CARBON NANOTUBES AND ASBESTOS FIBERS: INTERDISCIPLINARY RESEARCH ON EMERGING AND RE-EMERGING CONTAMINANTS

Interdisciplinarity unifies and integrates knowledge and must include an interaction, overlap, sharing of insights or bridging of disciplines among two or more disciplines from a theoretical, practical-outcome or problem-oriented approach. It borrows or applies tools between disciplines and it may lead to the emergence of a new discipline and new fields of knowledge.

Franks et al., Studies in Higher Education, 2007

Agnes B. Kane, MD, PhD
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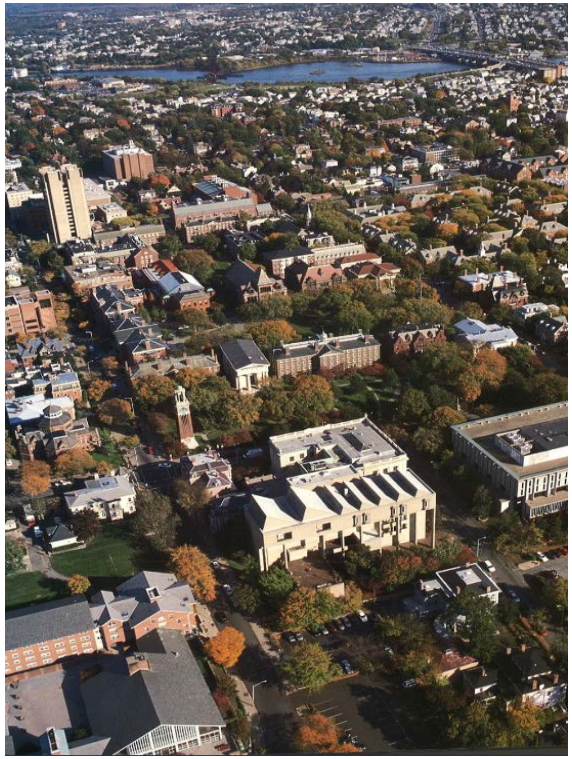
School of Engineering
Director, IMNI

Supported by research grants from NIEHS, US EPA, and NSF and training grants from NIEHS, the Department of Education, and the Superfund Research Program.

Institute for Molecular and Nanoscale Innovation

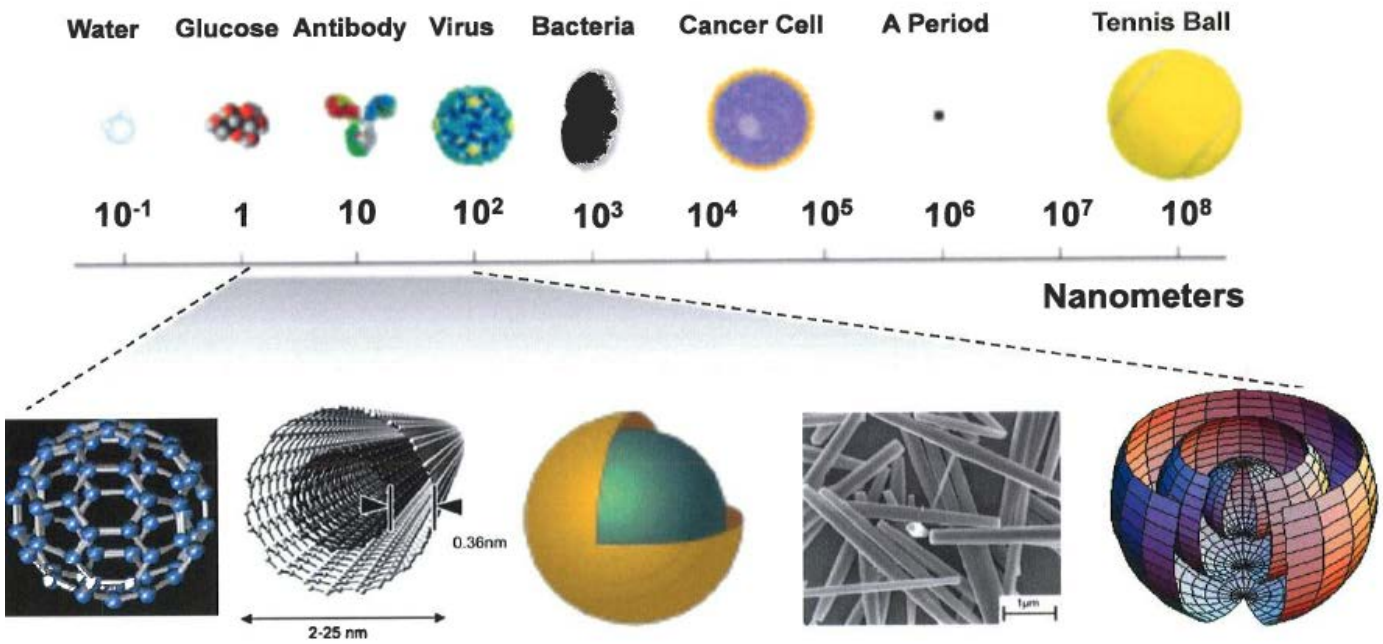
http://www.brown.edu/Departments/IMNI/



Brown University

NANOTECHNOLOGY

Working at the atomic, molecular and supramolecular levels, in the length scale of approximately 1-100 nm range, in order to understand and create materials, devices and systems with fundamentally new properties and functions because of their small structure. *Definition on http://nano.gov*



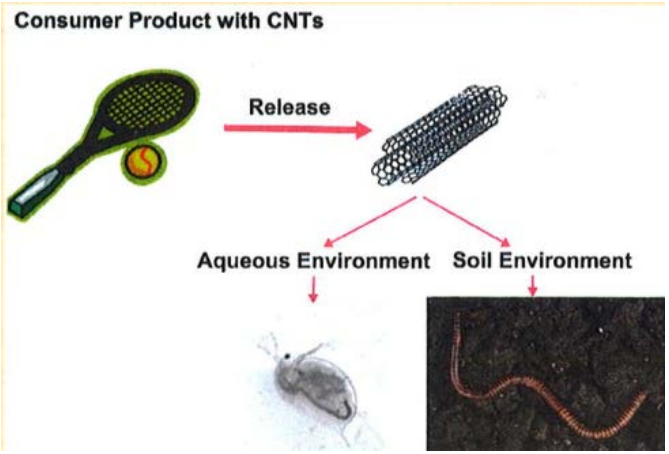
Modified from McNeil, 2005

NANOTECHNOLOGY: A POTENTIAL THREAT

A. Maynard, NIOSH

- Is Nanotechnology Dangerous? *Robert F. Service, Science, November 24, 2000*
- The Potential Environmental Impact of Engineered Nanomaterials. *Vicki L. Colvin, Nature Biotechnology, October, 2003*
- Researchers Find Nanotubes May Pose Health Risks Similar to Asbestos *The New York Times, May 21, 2008*

Nanotechnology research and development is an interdisciplinary enterprise, requiring the active involvement of engineers, chemists, physicists, and biologists to realize its full potential. Nanotechnology must also be developed responsibly, and this requires proactive management of its potential adverse effects on human health and the environment.



Barriers to Interdisciplinary Research

- Different traditions of teaching and learning
- Institutional expectations and conventions
- Different languages and terminology
- Establishing trust and mutual respect
- Uncertainty about funding publications

Franks et al., Studies in Higher Education, 2007

History of Asbestos-Related Diseases

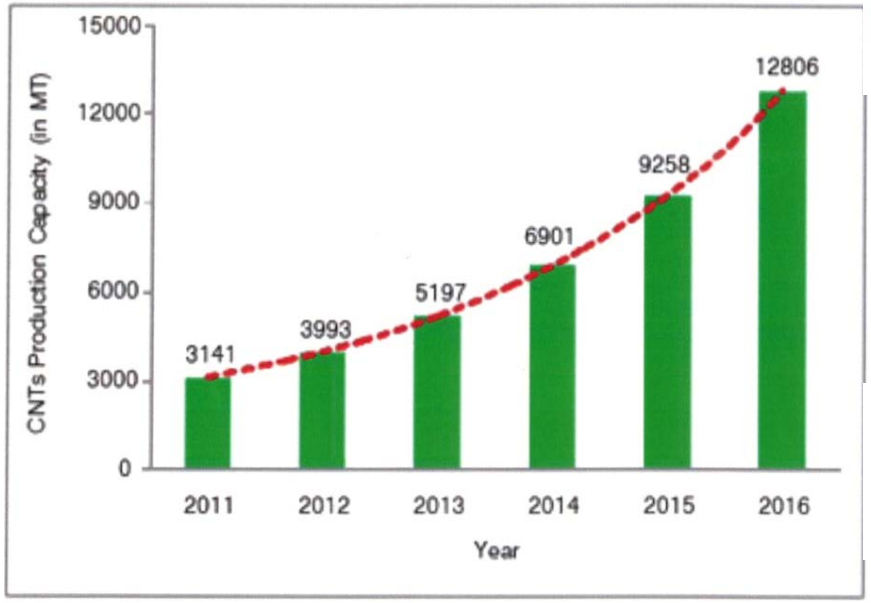
Becklake, Am. Rev. Resp. Dis. 114:187-227,1976

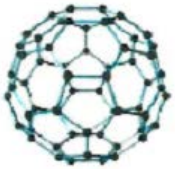
Disease	Established Casual Association
Asbestosis	1930
Lung Cancer	1955
Mesothelioma	1965
Cancer of Larynx	2006
Nanodiseases	????

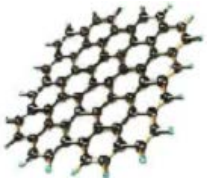
Libby, Montana: Superfund NPL, 2002

Projected Global Carbon Nanotube Market

www.nanowerk.com







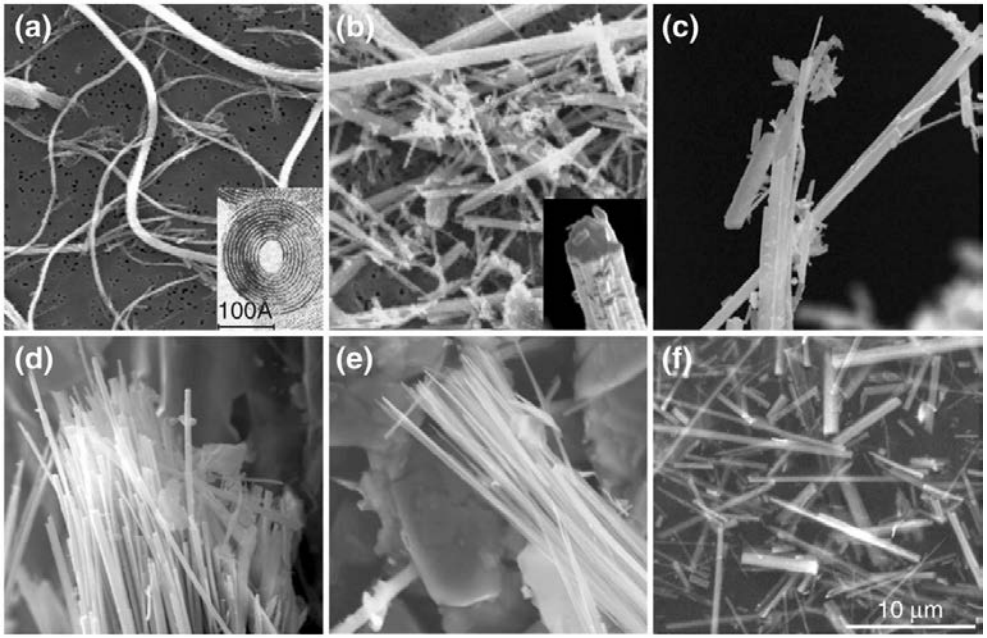
U.S. National Nanotechnology Initiative: $16.5 billion investment since 2001

1,300 commercial products: cars, sports equipment, electronics, batteries, sensors, defense, biomedical applications

THE ASBESTOS-CARBON NANOTUBE ANALOGY

Asbestos Fibers

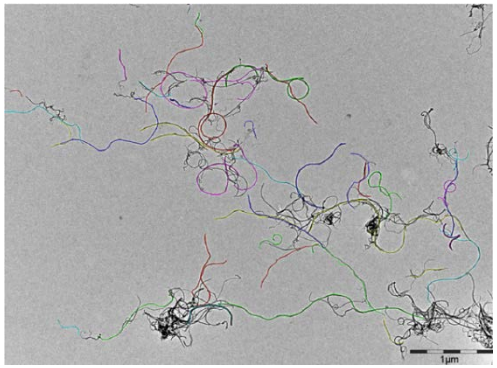
Chrysotile crocidolite anthophyllite

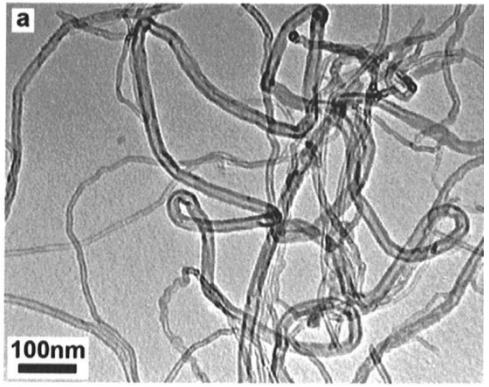


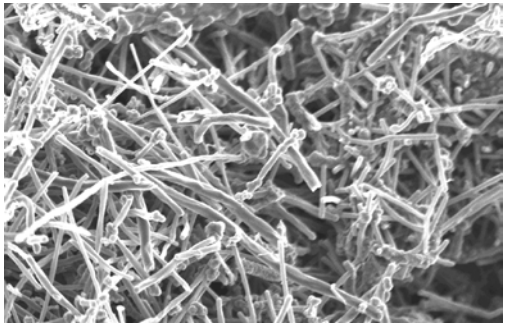
winchite-richterite tremolite amosite

U.S. Geological Survey

Carbon Nanotubes







Properties of Fibers Relevant for Biological Activity

1. **Surface reactivity**
2. **Durability and biopersistence**
3. **Fibrous shape and dimensions**

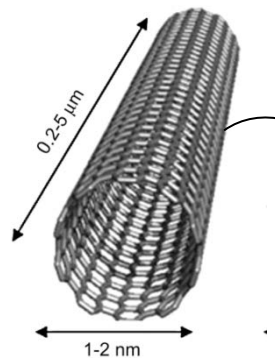
PROPERTIES OF FIBERS RELEVANT FOR BIOLOGICAL ACTIVITY

Surface Reactivity of Asbestos Fibers and Carbon Nanotubes

Crocidolite asbestos
$Na_2\ Fe^{2+}{}_3Fe^{3+}{}_2\ (Si_8O_{22})(OH)_2$

Fenton chemistry:

$$H_2O_2 \xrightarrow{Fe^{2+}} OH^{\bullet}$$

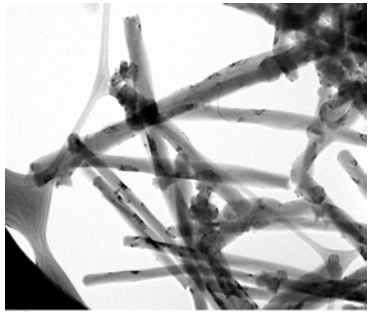


Reilly *et al* (2007) JNM, 48: 1039-1042

Surface e- donor:

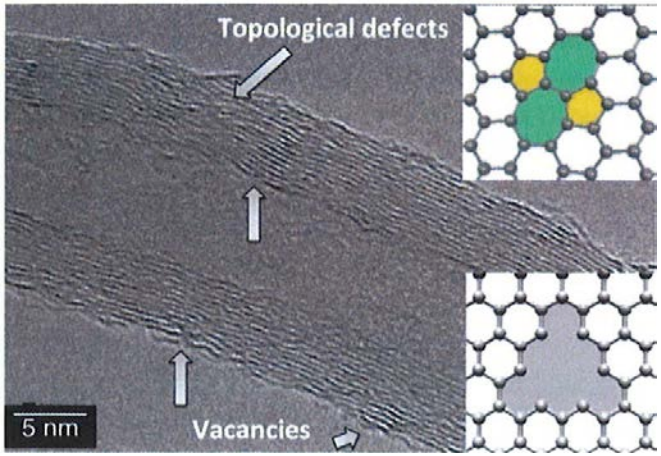
$$O_2 \xrightarrow{e^-} O^{-\cdot}{}_2$$

Iron Catalyst Residues

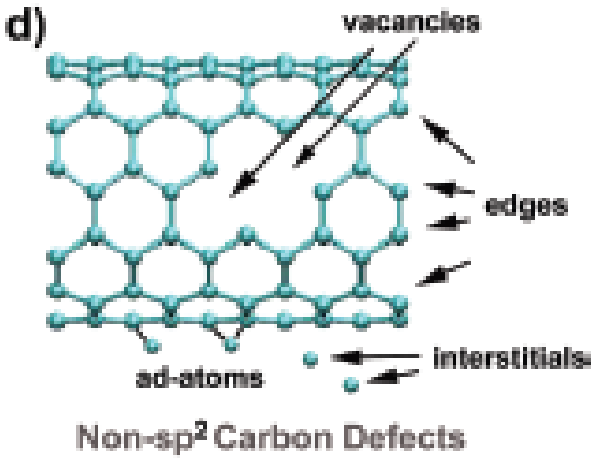


Carbon nanotubes

Surface Defects and Impurities in Carbon Nanotubes



Stone-Thrower-Wales defects

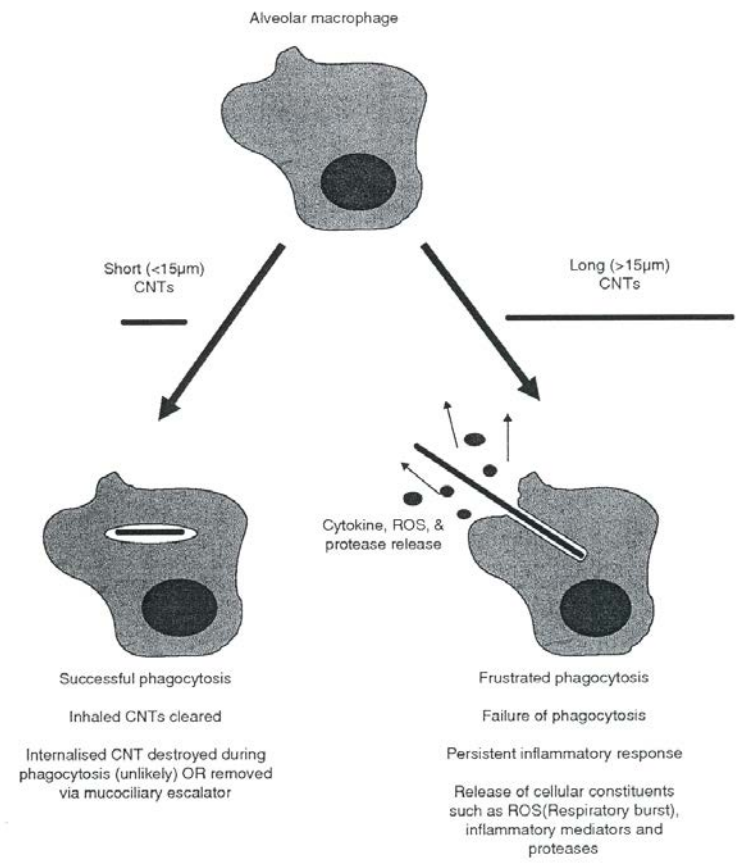


Terrones, ACS Nano, 2010

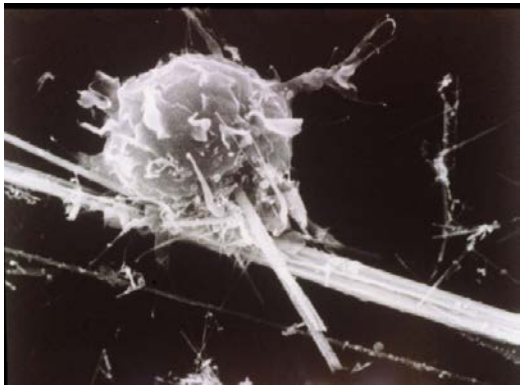
PROPERTIES OF FIBERS RELEVANT FOR BIOLOGICAL ACTIVITY

Fibrous Shape and Dimensions

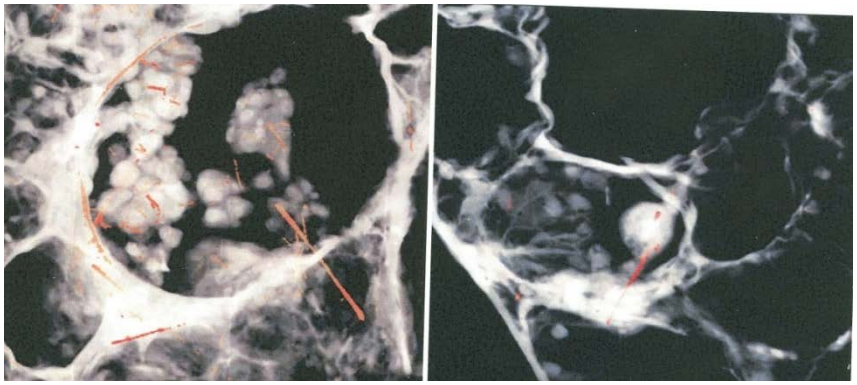
Long Fibers Induce Frustrated Phagocytosis and Impair Clearance



Incomplete or Frustrated Phagocytosis by Macrophages



Penetration into Alveolar Walls



J. Brain, Harvard School of Public Health

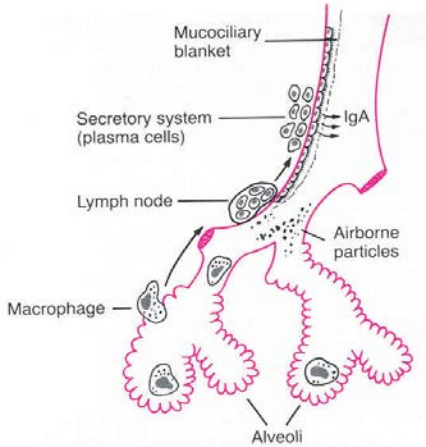
Johnston HJ, Hutchison GR, Christensen FM, Peters S, Hankin S, et al. "A Critical Review of the Biological Mechanisms Underlying the in Vivo and in Vitro Toxicity of Carbon Nanotubes: The Contribution of Physico-chemical Characteristics." Nanotoxicology 4, 207-46, 2010.

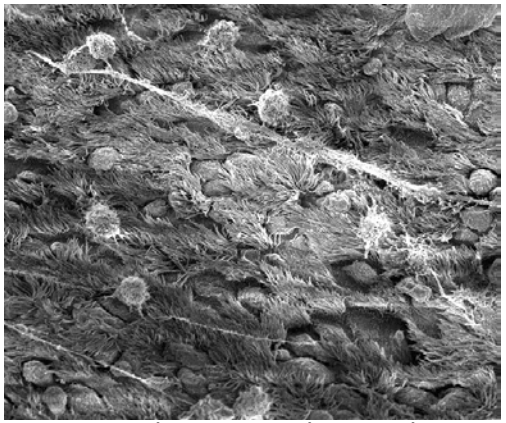
INTRATRACHEAL INSTILLATION OF CARBON NANOTUBES CAUSES IMPAIRED LUNG CLEARANCE AND TRANSLOCATION TO THE PLEURAL SPACE

Alison Elder and Gunter Oberdorster, University of Rochester

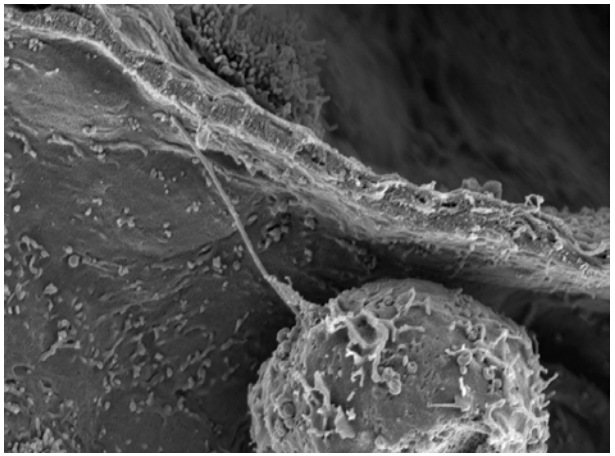
Lung Clearance Mechanisms

Daniele, Immune defenses of the lungs, 1988



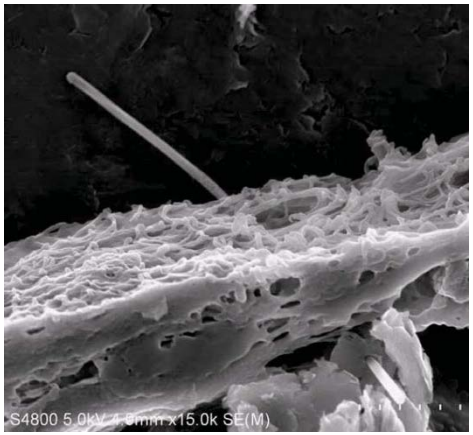


Long carbon nanotubes on the mucociliary escalator after 7 days



Frustrated phagocytosis of a carbon nanotube by an alveolar macrophage after 7 days

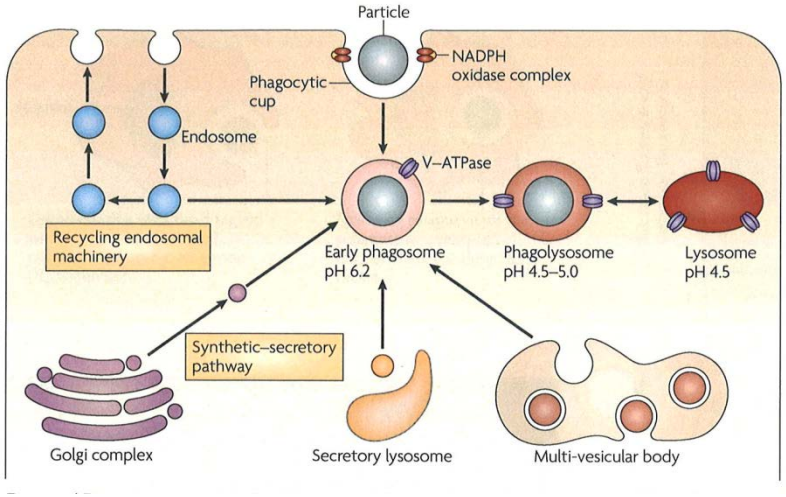
Penetration Into the Pleural Space



Robert Mercer, NIOSH SEM

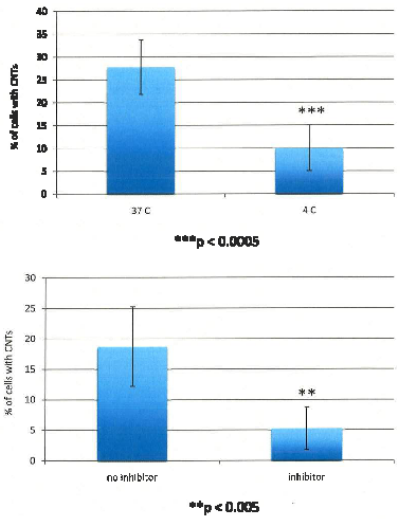
HOW DO FIBROUS NANOSTRUCTURES ENTER CELLS?

Endocytosis and Phagocytosis



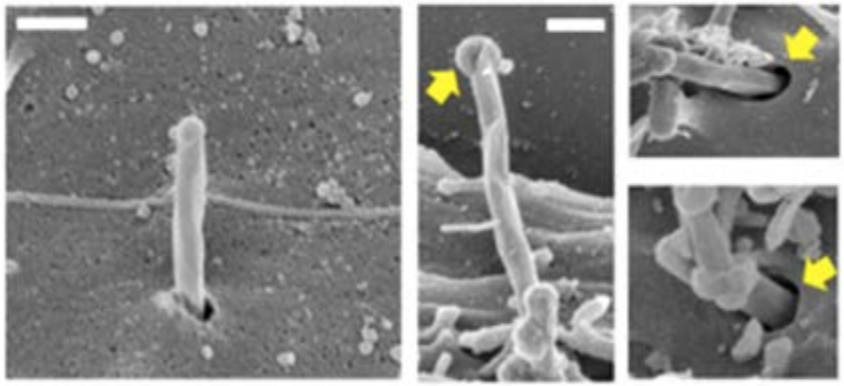
Russell et al. Nat. Rev. Immunol. 9:594, 2009

Energy-Dependent Endocytosis of Carbon Nanotubes by Liver Cells



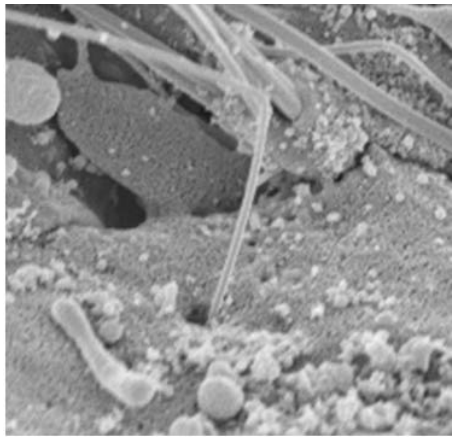
Incomplete Uptake or Frustrated Endocytosis

Carbon Nanotubes

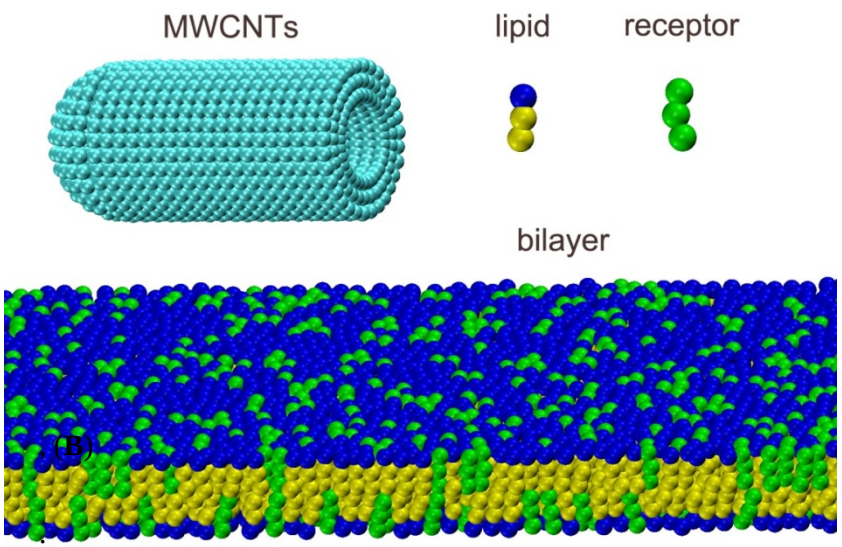


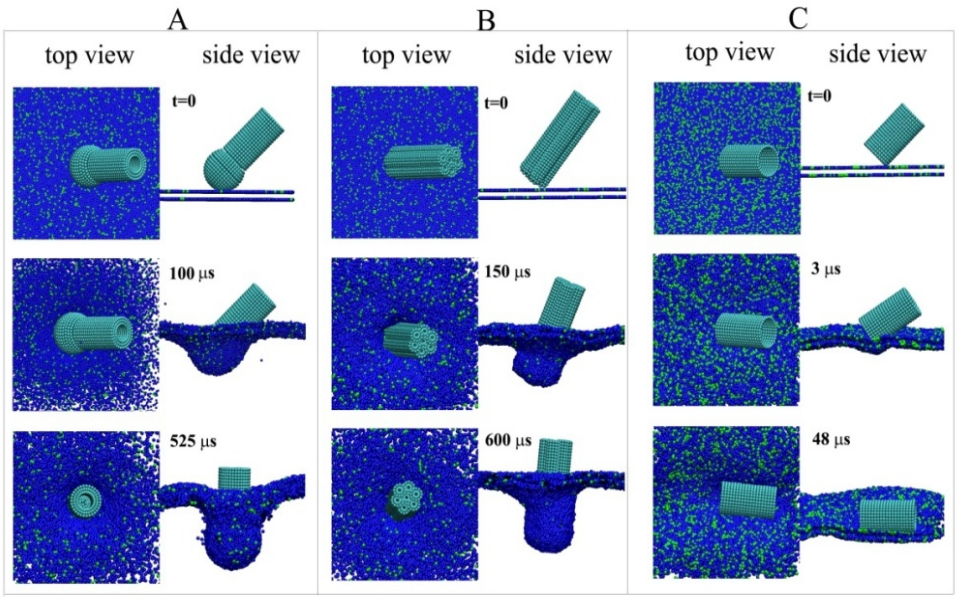
Shi et al. Nat. Nanotech. 18:714, 2011

Gold Nanowires



MOLECULAR DYNAMICS SIMULATION OF ENDOCYTOSIS OF CARBON NANOTUBES



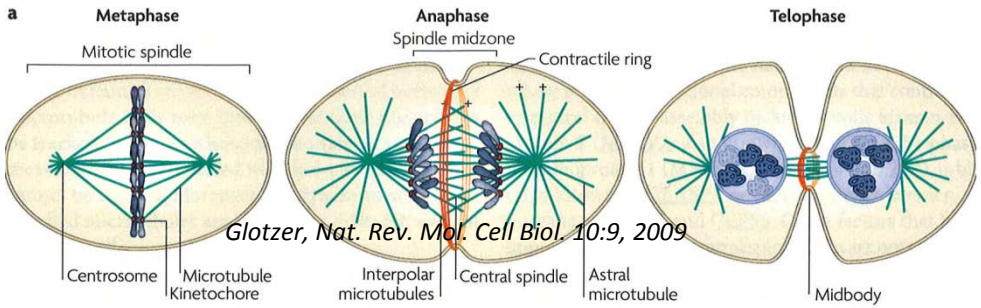


capped nanotube nanotube bundle uncapped bundle

- Capped carbon nanotubes are recognized as spheres by target cells.
- Elastic strain in the plasma membrane provides a driving force to rotate fibrous nanostructures to a high contact angle to minimize total elastic energy.
- If side walls contact the cell membrane, receptor density is not high enough to initiate endocytosis.

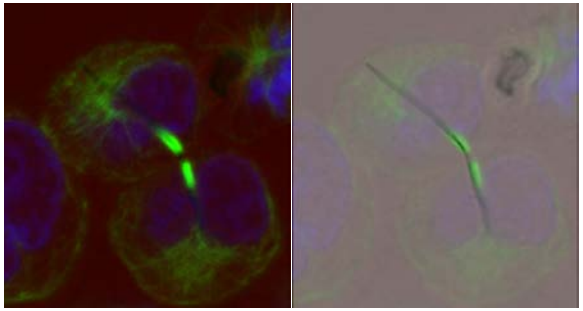
Xinghua Shi, Annette Von dem Bussche, Robert Hurt, Agnes Kane, Huajian Gao
School of Engineering and Department of Pathology and Laboratory Medicine
Nat. Nanotechnol. 18: 714-719, 2011

ASBESTOS FIBERS AND CARBON NANOTUBES INDUCE MICRONUCLEI AND MITOTIC ABNORMALITIES IN HUMAN LUNG EPITHELIAL CELLS

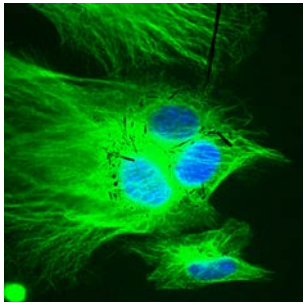


Glotzer, Nat. Rev. Mol. Cell Biol. 10:9, 2009

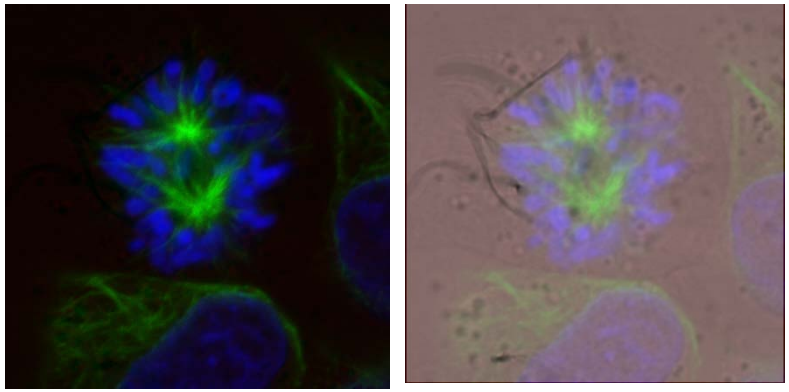
Microtubules-green fluorescence; nuclei and chromosomes-blue fluorescence



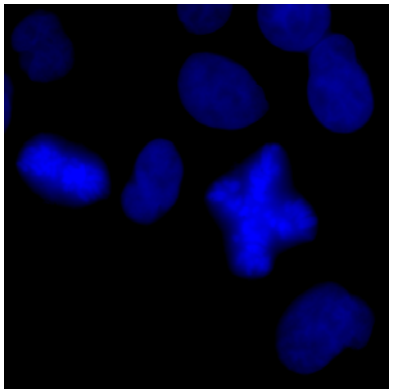
Carbon nanotube localized in midbody. Confocal microscopy- fluorescence and DIC.



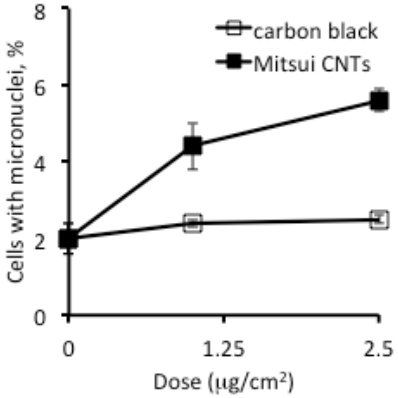
Carbon nanotubes induce multinucleated daughter cells.



Carbon nanotubes interfere with chromosomal segregation. Confocal microscopy- fluorescence and DIC.

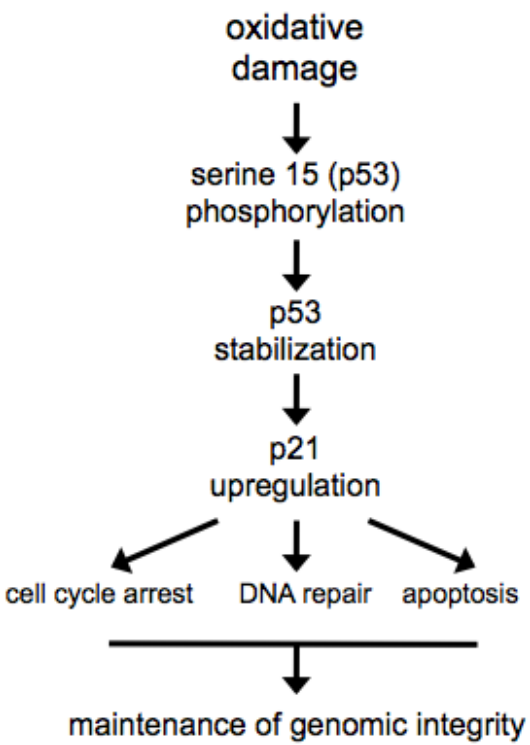


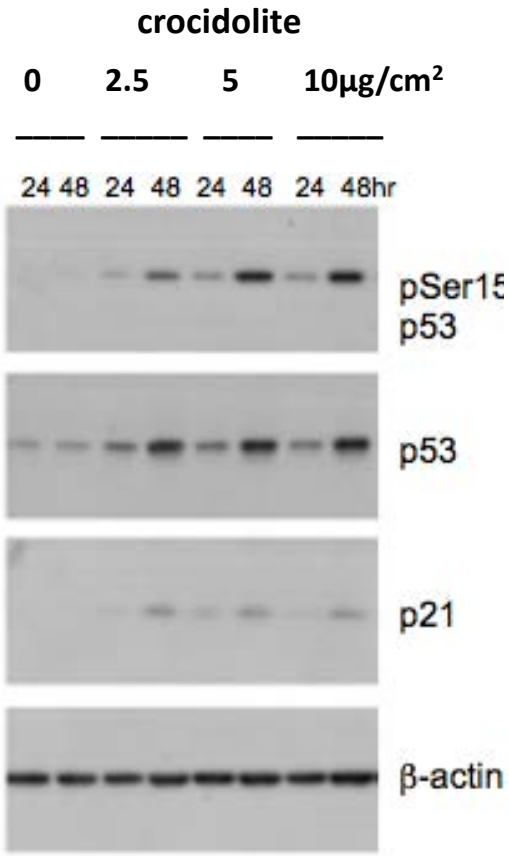
Asbestos fibers induce multipolar mitoses.



Lagging chromosomes produce micronuclei in daughter cells

ASBESTOS FIBERS AND CARBON NANOTUBES ACTIVATE OXIDATIVE STRESS, INFLAMMATORY, AND DNA DAMAGE PATHWAYS





Unregulated Gene Expression

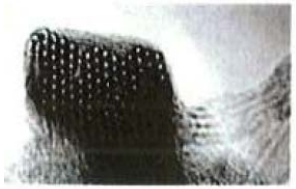
Pathway	Asbestos	CNTs
Oxidative Stress:		
Superoxide dismutase	10x	10X
Glutathione reductase	3x	4x
Glutathione-peroxidase	4x	6x
DNA Damage:		
BCL2	3x	9x
GADD45	---	2.4x
Sestrin	3x	7x
Inflammation:		
Cyclooxygenase 2	7.5x	10x
RANTES	8x	9x
IL-6	34x	110x

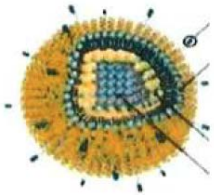
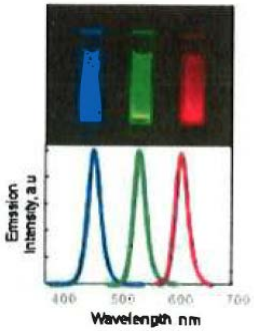
Pietruska et al., XRCCI deficiency sensitizes human lung cells to genotoxicity by crocidolite asbestos and Libby amphibole Environ. Health Perspect. 118:1707, 2010

INTERDISCIPLINARY TEACHING AND RESEARCH

Small Wonders -- Science, Technology, and Human Health Impacts of Nanomaterials

EN2910 – S01 and BIOL2840G – S01

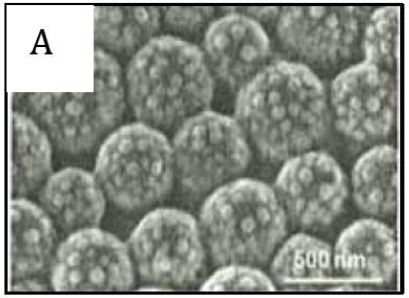


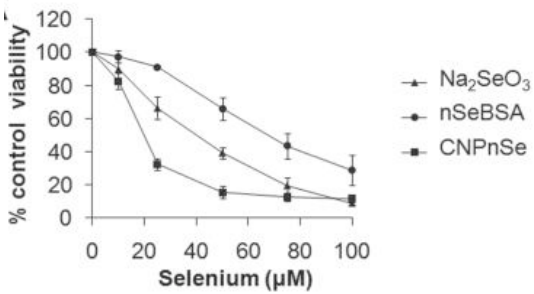



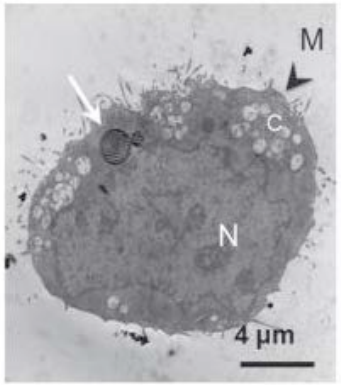
<u>Instructors</u>
Professor Robert Hurt, Engineering
Professor Agnes Kane, Pathology and Laboratory Medicine

Selenium – Carbon Nanoparticles for Treatment of Malignant Mesothelioma

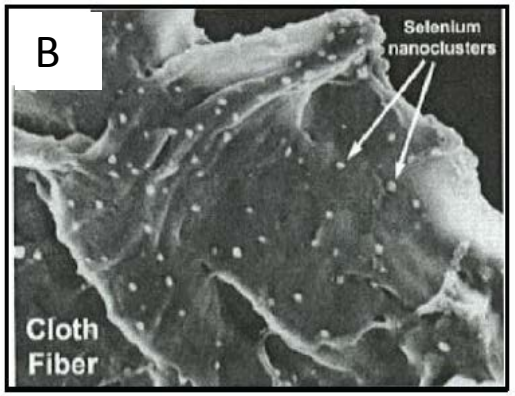
Vanesa Sanchez, Pathobiology Graduate Student and Love Sarin, Engineering Graduate Student *Sarin et al. Advanced Materials 10: 5207-5211, 2010*



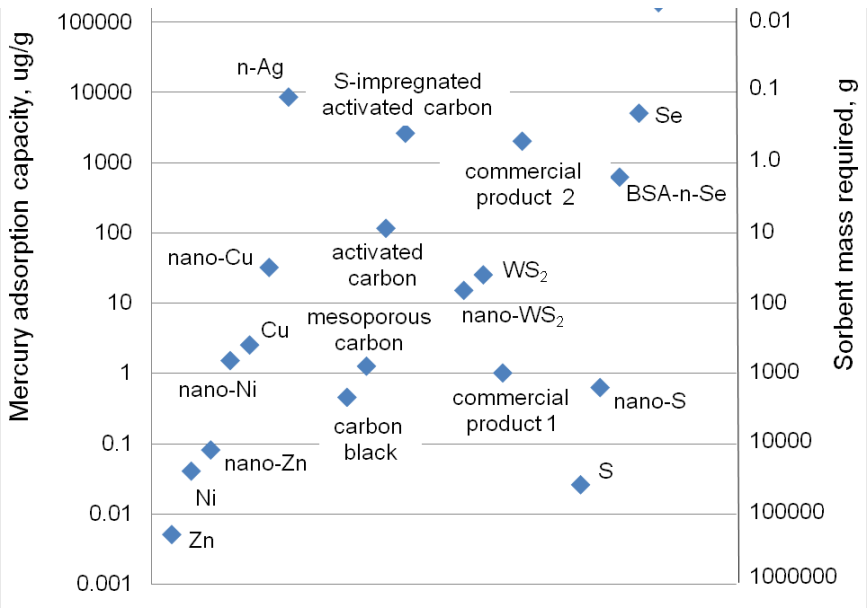




SELENIUM NANOPARTICLES FOR CAPTURE OF MERCURY VAPOR

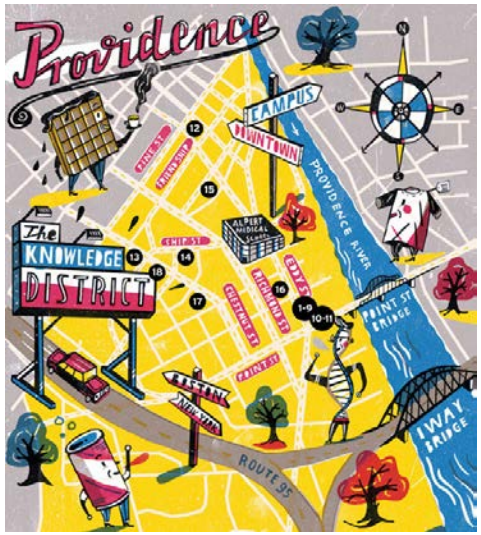


Lee et al., Environ Sci Technol 43: 5912-5920, 2009



Johnson et al., Environmental Science and Technology, 2008

Love Sarin, Ph.D.
Founder and President
Banyan Environmental, Inc.
Providence, RI



Transition from an Industrial to a Knowledge-Based Economy in Rhode Island

Interdisciplinary Training in Applications and Implications of Nanotechnology

Department of Education GAANN Training Grant, 2009-2014

Director: Robert Hurt, Ph.D.
Co-Director: Agnes B. Kane, M.D., Ph.D.

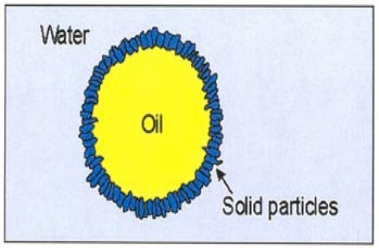
1. Supports predoctoral students who will pursue interdisciplinary research and teaching in the applications and implications of nanotechnology.
2. GAANN fellows will be supervised by co-mentors who are actively engaged in externally-funded research on the nano-bio interface, nanoscale imaging, nanoscale tissue engineering, and the environmental and human health impacts of nanotechnology.

Megan Creighton (left)
Robert Hurt (mentor-right)

GANN FELLOW

MEGAN CREIGHTON
Graduate Student/Engineering
Co-Mentors:
Robert Hurt/Agnes Kane
Thesis Topic:
Nanoparticle-based dispersants to stabilize oil-water emulsions
Funding:
Gulf of Mexico Research Institute

Deepwater Horizon Disaster, 2010



APRIL RODD

Institute for Molecular and Nanoscale Innovation

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Summary

1. Nanotechnology has applications for energy generation, electronics, medicine, aerospace, and defense.
2. Cell toxicity and adverse health effects are potential implications of nanotechnology.
3. The physical and chemical properties of nanomaterials responsible for cell toxicity are related to geometry, length, surface redox reactivity and biopersistence.
4. Commercial carbon nanotubes induce DNA damage and mitotic abnormalities in lung epithelial cells and mesothelial cells similar to asbestos fibers.

How can engineers minimize adverse environmental and health impacts: "safety by design" ?

NIEHS

Superfund Research Program