Health Risk Assessment of Manufactured Nanomaterials: More Than Just Size

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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-TiO₂, 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

Ecopaint

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

Environmental Interactions, Transformations, and Fate? Potential Health Effects?
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Air Pollution Control: Nano-metals
\(\text{Al}_2\text{O}_3; \text{Transition Metals; CeO}_2; 5 - 10\text{nm}\)

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:
\(\uparrow > 50\% \text{ in each: benzene; } 1,3\text{-butadiene; acetaldehyde (Air Toxics)}\)
\(\downarrow 80\% \text{ PAHs (Air Toxic)}\)
\(\downarrow 8-20\% \text{ NOx (NAAQ)}\)
\(\uparrow 50-100\% \text{ CO (NAAQ)}\)
Risk Assessment of Nanotechnology

Reports: Uncertainties in Nanotechnology Risk Assessment

- Spring 2004 Swiss Report
- Reinsurance Company
- July 2004 UK Royal Society Report
- August 2004 German NanoSafe Report
- November 2004 UK HSE Report
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Publications: Uncertainties in Nanotechnology Risk Assessment

Dreher, Toxicol. Sci., 2004
Hood, Environ. Hlth. Perspect., 2004
Oberdorster et al., Environ. Hlth. Perspect., 2005
Reijeiders, J. Cleaner Production, 2005

Tsuji et al., Toxicol Sci., 2005
Thomas & Sayre, J. AWMA, 2005
Biswa & Wu, Toxicol. Sci., 2005
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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
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What do we know about nanoparticle toxicology?

Particle Toxicology Database: PubMed 2004–1982

# of Publications

Toxicity Search Query

Nanomaterials
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Size: Deposition, Translocation and Fate of Nanoparticles


($^{99m}$Tc nano-CB, 5 - 10nm)
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Size: Deposition, Translocation, and Fate

Translocation of Pulmonary Deposited Carbon Black Nanoparticles to Other Organs

Excess Carbon-13 Concentration after 5 days Ultrafine $^{13}$C Exposure

(297 μg/m$^3$; CMD = 31 nm; GSD = 1.76)

(n=4, Striatum n=3)

Local versus Systemic Health Effects

G. Oberdorster et al., US EPA, PM BOSC Review, 2005
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What do we know about the toxicity of nanomaterials used in pollution remediation and control?

### PubMed Search Results

<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Number Citations on Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Nanotubes</td>
<td>9</td>
</tr>
<tr>
<td>Fullerenes</td>
<td>37</td>
</tr>
<tr>
<td>Dendrimer</td>
<td>29</td>
</tr>
<tr>
<td>Nano (ultrafine)-TiO$_2$</td>
<td>16</td>
</tr>
<tr>
<td>Nano-Zero Valent Iron</td>
<td>0</td>
</tr>
<tr>
<td>Nano-Cerium Dioxide</td>
<td>0</td>
</tr>
<tr>
<td>Nano (ultrafine)-ZnO</td>
<td>11</td>
</tr>
<tr>
<td>Ceramic Nanoparticles</td>
<td>0</td>
</tr>
</tbody>
</table>
Health Risk Assessment of Nanomaterials

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

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
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Single Wall Carbon Nanotube Pulmonary Toxicity

Size vs. Shape vs. Surface Properties

FIGURE 2. Comparison with cytotoxicity to AM among SWNTs, MWNT10, and C₆₀ at different dosage. Results are mean ± SE of triplicate experiments, $P < 0.05$.  

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Single Wall Carbon Nanotube Pulmonary Toxicity

Intact versus Ground CNTs

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Single Wall Carbon Nanotube Dermal Toxicity

Hydroxyl Radical Formation
(Oxidative Stress)

Cellular Toxicity
(Epidermal Keratinocytes)

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

C. M. Sayes et al., Nano Letters 4(10):1881-1887, 2004
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In Vitro Toxicity of Fullerenes
(Dermal Fibroblasts; Liver Cells; Astrocytes)

LC₅₀:
NHA - 2 ppb
HDF - 20 ppb
HepG2 - 50 ppb

C. M. Sayes et al., Biomaterials 26:7588-7595, 2005
# Health Risk Assessment of Nanomaterials

## Comparative In Vitro Toxicity of Fullerenes

<table>
<thead>
<tr>
<th>Toxicants</th>
<th>LC$_{50}$, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{60}(OH)_{24}$</td>
<td>&gt; 100,000</td>
</tr>
<tr>
<td>Ethanol*</td>
<td>17,000</td>
</tr>
<tr>
<td>THF</td>
<td>11,000</td>
</tr>
<tr>
<td>Toluene</td>
<td>1,600</td>
</tr>
<tr>
<td>Paraquat</td>
<td>100</td>
</tr>
<tr>
<td>Benzo[a]pyrene*</td>
<td>10</td>
</tr>
<tr>
<td>nano-C$_{60}$</td>
<td>0.02</td>
</tr>
<tr>
<td>Dioxin*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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

 Courtesy of C. M. Sayes, Rice University, CBEN
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**In Vivo Toxicity of Fullerenes**

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

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

Generation, Size, and Charge

Cationic  Anionic  Cationic  Anionic  Cationic

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.

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Pulmonary Toxicity of Fine vs. Nano-TiO$_2$
Size vs. Surface Properties

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Nano-TiO₂: 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 TiO₂, nano-dot TiO₂, nano-tube TiO₂ suggests that size/surface area alone does not regulate pulmonary toxicity of nano-TiO₂.

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)