NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

NTRC | NANOTECHNOLOGY RESEARCH CENTER

Building a Risk Management Program for Nanomaterials

Kenneth F. Martinez, MSEE, CIH
Laura Hodson, MSPH, CIH
Charles Geraci, PhD, CIH

Nanotechnology Research Center
Education and Information Division
National Institute for Occupational Safety and Health

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CDC Workplace Safety and Health

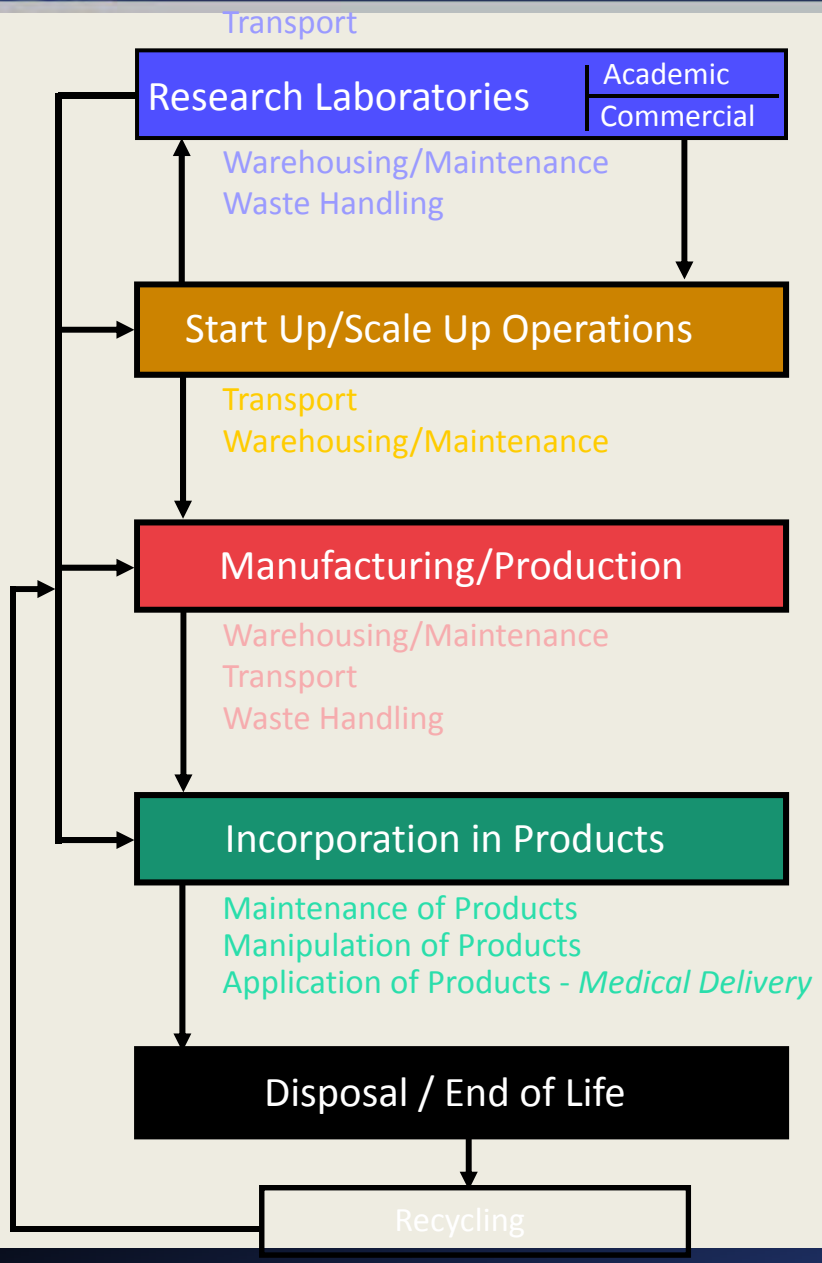
NIOSH

Nanotechnology

- Illustrates the challenges to society of a new technology
  - Beneficial properties
  - Potential hazard
  - What to do when information is lacking or uncertain

Exposure

- Workers generally the first people in society exposed to a new technology
- Nanotechnology is not an exception
- More than 1,000 nano-enabled products in commerce
- Workers make and use them


Transport
Research Laboratories
Academic
Commercial
Warehousing/Maintenance
Waste Handling
Start Up/Scale Up Operations
Transport
Warehousing/Maintenance
Manufacturing/Production
Warehousing/Maintenance
Transport
Waste Handling
Incorporation in Products
Maintenance of Products
Manipulation of Products
Application of Products - Medical Delivery
Disposal / End of Life
Recycling

Nanotechnology

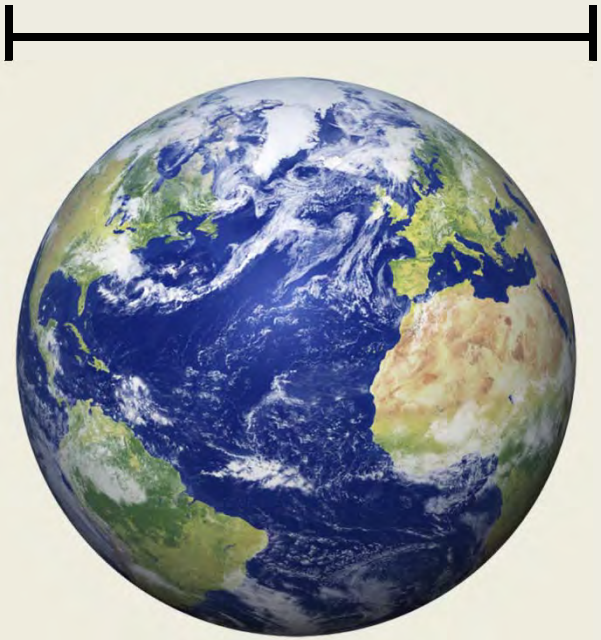
- Development of materials at the atomic, molecular, or macromolecular levels with at least one dimension in the range of 1-100 nanometers
- Creating and using structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size
- Ability to control or manipulate matter on the atomic scale

Nanomaterials

- 1 -100 nanometer size
- Special properties
- Naturally occurring (incidental) and specifically engineered

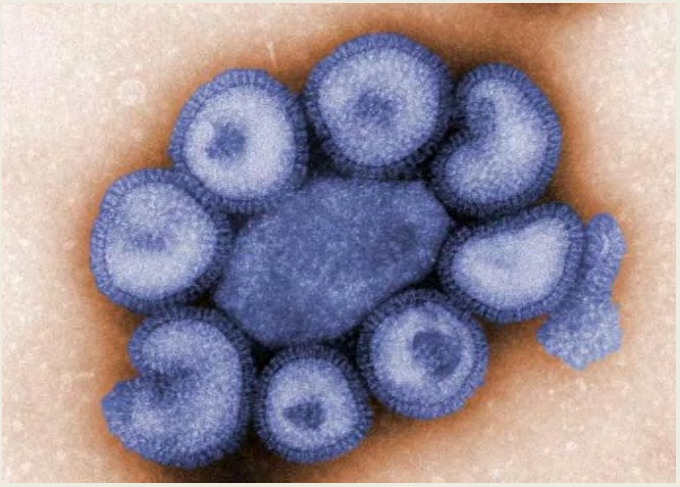
How little is “nano?”

If the diameter of the Earth represented
1 meter…

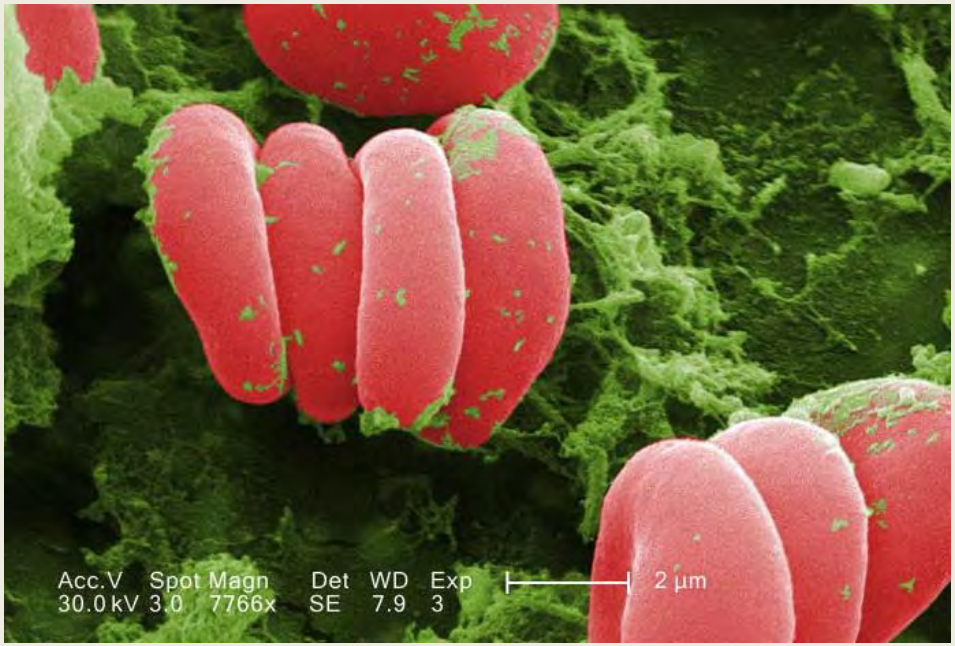


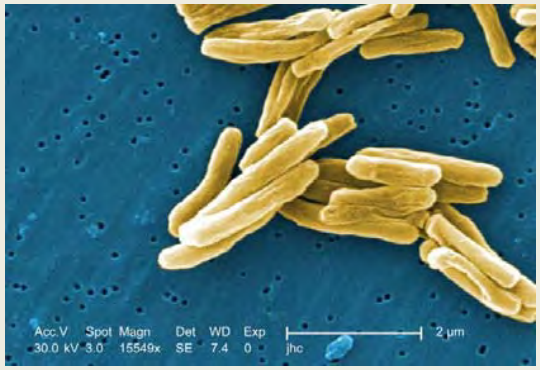
…1 nanometer
would be the size of a dime.

Size of Nanoparticles Relative to Microorganisms and Cells



Influenza virus
75-100 nm





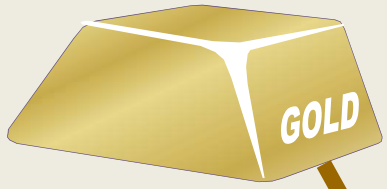
Tuberculosis bacteria
2,000 nm

Red blood cells
8,000 nm

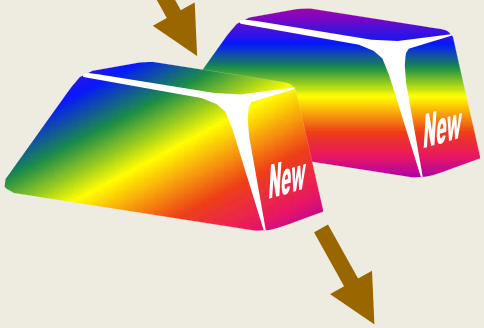
Not only smaller, but different

Same Properties

60 nm bar



30 nm bar

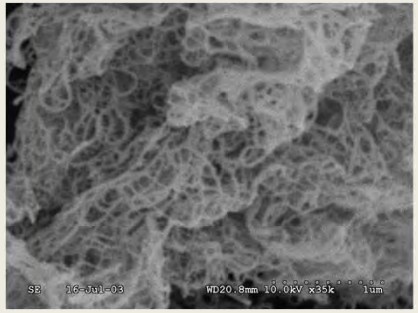


New Properties

- Lower melting point
- Useful as catalyst
- Different color
- Different conductivity

Nanoparticles: They have been around a while. Particles < 100 nm, Natural and Anthropogenic Sources

Natural	Anthropogenic	
	Incidental	Engineered
Forest Fires	Combustion engines	Controlled size and shape
Volcanoes	Incinerators	Semiconductors, carbon
Viruses	Jet engines	Metal oxides, polymers
Gas-to-particles	Welding fumes	Nanospheres, -wires, needles, -tubes, -shells, -rings, -platelets

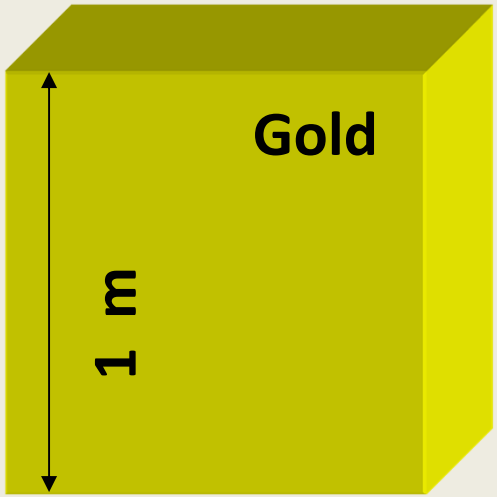


Engineered Nanomaterials

- Carbons
  - e.g., Fullerenes, nanotubes, nanofibers
- Oxides
  - e.g., TiO_2, ZnO, SiO_2, CeO_2, Fe_3O_4
- Metals
  - e.g., Ag, Fe, Al, Si, Zn, Cu, Ni
- Semiconductors
  - e.g., CdSe, CdS, InAs, InP
- Polymers/organics
  - e.g., liposomes, dendrimers
- Hybrids
  - e.g., nanoshells

Small Size → Large Surface Area

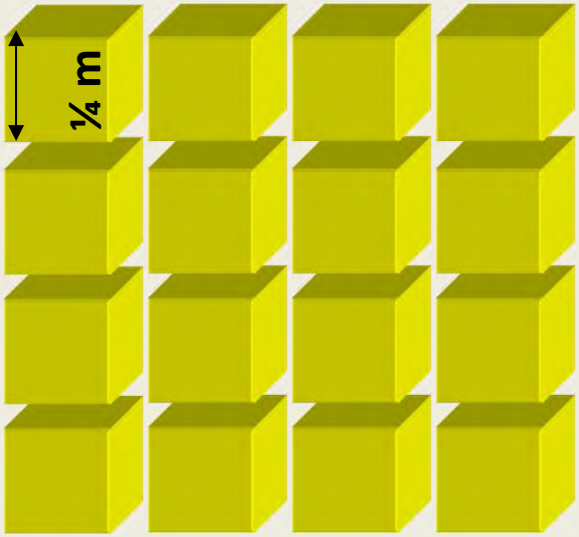
Each side = 1 meter



Mass ≈ 43,000 lb
SA = 6 m²

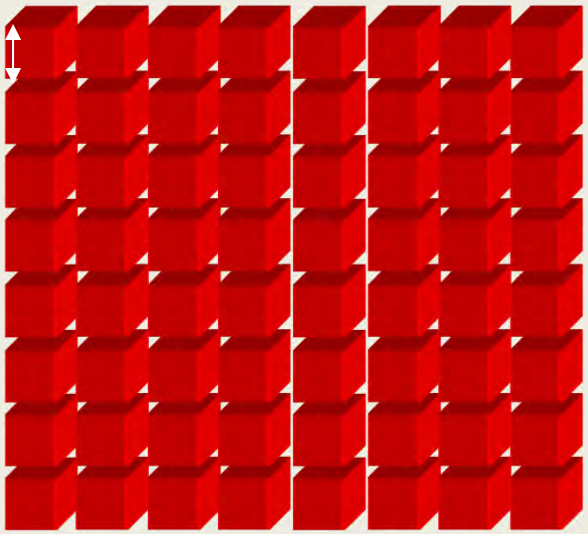
≈ 8 ft x 8 ft room

Each side = ¼ meter



Mass ≈ 43,000 lb
SA = 24 m²

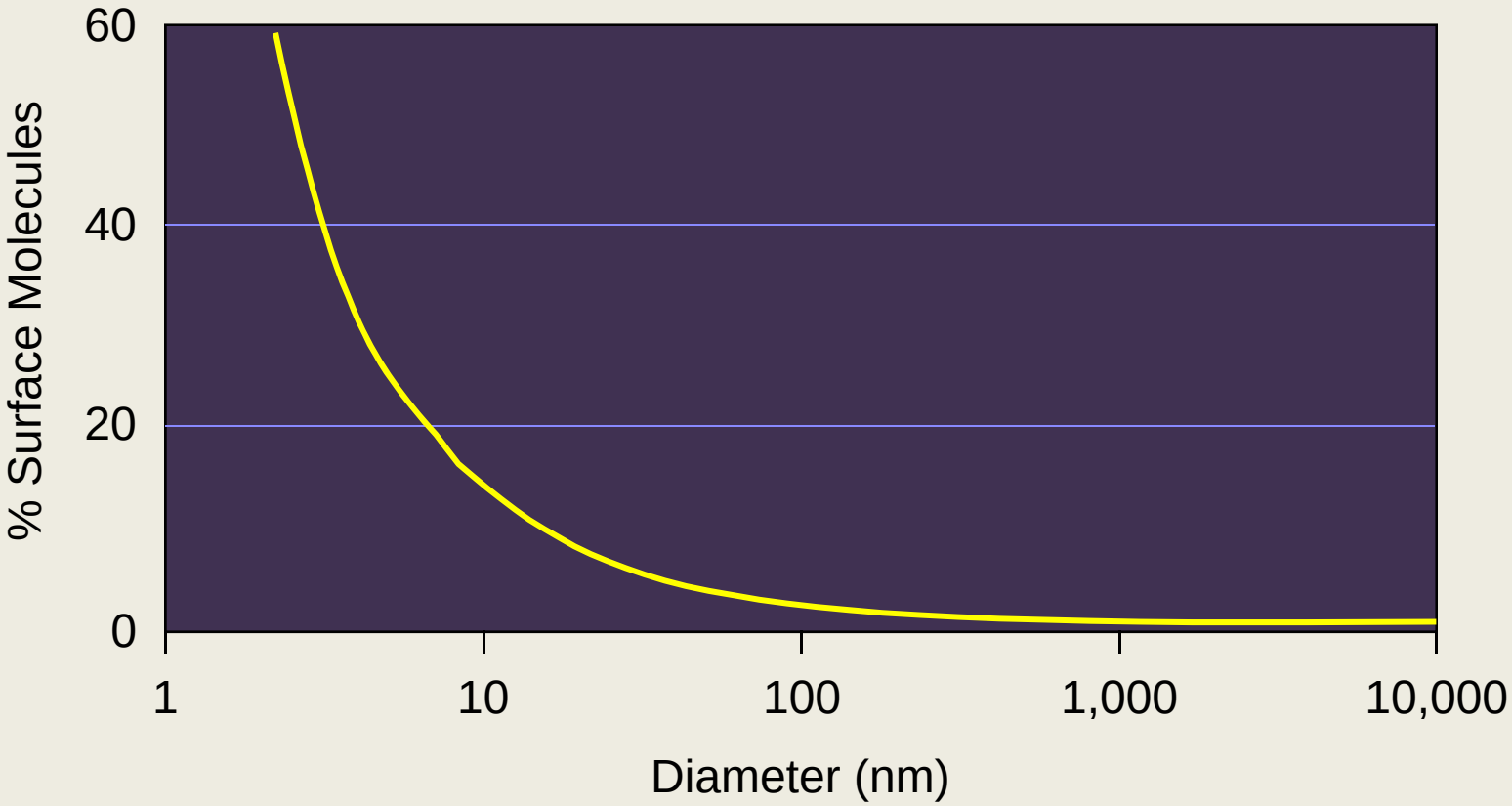
Each side = 1 nanometer



Mass ≈ 43,000 lb
SA ≈ 6 billion m²
≈ 2500 sq miles

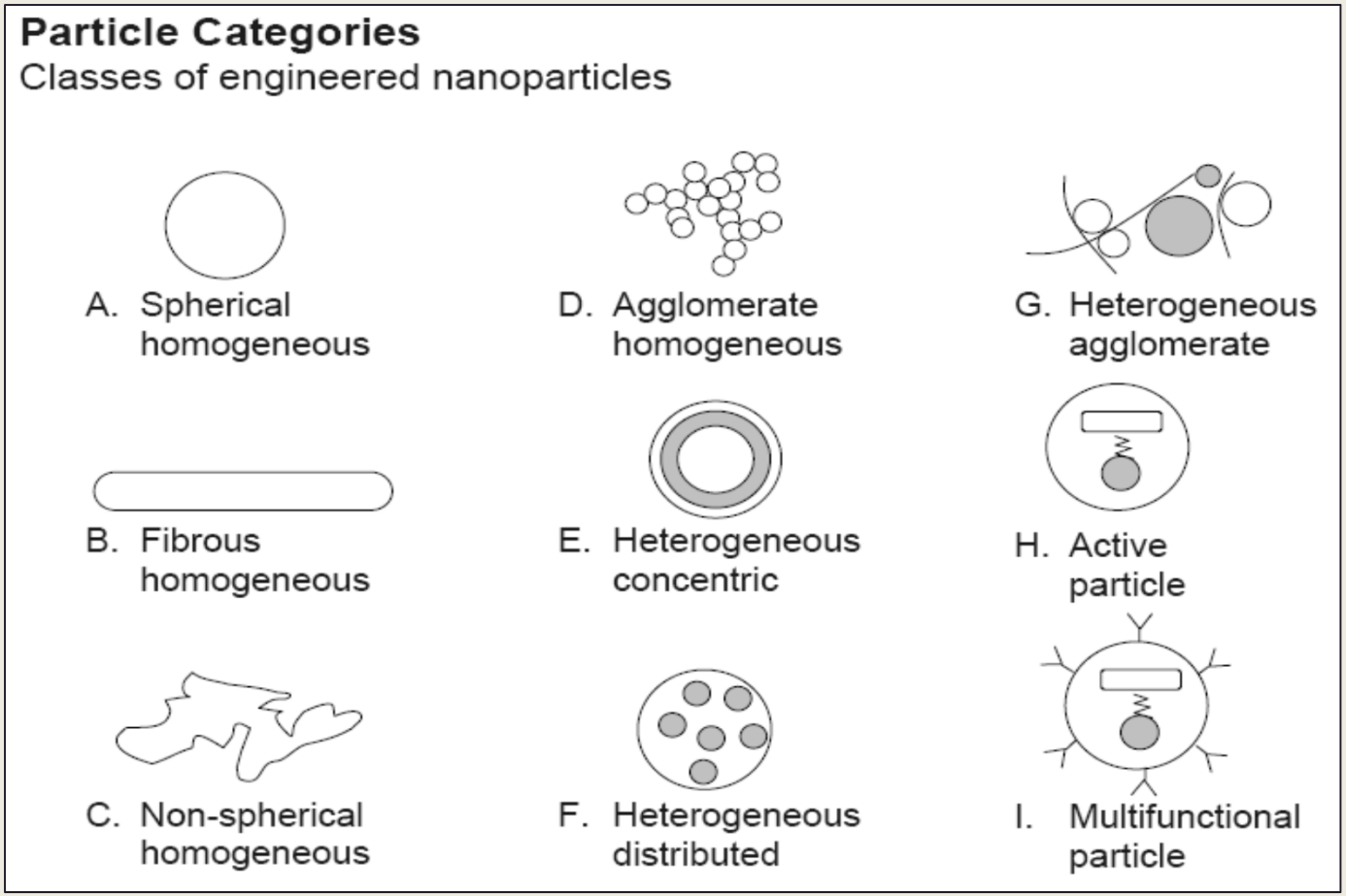
State of Delaware:
< 2000 sq miles

Why are nanomaterials potentially dangerous?



Source: Kelly [2009]

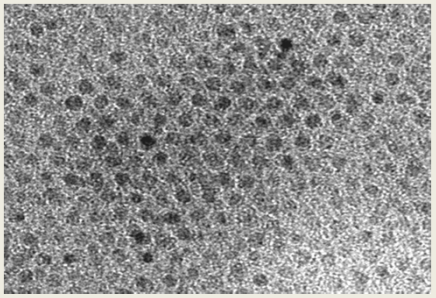
What could a “nanoparticle” be?



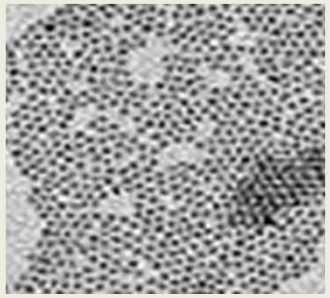
Source: Dr. A . Maynard: Woodrow Wilson International Center for Scholars

Size-Dependent Properties

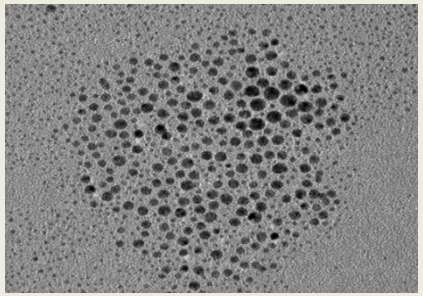
Fe_3O_4, Magnetite (4 nm)

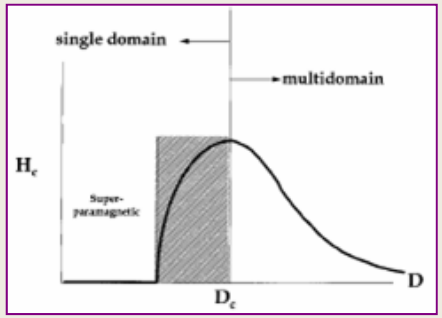


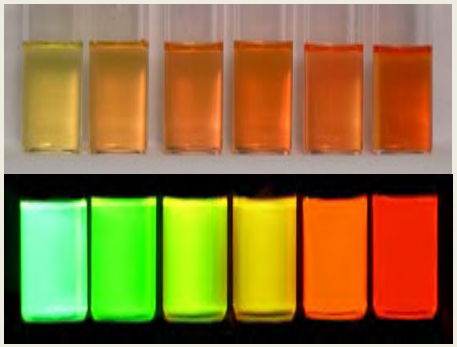
CdSe (8 nm)

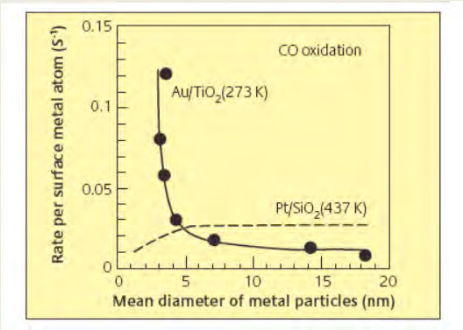


Gold (~ 10 nm)









Magnetism

Emission

Reactivity

Parameters That Could Affect Nanoparticle Toxicity

- Size
- Shape
- Composition
- Solubility
- Crystalline structure
- Charge
- Surface characteristic
- Agglomeration
- Impurities
- Attached functional groups

Why is nanotechnology of great interest?

- Imparts useful properties to materials
  - Stronger
  - Lighter
  - More durable
- Different melting temperatures
- Enhanced electrical conductivity
- More transistors on integrated chip
- Enhanced chemical reactivity

All of these point to the possibility of creating new and very powerful applications.

Applications of Nanotechnology

Agriculture	More efficient, targeted delivery of plant nutrients, pesticides
Automotive	Lighter, stronger, self-healing materials
Biomedical	Targeted therapeutics, enhanced detection, new structural materials
Energy	More efficient fuel cells, solar collectors
Environmental	New pollution control and remediation tools, sensors
Food	New safety sensors, food preservatives, nutrient additives
Materials	Self-cleaning glass, stain resistant, stronger materials, body armor
Water	New purification approaches

A Nano History

- 300 AD Lycergus Cup with nano gold
- 6th to 15th Century stained glass
- 13th to 18th Century Demacus saber blades contain carbon nanofiber

Early Nano-Enabled Consumer Products are on the Market Now [Gibbs 2006]

Samsung Nano SilverSeal Refrigerator

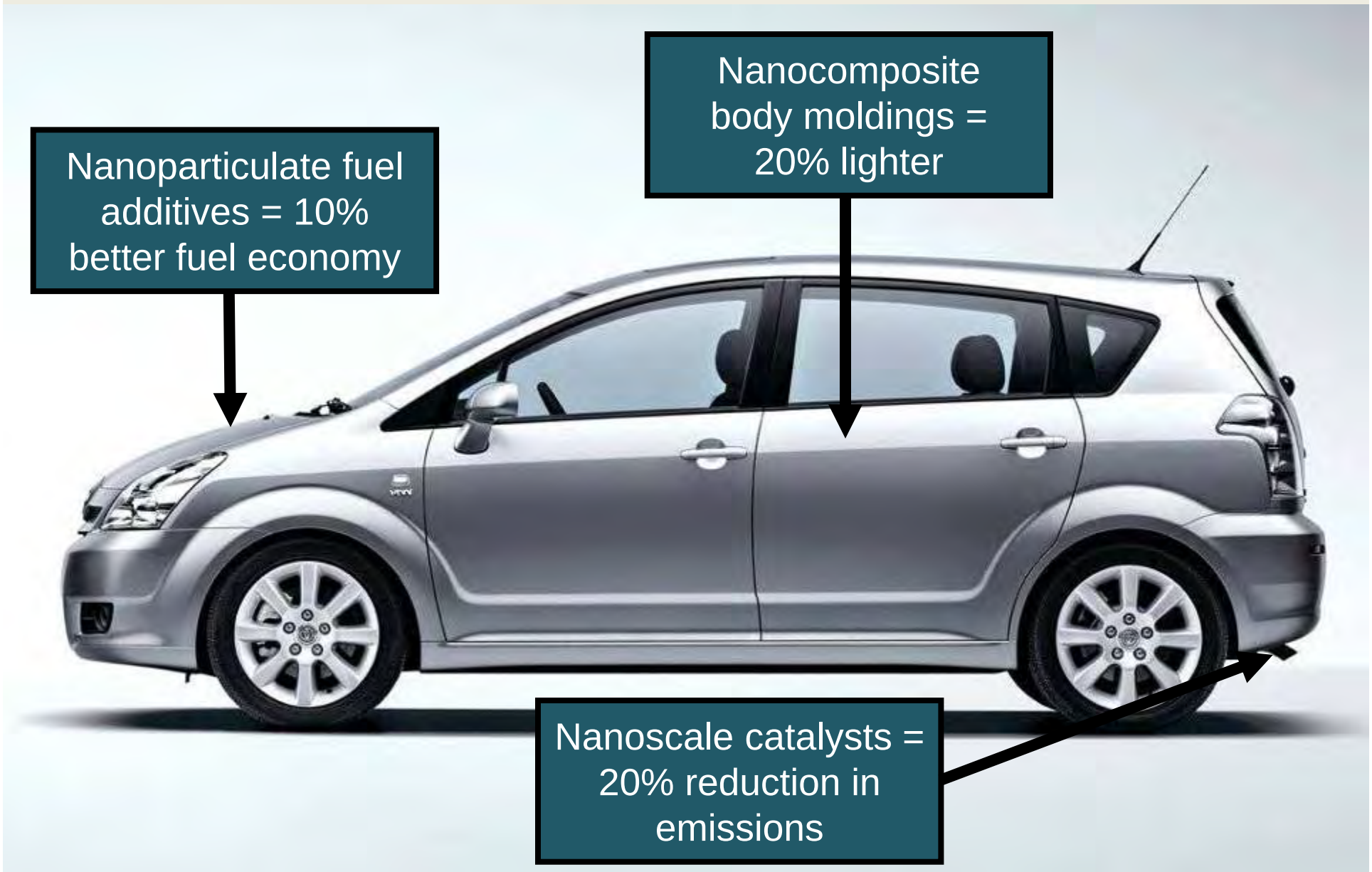
Kodak EasyShare LS633 camera

Eddie Bauer Ruston Fit Nano-Care khakis

Wilson Double Core tennis balls

Laufen Gallery washbasin with Wondergliss

Smith & Nephew Acticoat 7 antimicrobial wound dressing

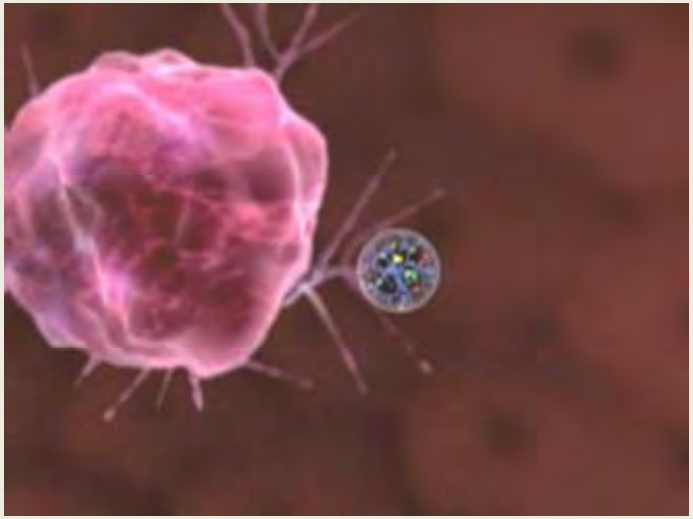


Source: Gibbs [2006]

Nanotechnology: Biochemical applications

Cancer treatment (nano.cancer.gov)

- Potential for:
  - Disease sensing
  - Diagnosis
  - Targeted therapy



- FDA has approved numerous Investigational New Drug (IND) applications for nano-formulations, enabling clinical trials for breast, gynecological, solid tumor, lung, mesenchymal tissue, lymphoma, central nervous system and genito-urinary cancer treatments.

Picture source: Burnham Institute

Nanomaterials: What is available and might be your 'next exposure'?

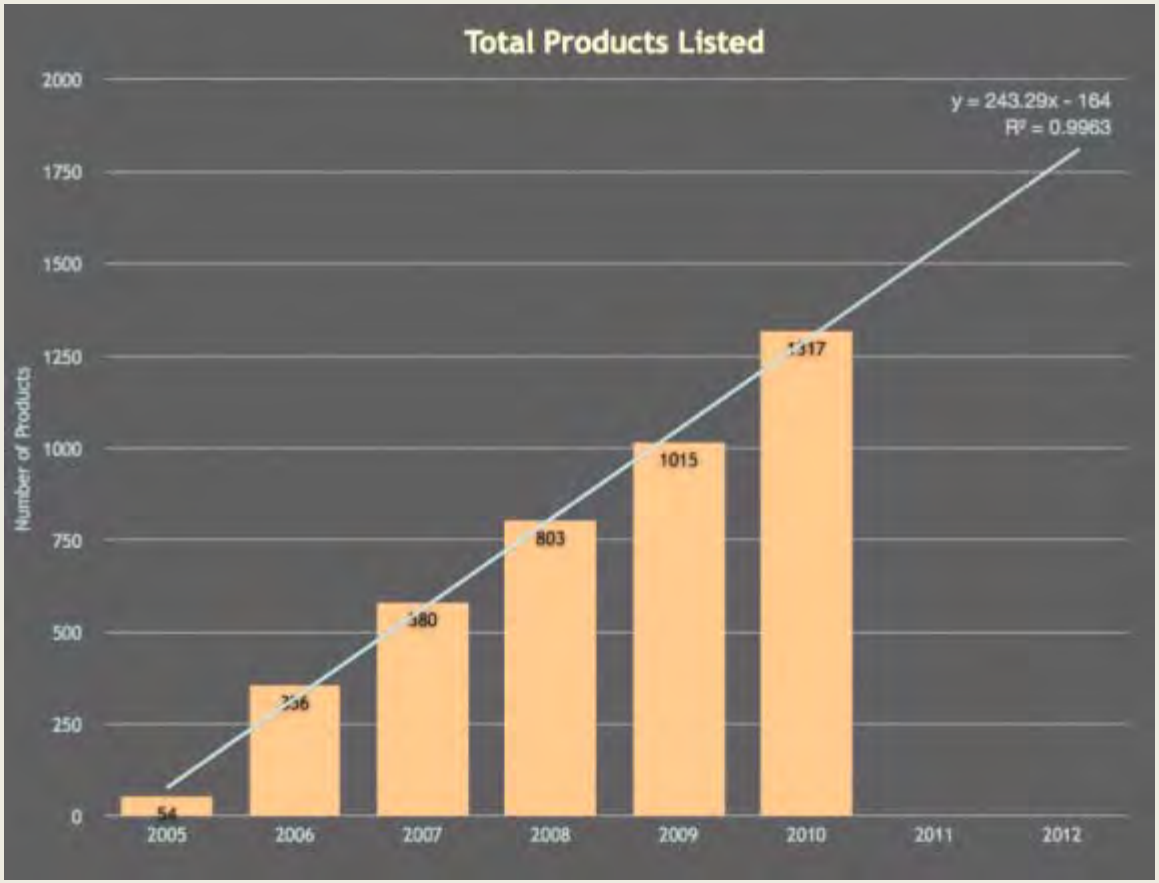
Look at the material supply chain.

Nano Werk Nanomaterial Database:

2,921 materials from 319 suppliers

Nanomaterials only, <u>not</u> Nano-intermediates or products, e.g., nanocomposite

1317 Commercial Products as of 2010



Source Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies

How can the benefits of nanotechnology be realized while proactively minimizing the potential risk?

A history we don't want to repeat

Asbestos

- Great properties
  - Fire retardant, insulator
- Bad health effects
  - Mesothelomia, asbestosis, lung cancer
  - Long latency period
- Regulated beginning in late 1970's
  - EPA 1970 Clean Air Act, 1986 AHERA
  - OSHA 1972 29 CFR 1910.1001
- Lawsuits (try googling asbestos or watching daytime TV)
  - Longest most expensive mass tort in U.S. history

The Real World Question- Nanomaterials: Are There Risks?

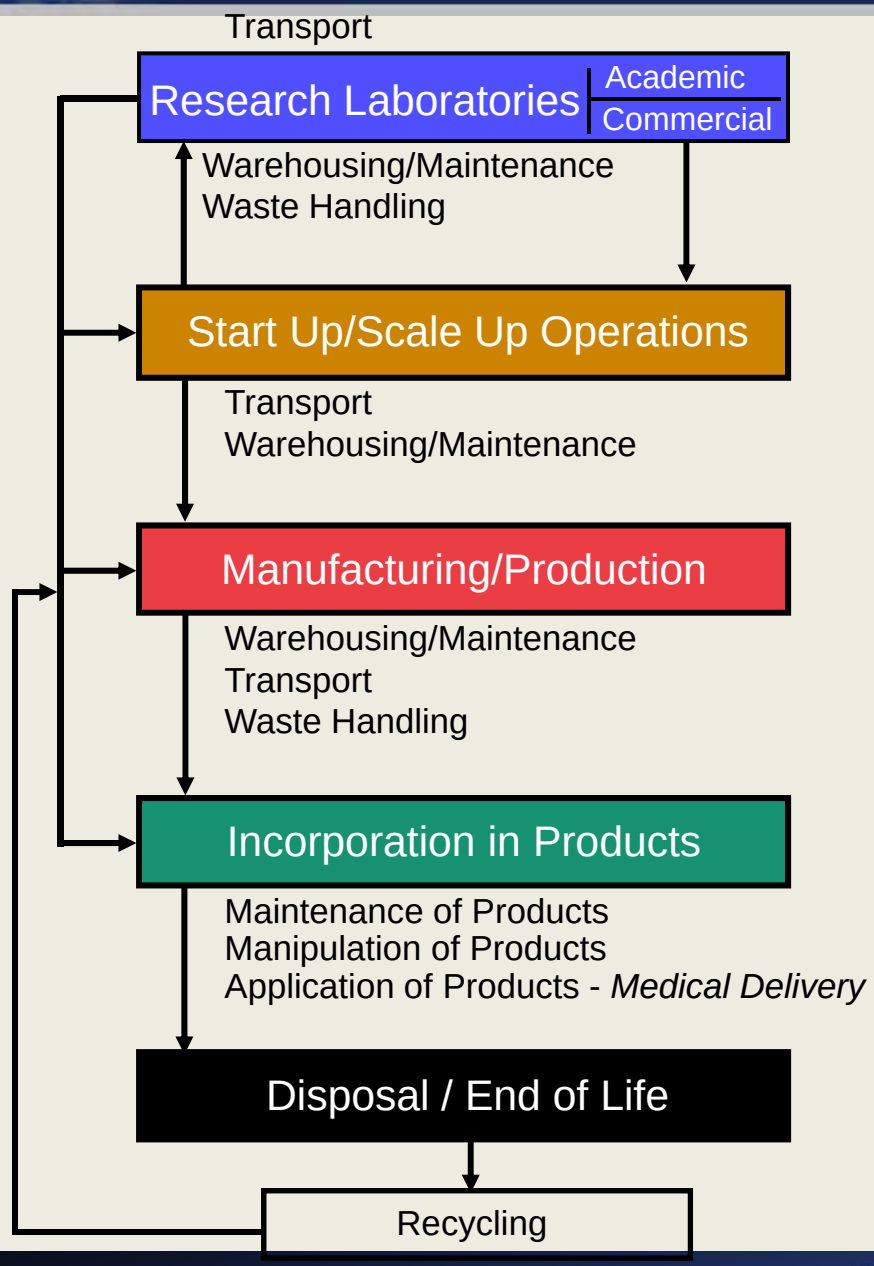
RISK = HAZARD x EXPOSURE

Hazard: Biological activity – toxicity. What is known?

Exposure: Where, to what, to what extent, and can it be measured?

Unknowns and uncertainties = Risk Management approach

Track through the life cycle



The Classic Risk Model

Hazard Identification
Is there reason to believe this could be harmful?

Exposure Assessment
Will there be exposure in real-world conditions?

Risk Characterization
Is substance hazardous and will there be exposure?

Risk Management
Develop procedures to minimize exposures

Nanotoxicology- key findings

- Pulmonary exposure to:
  - SWCNT causes rapid and persistent fibrosis in mice
  - MWCNT can reach the intrapleural space in mice (site of mesothelioma for asbestos)
  - SWCNT can interfere with cell division (in petri dish)
- Certain nanoparticles (SWCNT or TiO_2) can cause cardiovascular dysfunction in mice
- MWCNT or TiO_2 nanowires can induce inflammatory mediators in certain regions of the brain in mice

Toxicology Take-Home Message

Exposure limits for the large form of the material may not be protective for the nano size.

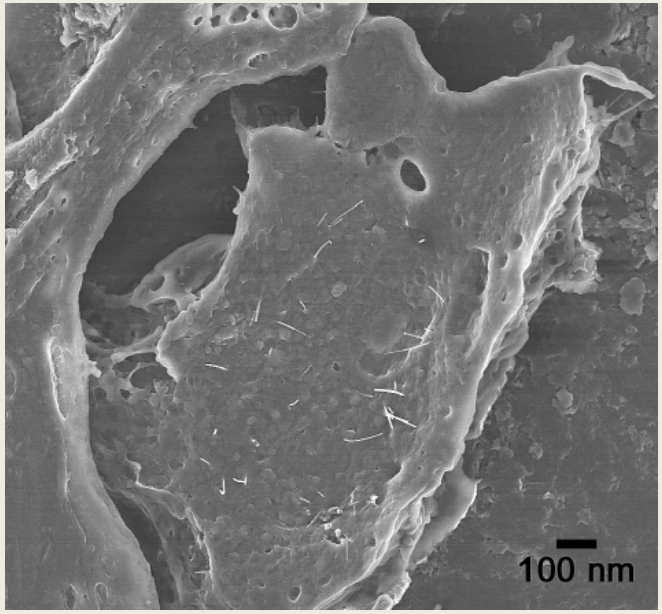


Image courtesy R. Mercer, NIOSH

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Exposure Assessment

- Critical component of risk management
- Identifies populations at risk
- Characterize the exposure, therefore better understanding of risk
  - Nature of exposure: low v. high, short v. long
  - Extent of exposure: few or many
  - Complexity of the exposure
  - Place the exposure on the life cycle
- Verify controls

Small Literature on Exposure

- Relative newness of exposure scenarios
- Uncertainties of what metric to use
- Difficult getting entrance to worksites
- Not a wide range of operations assessed
- Little information on downstream users

Multiple Metrics Can Be Used to Assess Exposure

- **Mass**: Links to historical data; lacks sensitivity and specificity
- **Size distribution**: More information not always easy, not specific
- **Number concentration**: Fairly simple with monitors, not specific to particles, recent correlation of number in ambient air to biomarkers of coronary heart disease
- **Surface area**: Some relevance based on toxicology and technology is available

"Each one may be right"

Exposure Scenarios Evaluated

Graded Approach to Measurement

- Step 1
  - Particle counters and simple size analyzers to screen the area and process
- Step 2
  - Filter based samples for electron microscopy and elemental analysis, collected **at Source**
- Step 3
  - Filter based samples for electron microscopy and elemental analysis, collected **at Personal Breathing Zone**
- Step 4
  - Less portable aerosol sizing equipment

Recent Published Summary of Field Exposure Assessments

Journal of Occupational and Environmental Hygiene March 2010

Nanoparticle Emission Assessment Technique (NEAT) for the Identification and Measurement of Potential Inhalation Exposure to Engineered Nanomaterials — Part A

and

Part B: Results from 12 Field Studies

M. Methner, L. Hodson, C. Geraci

National Institute for Occupational Safety and Health (NIOSH), Nanotechnology Research Center, Cincinnati, Ohio

Need for a Comprehensive Job-Exposure Matrix (JEM) for Each Worker

	Exposure Period 1	Exposure Period 2	Exposure Period 3	○ ○ ○
Job 1	Time (J_1, P_1)	Time (J_1, P_2)	Time (J_1, P_3)	○ ○ ○
Job 2	Time (J_2, P_1)	Time (J_2, P_2)	Time (J_2, P_3)	○ ○ ○
Job 3	Time (J_3, P_1)	Time (J_3, P_2)	Time (J_3, P_3)	○ ○ ○
○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ ○

Where time (J_i, P_j) is the worker's time on job i during exposure period j.

Emission versus Exposure Measurements

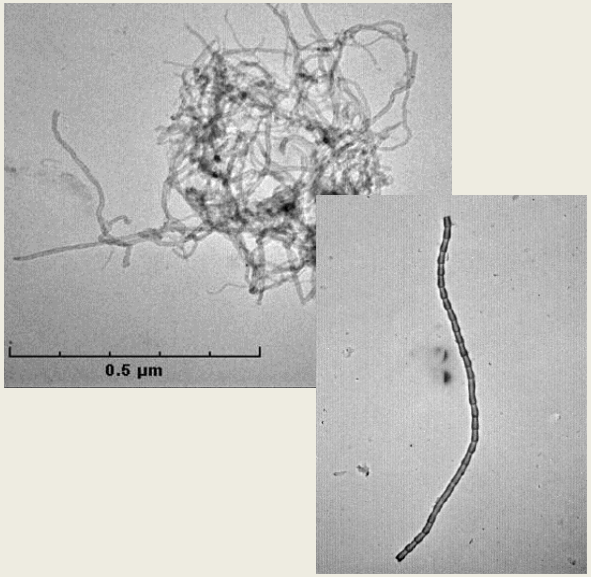
- Qualitative
  - Confirmation: e.g. TEM with elemental analysis
- Mass concentration
- Particle number
- Size distribution (count or mass by size)
- Surface area

Nanotechnology Field Studies Team

- Sampling Strategy
  - Integrated samples
    - *Core component of exposure assessment*
    - Filter-cassette based
      - Elements
      - Electron Microscopy
    - Area and personal breathing zone
    - Full-shift and task-based
  - Direct Reading Instruments
  - Wipe Samples

Correlate Simple and Complex Measurements

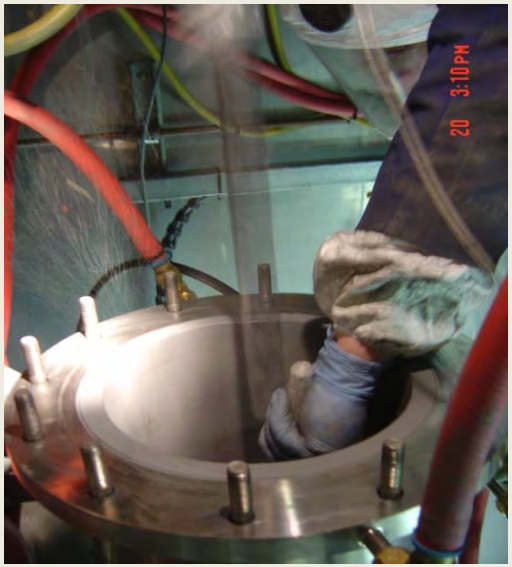
Electron microscopy

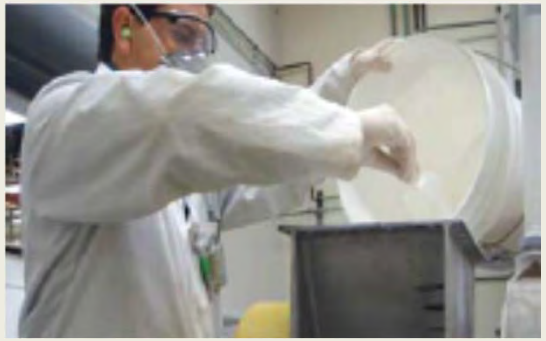


Elemental Analysis

Particle Counters and Size Analyzers

Potential Exposure Examples

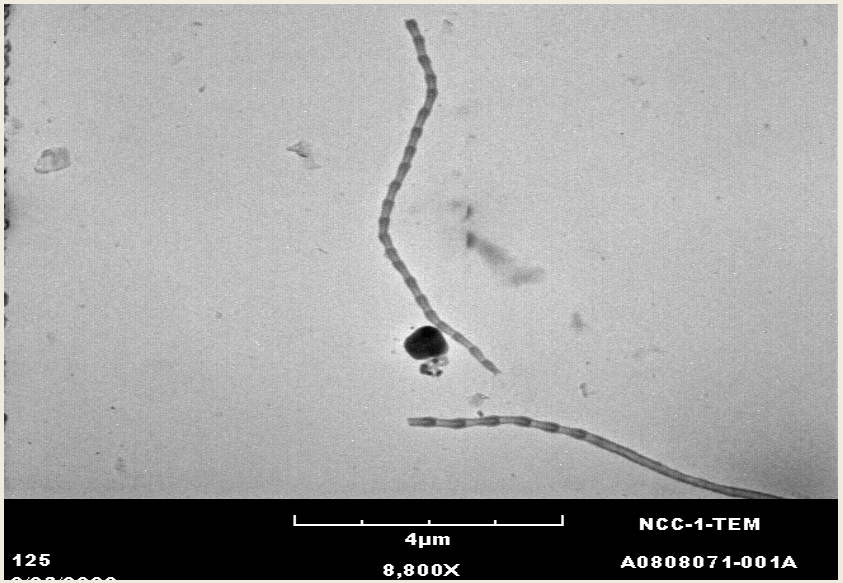


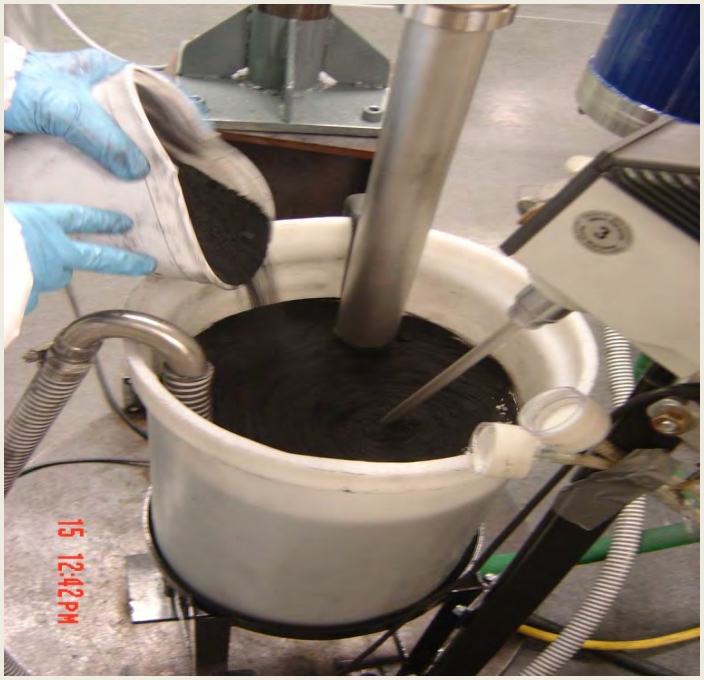


Photos courtesy of M. Methner, NIOSH

Weighing small quantity of CNF's inside ventilated balance enclosure

PBZ shows CNF's can escape ventilated enclosure!



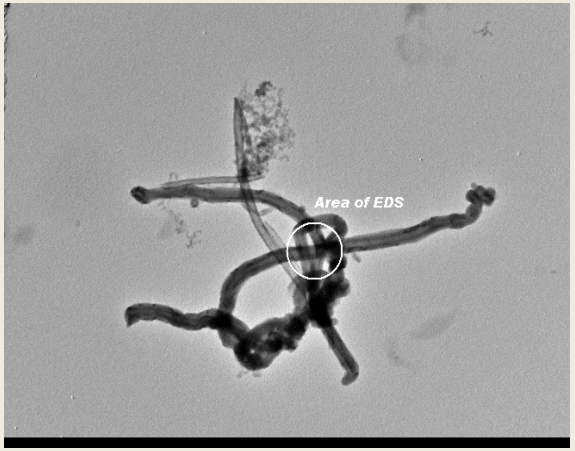


Adding MWCNT's to vortex mixer

At source sample shows release occurred

Weighing CNF's inside laboratory fume hood

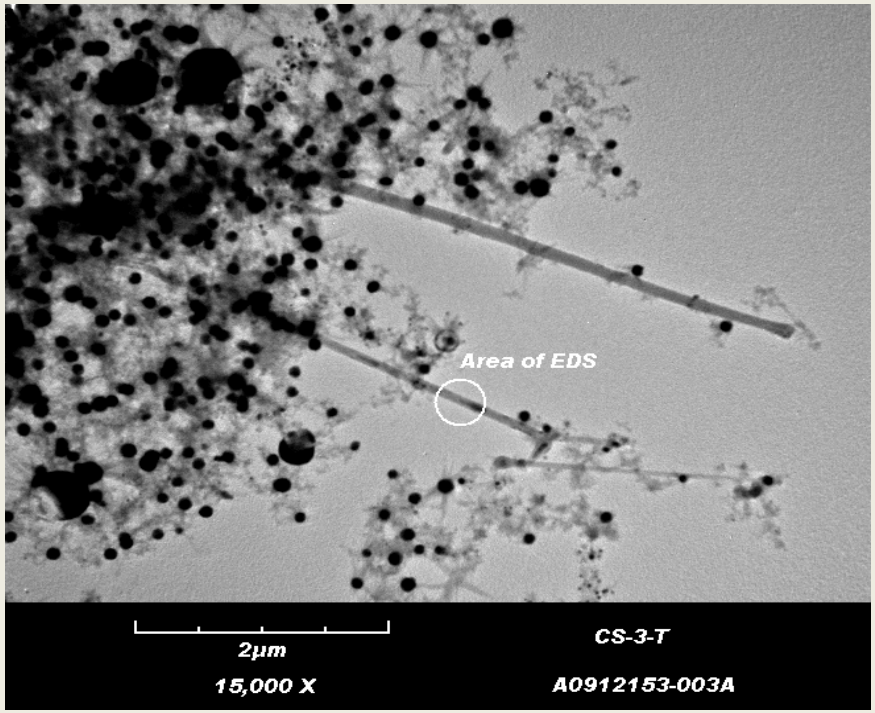
PBZ indicates CNF's reach breathing zone and could escape and contaminate adjacent areas/entire lab



Workplace photos courtesy of M. Methner, NIOSH.

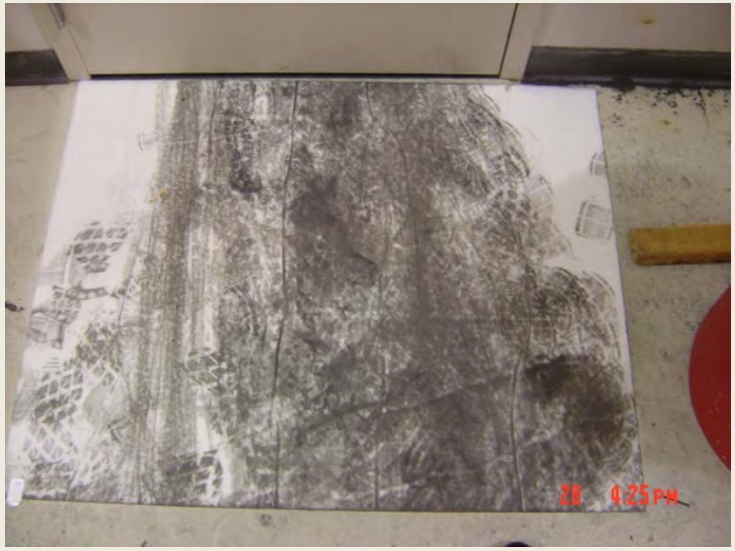
Harvesting SWCNTs from a Carbon Arc Reactor

Task-based PBZ air sample analyzed via TEM w/ EDS



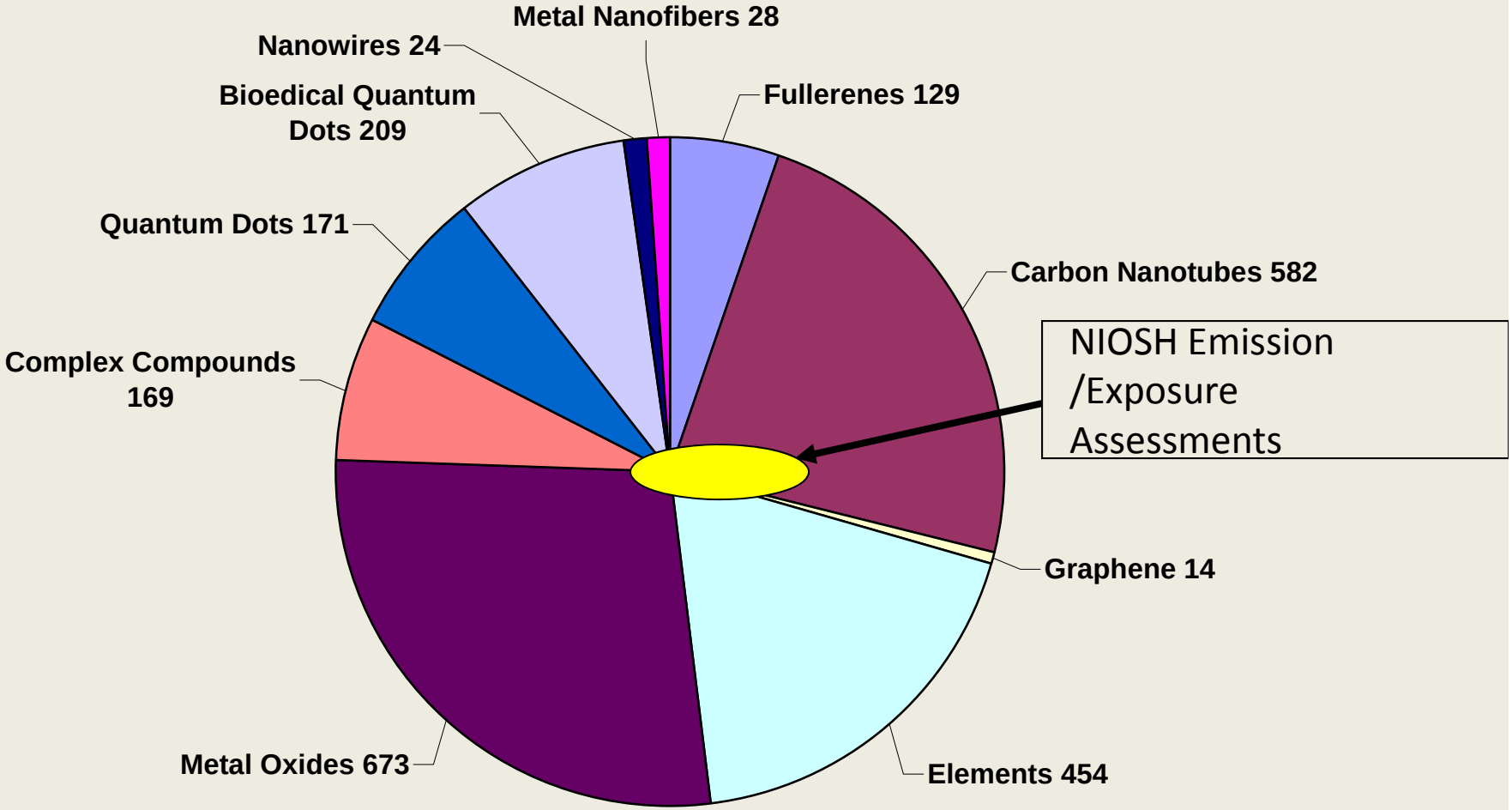
Using HEPA vac to clean outer surface of trays of spilled material

Dark specs are clumps of raw CNF's that accumulate during tray loading



"Sticky mats" are used at the exit of the tray loading room – This mat was changed prior to transporting trays to the furnace area. This accumulation is due to 6 trips out to the furnace.

The Exposure Experience: What progress has been made??



Source of distribution database is NanoWerk, 2010.

Exposure Data: Conclusions/Challenges

- We have addressed a small piece of the pie
- Exposures do occur in the workplace
- Exposure limits are being developed
- Mass is still the primary metric for exposure
- Direct-reading approaches have a place
- Additional metrics need to be explored: fiber count?
- Confirmatory methods are needed
- Controls can be effective

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Is there reason to believe this could be harmful?

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Will there be exposure in real-world conditions?

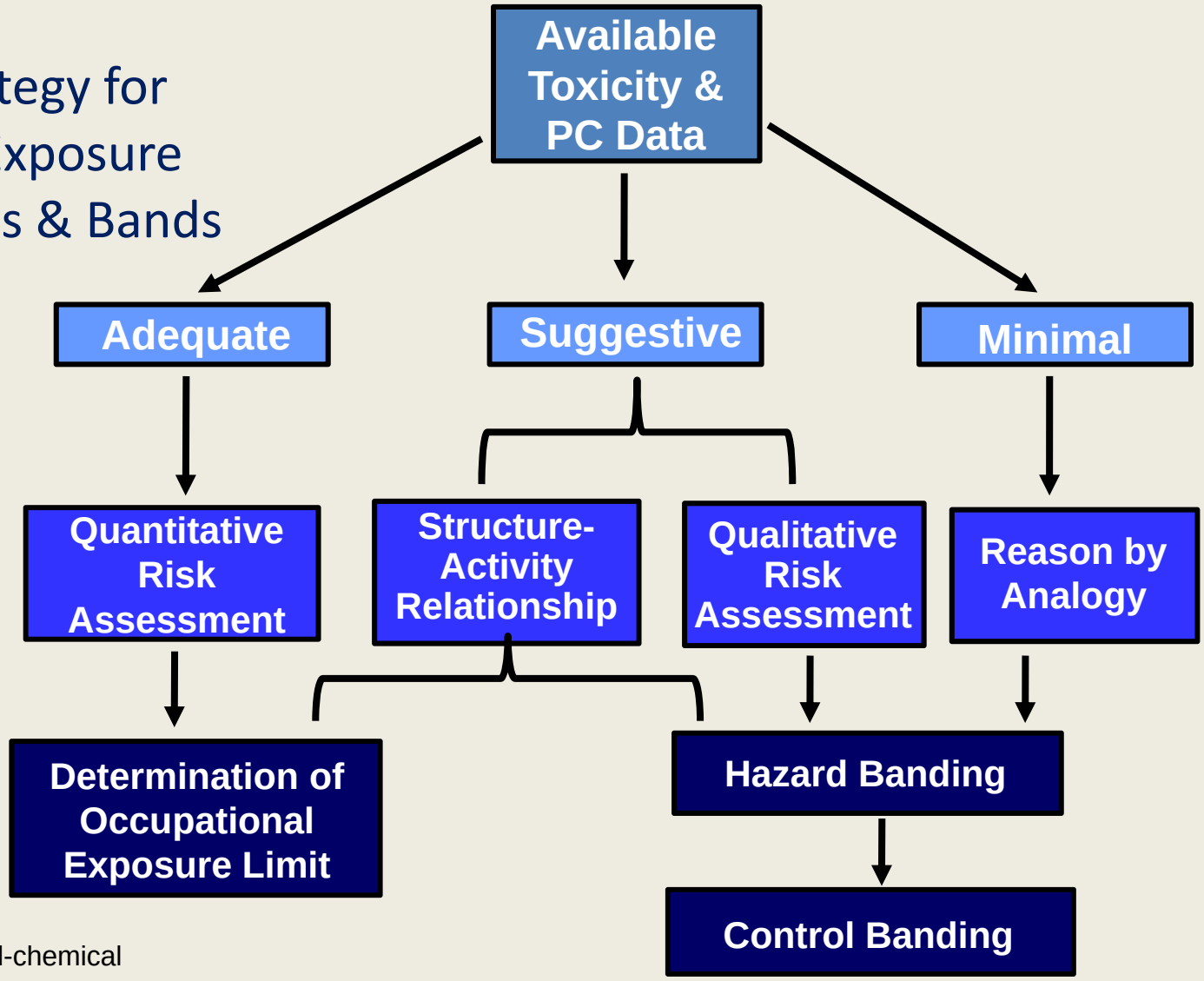
Risk Characterization
Is substance hazardous and will there be exposure?

Risk Management
Develop procedures to minimize exposures

Quantitative Risk Assessment (QRA)

- The estimation of the severity and likelihood of adverse responses associated with exposure to a hazardous agent
- Can be used to estimate the exposure concentrations that are likely—or unlikely—to cause adverse health effects in workers
- Two sources for prediction
  - Animal data
  - Human (epidemiologic) data

Possible Strategy for Developing Exposure Control Limits & Bands

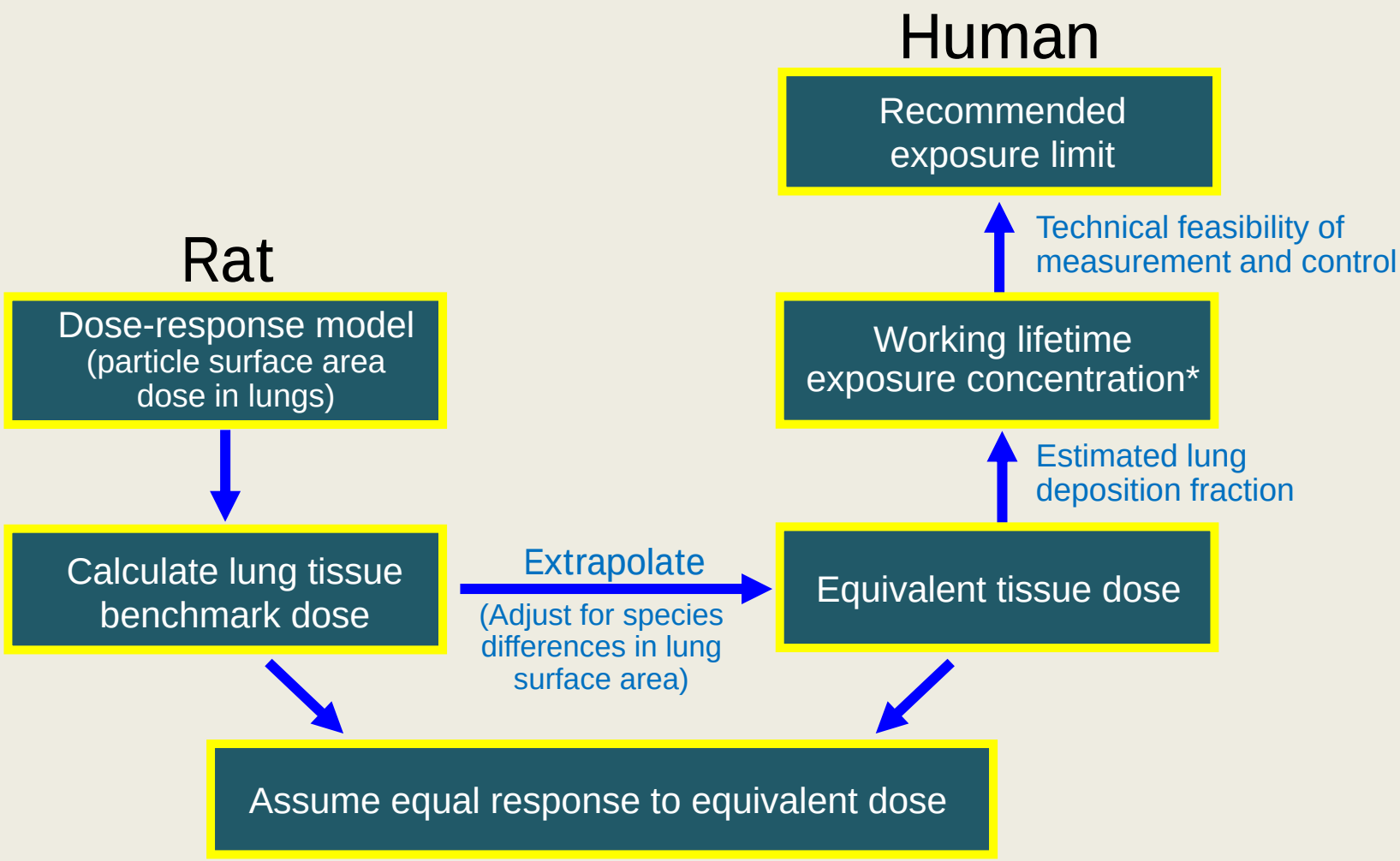


PC: physical-chemical

[Adapted from Schulte et al. 2010, J Nanopart Res]

Quantitative Risk Assessment in Developing Recommended Exposure Limits for Inhaled Particles

Based on Kuempel et al. [2006]



*Dose associated with specified level of risk.

CNT Risk Assessment
NIOSH systematically reviewed:

- 54 laboratory studies of animals exposed to CNT or CNF published between 2001–2012
- 44/54 reported pulmonary inflammation
- 27/54 granuloma
- 23/54 pulmonary fibrosis

  - These findings are relevant to human health -

- Similar health effects have been seen in workers exposed to particulates in dusty jobs
- Laboratory studies followed by exposure and epidemiology data show consistent trends for fine dusts

CNT Risk Assessment Dose-Response

NIOSH conducted quantitative risk assessments on studies with sufficient dose-response data.

- Included 2 subchronic 90-day inhalation studies [Ma-Hock et al. 2009; Pauluhn 2012]
- 5 additional studies by other routes and durations [Lam et al. 2004; Muller et al. 2005; Shvedova et al. 2005, 2008; Mercer et al. 2011]

The Classic Risk Model

Hazard Identification
Is there reason to believe this could be harmful?

Exposure Assessment
Will there be exposure in real-world conditions?

Risk Characterization
Is substance hazardous and will there be exposure?

Risk Management
Develop procedures to minimize exposures

Overall Company Health and Safety Program

- Management Leadership
  - Policies
  - Standards
- Employee Participation
- Planning
- Implementation
  - Risk Management
  - Training
  - Communication
  - Safe Practices
- Evaluation
- Corrective Actions
- Compliance Plan

Nanomaterial Risk Management Program

- Hazard Determination
- Process Review
- Exposure Evaluation
- Risk Characterization
- Controls

Hierarchy of Controls

Elimination
↓
Substitution
↓
Isolation
↓
Engineering Controls
↓
Administrative Controls
- Biological Monitoring
- Medical Screening and Surveillance

↓
Personal Protective Equipment

Closing Risk Management Gaps
Is Basic Guidance Available?

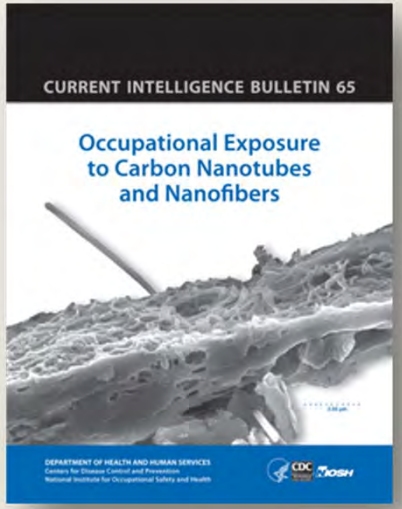
NIOSH Current Intelligence Bulletins (CIBs)

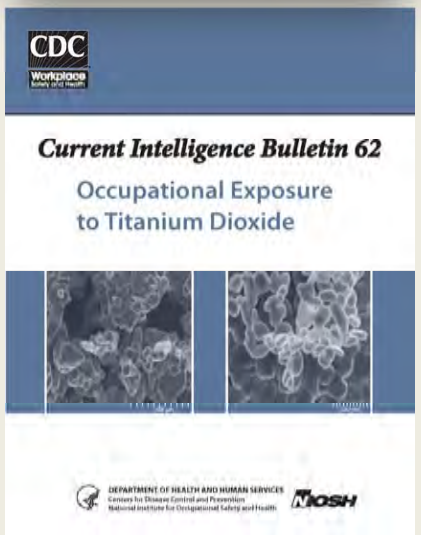
- **Describes the hazards**
- **Exposure limits**

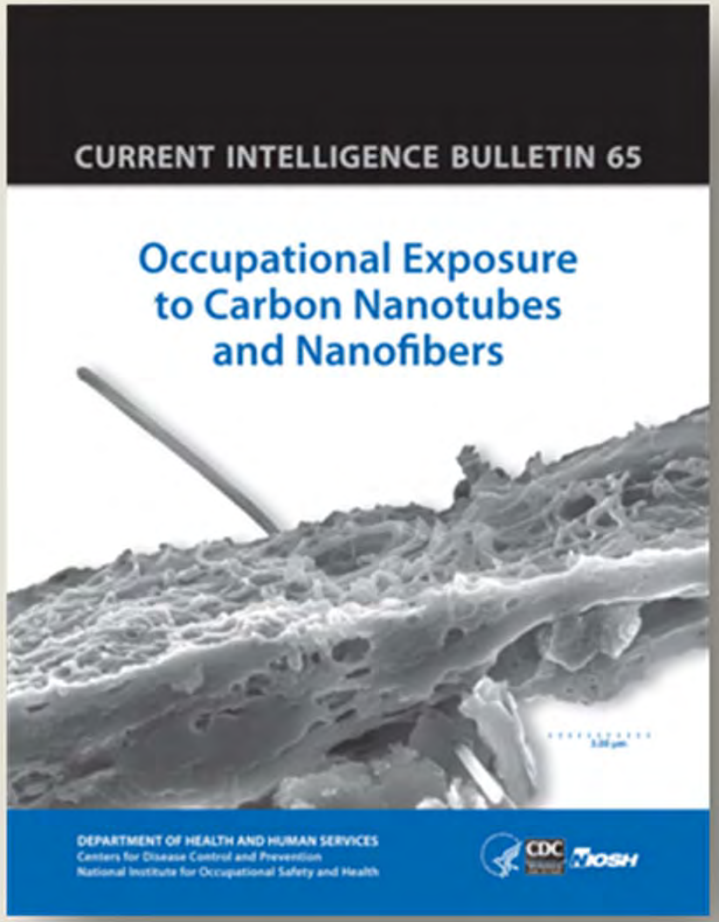
NIOSH RELs:

  - 300 µg/m3 for nano TiO_2
  - 1 µg/m3 for CNT and CNF

- **How and where to measure**
- **Limits of controls**



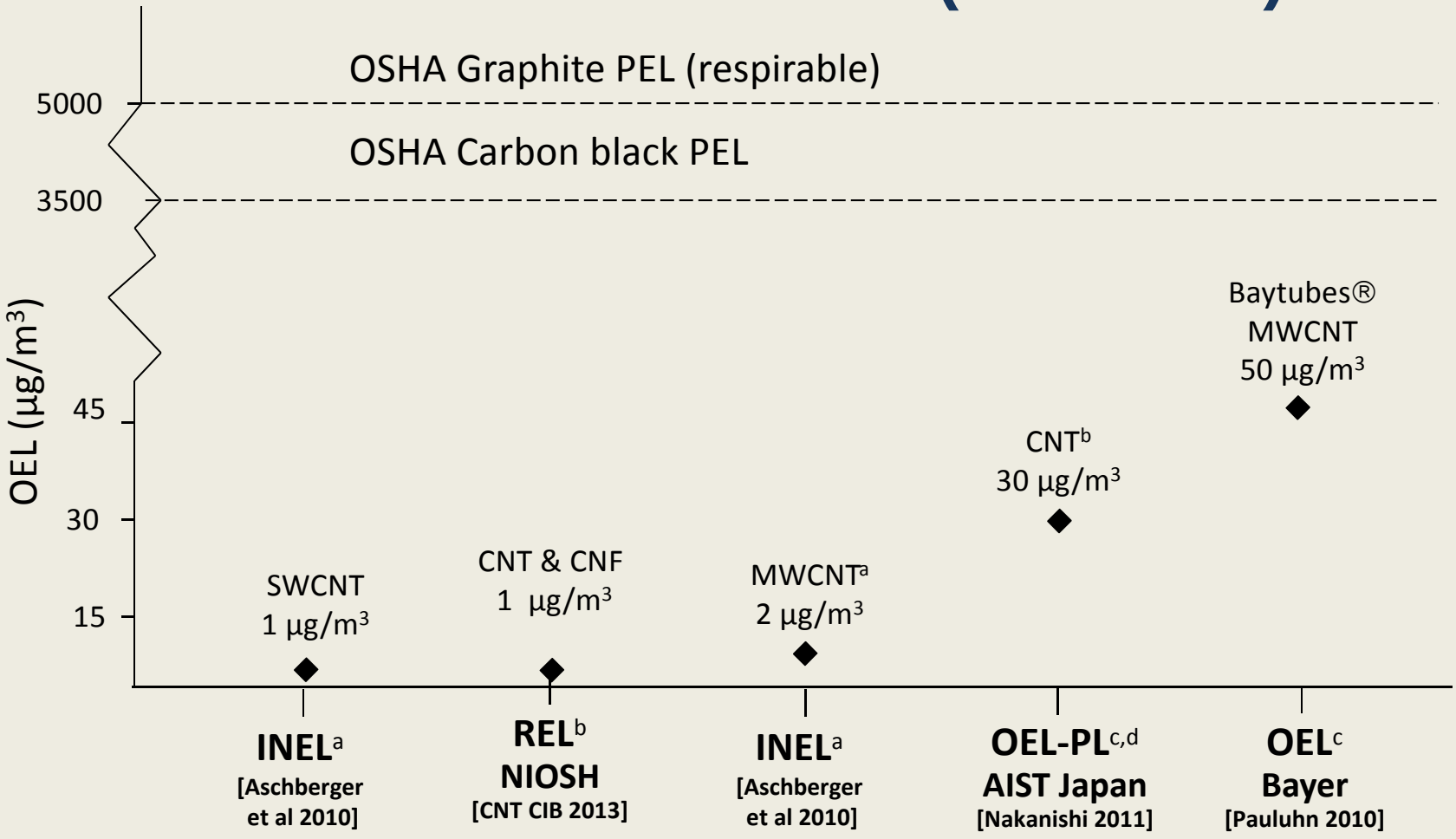




Document Contents

- Summary of hazards (toxicology)
- Dose-response risk assessment
- Evaluation of worker exposures
- NIOSH Recommended Exposure Limit (REL)
- Exposure assessment guidance
- Evaluation of controls
- Medical screening and surveillance
- Research needs

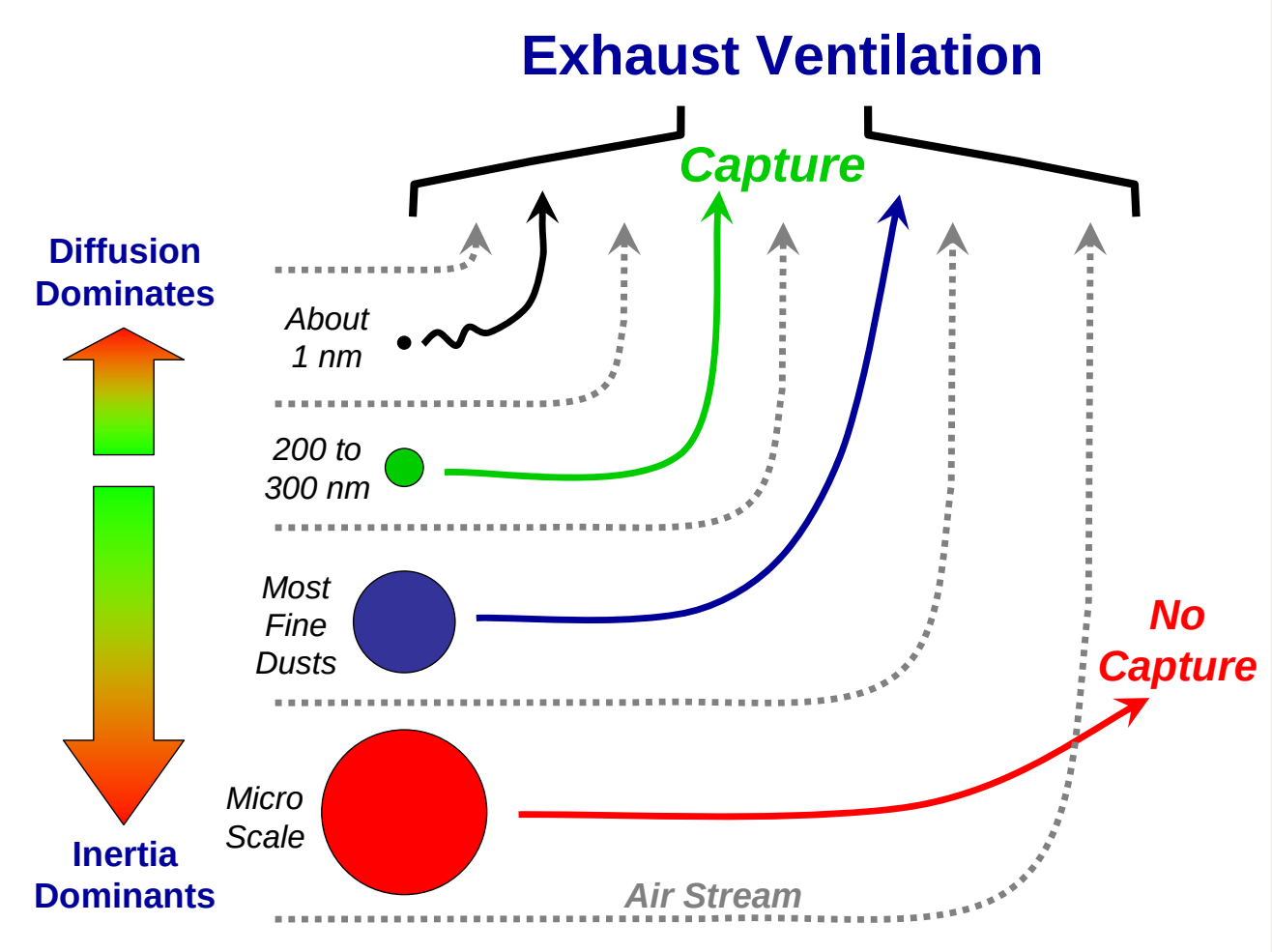
OELs for CNT/CNF (8-hr TWA)



BSI—0.01 f/ml *[benchmark exposure limit-BEL] for high aspect ratio nanomaterials (1/10th asbestos OEL).*

[a] Indicative No-effect Level; [b] Recommended Exposure Limit; [c] Occupational Exposure Limit; [d] Period-limited (15-yr)

Conventional Controls Should Work



Factors Influencing Control Selection

mild / reversible → Occupational Health Hazard → severe / irreversible

kilograms

Quantity

milligrams

Engineered Local Exhaust Ventilation

Closed Systems

Exposure Risk

8 hours

Task Duration

15 minutes

slurry/suspension → agglomerated → highly disperse

Physical Form

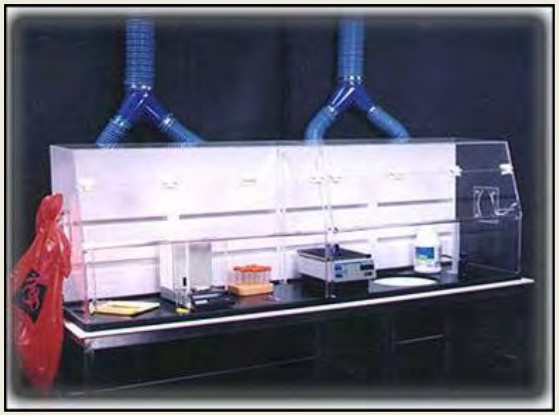
Special thanks to Donna Heidel, NIOSH

Manufacturing Containment

Photos courtesy Nanocomp Technologies, Inc.

Controls for Laboratory-Scale Work

- Effective controls that factor budget and space limitations are available
- Select controls based on task-based exposure risks



Case Study: Use of LEV during reactor cleanout

Average percent reduction from the use of a local exhaust ventilation unit:

96 +/- 6% based on particle counts

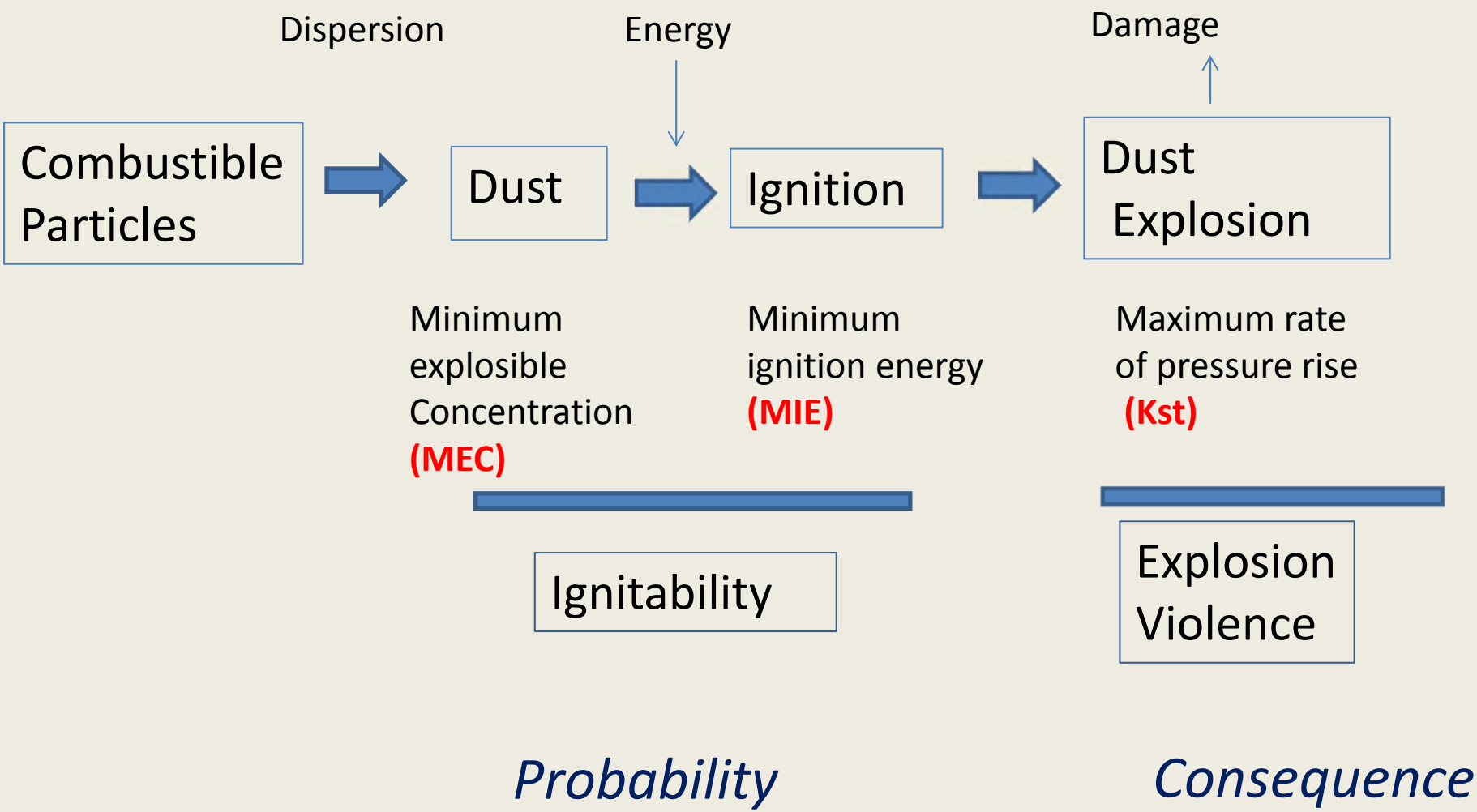
88 +/- 12% based on mass

Don't forget other nanofabrication hazards

- Toxic gases and chemicals
- High temperatures >600°C
- High pressures
- Lasers
- Strong magnetic fields

Fire and Explosion Safety

- Experiments thus far indicate moderate combustibility



Adapted from Dobashi, 2008

Fire and explosion risks from metal nanomaterials

Material	MIE mJ	Kst bar m/s
Al 35 nm	< 1	349
Al 100 nm	<1	296
Al 40 um	59.7 mJ	77

Wu et al 2010

Material	MIE (mJ)
Ti 35 nm	< 1
Ti 100 nm	<1
Ti 8 um	22
Fe 15 nm	<1
Fe 64 nm	<1
Fe 150 um	Would not ignite

Wu et al 2009

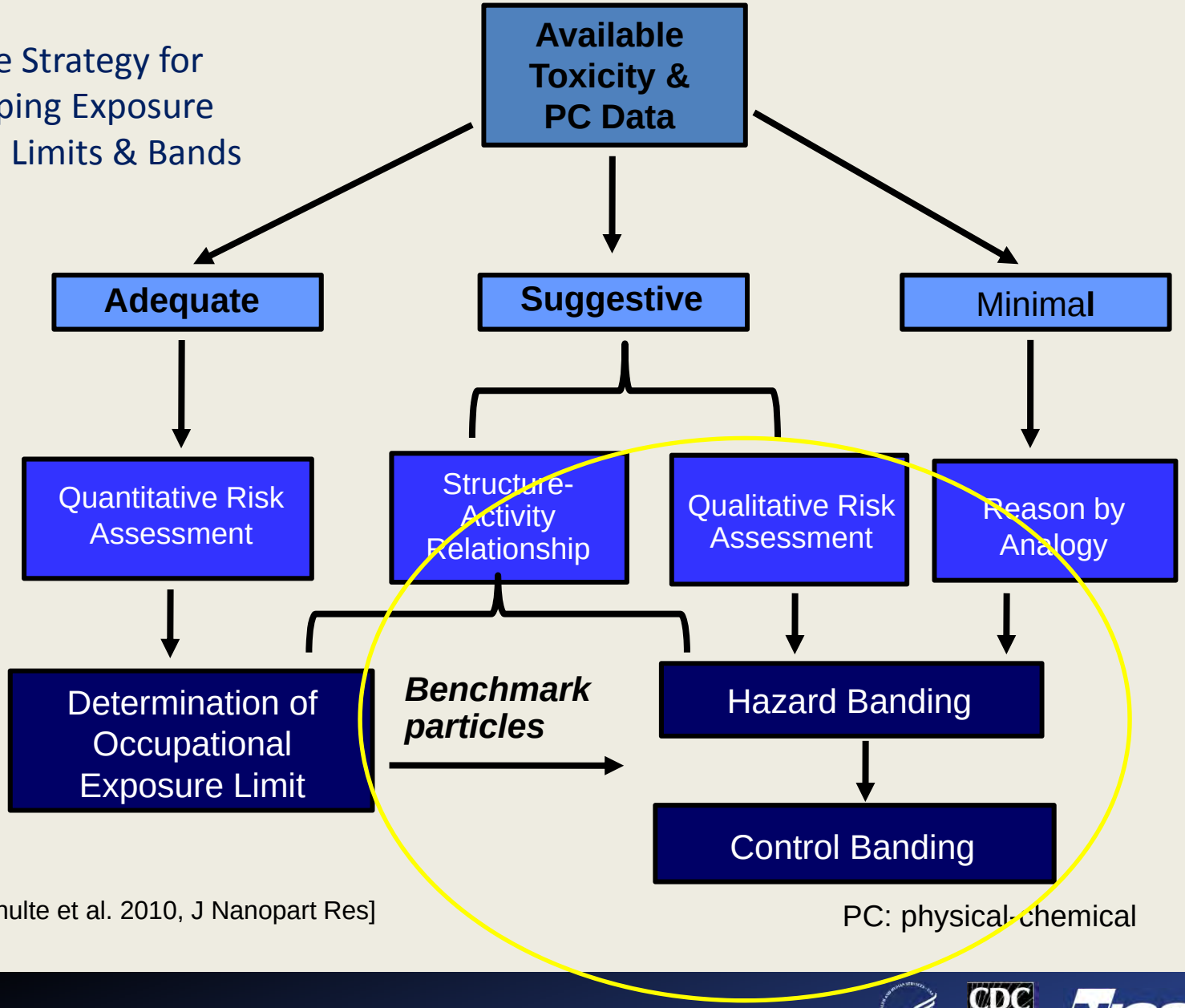
Recommendations

Personal Protective Equipment

- Provide respiratory protection when exposures can't be controlled below the REL
- Provide protective clothing and gloves when there is potential for contact contaminated surfaces (i.e., when technical methods to control exposure are unsuccessful)

Inadequate glove and wrist protection can cause dermal exposure

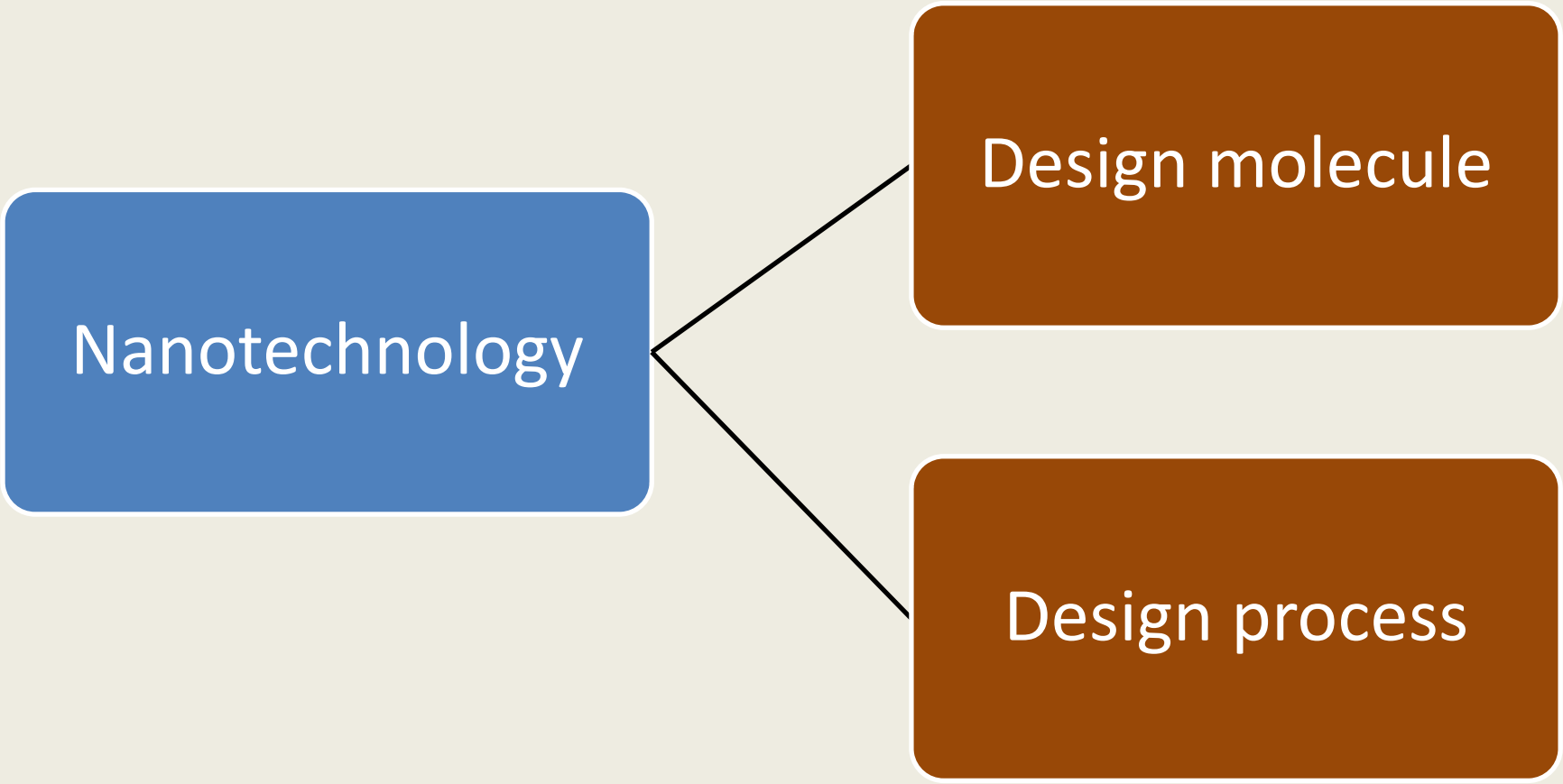
Possible Strategy for Developing Exposure Control Limits & Bands



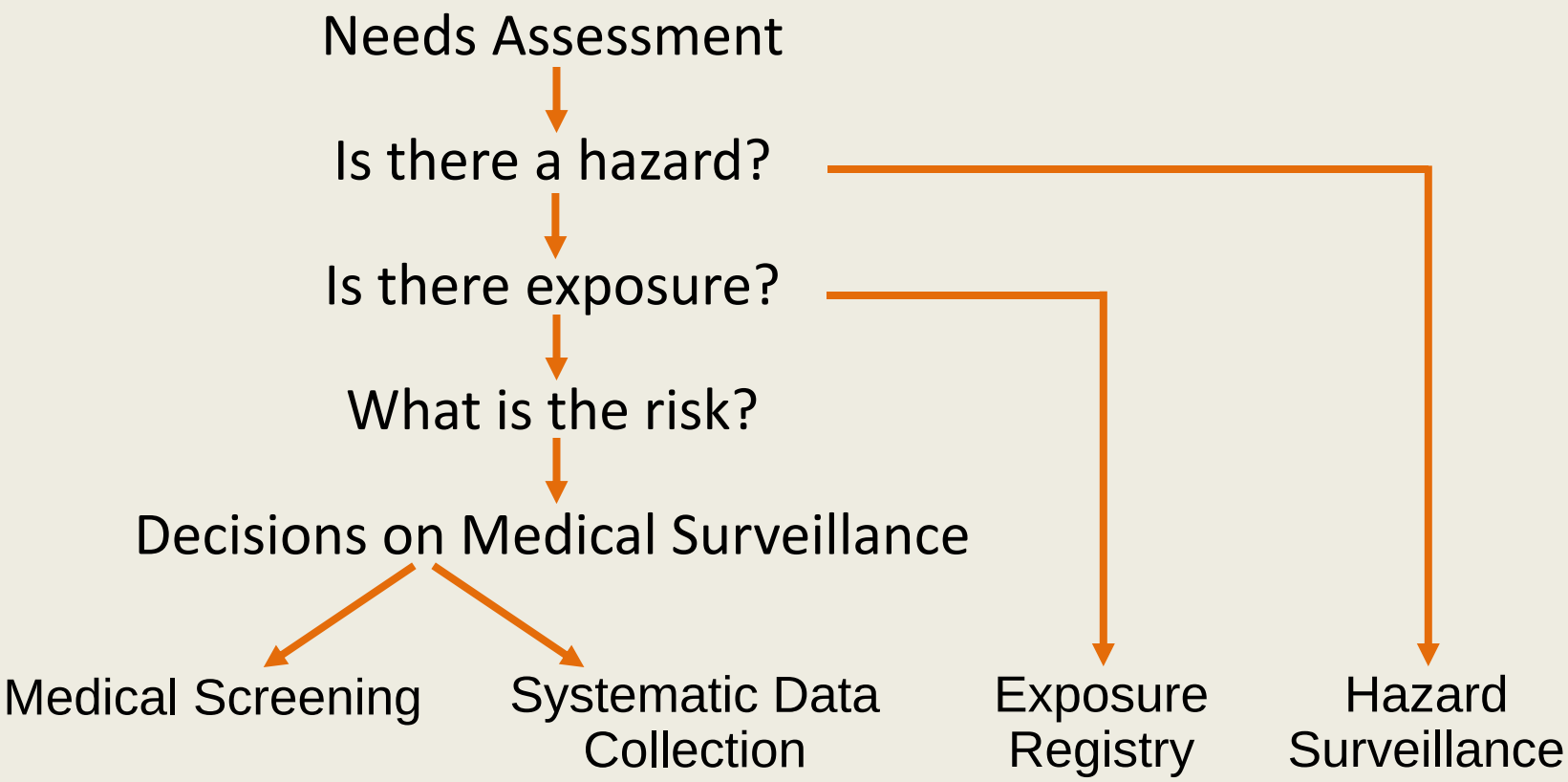
[Adapted from Schulte et al. 2010, J Nanopart Res]

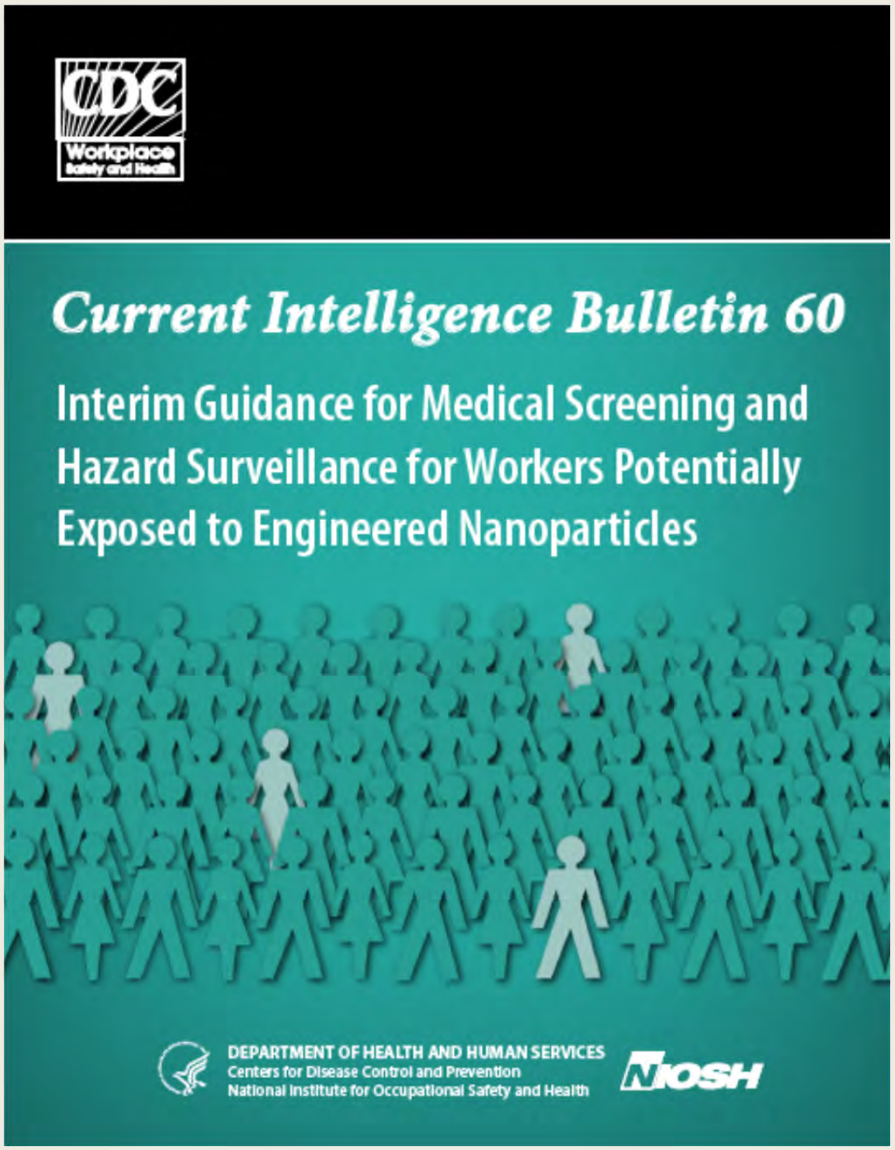
PC: physical-chemical

Prevention through Design (PtD)



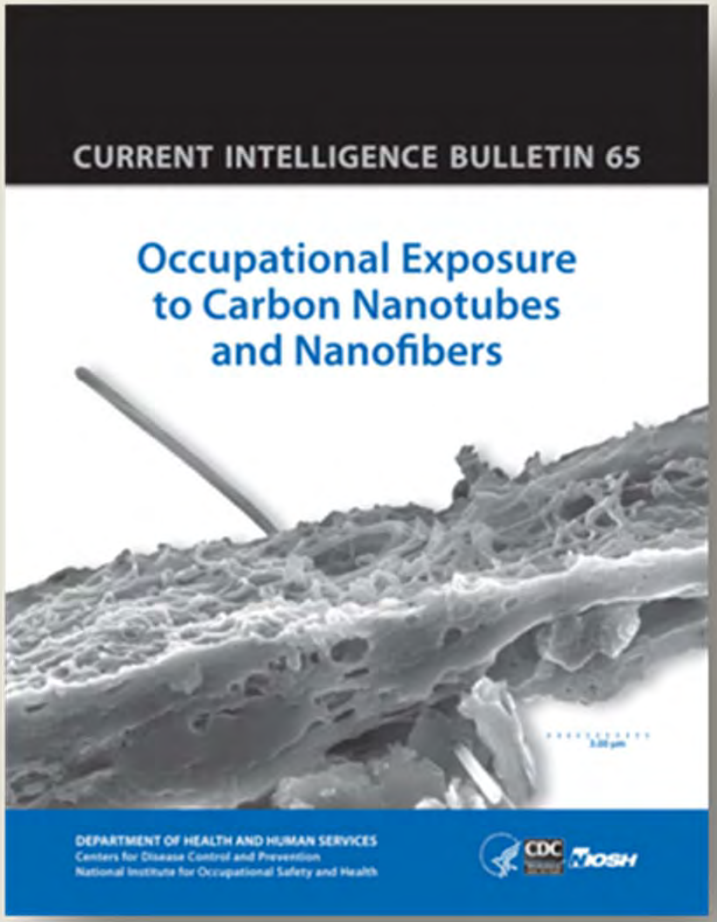
Issues in Medical Surveillance for Workers in Nanotechnology





Interim Guidance Issued by NIOSH

- Value of medical screening
- Lack of specific health end point
- Hazard Surveillance
- Potential for Exposure Registry



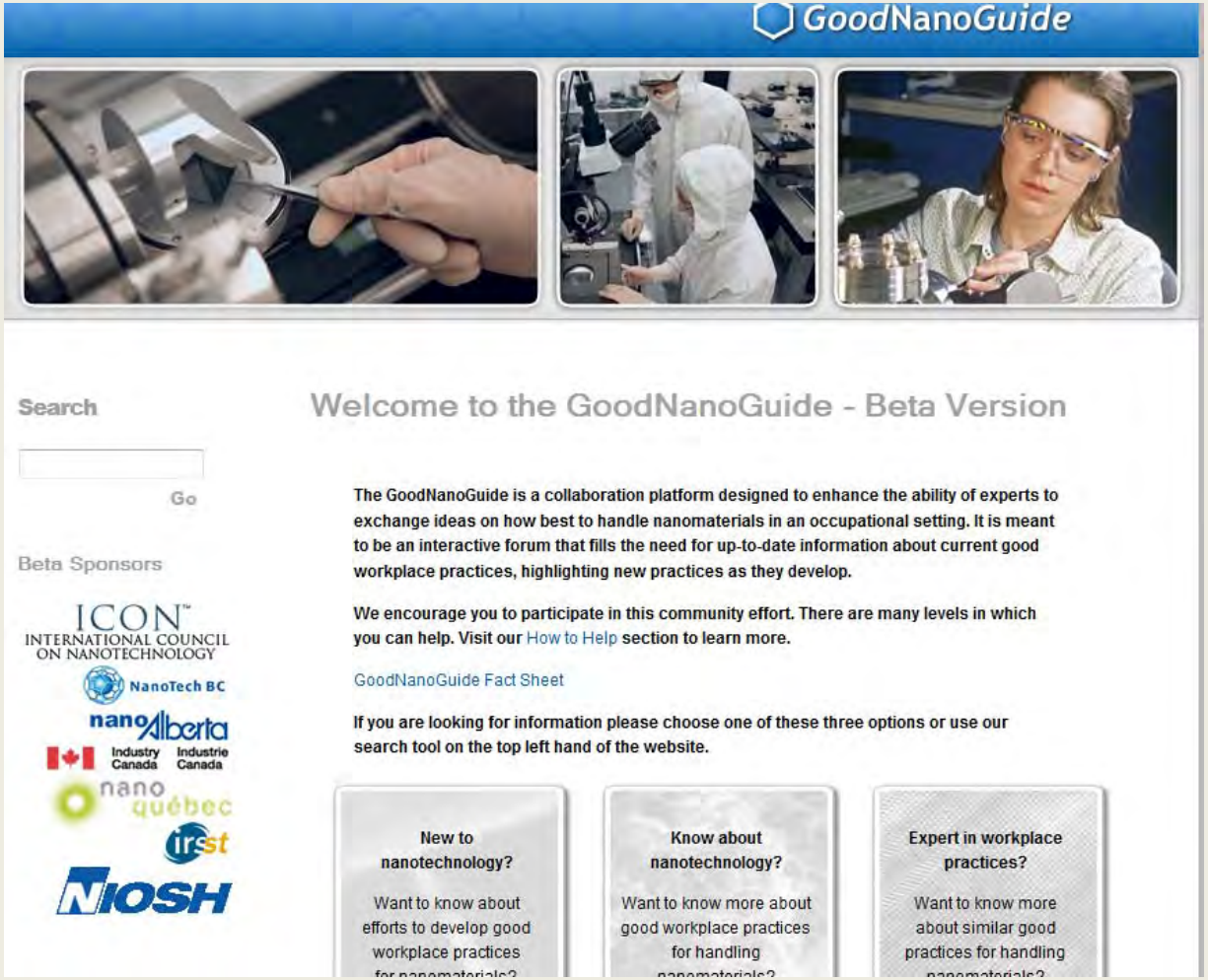
Medical screening and surveillance guidance for workers exposed >REL

- Baseline evalution
- Spirometry test
- Baseline chest Xray
- Other examinations or medical test as deemed appropriate by health-care professional

Next Phase of Effort

- Assess extent of compliance with precautionary guidelines
- Consider what workers should be registered
- Consider epidemiologic studies
  - Prospective studies
  - Cross-sectional studies—biomarkers

Shared Experience



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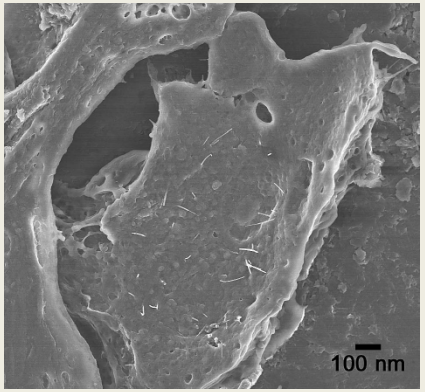
Recent Virtual Journal Issues:
March 2011

Where do we go from here?

NIOSH needs to remain at the forefront of U.S. research to understand the occupational health implications of engineered nanomaterials, and to apply that knowledge to develop risk management practices to prevent work related injuries and illnesses.



Finding Answers to the Central Occupational Health Questions

- How might workers be exposed to nanoparticles during manufacturing and handling of nanomaterials?
- How do engineered nanomaterials interact with the body's systems?
- What effects might engineered nanomaterials have on the body's systems?
- How can adverse health effects be prevented?

Take Home Message

- Nanotechnology- it's just chemistry (and physics and biology).
- The potential risks can be effectively managed in the workplace.
- Companies can reapply controls developed for pharmaceutical and other chemical process containment.