NIOSH’s Progress towards Developing a Categorical Approach to Nanomaterials Risk Assessment and Developing the Database

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NIOSH Research on Engineered Nanomaterials (EMNs) Risk Assessment Program Area

**Burden**
- Potential occupational exposure associated with production & use of ENMs

**Need**
- Evidence-based risk assessments to support effective risk management recommendations

**Impact**
- Responsible and sustainable development of the technology – including healthy workers
Key questions:

What options are available to reduce the hazards or exposures?

How can risk assessment be used to evaluate the merits of the various options?

[NAS 2009; NAS 1983]
Risk Assessment Guidance - Relevant to Nanomaterials and Occupational Safety and Health

- Standard principles and practices apply to nanomaterials
- New methods are being developed to utilize data from alternative testing strategies

NIOSH (2017)
NIOSH/NTRC Risk Assessment Objectives

• Assessing hazard potency among well-studied materials
  – which vary in size, shape, solubility, density, functionalization, etc.

• Predicting hazard potency groups among a wide range of ENMs
  – using limited data on new ENMs in a validated framework based on well-studied materials

• Providing information for risk management decision-making
  – considering the workplace health & safety applications
NIOSH Framework to Derive Occupational Exposure Limits or Bands for ENMs

[Drew NM, Kuempel ED. Toxicology and Risk Assessment Conference, April 24, 2018, Cincinnati, Ohio]
Control Banding

Hazard Banding by Severity of Effect

Exposure Banding
Frequency, duration, & amount; energy & dustiness

Performance-based Exposure Control Limits

Airborne concentration, 8-hr TWA (μg/m³)

- Closed Systems & Robotics
- Containment Systems
- Ventilated Enclosures
- Local Exhaust Ventilation
- General Ventilation

[Also the OEB airborne concentrations]

Benefits of Categorical (Grouping) Approach

- More efficient use of data
- Reduced costs and animal use
- Increased sample size
- Greater robustness of results
- Increased biological plausibility for other materials within biological mode-of-action categories

Methods

I. Develop proof-of-concept framework for hazard potency grouping and prediction  
   ✓ Completed

II. Build a more comprehensive database  
    ❑ In progress

III. Extend/evaluate models/frameworks and apply in hazard grouping and OEB estimation  
    ❑ In progress

Opportunities for collaboration
A quantitative framework to group nanoscale and microscale particles by hazard potency to derive occupational exposure limits: Proof of concept evaluation

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Includes data from US and EU collaborators! ENPRA, NanoGo, NIOSH and others
Physicochemical Properties for Predicting Hazard Potency

- Random forest methods used to identify the important physicochemical predictors of pulmonary toxicity
- Proof-of-concept model built with 18 materials with limited physicochemical information
- Group assignments were correctly predicted for five of six new ENMs.

[Drew et al. 2017. RTP 89:253-267]
Comparative Potency Analysis

Comparative Risk Estimate

ExR₂ = k (ExR₁)

[Kuempel et al. 2012 JNR 14:1029; adapted from Sobels 1977,1993; Schoeny & Margosches 1989; Sutter 1995]
Dose-Response Modeling

**Benchmark Dose (BMD):** The dose associated with the benchmark response (BMR)

**BMDL:** Statistical lower confidence limit on the BMD (used as the PoD)

**OEL noncancer endpoint**

**Response**

**Dose**

**BMR:** Predetermined change in response rate relative to background (e.g., added 10%)

[Adapted from U.S. EPA BMDS]
Hazard Potency Estimates and Grouping*

by Acute Inflammation (background + 4% PMNs, at 0-3 d post-exposure)

*Hierarchical Clustering used to group similar materials

[Drew et al. 2017. RTP 89:253-267]
Challenges for Data Analysis

• Large amounts of data available, yet considerable heterogeneity due to experimental design differences

• Dose-response data are often insufficient for modeling
  – Few dose groups or number of animals per group
  – Missing data for key parameters

• Obtaining comprehensive data sets with adequate dose-response and physicochemical properties data
Extending the Database

• Systematic literature review
• NIOSH toxicology studies
• Data from research collaborators
• *In vivo* and *in vitro* data
• Toxicological endpoints over time
• Early markers and gene expression
• Material characterization
Proposed Structure of NIOSH Nanotoxicology Database

- **Endpoints Table**: Individual data from each assay
  - Key: Response ID

- **Experiment Table**: In vivo/in vitro study features
  - Key: Experiment ID

- **Study Table**: Contains all studies in database
  - Key: Experiment ID
  - Key: Study ID
  - Key: Material ID

- **Assay Table**: Response assay description
  - Key: Study ID

- **Materials Table**: Physicochemical properties
  - Key: Study ID

[Similar to and compatible with ISA-TAB-Nano & other database standards]

[Figure by Theresa Boots]
Utility of Data Templates

• Standardize data format and compatible software
• Ensure inclusion of essential variables
• Simplify data entry and minimize errors
• Improve utility of nanotoxicology data for risk analyses
• Facilitate data sharing
Toxicogenomics Database Workflow

Initial Database Sources
- GEO
- EPA AcTOR
- Array Express
- NTP
- NIOSH

Identify Unique Datasets
- Compare databases, overlaps
- Evaluate results from different search terms

Select Datasets based on Inclusion Criteria
- Assay platform type
- Experimental sample type
- Relevance to engineered nanomaterials
- Relevance to risk assessment for occupational safety and health

[Medvedovic and Davidson 2017 - Toxicogenomics Database Protocol for ENMs Risk Assessment]
Exploring Differential Gene Expression and ENM Exposure

Lung Disease Model Biclusters

ENM Biclusters: Acute Inflammation

[Davidson SE, Kuempel ED, Medvedovic M (2018). Exploring the Use of Toxicogenomics in Risk Assessment of Nanomaterials. Toxicology and Risk Assessment Conference, April 24, Cincinnati, Ohio].
What's Known

- Standard risk assessment methods are generally applicable to EMNs
- Toxicology data from well-studied materials can be used as benchmarks
- Exposure measurement methods are generally available
- Engineering controls can be effective at controlling exposures
- Proof-of-concept models for hazard/safety assessment have been developed

What's Still to Know/Do

- Data integration across toxicological assays and endpoints
- Extension and validation of predictive models
- Implementation of validated frameworks to wide range of ENMs
- Further linkage of steps in risk assessment and management
Possible Areas of Research Collaboration in Risk Assessment of ENMs

• Data sharing to build a comprehensive database
• Identifying minimally acceptable data requirements
• Comparing and cross-validating methods and frameworks
• Integrating comparable data and complementary methods
• Implementing validated models for hazard/safety assessments
NIOSH Resources

• Risk Assessment Practices *Draft*
  [https://www.cdc.gov/niosh/docket/review/docket316/](https://www.cdc.gov/niosh/docket/review/docket316/)

• Occupational Exposure Banding *Draft*
  [https://www.cdc.gov/niosh/docket/archive/docket290.html](https://www.cdc.gov/niosh/docket/archive/docket290.html)

• NIOSH Current Intelligence Bulletins:
  – Silver Nanomaterials *Draft*
    [https://www.cdc.gov/niosh/docket/review/docket260a/](https://www.cdc.gov/niosh/docket/review/docket260a/)
  – Carbon Nanotubes and Nanofibers
  – Titanium Dioxide
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Thank you!

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