Measurement and Standardization Needs for Predicting Nano-Biointeractions

Kristen M. Kulinowski, PhD

9 June 2008

Washington, DC

Addressing Applications & Implications

http://cben.rice.edu

The Center for Biological & Environmental Nanotechnology

An NSF center of excellence in nanotechnology research & education

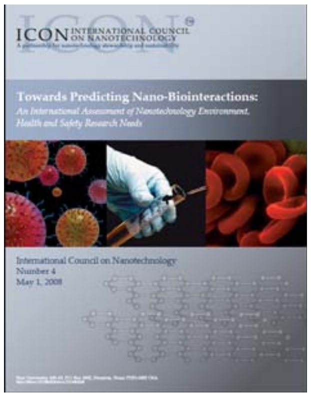
http://icon.rice.edu

The International Council on Nanotechnology

A unique multi-stakeholder forum for addressing the potential risks of nanotechnology

Recent Knowledge Transfer Highlights

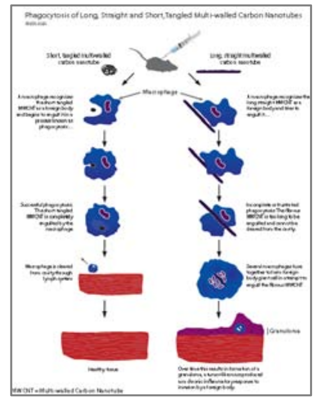
NanoEHS Research Needs



Towards Predicting Nano-bio Interactions

Backgrounders on High-Impact Research

Nanoparticles and Amyloid Diseases



Nanotubes and Mesothelioma

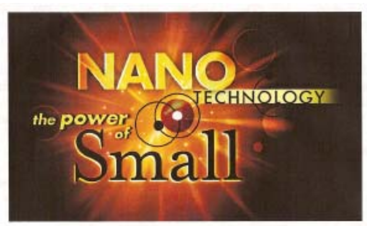
CBEN Testimony

Colvin at House Science Committee

New Resource for OEHS Practitioners

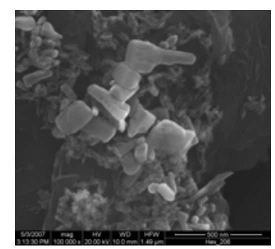
ICON Wiki on occupational practices

CBEN in Nationally Syndicated TV Show



Power of Small series on PBS

Partnership with Consumers Union



Research on NPs in sunscreens

Our 2007-8 highlights illustrate diverse, effective and innovative accomplishments

Risk: Three Areas of Concern

End-of-use issues:
Ecological impacts

Direct consumer contact

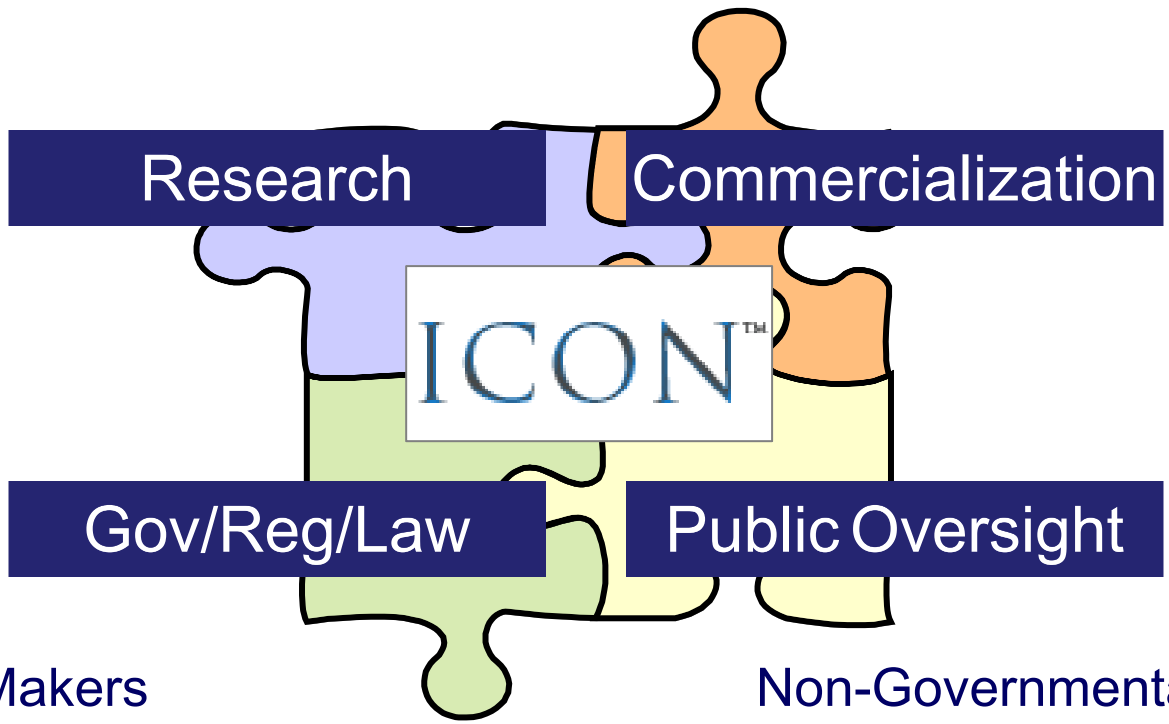
Worker and laboratory safety

What do we know about nano's impacts on EHS?
What are the barriers to effective risk management of nanomaterials?

ICON: A New Model for Interaction

Academics
Industry
Government

Industry
Trade Groups



Gov Policy Makers
Regulators
Lawyers

Non-Governmental Organizations
Social/Ethical Researchers

Information regarding potential environmental and health risks of nanotechnology to foster risk reduction and maximize societal benefit.

Virtual Journal of NanoEHS

nanoEHS VIRTUAL JOURNAL

The Virtual Journal of Nanotechnology Environment, Health and Safety

HOT PAPER: "Nucleation of protein fibrillation by nanoparticles," Linse, S., C. Cabaleiro-Lago, Xue, W.-F., Lynch, I., Lindman, S., Thulin, E., Radford, S. E., Dawson, K. A. (2007). Proceedings of the National Academy of Sciences of the United States of America XXX(XXXX): XXX.

This work explores the role that nanoparticles play in accelerating the rate of a process called protein fibrillation, which has been linked to amyloid diseases. Amyloid diseases are a broad class of ailments that result when amyloid proteins misfold and form insoluble fibrous plaques (fibrils) that deposit in the tissues of the body. Linse et al. noted an increased rate of protein fibrillation when beta 2-microglobulin, an amyloid protein associated with complications from kidney dialysis, was put into solution with nanoparticles. Four different types of nanoparticles (copolymer particles of N-iso-propylacrylamide (NIPAM) and N-tert-butylacrylamide (BAM), cerium oxide particles, CdSe or CdSe/ZnS quantum dots and multi-walled carbon nanotubes) each accelerated the production of small seeds upon which fibrils form most effectively. However this study did not determine that nanoparticles can cause human disease.

For a general overview on nanoparticles and amyloid diseases, see here.

For questions and answers about nanoparticles and amyloid diseases, see here.

More information.

Recent Additions the full issue

ZnO – nanostructures, defects and devices
Schmidt-Mende L, MacManus-Driscoll JL
Materials Today
Materials Today, 2007, 10 (5): 40-48.

Details

Recent Virtual Journal Issues:
April 2007
March 2007
February 2007
January 2007
December 2006
November 2006
October 2006
September 2006
August 2006
July 2006
June 2006
May 2006

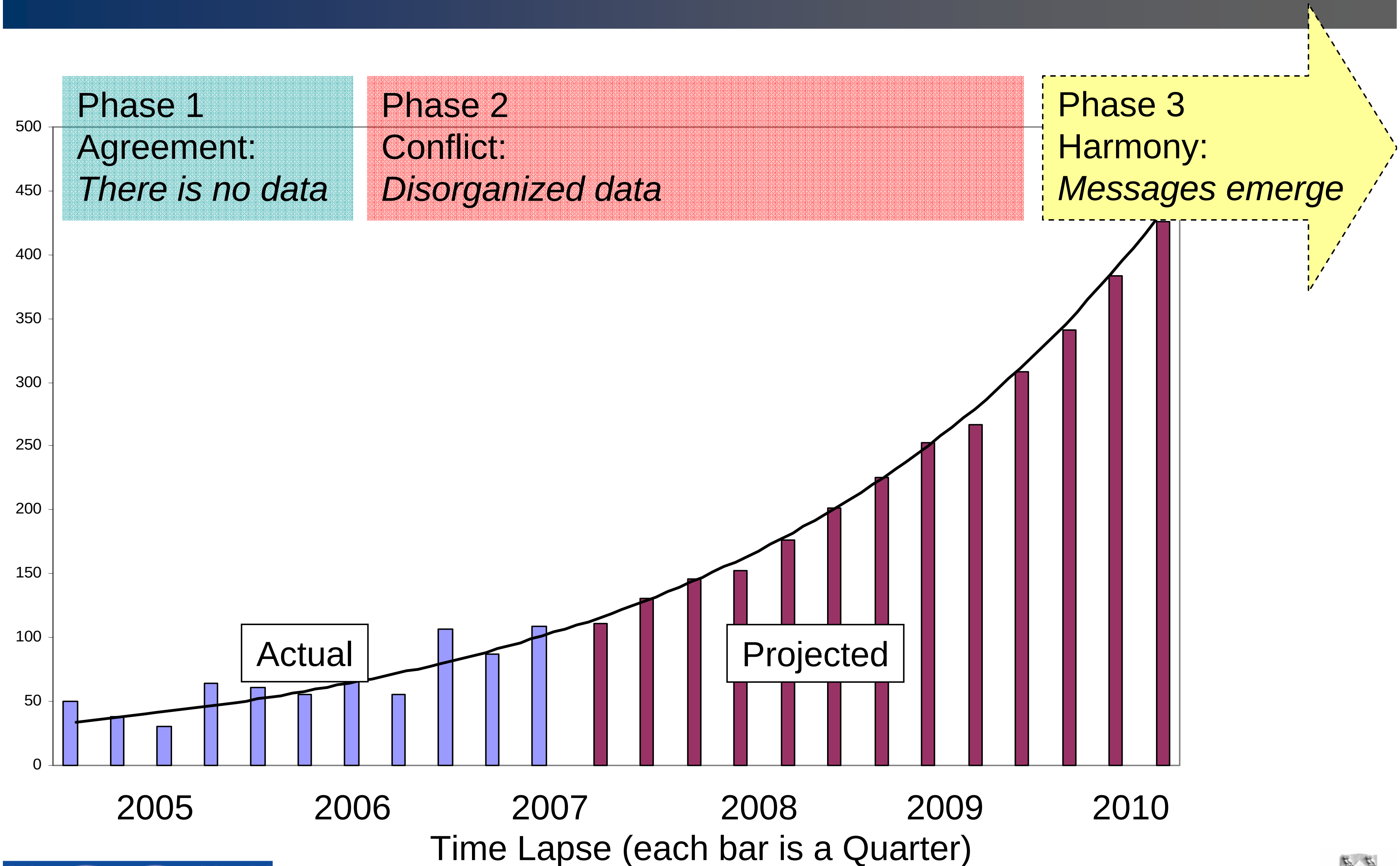
Other issue: Go

Database of citations to peer-reviewed nanoEHS papers

- Database launched August 2005
- Monthly updates
- Familiar, user-friendly format
- RSS feed
- Over 2000 records
- Backgrounders on key literature

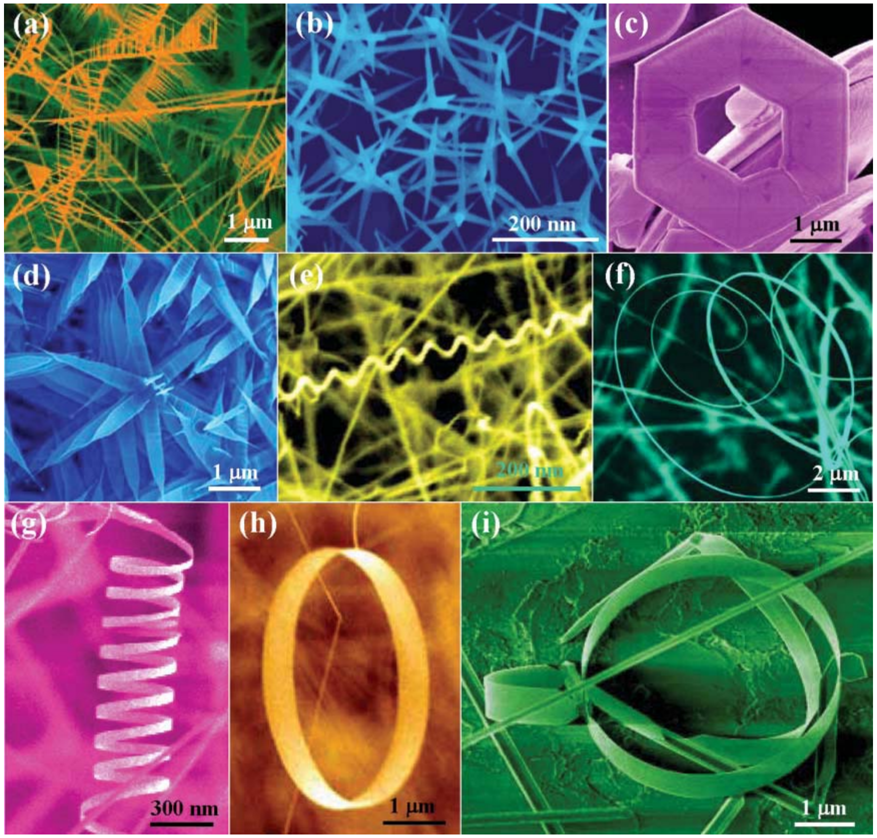
http://icon.rice.edu/virtualjournal.cfm

Growth Rate of EHS Publications



Risk Assessment for Nano is Complicated

Credit: Zhong Lin Wang

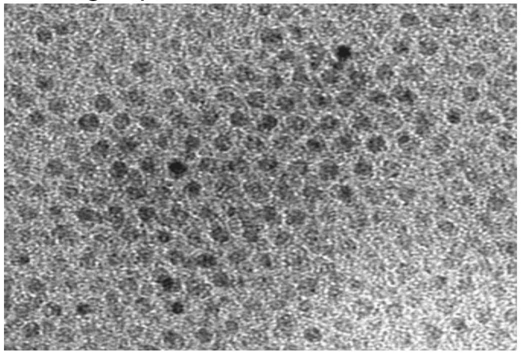


A few of the barriers

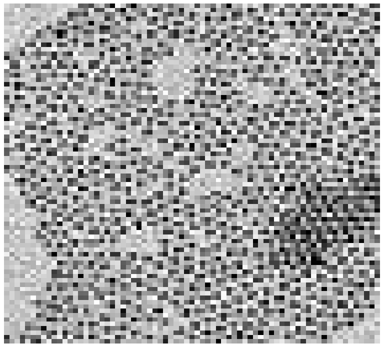
- Distinctive properties
- Nanomaterial diversity and variability
- Lack of standards
- Measurement tools

Nanomaterials: Distinctive Properties

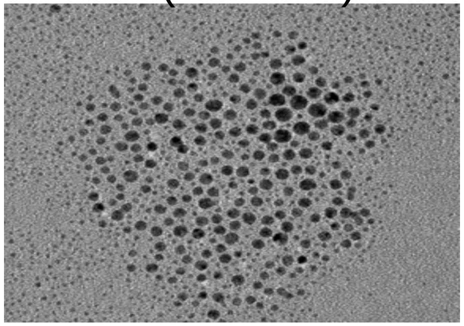
Fe_3O_4, Magnetite (4 nm)

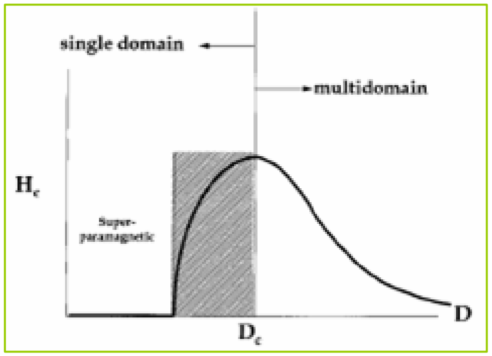


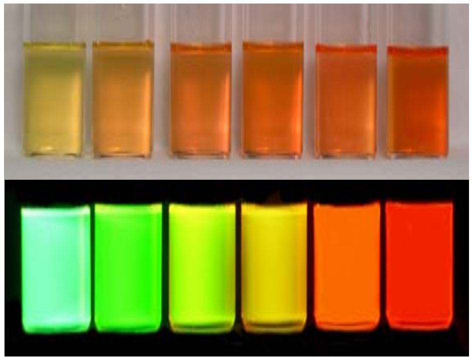
CdSe (8 nm)

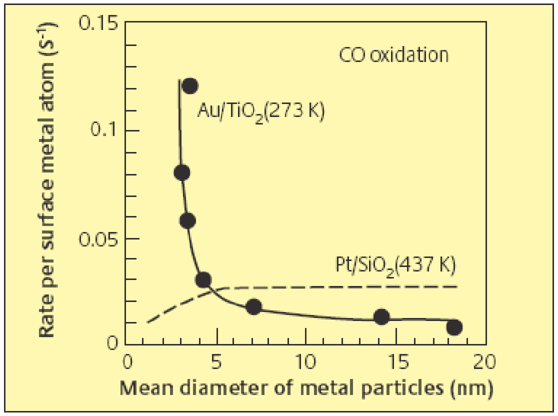


Gold (~ 10 nm)









Taken from M. Haruta Nature, 2005

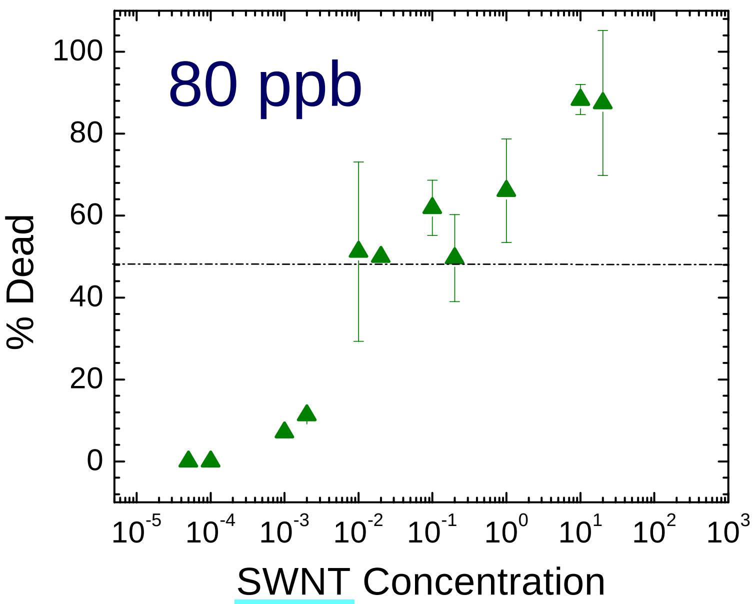
Size-Dependent Magnetism

Size-Dependent Emission

Size-Dependent Reactivity

Nanomaterial Diversity

Are single-walled carbon nanotubes toxic?



Colvin, et al. unpublished

- 20 major types of SWNT
- 4 manufacturing types (trace impurities)
- Lengths ranging from 5 – 300 nm
- 5 methods of purification
- 10 possible surface coatings

> 50,000 SWNT samples

How can better tools for predicting nanomaterial risk be developed?

International NanoEHS Research Needs

GRAND CHALLENGE: Computational Models that Predict Interactions of Engineered Nanomaterials with Organisms and the Environment

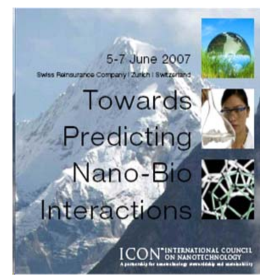
Workshop 1: Towards Nanomaterial Classes

- Develop classification of NMs based on material type
- Determine present and future applications
- Describe potential hot spots in lifecycle
- Describe properties important to biointeraction

NIH Campus Jan 2007

Workshop 2: Towards Predictive Models

- Elucidate mechanisms of nano-biointeractions
- Elucidate interactions at cell-free, cellular, tissue and whole animal levels
- Develop prioritized strategies and timelines



Swiss Re June 2007

OVERALL GOAL OF WORKSHOPS: Prioritized Research for Predicting Biointeractions for Nanomaterials of Commercial Relevance

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Key Findings from Workshop 1

CHALLENGE: Nanomaterial properties are not static throughout lifecycle

Tools and models must be developed that can describe the dynamic nature of nanomaterials throughout their lifecycle.

CHALLENGE: Chemical composition is not the ideal or sole property on which to focus

A set of screening tools is needed to correlate the <u>functional</u> properties of nanomaterials with their potential for biological interaction.

CHALLENGE: Exposure scenarios are too diverse to draw general conclusions

Exposure assessment studies are needed to enable predictions about implications of physicochemical properties for net dose.

Key Findings from Workshop 2

CHALLENGE: Nanoparticle surfaces undergo changes during interactions in biological environments

Quantitative models are needed to describe how the properties of NPs control the nature and extent of biomolecular interactions at their surface.

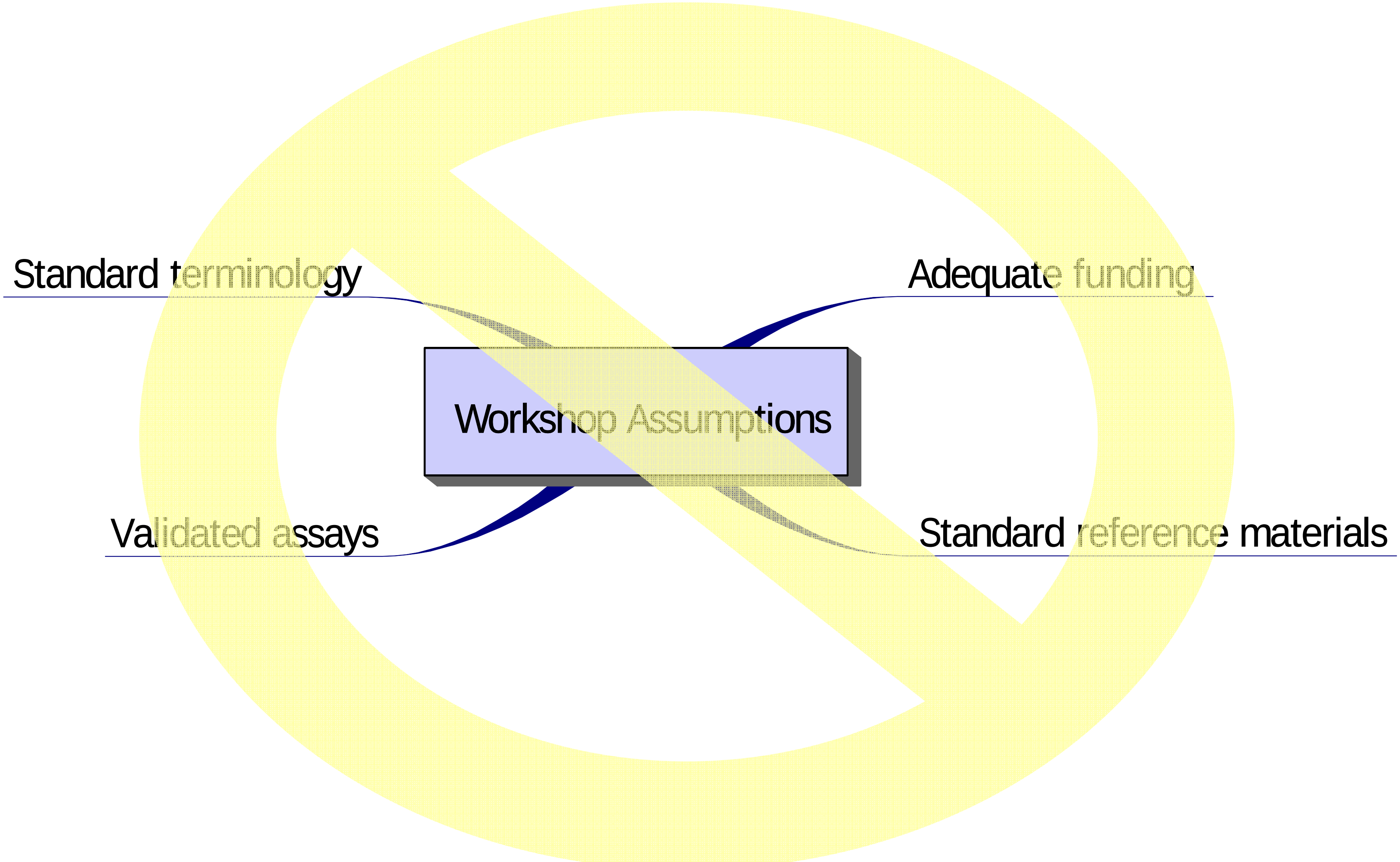
CHALLENGE: Existing mass-based metrics of measuring dose and dose rate may underestimate NP impacts

Dose and dose rate may need to be validated independently for NPs**.**

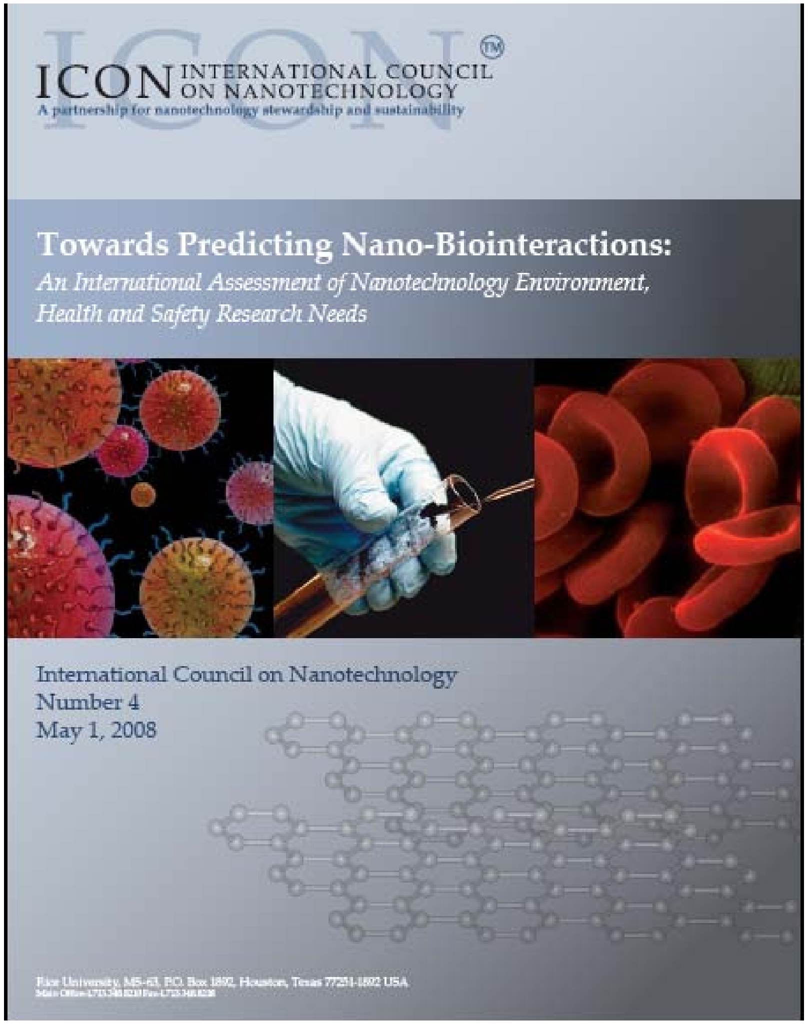
CHALLENGE: In vitro assays are practical given nanomaterial diversity but may be poor predictors of in vivo endpoints

Better biomarkers are essential to address the vast diversity of NP types and to develop strong correlative models for predicting in vivo endpoints based on in-vitro results**.**

Workshop 2 Assumptions



Cross-Cutting Issues between WS 1 and 2



Many outstanding needs

- Lack of standards for terminology, characterization, and materials
- Metrology and tools to characterize and measure nanomaterials and to monitor their presence in the environment and in biological media
- Test methodologies to characterize potential mobility of embedded nanomaterials
- Evaluation of the appropriateness of in vitro tests to characterize nanomaterial interactions more broadly,
- Standardization of biological materials used in testing

Highest Priority Research (2-yr Goals)

Research to Predict Nano-Biointeractions

- Understand which NM characteristics are most important for biointeractions
- Establish validated NMs that have been tested in vitro and in vivo
- Develop tools for in vitro testing that map onto in vivo endpoints
- ➡ Develop new techniques for imaging NMs in biological media and organisms
- Determine fate and interactions of NMs in reference organisms
- Design framework for data sharing and ontologies

Highest Priority Research (2-5 yr Goals)

Research to Meet Risk Management Needs

- ➡ Identify/develop tools for detecting and characterizing presence of NMs in the workplace and the environment
- ➡ Validate the effectiveness of personal protective equipment in limiting exposure
- ➡ Establish test methods for evaluating the stability and mobility of NMs in liquid and solid matrices
- ➡ Develop portable tools to monitor a wide range of nanomaterials in the workplace and environment
- ➡ Determine the bioavailability of nanomaterials throughout the lifecycle

~~No~~ Few Standards

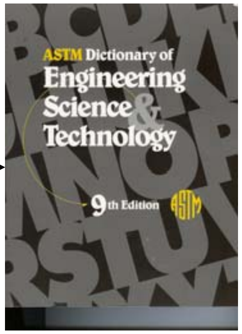
Standard: a technical document that is a basis for manufacturing, management, codes & regulations

Scientific data

Public reports

Industry practices

→ **Standards** →



First goal: Terminology and nomenclature
Second goal: Product stewardship

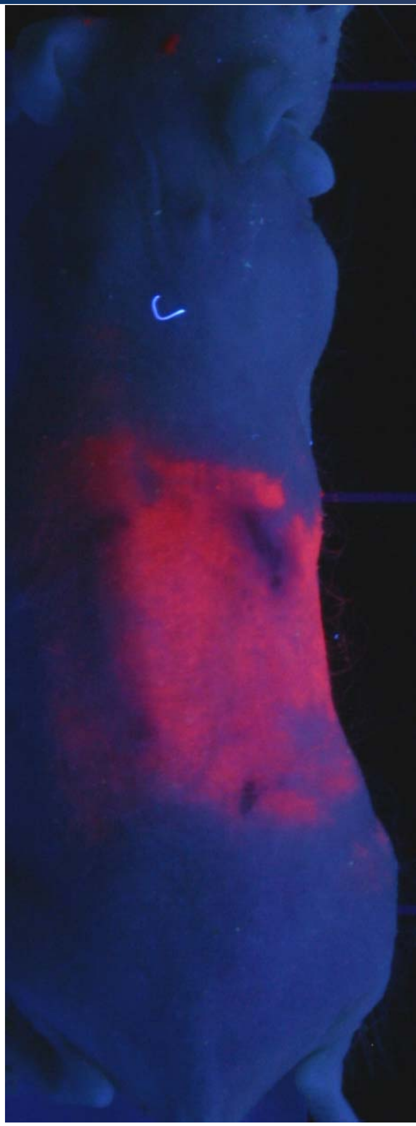
How Standards Impact Risk Management

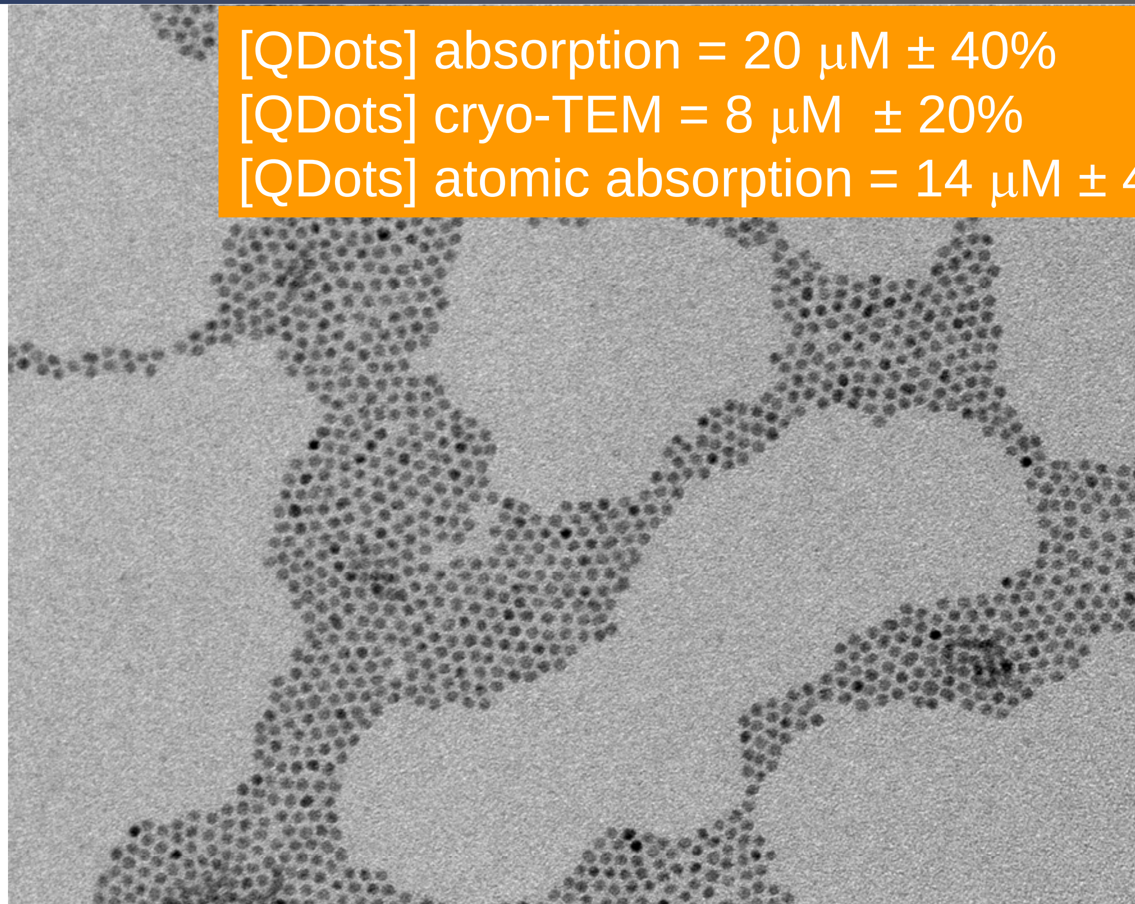
Terminology	TSCA: new chemical? OSHA: Material Safety Data Sheet Data in literature can’t be easily compared

Metrology/characterization	Occupational exposure: No standard detection equipment Environmental monitoring not easy

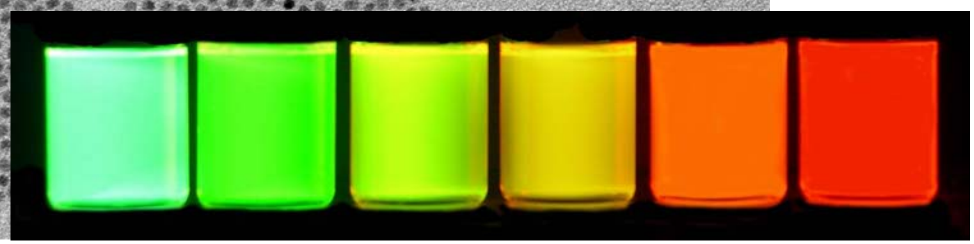
EHS	No standard test battery for tox screening No standard practices for occupational handling

Example: Standard Characterization Methods Needed!





[QDots] absorption = 20 μM ± 40%
[QDots] cryo-TEM = 8 μM ± 20%
[QDots] atomic absorption = 14 μM ± 40%



V.L. Colvin w/ Paul Howard (NCTR), Nigel Walker (NIEHS)

Nanotechnology Stds Activities

- Chair, Vicki Colvin

Subcommittees

- E56.01 Terminology & Nomenclature*
  - Colvin sub-chair
- E56.02 Characterization
- E56.03 Environment, Health, and Safety
  - Kulinowski sub-chair

Limited stakeholder engagement in these processes

- ANSI-Accredited U.S. Technical Advisory Group (TAG) to ISO/TC 229 *Nanotechnologies*
- www.ansi.org/nsp

- Technical committee on nanotech (ISO/TC 229)
  - Working Group (WG) 1 - Terminology and Nomenclature – Leadership assigned to Canada
  - Working Group (WG) 2 - Measurement and Characterization – Leadership assigned to Japan
  - Working Group (WG) 3 - Health, Safety and Environment – Leadership assigned to United States

ASTM Nano Standards

Active standards

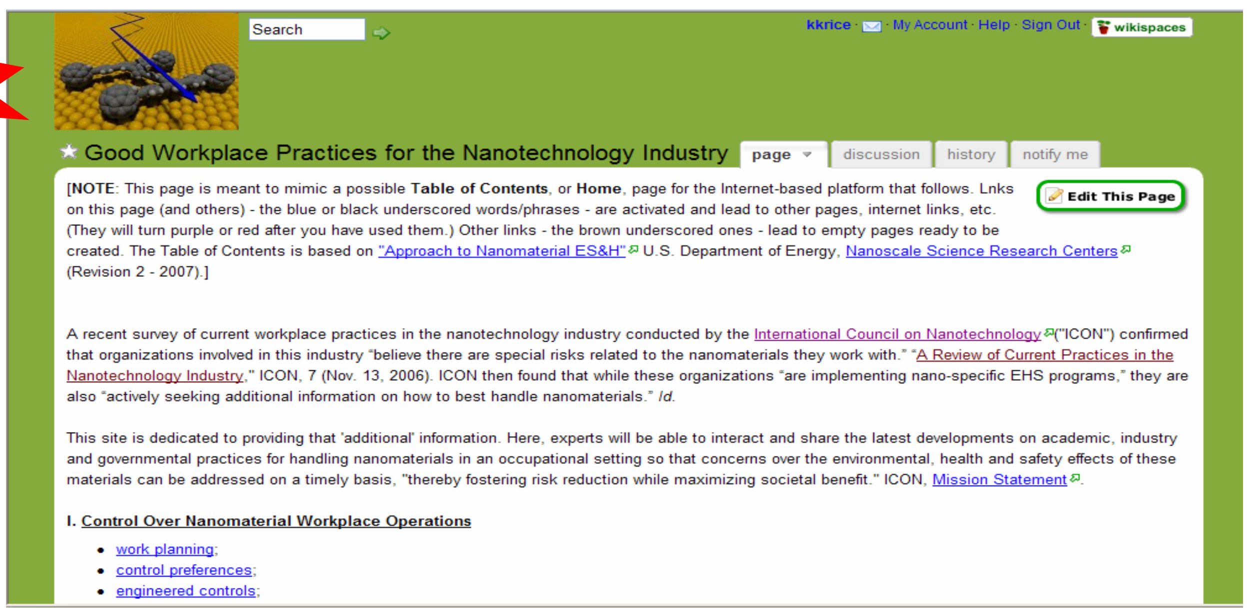
- **E2456-06 Standard Terminology Relating to Nanotechnology**
- **E2524-08 Standard Test Method for Analysis of Hemolytic Properties of Nanoparticles**
- **E2525-08 Standard Test Method for Evaluation of the Effect of Nanoparticulate Materials on the Formation of Mouse Granulocyte-Macrophage Colonies**
- **E2526-08 Standard Test Method for Evaluation of Cytotoxicity of Nanoparticulate Materials in Porcine Kidney Cells and Human Hepatocarcinoma Cells**
- **E2578-07 Standard Practice for Calculation of Mean Sizes/Diameters and Standard Deviations of Particle Size Distributions**
- **E2535-07 Standard Guide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings**

Proposed New Standards

- WK8705 Measurement of particle size distribution of nanomaterials in suspension by Photon Correlation Spectroscopy (PCS)
- WK8997 Standard Practice for Analysis of Hemolytic Properties of Nanoparticles
- WK9326 Standard Practice for Evaluation of the Effect of Nanoparticulate Materials on the Formation of Mouse Granulocyte-Macrophage Colonies
- WK9327 Standard Practice for Evaluation of Cytotoxicity of Nanoparticulate Materials on Porcine Kidney Cells
- WK9952 Standard Practice for Measuring Length and Thickness of Carbon Nanotubes Using Atomic Force Microscopy Methods
- WK10417 Standard Practice for the Preparation of Nanomaterial Samples for Characterization

Future Directions

- Identify promising metrology and methodologies for monitoring nanomaterials in the workplace and the environment
- Identify tools for detecting the presence and characteristics of nanomaterials in biological systems
- Develop a minimum set of experimental data to be submitted with a technical manuscript to allow for greater reproducibility and comparison of nano-biointeractions research
- Identify model biological systems and model nanoparticles for nano-biointeractions research
- **ICON Good Workplace Practices Wiki**



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Good Workplace Practices for the Nanotechnology Industry

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Edit This Page

[NOTE: This page is meant to mimic a possible **Table of Contents**, or **Home**, page for the Internet-based platform that follows. Lnks on this page (and others) - the blue or black underscored words/phrases - are activated and lead to other pages, internet links, etc. (They will turn purple or red after you have used them.) Other links - the brown underscored ones - lead to empty pages ready to be created. The Table of Contents is based on "Approach to Nanomaterial ES&H" U.S. Department of Energy, Nanoscale Science Research Centers (Revision 2 - 2007).]

A recent survey of current workplace practices in the nanotechnology industry conducted by the International Council on Nanotechnology ("ICON") confirmed that organizations involved in this industry "believe there are special risks related to the nanomaterials they work with." "A Review of Current Practices in the Nanotechnology Industry," ICON, 7 (Nov. 13, 2006). ICON then found that while these organizations "are implementing nano-specific EHS programs," they are also "actively seeking additional information on how to best handle nanomaterials." *Id.*

This site is dedicated to providing that 'additional' information. Here, experts will be able to interact and share the latest developments on academic, industry and governmental practices for handling nanomaterials in an occupational setting so that concerns over the environmental, health and safety effects of these materials can be addressed on a timely basis, "thereby fostering risk reduction while maximizing societal benefit." ICON, Mission Statement.

I. Control Over Nanomaterial Workplace Operations

- work planning;
- control preferences;
- engineered controls;

Addressing Applications & Implications

http://cben.rice.edu

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http://icon.rice.edu

The International Council on Nanotechnology

A unique multi-stakeholder forum for addressing the potential risks of nanotechnology

Prioritized Research Needs I

Research to Predict Nano-Biointeractions	Near-term 2 years	Mid-term 5 years	Long-term 7-10 years
Nanomaterial characterization			
1. Establish minimum NM physicochemical properties for characterization.	✓		
2. Establish validated correlation between physicochemical properties and biointeractions.		✓	
Standard terminology			
3. Establish common vocabulary/terminology for materials and assays.	✓		
Standard reference nanomaterials			
4. Establish validated reference NMs that have been tested *in vitro* and *in vivo*.	✓		
5. Establish tight control of nanoparticle reference materials.		✓	
Techniques for detecting Nanomaterials in biological media			
6. Develop new techniques for imaging NMs in biological media and organisms to supplement TEM	✓		
In vivo tests and correlation to in vitro tests			
7. Quantitatively determine the fate and interactions of engineered NMs within reference organisms, including dose and dose-rate effects.	✓		
8. Develop a fundamental understanding of NM interaction with cell-signaling pathways.		✓	
9. Identify nano-biointeractions for chronic exposure.			✓
10. Validate SARs based on *in vitro* and *in vivo* data.			✓

Prioritized Research Needs II

In vitro test validation			
11. Identify standard *in vitro* biological media and tests based on *in vivo* tests.	✓		
12. Evaluate interactions of a range of engineered NMs with standard *in vitro* tests and evaluate vs. *in vivo*.	✓		
13. Establish validated correlation between physicochemical properties and biointeractions.		✓	
14. Validate standard *in vitro* biological media and assays vs. *in vivo* tests.		✓	
15. Correlate engineered NMs *in vitro* and *in vivo* for model systems.		✓	
16. Explore interactions of a broad range of engineered NMs with complex coatings with standardized *in vitro* tests.		✓	
17. Complete mechanistically based QSAR studies.		✓	
18. Develop engineered NM-specific, high-throughput screening methods with supplemental modeling.			✓
19. Validate SARs based on *in vitro* and *in vivo* data.			✓
Model development			
20. Design framework(s) for data sharing and ontologies.	✓		
21. Explore applicability of established modeling algorithms.	✓		
22. Establish data-sharing structures.		✓	
23. Establish mechanistically based QSAR studies.		✓	
24. Validate SARs based on in vitro and in vivo data.			✓
25. Validate algorithms and training sets for computational models.			✓
26. Develop engineered NM-specific, high-throughput screening methods with supplemental modeling.			✓

NM = Nanomaterial

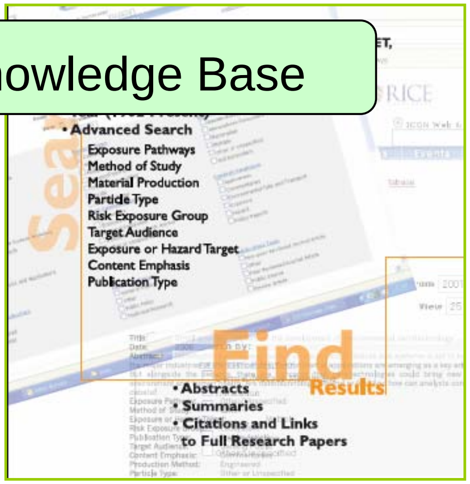
Prioritized Research Needs III

Research to Meet Risk Management Needs	Near-term 2 years	Mid-term 5 years	Far-term 7-10 years
Metrology for risk management			
1. Identify metrology techniques capable of characterizing the presence of engineered NMs in the workplace and environment.	✓		
2. Validate the effectiveness of personal protective equipment in limiting exposure.	✓		
3. Develop portable tools to monitor a wide range of NMs in the workplace and environment.		✓	
Assessment of bioavailability			
4. Determine the bioavailability of NMs throughout the lifecycle.		✓	
Characterization of potential mobility of embedded NMs			
5. Establish test methodologies to evaluate the stability and mobility of NMs in liquid and solid matrices.	✓		
6. Complete evaluation of stability and mobility of NMs in common liquid and solid matrices.		✓	

NM = Nanomaterial

Quality Information about Risks & Benefits

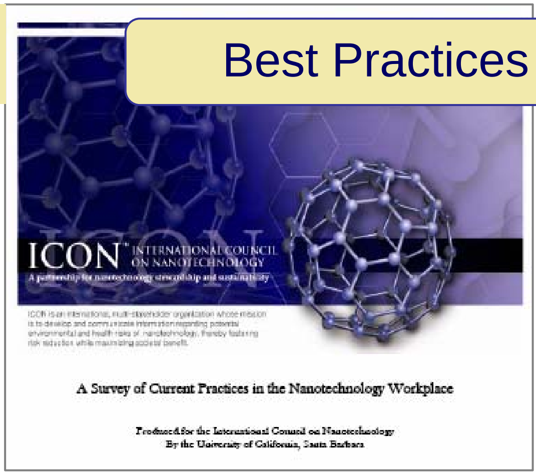
Knowledge Base



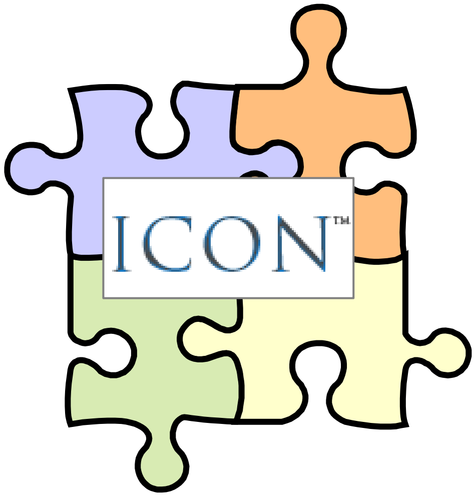
Database/VJ on nanoEHS research

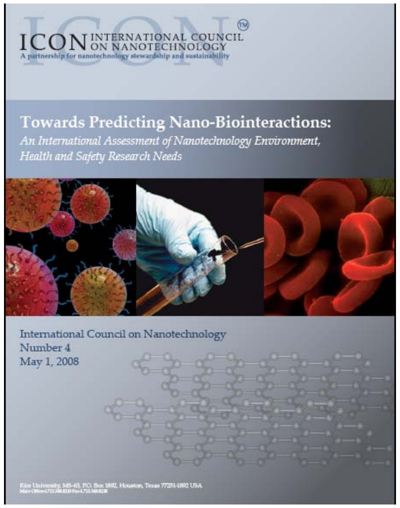
New ES&T paper:
DOI: 10.1021/es702158q

Best Practices



Survey of current workplace practices





International nanoEHS research needs assessment

Communications

ICONsultations with diverse stakeholders

ICON Working Groups

RICE

Acknowledgments

Workshop Steering Team Members

- Cate Alexander Brennan, National Nanotechnology Coordination Office
- John Balbus, Environmental Defense
- David Berube, University of South Carolina
- Vicki Colvin, Rice University
- Scott Cumberland, The Clorox Company
- Kenneth Dawson, University College Dublin
- Thomas Epprecht, Swiss Reinsurance Company
- Mike Garner, Intel Corporation
- Tracy Hester, Bracewell & Giuliani, LLP
- Kristen Kulinowski, Rice University
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- Jennifer Sass, Natural Resources Defense Council
- Hideo Shindo, NEDO Japan
- Vicki Stone, Napier University
- Sally Tinkle, National Institute of Environmental Health Sciences

- David Johnson, Rice University

Major Sponsors

ICON

NSF Grant BES-0646107

In-Kind Sponsors

National Institutes of Health

Swiss Re

E2456-06 Standard Terminology Relating to Nanotechnology

- Agglomerate
- Aggregate
- Fine particle
- Nano
- Nanoparticle
- Nanoscale
- Nanoscience
- Nanostructured
- Nanotechnology
- Non-transitive nanoparticle
- Particle
- Transitive nanoparticle
- Ultrafine particle

nanoparticle, *n—in nanotechnology*, a sub-classification of ultrafine particle with lengths in two or three dimensions greater than 0.001 micrometer (1 nanometer) and smaller than about 0.1 micrometer (100 nanometers) and which may or may not exhibit a size-related intensive property.

DISCUSSION—This term is a subject of controversy regarding the size range and the presence of a size-related property. Current usage emphasizes size and not properties in the definition. The length scale may be a hydrodynamic diameter or a geometric length appropriate to the intended use of the nanoparticle.

This document is available at no cost at http://www.astm.org

Std Occupational Guide

E2535: Standard Guide for Handling Unbound Engineered Nanoparticles in Occupational Settings

Standard Guide for Handling Unbound Engineered Nanoparticles in Occupational Settings[1]

This standard is issued under the fixed designation E XXXX; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

INTRODUCTION

Nanometer-scale particles (nanoparticles) are encountered in nature and in industry in a variety of forms and materials. Engineered nanoparticles as a class comprise a range of materials differing in shape, size, and chemical composition, and represent a broad range of physical and chemical properties. Workers within some nanotechnology-related industries and operations have the potential to be exposed to these engineered nanoparticles at levels exceeding ambient nanoparticle concentrations through inhalation, dermal contact and ingestion when not contained on or within a matrix (unbound). Occupational health risks associated with manufacturing, processing and handling unbound nanoparticles, agglomerates or aggregates of nanoparticle are not yet clearly understood. Dominant exposure routes, potential exposure levels and any material hazard are expected to vary widely among particular nanoparticle materials and handling contexts. Additional research is needed to understand the impact of these exposures on employee health and how best to devise appropriate exposure monitoring and control strategies. Until clearer understandings emerge, the limited evidence available suggests caution when potential exposures to unbound engineered nanoparticles (UNP) may occur.

- Technical Contact: Steven Brown (Intel)
- Passed final ballot 9/15/2007