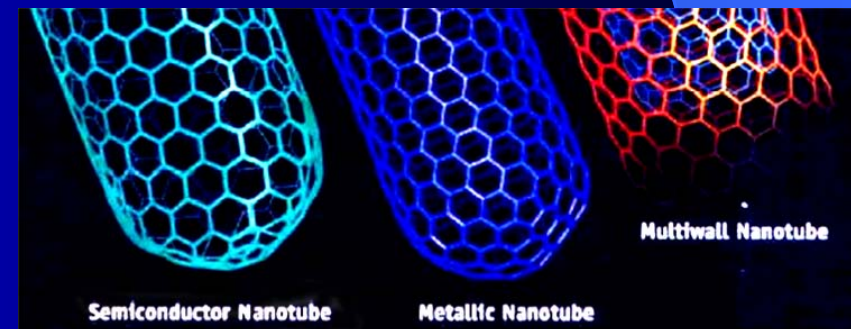


# *Health Risk Assessment of Manufactured Nanomaterials: More Than Just Size*

Kevin Dreher, Ph.D.  
National Health and Environmental Effects Laboratory  
U.S. Environmental Protection Agency  
Research Triangle Park, NC  
[dreher.kevin@epa.gov](mailto:dreher.kevin@epa.gov)

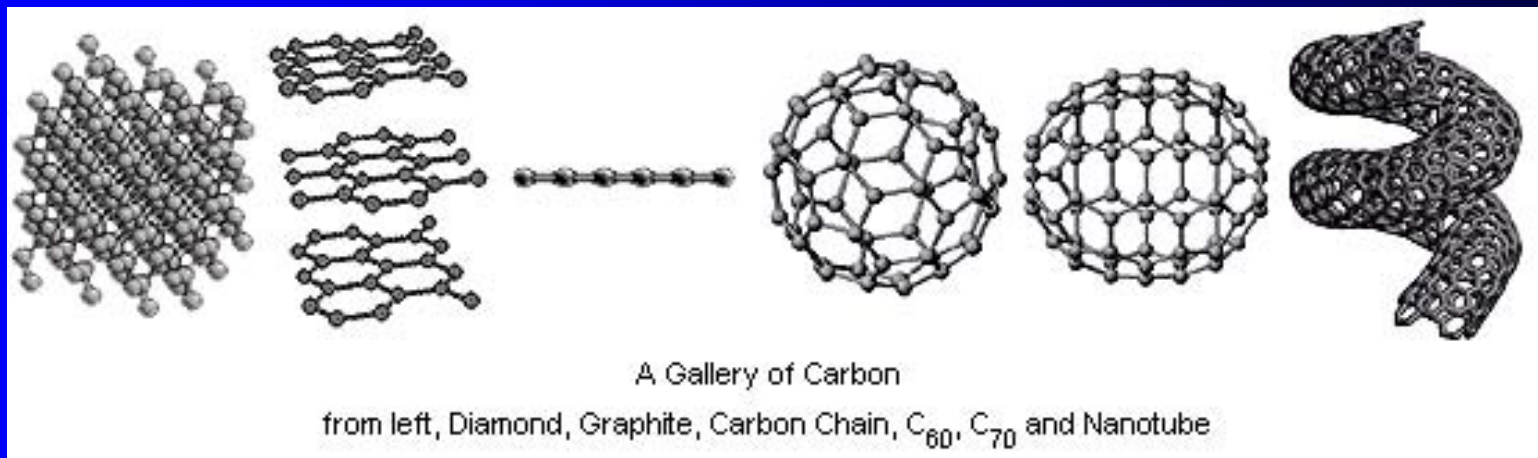
Nanotechnology for Remediation Technical  
Workshop  
US Department of Commerce  
Oct. 20-21, 2005  
Washington, DC



# Health Risk Assessment of Nanomaterials

## *Outline*

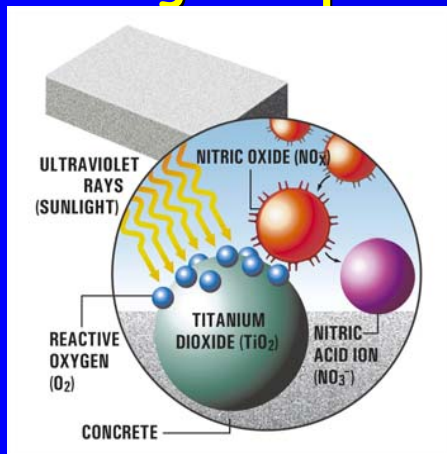
1. Nanotechnology and Air Pollution Control
2. Uncertainties in Nanotechnology Risk Assessment
3. Toxicity of Nanomaterials (Nanotoxicology):
  - CNTs, fullerenes, dendrimers, nano-metals
  - focus on health effects
  - insights into factors regulating particle toxicity:  
"more than just size" and "unique toxicities"
4. Summary



# Health Risk Assessment of Nanomaterials

*Air Pollution Control: Photo-Catalytic Nano-TiO<sub>2</sub>, ZnO*

**Paving and painting out pollution**



**Self cleaning glass/surfaces**



-2002, nanoTiO<sub>2</sub>\cement, Milan, Italy, 60% decrease in near road side NO<sub>x</sub> levels

-Second Generation: Doped with V, Pd, or Nd allows photo-catalytic activity with sun light

-EU Photocatalytic Innovative Coverings Applications for Depollution Assessment (PICADA) NO<sub>x</sub> reduction



**Air**

*Environmental Interactions, Transformations, and Fate?  
Potential Health Effects?*

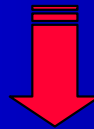
# Health Risk Assessment of Nanomaterials

*Air Pollution Control: Nano-metals  
(Al<sub>2</sub>O<sub>3</sub>; Transition Metals; CeO<sub>2</sub>: 5 - 10nm)*

*Fuel Additives: Better Fuel Economy and Reduced Emissions*

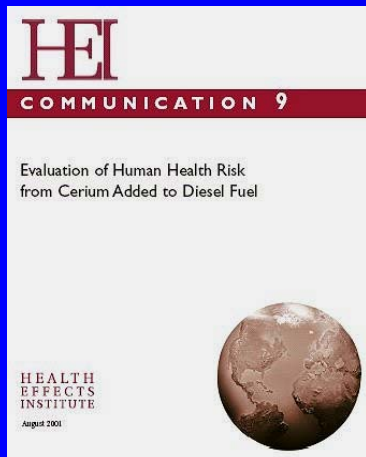


- On and Off Road Diesel\Gas Additive:
  - Oxonica: Envirox® (nano-Cerium Oxide; 10nm);
  - Nanotech Fuel Corporation: Fuel Reformulator
- Dept. of Defense



*Air*

*Environmental Interactions, Transformations, Fate?  
Potential Health Effects?*



**Diesel Exhaust:**

- ↑ >50% in each: benzene; 1,3-butadiene; acetaldehyde (Air Toxics)
- ↓ 80% PAHs (Air Toxic)
- ↓ 8-20% NO<sub>x</sub> (NAAQ)
- ↑ 50-100% CO (NAAQ)

# Risk Assessment of Nanotechnology

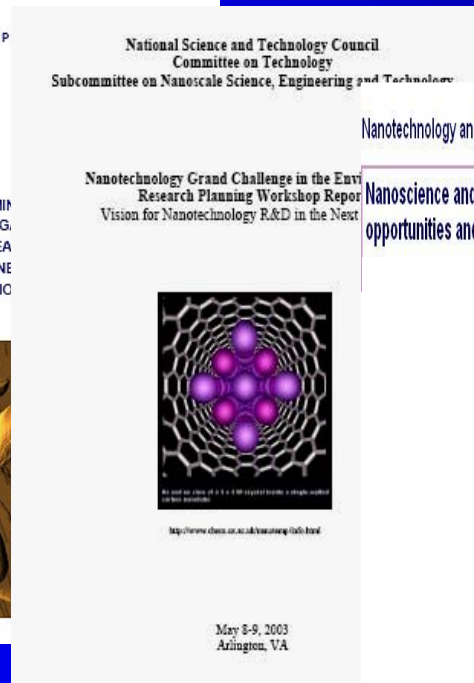
## Reports: Uncertainties in Nanotechnology Risk Assessment



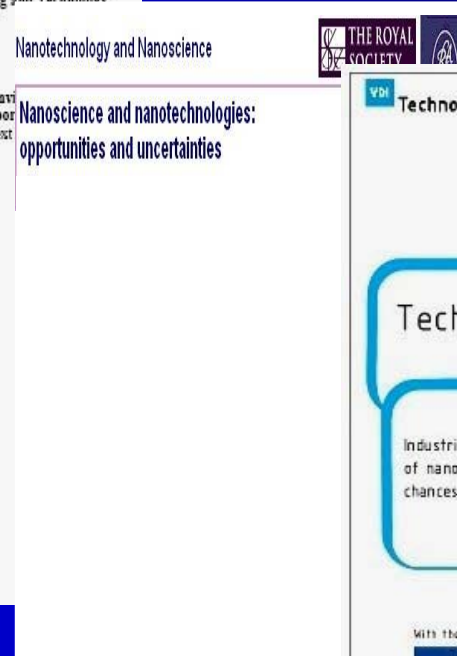
**Spring, 2004  
Swiss Report  
Reinsurance  
Company**



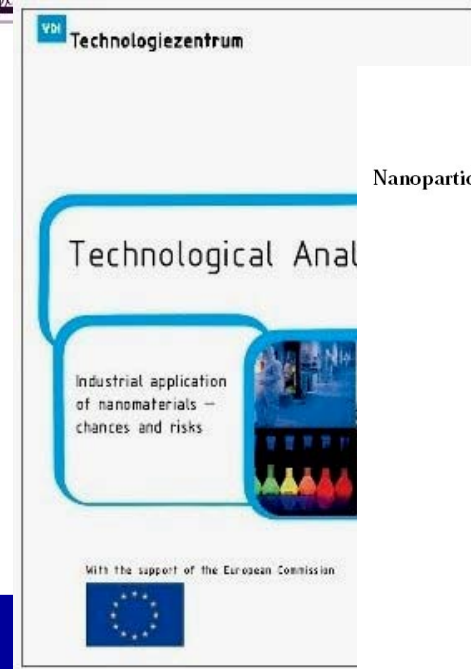
**2004  
European  
Commission**



**April 2004  
NNI Report  
Grand Challenge:  
"Nanotechnology in  
the Environment"**



**July 2004  
UK Royal  
Society  
Report**



**August 2004  
German  
NanoSafe  
Report**



**Nov. 2004  
UK HSE  
Report**

# Risk Assessment of Nanotechnology

## Publications: Uncertainties in Nanotechnology Risk Assessment

### TOXICOLOGICAL HIGHLIGHT

Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles

Karin L. DeWalt<sup>1</sup>

<sup>1</sup>Atlanta South of Emory Research Laboratory, US Environmental Protection Agency



### Nanotechnology: Looking As We Leap

The articles highlighted in this issue of "Publications" of Single-Wall Carbon Nanotubes in May 7 and 9/ Days after Introduction published by Chu-Wing Lam, John T. James, Robert McChesney, and Robert L. Hazen (pp. 125-31) and "Comparative Pulmonary Toxicity Assessment of Single-Wall Carbon Nanotubes" by D. B. Warburton, B. R. Larrance, K. L. Road, D. H. Raach, G. A. M. Reynolds, and T. R. Webb (pp. 117-125).

In an effort to coordinate research and application across various disciplines, the National Center for Environmental Health Research Laboratory, US Environmental Protection Agency, is publishing this special issue. The articles in this issue are intended to provide a comprehensive overview of the current state of nanotechnology research and its potential applications. The articles are organized into three main sections: (1) Environmental Health Research, (2) Environmental Policy, and (3) Environmental Education. The articles in this issue are intended to provide a comprehensive overview of the current state of nanotechnology research and its potential applications.

Manufactured nanoparticles and nanotubes that are currently being used in a wide variety of consumer products, including cosmetics, food, and pharmaceuticals. The articles in this issue are intended to provide a comprehensive overview of the current state of nanotechnology research and its potential applications.

**Dreher, Hood, Perspect., 2004**  
**Hood, Environ. Hlth. Perspect., 2004**  
**Oberdorster et al., Environ. Hlth. Perspect., 2005**

### Review

#### Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles

Joseph J. Schauer, et al. Environmental Health Perspectives 113(11):1508-1510 (2005)

Although nanotechnology has captured the imagination of the public, its potential for harm is still uncertain. This review examines the current state of knowledge on the toxicity of ultrafine particles (UFPs) and discusses the challenges of nanotoxicology. UFPs are particles with diameters less than 2.5 micrometers (µm) and are found in both indoor and outdoor environments. They are known to be highly reactive and can penetrate deep into the lungs, where they can cause inflammation and oxidative stress. The review discusses the need for further research on the toxicity of UFPs and the challenges of nanotoxicology.

### CRITICAL REVIEW

#### Nanoparticles and the Environment

Pravin Biswas, et al. Environmental Science and Technology 39(10):1107-1115 (2005)

This critical review examines the environmental impacts of nanoparticles. It discusses the sources, transport, and fate of nanoparticles in the environment. It also discusses the potential for nanoparticles to cause environmental damage and the need for further research on their toxicity. The review highlights the challenges of studying the environmental impacts of nanoparticles and the need for a multidisciplinary approach to this research.

### ARTICLE IN PRESS

#### Cleaner nanotechnology and hazard reduction of manufactured nanoparticles

L. Reijnders, et al. Environmental Health Perspectives 113(11):1511-1514 (2005)

This article discusses the need for cleaner nanotechnology and the reduction of hazards associated with manufactured nanoparticles. It discusses the challenges of studying the toxicity of nanoparticles and the need for a multidisciplinary approach to this research. The article highlights the need for further research on the toxicity of nanoparticles and the need for a multidisciplinary approach to this research.

### FORUM SERIES

#### Research Strategies for Safety Evaluation of Nanoparticles: Part I. Evaluating the Human Health Implication to Nanoscale Materials

Kathryn Thomas, et al. Environmental Health Perspectives 113(11):1515-1520 (2005)

This forum series discusses research strategies for the safety evaluation of nanoparticles. It discusses the challenges of studying the toxicity of nanoparticles and the need for a multidisciplinary approach to this research. The forum series highlights the need for further research on the toxicity of nanoparticles and the need for a multidisciplinary approach to this research.

### DISCUSSION

#### Challenges Associated with Nanoscale Materials

This discussion highlights the challenges associated with nanoscale materials. It discusses the need for further research on the toxicity of nanoparticles and the need for a multidisciplinary approach to this research. The discussion highlights the need for further research on the toxicity of nanoparticles and the need for a multidisciplinary approach to this research.

### INFORMATION

#### Nanotechnology: The Great Potential for Improving Environmental Protection

This information section discusses the potential of nanotechnology for improving environmental protection. It discusses the challenges of studying the toxicity of nanoparticles and the need for a multidisciplinary approach to this research. The information section highlights the need for further research on the toxicity of nanoparticles and the need for a multidisciplinary approach to this research.

### Research Strategies for Safety Evaluation of Nanomaterials, Part IV: Risk Assessment of Nanoparticles (Symposium Summary)

Joey S. Tsuij, Andrew D. Maynard, Paul C. Howard, John T. James, Chu-Wing Lam, David B. Warburton, Annette B. Sastanari

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<sup>3</sup>Woodrow Wilson International Center for Scholars, Washington, DC 20004-3007

<sup>4</sup>maynard@wwic.edu

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<sup>6</sup>paull.howard@hhs.gov

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<sup>10</sup>Chu-Wing.Lam@jsc.nasa.gov

<sup>11</sup>DuPont Haskell Laboratory, Newark, DE 19714; david.b.warburton@usdot.gov

<sup>12</sup>Environ@haskell.com; 77002\_sastanari@enviroincorp.com

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### 1. Introduction

Nanotechnology is characterized by the use of small manufactured particles (0-100 nm), which are called nanoparticles or ultrafine particles. It has been argued that nanotechnology holds the promise to define the concept of "zero and pollution" (1). As a new material use it has been suggested that nanotechnology promises to drastically reduce consumption of energy such as solar cells and will make much needed improvements in clean technology applications (2). Nanotechnology has also been argued to allow for greater selectivity in chemical reactions, and

to contribute to improved energy efficiency (3). However, the emergence of nanotechnology is not without risks. The use of ultrafine particles (UFPs) as a new material use it has been suggested that nanotechnology promises to drastically reduce consumption of energy such as solar cells and will make much needed improvements in clean technology applications (2). Nanotechnology has also been argued to allow for greater selectivity in chemical reactions, and

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### 2. Environmental Protection

The environmental protection of nanotechnology is a topic that is receiving increasing attention. It is clear that the use of nanoparticles in a wide variety of consumer products, including cosmetics, food, and pharmaceuticals, has the potential to cause environmental damage. It is therefore essential that we take steps to protect the environment from the potential hazards of nanoparticles. This requires a multidisciplinary approach to this research, involving scientists from a wide range of disciplines, including toxicology, environmental health, and public health.

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**Tsuji et al., Toxicol Sci., 2005**

**Thomas & Sayre, Toxicol Sci., 2005**

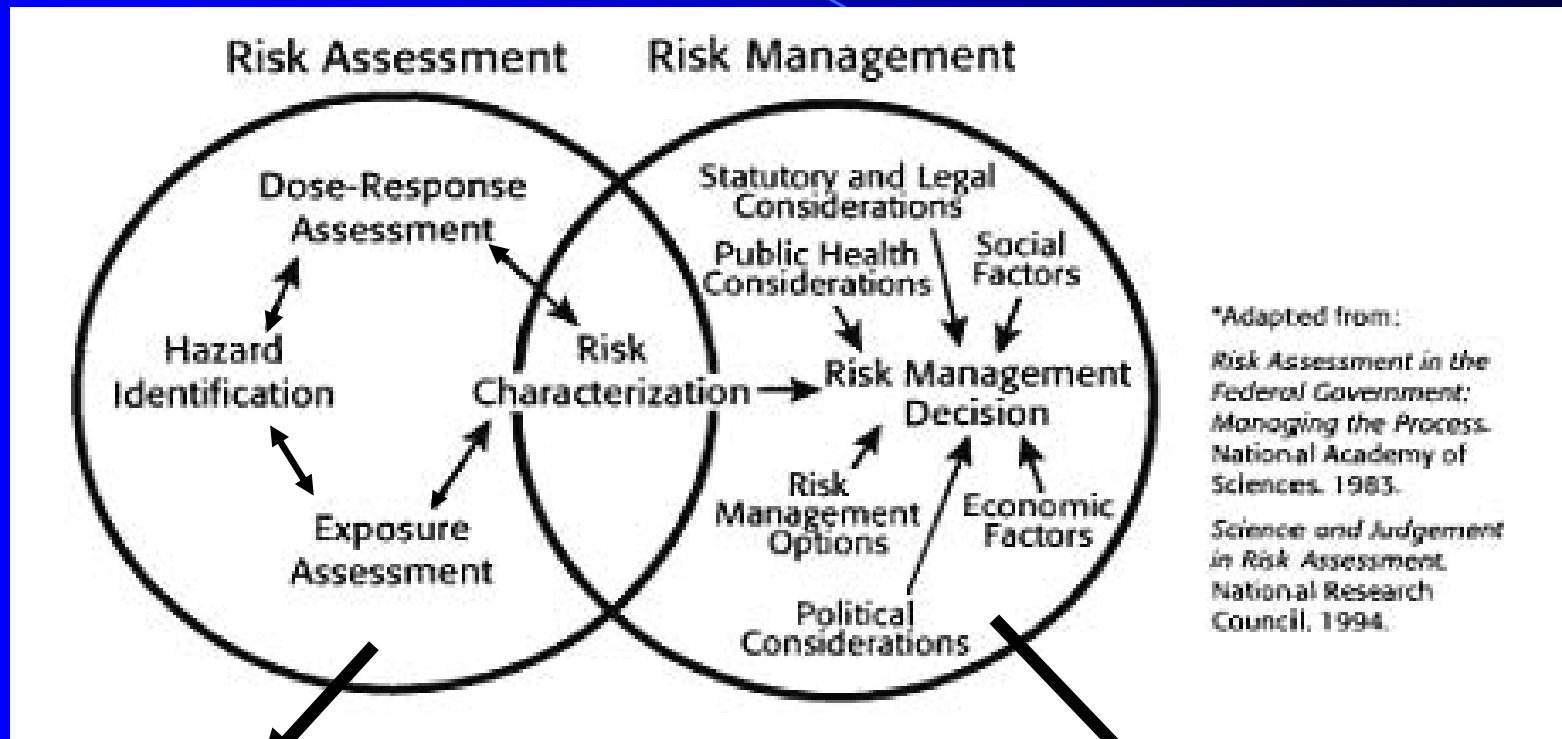
**Biswas & Wu, J. AWMA, 2005**

**J. Cleaner Production, 2005**

**Reijnders, J. Cleaner Production, 2005**

# Risk Assessment of Nanotechnology

## *Uncertainties*



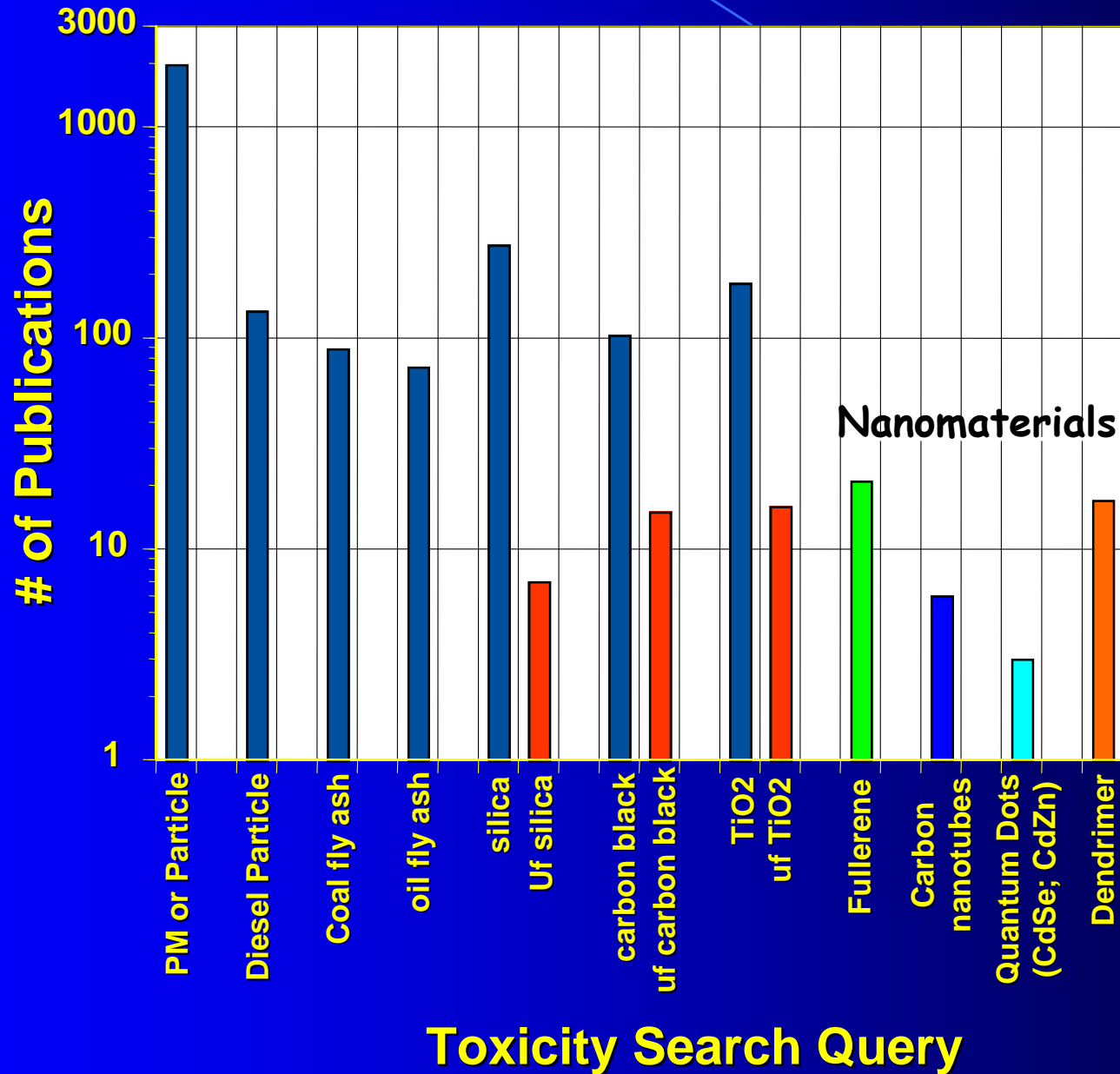
- ➔ - Health, Ecological, Environmental Effects
- ➔ - Hazard Identification (tox. metric)
- Nomenclature
- Exposure/Detection
- Fate, Transport, Transformation
- Waste Generated
- Production Volume

- Worker Protection
- Spill Clean Up and Monitoring
- Chemical Hygiene Plans
  - worker protection
  - handling waste
  - monitoring
  - spill control and clean up

# Health Risk Assessment of Nanomaterials

*What do we know about nanoparticle toxicology?*

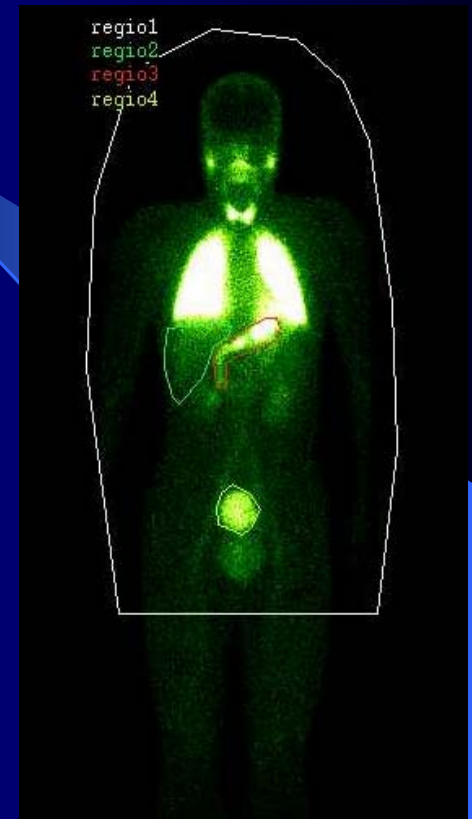
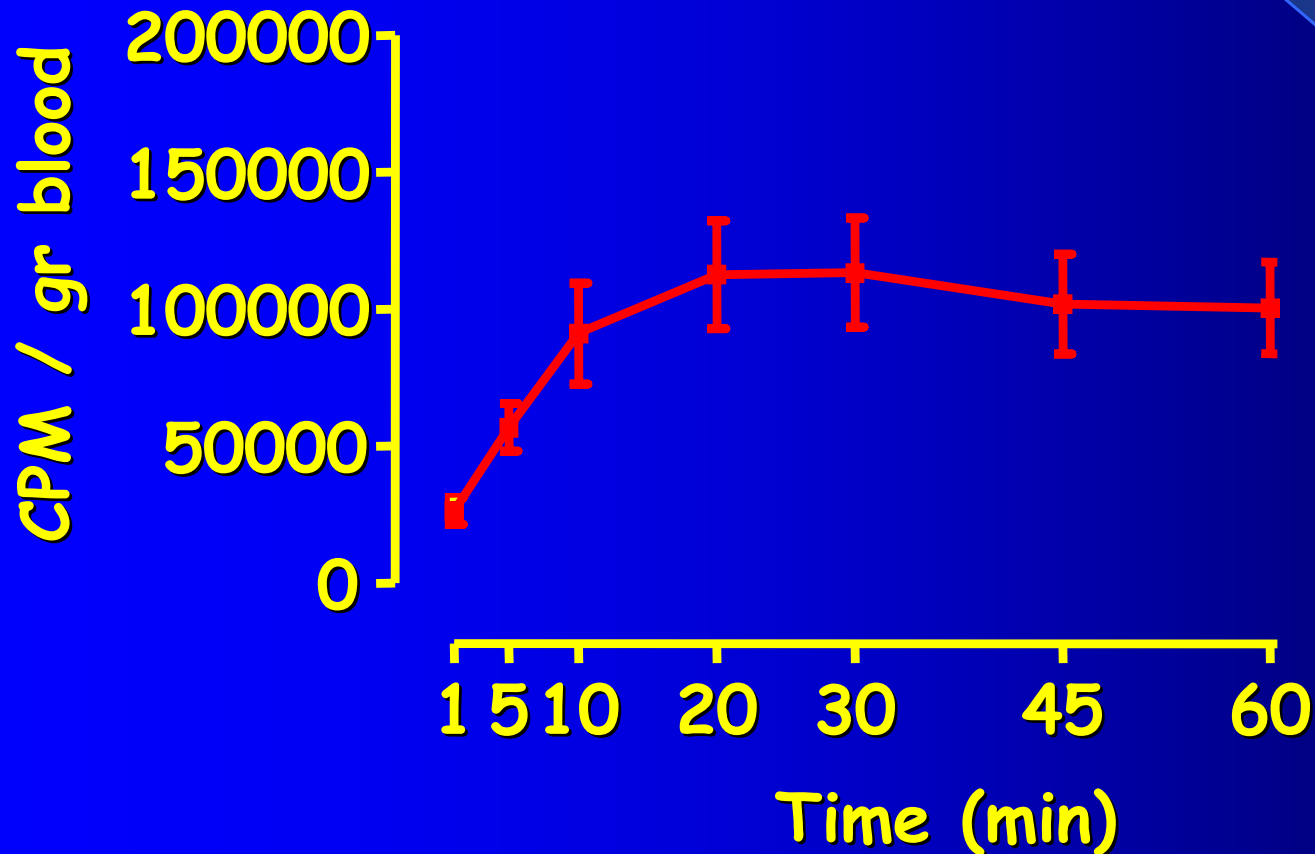
Particle Toxicology Database: PubMed 2004-1982





# Health Risk Assessment of Nanomaterials

*Size: Deposition, Translocation and Fate of Nanoparticles*

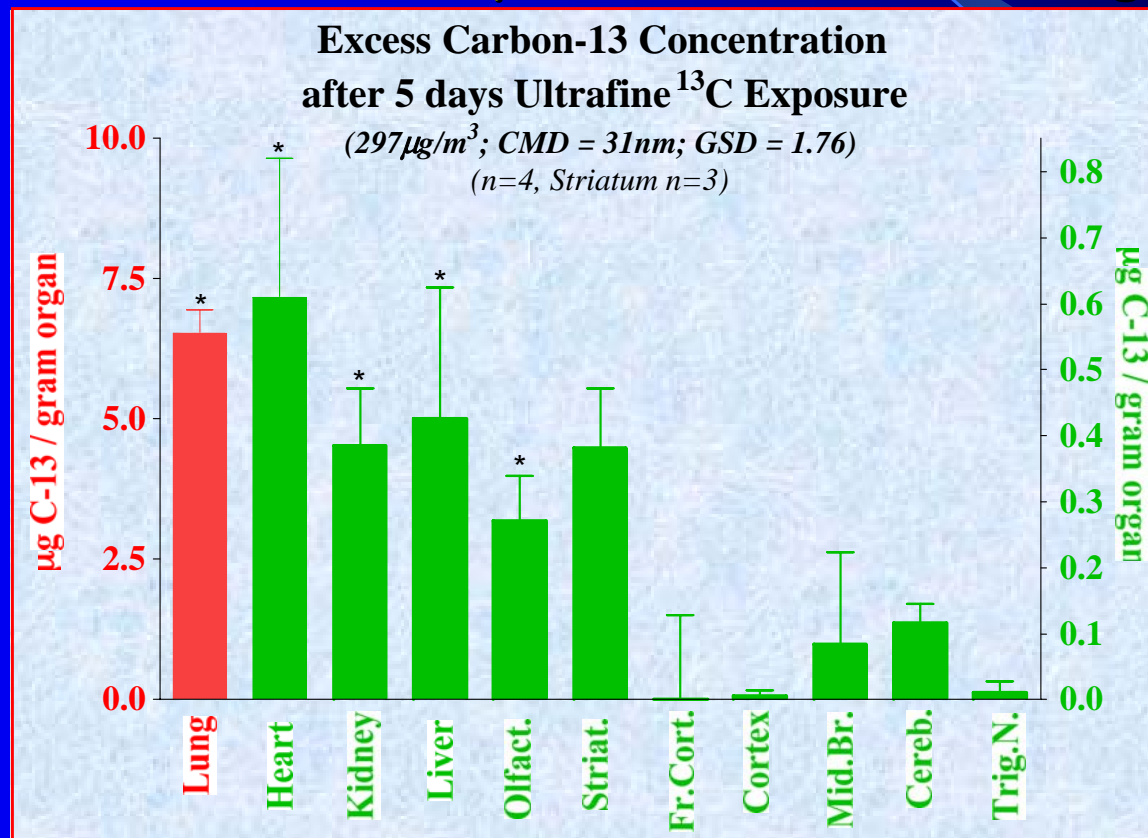


Nemmar et al., *Circulation*, 105:411-414, 2002  
( $^{99m}\text{Tc}$  nano-CB, 5 - 10nm)

# Health Risk Assessment of Nanomaterials

*Size: Deposition, Translocation, and Fate*

## Translocation of Pulmonary Deposited Carbon Black Nanoparticles to Other Organs



*Local versus Systemic Health Effects*

G. Oberdorster et al., US EPA, PM BOSC Review, 2005

# Health Risk Assessment of Nanomaterials

*What do we know about the toxicity of nanomaterials used in pollution remediation and control?*

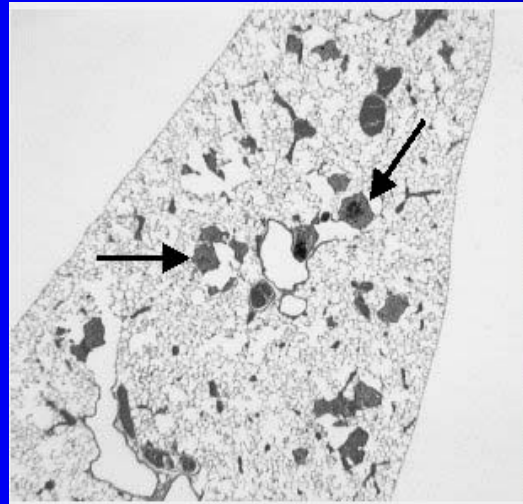
## PubMed Search Results

Nanomaterial	Number Citations on Toxicity
Carbon Nanotubes	9
Fullerenes	37
Dendrimer	29
Nano (ultrafine)-TiO <sub>2</sub>	16
Nano-Zero Valent Iron	0
Nano-Cerium Dioxide	0
Nano (ultrafine)-ZnO	11
Ceramic Nanoparticles	0

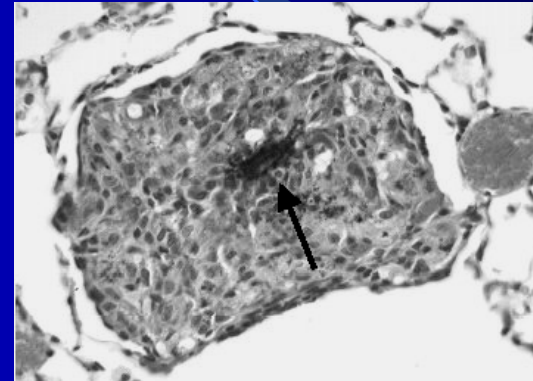
Limited Toxicological Database

# Health Risk Assessment of Nanomaterials

- Single Wall Carbon Nanotube Pulmonary Toxicity
- Adequacy of Existing Particle Toxicology Databases



Multiple Granulomas in Rat Lung  
Following SWCNT Exposure



Magnification of SWCNT  
Induced Granuloma

1. Comparative toxicological assessment using equivalent mass exposure:  
SWCNT = Quartz >> nano-Carbon Black > SiO<sub>2</sub> > Graphite, yet MSDS  
sheet reference graphite for health hazard specifications:  
SWCNT = Quartz
2. SWCNT lung injury with little or no inflammation, new mechanism of lung  
injury

-D. B. Warheit et al., *Toxicological Sciences* 77:117-125, 2004

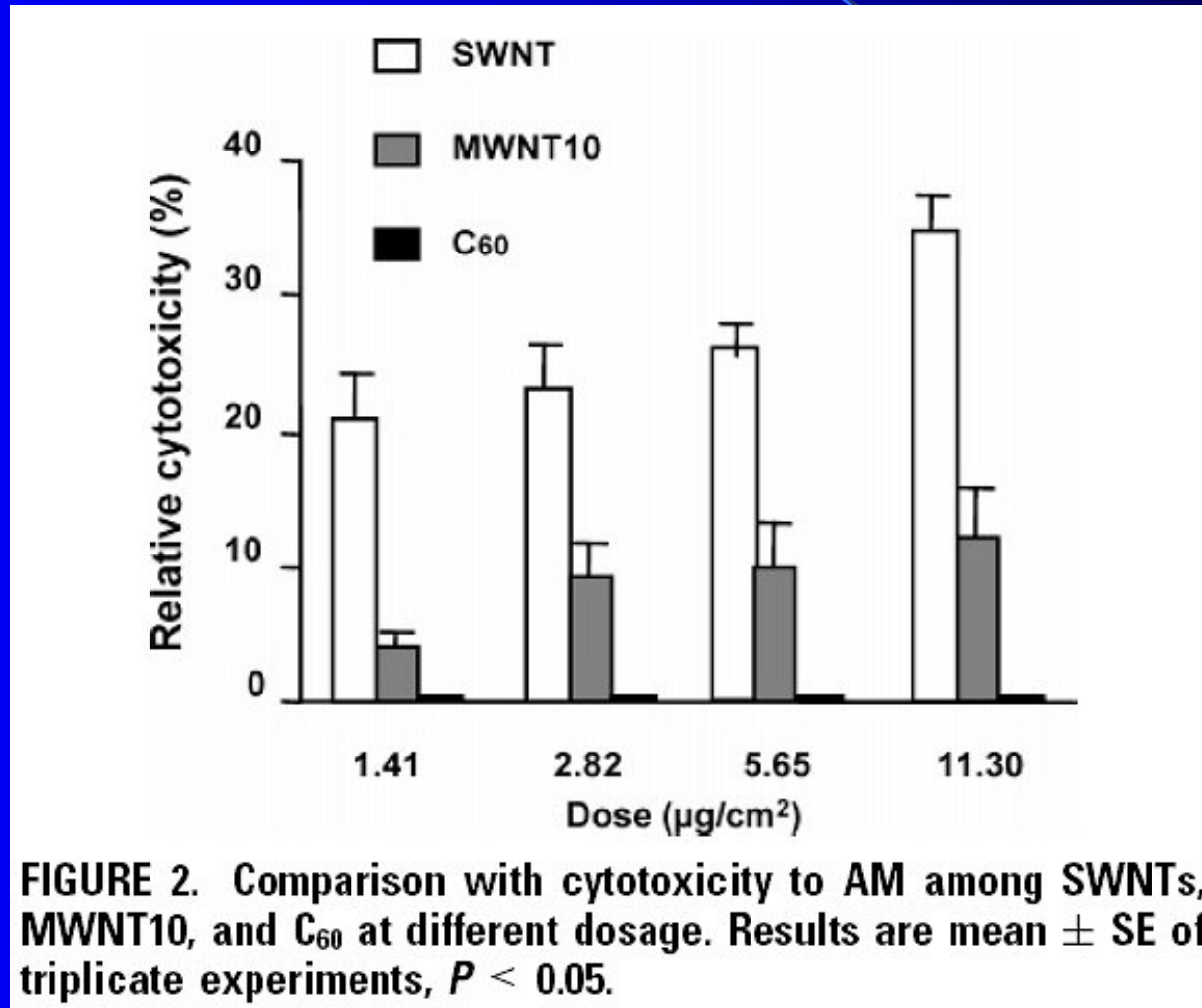
-C-W. Lam et al., *Toxicological Sciences* 77:126-134, 2004

-A, Shvedova et al., *Am. J. Physiol: Ling Cell Molec. Physiol.* 289:L698-L708 ,2005

# Health Risk Assessment of Nanomaterials

## *Single Wall Carbon Nanotube Pulmonary Toxicity*

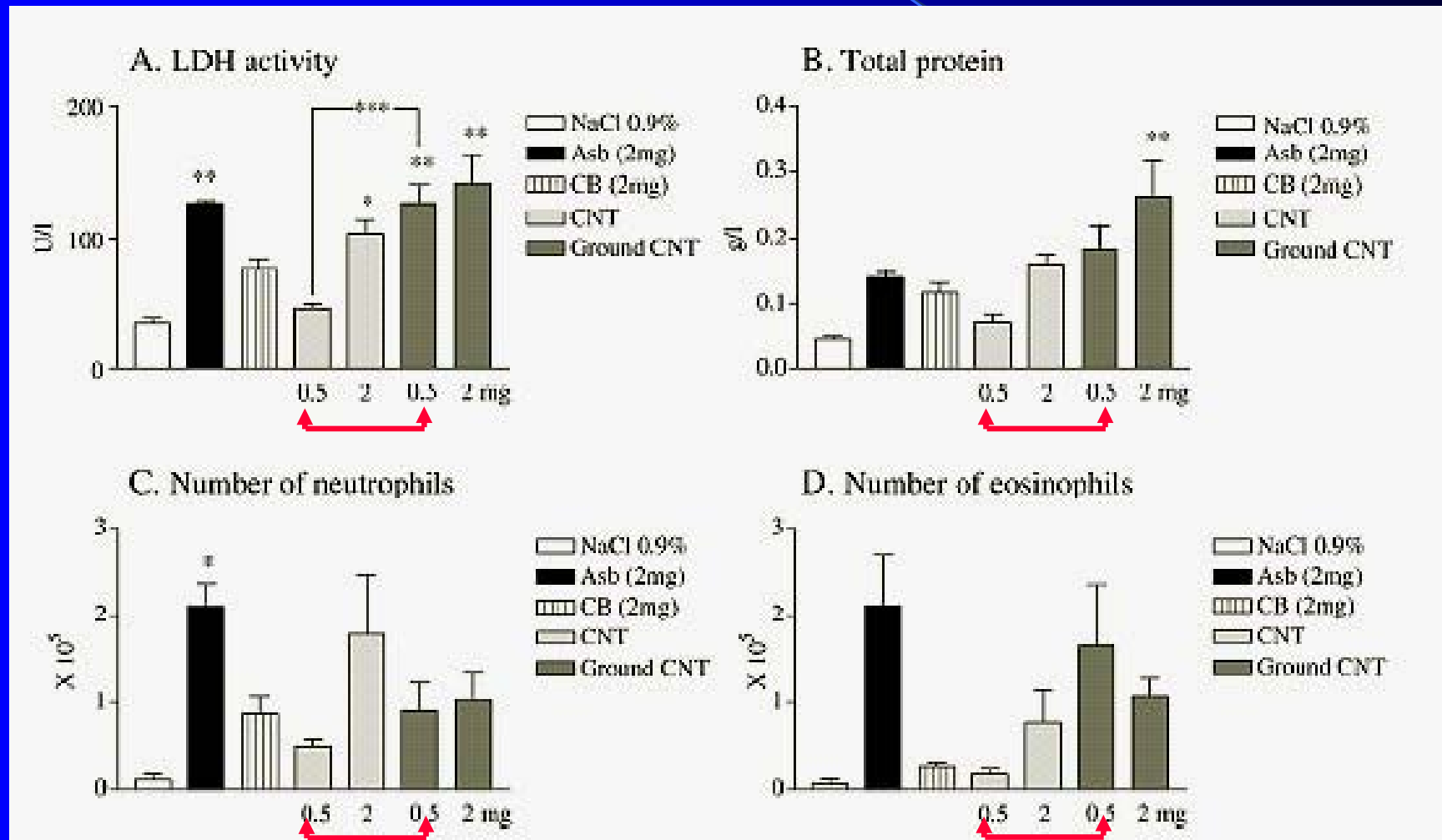
### *Size vs. Shape vs. Surface Properties*



# Health Risk Assessment of Nanomaterials

## Single Wall Carbon Nanotube Pulmonary Toxicity

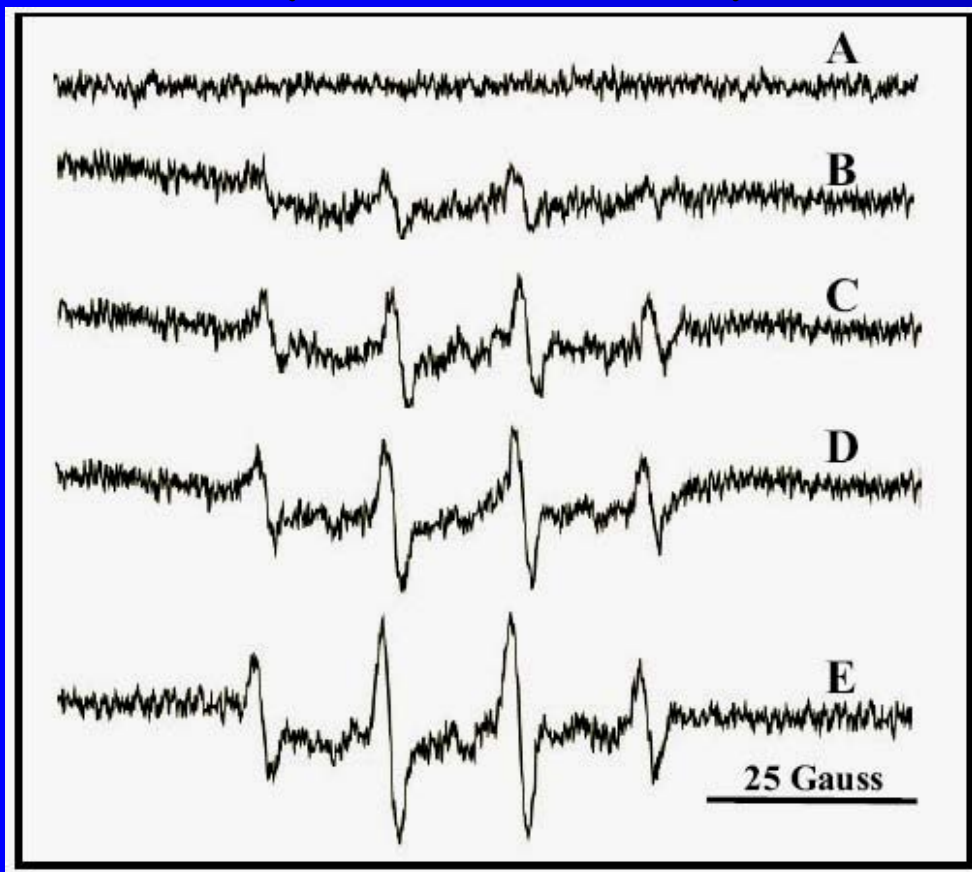
### Intact versus Ground CNTs



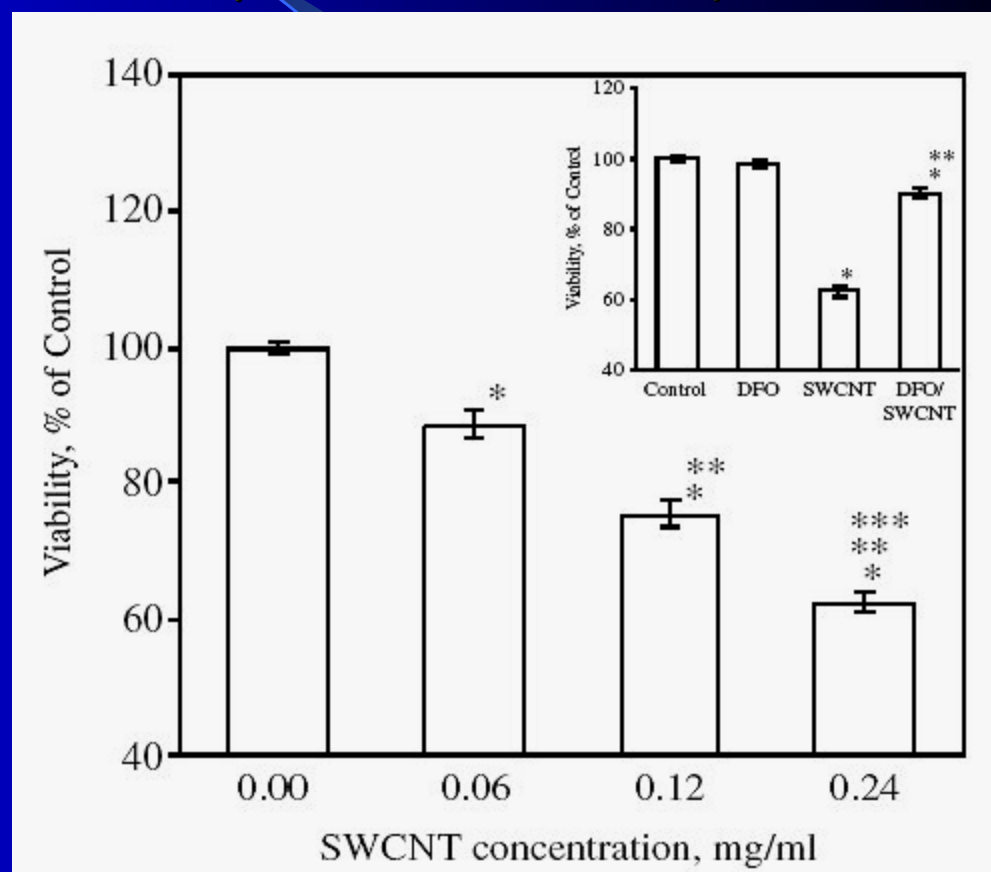
# Health Risk Assessment of Nanomaterials

## Single Wall Carbon Nanotube Dermal Toxicity

### Hydroxyl Radical Formation (Oxidative Stress)



### Cellular Toxicity (Epidermal Keratinocytes)

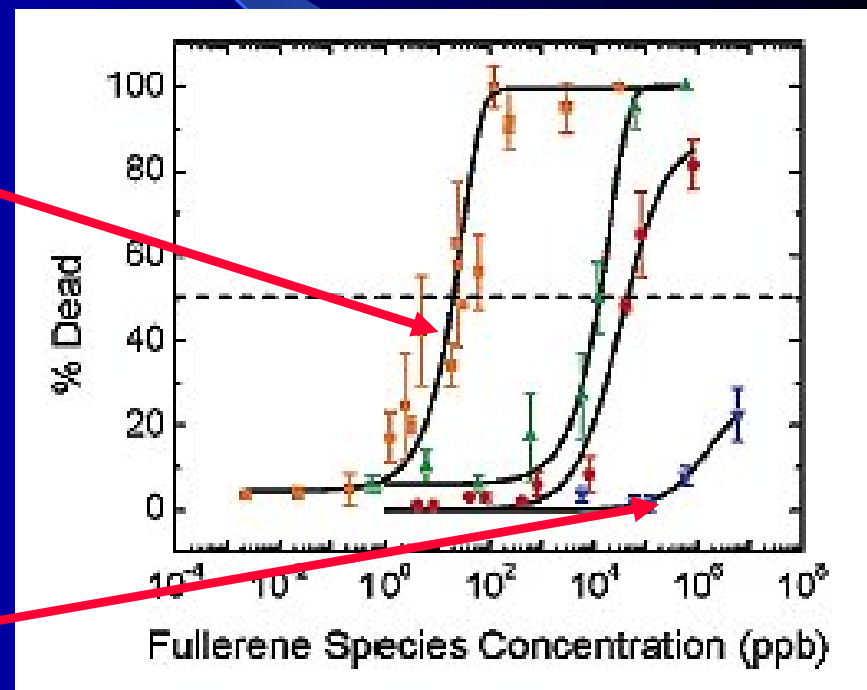


A. Shvedova et al., *J. Toxicol. Environ. Health, Part A*, 66:1909-1926, 2003  
N.A. Monteiro-Riviere et al., *Toxicol. Lett.* 155:377-384, 2005. (MWCNTs)

# Health Risk Assessment of Nanomaterials

## *In Vitro Dermal Toxicity of Fullerenes: Size vs. Surface Properties*

Fullerene Species	Structure	Live Stain	Dead Stain
$C_{60}$			
$C_3$			
$Na^{+}_{2-3} [C_{60}O_{7-9}(OH)_{12-15}]^{(2-3)-}$			
$C_{60}(OH)_{24}$			





# Health Risk Assessment of Nanomaterials

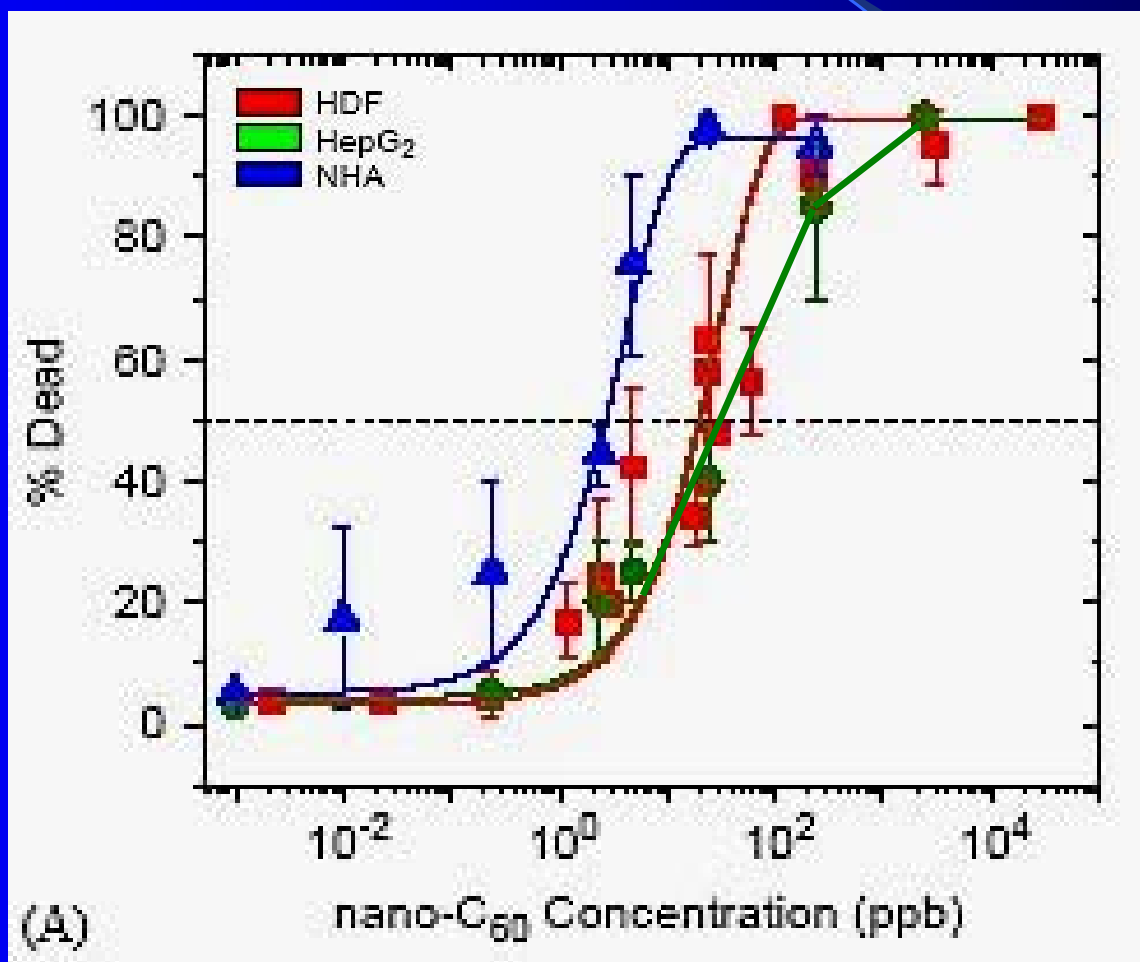
## *In Vitro Toxicity of Fullerenes (Dermal Fibroblasts; Liver Cells; Astrocytes)*

$LC_{50}$ :

NHA - 2ppb

HDF - 20ppb

HepG2 - 50ppb

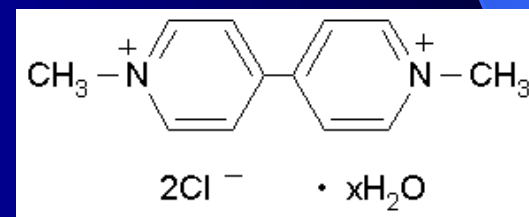


*C. M. Sayes et al., Biomaterials 26:7588-7595, 2005*

# Health Risk Assessment of Nanomaterials

## *Comparative In Vitro Toxicity of Fullerenes*

Toxicants	LC <sub>50</sub> , mg/kg
<b>C<sub>60</sub>(OH)<sub>24</sub></b>	<b>&gt; 100,000</b>
<b>Ethanol*</b>	<b>17,000</b>
<b>THF</b>	<b>11,000</b>
<b>Toluene</b>	<b>1,600</b>
<b>Paraquat</b>	<b>100</b>
<b>Benzo[a]pyrene*</b>	<b>10</b>
<b>nano-C<sub>60</sub></b>	<b>0.02</b>
<b>Dioxin*</b>	<b>0.001</b>



**Paraquat**

\*National Institute of Health,  
Registry of Cytotoxicity Data (ZEBET)

Courtesy of C. M. Sayes, Rice University, CBEN

# Health Risk Assessment of Nanomaterials

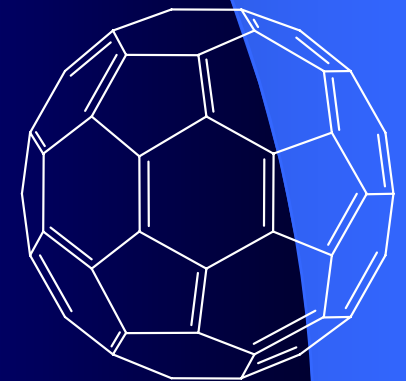
## *In Vivo Toxicity of Fullerenes*

***In Vivo* Biological Behavior of a Water-Miscible Fullerene:  $^{14}\text{C}$  labeling, Absorption, Distribution, Excretion, and Acute Toxicity.**

Y.S. Tokuyama et al., *Chem. Biol.*, 2(6):385-389, 1995.

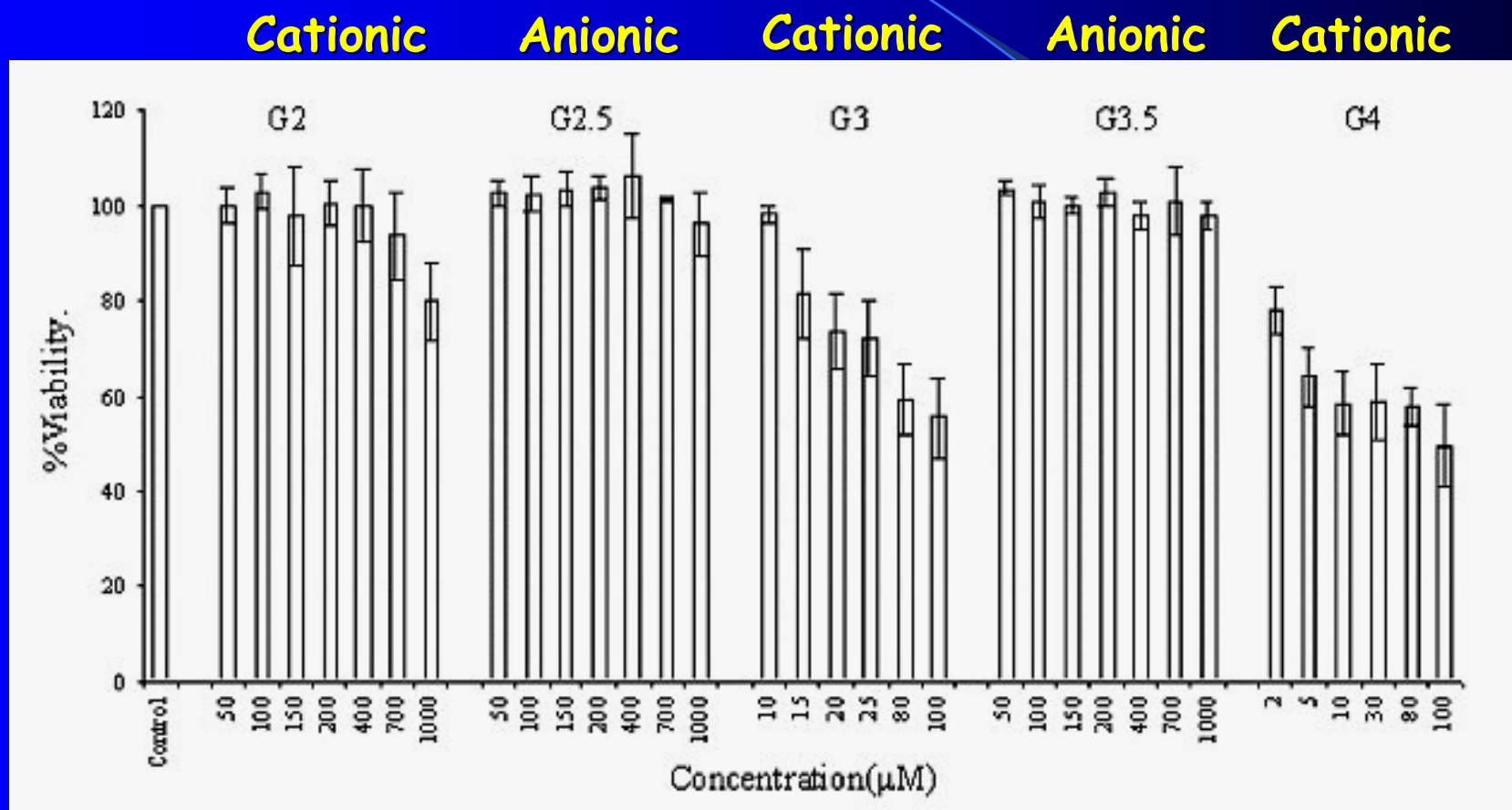
**Novel Harmful Effects of [60]Fullerene on Mouse Embryos *In Vitro* and *In Vivo***

T. Tsuchiya et al., *FEBS Lett.* 393(1):139-145, 1996.



# Health Risk Assessment of Nanomaterials

## *In Vitro Intestinal Toxicity of Dendrimers Generation, Size, and Charge*



- R. Jevprasesphant et al., *Intl. J. Pharmaceutics*, 252:263-268, 2003.  
R. Jevprasesphant et al., *Pharmaceutical Res.*, 20(10):1543-1550, 2003.  
D. Fischer et al., *Biomaterials*, 24:1121-1131, 2003

# Health Risk Assessment of Nanomaterials

## Organ Distribution of Dendrimers

### PAMAM. Gen. 5, d=5nm, Positive vs. Negative Charge

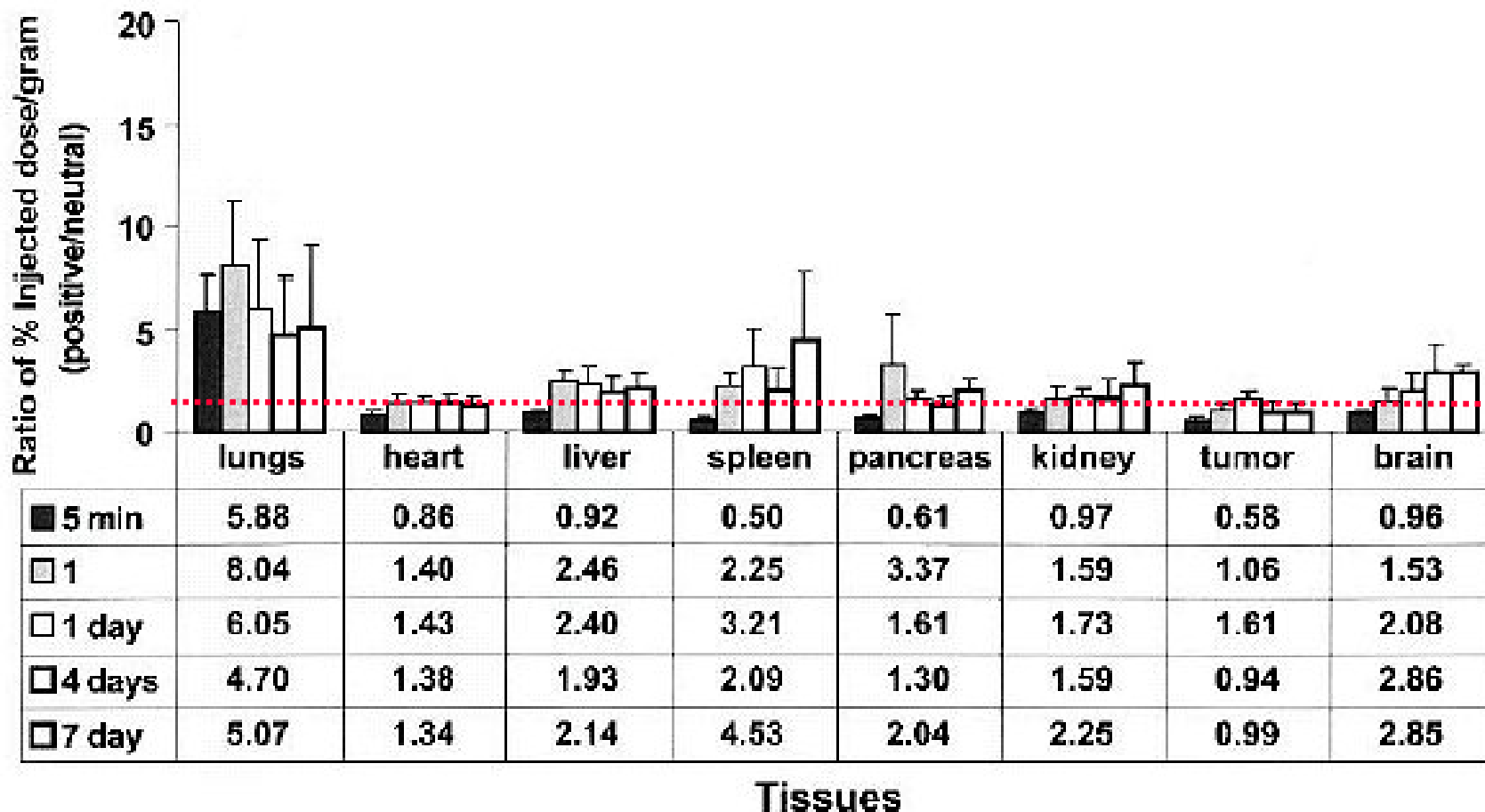
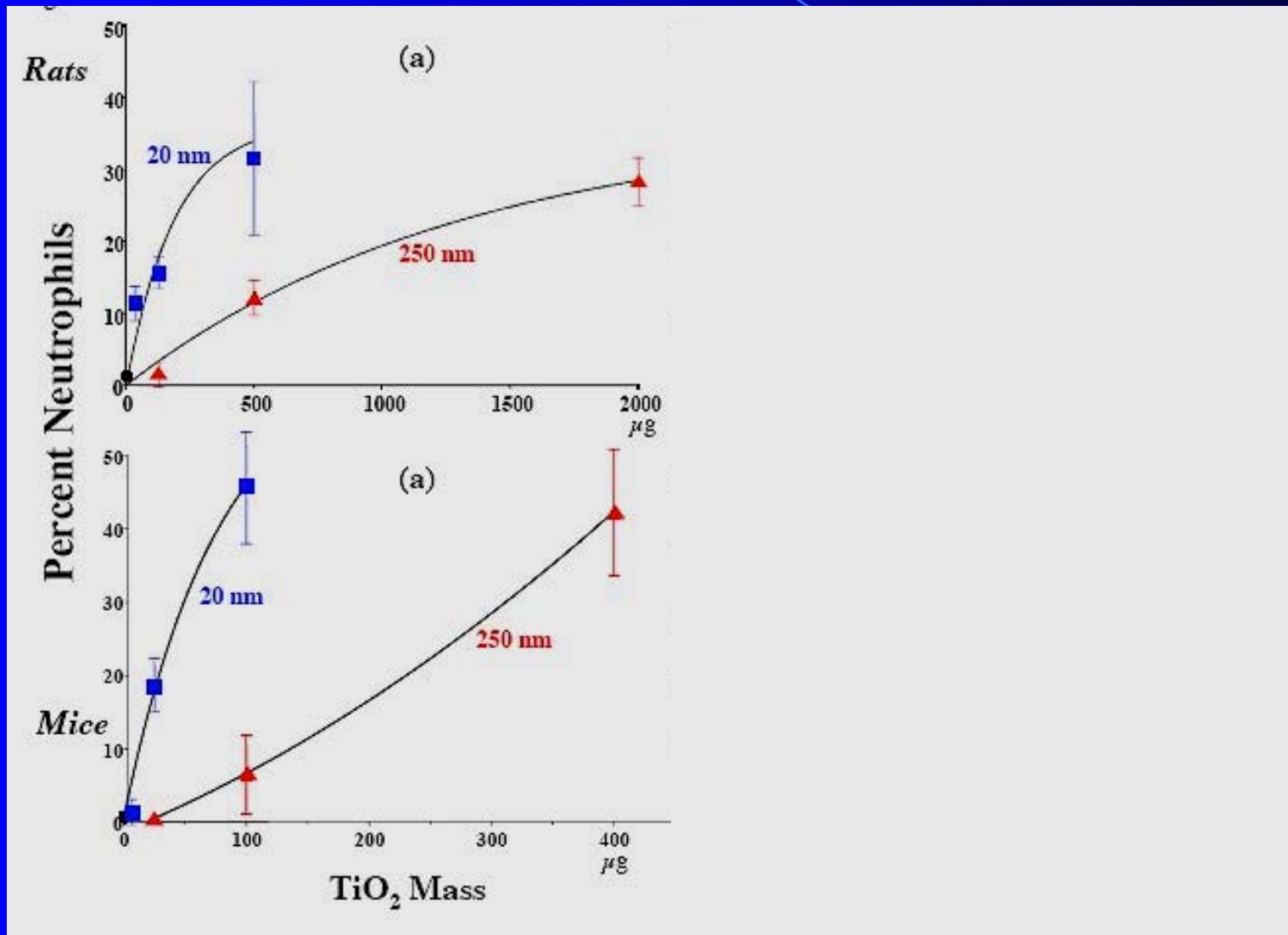


Fig. 3. Ratio of the percent injected dose per gram of organ (% ID/g) of positive surface dendrimer (PSD) relative to that of the neutral surface dendrimer (NSD) in tissues of C57BL/6J mice (B16 melanoma model). The bars show mean ratios and error bars show total standard deviation.

# Health Risk Assessment of Nanomaterials

## *Pulmonary Toxicity of Fine vs. Nano-TiO<sub>2</sub> Size vs. Surface Properties*



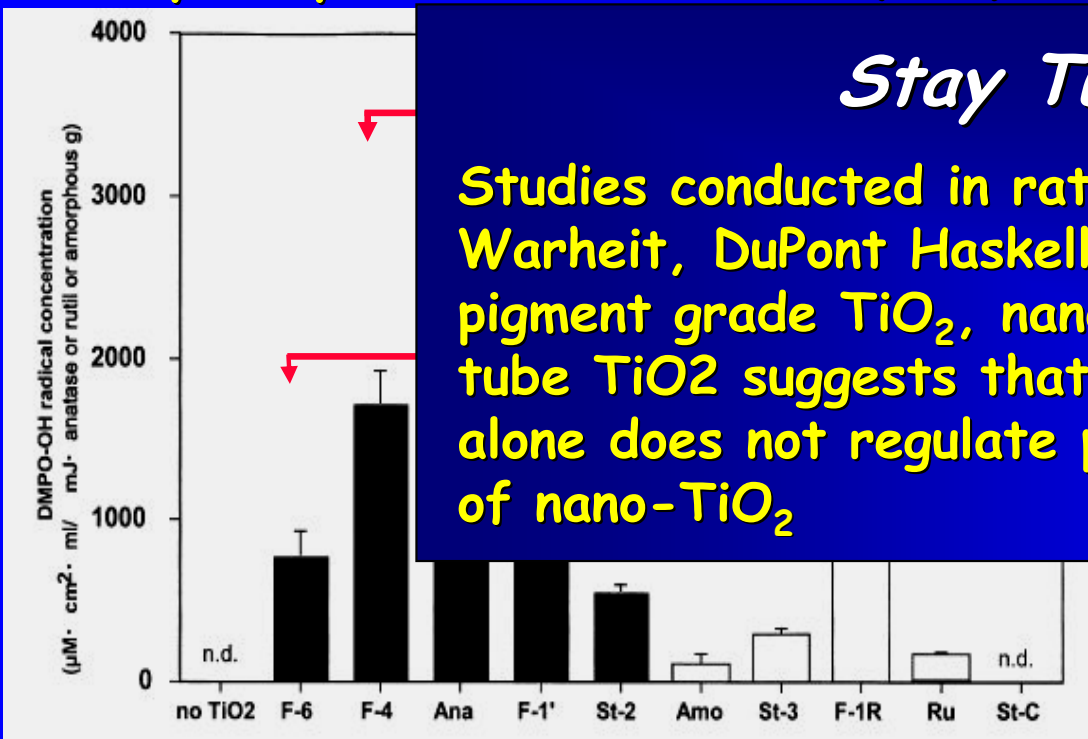
**Oberdorster<sup>3</sup>, *Environ. Health Perspec.*, 2005.**

# Health Risk Assessment of Nanomaterials

## Nano-TiO<sub>2</sub>: Size vs. Surface Properties

### Oxidative Stress

### Hydroxyl Radical Production (ESR)



**Stay Tuned**

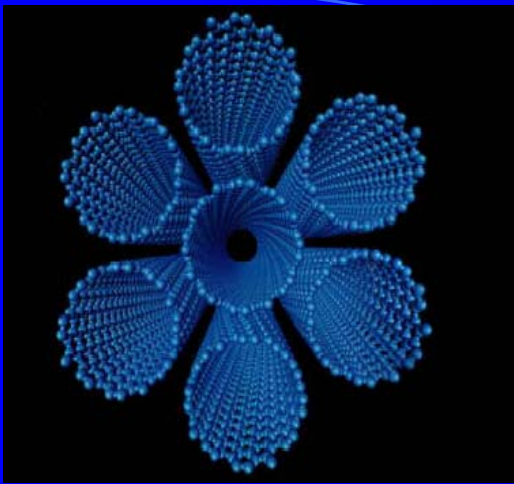
Studies conducted in rats by Dr. David Warheit, DuPont Haskell Laboratory with pigment grade TiO<sub>2</sub>, nano-dot TiO<sub>2</sub>, nano-tube TiO<sub>2</sub> suggests that size/surface area alone does not regulate pulmonary toxicity of nano-TiO<sub>2</sub>

### Test Samples

	Size (nm)	Surface Area (m <sup>2</sup> /g)
	15	105
	30	53
	30	53
Amo	Amorphous	17
St3	1/99	37

F6 F4 Ana Amo St3

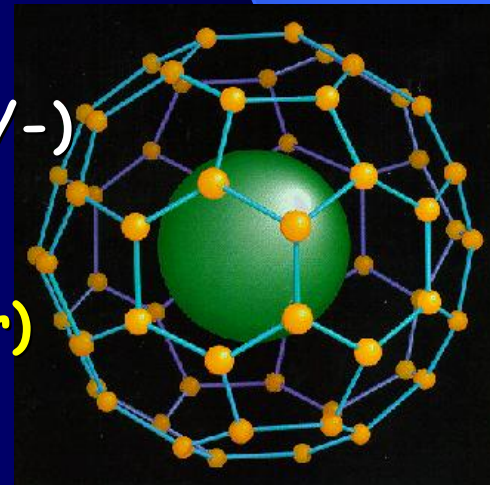
Uchino et al. *Toxicol. In Vitro*, 16:629-635, 2002



# Health Effects Nanomaterials (Nanotoxicology)

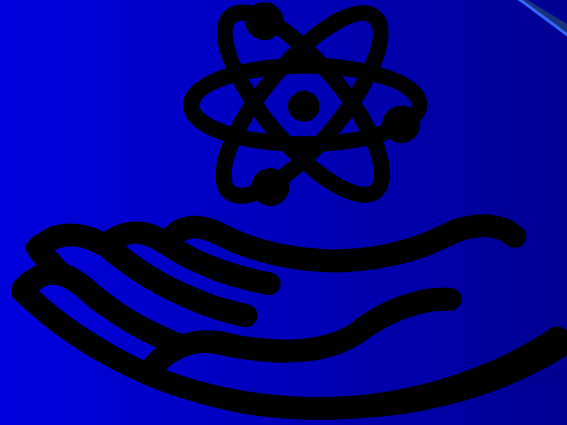
## *Summary*

- Multi-disciplinary and coordinated approach is required
- Health effects and hazard identification:
  - particle toxicity is multi-factorial: "more than just size";  
(metric of toxicity >>> exposure assessment and standards)
  - local vs. systemic toxicity (the latter maybe more responsive)
  - nanomaterials have "unique toxicities";
  - have we measured the toxicity associated with unique properties?? (photo-catalytic properties)
  - detecting nanomaterials in environmental and biological systems remains a challenge: (exposed, +/-)
- Health effects associated with interactions of nanomaterials or nanotechnology applications with co-pollutants in environmental media (air, soil, water) are unknown





# Risk Assessment of Nanomaterials



**Risk assessment is critical to ensure the responsible development of the beneficial applications of nanotechnology**

*(NNI Strategic Plan: Goal 4, December 2004;  
NNI at Five Years: Societal Concerns and Potential Risks, May 2005)*