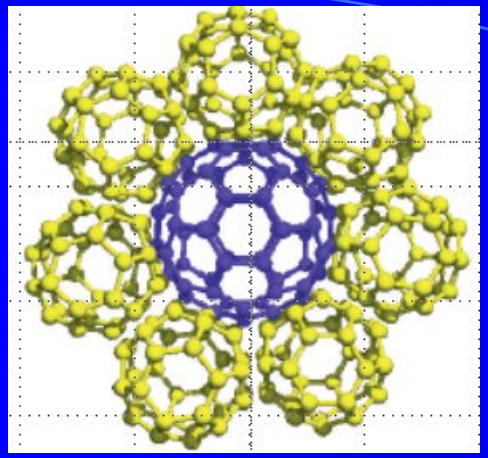
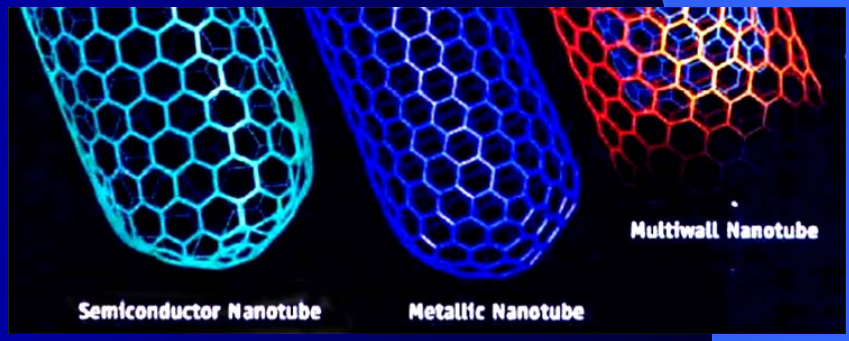


Health Risk Assessment of Manufactured Nanomaterials: More Than Just Size

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

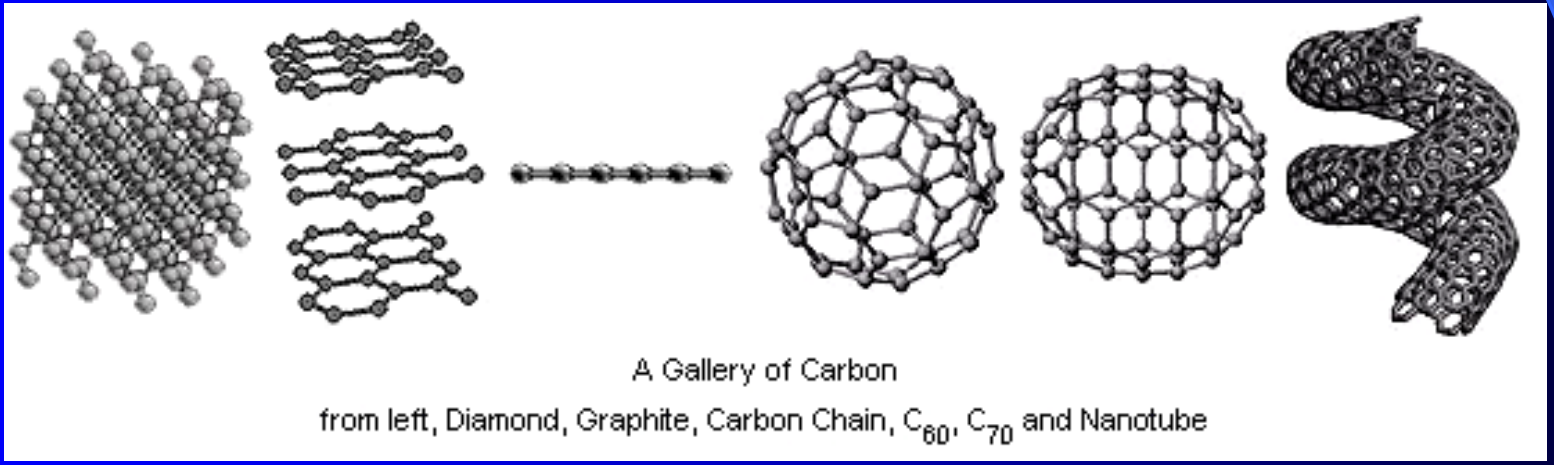
Nanotechnology for Remediation Technical Workshop
US Department of Commerce
Oct. 20-21, 2005
Washington, DC



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



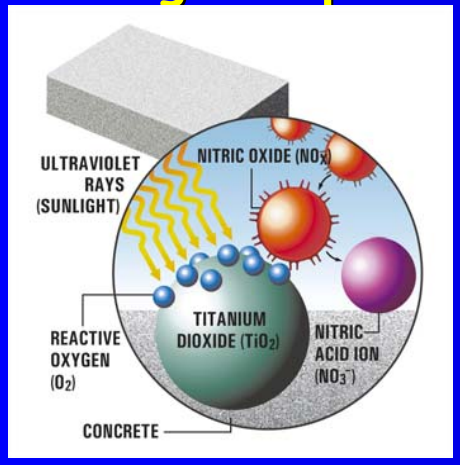
A Gallery of Carbon

from left, Diamond, Graphite, Carbon Chain, C_{60}, C_{70} and Nanotube

Health Risk Assessment of Nanomaterials

Air Pollution Control: Photo-Catalytic Nano-TiO_2, ZnO

Paving and painting out pollution



-2002, nanoTiO2\cement, Milan, Italy, 60% decrease in near road side NOx levels

Self cleaning glass/surfaces

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

-EU Photocatalytic Innovative Coverings Applications for Depollution Assessment (PICADA) NOx reduction

Air

Environmental Interactions, Transformations, and Fate?

Potential Health Effects?

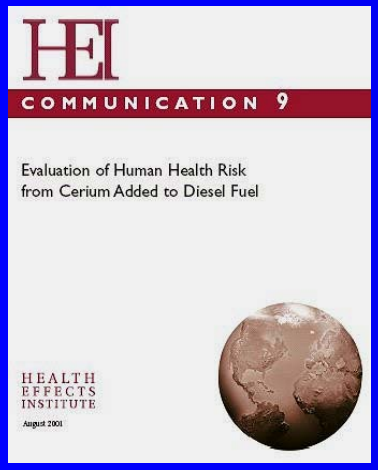
Health Risk Assessment of Nanomaterials

Air Pollution Control: Nano-metals
(Al_2O_3; Transition Metals; CeO_2: 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

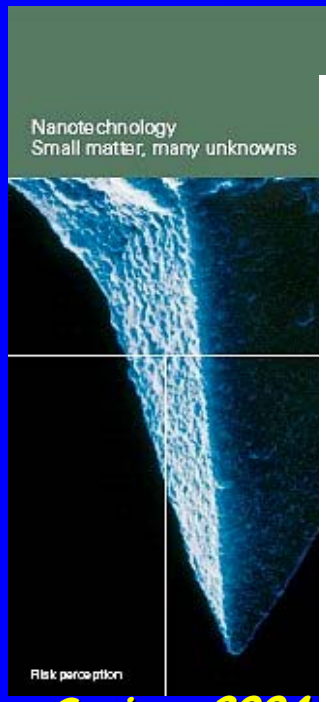
Air
Environmental Interactions, Transformations, Fate?
Potential Health Effects?



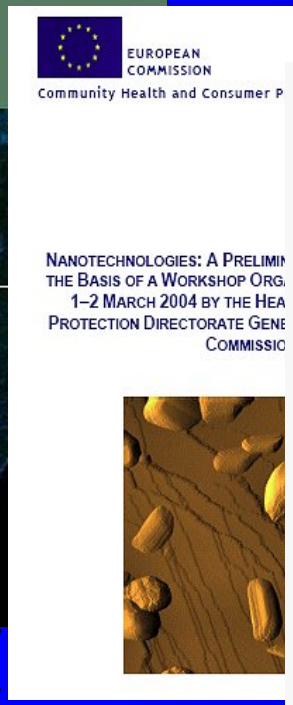
Diesel Exhaust:
↑>50% in each: benzene; 1,3-butadiene; acetaldehyde (Air Toxics)
↓80% PAHs (Air Toxic)
↓8-20% NOx (NAAQ)
↑50-100% CO (NAAQ)

Risk Assessment of Nanotechnology

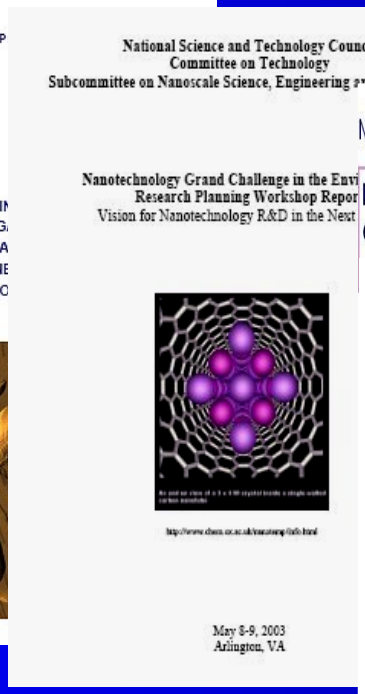
Reports: Uncertainties in Nanotechnology Risk Assessment



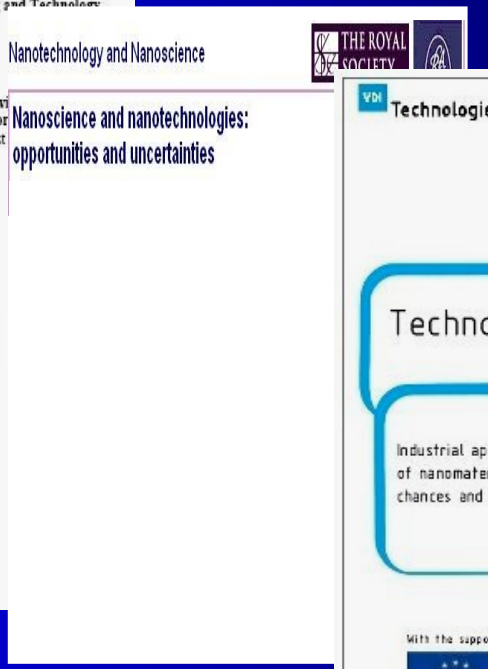
Spring, 2004
Swiss Report
Reinsurance Company



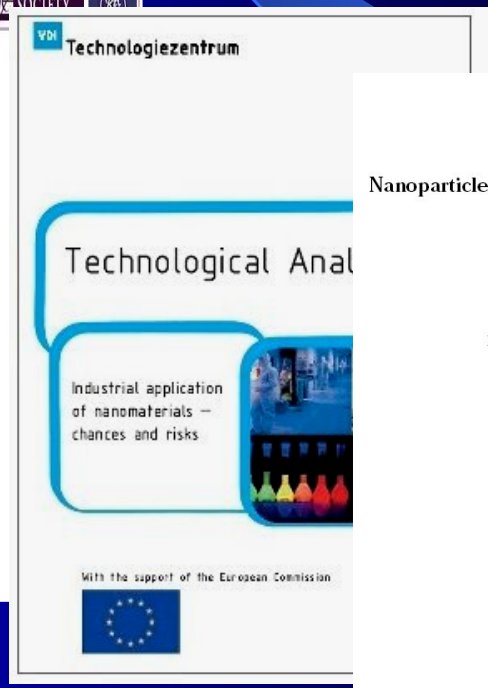
2004
European Commission



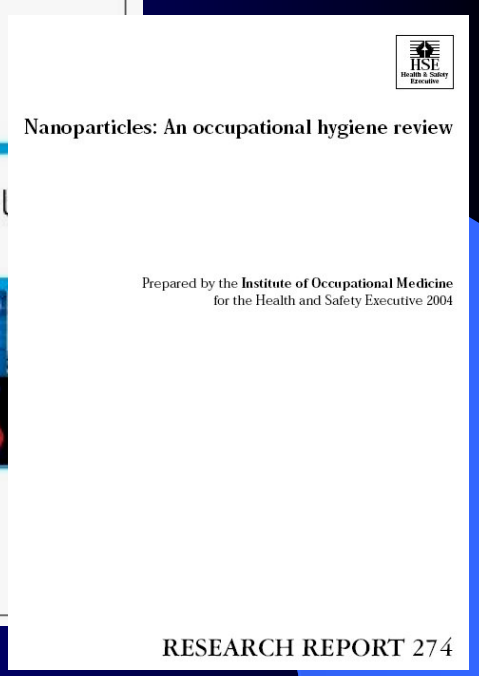
April 2004
NNI Report
Grand Challenge:
"Nanotechnology in the Environment"



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 N

Kevin L. Dreher

Dreher, Toxicol.Sci., 2004


Environews . Focus

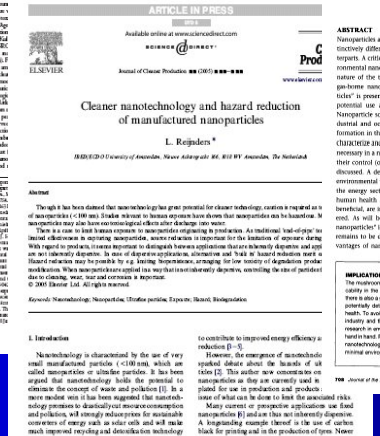
Nanotechnology: Looking As We Leap

Hood, Environ. Hlth. Perspect., 2004


Review

Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles

Oberdorster et al., Environ. Hlth. Perspect., 2005


ARTICLE IN PRESS

Cleaner nanotechnology and hazard reduction of manufactured nanoparticles

L. Reijnders *

Reijeiders, J. Cleaner Production, 2005


CRITICAL REVIEW

Nanoparticles and the Environ

Pratim Biswas

Chang-Yu Wu

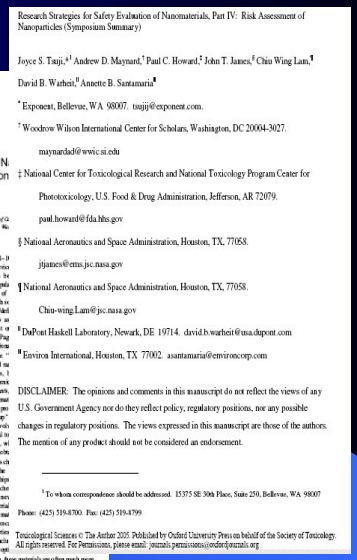
Biswas & Wu, J. AWMA, 2005


FORUM SERIES

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

Karlton Thomas* and Philip Sayre†

Thomas & Sayre, Toxicol. Sci., 2005

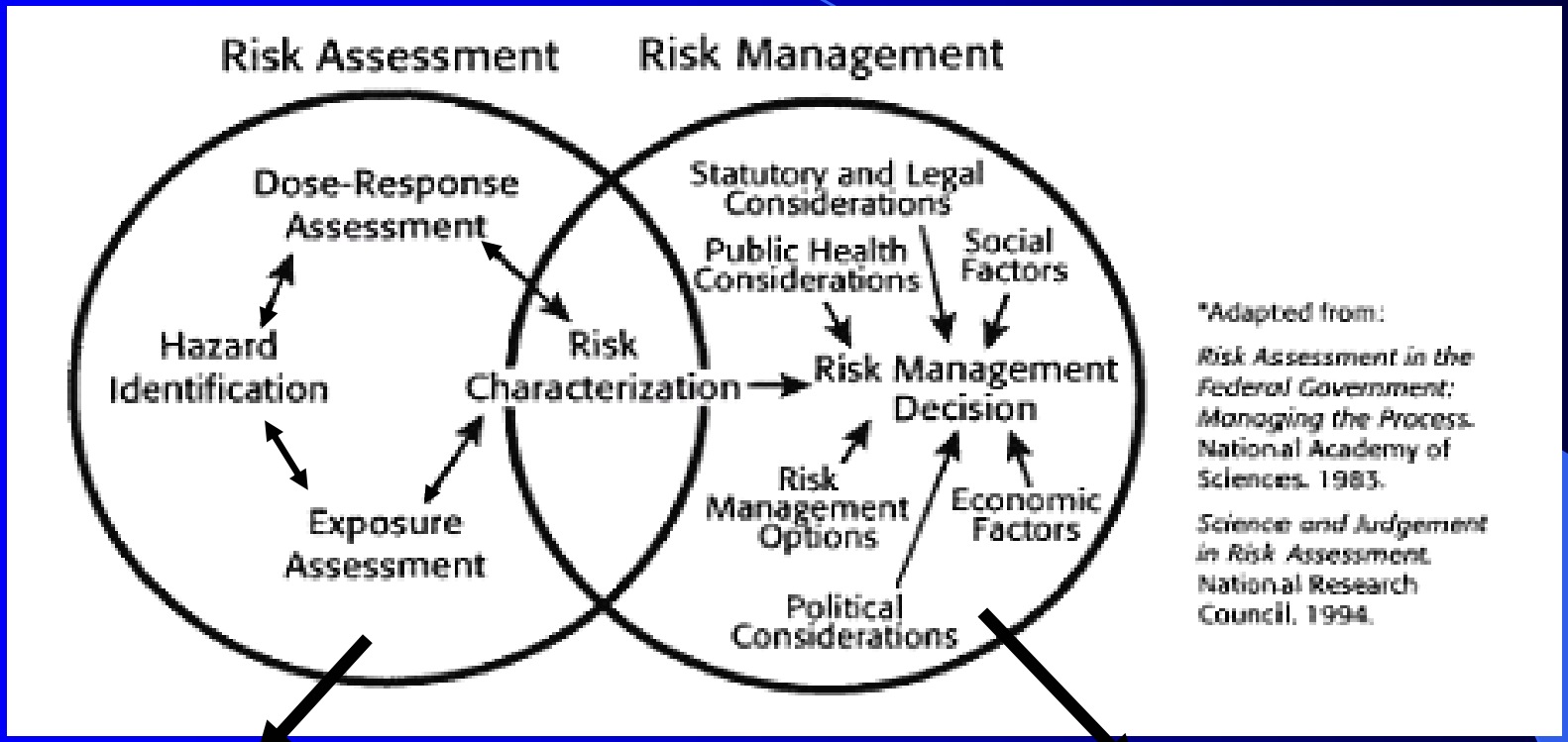

Research Strategies for Safety Evaluation of Nanomaterials, Part IV: Risk Assessment of Nanoparticles (Symposium Summary)

Joyce S. Tsuji,*,1 Andrew D. Maynard,† Paul C. Howard,‡ John T. James,§ Chiu Wing Lam,¶ David B. Warheit,‖ Annette B. Santamaria#

Tsuji et al., Toxicol Sci., 2005

Risk Assessment of Nanotechnology

Uncertainties



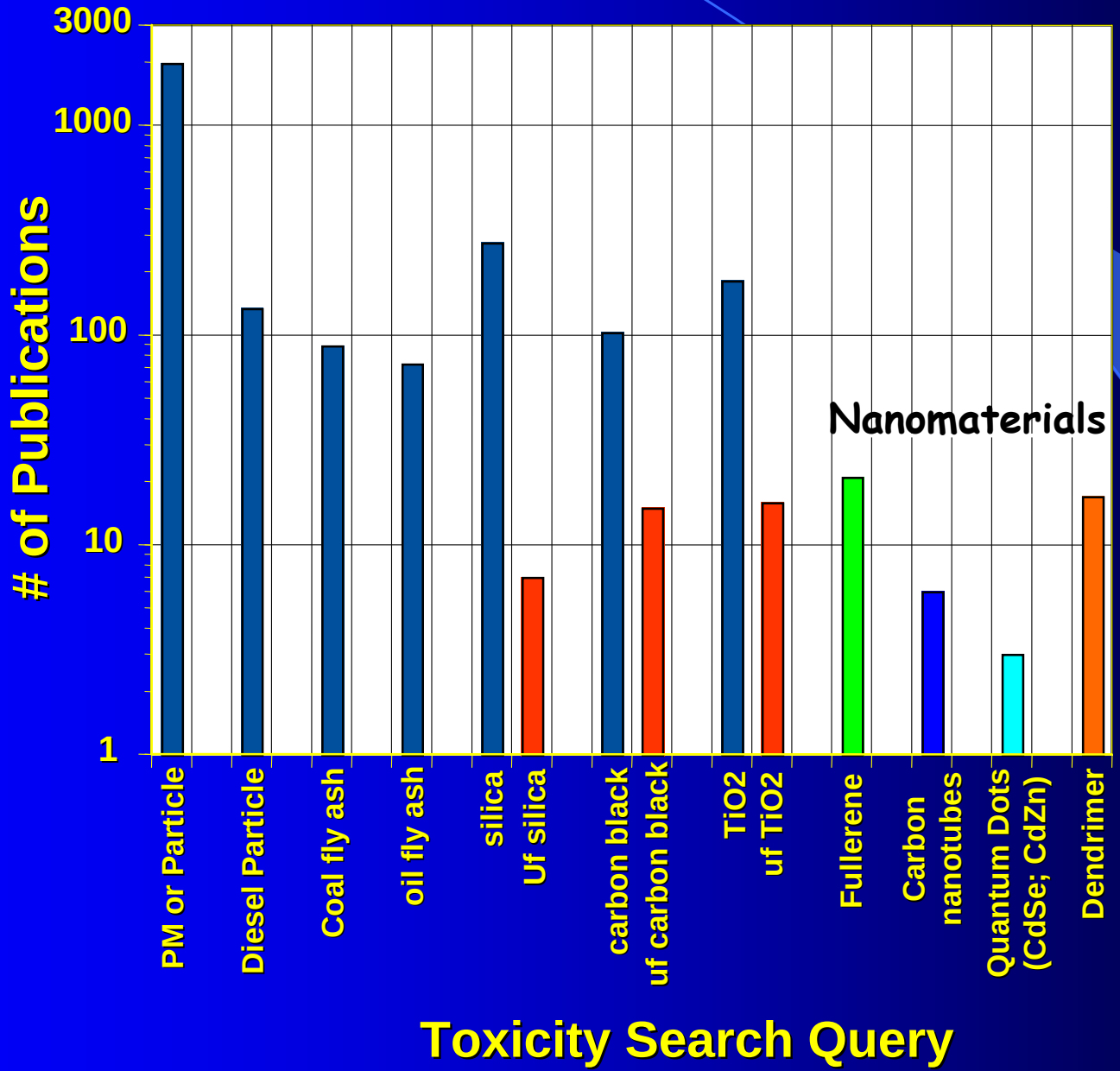
- -Health, Ecological, Environmental Effects
- -Hazard Identification (tox. metric)
- -Nomenclature
- -Exposure/Detection
- -Fate, Transport, Transformation
- -Waste Generated
- -Production Volume

- -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

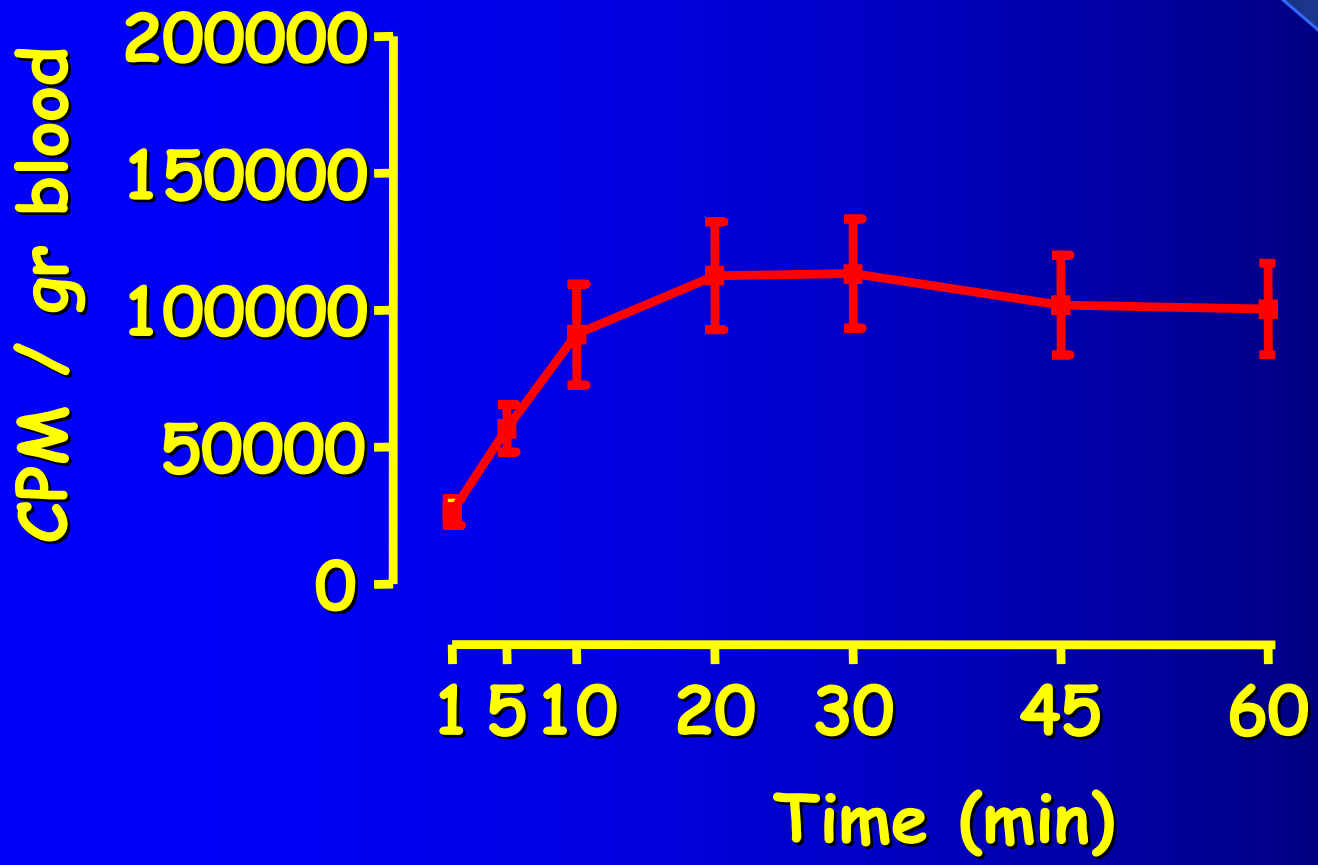
What do we know about nanoparticle toxicology?

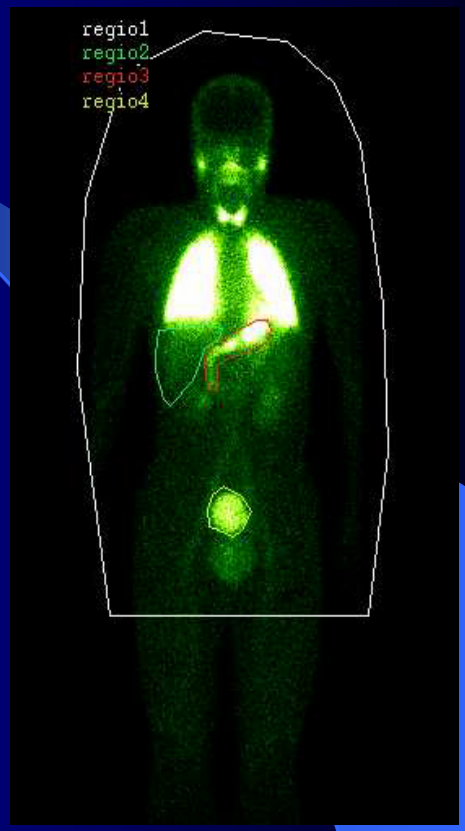
Particle Toxicology Database: PubMed 2004-1982



Health Risk Assessment of Nanomaterials

Size: Deposition, Translocation and Fate of Nanoparticles



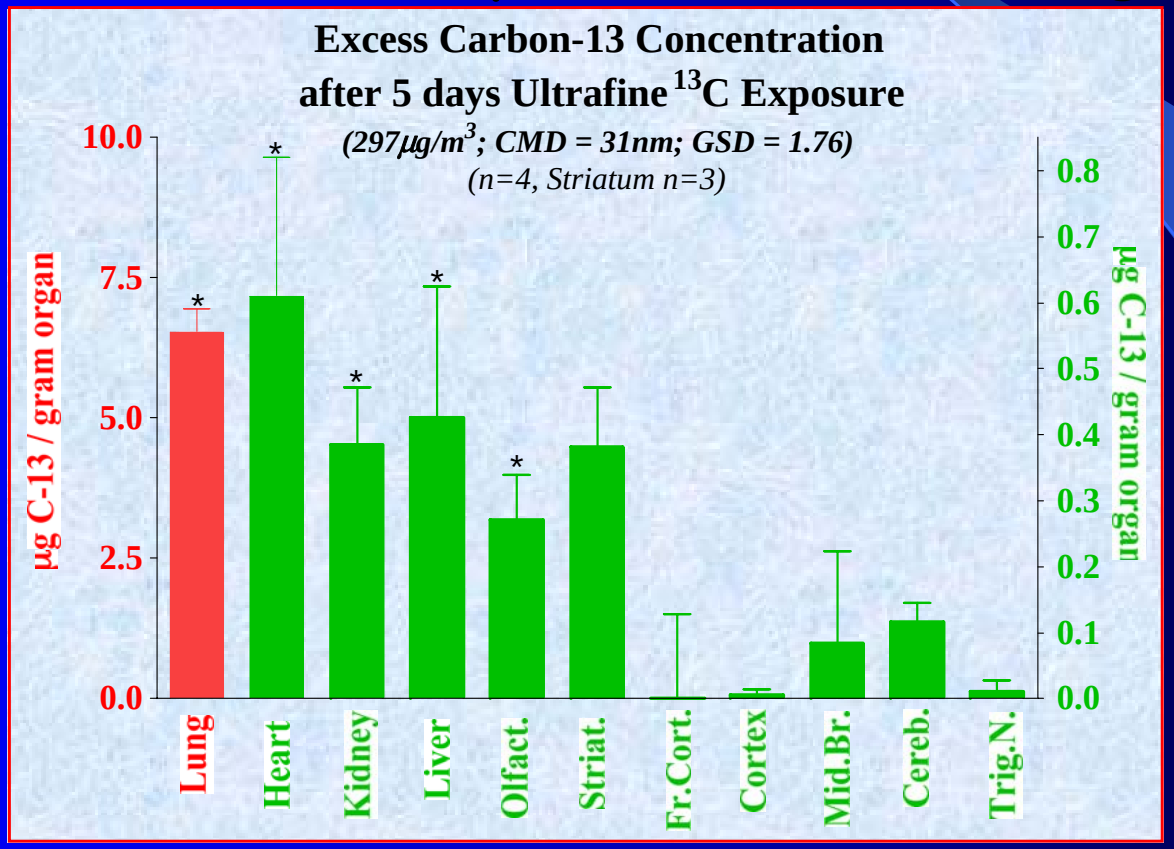


Nemmar et al., *Circulation*, 105:411-414, 2002
(^{99m}Tc nano-CB, 5 - 10nm)

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?

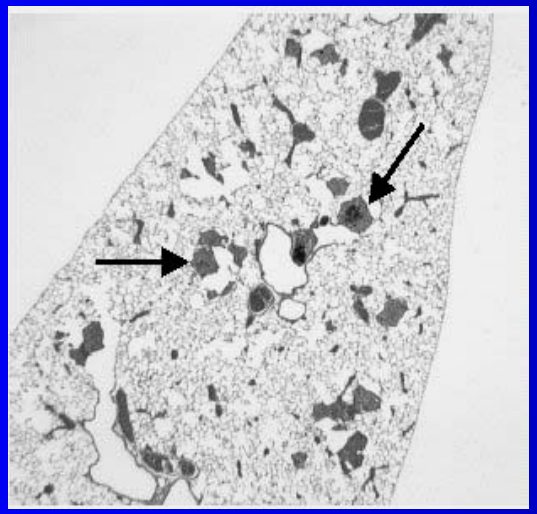
PubMed Search Results

Nanomaterial	Number Citations on Toxicity
Carbon Nanotubes	9
Fullerenes	37
Dendrimer	29
Nano (ultrafine)-TiO_2	16
Nano-Zero Valent Iron	0
Nano-Cerium Dioxide	0
Nano (ultrafine)-ZnO	11
Ceramic Nanoparticles	0

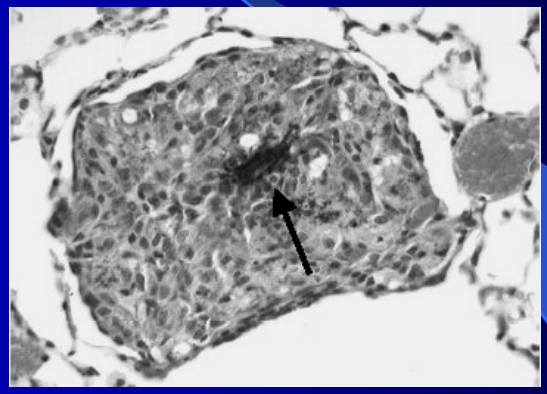
Limited Toxicological Database

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 > SiO2 > 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

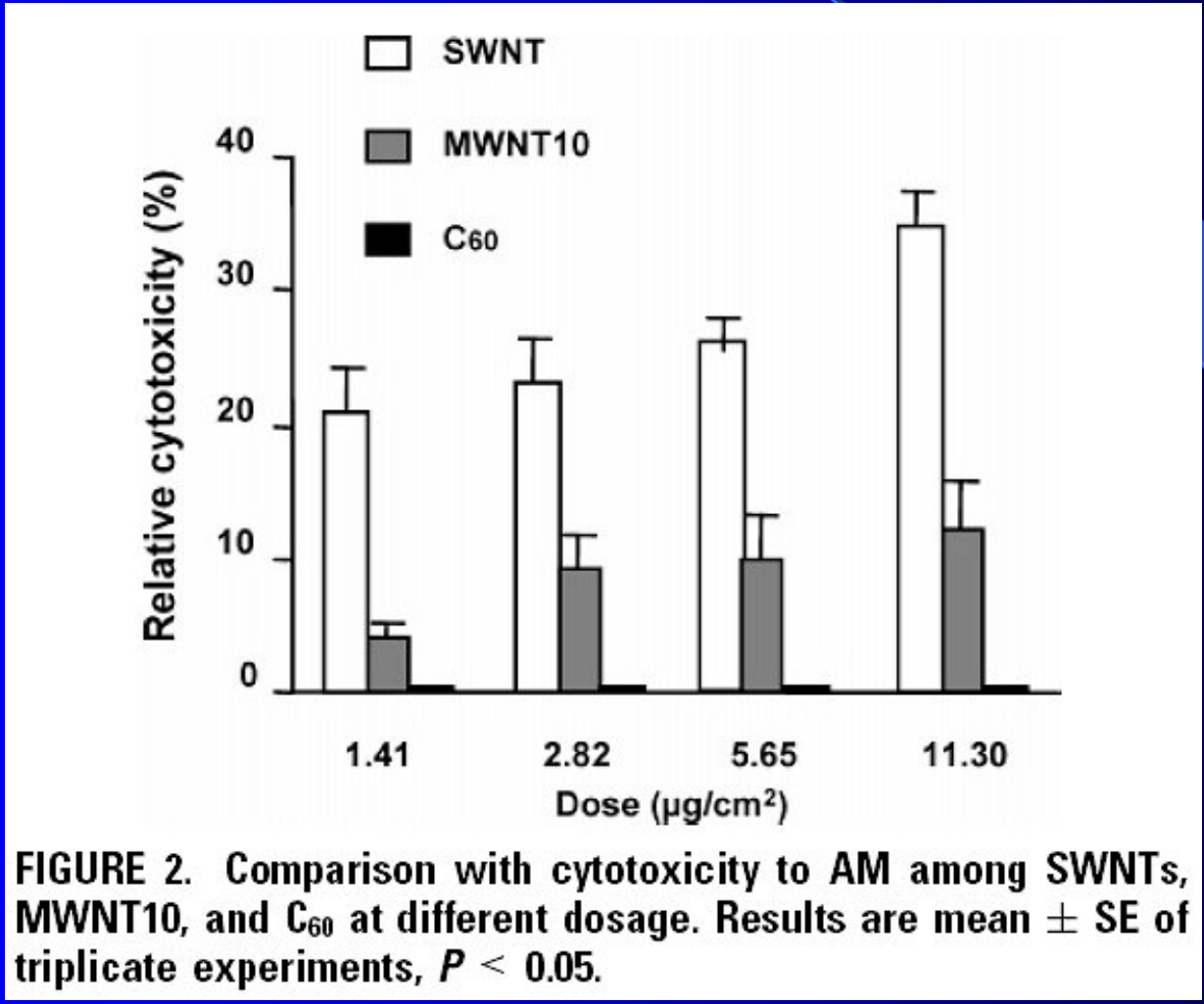


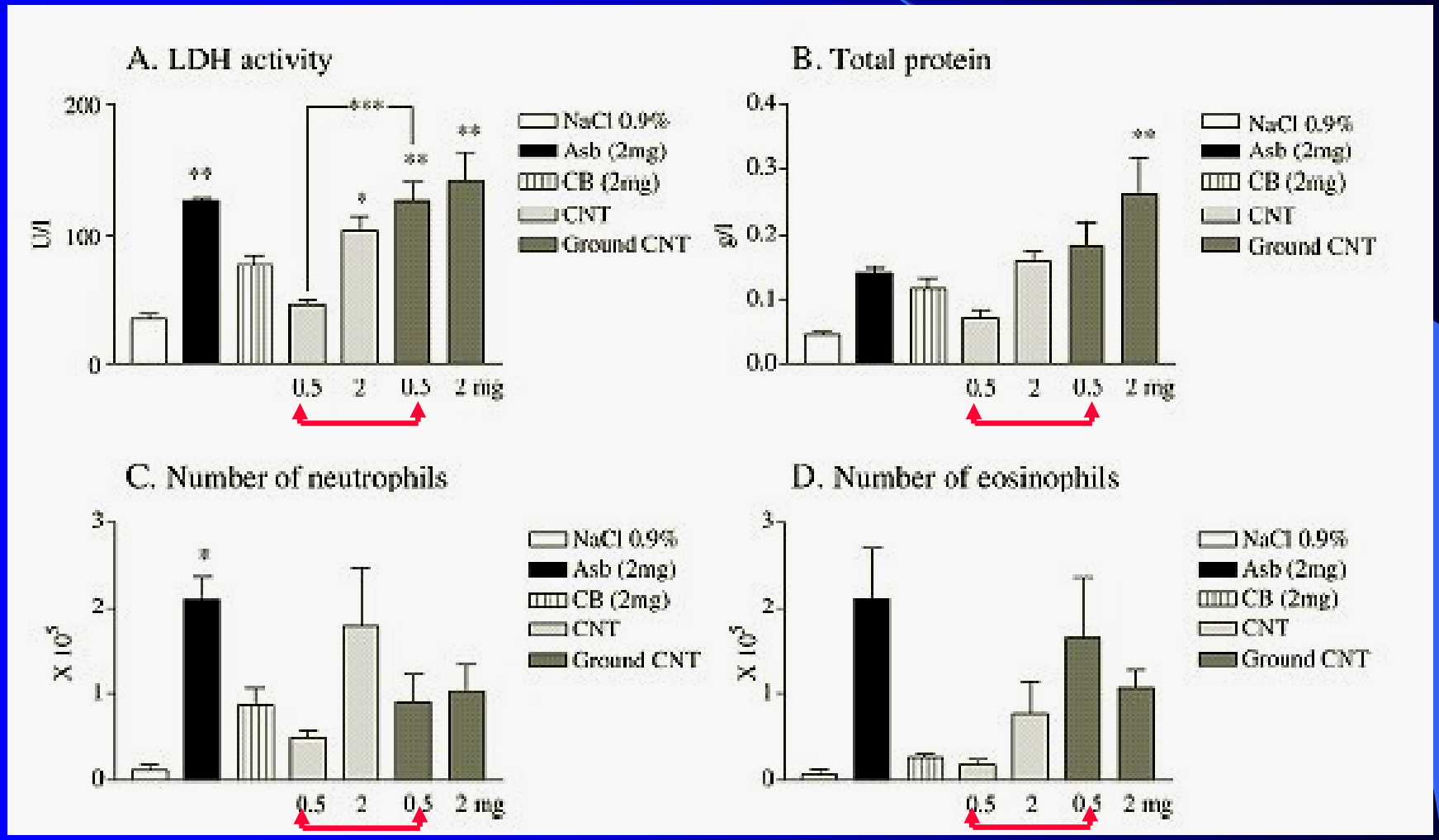
FIGURE 2. Comparison with cytotoxicity to AM among SWNTs, MWNT10, and C_{60} at different dosage. Results are mean ± SE of triplicate experiments, $P < 0.05$.

G. Jia et al., *Environ. Sci. Technol.*, 39:1378-1383, 2005

Health Risk Assessment of Nanomaterials

Single Wall Carbon Nanotube Pulmonary Toxicity

Intact versus Ground CNTs

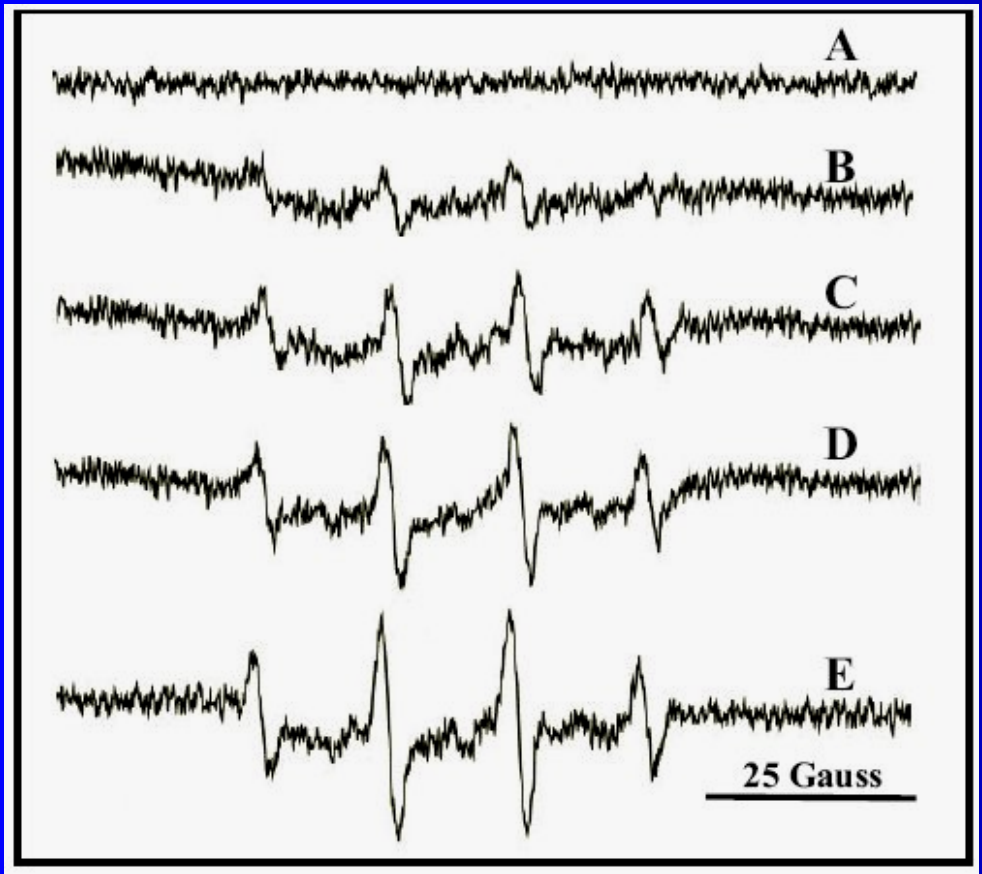


J. Muller et al., *Toxicol. Appl. Pharmacol.*, 207: 221-231, 2005

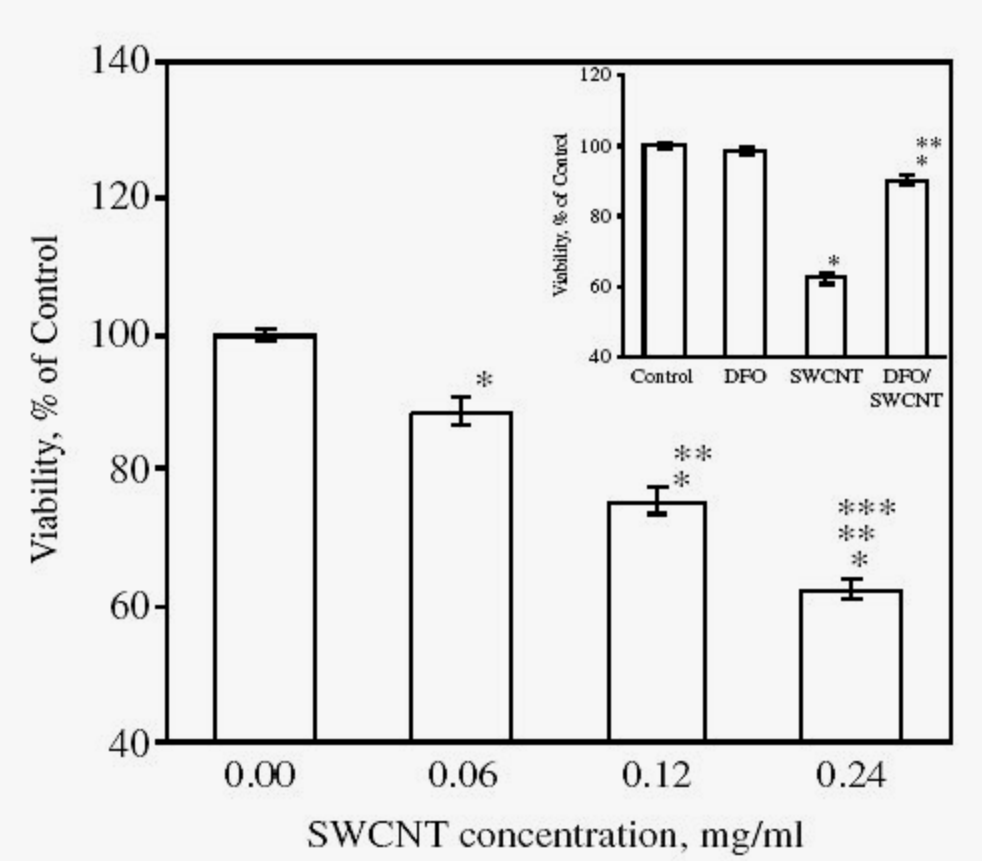
Health Risk Assessment of Nanomaterials

Single Wall Carbon Nanotube Dermal Toxicity

Hydroxyl Radical Formation (Oxidative Stress)



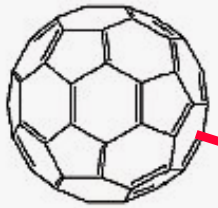
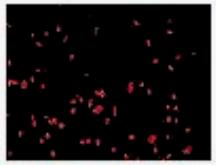
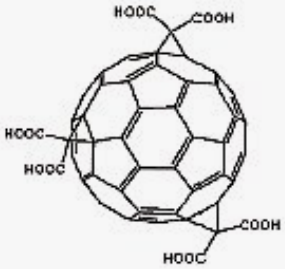
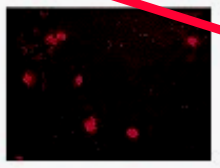
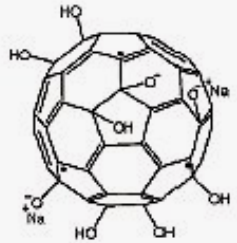
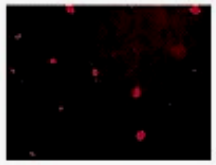
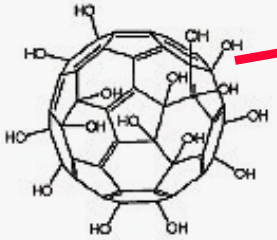
Cellular Toxicity (Epidermal Keratinocytes)

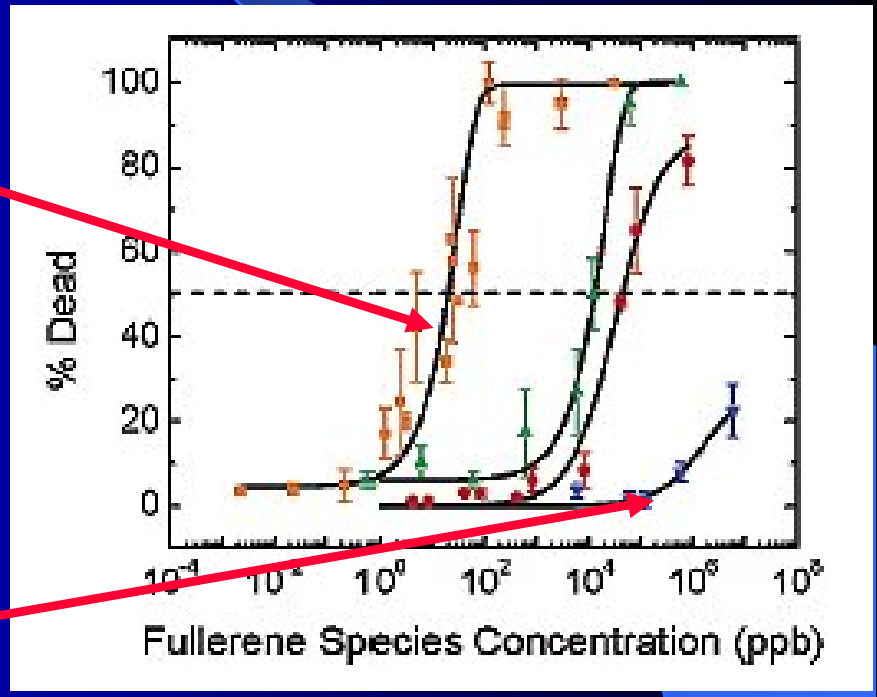


A. Shvedova et al., *J. Toxicol. Environ. Health*, Part A, 66:1909-1926, 2003
N.A. Monteiro-Riviere et al., *Toxicol. Lett.* 155:377-384, 2005. (MWCNTs)

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			
$Na^{+}_{2\text{-}3}$ $[C_{60}O_{7\text{-}9}(OH)_{12\text{-}15}]^{(2\text{-}3)-}$			
$C_{60}(OH)_{24}$			



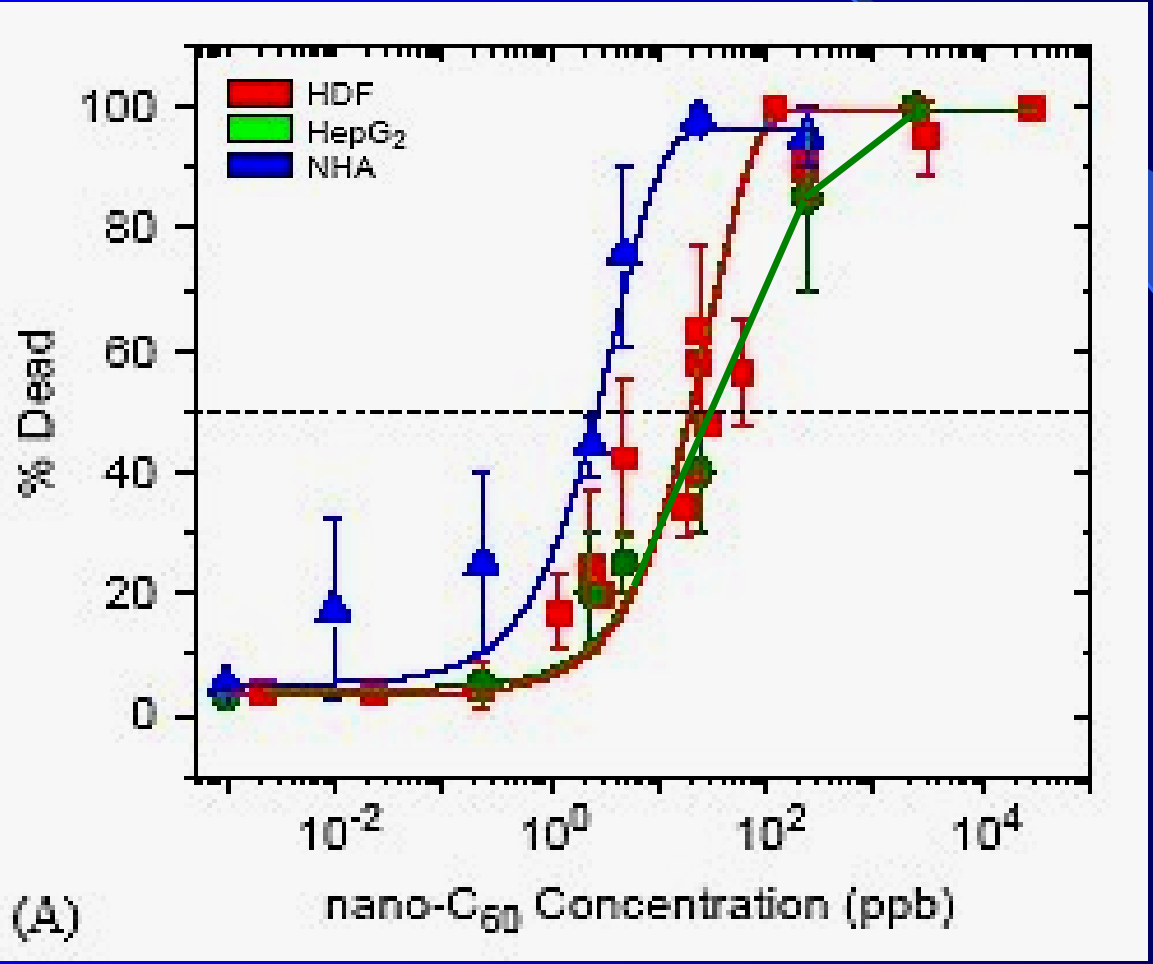
C. M. Sayes et al., *Nano Letters* 4(10):1881-1887, 2004

Health Risk Assessment of Nanomaterials

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

LC_{50}:

NHA-2ppb
HDF-20ppb
HepG2-50ppb



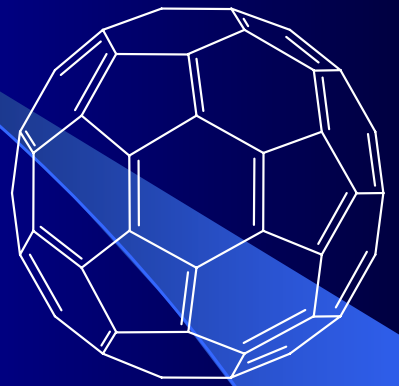
C. M. Sayes et al., *Biomaterials* 26:7588-7595, 2005

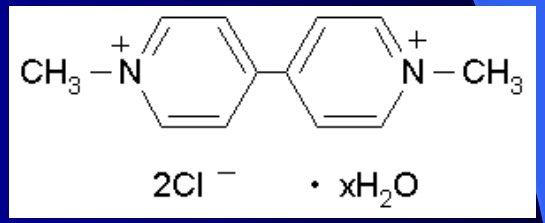
Health Risk Assessment of Nanomaterials

Comparative In Vitro Toxicity of Fullerenes

Toxicants	LC_{50}, mg/kg
$C_{60}(OH)_{24}$	> 100,000
Ethanol*	17,000
THF	11,000
Toluene	1,600
Paraquat	100
Benzo[a]pyrene*	10
nano-C_{60}	0.02
Dioxin*	0.001

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





Paraquat

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

Health Risk Assessment of Nanomaterials

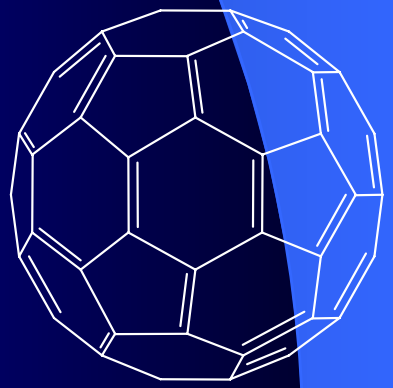
In Vivo Toxicity of Fullerenes

In Vivo **Biological Behavior of a Water-Miscible Fullerene: ^{14}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.

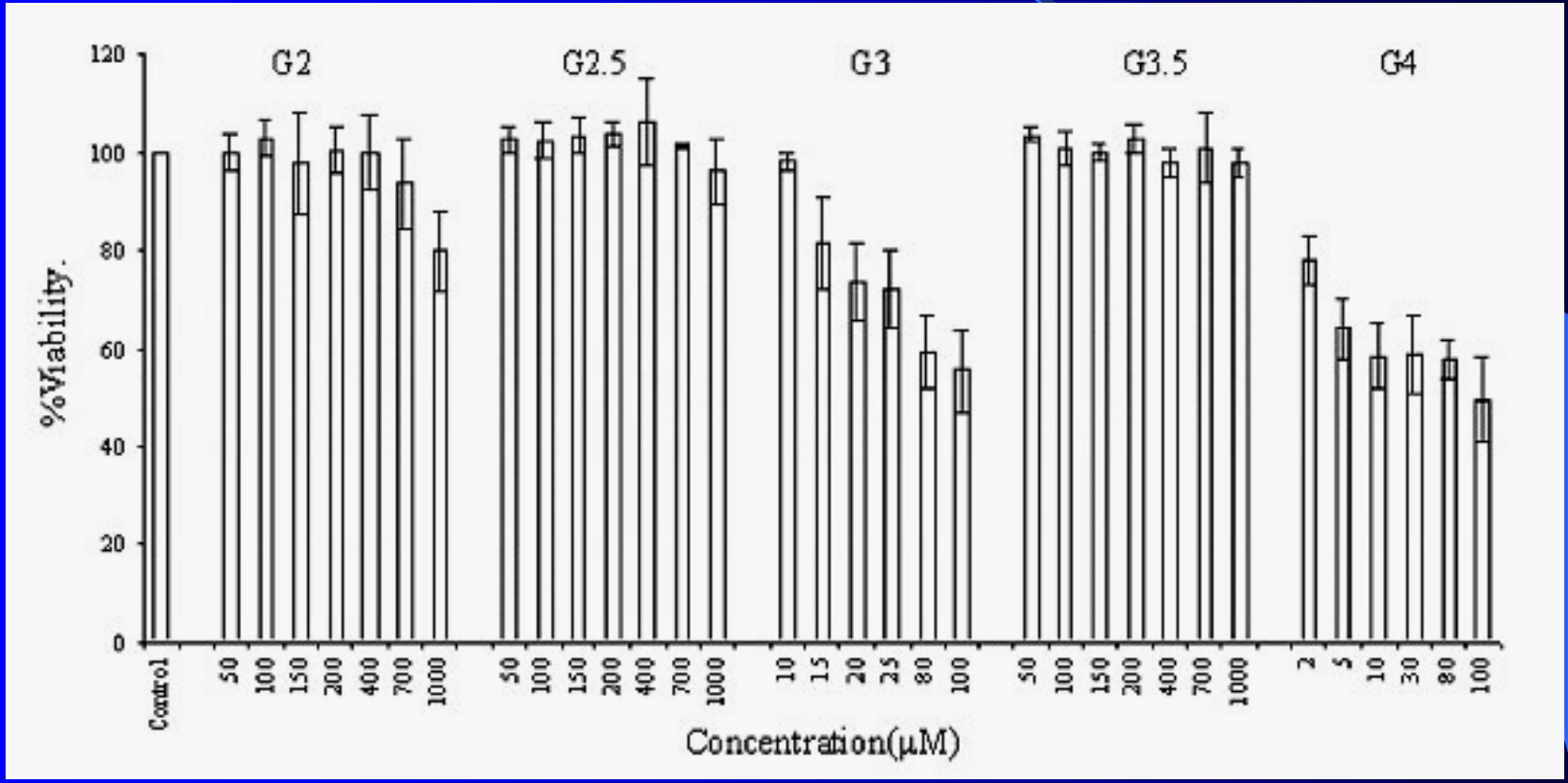


Health Risk Assessment of Nanomaterials

In Vitro Intestinal Toxicity of Dendrimers

Generation, Size, and Charge

Cationic Anionic Cationic Anionic Cationic

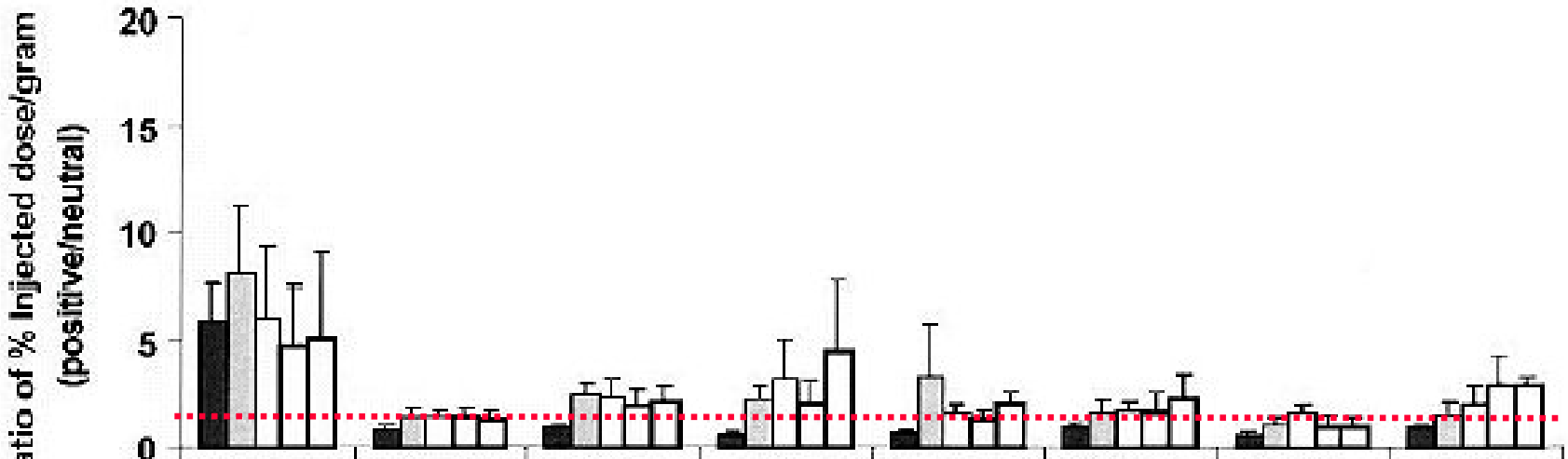


R. Jevprasesphant et al., *Intl. J. Pharmaceutics*, 252:263-268, 2003.
R. Jevprasesphant et al., Pharmaceutical Res., 20(10):1543-1550, 2003.
D. Fischer et al., Biomaterials, 24:1121-1131, 2003

Health Risk Assessment of Nanomaterials

Organ Distribution of Dendrimers

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



	lungs	heart	liver	spleen	pancreas	kidney	tumor	brain
5 min	5.88	0.86	0.92	0.50	0.61	0.97	0.58	0.96
1	8.04	1.40	2.46	2.25	3.37	1.59	1.06	1.53
1 day	6.05	1.43	2.40	3.21	1.61	1.73	1.61	2.08
4 days	4.70	1.38	1.93	2.09	1.30	1.59	0.94	2.86
7 day	5.07	1.34	2.14	4.53	2.04	2.25	0.99	2.85

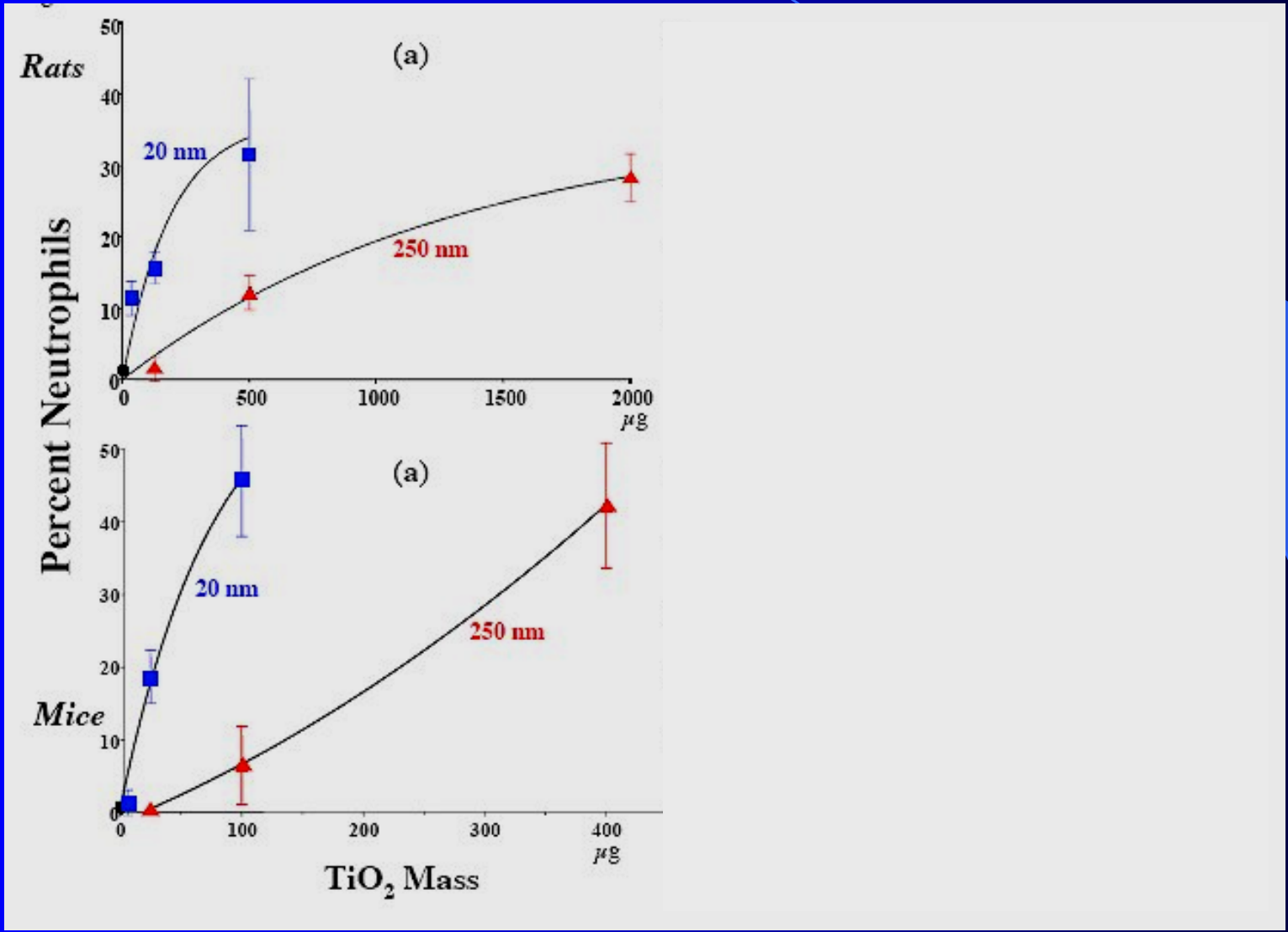
Tissues

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.

S.S. Nigavekar et al., *Pharmaceutical Res.* 21(3):476-483, 2004

Health Risk Assessment of Nanomaterials

Pulmonary Toxicity of Fine vs. Nano-TiO_2 Size vs. Surface Properties

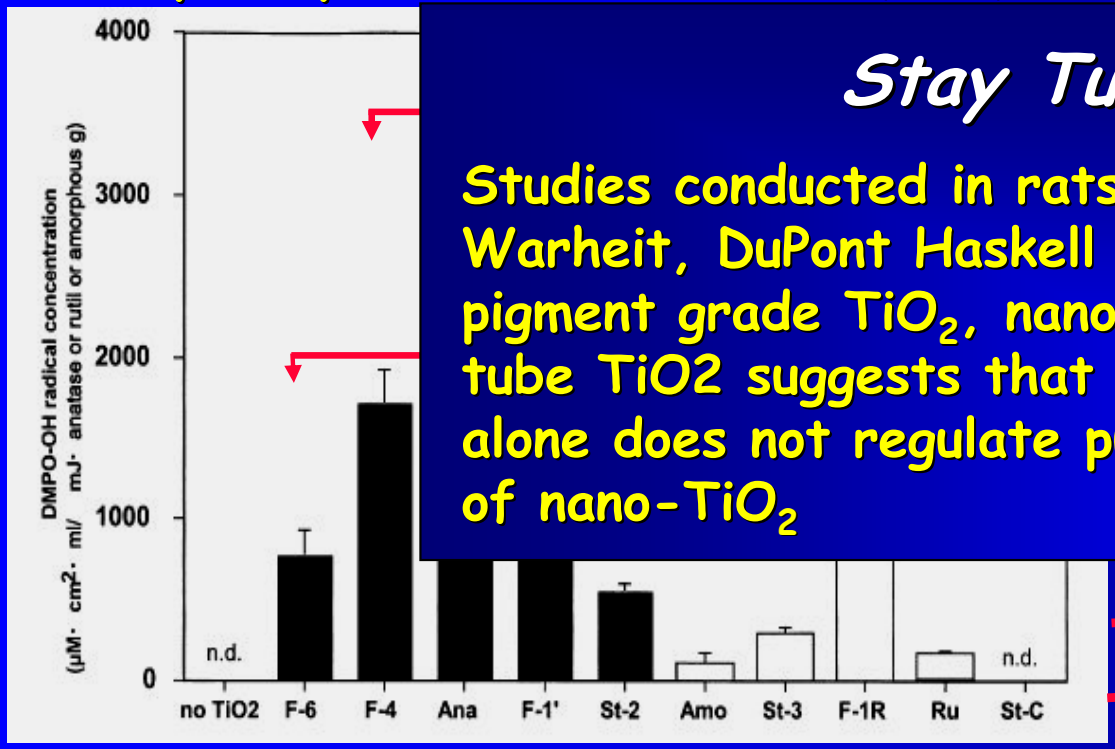


Oberdorster[3], *Environ. Health Perspec.*, 2005.

Health Risk Assessment of Nanomaterials

Nano-TiO_2: Size vs. Surface Properties

Oxidative Stress
Hydroxyl Radical Production (ESR)



F6 F4 Ana Amo St3

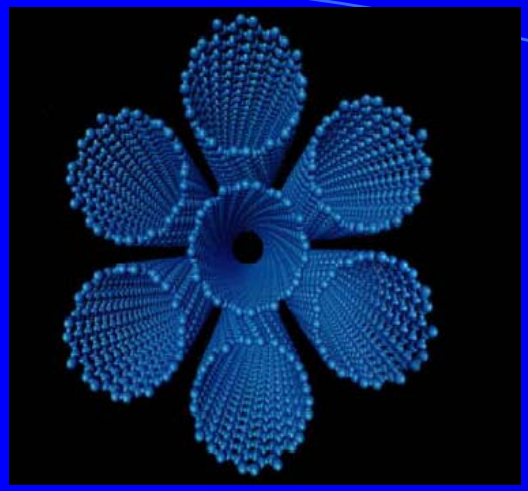
Stay Tuned

Studies conducted in rats by Dr. David Warheit, DuPont Haskell Laboratory with pigment grade TiO_2, nano-dot TiO_2, nano-tube TiO2 suggests that size/surface area alone does not regulate pulmonary toxicity of nano-TiO_2

st Samples

		Size (nm)	Surface Area (m^2/g)
		15	105
		30	53
		30	53
Amo	Amorphous	17	96
St3	1/99	37	44

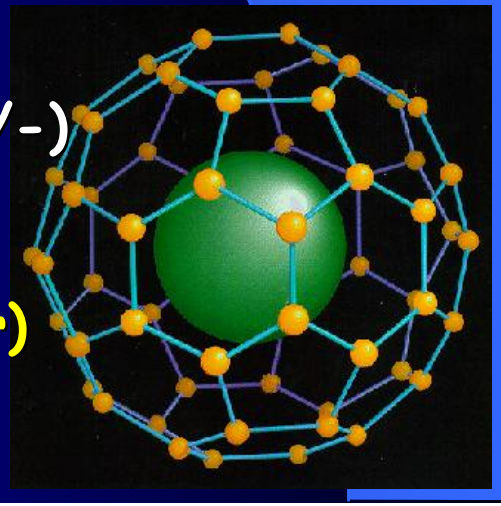
Uchino et al. *Toxicol. In Vitro*, 16:629-635, 2002



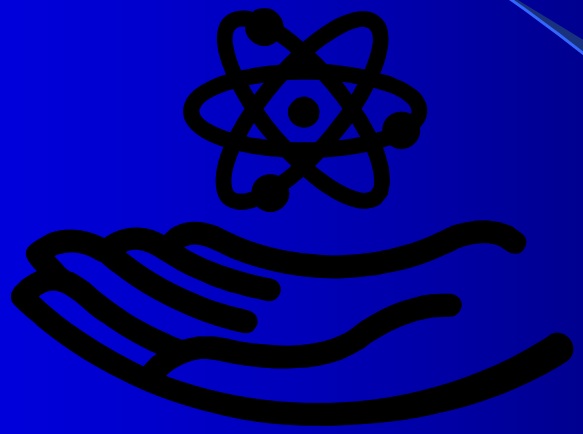
Health Effects Nanomaterials (Nanotoxicology)

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)