Nanotechnology Updates for the Biosafety Lab

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COLDEN CORPORATION
Occupational Health, Safety & Environmental Consultants

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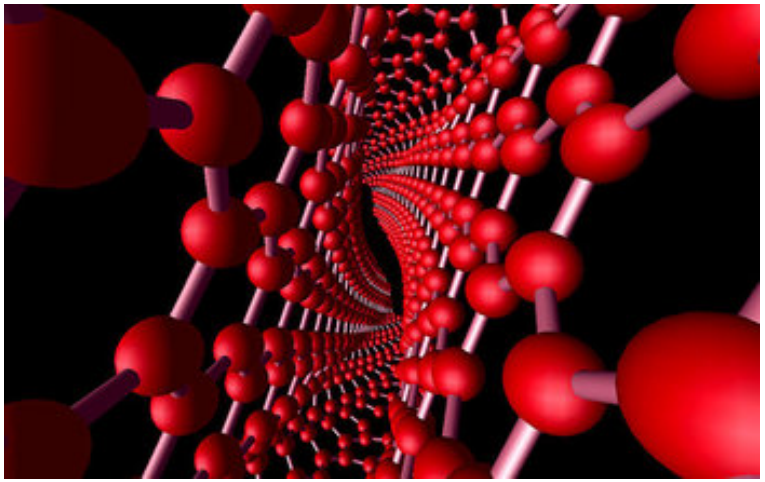
Outline

- 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)

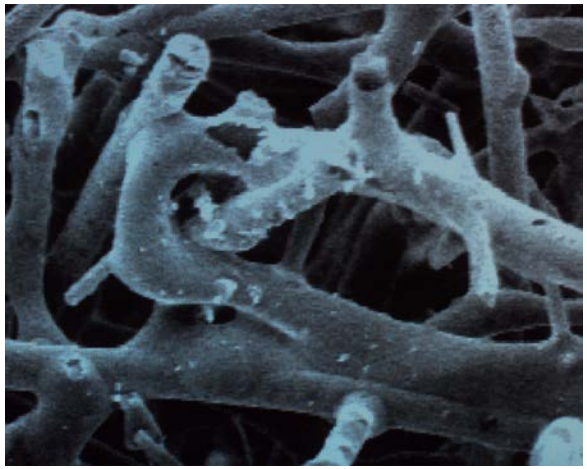


ENM high-volume examples:

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

Image credit: Vin Crespi, Pennsylvania State Physics. Creative Commons license.
http://www.nsf.gov/news/news_images.jsp?cntn_id=130586&org=NSF

Nanotechnology and Advanced Materials



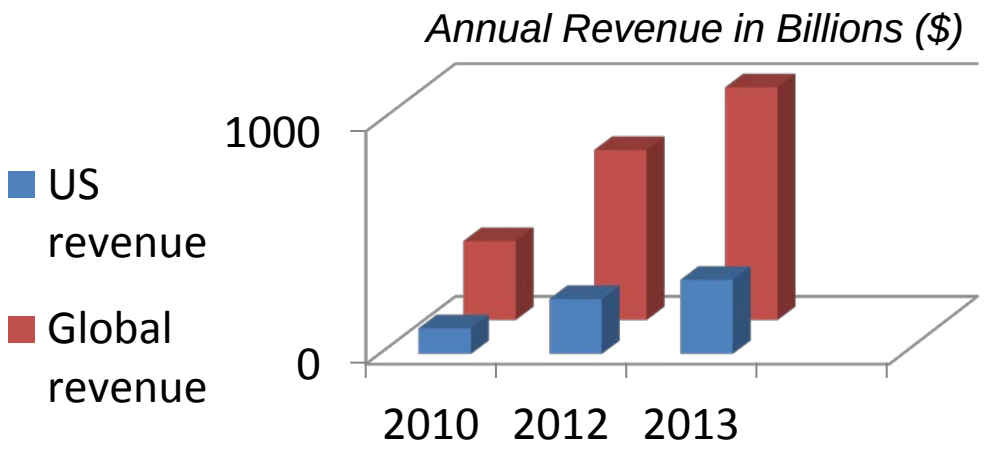
- Next Generation
  - Ex: Aerogels, superomniphobic, auxetic, smart materials
- Functional
  - Ex: Biomaterials, NEMs
- Self-Assembly
  - Ex: Self-healing materials, controlled self-assembly such as 3D printers to create sequences for DNA, RNA, or proteins

Zappa, Policy Horizons Canada. 13 Emerging Nanotechnologies And Materials That Will Change The World. May 2014. http://www.businessinsider.com/13-emerging-nanotechnologies-and-next-generation-materials-2014-4

Image: Aerogel. NASA 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.



Financial data from Lux Research report excerpt (February 2014) based on NSF and NNCO-funded study. https://portal.luxresearchinc.com/research/report_excerpt/16215

Nanomaterial Lifecycle

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

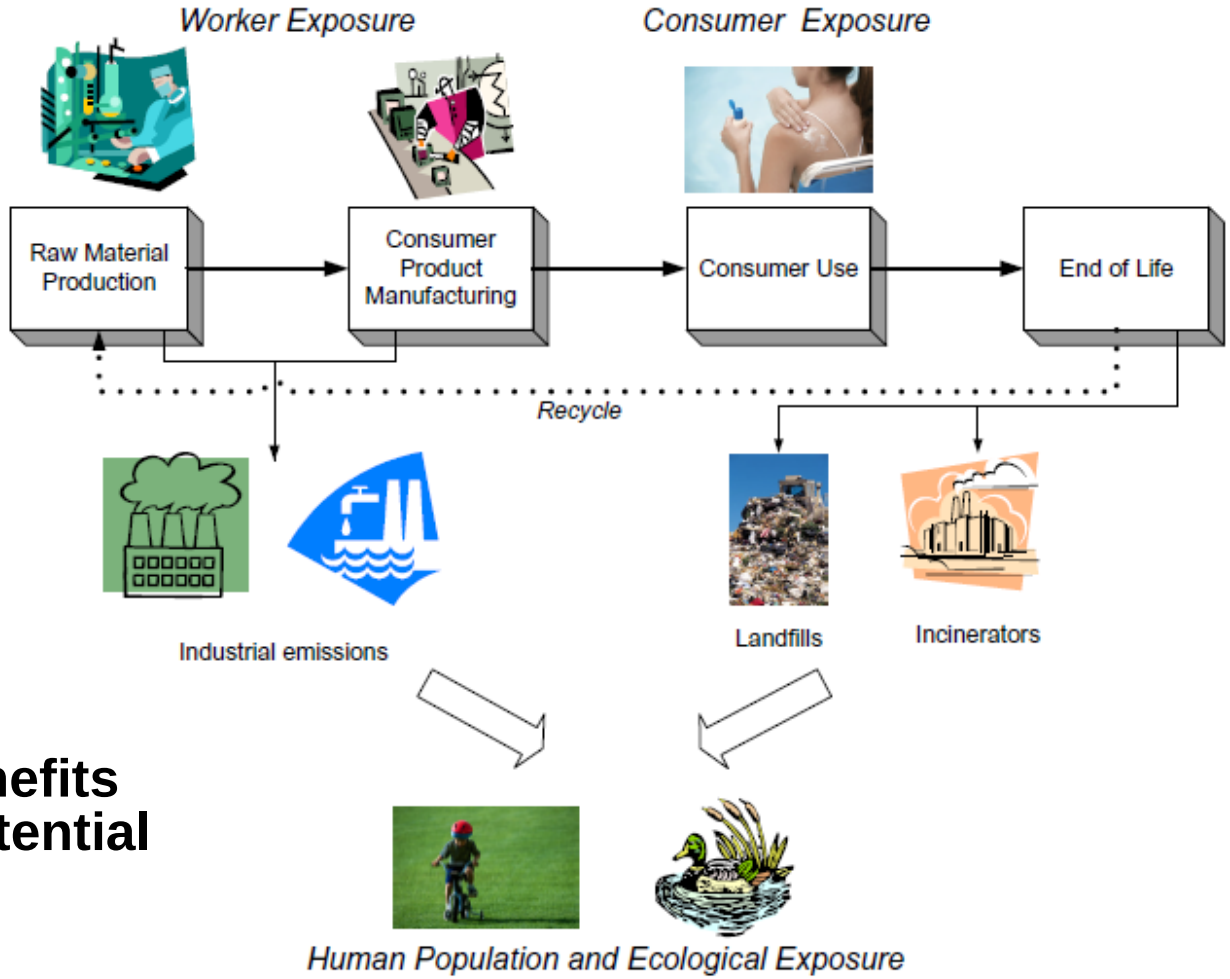


Fig: US EPA 100/B-07/001, Figure 16, 2007

How to maximize nanotechnology benefits while minimizing potential adverse impact?

Nanotechnology Risk Assessment and Management

Challenges	Current/Future Directions
▪ 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	▪ 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

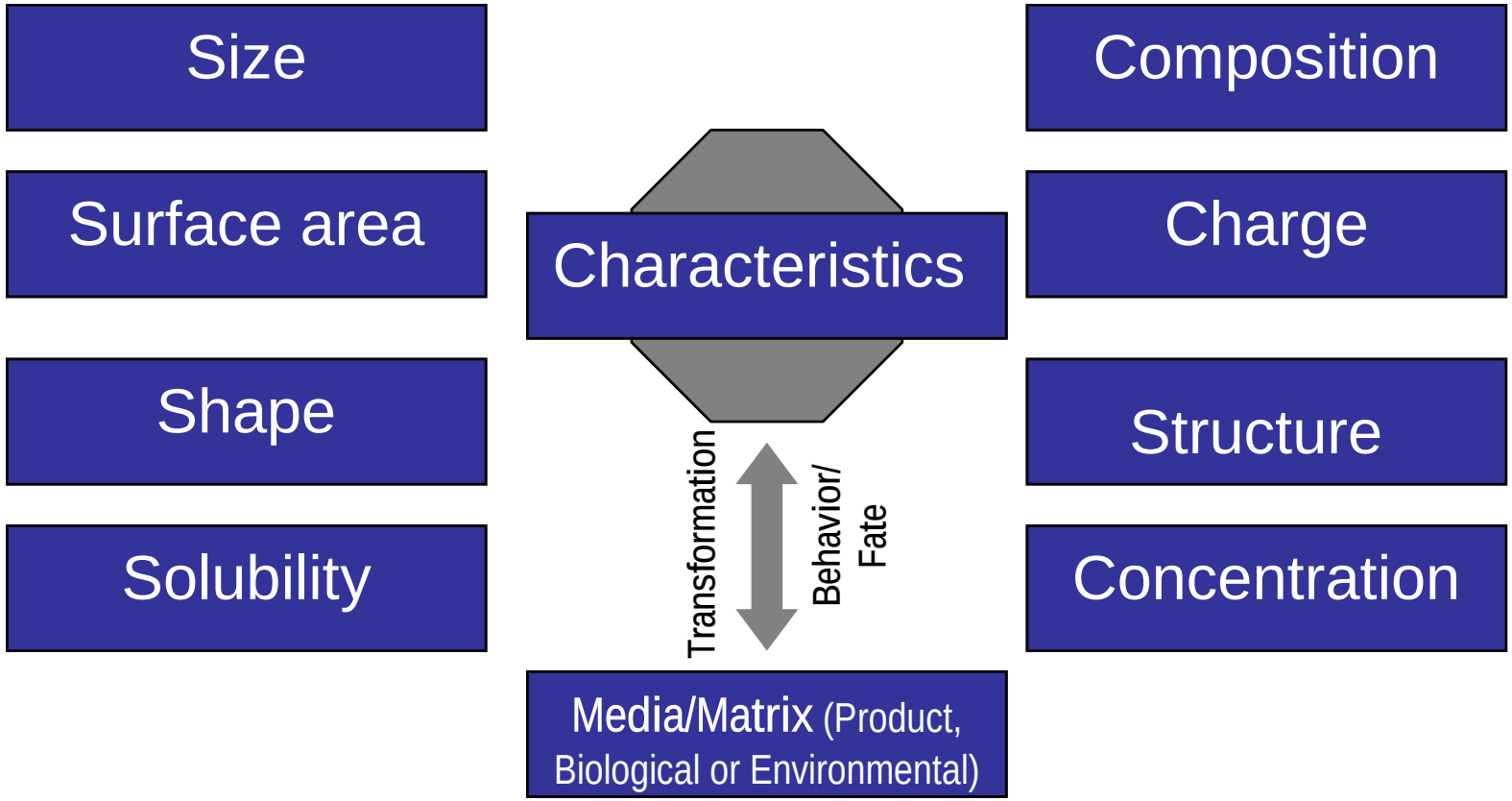


Figure: Shepard M. © 2014.

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

<u>Approaches for practitioners:</u>

- 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

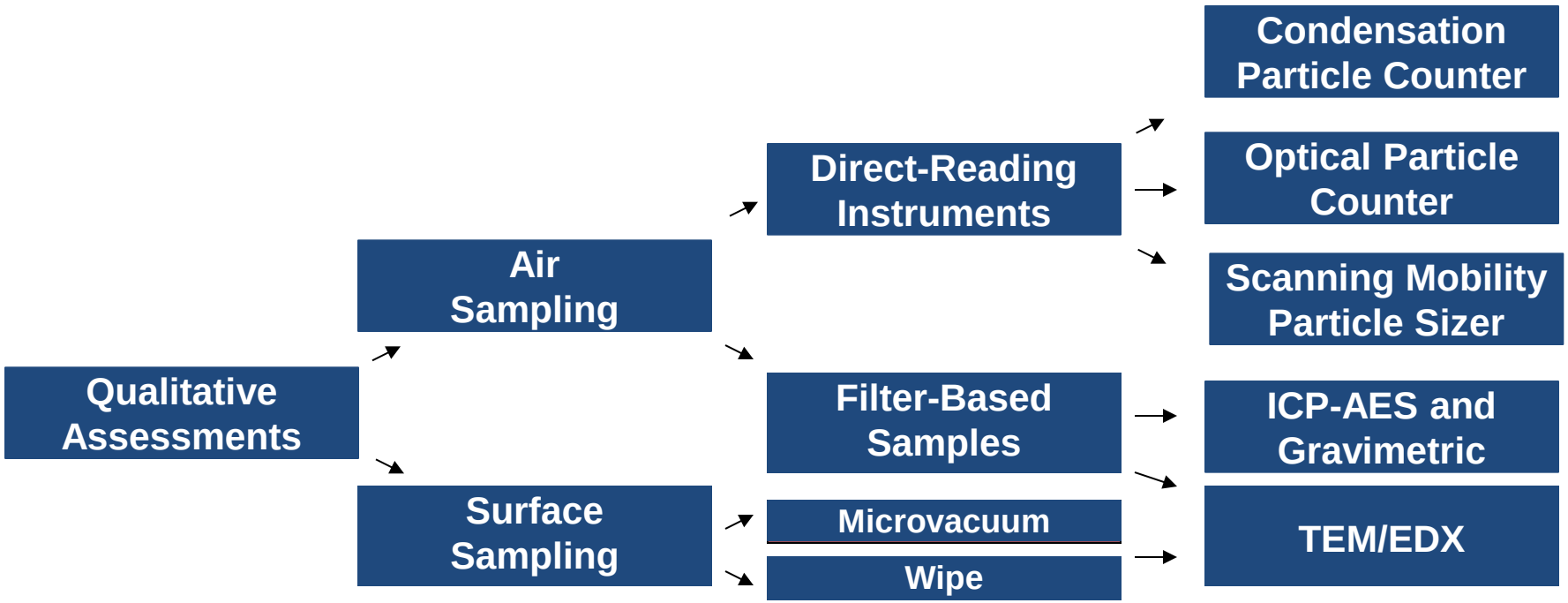
- 1 µg/m^3 elemental carbon 8-hr TWA for CNTs/CNFs (NIOSH, 2013)
- 0.3 mg/m^3 10-hr TWA for nanoscale titanium dioxide (NIOSH, 2011)
- 0.3 mg/m^3 TWA as an upper bound categorical guideline adjusted for other poorly soluble low toxicity (PSLT) nanoparticles (Schulte et al., 2010; NIOSH, 2011)
- 0.06 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/m^3
  - 40,000 p/cc for granular ENMs with density < 6,000 kg/m^3
  - 10,000 f/m^3 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)*

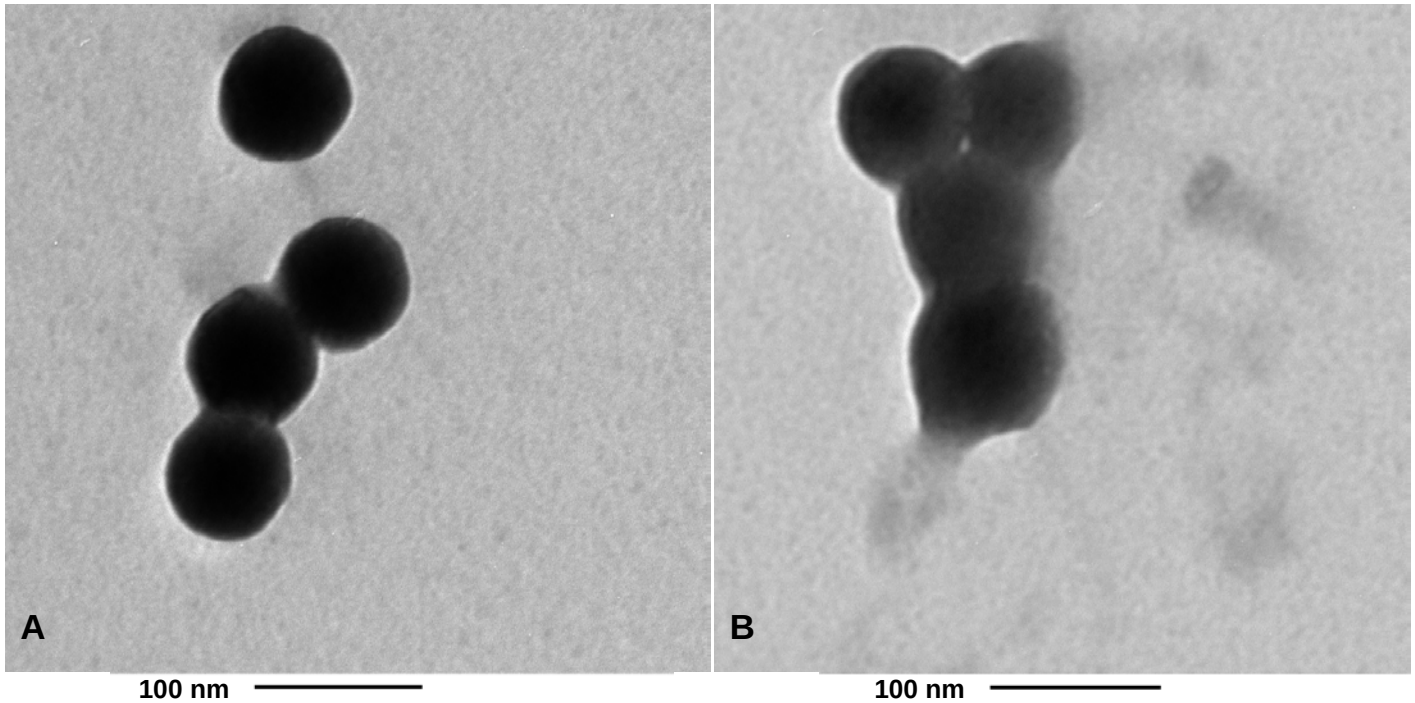
Exposure Assessment: Example Sampling Framework



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

Air sampling approach from Shepard and Brenner, Ann Occ Hyg, 2014
Figure: Shepard M. © 2014.

NOAA in Surface Vacuum Samples



A. Microvacuum sample collected on handle/control panel of HEPA vacuum used in bulk slurry delivery area in the subfab (MCE 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 WWT tank, acidic slurry system (PC filter), by TEM/EDX. 40,000x. ©CNSE ; images by iATL 77.7x74.9 nm; 89.5x87.1 nm. EDX: SiAl (90 wt-%) CaCrFe.

Shepard and Brenner, Int J Occup Environ Health, 2014

Risk Management and Control of Workplace ENM Exposures

Examples of exposure factors to consider include:

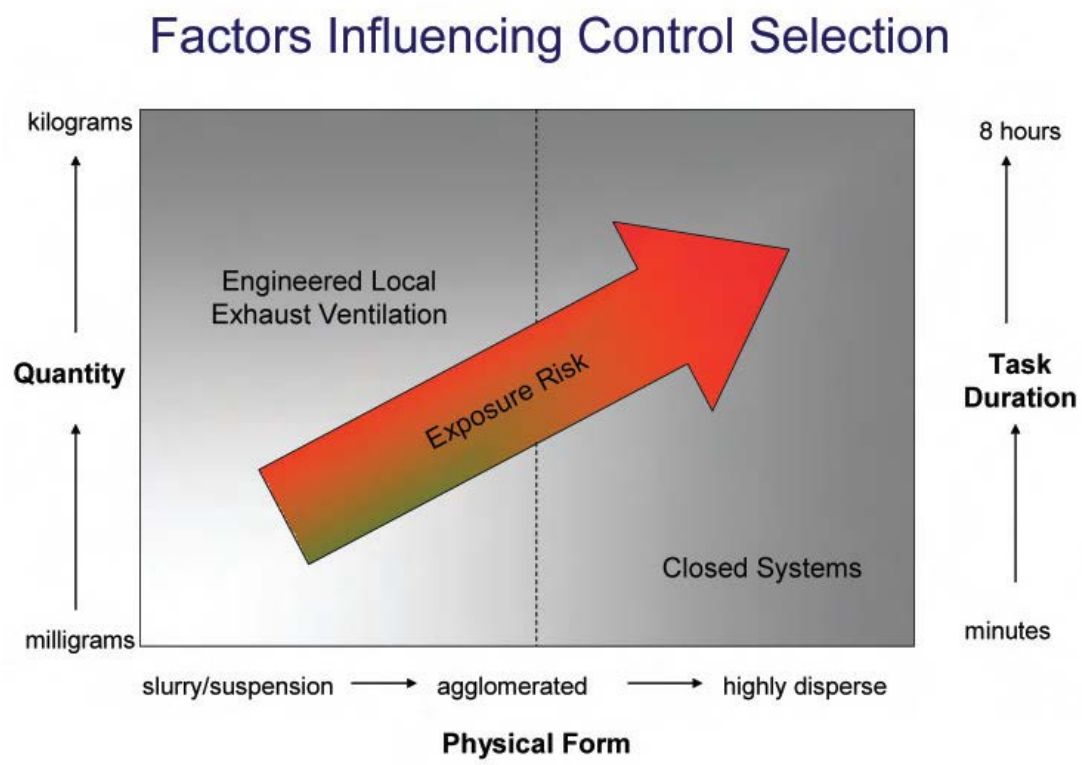


Figure: NIOSH 2009-125, Figure 8-3, March 2009.

Control Banding (CB) Framework

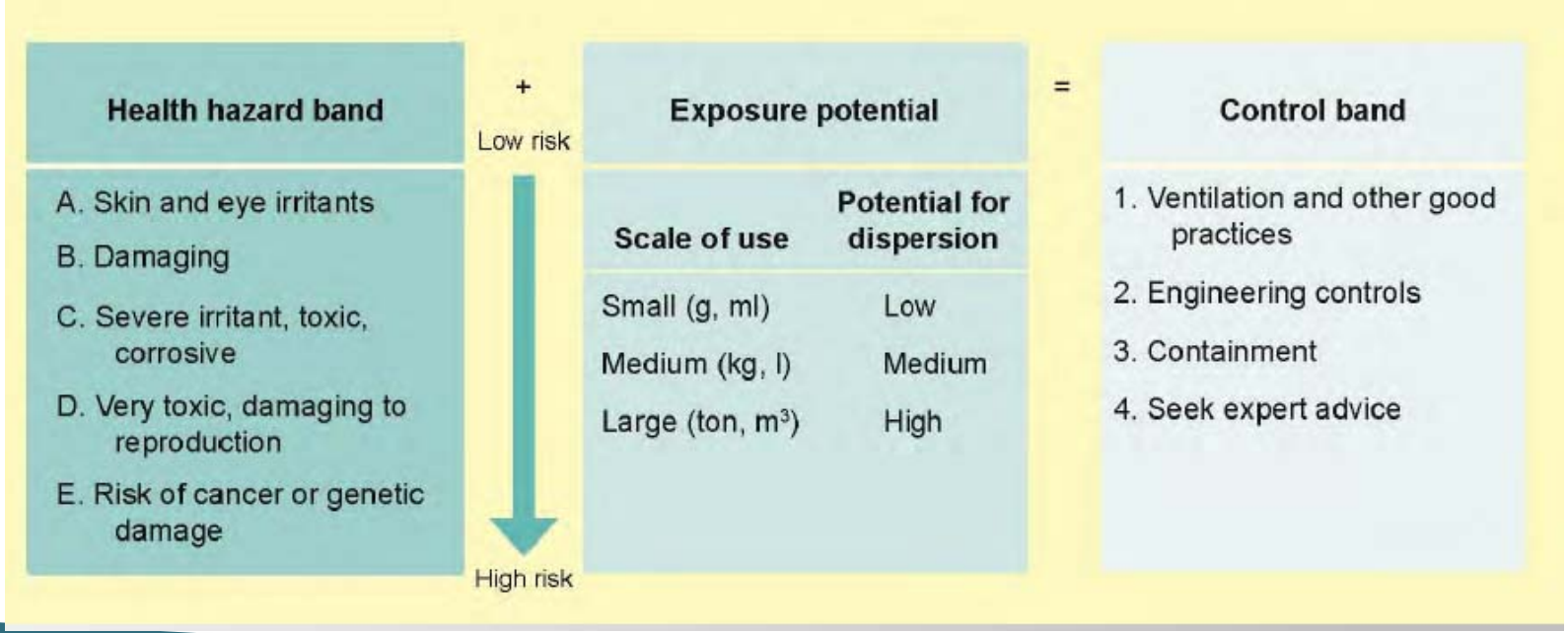
Risk assessment and management approach used where toxicological and/or exposure data are limited.

Uses categories (bands) to describe:

- Hazard (severity)
- Exposure (probability)

Recommends a set of controls:

- Limited number of approaches
- Applies existing knowledge



Health hazard band	+	Exposure potential		=	Control band
	Low risk				
A. Skin and eye irritants		Scale of use	Potential for dispersion		1. Ventilation and other good practices
B. Damaging		Small (g, ml)	Low		2. Engineering controls
C. Severe irritant, toxic, corrosive		Medium (kg, l)	Medium		3. Containment
D. Very toxic, damaging to reproduction		Large (ton, m^3)	High		4. Seek expert advice
E. Risk of cancer or genetic damage					
	High risk				

Figure: COSSH Essentials (UK).

ENM Control/Risk Banding Approaches

- Precautionary Matrix (SUI)
  http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en
- CB Nanotool (US DOE/LLNL)
  http://controlbanding.net/
- ANSES CB tool (FR)
  https://www.anses.fr/en/content/tool-control-banding-risks-associated-nanomaterials
- ISO 12901-2
- Stoffenmanger Nano (NL)
  https://nano.stoffenmanager.nl/
- GoodNanoGuide (US)
  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

Characteristic	ANSES *[1]*	CB Nanotool *[2]*	ISO 12901-2 *[1]*	Precautionary Matrix *[2]*
Hazard bands	1 to 5	1 to 4	1 to 5	1 to 9
Hazard classification	Hazard class, properties	Toxicity, properties	Hazard class, toxicity, properties	Solubility, reactivity, toxicity
Exposure bands	1 to 4	1 to 4	1 to 4	1 to 9
Exposure classification	Physical state, process	Amount, dustiness, other conditions	Amount, emission potential	Amount, frequency, form
Control bands or risk levels	5 bands	4 bands	5 bands or 3 risk levels	2 risk levels
Uncertainty/ Unknowns	Set to max. band	Assigned 75% of max. points	Considered (+1 band from bulk or analogous)	Assigned max. points

Criteria: *[1]* – Binary; *[2]* – Scoring

Figure: Shepard M. © 2014.

Model Parameters

	ANSES	CB Nanotool	ISO 12901-2	Precautionary Matrix
Material Characteristic:				
Size	o	+	o	o
Shape/fibrous	+	+	+	+
Solubility	+	+	+	+
Reactivity	+	+	o	+
Toxicity	-	+	+	+
Exposure Characteristic:				
Duration of exposure	-	+	-	-
Frequency of exposure	-	+	-	+
No. exposed	-	+	-	-
Amount	-	+	+	+
Physical form	+	o	+	+
Type of process or dustiness	+	+	+	+

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/

Probability

Severity

	Extremely Unlikely (0-25)	Less Likely (26-50)	Likely (51-75)	Probable (76-100)
Very High (76-100)	RL 3	RL 3	RL 4	RL 4
High (51-75)	RL 2	RL 2	RL 3	RL 4
Medium (26 -50)	RL 1	RL 1	RL 2	RL 3
Low (0-25)	RL 1	RL 1	RL 1	RL 2

RL 1: General Ventilation
RL 2: Fume hoods or local exhaust ventilation
RL 3: Containment
RL 4: Seek specialist advice

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

ISO 12901-2 Exposure Banding

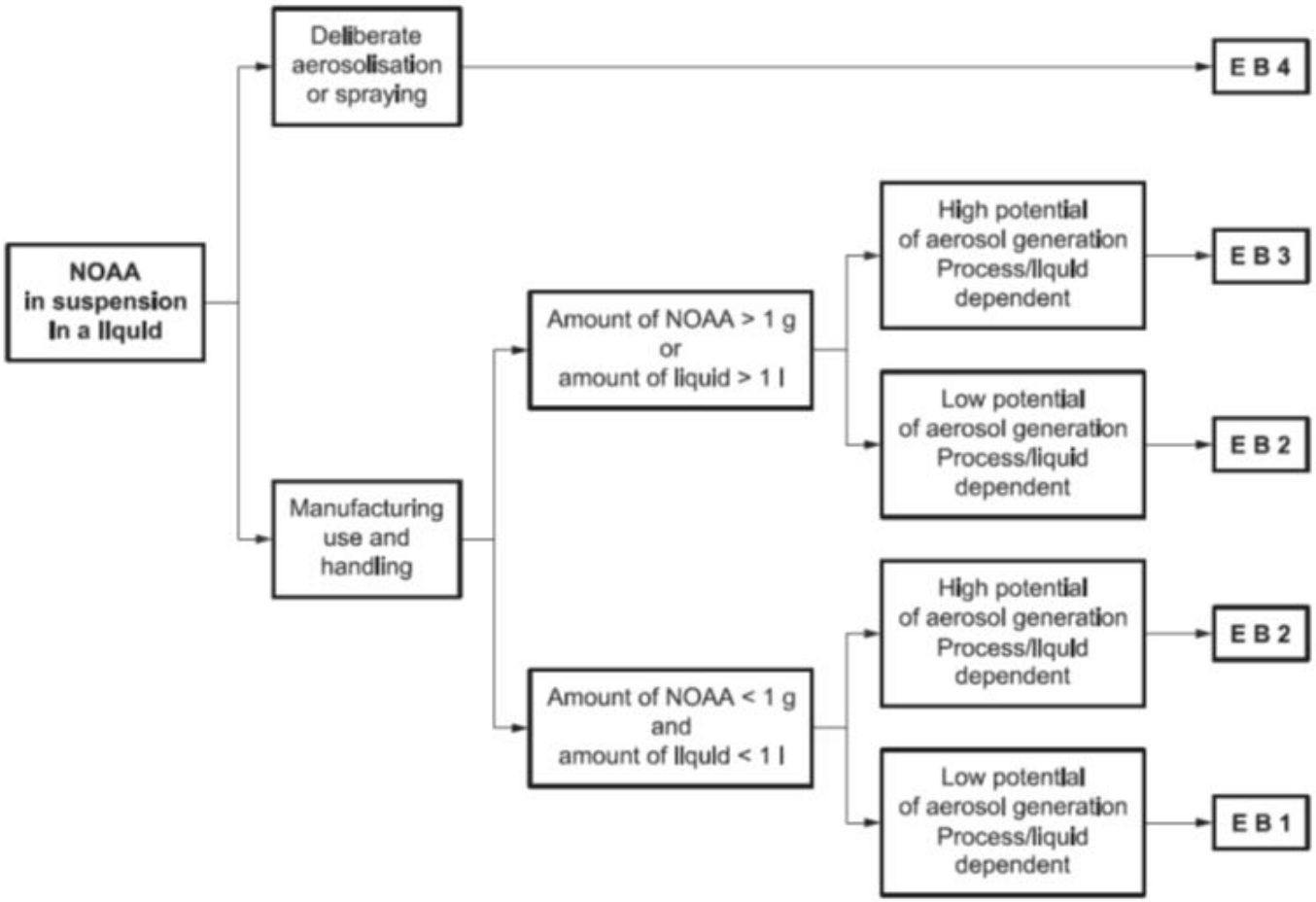


Figure 5 — Exposure banding process: NOAA in suspension in a liquid

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Training Resources

Nomenclature & Glossary

OHS Reference Manual

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

Nanoparticles in:	Dry Powder	Liquid Dispersion	Solid Polymer Matrix	Nonpolymer Matrix
	Potential Hazard	Potential Hazard	Potential Hazard	Potential Hazard

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.

Second and Third Steps: Risk Assessment and Management

Material Unpacking	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Synthesis	Exposure Potential	Exposure Potential		
	Controls	Controls		
Weighing and Measuring	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Dispersing	Exposure Potential	Exposure Potential		
	Controls	Controls		
Mixing	Exposure Potential	Exposure Potential		
	Controls	Controls		
Spraying	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Machining	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Packing	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Process Equipment Cleaning	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential
	Controls	Controls	Controls	Controls
Workspace Cleaning	Exposure Potential	Exposure Potential	Exposure Potential	Exposure Potential

Key Initiatives and Organizations

- National Nanotechnology Initiative (NNI) 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/TS 12901-1:2012 - *Nanotechnologies - Occupational risk management applied to engineered nanomaterials Part 1: Principles and approaches*

- ISO/TS 12901-2:2014 - *Nanotechnologies - Occupational risk management applied to engineered nanomaterials - Part 2: Use of the control banding approach*

- 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

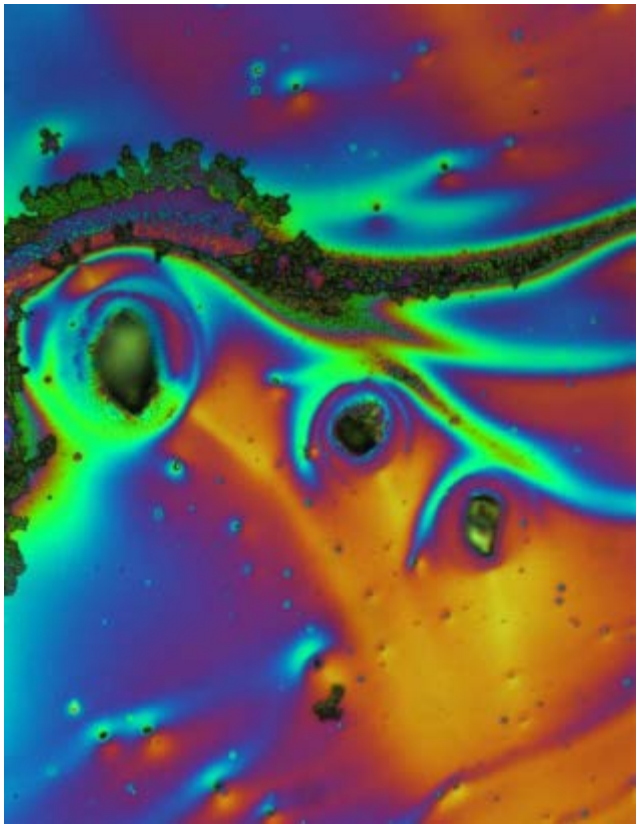
Vice Chair – Paul Webb

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

- Brouwer, DH. (2012) Control Banding Approaches for Nanomaterials. *Ann Occup Hyg* 56(5):506-514
- Dimitri, J., Rickabaugh, K., Webb, P., Shepard, M. *Industrial Hygiene Practices for Assessing Nanomaterials Exposures* (Nov 2013), The Synergist, AIHA, pp24-27
- Dimitri, J., Shepard, M., Webb, P., Baker, J. *Nanomaterials: The Next Wave* (February 2015), The Synergist, AIHA, pp28-31
- *Good NanoGuide* www.goodnanoguide.org
- Kuhlbusch et al. (2011) Nanoparticle exposure at nanotechnology workplaces: A review. *Particle and Fibre Toxicology* 8(22)
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- West,G., Lippy, B., Marsick, D., Cooper, M. *Unknown Risks: Nanomaterials in Construction* (Oct 2014), The Synergist, AIHA, pp22-23
- *Join the AIHA Nanotechnology Working Group*

Questions and Comments

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Thank you for your attention!

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