Nanotechnology Updates for the Biosafety Lab

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Northeast Biological Safety Association
October 2, 2015
Outline

- Nanotechnology
  - Overview
  - Emerging nanotechnologies and next generation products
  - Workplace and Biosafety impact
- Current practices and updates in nano risk assessment and management
- Initiatives and resources
Nanoscale Sciences and Technologies

Manipulation at the atomic or molecular level for novel properties.

- Engineered nanomaterials (ENMs)
- Nano-objects and their agglomerates and aggregates (NOAA)

ENM high-volume examples:

- Carbon nanotubes (CNTs), nanofibers (CNFs), graphene
- Titanium dioxide
- Silver

Nanotechnology and Advanced Materials

- **Next Generation**
  - Ex: Aerogels, superomniphobic, auxetic, smart materials

- **Functional**
  - Ex: Biomaterials, NEMs

- **Self-Assembly**
  - Ex: Self-healing materials, controlled self-assembly such as 3D printers to create sequences for DNA, RNA, or proteins

Image: Aerogel. NASA [http://www.nasa.gov/centers/ames/images/content/140926main_ACD97-0042-16.jpg](http://www.nasa.gov/centers/ames/images/content/140926main_ACD97-0042-16.jpg)
Nanotechnology Growth

- Funding for emerging nanotechnology grew 40-45% per year from 2010-2013.
- Worldwide revenue from ENMs, nano-intermediates, and nano-enabled products continues to grow and is predicted to reach $4.4 trillion by 2018.

Nanomaterial Lifecycle

Lifecycle perspective in risk assessment for a nano-enabled consumer product

How to maximize nanotechnology benefits while minimizing potential adverse impact?

Fig: US EPA 100/B-07/001, Figure 16, 2007
Nanotechnology Risk Assessment and Management

**Challenges**
- Gaps in toxicity and exposure data; uncertainty re: metrics
- Numerous materials, properties, applications, and potential transformations throughout the lifecycle
- Limitations or lack of validated methods for detection and measurement
- Little standardization in data analysis and reporting

**Current/Future Directions**
- Screening and categorical approaches
- Coordinated research efforts by materials scientists, toxicologists, IHs
- Prevention through Design
- Control/risk banding models
- Precautionary approach – As low as reasonably practicable
- Government-industry-academic partnerships
Physicochemical properties and characteristics of ENMs

- Size
- Surface area
- Shape
- Solubility
- Composition
- Charge
- Structure
- Concentration

Characteristics

Transformation
Behavior
Fate

Media/Matrix (Product, Biological or Environmental)
ENMs in the Workplace

- Estimated 6 million workers in nanotechnology fields by 2020 including 2 million in the US (Roco et al. 2010)
- Workers have the potential for exposure to materials with novel sizes, configurations and physical chemical properties
- Existing mass-based occupational exposure limits (OELs) for parent/bulk materials may not be sufficiently protective

Convergence and advanced materials
Biotechnology       Nanotechnology
Biosafety Levels    Nanomaterial Risk Levels
Nanotechnology and Biosafety

- Nanomedicine
  - Drug delivery
  - Nanodevices
  - Biosensors
  - Bioimaging

- Other nanobioscience applications
  - 3D printing for DNA, RNA, proteins
  - Nano-enabled products

- *In vivo* and *in vitro* toxicity testing of ENMs used in diverse industries
Workplace Risk Assessment and Management

After identification of hazards from ENMs or nano-enabled products:

- **Hazard Characterization**: Evaluate data on physiochemical properties and toxicity. Consider solubility, size, shape, form, charge, surface chemistry, composition, crystallinity, etc.

- **Exposure Assessment**: Use the most practical method to evaluate data on exposure conditions (e.g., process, physical state, amount, task frequency, duration, etc.). Document approach/results.

- **Risk Characterization**: Follow screening methods, banding models, and other recommended approaches. Consider uncertainty.

- **Risk Management**: Apply the hierarchy of controls. Communicate risks and periodically re-evaluate and improve where feasible.

See also The Synergist Nov 2013 online edition, supplemental table (Dimitri J, Rickabaugh K, Webb P and Shepard M, with table adapted from BSI 2007).
Hazard Identification and Evaluation

- Hazard identification can be challenging due to lack of or insufficient reporting on labels and SDSs
- Hazard evaluation is increasingly relying on screening methods and categorical approaches

Approaches for practitioners:
- Hazard banding
  - Ex. BSI 2007 approach: 1. Fibrous; 2. CMAR; 3. Insoluble; and 4. Soluble
- Hazard categorization using control banding models
- Occupational exposure banding (OEB) - NIOSH research indicates further data and model testing/validation are necessary
Exposure Assessment and Control

- Exposure modeling and sampling approaches (Ex: NIOSH NEAT v2)
- Surveillance and biomonitoring
- Control banding/risk banding
- Prevention through design approaches
  - Safer engineered nanomaterials
- Traditional hierarchy of controls
  - Nanoparticles follow classical laws of aerosol physics
ENM Sampling Approaches

Vary from screening level to more comprehensive approaches. Metrics may include:

- Number
- Mass
- Size
- Surface area

**Typically use a combination of approaches – direct reading instruments and filter-based samples**
Limitations in Sampling Approaches

- **Measurement**
  - Validated methods lacking
  - Time-resolved devices non-specific
  - Electron microscopy methods resource-intensive
  - Differentiation from incidental ultrafine particles

- **Interpretation**
  - Metrics and correlation to biological activity
  - Comparative values limited
  - Consensus lacking on size ranges to include and data analysis methods
Reference Values: Mass

- 1 µg/m³ elemental carbon 8-hr TWA for CNTs/CNFs (NIOSH, 2013)
- 0.3 mg/m³ 10-hr TWA for nanoscale titanium dioxide (NIOSH, 2011)
- 0.3 mg/m³ TWA as an upper bound categorical guideline adjusted for other poorly soluble low toxicity (PSLT) nanoparticles (Schulte et al., 2010; NIOSH, 2011)
- 0.06 x Bulk OEL for insoluble, non-fibrous ENMs (BSI, 2007)
- Nanosilver – NIOSH Roundtable on OELs at AIHce 2016
Reference Values: Number

- Benchmark levels above background exposures for biopersistent particles 1-100 nm (IFA, 2009, 2011)
  - 20,000 p/cc for granular ENMs with density > 6,000 kg/m³
  - 40,000 p/cc for granular ENMs with density < 6,000 kg/m³
  - 10,000 f/m³ for CNTs as a provisional fiber concentration

- 20,000 p/cc above background (BSI, 2007)

- Literature:
  - Relative difference: Task/Background > 1
  - Absolute difference: Task – Background > 0
  - Confidence intervals
  - Statistically significant difference between task and background

*Differences in metric being compared (max, median, GM, AM)
Exposure Assessment: Example Sampling Framework

ICP-AES: inductively coupled plasma - atomic emission spectroscopy.
TEM/EDX: transmission electron microscopy/energy dispersive x-ray spectroscopy.
NOAA in Surface Vacuum Samples

A. Microvacuum sample collected on handle/control panel of HEPA vacuum used in bulk slurry delivery area in WWT tank, acidic slurry system (PC filter), by TEM/EDX. 40,000x. ©CNSE; images by iATL. 79.2 x 80.6 nm. EDX: Si (90 wt-%) CaCr.

B. Microvacuum sample collected on access cover to the subfab (MCE filter), by TEM/EDX. 40,000x. ©CNSE; images by iATL. 77.7 x 74.9 nm; 89.5 x 87.1 nm. EDX: SiAl (90 wt-%) CaCrFe.

Risk Management and Control of Workplace ENM Exposures

Examples of exposure factors to consider include:

Factors Influencing Control Selection

Figure: NIOSH 2009-125, Figure 8-3, March 2009.
Control Banding (CB) Framework

Risk assessment and management approach used where toxicological and/or exposure data are limited.

Uses categories (bands) to describe:
- Hazard (severity)
- Exposure (probability)

Recommends a set of controls:
- Limited number of approaches
- Applies existing knowledge

Figure: COSSH Essentials (UK).
ENM Control/Risk Banding Approaches

- Precautionary Matrix (SUI)

- CB Nanotool (US DOE/LLNL)
  [http://controlbanding.net/](http://controlbanding.net/)

- ANSES CB tool (FR)

- ISO 12901-2

- Stoffenmanger Nano (NL)
  [https://nano.stoffenmanager.nl/](https://nano.stoffenmanager.nl/)

- GoodNanoGuide (US)
  [https://nanohub.org/groups/gng/matrix](https://nanohub.org/groups/gng/matrix)

- Genaidy et al., 2009 for CNF production

- Others
Considerations in Model Selection or Development

- Type of model and output (CB or risk levels)
- Scope/application
- Source domains
- Number of bands
- Parameters
- Classification criteria
- Uncertainty
## Model Characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard bands</td>
<td>1 to 5</td>
<td>1 to 4</td>
<td>1 to 5</td>
<td>1 to 9</td>
</tr>
<tr>
<td>Hazard classification</td>
<td>Hazard class, properties</td>
<td>Toxicity, properties</td>
<td>Hazard class, toxicity, properties</td>
<td>Solubility, reactivity, toxicity</td>
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<tr>
<td>Exposure bands</td>
<td>1 to 4</td>
<td>1 to 4</td>
<td>1 to 4</td>
<td>1 to 9</td>
</tr>
<tr>
<td>Exposure classification</td>
<td>Physical state, process</td>
<td>Amount, dustiness, other conditions</td>
<td>Amount, emission potential</td>
<td>Amount, frequency, form</td>
</tr>
<tr>
<td>Control bands or risk levels</td>
<td>5 bands</td>
<td>4 bands</td>
<td>5 bands or 3 risk levels</td>
<td>2 risk levels</td>
</tr>
<tr>
<td>Uncertainty/Unknowns</td>
<td>Set to max. band</td>
<td>Assigned 75% of max. points</td>
<td>Considered (+1 band from bulk or analogous)</td>
<td>Assigned max. points</td>
</tr>
</tbody>
</table>


Figure: Shepard M. © 2014.
# Model Parameters

<table>
<thead>
<tr>
<th>Material Characteristic:</th>
<th>ANSES</th>
<th>CB Nanotool</th>
<th>ISO 12901-2</th>
<th>Precautionary Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>o</td>
<td>+</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Shape/fibrous</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Solubility</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reactivity</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td>Toxicity</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

## Exposure Characteristic:

<table>
<thead>
<tr>
<th>Exposure Characteristic:</th>
<th>ANSES</th>
<th>CB Nanotool</th>
<th>ISO 12901-2</th>
<th>Precautionary Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Frequency of exposure</td>
<td>-</td>
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<td>-</td>
<td>+</td>
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<td>No. exposed</td>
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<td>-</td>
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<tr>
<td>Amount</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Physical form</td>
<td>+</td>
<td>o</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Type of process or dustiness</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Key:**
- + present
- - not present
- o partially addressed

Figure: Shepard M. © 2014.
## CB Nanotool: Parameters & Weighting

### Severity:
- **Nanomaterial**: 70% of Severity score
  - Surface Chemistry (10 pts)
  - Particle Shape (10 pts)
  - Particle Diameter (10 pts)
  - Solubility (10 pts)
  - Carcinogenicity (6 pts)
  - Reproductive Toxicity (6 pts)
  - Mutagenicity (6 pts)
  - Dermal Toxicity (6 pts)
  - Asthmagen (6 pts)
- **Parent Material**: 30% of Severity score
  - Occupational Exposure Limit (10 pts)
  - Carcinogenicity (4 pts)
  - Reproductive Toxicity (4 pts)
  - Mutagenicity (4 pts)
  - Dermal Toxicity (4 pts)
  - Asthmagen (4 pts)

### Probability:
- Estimated amount (25 pts)
- Dustiness/mistiness (30 pts)
- Number of workers (15 pts)
- Frequency of operation (15 pts)
- Duration of operation (15 pts)

*indicates maximum points

http://controlbanding.net/
## CB Nanotool: Risk Matrix

http://controlbanding.net/

<table>
<thead>
<tr>
<th>Probability</th>
<th>Extremely Unlikely (0-25)</th>
<th>Less Likely (26-50)</th>
<th>Likely (51-75)</th>
<th>Probable (76-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>RL 3</td>
<td>RL 3</td>
<td>RL 4</td>
<td>RL 4</td>
</tr>
<tr>
<td>High</td>
<td>RL 2</td>
<td>RL 2</td>
<td>RL 3</td>
<td>RL 4</td>
</tr>
<tr>
<td>Medium</td>
<td>RL 1</td>
<td>RL 1</td>
<td>RL 2</td>
<td>RL 3</td>
</tr>
<tr>
<td>Low</td>
<td>RL 1</td>
<td>RL 1</td>
<td>RL 1</td>
<td>RL 2</td>
</tr>
</tbody>
</table>

**Severity**
- Very High (76-100)
- High (51-75)
- Medium (26-50)
- Low (0-25)

**Example:** Risk framework for the CB Nanotool control banding model (Paik et al. 2008, Zalk et al. 2009).

- RL 1: General Ventilation
- RL 2: Fume hoods or local exhaust ventilation
- RL 3: Containment
- RL 4: Seek specialist advice
ISO 12901-2 Exposure Banding

Figure 5 — Exposure banding process: NOAA in suspension in a liquid
Nanomaterial Occupational Risk Management Matrix

This section provides a conceptual framework for occupational risk management designed to control and minimize exposures to engineered nanomaterials in the presence of uncertainty. Each organization should have a management structure to assess and minimize risk.

Below is the GoodNanoGuide OHS matrix in which the potential handling hazards of nanomaterials are rows labeled by the leftmost column, and the various physical forms of the nanoparticles are in four vertical columns (if you would like to approach this topic in a narrative style, please refer to the OHS Reference Manual).

First Step: Identify

<table>
<thead>
<tr>
<th>Nanoparticles in:</th>
<th>Dry Powder</th>
<th>Liquid Dispersion</th>
<th>Solid Polymer Matrix</th>
<th>Nonpolymer Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potential Hazard</td>
<td>Potential Hazard</td>
<td>Potential Hazard</td>
<td>Potential Hazard</td>
</tr>
</tbody>
</table>
Good NanoGuide

Dry Powder Weighing-Measuring Controls

Operations

Weighing and Measuring dry powders when there is the potential for aerosolization and release of nanomaterials into the workplace atmosphere.

Controls

- Ventilated Laboratory Hood or local exhaust enclosure with HEPA* exhaust filtration
- If an exhausted enclosure is not available, PPE should be used to minimize potential for respiratory, dermal and eye exposure
- Latex or nitrile clean room gloves
- Wet cleaning of laboratory hood surfaces or local exhaust enclosure following conclusion of handling operations
- The filtered air must not be recirculated into the workplace.
Key Initiatives and Organizations

- National Nanotechnology Initiative (NNI) [www.nano.gov](http://www.nano.gov)
- NIOSH
  - Nanotoxicology
  - Nanotechnology Field Research Team
- ISO Technical Committee on Nanotechnologies (TC 229)
  - WG 2 Measurement and Characterization
  - WG 3 Health, Safety and Environmental Aspects
- OECD Working Party on Manufactured Nanomaterials
  - Database on human health and environmental safety research
  - Harmonized test guidelines for nanotoxicology
  - Safety testing for representative ENMs
ISO TC 229 WG 3

Related to occupational health and safety:

- ISO/TR 12885:2008 - Nanotechnologies - Health and safety practices in occupational settings relevant to nanotechnologies
  - Under consideration for revision - led by the US (Vladimir Murashov, NIOSH)


- ISO/DTR 18637 - General framework for the development of occupational exposure limits for nano-objects and their aggregates and agglomerates – under development, led by the US (Vladimir Murashov, NIOSH)

- Potential for future work items:
  - exposure measurement techniques for specific nanomaterials
  - engineering controls for specific nanomaterials and manufacturing processes

*Potential future work items from Heather Benko, ANSI, via email August 18, 2015*
AIHA Nanotechnology Working Group (NTWG)

2015-2016 Leadership Team
Chair – Michele Shepard
Vice Chair – Paul Webb
Secretary – John Baker
Secretary-Elect – Amanda Archer

AIHA Liaison – Thursa L. Pecoraro, tla@aiha.org

Visit our webpage under Volunteer Groups @AIHA: www.aiha.org/insideaiha/volunteergroups/Pages/NTWG.aspx
Nanotechnology Health & Safety Resources

- Good NanoGuide [www.goodnanoguide.org](http://www.goodnanoguide.org)
- Kuhlbusch et al. (2011) Nanoparticle exposure at nanotechnology workplaces: A review. *Particle and Fibre Toxicology* 8(22)
- NIOSH Nanotechnology – Publications, blog, other resources [http://www.cdc.gov/niosh/topics/nanotech/](http://www.cdc.gov/niosh/topics/nanotech/)
- Join the AIHA Nanotechnology Working Group
Questions and Comments

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