UPDATES IN NANOTOXICOLOGY: NEW CONCEPTS OF DOSE & IMPLICATIONS FOR OCCUPATIONAL HEALTH

Dhimiter Bello, ScD, MSc
Associate Prof., Exposure Biology
Department of Work Environment
University of Massachusetts Lowell
Visiting Scientist, MIPS/HSPH

Outline

A. Engineered Nanomaterials (ENM)
   - Definitions, Types, ENM vs. UFP & Use

B. Nanotoxicology
   - Metrics, Biokinetics, Disease

C. NanoEHS Issues – Catching up?
   - Instruments, Regulations

D. Discussion

dhimiter_bello@uml.edu
Outline

A. Engineered Nanomaterials (ENM)
   - Definitions, Types, ENM vs. UFP

B. Nanotoxicology
   - Metrics, Biokinetics, Disease

C. NanoEHS Issues
   - Instruments, Regulations, PPE

D. Case Study & Discussion

dhimiter_bello@uml.edu

Nano Vocabulary

Engineered Nanomaterial (ENM):
- Intentionally produced
- One or more dimensions in the nanoscale (1-100 nm)
- Exhibit novel properties compared to the bulk counterpart

<table>
<thead>
<tr>
<th>Nanostructure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticle</td>
<td>Nano-object with all three external dimensions in the nanoscale.</td>
</tr>
<tr>
<td>Nanoplate</td>
<td>Nano-object with one external dimension in the nanoscale and the two other external dimensions significantly larger.</td>
</tr>
<tr>
<td>Nanofibre</td>
<td>Nano-object with two similar external dimensions in the nanoscale and the third dimension significantly larger.</td>
</tr>
<tr>
<td>Nanotube</td>
<td>Hollow nanofibre.</td>
</tr>
<tr>
<td>Nanorod</td>
<td>Solid nanofibre.</td>
</tr>
<tr>
<td>Nanowire</td>
<td>Electrically conducting or semi-conducting nanofibre.</td>
</tr>
<tr>
<td>Quantum dot</td>
<td>Crystalline nanoparticle that exhibits size-dependent properties due to quantum confinement effects on the electronic states.</td>
</tr>
</tbody>
</table>
Naturally Occurring & Incidental Nanoparticles (Ultrafine Particles)

- **Viruses & Other Microorganisms**
  - Viruses, 10-70nm

- **Incidental – Natural**
  - Volcanoes, Wild Fires, Desert Storms, Ocean Spray

- **Incidental – Anthropogenic**
  - Combustion, Welding, Paint pigments

Rotavirus, 76.5nm
Inflammation of GI tract

What’s so special about nanoscale?

1. Quantum effects dominate properties;
2. Scale at which much of biology occurs;
3. Surface & interface play a large role in materials properties & interactions

Nano Scale

Yokel & MacPhail J.Occ. Med. Toxy 2011, 6/7
Novel properties at the nanoscale

- Sunscreens, TiO2 & ZnO nano vs macro

http://www.nanoandme.org/nano-products/cosmetics-and-sunscreen/


Novel Properties: Engineered Water NanoStructures (EWNS)

- EWNS have ~10 electrons per structure
- LIFETIME (~10 min)

Demokritou et al 2013

Center for Nanotechnology and Nanotoxicology at Harvard School of Public Health
Novel Surface Inactivation

Pyriotakis et al 2013

Center for Nanotechnology and Nanotoxicology
at Harvard School of Public Health

Snapshot of commercially available ENM

http://www.nanowerk.com/phpscripts/n_dbsearch.php
### Commercial Nanomanufacturing in NL

<table>
<thead>
<tr>
<th>Sector</th>
<th>Functional Property</th>
<th>Exposure Situation</th>
<th>Market Penetration (%)</th>
<th>Average Number of Companies per Sector</th>
<th>Average Number of Exposed Workers per Company</th>
<th>Number of Potentially Exposed Workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of wet concrete</td>
<td>Pozzolanic activity</td>
<td>Mechanical mixing of nano-concentrations and -composites (powder and liquid) with relatively low energy levels</td>
<td>80</td>
<td>190</td>
<td>8</td>
<td>152</td>
</tr>
<tr>
<td>Protection of concrete</td>
<td>EO22 and ZnO for UV absorption</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Paint production</td>
<td>EO22 for absorption of alcohols</td>
<td>Not applicable</td>
<td>1</td>
<td>29</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Paper production</td>
<td>Nano-ink for strength and durability</td>
<td>Mechanical mixing of nano-concentrations powder and product with relatively low energy levels</td>
<td>1</td>
<td>878</td>
<td>6.3</td>
<td>56</td>
</tr>
<tr>
<td>Plastic production</td>
<td>Nanoclay or nano silica for strength and durability, Ag for antimicrobial effect, ZnO2 as scratch-resistant coating</td>
<td>Not applicable</td>
<td>100</td>
<td>150</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>Tire production</td>
<td>Carbon black in filler and nano silica for strength and durability</td>
<td>Mechanical mixing of nano-concentrations powder with relatively low energy levels</td>
<td>100</td>
<td>150</td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>Tower production</td>
<td>Rheological properties</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100</td>
<td>150</td>
<td>1</td>
<td>499</td>
</tr>
</tbody>
</table>

Bekker et al, AnnHyg 2012
Commercial Uses

~20% of building materials contain nano ENM (Source: Harvard School of Design)

<table>
<thead>
<tr>
<th>MNMs</th>
<th>Architectural/Construction Materials</th>
<th>Expected Benefits</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>concrete</td>
<td>mechanical durability; crack prevention</td>
<td>5, 9, 16, 134</td>
</tr>
<tr>
<td></td>
<td>ceramics</td>
<td>enhanced mechanical and thermal properties</td>
<td>17, 18</td>
</tr>
<tr>
<td></td>
<td>solar cell</td>
<td>effective electron mediation</td>
<td>6, 22</td>
</tr>
<tr>
<td></td>
<td>concrete</td>
<td>reinforcement in mechanical strength</td>
<td>5, 6, 8, 9, 114</td>
</tr>
<tr>
<td></td>
<td>ceramics</td>
<td>corrosion, light transmission; fire resistant</td>
<td>115, 116</td>
</tr>
<tr>
<td></td>
<td>window</td>
<td>flame-generating; anti-reflection</td>
<td>6, 22</td>
</tr>
<tr>
<td></td>
<td>window</td>
<td>superhydrophobic; anti-fogging; fouling resistance</td>
<td>7, 10, 20, 24</td>
</tr>
<tr>
<td></td>
<td>solar cell</td>
<td>non-utility electricity generation</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>concrete</td>
<td>increased compressive strength; abrasion-resistant</td>
<td>5, 114</td>
</tr>
<tr>
<td></td>
<td>G4 nanoparticles</td>
<td>steel</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ag nanoparticles</td>
<td>coating/painting</td>
<td>11</td>
</tr>
</tbody>
</table>

~60 studies in all, 25 studies in workplaces

- Area Samplers
- Number concentration & size distribution + STEM/EDS
- Need for standardization & harmonization of measurements & approaches
- Collection of systematic contextual information
- Tiered Approach to understanding nature of exposures
Where do Exposures to ENM OCCUR?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Range of arithmetic means during activity</th>
<th>Number conc. by SMPS (particles/cm³)</th>
<th>Surface area concentration by LQI-DC (µm²/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production—commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>1,661–39,087 (n = 12)</td>
<td>25–74 (n = 8)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>1,339–23,566 (n = 8)</td>
<td>21–69 (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Production—non-commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>3,887–21,441 (n = 7)</td>
<td>43–129 (n = 6)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>2,040–12,919 (n = 7)</td>
<td>35–93 (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Downstream use—commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>6,272–7,8376 (n = 9)</td>
<td>17–88 (n = 11)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>6,242–32,515 (n = 7)</td>
<td>11–51 (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Downstream use—non-commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>234–380,404 (n = 57)</td>
<td>36–173 (n = 13)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>199–34,507 (n = 55)</td>
<td>27–147 (n = 10)</td>
<td></td>
</tr>
</tbody>
</table>

Brouwer et al J Nanoparticle Res 2013
Nano carbon black

Image: D. Bello

Image: D. Bello
ENM have made their way into toner formulations & do become airborne

Bello et al 2013 Nanotoxicology

Nanotoxicology Highlights

- BIOKINETICS & TRANSLOCATION
- DOSE METRICS
- SURFACE ACTIVITY/ ROS
- High Aspect Ratio Materials
Inhalation – Primary Exposure Pathway

CONCERNS

Phagocytosis
Clearance by mucociliary escalator
Unique Tox Behavior
Translocation to other organs

The Lung

Distance to RBC/capillaries & Sensitive CELLS: Macrophages & Dendritic

- SA, 140 m²
- >5x10⁸ alveoli

Alveolar Wall, <1 um

Source: Oberdörster et al 2005 EHP 113 7

Source: Urmira Kodavanti
Gut & Skin

GI Tract, S.Int. SA, 200 m²
Barrier, 20-25 um thick

SKIN: SA, 2 m²
Barrier, 30-50 um

HD blood > 34nm
Little translocation
If +, retained in the lungs, TOXIC

HD blood between 6-34 nm

CHARGE governs transl. to LN…
+

+/– enable fast translocation
(within 3 -30 min)

HD blood < 6nm
Fast translocation & clearance in urine

SIZE & CHARGE RULE...
Choi et al 2010 Nature Biotechnology
doi:10.1038/nbt.1696

Kreyling Nature Biotech 2010
Figure 5. Phagocytosis and clearance of particles by alveolar macrophages is effective for fine particle, but inefficient for nanoparticles (<100 nm).

Figure 6. In vivo retention of inhaled nanosized and larger particles in alveolar macrophages (left side) and in exhaustively lavaged lungs (epithelial and interstitial retention, right side) 24 h post exposure. The alveolar macrophage is a most important defense mechanism in the alveolar region for fine and coarse particles, yet inhaled single NP are not efficiently phagocytized by alveolar macrophages.
SIZE & CHARGE RULE...
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CHARGE governs transl. to LN...
+, Little translocation
-/+ or – enable fast translocation
(within 3 -30 min)

HD blood < 6nm
Fast translocation & clearance in urine

Kreyling Nature Biotech 2010

Translocation Out of the Exposure Organ
Technicium-labeled aerosol to expose human volunteers, WB Gamma camera

Nemmar et al, Circ, 2002; 105 (4): 411-41
Leaching of Tc label; much, much less translocation
Humans: Limited Extra-pulmonary Translocation
(based on limited data)

Human, $^{99m}$Tc-EC-NP, 20 breaths,
100 nm CMD, $10^5$ cm$^{-3}$

- NP accumulation in secondary target organs <1% by number
- ng mass
- Consistent with rodent data

Moller et al AJRCM 2008 & Wiebert et al 2004

Systemic translocation of Ir NP towards 2nd target organs
Slide courtesy of W. Kreyling

WKY rat, $^{152}$Ir NP, 1 hr exposure
15 nm CMD, $10^7$ cm$^{-3}$, 0.2 mg/m$^3$

Long-term translocation kinetics
same exposure

Kreyling et al., 2002

Same for: spleen, heart, kidneys, brain

Helmholtz Zentrum München
German Research Center for Environmental Health