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
Health Risk Assessment of Nanomaterials

Air Pollution Control: Photo-Catalytic Nano-TiO₂, ZnO

Paving and painting out pollution

Self cleaning glass/surfaces

-2002, nanoTiO₂/cement, Milan, Italy, 60% decrease in near road side NOx 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) NOx reduction

Air

Environmental Interactions, Transformations, and Fate? Potential Health Effects?
Health Risk Assessment of Nanomaterials

Air Pollution Control: Nano-metals
\[(\text{Al}_2\text{O}_3; \text{Transition Metals}; \text{CeO}_2: 5-10\text{nm})\]

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

Reports: Uncertainties in Nanotechnology Risk Assessment
Risk Assessment of Nanotechnology

Publications: Uncertainties in Nanotechnology Risk Assessment

Dreher, Toxcol. Sci., 2004
Hood, Environ. Hlth. Perspect., 2004
Oberdorster et al., Environ. Hlth. Perspect., 2005
Reijeiders, J. Cleaner Production, 2005
Tsuji et al., Toxcol Sci., 2005
Biswa & Wu, J. AWMA, 2005
Thomas & Sayre, Toxcol 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

Risk Assessment
- Dose-Response Assessment
- Hazard Identification
- Exposure Assessment

Risk Management
- Statutory and Legal Considerations
- Public Health Considerations
- Social Factors
- Risk Management Options
- Political Considerations
- Economic Factors

Risk Characterization
Risk Management Decision

*Adapted from:
Health Risk Assessment of Nanomaterials

What do we know about nanoparticle toxicology?

Particle Toxicology Database: PubMed 2004-1982

Toxicity Search Query

# of Publications

PM or Particle
Diesel Particle
Coal fly ash
oil fly ash
silica
uf silica
carbon black
uf carbon black
TiO2
uf TiO2
Fullerene
Carbon nanotubes
Quantum Dots (CdSe; CdZn)
Dendrimer

Nanomaterials
Health Risk Assessment of Nanomaterials

Size: Deposition, Translocation and Fate of Nanoparticles

![Graph showing CPM per gram of blood over time (min).](image)


($^{99m}$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

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

$(297\mu g/m^3; \text{CMD} = 31nm; \text{GSD} = 1.76)$

$(n=4, \text{Striatum} n=3)$

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

<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>

Limited Toxicological Database
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
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 C₆₀ at different dosage. Results are mean ± SE of triplicate experiments, P < 0.05.

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)

Health Risk Assessment of Nanomaterials

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

Health Risk Assessment of Nanomaterials

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

\[ \text{LC}_{50}: \]
- 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>0.0001</td>
</tr>
</tbody>
</table>

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

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

![Paraquat](image)
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.  

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

**In Vitro Intestinal Toxicity of Dendrimers**

*Generation, Size, and Charge*

### Organ Distribution of Dendrimers

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

![Graph showing organ distribution of dendrimers](image)

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

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

Health Risk Assessment of Nanomaterials

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)