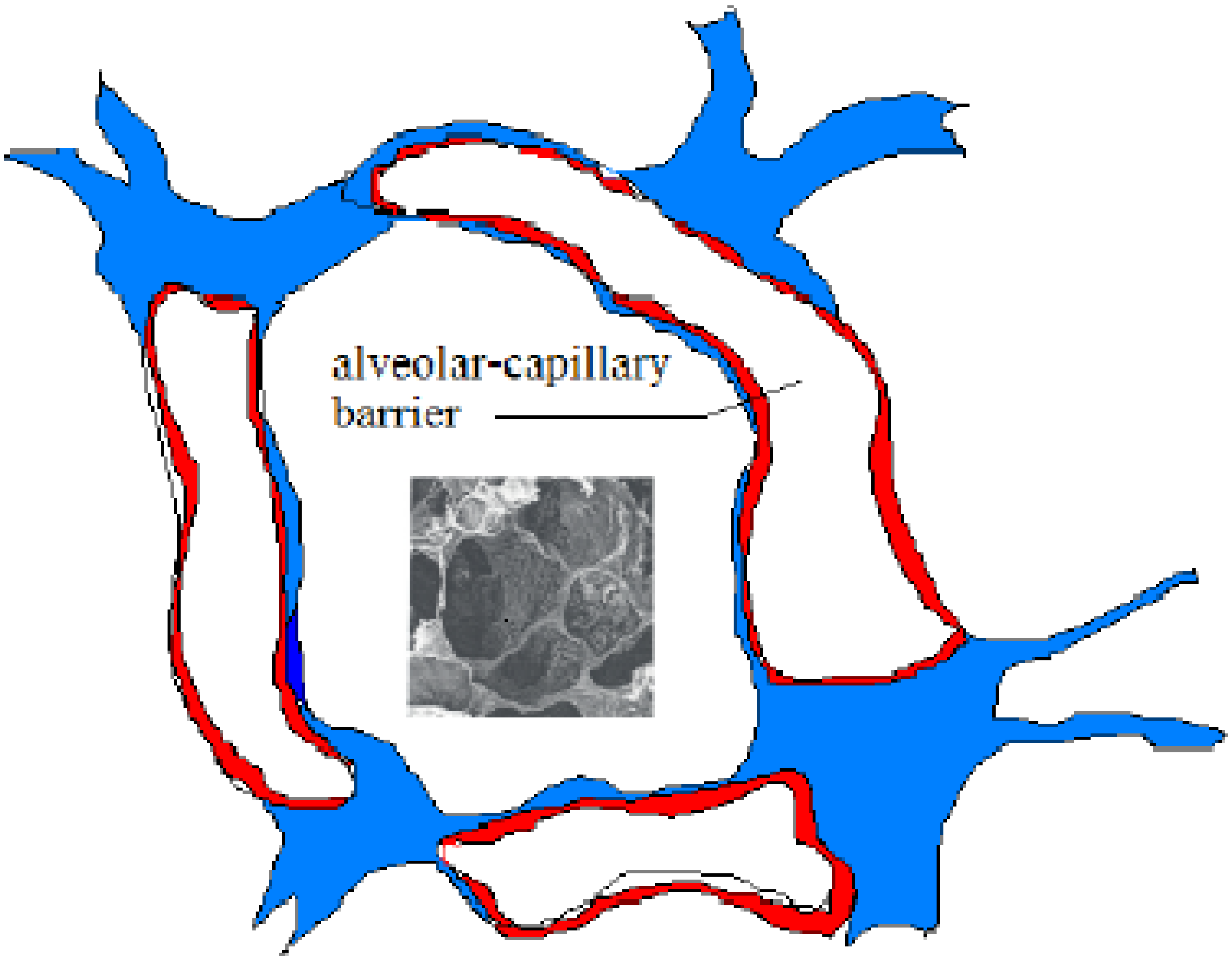


Figure 11.1 The respiratory system. Adapted from *Handbook of Air Pollution* USPHS 999-AP-44 (1968).

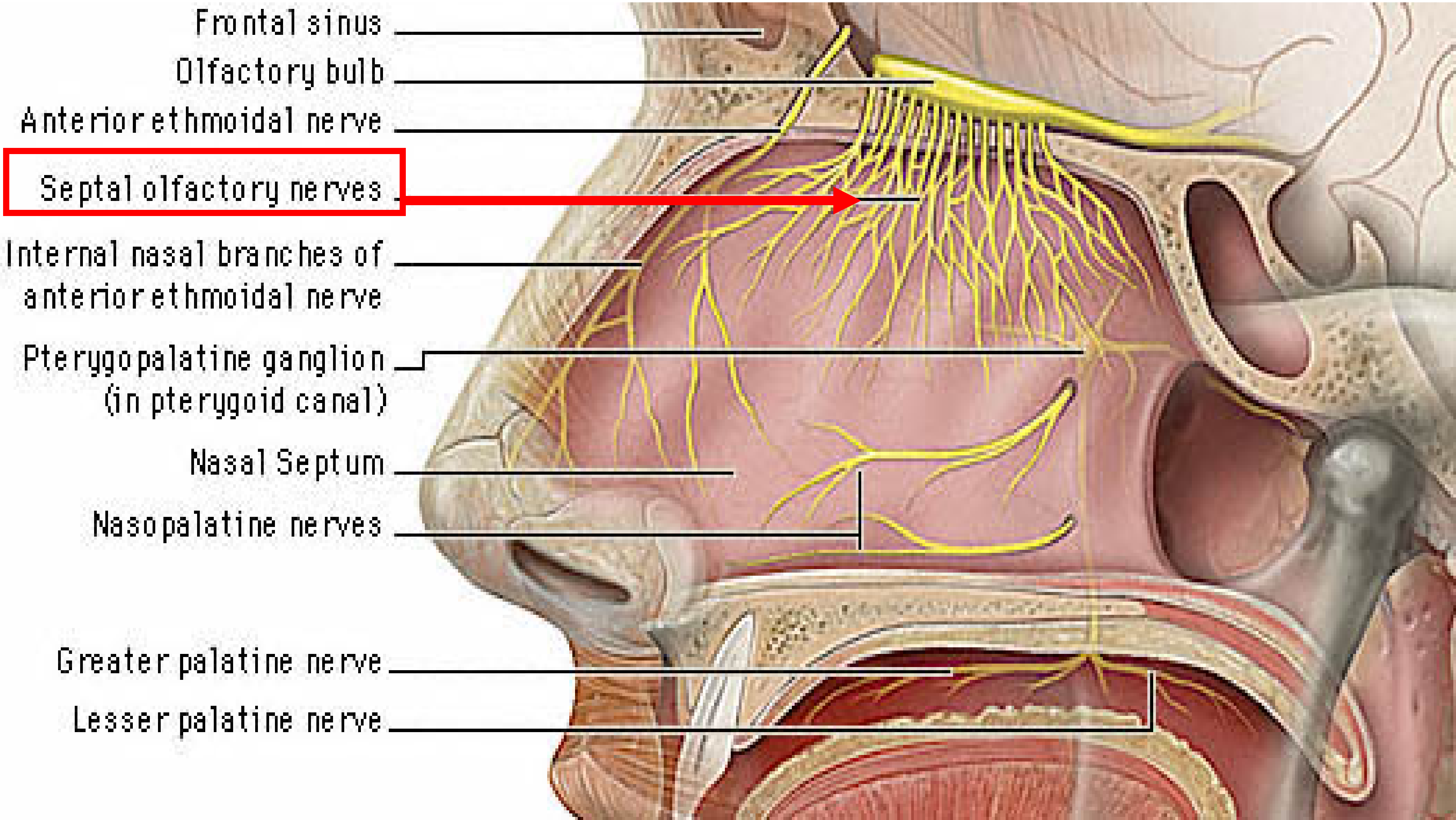
Cross-section of alveoli



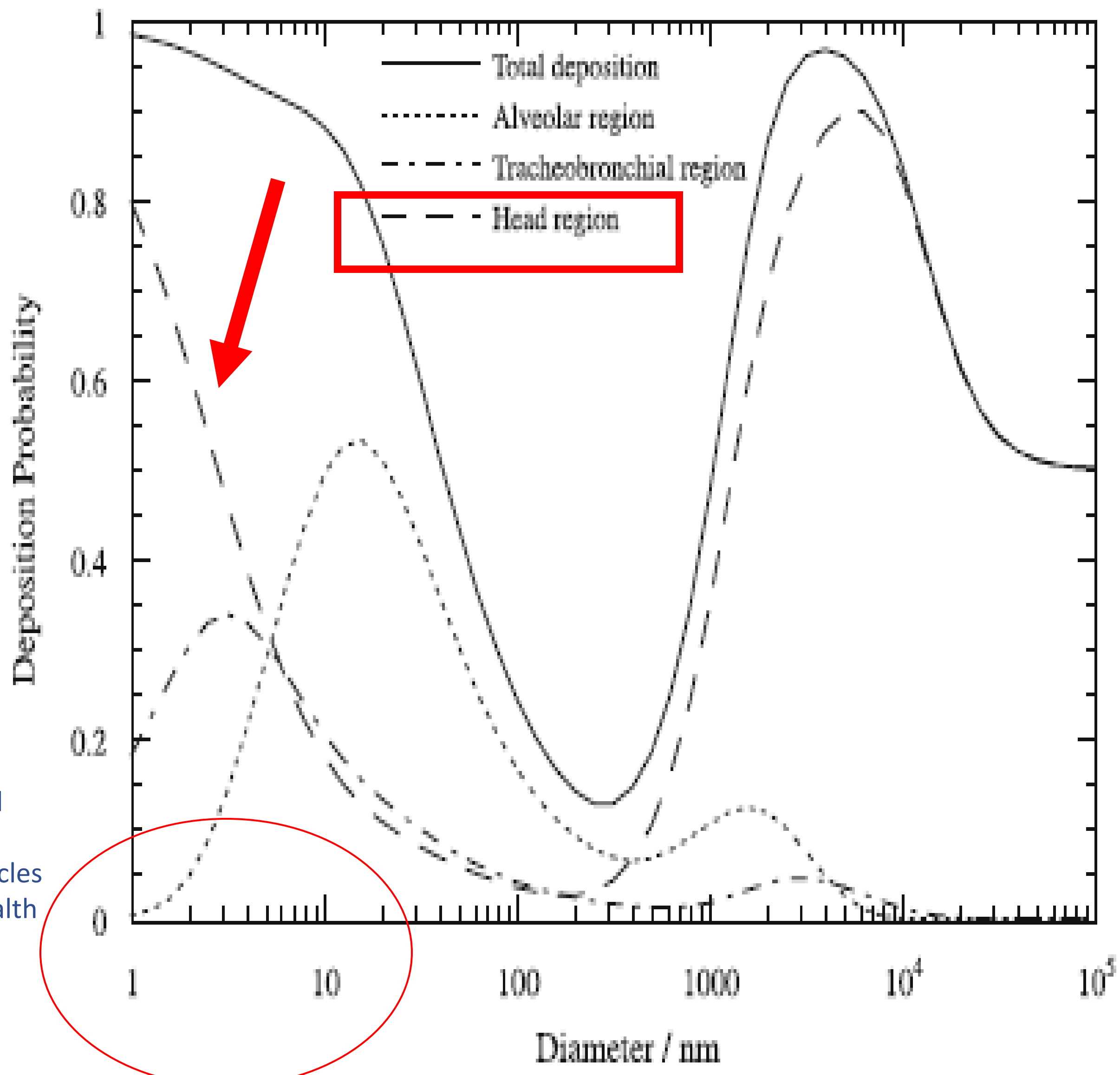
Shows a very thin (500 nm) separation between blood and air. An SEM image of the alveoli is shown in the inset

Hoet et al. J Nanobiotech 2004.

Olfactory nerve exposure and central nervous system effects



Modeled Total Particle Deposition Probability



Source: Maynard and Kuempel, "Airborne nanostructured particles and occupational health (2005)"

Emphasis on CNT Toxicity

- Many studies published in the last 3-5 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.

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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

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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

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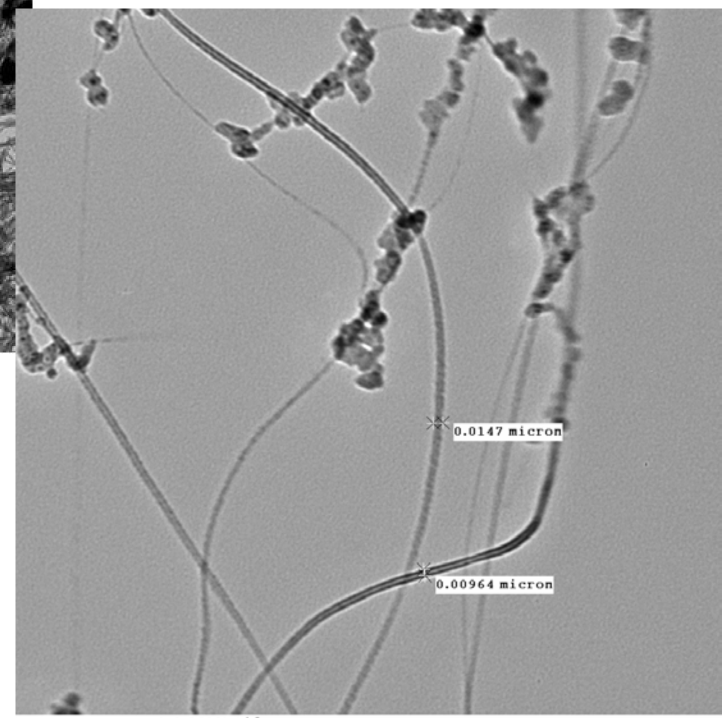


nanocomp source-4-1 0608'.tif
CNT source 0608'-4-1
Cal: 955.975pix/micron

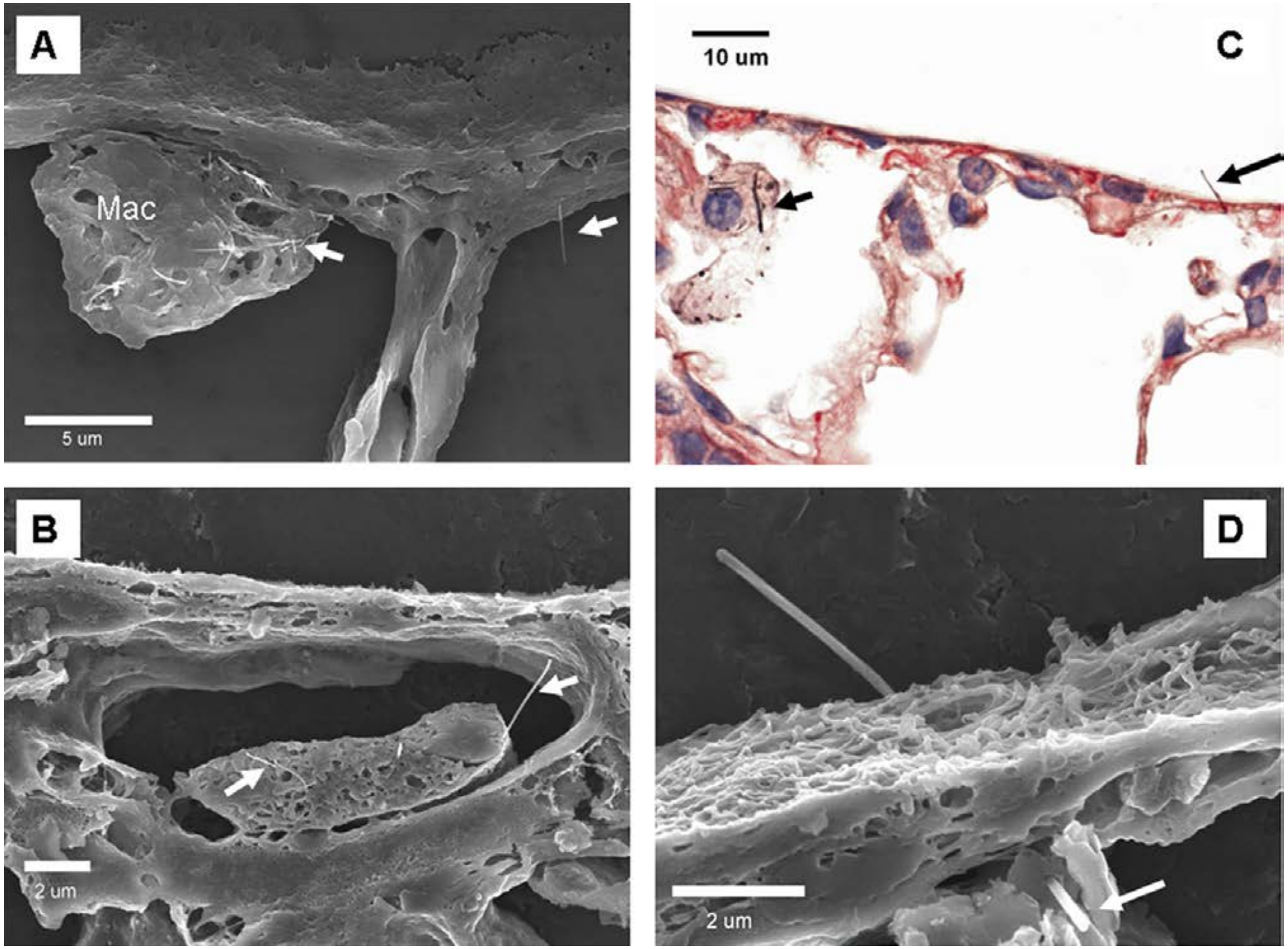
TEM Mode: Imaging
Microscopist: Candace

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.

Mercer, et al., Distribution and persistence of pleural penetrations by multi-walled carbon nanotubes, *Part. Fibre Tox.*, 2010.



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CNTs cause Mesothelioma?, Cont.

Poland: “Here we show that exposing the mesothelial lining of the body cavity of mice, as a surrogate for the mesothelial lining of the chest cavity, to long multiwalled carbon nanotubes results in asbestos-like, length-dependent, pathogenic behaviour… Our results suggest the need for further research and great caution before introducing such products into the market if long-term harm is to be avoided.”

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

Dec 2014 – IARC designates “certain MWCNTs” as 2B, Suspect Human Carcinogen

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NIOSH Recommended Exposure Limit (REL)

- NIOSH (2013) Current Intelligence Bulletin 65 - Occupational Exposure to Carbon Nanotubes and Nanofibers. U.S. National Institute for Occupational Safety and Health DHHS (NIOSH) Publication No. 2013-145
- Reviewed in detail the toxicology literature concerning the acute health effects associated with CNTs and CNFs

NIOSH, Cont.

- Proposed an REL of 1 μg/m^3 of airborne elemental carbon as an 8-hour TWA respirable mass concentration
- Exposures are to be measured and compared to the REL using NIOSH Method 5040, titled "Diesel Particulate Matter (as Elemental Carbon)"
- Elemental carbon is used as a surrogate for actually measuring CNTs or CNFs

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NIOSH, Cont.

The 1 μg/m^3 value was selected based on:

- The level of quantification (LOQ) of Method 5040: NIOSH estimates that "under optimum conditions an LOQ of 1 μg/m^3 can be obtained for an 8-hr respirable sample collected on a 25-mm filter at a flow rate of 4 liters per minute (lpm)."
- At the REL, NIOSH estimates that the "maximum likelihood estimate" of "minimal lung effects" as 2.4 – 33%, and the maximum likelihood estimate of "slight or mild lung effects" as 0.23 – 10%

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Concerns with the NIOSH REL

- the REL may not actually be protective of worker health regarding acute health effects
- the risk assessment and the REL did not consider mesothelioma as an end point, even though there is considerable animal data indicating that this is a distinct possibility
- NIOSH is proposing a mass-based exposure limit for CNTs and CNFs

Mass-Based Exposure Limit

- Primary reason: standard industrial hygiene sampling equipment (i.e., personal sampling pump and filter cassette) and an existing analytical method can be used to evaluate exposures and compare them to the exposure limit
- However, very small mass concentrations of nanoparticles can represent a very high number concentration

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Example Calculation

- Assume that an occupational hygienist is evaluating an exposure to CNTs using NIOSH Method 5040 and finds an elemental carbon concentration of 1 $\mu g/m^3$, just equal to the NIOSH REL.
- Assume further that the measured aerosol consisted of CNTs with a diameter (d) of 10 nm, a length (L) of 2000 nm, and a density (ρ) of 1.4 g/cm^3

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Example Calculation, Cont.

Volume of 1 CNT:

$$V = \frac{\pi d^2 L}{4} = \frac{\pi (10^{-8} m)^2 (2x10^{-6} m)}{4} = 1.6x10^{-22} m^3$$

Mass of 1 CNT:

m = ρV = (1400 kg/m^3)(1.6x10^{-22} m^3)

= 2.2 x 10^{-19} kg x 10^9 µg/kg = 2.2 x 10^{-10} µg

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Example Calculation, Cont.

We can now convert from the mass concentration of the REL to the equivalent number concentration:

$$n = \frac{c}{m} = \frac{1\mu g / m^3}{2.2x10^{-10}\mu g / CNT} = 4.6x10^9 CNT / m^3 x10^{-6} m^3 / cm^3 = 4,600 CNT / cm^3$$

This is an extremely high number concentration, especially compared to asbestos, which we know causes mesothelioma and has a PEL of 0.1fibers/cm^3

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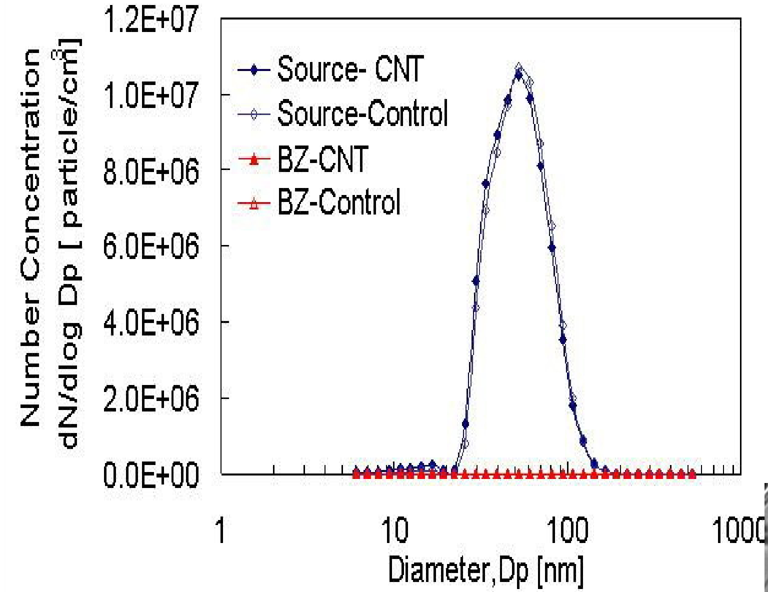
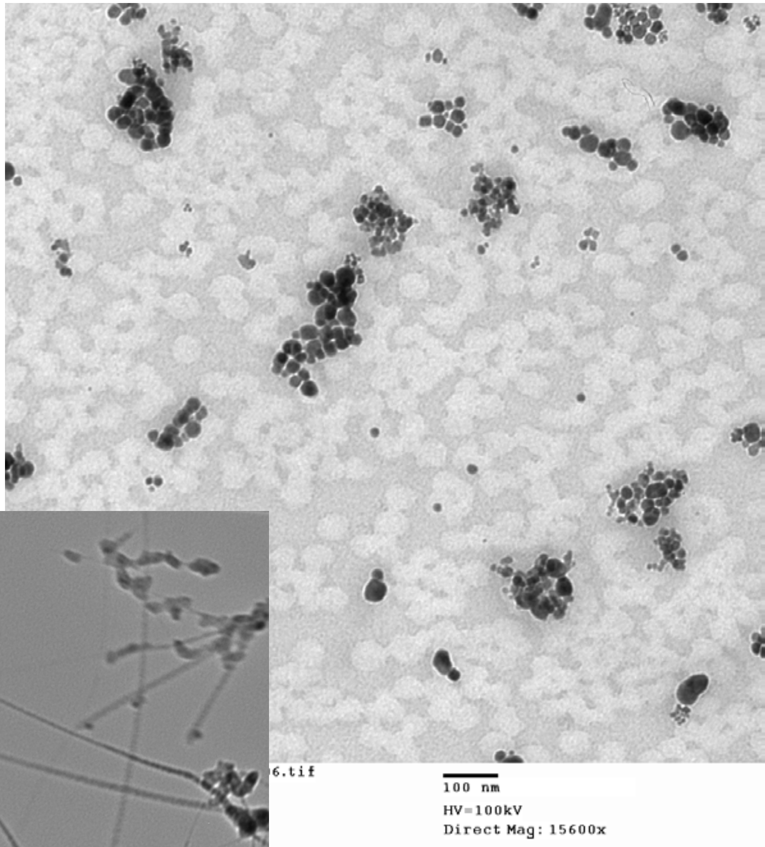
Additional Considerations

- This calculation assumed CNTs with one set of dimensions: smaller or larger CNTs will have different number concentrations corresponding to the REL
- The EC as measured by Method 5040 may be from another source – e.g., carbon soot from the CNT production process, diesel exhaust, etc.

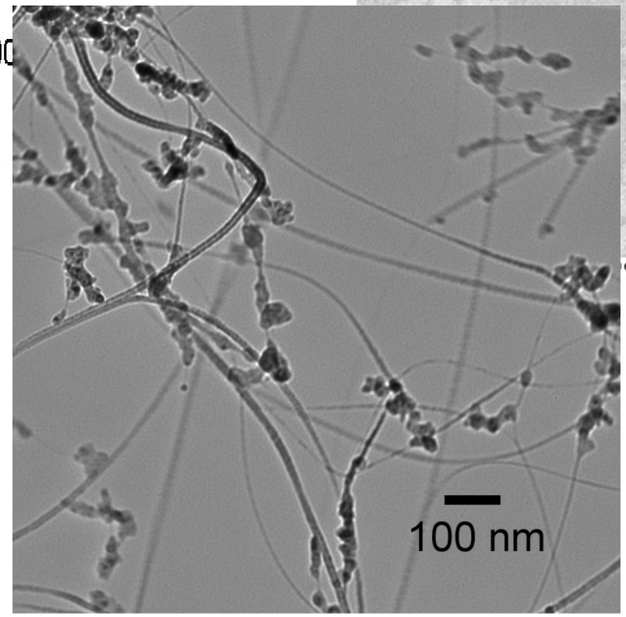
Released from CNT furnaces



Furnace 1



Furnace 2



NIOSH’s Comment

The recommended exposure limit is in units of mass/unit volume of air, which is how the exposures in the animal studies were quantified and it is the exposure metric that generally is used in the practice of industrial hygiene. In the future, as more data are obtained, a recommended exposure limit might be based on a different exposure metric better correlated with toxicological effects, such as CNT/CNF number concentration.

Other Information

- The Current Intelligence Bulletin also contains a great deal of information on engineering controls, respiratory protection, and good work practices to minimize worker exposure while further work is done to refine the CNT REL.
- A copy of the CIB is included in the on-line materials for this session

EU Approach

- German Institute for Occupational Safety and Health (IFA) has developed what are called benchmark levels of evaluating ENP exposures
- Use what IFA considers to be likely predictors of ENP toxicity, i.e., size, shape, density and biopersistence, to distinguish four groups, each with a "nano reference value (NRV)."

Nano Reference Values

- Group 1 consists of "rigid, biopersistent nanofibers for which effects similar to those of asbestos are not excluded" (e.g., CNTs) with a NRV of 0.01 fibers/cm^3 (also the BSI standard)
- Group 2 includes "biopersistent granular nanomaterial in the range of 1 and 100nm" with a density greater than 6000 kg/m^3 (e.g., gold, silver) with a NRV of 20,000 particles/cm^3 (above background)

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NRVs, Cont.

- Group 3 is similar to Group 2, but for materials with a density less than 6000 kg/m^3 (e.g.,TiO_2, ZnO) with a NRV of 40,000 $particles/cm^3$ (above background)
- Group 4, "non-biopersistent granular nanomaterial in the range of 1 and 100 nm," (*e.g.*, sodium chloride) is considered to have toxicity similar to the material at larger sizes, so the applicable OEL for that material is used

NIOSH vs. EU CNT REL

NIOSH: 4600 CNTs/cm^3 (our example)

EU: 0.01 CNTs/cm^3

They only differ by a factor of 460,000!

EU mass conc = = 2.2 x 10^{-6} μg/m^3!!!

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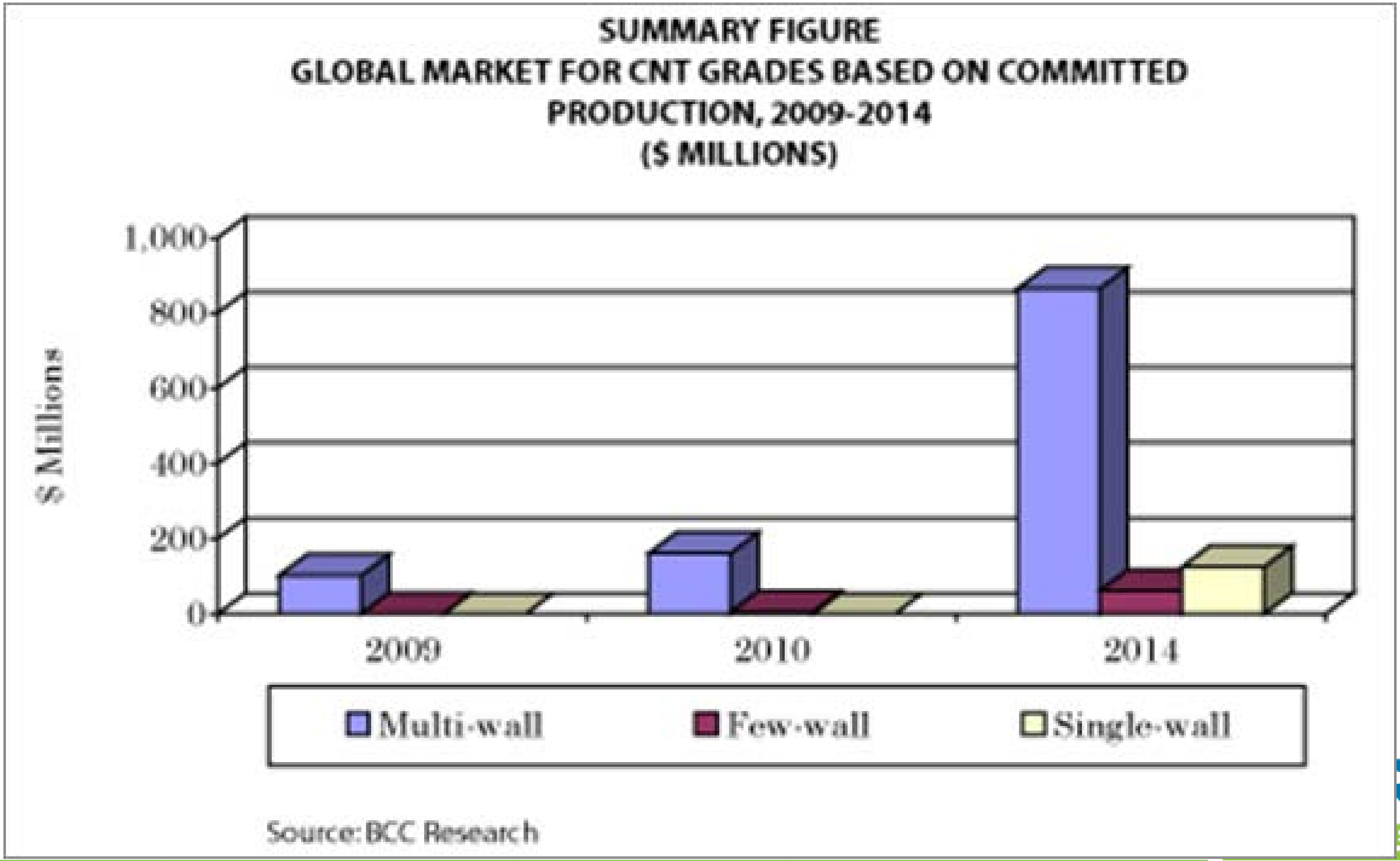
CNT Market Forecast



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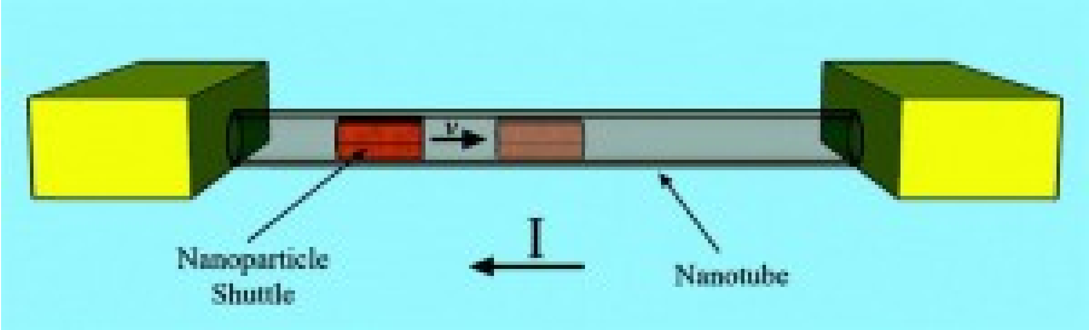
	Manufacturers	Annual production capacity (Metric tonnes)	Processing routes	Country
SWCNTs	Unidym, Inc. (acquired by Wisepower Co.), http://www.unidym.com	1.5	High-pressure carbon monoxide (HiPco)	USA
	Toray Industries, Inc. http://www.toray.com	1.5	CCVD	Japan
	Mitsubishi Rayon Co. Ltd. http://www.mrc.co.jp/english/index.html	1.2	CVD	Japan
	SouthWest NanoTechnologies Inc. http://www.swentnano.com	1.0	Cobaltmolybdenum catalyst (CoMoCAT)®	USA
	Kleancarbon Inc. http://www.kleancarbon.com	1.0	CVD	Canada
MWCNTs	Showa Denko K.K http://www.sdk.co.jp/english	500	CCVD	Japan
	CNano Technology Limited http://www.cnanotechnology.com	500	CCVD	USA
	Nanocyl S.A., http://www.nanocyl.com*	400	CCVD	Belgium
	Bayer MaterialScience AG http://www.bayermaterialscience.com	260	CCVD	Germany
	Arkema Inc. http://www.arkema-inc.com	50	CCVD	France
	Hyperion Catalysis International, Inc. http://www.hyperioncatalysis.com	50	CVD	USA

Carbon nanotube uses

Two use scenarios:

1) as a fibrous filler in a polymer nanocomposite for use in tennis racket frames

2) As a new generation memory device



Risks and Benefits of Two CNT Products Properties to Consider		
Property	**Tennis Racket**	**Memory Device**
Importance to society	Low	Very high
Value added to the device	Low	Very high
Quantity used per device	Very high (grams)	Very low (nanograms)
Physical form during device manufacture	Dry powder	Suspended in liquid
Potential for occupational exposure	Very high	Very low
Potential for consumer exposure	Low	Very low
Quantity at end of life disposal	Very high	Very low

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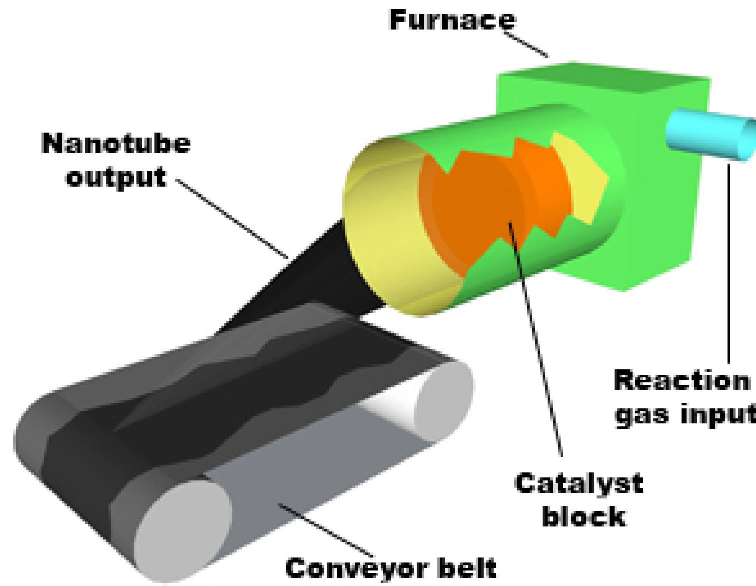
CNTs in Inherently-safe Form?

nanocomp TECHNOLOGIES, INC.



Approach to Sustainable Nanotechnology

- In view to the uncertain, but probable, adverse health effects of at least *some* ENPs, we must follow a *precautionary* approach to technological development
- Assume that *any* exposure measurably above background may be hazardous
- The risks and benefits of *each* technology must be evaluated on a *case-by-case* basis

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