

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

Eileen D Kuempel PhD

Risk Assessment Critical Area Coordinator, NIOSH/NTRC

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NIOSH Research on Engineered Nanomaterials (EMNs)

Risk Assessment Program Area

Burden

- Potential occupational exposure associated with production & use of ENMs

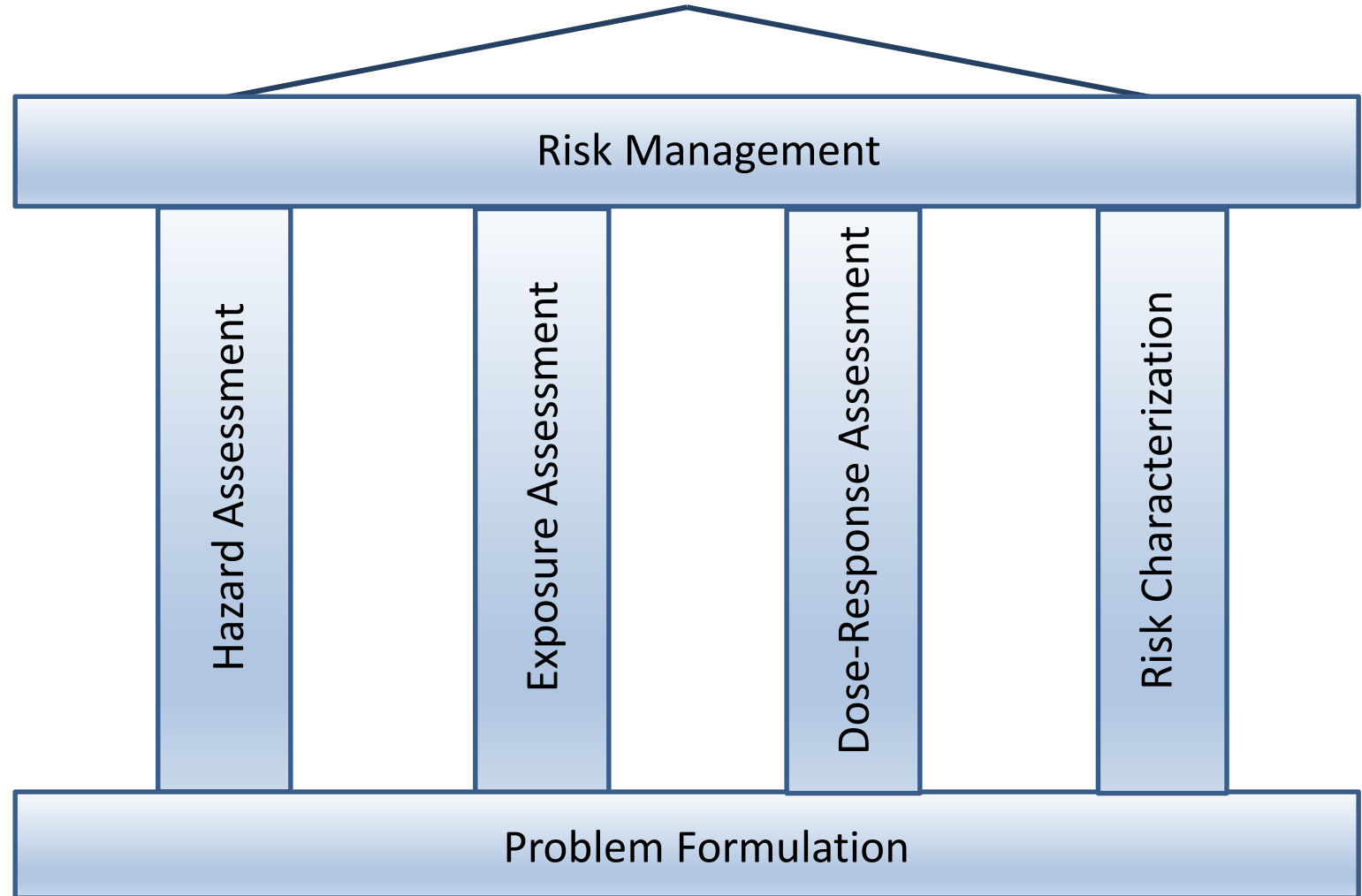
Need

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

Impact

- Responsible and sustainable development of the technology – including healthy workers

Risk Assessment Paradigm



Key questions:

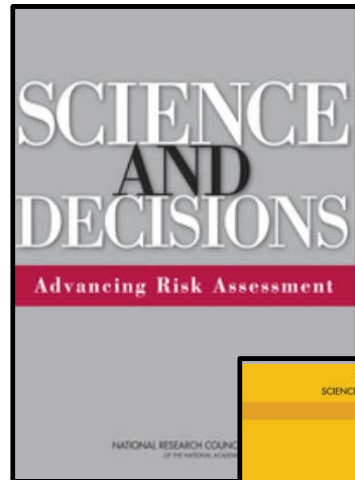
What options are available to reduce the hazards or exposures?

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

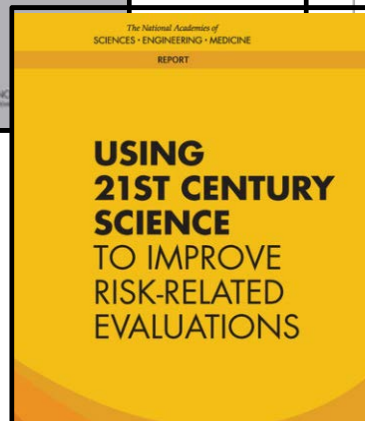
[NAS 2009; NAS 1983]

Risk Assessment Guidance - Relevant to Nanomaterials and Occupational Safety and Health

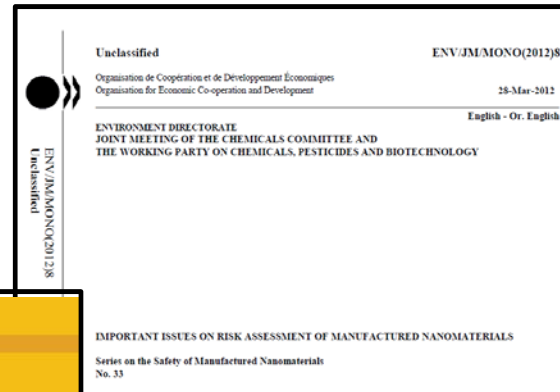
- Standard principles and practices apply to nanomaterials
- New methods are being developed to utilize data from alternative testing strategies



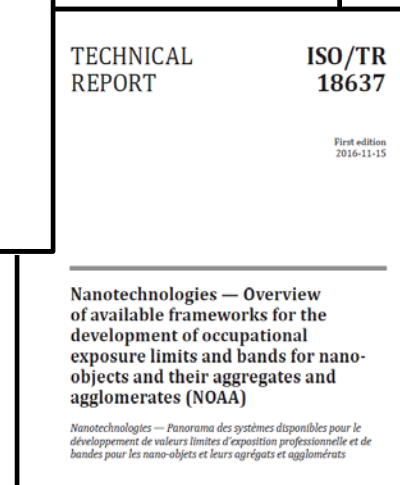
NAS (2009)



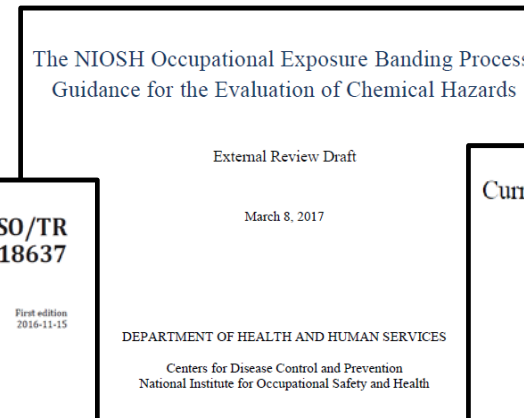
NAS (2017)



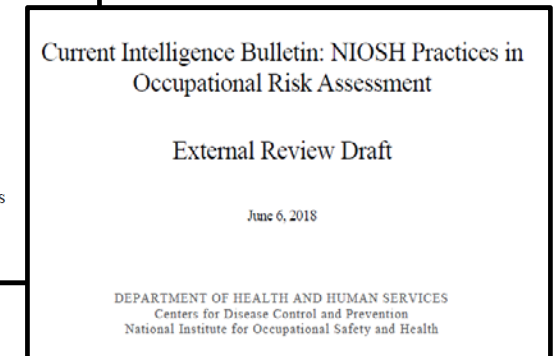
OECD (2012)



ISO (2016)



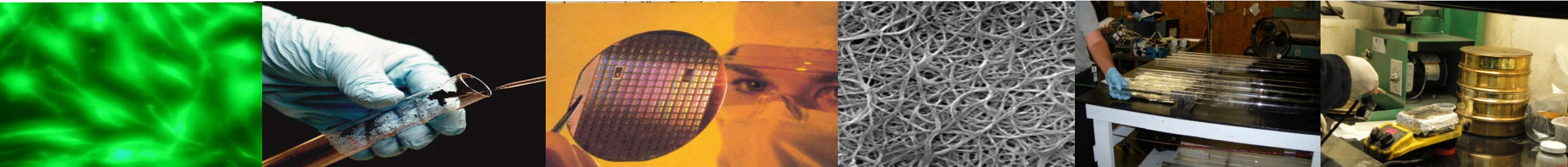
NIOSH (2017)



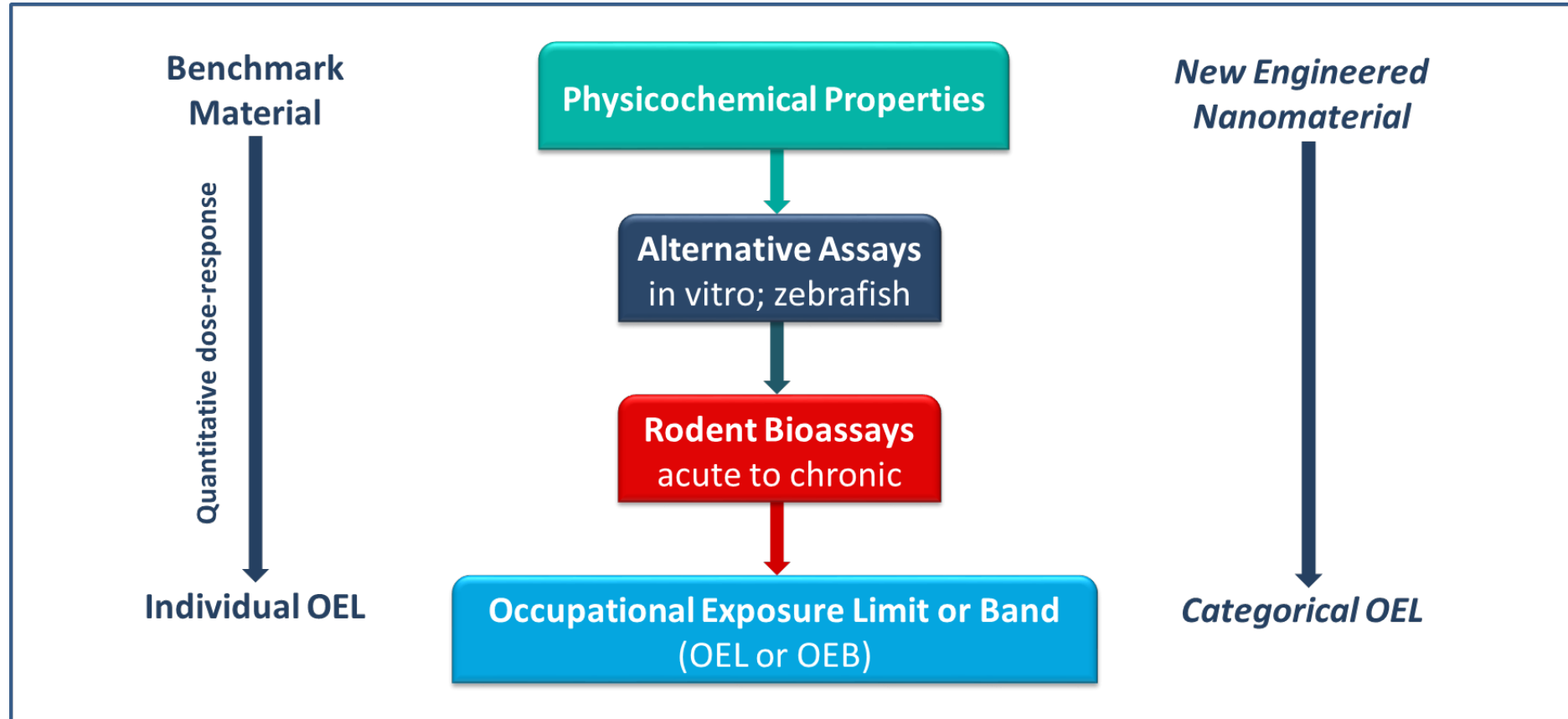
NIOSH (2018)

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



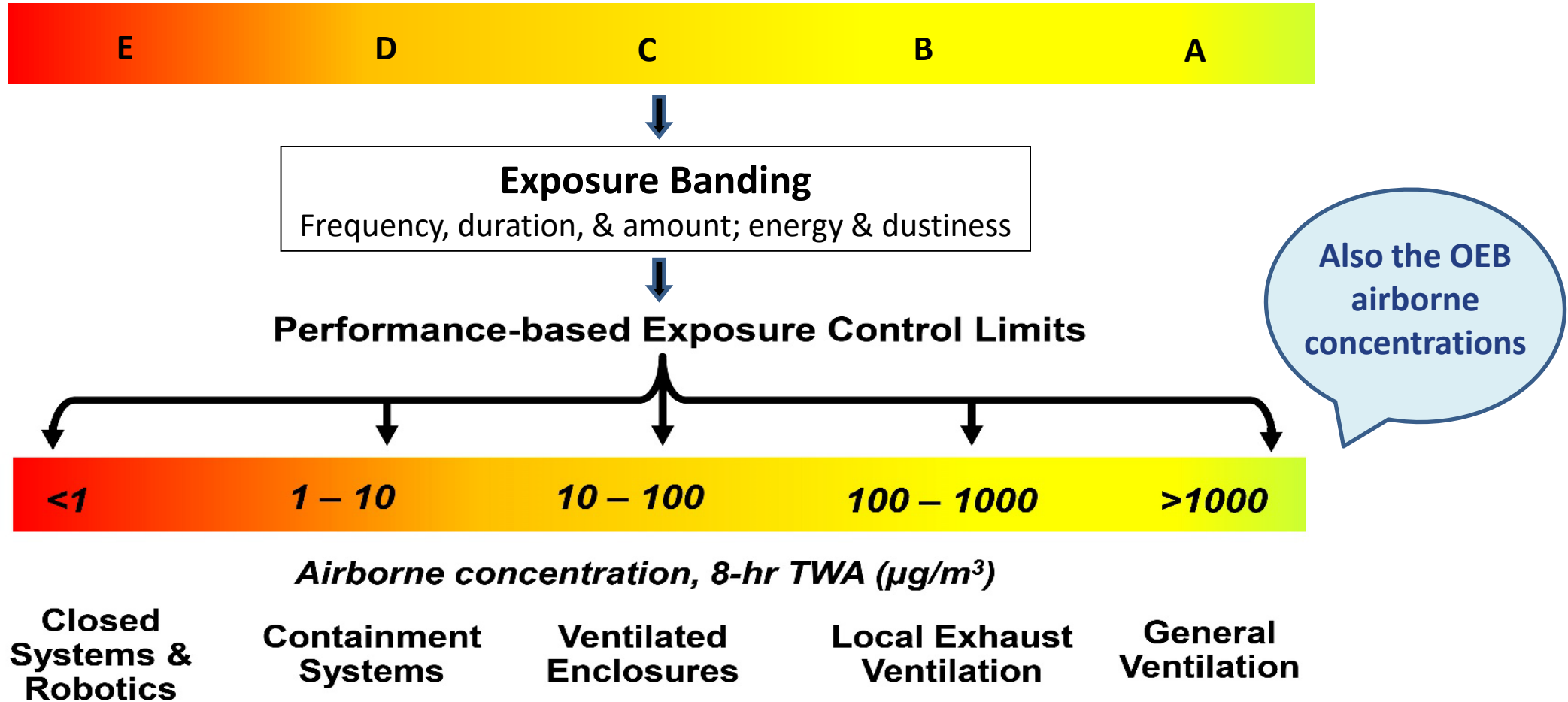
NIOSH Framework to Derive Occupational Exposure Limits or Bands for ENMs



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

Control Banding

Hazard Banding by Severity of Effect



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*

Developing a Framework to Group Nanomaterials

Regulatory Toxicology and Pharmacology 89 (2017) 253–267



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journal homepage: www.elsevier.com/locate/yrtph



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



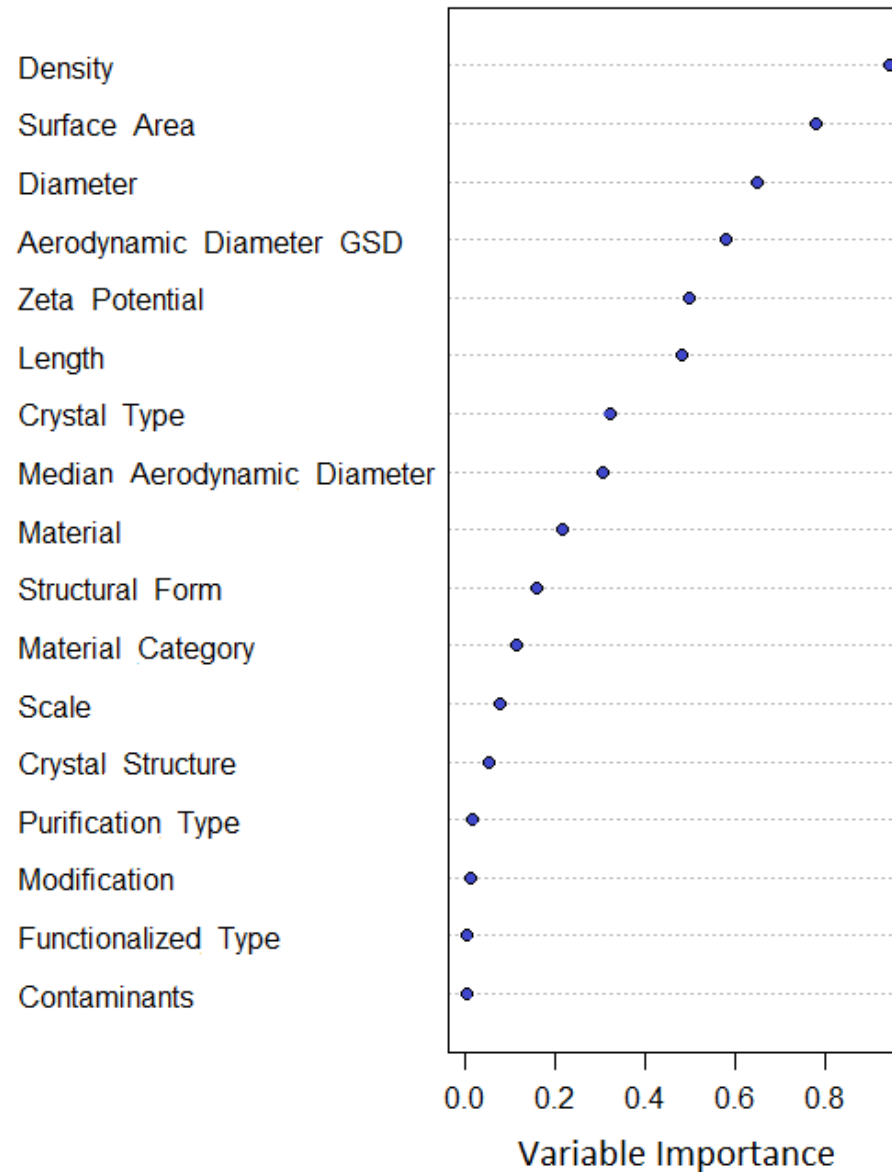
Nathan M. Drew^{a,*}, Eileen D. Kuempel^a, Ying Pei^b, Feng Yang^b

^a National Institute for Occupational Safety and Health (NIOSH), Nanotechnology Research Center (NTRC), Cincinnati, OH 45226, USA

^b West Virginia University, Department of Industrial and Management System Engineering, Morgantown, WV 26506, USA

*Includes data from US and EU collaborators!
ENPRA, NanoGo, NIOSH and others*

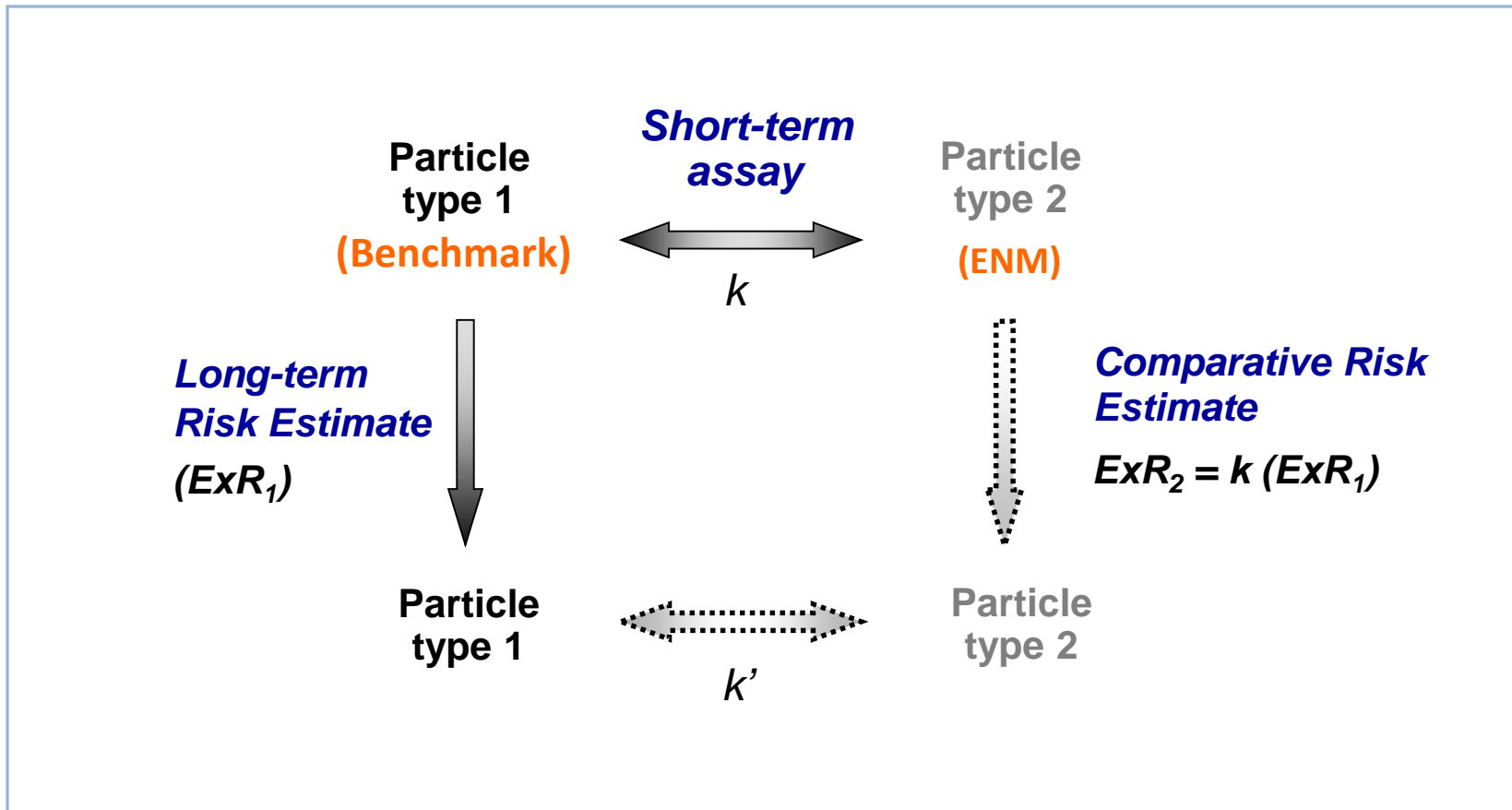
Physicochemical Properties for Predicting Hazard Potency



- ✓ 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.

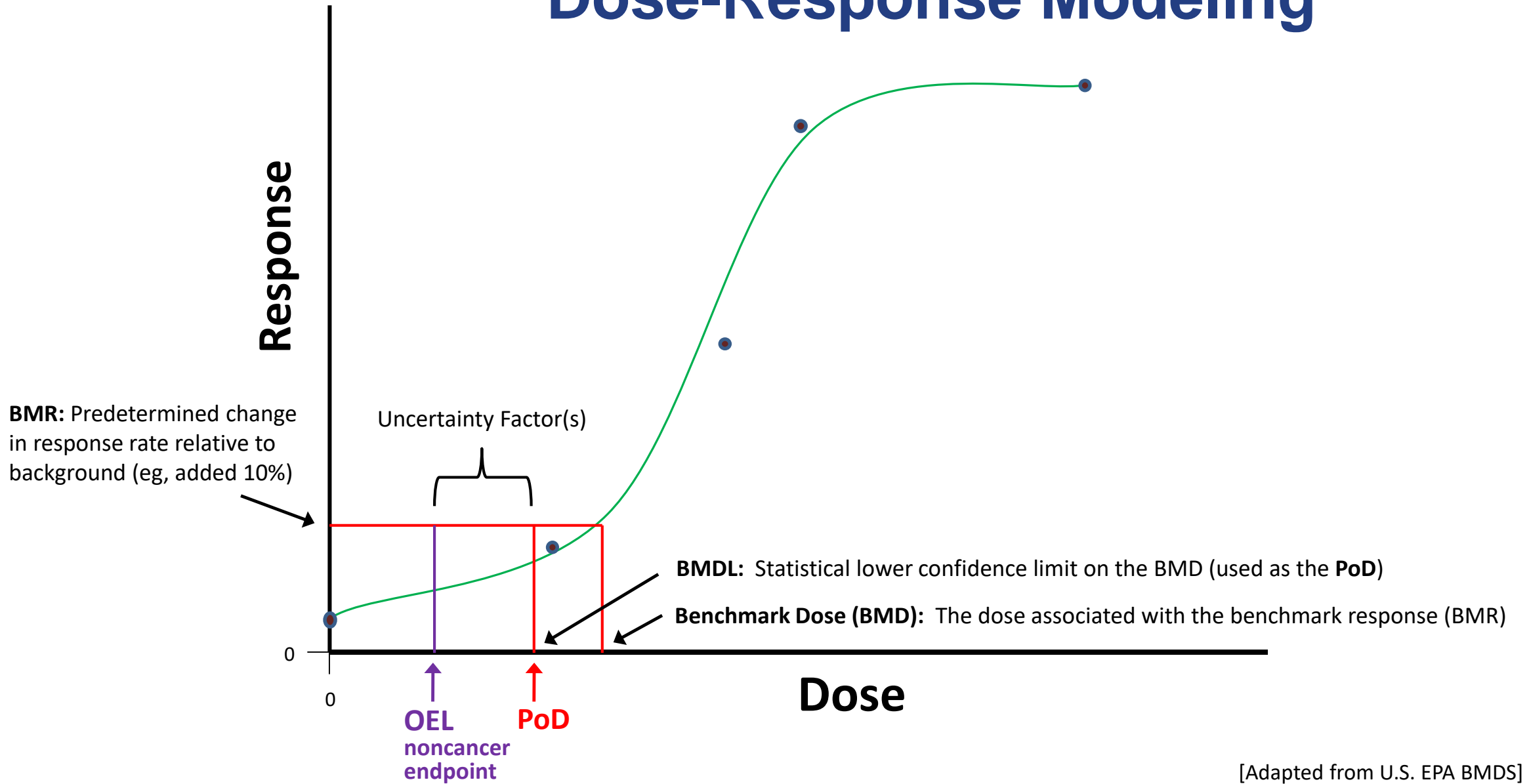
[Drew et al. 2017. RTP 89:253-267]

Comparative Potency Analysis



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

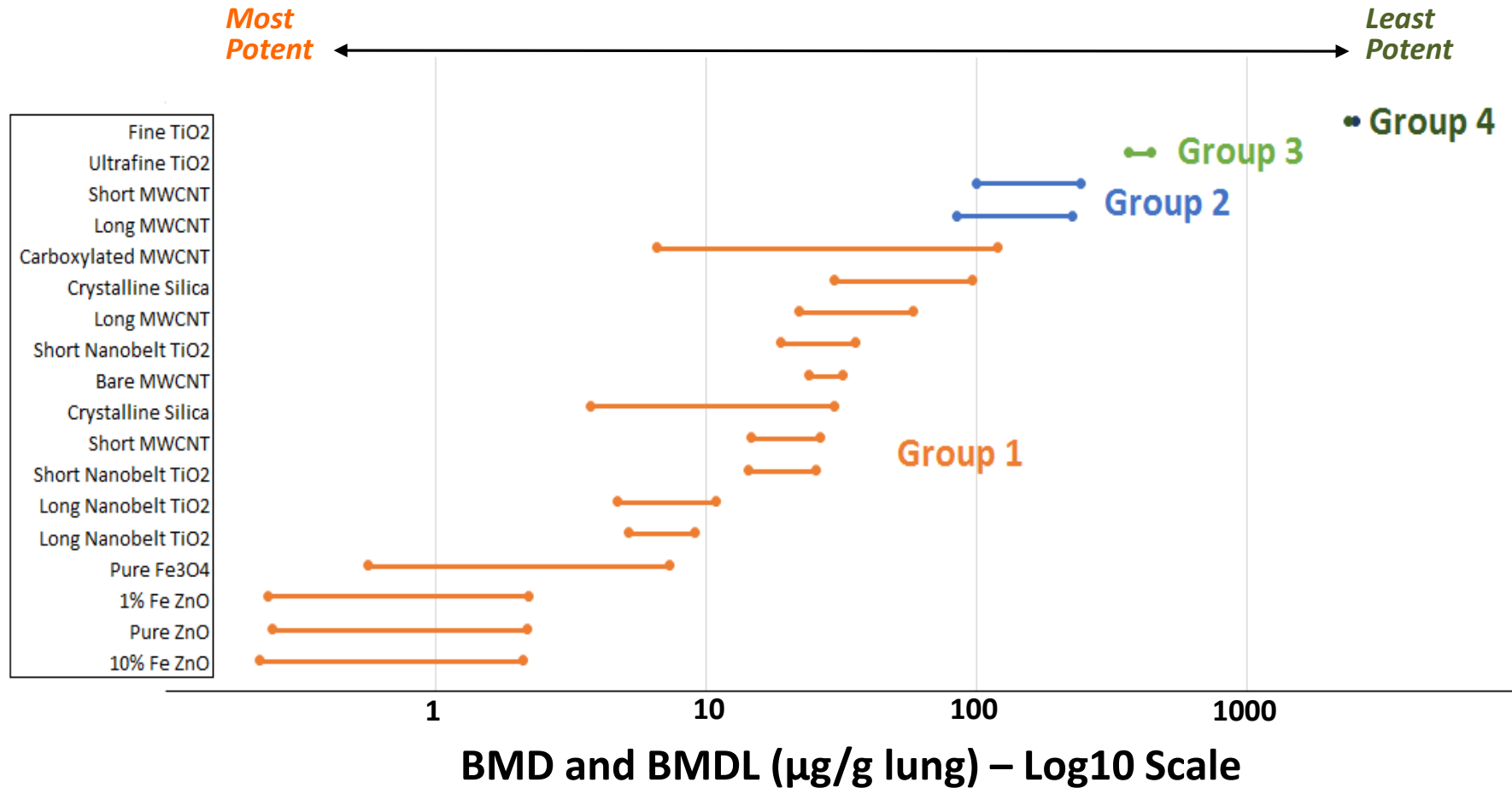
Dose-Response Modeling



[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]

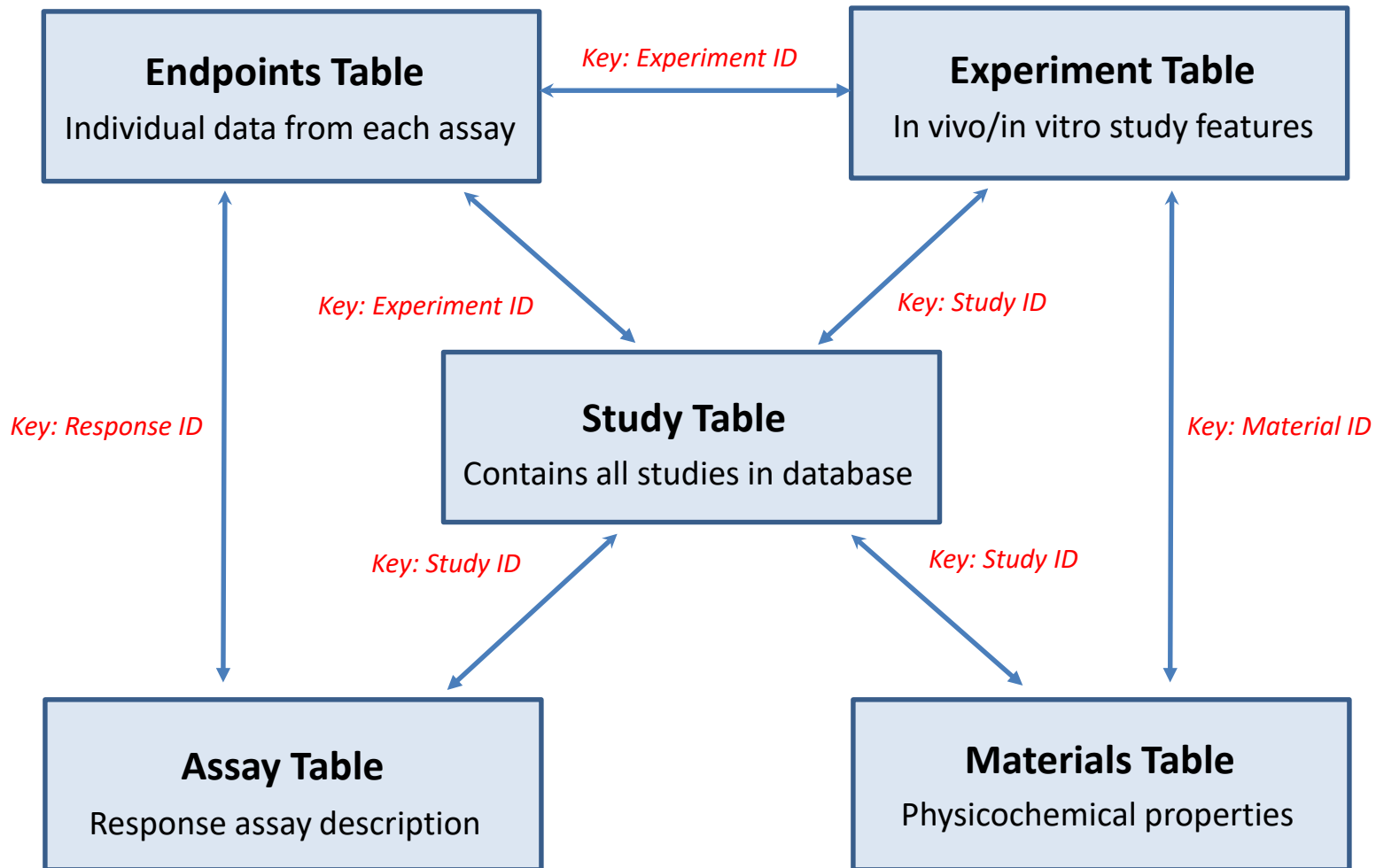
Challenges for Data Analysis

- 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



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

[Figure by Theresa Boots]

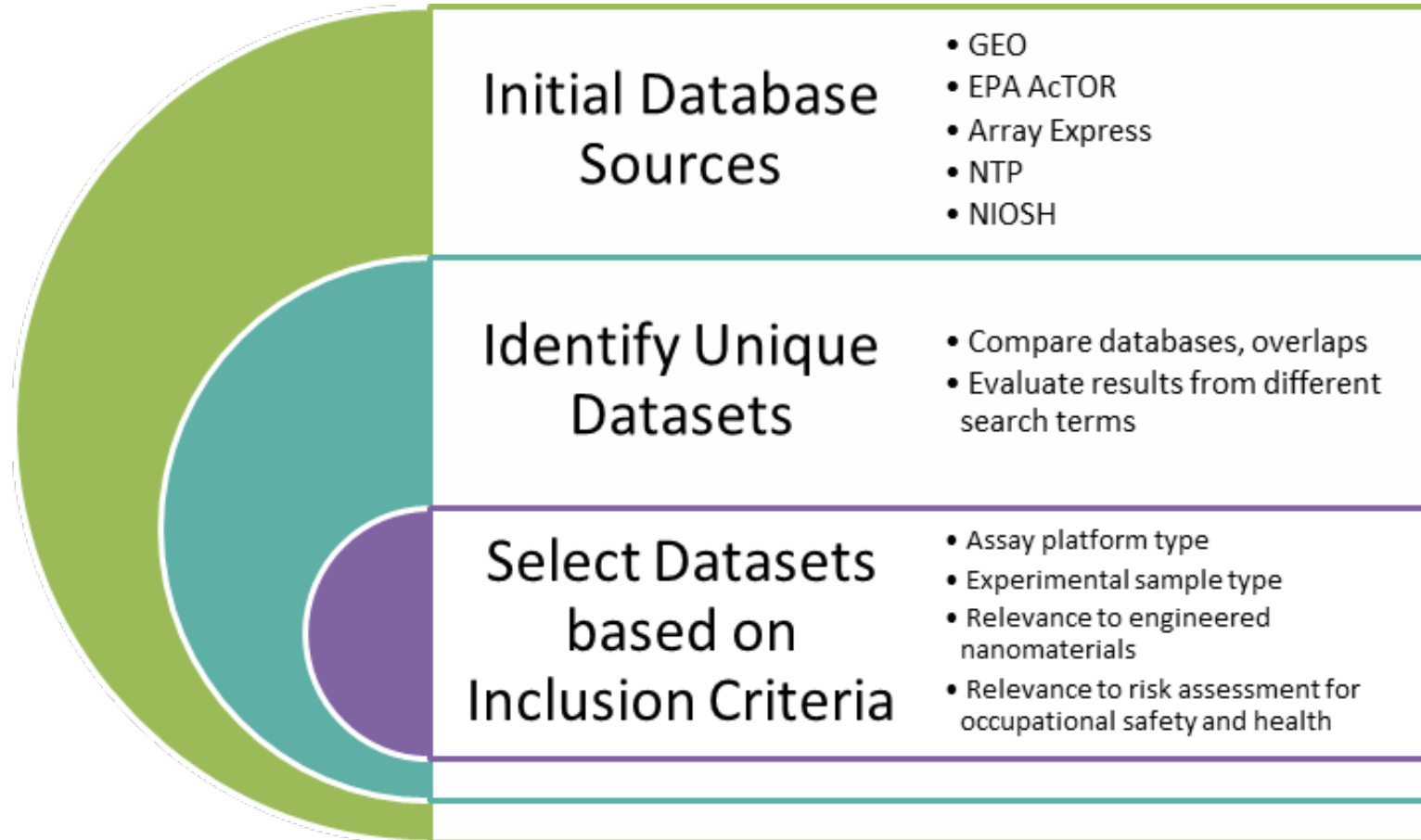
Utility of Data Templates

- 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

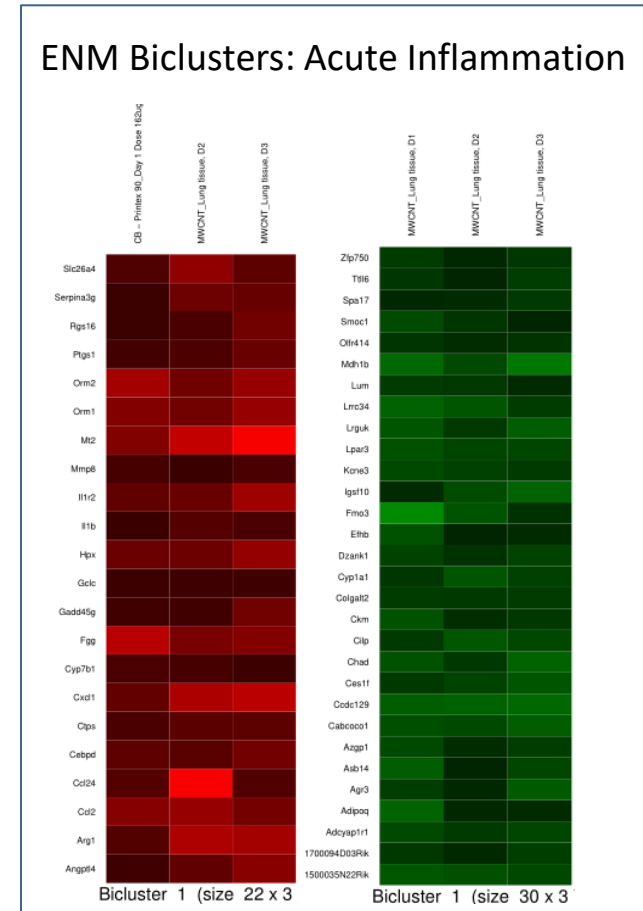
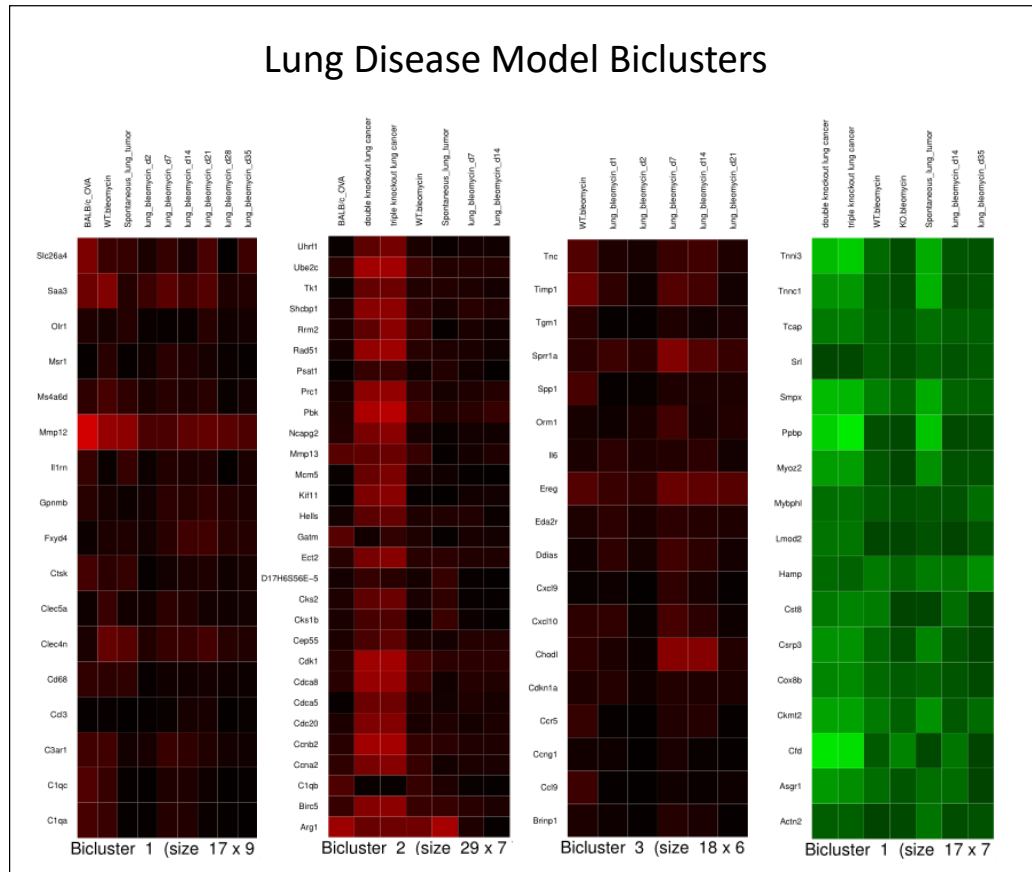
	A	B	C	D	E	F	G	H
1	Study_ID	In_vivo	In_vitro	Species	Cell_type	Experiment_ID_List	Response_ID_List	Material_ID_List
2								

	A	B	C	D	E	F	G
1	Experiment_ID	Subject_ID	EP_ID	Assay_ID	Response_ID	Value	Units
2							

Toxicogenomics Database Workflow



Exploring Differential Gene Expression and ENM Exposure



[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].

Risk Assessment to Inform Risk Management of EMNs

Relatively Well 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/>
- Occupational Exposure Banding *Draft*
<https://www.cdc.gov/niosh/docket/archive/docket290.html>
- NIOSH Current Intelligence Bulletins:
 - Silver Nanomaterials *Draft*
<https://www.cdc.gov/niosh/docket/review/docket260a/>
 - Carbon Nanotubes and Nanofibers
<https://www.cdc.gov/niosh/docs/2013-145/>
 - Titanium Dioxide
<https://www.cdc.gov/niosh/docs/2011-160/>



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Outside NIOSH Research Collaborators

Mark Widder, BS, *US Army Center for Environmental Health Research*

Feng Yang, PhD, Ying Pei, MS *West Virginia University*

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Lang Tran, PhD, *Institute of Occupational Medicine, Edinburgh*

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NIOSH Nanotechnology Research Center (NTRC) Co-Managers & Coordinator

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Laura Hodson, MS, CIH



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Thank you!

ekuempel@cdc.gov

www.cdc.gov/niosh/topics/nanotech

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safety and health research.