Nanoparticles and Health

Contra Costa County
Hazards Materials Commission
March 22, 2012

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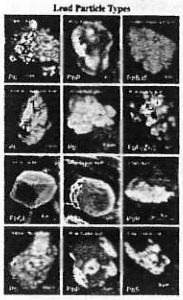
University of California

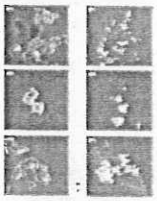
My Career Has Been All About Particulate Matter!!

Asbestos

Silica

Lead





Beryllium

Welding Fume

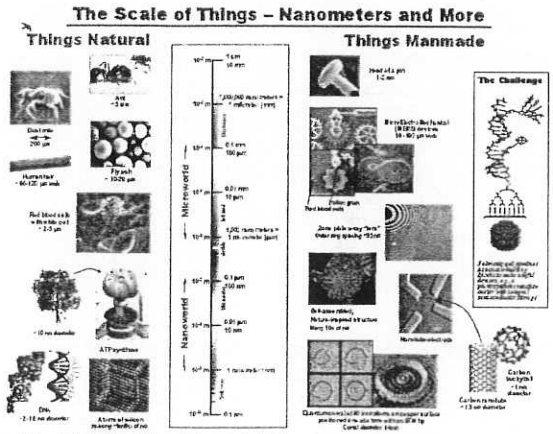
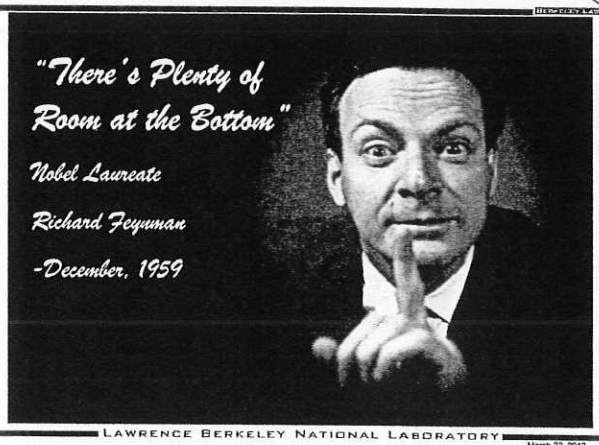


Figure 1. Diagram indicating relative scale of nanosized objects.
(From NNI website, courtesy Office of Basic Energy Sciences, U.S. Department of Energy.)

Where it all began (folklore review)

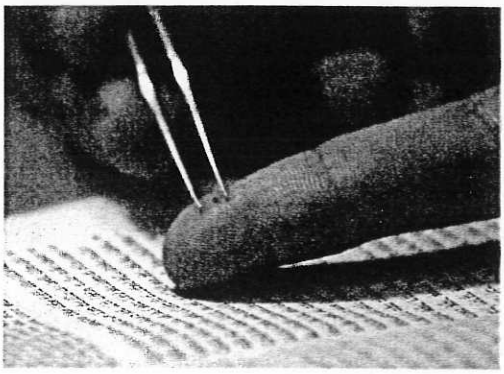


The Challenge

"What I want to talk about is the problem of manipulating and controlling things on a small scale."

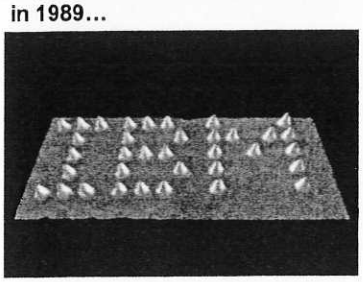
"Why cannot we write the entire 24 volumes of the Encyclopedia Brittanica on the head of a pin?"

Bible on Head of a Pin, 2007



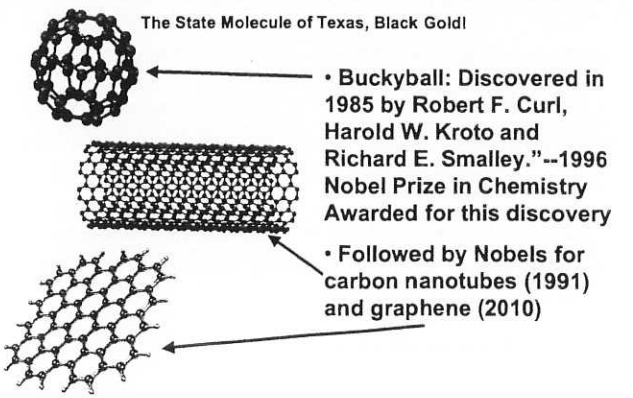
Iconic IBM Advertisement

Feynman's dream comes to life in 1989…



- **IBM scientists Don Eigler and Erhard Schweizer arrange 35 xenon atoms with an Scanning Tunneling Microscope to spell out the company name**

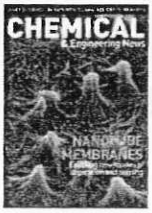
3 Nobel Prizes for Nanocarbon



The State Molecule of Texas, Black Gold!

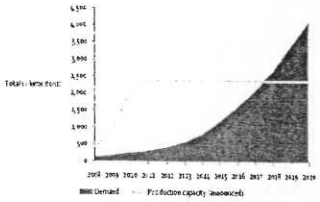
- **Buckyball: Discovered in 1985 by Robert F. Curl, Harold W. Kroto and Richard E. Smalley."--1996 Nobel Prize in Chemistry Awarded for this discovery**
- **Followed by Nobels for carbon nanotubes (1991) and graphene (2010)**

Futuristic Applications of Carbon Nanotubes



The Hype Cycle: Carbon Nanotubes

- **Sporting goods, aerospace/defense, wind turbines automobile industry, batteries, electronics, filtration**



Wikipedia: Hype Cycle

Quoted from: David Hwang of Lux Research

What Are the Issues with Engineered NanoParticles, ENP?

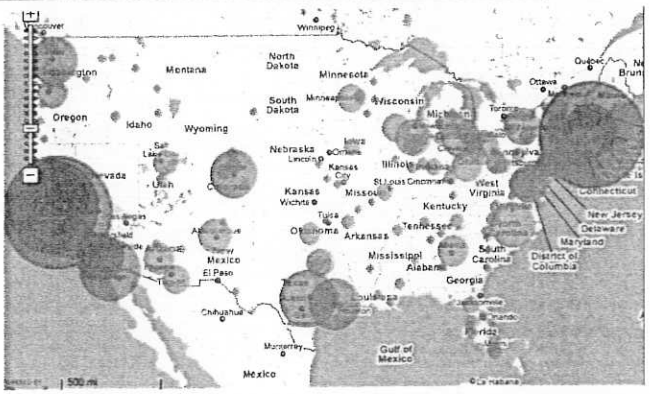
- **What are ENP**
- **What are the reasons for concern about ENP**
- **What has been shown about toxicity of ENP**

Early nanotechnologist!

Primary EH&S Issue: *Unbound Engineered Nanoparticles*

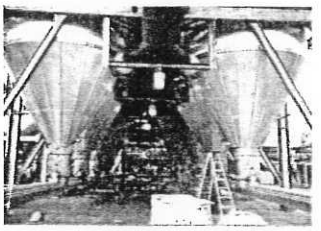
- **Not firmly attached to a surface**
- **Not part of a bigger item (e.g., microchip, cell wall)**
- **Can result in exposure via inhalation, skin absorption or ingestion (or other nanospecific routes of exposure!)**

US Nanotechnology Hot Spots



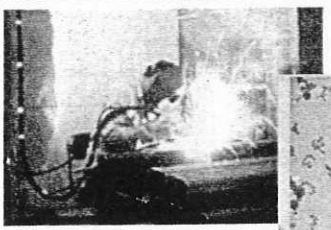
ENP Have Been Produced Commercially for Decades

- Carbon black–100 years
- Fumed silica
- Iron oxide
- Titanium dioxide
- Aluminum oxide
- Zirconium oxide
- Nanoclays



Aeropulse Carbon Black Factory
From their web site

Not All Nanoparticles Are *Engineered*



Welding fume

Oxides of zinc, iron, chromium, aluminum, or nickel mostly in the nano-range when fresh

Picture - UC San Francisco

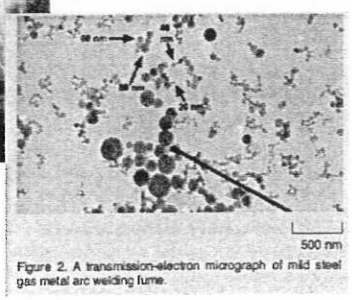
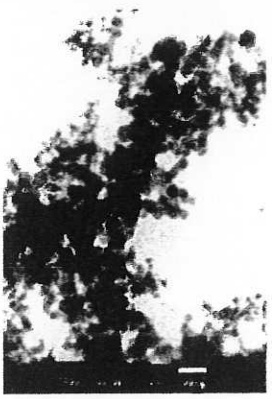
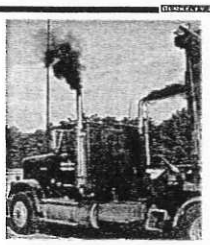


Figure 2. A transmission-electron micrograph of mild steel gas metal arc welding fume.

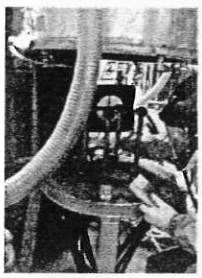
Not All Nanoparticles Are *Engineered*

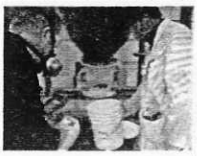




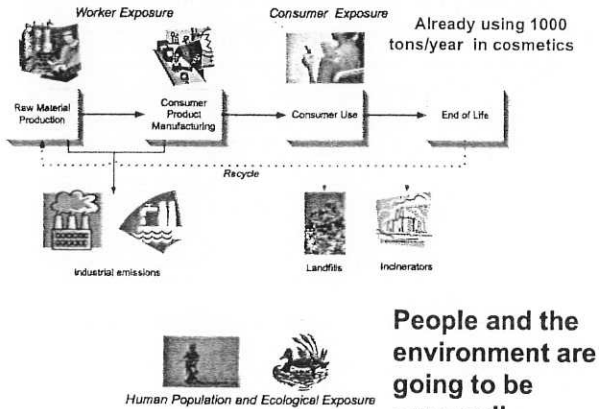
Nanoscale soot plus carbon monoxide, carbon dioxide, sulphur dioxide, nitrogen oxides, formaldehyde, benzene and polycyclic aromatic hydrocarbons

Factories Are Gearing Up to Produce Engineered Nanoparticles





But What Are the Risks?



Already using 1000 tons/year in cosmetics

People and the environment are going to be exposed!

Figure 16. Life Cycle Perspective to Risk Assessment

We Are All Nanoparticle Consumers in 2012

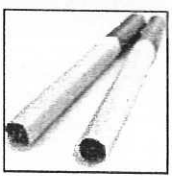
By 2009, nanomaterials are extensively incorporated into >600 consumer products

2008 Easton Stealth Comp Youth Baseball Bat CNT -11oz. LCN6
[LCN6]

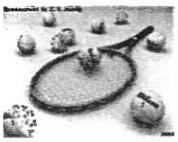
2008 Easton Stealth Comp Youth Baseball Bat CNT -11oz LCN6

Easton Stealth Comp Features

- CNT Carbon Nanotube technology an Patented iMX™ - Integrated MatriX technology strengthens composite structures, optimizing designs and materials for maximum performance



Carbon Nanotubes Are Here Already !



CNTs make sports equipment stronger, lighter, more profitable, cooler!

2008 Easton Stealth Comp Youth Baseball Bat CNT -11oz. LCN6 [LCN6] $249.95

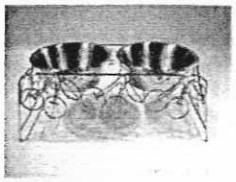
2008 Easton Stealth Comp Youth Baseball Bat CNT -11oz. LCN6

Easton Stealth Comp Features:

- CNT Carbon Nanotube technology and Patented IMX™ - Integrated MatriX technology strengthens composite structures, optimizing designs and materials for maximum performance

>500 consumer products that contain nanomaterials at last count!

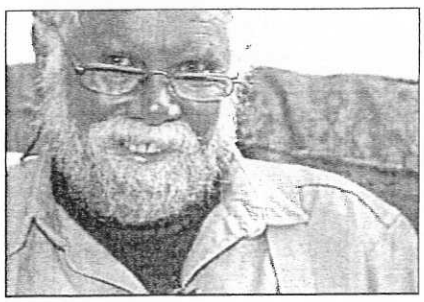
Products with Nano Materials in 2009



Drinking Too Much Nano Silver?

- Man turned blue from drinking nano silver particles



Some People Are Showing Their Concern!

FIND YOUR SUNSCREEN

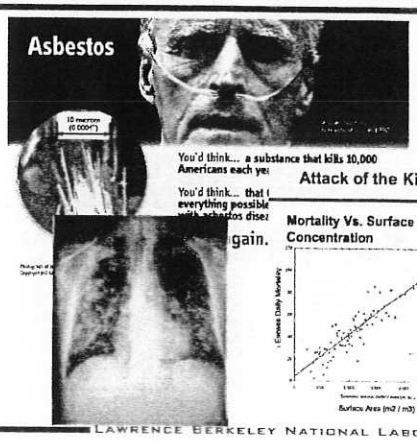
- Water-resistant/sweatproof
- Marketed for children/babies
- Good UVA protection
- No nano-particles

Nanoscale May Be Fundamentally Different

- Properties of nanoscale materials may be fundamentally different from bulk materials of same chemical composition
- Among the new properties of nanoscale materials may be:
  - —New toxicological properties
  - —New environmental hazards

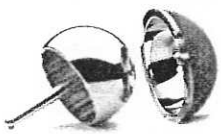
Size-specific phenomena and new properties

Asbestos, Silica, Environmental Ultrafines



Thousands of People Are Suffering NOW Due to Nanoparticle Exposure

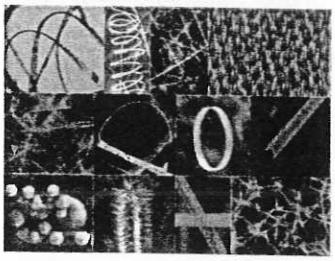
- A recent shift toward metal-on-metal artificial joints--Wear of these joints causes creation of toxic metal oxide nanoparticles (30-100 nm Co, Cr, Mo)--- resulting in persistent tissue inflammation, bone loss and ultimately joint failure as well as possible systemic cardiovascular and neurotoxicity



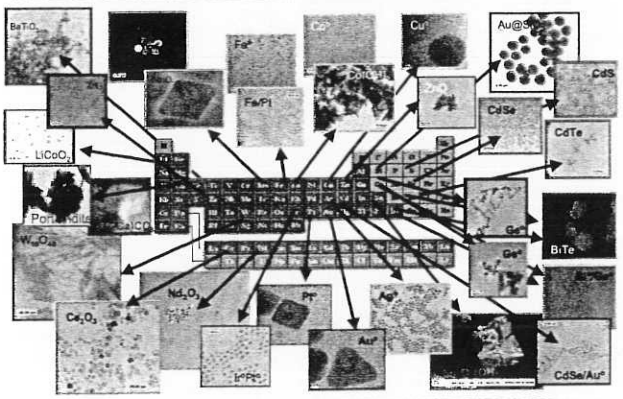
It Is Not Going To Be Easy To Sort Out

- Many variables may effect toxicity
  - — Size
  - — Shape
  - — Chemistry
  - — Crystal structure
  - — Water solubility
  - — Surface area
  - — Surface coating
  - — Agglomeration state
  - — Density
  - — Dispersability
  - — Porosity
  - — Surface charge
  - — Conductivity
  - — Contaminants
  - — Manufacturing method

One chemistry but many forms of nanoscale ZnO!!



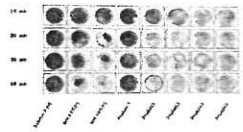
Extremely Broad Chemistries



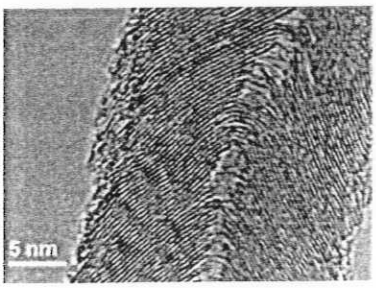
This from one set of labs at the University of New Mexico

Uses of Tests Not Compatible with Nanoparticles

- MTT test--measures mitochondrial toxicity
- Lack of red indicates inactive mitochondria
- Early studies said carbon nanotubes showed high toxicity in this test
- In fact, CNTs interfere with this assay and make it almost useless



Nanotube, NOT!!

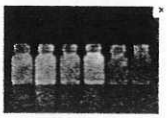


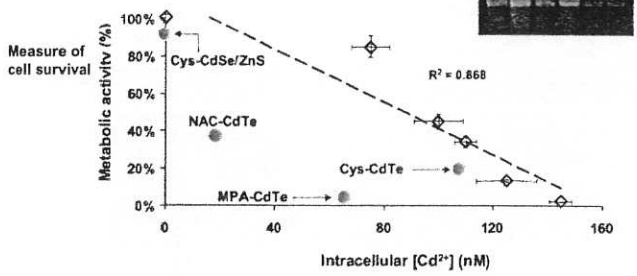
- Representative "carbon nanotube" from Mitchell et al (2007) inhalation study is in fact a nanofiber.
- Cheap Tubes!
- The authors didn't know the difference!

Common Drivers of "Nanotoxicity"

- Intrinsic elemental toxicity
  - — Individual atoms or ions interfere with biological systems
  - — Lead, cadmium, fluoride, etc
    - Usual dose metric is mass
- Surface area/reactivity driven toxicity
  - — Surface catalyzes damaging reactions
    - Surface area is likely the most relevant dose metric
- Morphology-driven toxicity
  - — Fiber toxicity
  - — Asbestos, fibrous zeolites, MMMF
    - Usual dose metric is particle count

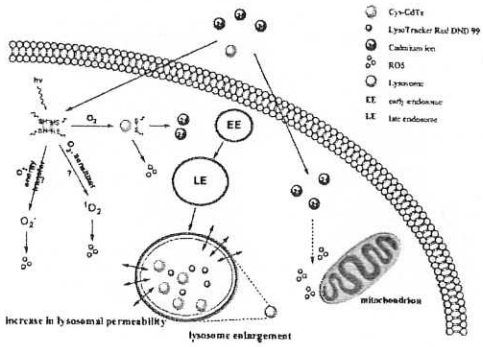
"Elementally Toxic" Cd Quantum Nanodots:





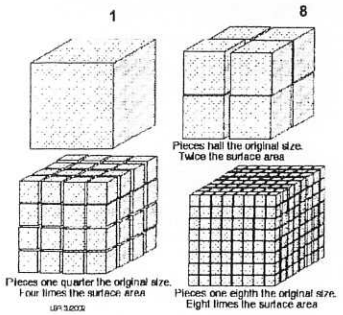
- Cd2+ Accounts for only Part of Net Toxicity (2007)

Duel Mechanisms: CdTe Toxicity

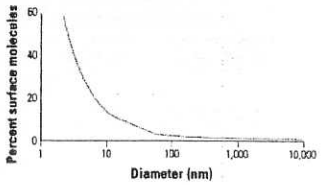


- ROS derived from Cd ion and intact particles

Nanoparticle Surface Area is Huge!



- More surface area = more catalysis
- Approaches 100% of atoms on the surface
- Catalytic generation of ROS= oxidative stress
- This clearly drives "excess" toxicity of some nanoparticles

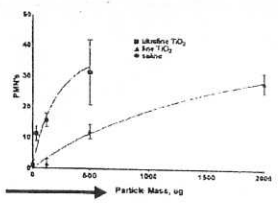


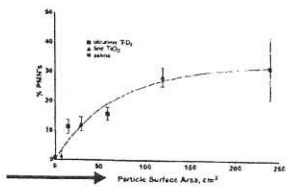
•www.gly.uga.edu/railsback/1121WeatheringArea.jpeg

Surface Area May Be Critical Metric

Metals/oxides of low solubility and low elemental toxicity, e.g. Ti, Zr, Ba, Au, polymers, fullerenes

- Toxicity of ultrafine TiO2 appears much higher than fine TiO2 *per unit mass*
- Toxicity is equivalent when *surface area* is the exposure metric



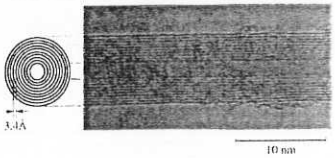


Measured polymorphonuclear neutrophils in lung lavage fluid, an index of inflammation

Oberdorster, Int Arch Occup Environ Health. 2001 Jan;74(1):1-8.

Carbon Nanotubes (CNTs)

www.gly.uga.edu/schroeder/geol6550/CM07.html

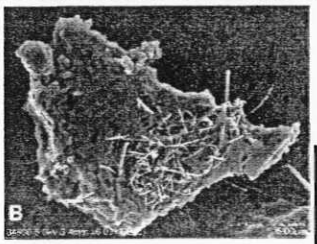


Crossections of Two Similar Appearing *Nanotubes*

- Chrysotile asbestos (left)
- Multiwalled carbon nanotube (above)

Similar toxicity?

CNT Toxicity



•Carbon Nanotube Bundle

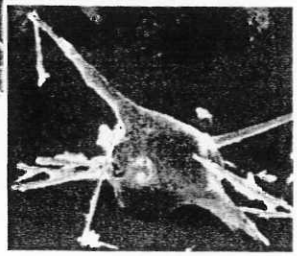
•CNTs are fairly durable in lung tissue

•Inhalation of CNTs causes formation of granulomas and diffuse fibrosis

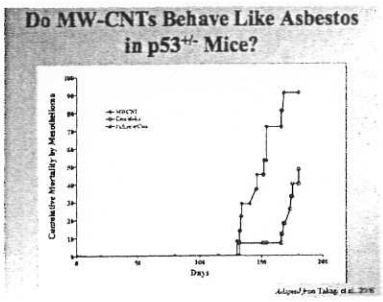
•Injection IP may cause mesothelioma

Frustrated Phagocytosis

•Crocidolite Asbestos



What About Mesothelioma?



- ✓ In this study, long MWCNTs appeared to be the most potent mesothelioma agents ever tested!
- ✓ Lots of criticism of this assay, so the question remains open.

Are CNTs Just Synthetic Graphite?

Section 1 Product Identification

Chemical Name:	Carbon Fullerene
Formula:	Carbon
Chemical Family:	Synthetic Graphite
Synonyms:	Carbon Nanotubes
CAS Number:	7782-42-5 (Graphite)

•Current MSDS from Bay Area manufacturer of CNTs

Section 2 Composition and Information on Ingredients

Component	%	OSHA/PEL	ACGIH/TLV
Synthetic graphite	Up to 100%	15 mg/m^3 (total dust) 5 mg/m^3 (respirable fraction)	2 mg/m^3 TWA
Metallic impurity	Balance		

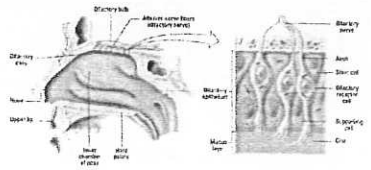
What Is a Safe Airborne Exposure Limit for CNTs?

- Graphite Standard (OSHA): 5 mg/m^3 averaged over 8 hours
- Carbon Black (ACGIH): 3.5 mg/m^3
- Bayer Corporation (*Baytube*: MWCNT): 0.05 mg/m^3*
- NIOSH MWCNT Proposal: 0.007 mg/m^3
- NIOSH MWCNT BMD Proposal: ~0.0007 mg/m^3

* For Bayer's "short-tangled" and thus "low toxicity" MWCNTs. Implication is that this standard may be inadequate for longer/less tangled and thus potentially more toxic MWCNTs.

Translocation from Nose to Brain

- **Known since 1941 that polio virus particles can enter the brain via the olfactory nerves**
- **Studies in monkeys with intranasally instilled gold ultrafine particles (< 100 nm) and in rats with inhaled carbon UFPs (36 mn) suggested that solid UFPs deposited in the nose travel along the olfactory nerve to the olfactory bulb**



Translocation along Axons

- **Long known that some nanoparticles deposited in rodent noses translocate along axons into the brain**
- **The same effect has been demonstrated from nerve endings in the trachea and bronchi**

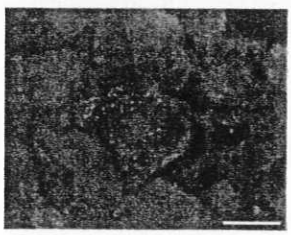


FIGURE 9.—Red rhodamine beads in a neuron cell body of the jugular ganglion demonstrate neuronal transport of particles from the trachea of a rat after intratracheal instillation of fluorescent beads. Bar = 20 μm.

Oxidative Stress in Coronary Arteries Caused by Inhalation of TiO2

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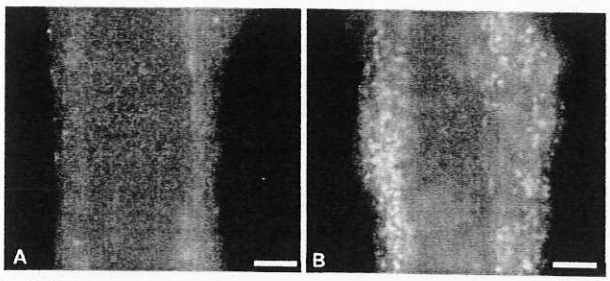
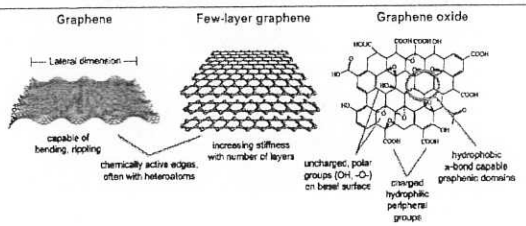


FIGURE 8.—TiO_2 NP inhalation causes oxidative stress in coronary arterioles. (A). Representative coronary arteriole from a sham-control rat. (B). Representative coronary arteriole from a rat exposed to 10 μg TiO_2 NP (measured lung deposition). Arterioles were incubated with dihydroethidium (DHE, 10^{-4} M, 20 minutes). Superoxide oxidizes DHE to form ethidium bromide. Ethidium bromide is intercalated into nuclear DNA, and is fluorescent at 480 nm. Note the increased density of fluorescent nuclei in the microvascular wall of the NP exposed rat in B. Differences in dye loading are resolved by measuring background DHE fluorescence at 330 nm and subtracting this image from the ethidium bromide image. The remaining fluorescent light intensity is quantified with image analysis software. Measurements are made 24 hours after NP inhalation. Bar = 50 μm.

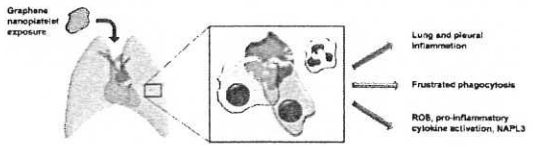
Graphene!

- Yet another Nobel prize (2010)!
- 3000 published papers in 2010!
- Possible use in composites, polymers, electrodes, super capacitors, inks, biomedical technologies
- Variations: Few layer graphene, graphene oxide, reduced graphene oxide,



Graphene

- Duch, 2011: Graphene oxide instilled into lungs of mice caused severe and persistent inflammation, cell death. Pristine graphene was much less toxic
- Schinwald, 2012: Aspiration and instillation of micron scale graphene plates caused significant lung inflammation with evidence of frustrated phygocytosis.



Regulation of Nanoparticles

Berkeley Nano Ordinance

- Berkeley Manufactured Nanoscale Materials Health and Safety Disclosure Ordinance, December 2006
- An "add on" to the HMBP process
- Only local nano ordinance, focused on disclosure
- Compels facilities that produce or handle manufactured engineered nanoscale materials to report what they are working with, describe known toxic effects and provide a plan on how the materials are handled safely.

Berkeley Nano Ordinance: Criticism

- No de minims quantities specified
- "Open" reporting format
- Limited amount of information captured
- Burdensome and may drive out startups

Cambridge, MA considered and rejected a similar ordinance in 2008

State of California Call-Ins

- California Health and Safety Code 699: Basis for requiring producers of specified nanomaterials to report on nanoparticles--quantity, detection methods, risks, protective steps etc
- Do you consider your waste or material to be hazardous waste
- Two stages complete
  - —Call 1: Carbon nanotubes
  - —Call 2: Assortment of metal and metal oxide nanoparticles

California/Federal OSHA

- No specific regulations for new engineered nanomaterials

EPA

EPA Has Many Possible Regulatory Roles WRT CNTs

- Prohibit/Regulate introduction of nanoparticles into commerce under TSCA:
  - —Underway for CNTs and other nanoparticles since 2008
- Regulate as a pesticide (FIFRA):
  - —Already underway for nano-silver
- Prohibit releases to air (Clean Air Act) or Water (Clean Water Act, Safe Drinking Water Act)
- Classify as hazardous Waste (RCRA)

EPA: TSCA

- Generally, you can only market and use chemicals that are on the EPA Toxic Substances Control Act (TSCA) inventory
- Carbon nanotubes are fundamentally new and are not among the 84,000 chemicals on that inventory...
- Most other "nano materials" are chemically identical to larger materials and thus not subject to regulation as new chemicals, yet

EPA Officially Announces The Regulation of CNT Import and Manufacturing

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPPT–2004–0122; FRL–8386–6]

Toxic Substances Control Act Inventory Status of Carbon Nanotubes

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: 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 when required under 40 CFR part 720 or part 723. In order to determine the TSCA Inventory status of a CNT, a manufacturer may submit to EPA a *bona fide* intent to manufacture or import under 40 CFR 720.25.

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FURTHER INFORMATI

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Information?

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OPPT–2004–0122.
docket are listed in
available at *http://*
Although listed in
information is not
e.g., Confidential B

Evolving EPA Rules for CNTs

- EPA receives at least 100 PMNs to import or manufacture nanomaterials, many for CNTs. Eventually the EPA enters into "5(E)" consent decrees with many (15 to date) of these companies, with the following typical requirements:
  - —Use the material only for the listed (semi-secret!) purposes
    - Examples: polymer composite materials, electronics, catalyst support
  - —Conduct a 90-day rat inhalation toxicity study on their material
  - —Require employees who may be exposed to use specified types of personal protective equipment at facilities under its control (full-face respirator/protective coveralls and gloves)
  - —*Only distribute the material to persons who agree to comply with all of the restrictions of the 5(e) order (except the tox study).*

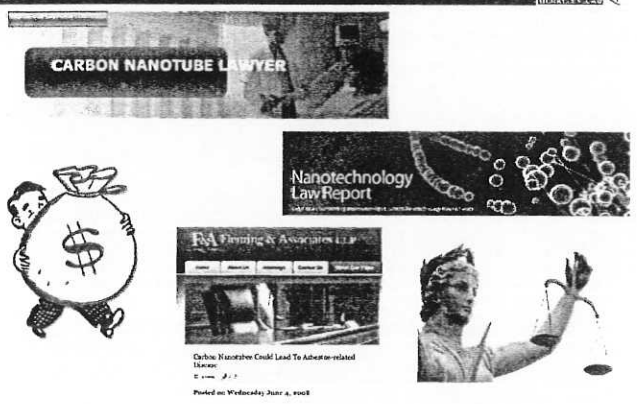
EPA Issues Significant New Use Rules (SNURs) for Multi-Walled Carbon Nanotubes

- After signing a Section 5(e) Consent Order, EPA generally promulgates a Significant New Use Rule (SNUR) that mimics the Consent Order to bind all other manufacturers and processors to the terms and conditions contained in the Consent Order for that exact, specific PMN material.
- The SNUR requires that manufacturers, importers and processors of PMN substances notify EPA via a SNUN at least 90 days before beginning any activity that EPA has designated as a "significant new use". These new use designations are typically those activities prohibited by the Section 5(e) Consent Order."
  - Significant new uses of multi-walled carbon nanotubes are deemed to occur when employees do not "use gloves impervious to nanoscale particles and chemical protective clothing;" and/or fail to "use a NIOSH-approved full-face respirator with an N-100 cartridge while exposed by inhalation in the work area."
  - "Significant new use" applies to the use of a substance outside of the list of approved uses in the PMN (e.g. catalyst support, filler, polymer).

General Research Exemption to SNURs

- SNUN Exception for Research: 40 CFR 721.47:
  - —Small quantity, only for R&D
  - —Standard lab procedures
  - —Only handled by "technically qualified individuals"
  - —Additional rules apply to R&D that exceeds the scope of "laboratory scale"

The Lawyers Are Mobilizing



Questions?