NIOSH Nanotechnology Efforts: Progress Report on Protecting H & S of Nanotech Workers

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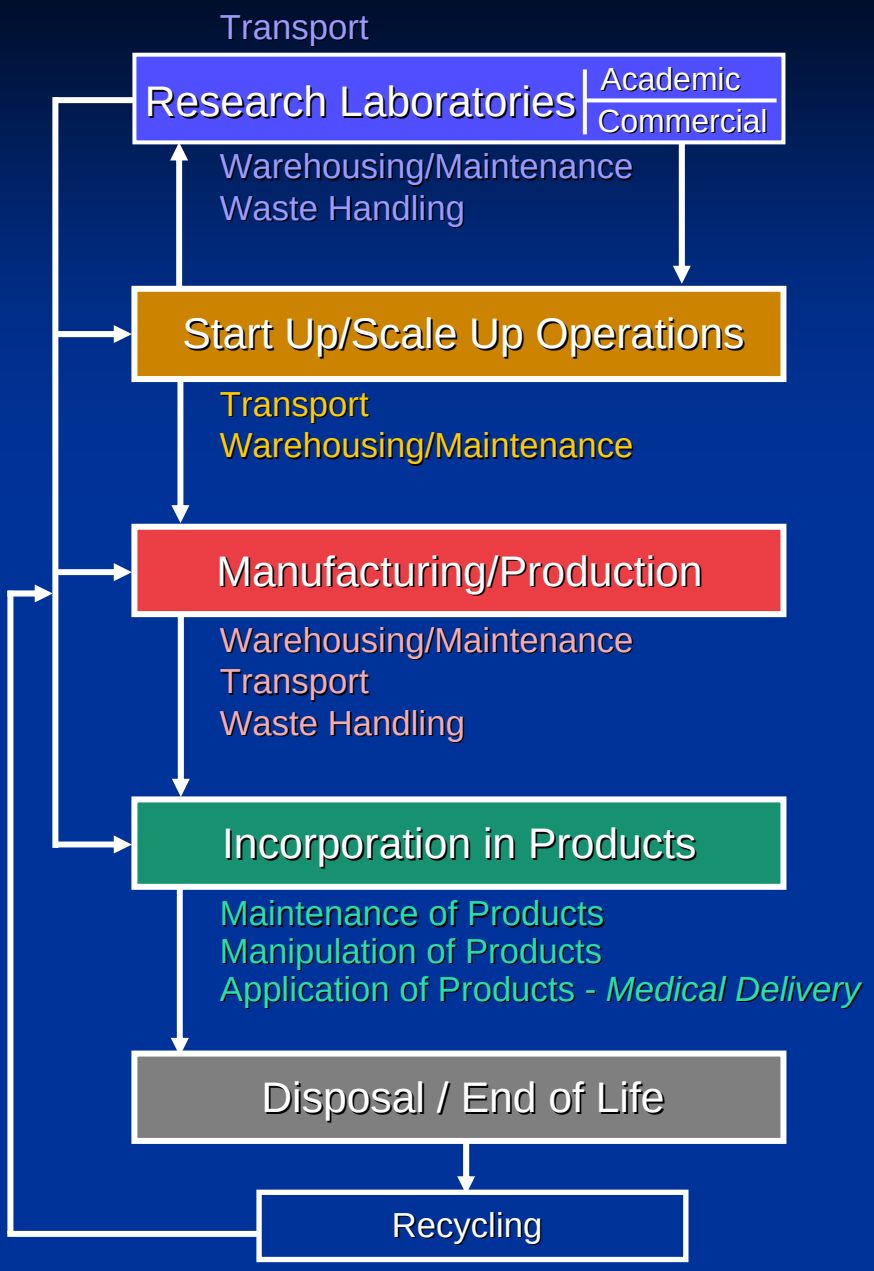
National Institute for Occupational Safety and Health

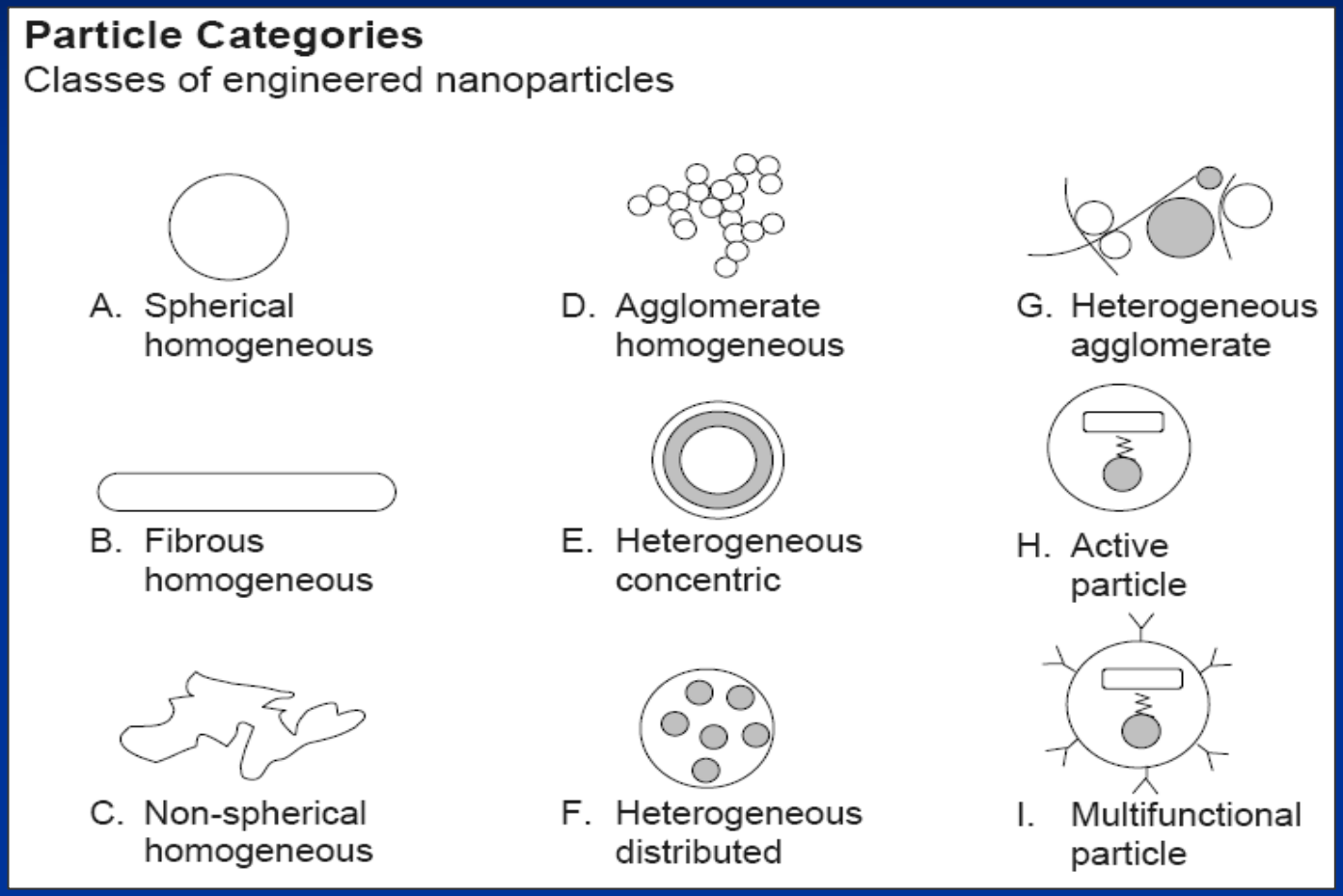
The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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

What could a “nanoparticle” be?



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

Parameters that could affect nanoparticle toxicity

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

Key elements in worker protection

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"

Key elements in worker protection

Hazard

Nanotoxicology
What do we know?
Are there "trends?"

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."

Perspective

Adapted from Maynard [2006]

- Nanomaterials have unique properties… but the body responds to foreign materials in limited ways
- Little is known of the health impact of engineered nanoparticles… but we are not starting from total ignorance

History of assessing particles

- Over 100 years of knowledge to draw on
  - Occupational exposures to fines and ultrafines
  - Air pollution epidemiology
  - Fiber carcinogenesis studies
  - Airborne radioactive particles

Basis for concern about health and safety effects of nanoparticles

- Initial animal inhalation studies of engineered nanomaterials
  - Pulmonary fibrosis, granulomas, and inflammation
  - Lung cancer, mesothelioma-like effects
  - Cardiovascular effects: oxidative stress, plaque

Effects of various engineered nanoparticles

Effect	Particle	Reference
Deposit in the alveoli	Ultrafine $Ti0_2$ SWCNT	Sager et al. 2008 Shvedova et al. 2005 Mercer et al. 2008
Evade phagocytosis	SWCNT	Mercer et al. 2008
Enter alveolar walls	SWCNT $Ti0_2$	Mercer et al. 2008 Oberdörster et al. 1994
Produce interstitial inflammation	Ultrafine carbon black	Nikula et al. 1995
Produce fibrosis	SWCNT	Shvedova et al. 2005 Mercer et al. 2008
Produce tumors	Ultrafine $Ti0_2$	Heinrich et al. 1995
Form granulomas	SWCNT	Shvedova et al. 2005

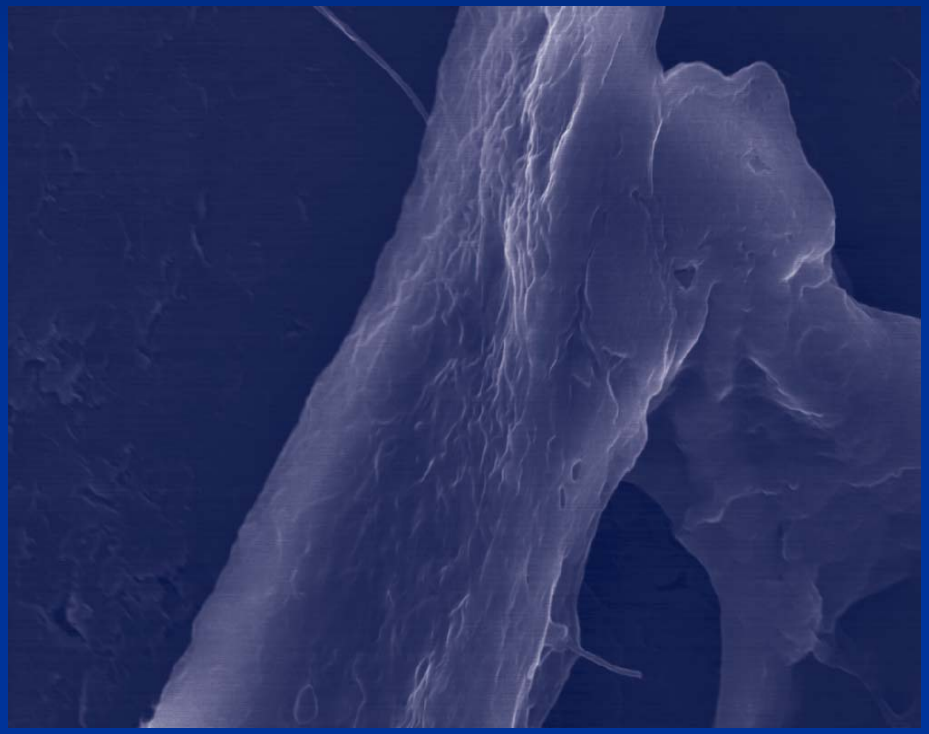
Source: Schulte et al. [2008]

Effects of various engineered nanoparticles cont'd

Effect	Particle	Reference
Enter circulatory system	Ultrafine carbon	Oberdörster et al. 2002
Form plaques on vessel walls	SWCNT	Li et al. 2007
Enter and move through circulatory system	Silver, iridium, elemental carbon (^{13}C) nanoparticles	Geiser et al. 2005
Enter various organs	Silver, iridium, elemental carbon (^{13}C) nanoparticles	Geiser et al. 2005
Enter cell nuclei	SWCNT, C_{60}	Porter et al. 2007a and b
Move from nose to brain	Carbon nanoparticles (^{13}C); manganese oxide nanoparticles	Oberdörster et al. 2004; Elder et al. 2006
Penetrate epidermis	Quantum dots	Ryman-Rasmussen et al. 2006

Source: Schulte et al. [2008]

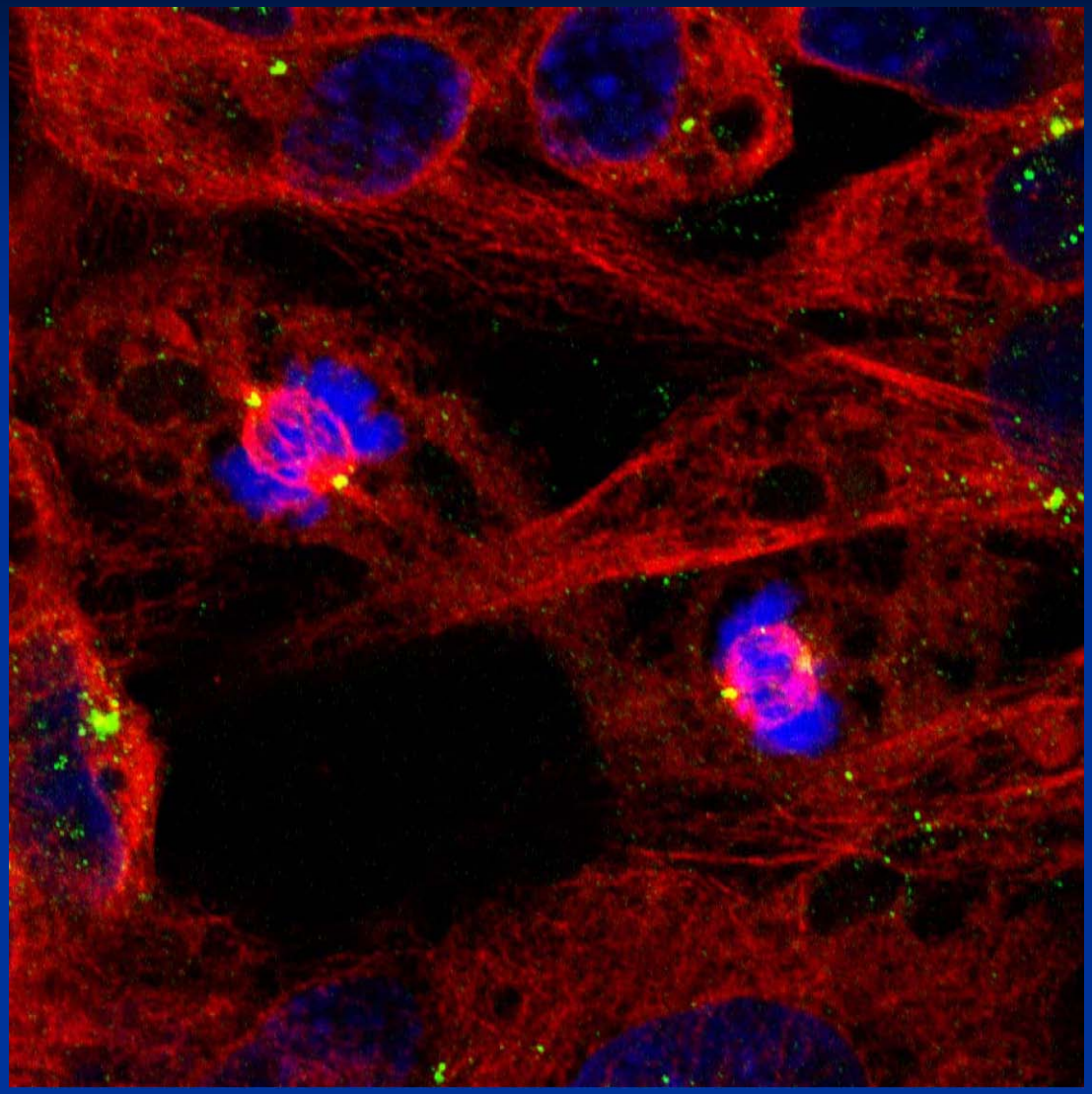
Nanotoxicology: key findings



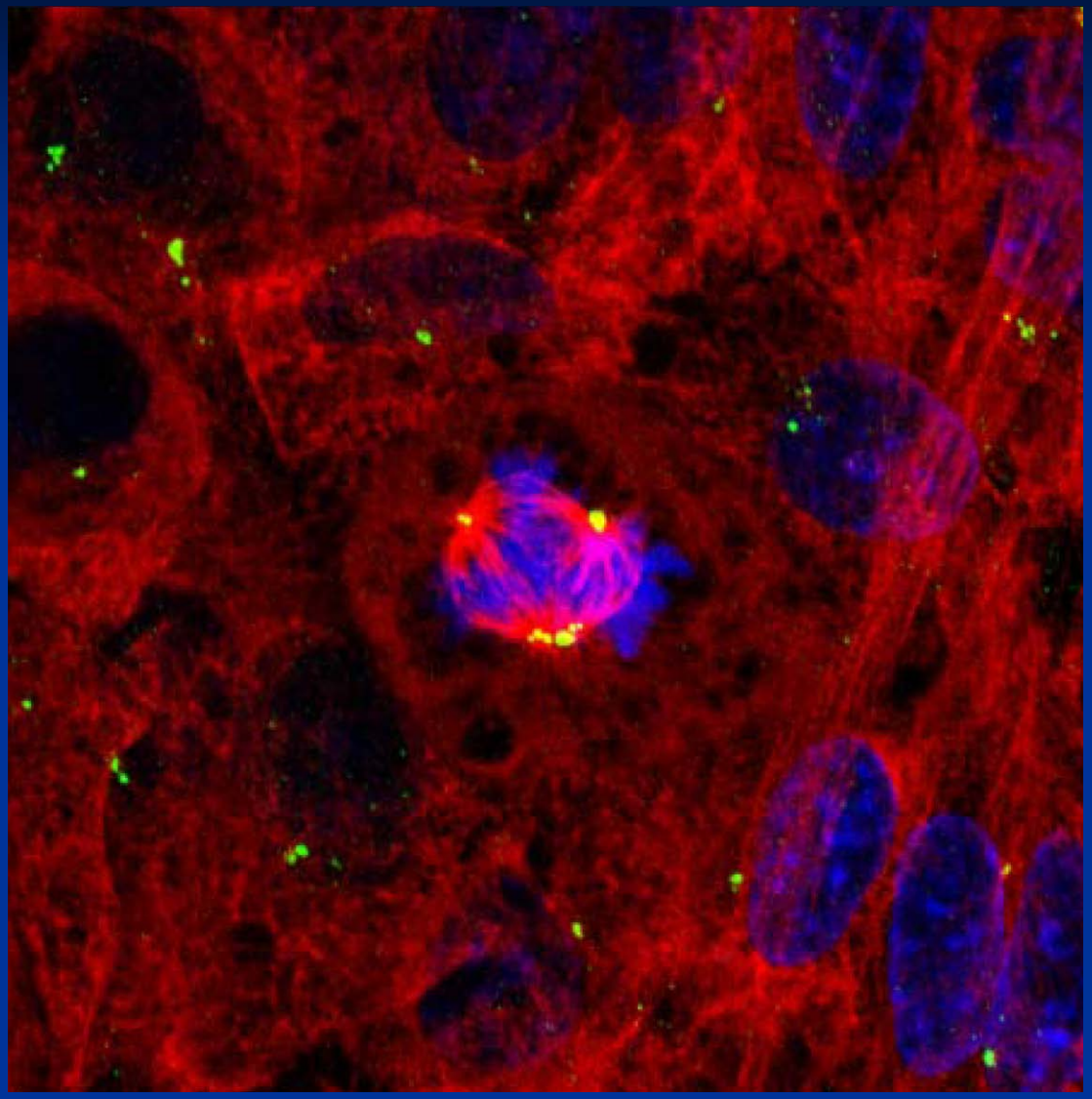
Courtesy of
R. Mercer, NIOSH

Carbon nanotubes

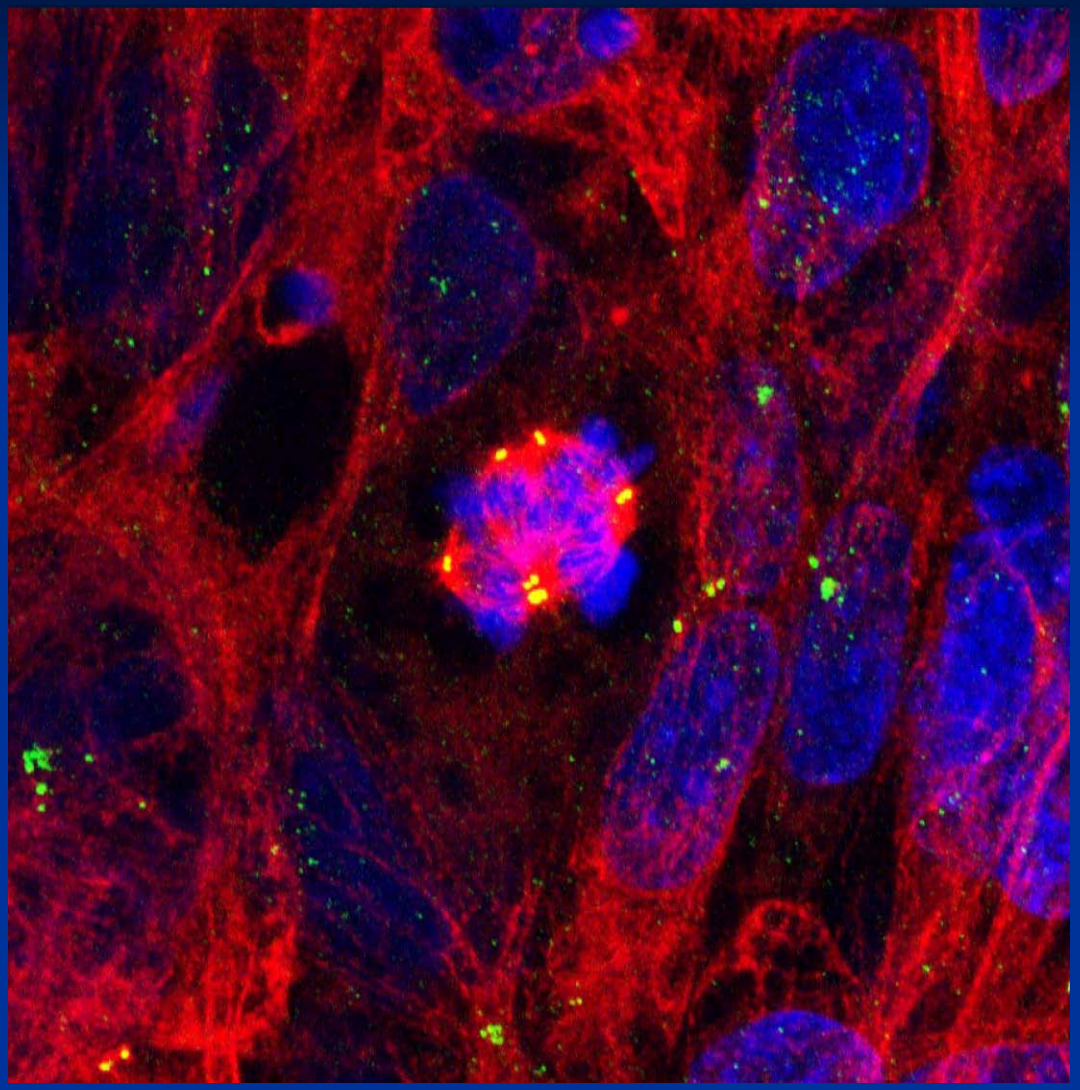
- Multi-walled nanotubes can reach the intrapleural space (site of mesotheliomia)
- Single-walled nanotubes can interfere with cell division



Two dividing control cells with normal centrosome morphology



Tripolar mitosis following exposure to .024 $\mu g/cm^2$ SWCNT



Four polar mitosis, nanotube association 24 hours following exposure to .024 $\mu g/cm^2$ SWCNT

Mitotic spindle aberrations

- Following acute and chronic exposure to carbon nanotubes
  - SWCNT enter the nucleus, are integrated with microtubules and centrosomes, are within the bridge separating dividing cells
    - Fragment the centrosome
    - Disrupt the mitotic spindle
    - Induce aneuploidy
    - Chemicals and fibers that induce centrosome damage, mitotic spindle damage and aneuploidy increase risk of cancer

Linda Sargent, Ph.D.
Molecular Genetics Laboratory, NIOSH

Key elements in worker protection

Exposure →

Can it be measured?
Where is it occurring?
Metric?

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."

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"

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

Examples of NIOSH field investigations: basic metrics

Type of Facility	Type of Particle, Morphology	Size of Particle	Range of "Potential" Exposure Concentrations
University Research lab	Carbon Nanofibers	Approx. 100 nm diameter, 1–10 microns long	60-90 µg/m^3 Total Carbon
Metal Oxide Manufacturer	TiO_2, Lithium Titanate, powder	100–200 nm	<100 nm: 1.4 µg/m^3 (TiO_2) Total dust: 4-149 µg/m^3 (TiO_2) <100 nm: ND (Li) Total dust: ND -3 µg/m^3 (Li)
Manufacturer	Carbon Nanofibers	Approx. 100 nm diameter, 1–10 microns long	15 - 1800 µg/m^3 Total carbon
Research and Development lab	Quantum Dots, spheres	2–8 nm	ND
Metal Oxide Manufacturer	Manganese, Silver, Nickel, Cobalt, Iron oxides, spheres	8–50 nm	67 - 3619 µg/m^3 Mg, Ag, Ni, Co, Fe
Research and Development lab (Pilot-Scale)	Aluminum, spheres	50–100 nm	40 - 276 µg/m^3 Al
Research and Development lab	Elemental metals: Silver, copper, TiO_2	15–40 nm	ND
Filter Media Manufacturer	Nylon 6 Nanofiber	70–300 nm diameter, continuous length	ND

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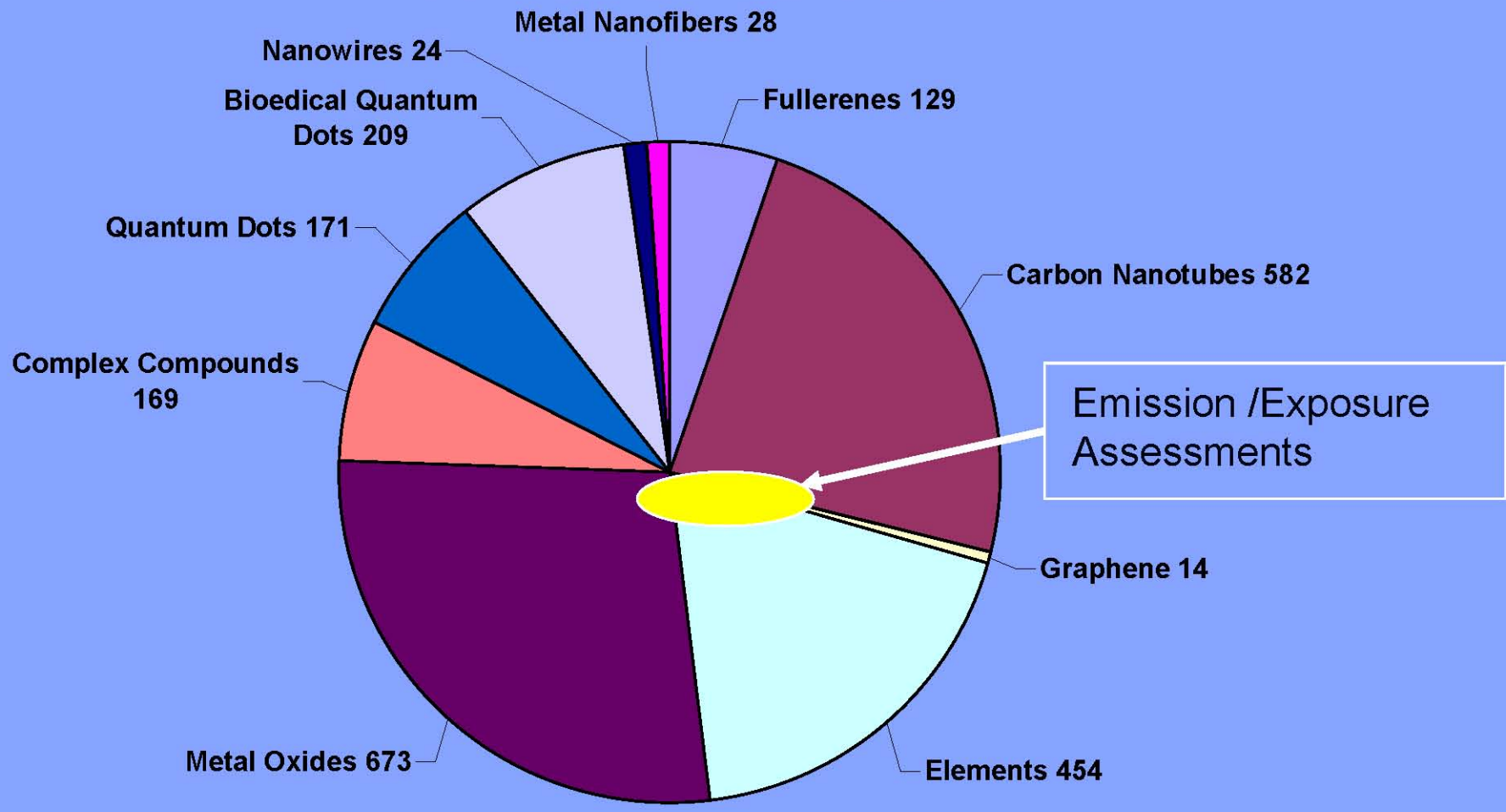
The Exposure Experience: What have we seen?

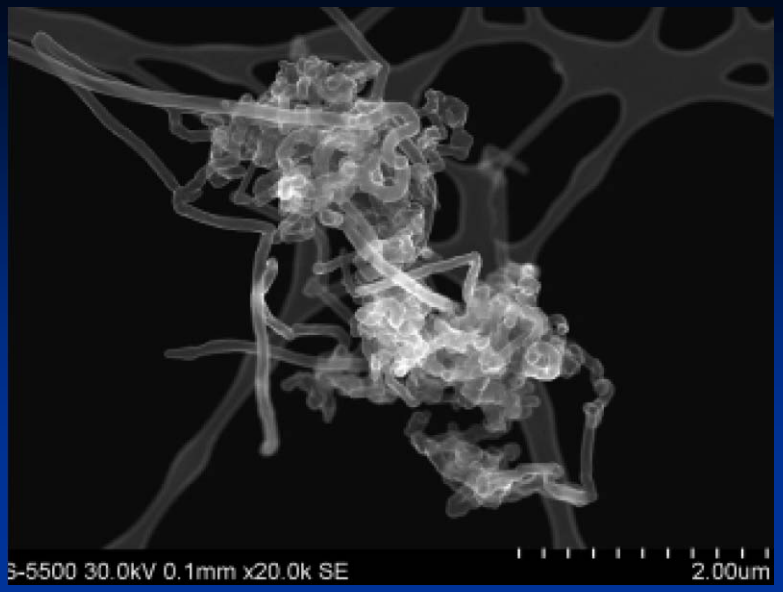


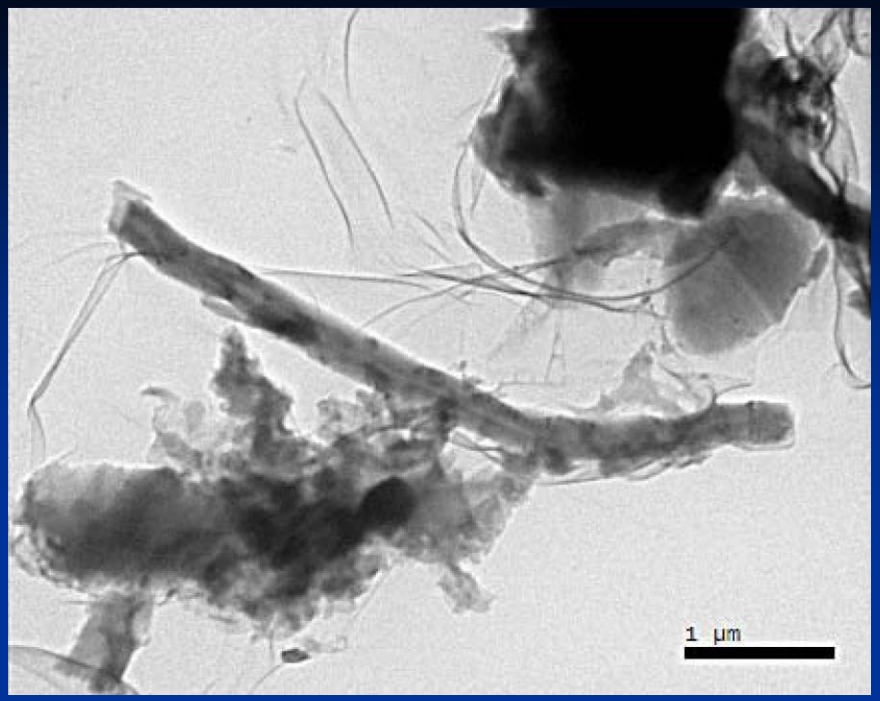
Source of distribution database: NanoWerk, 2010.

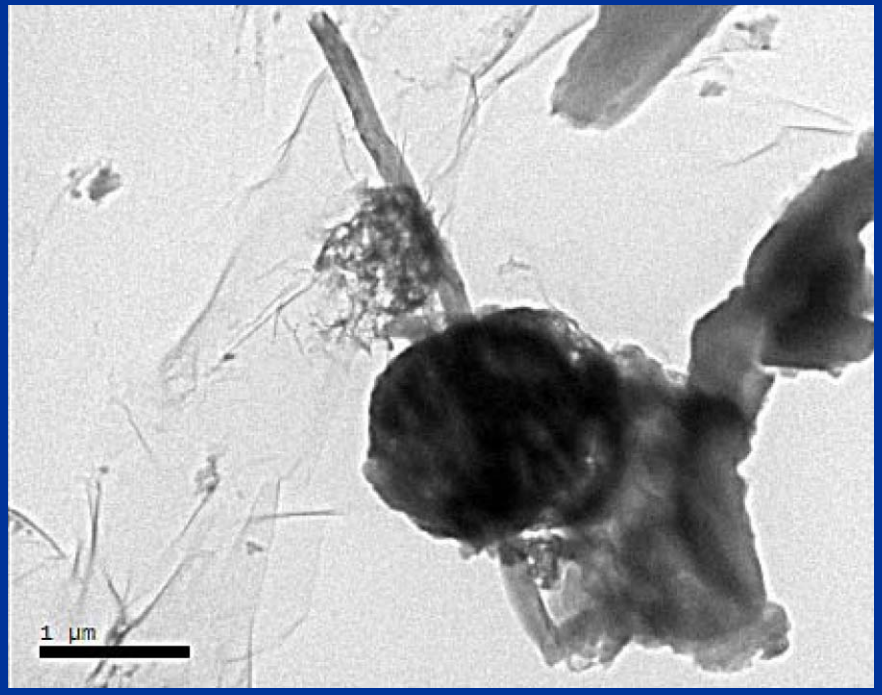
Need for a comprehensive job-exposure matrix (JEM) for each worker

	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.







Images from field air samples. Complex nanomaterial shapes in a complex matrix.

Key elements in worker protection

Hazard Identification

"Is there reason to believe this could be harmful?"

Exposure Assessment

"Will there be exposure in real-world conditions?"

Risk

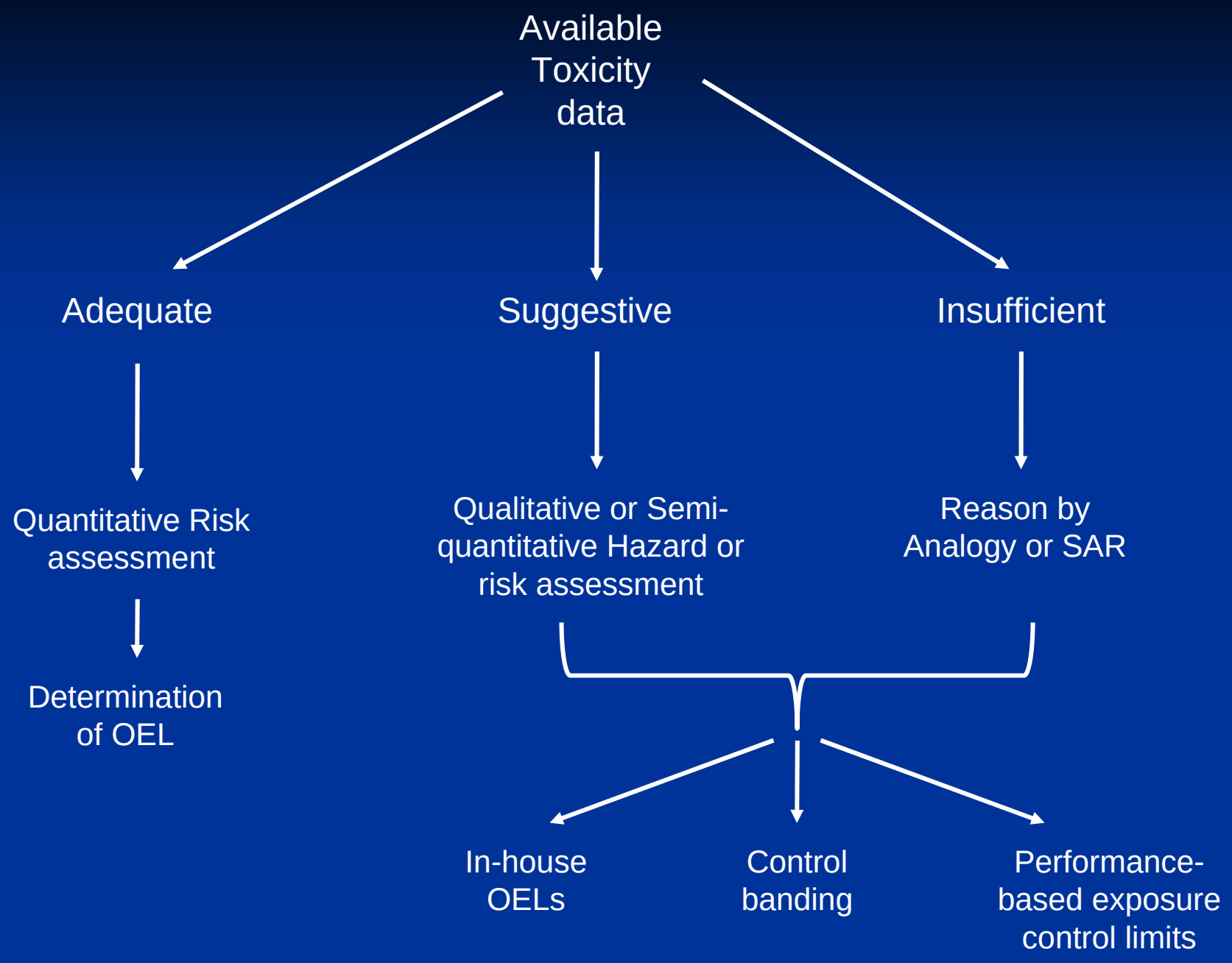
Hazard x Exposure

Risk Characterization

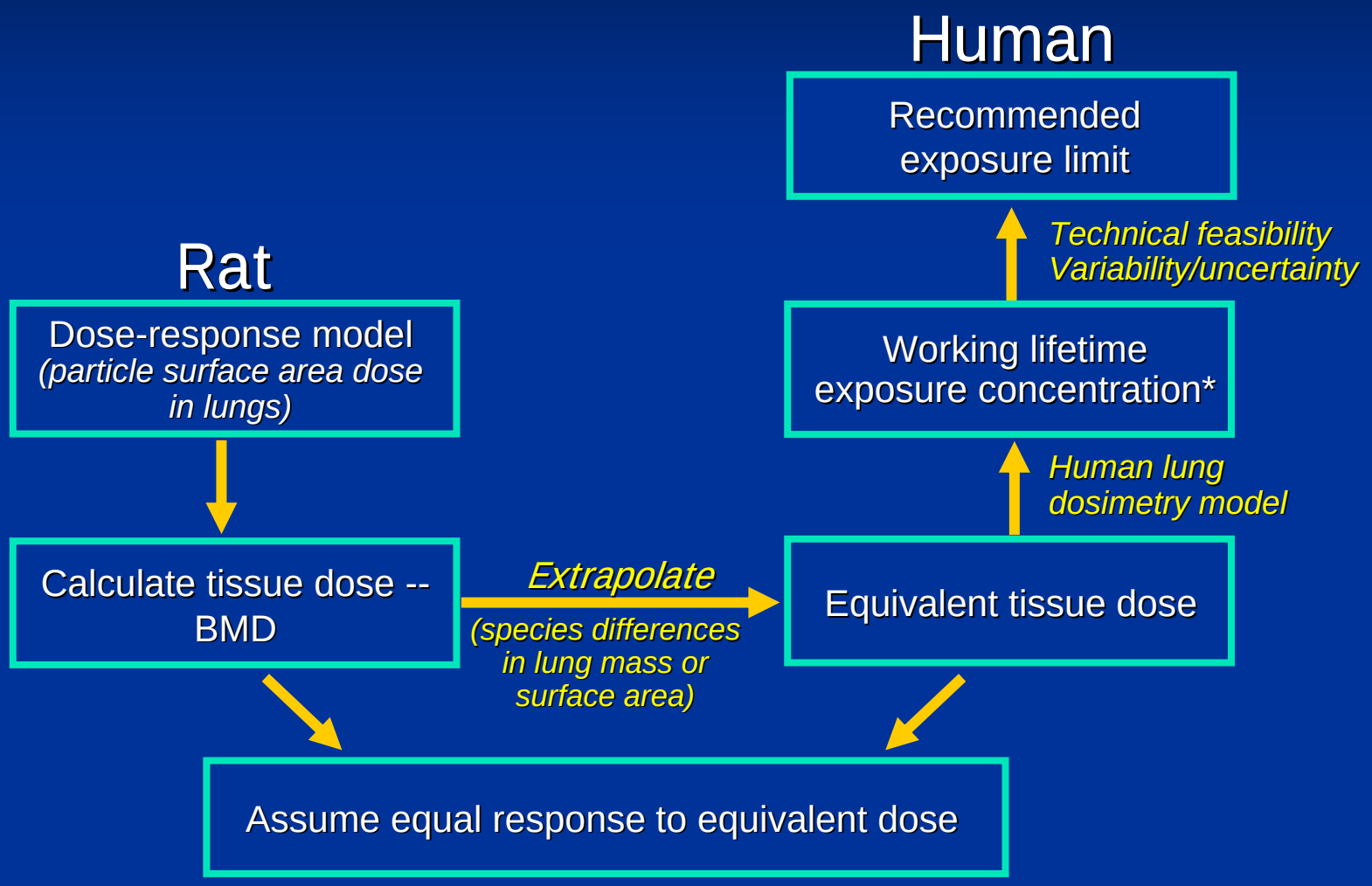
"Is substance hazardous *and* will there be exposure?"

Risk Management

"Develop procedures to minimize exposures."


Available Toxicity data
Adequate
Suggestive
Insufficient
Quantitative Risk assessment
Determination of OEL
Qualitative or Semi-quantitative Hazard or risk assessment
Reason by Analogy or SAR
In-house OELs
Control banding
Performance-based exposure control limits

Quantitative Risk Assessment in developing Recommended Exposure Limits for nanoparticles



*Compare rat-based risk estimates with confidence intervals from human studies

Risk assessment: ultrafine (nano) TiO_2

- NIOSH draft recommended exposure limits (RELs)
  - 1.5 mg/m3 fine TiO_2
  - 0.1 mg/m3 ultrafine TiO_2
  - Reflects greater inflammation & tumor risk of ultrafine on mass basis

- Key message: The OEL for a material in its "large" form may not be appropriate for the nano form.

Risk assessment: carbon nanotubes

- Use data from Ma-Hock (2009)
  - Wistar rats exposed 0.1, 0.5, 2.5 mg/m^3 multiwall carbon nanotubes (6 hr/day, 5 days/wk, 15 wks)
- OEL for a risk of pulmonary fibrosis at less than 1/1000 over a working lifetime
- Likely to be less than the limit of quantitation for organic carbon i.e., < 7 μg/m^3

Key elements in worker protection

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"Develop procedures to minimize exposures."

Recognize and Manage Risk

What works?
What has been used?
What can be reapplied?

Risk management

- Follow hierarchy of controls
- Establish OELs
- Utilize Prevention through Design
- Consider medical screening

Pieces in the big picture

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

Controls have been applied in research and pilot development work

Manufacturing containment

Courtesy of Nanocomp Technologies, Inc.

Manufacturing containment

Courtesy of Nanocomp Technologies, Inc.

Case study: use of LEV during reactor cleanout

Next version…

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

96 +/- 6% based on **particle counts**

88 +/- 12% based on **mass**

M. Methner,
JOEH June 2008

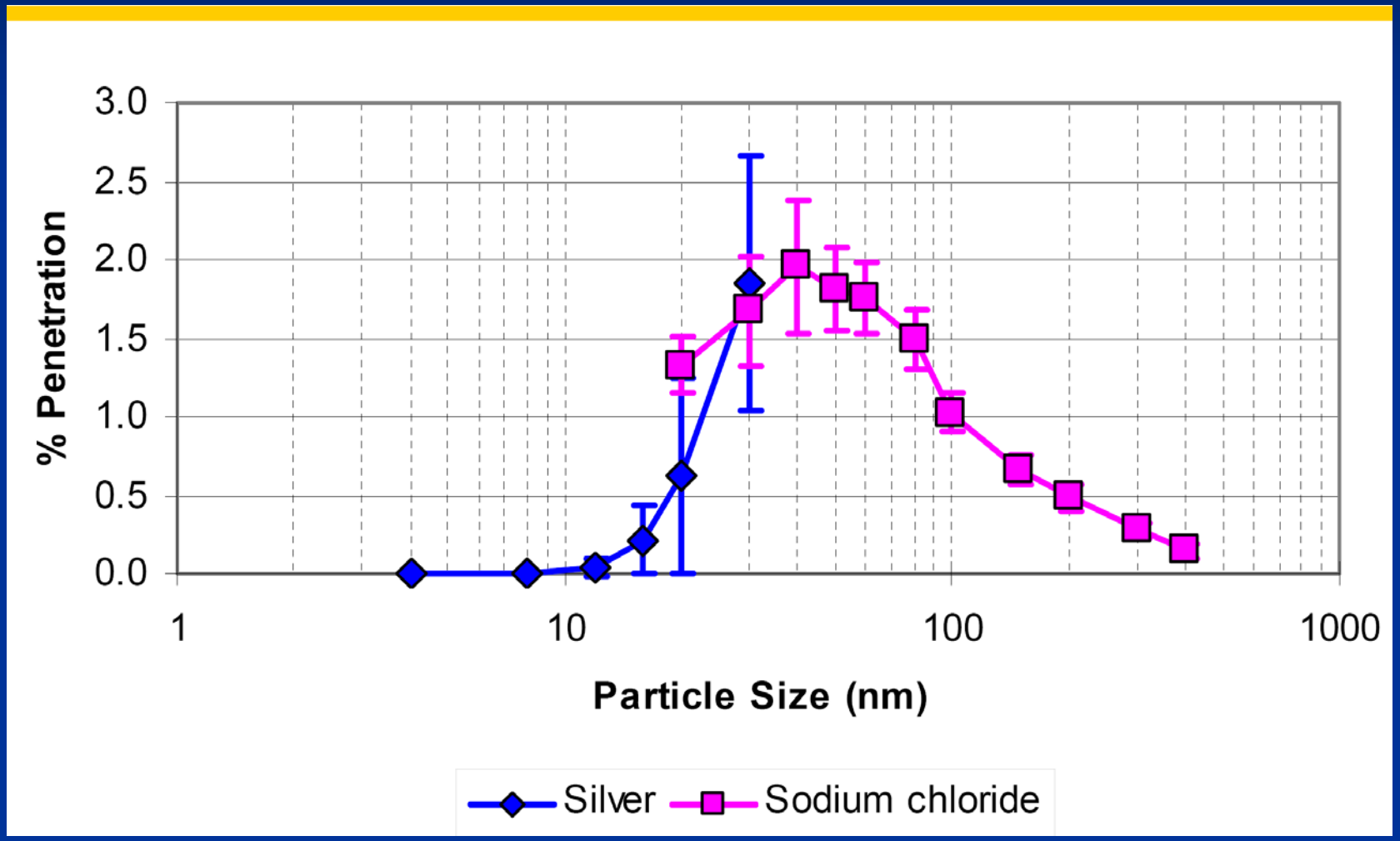
Effectiveness of LEV in Reducing Release of Aerosol During Reactor Cleanout Operations:

Mass Air Concentrations of Metal Oxides With/Without LEV Micrograms/cubic meter (μg/m^3)

Operation	Air Concentration "Without" LEV	Air Concentration "With" LEV	Percent Reduction in air concentration due to use of LEV (%)*
Manganese (Mn) Reactor cleanout	3,619	150	96
Silver (Ag) Reactor cleanout	6,667	1,714	74
Iron (Fe) Reactor cleanout	714	41	94
Background (Reactor area Prior to cleanout)	ND	ND	N/A
Mean (+/- S.D.)			**88 (+/- 12)**

* Percent reduction calculated as follows: [(Without LEV - With LEV)/ Without LEV] x 100

Filtration performance of an example NIOSH approved N95 filtering facepiece respirator



n=5; error bars represent standard deviations
TSI 3160; Flow rate 85 L/min

Exposure management
Control banding - concept

	Low Dustiness	Medium Dustiness	High Dustiness
Hazard Group A			
Small	1	1	1
Medium	1	1	2
Large	1	2	2
Hazard Group B			
Small	1	1	1
Medium	1	2	2
Large	1	3	3
Hazard Group C			
Small	1	1	2
Medium	2	3	3
Large	2	4	4
Hazard Group D			
Small	2	2	3
Medium	3	4	4
Large	3	4	4
Hazard Group E			
For all hazard group E substances, choose control approach 4			

Parameters

- Amount Used
- Dustiness
- Hazard Group (R-Phrase)

Control Approach

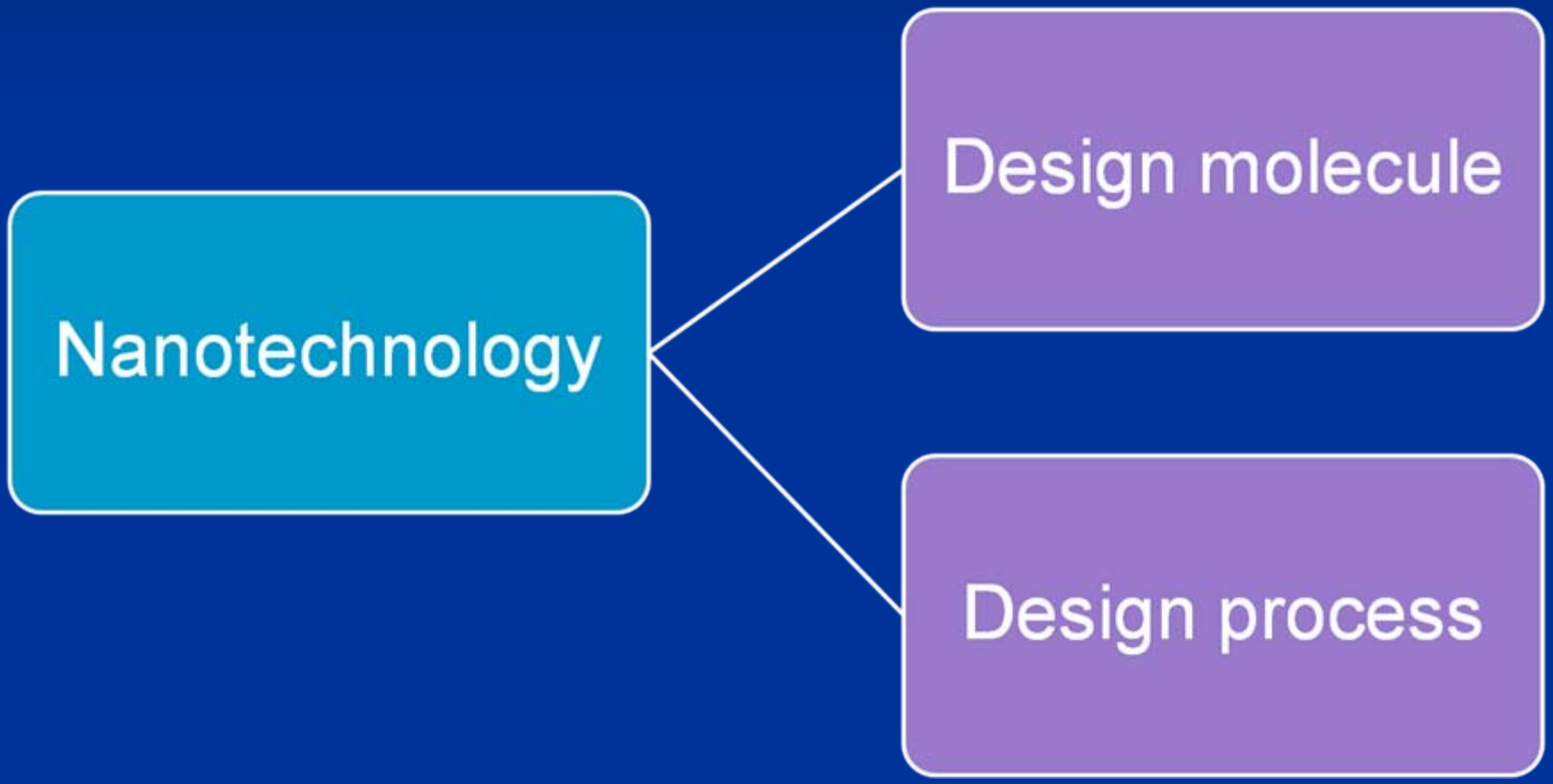
1. General Ventilation
2. Engineering Control
3. Containment
4. Specialist Advice

Source: T.J. Lentz, NIOSH

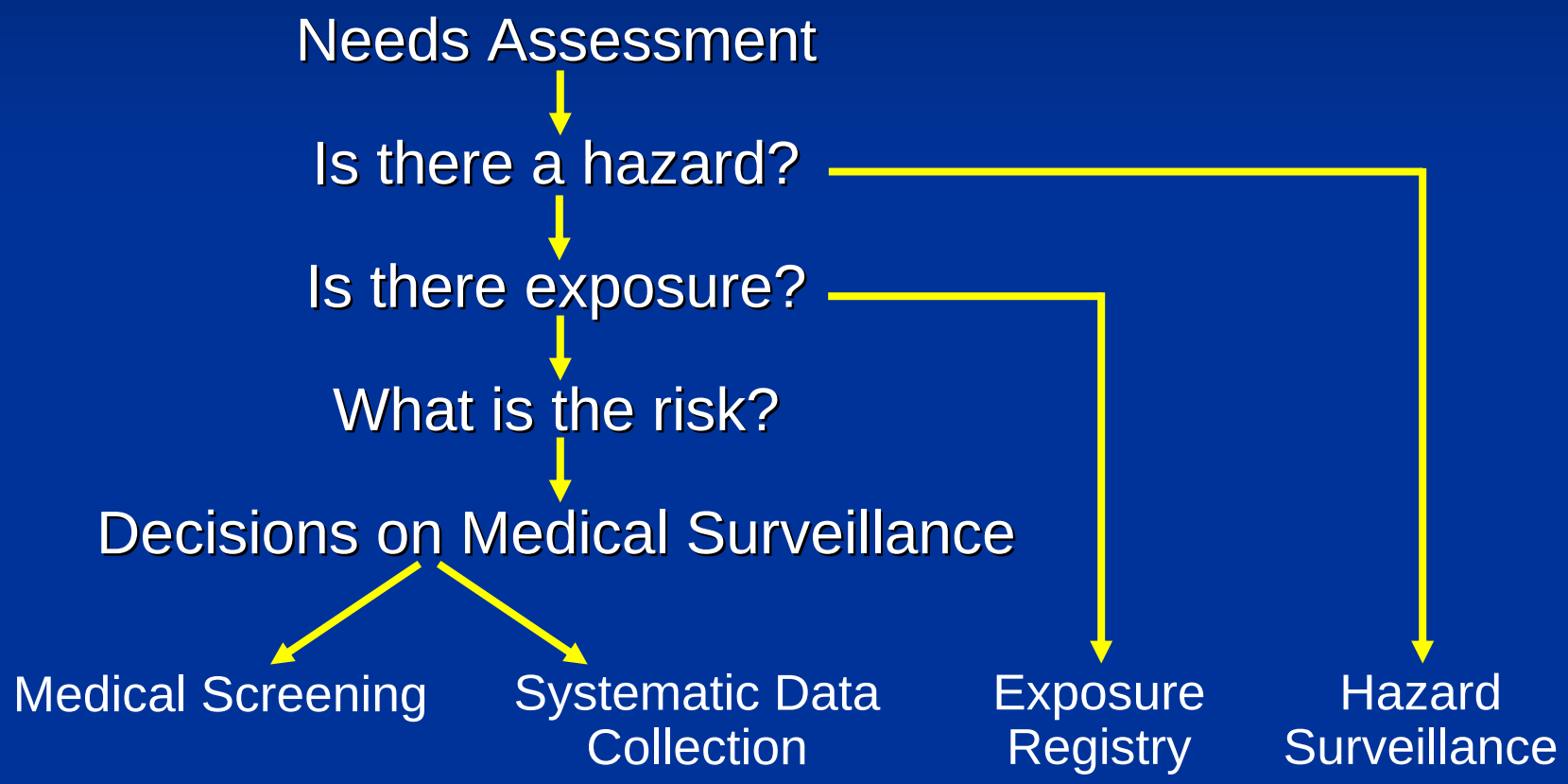
Establishment of OELs

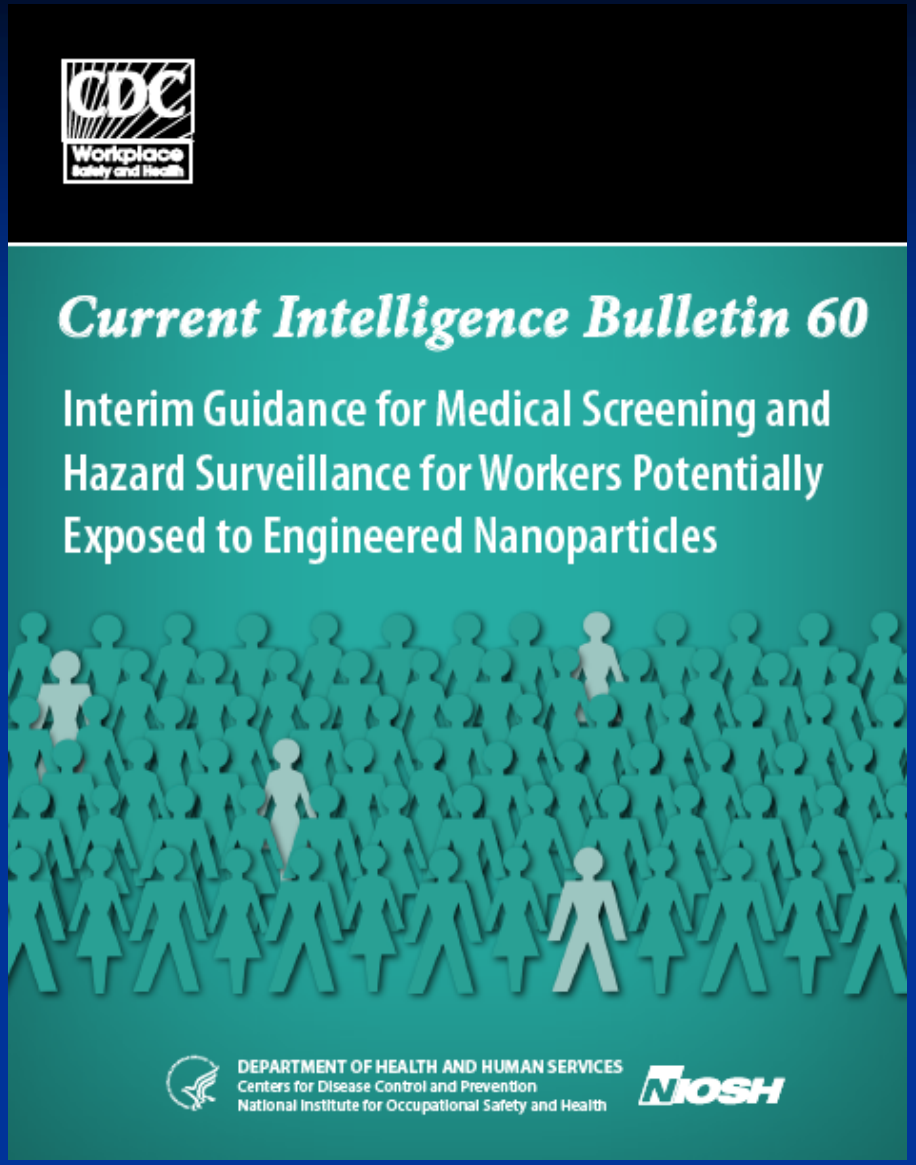
- No officially promulgated OELs
- 16 “unofficial” proposed OELs

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

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

etc.

Sector: **Food**

Sector: **Electronics**

Sector: **Medicine**

Sector: **Energy**

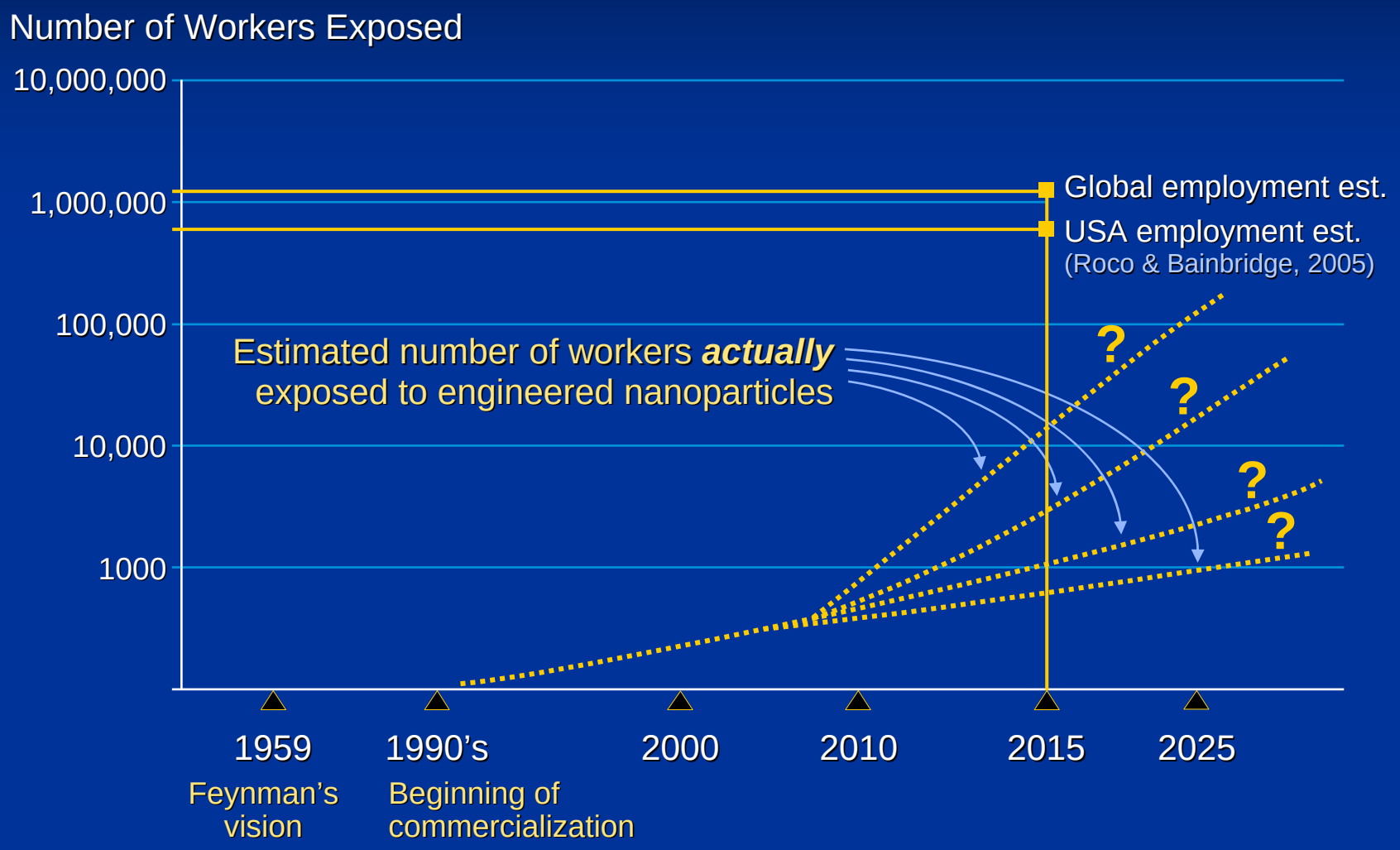
Sector: **Materials**

Workplaces	*Nanomaterial Type*			
	Carbon Nanotubes	Metal Oxides	Dendrimers	Fullerenes Metal Nanomaterials Nanowires Nanostructured Metals Nanoporous Materials Nanoscale Encapsulation
Laboratory Research				
Start up/Pilot				
Manufacturing				
Production				
Disposal				

Workplace x Sectors x Nanomaterials

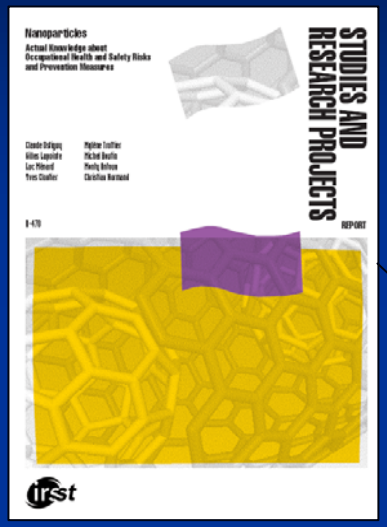
- Challenge:
  - Understand risk in each cell
  - Set priorities for research and guidance
  - Control risks

Dilemmas in identifying workers exposed to engineered nanoparticles

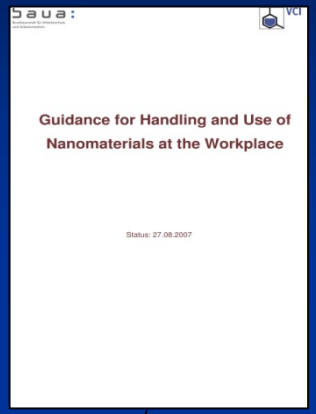


Source: Schulte [2009]

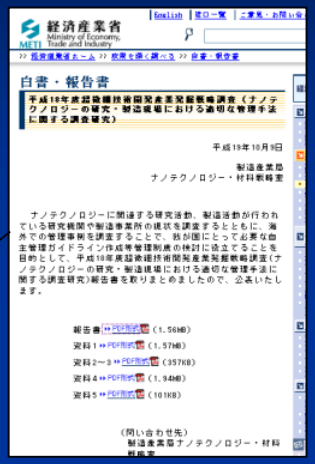
Government Guidance Documents



IRSST



BAuA
UK HSE



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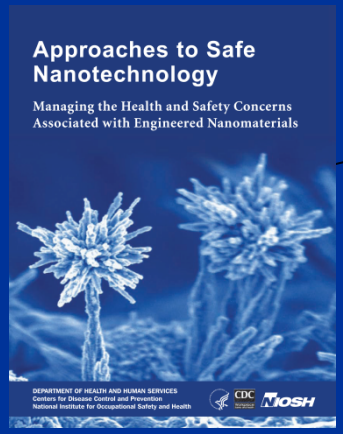
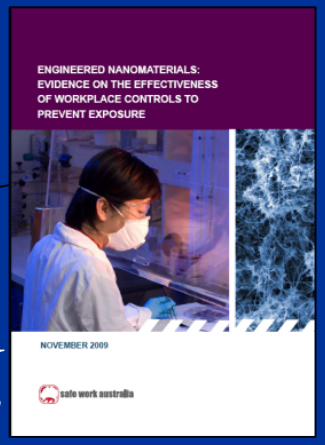
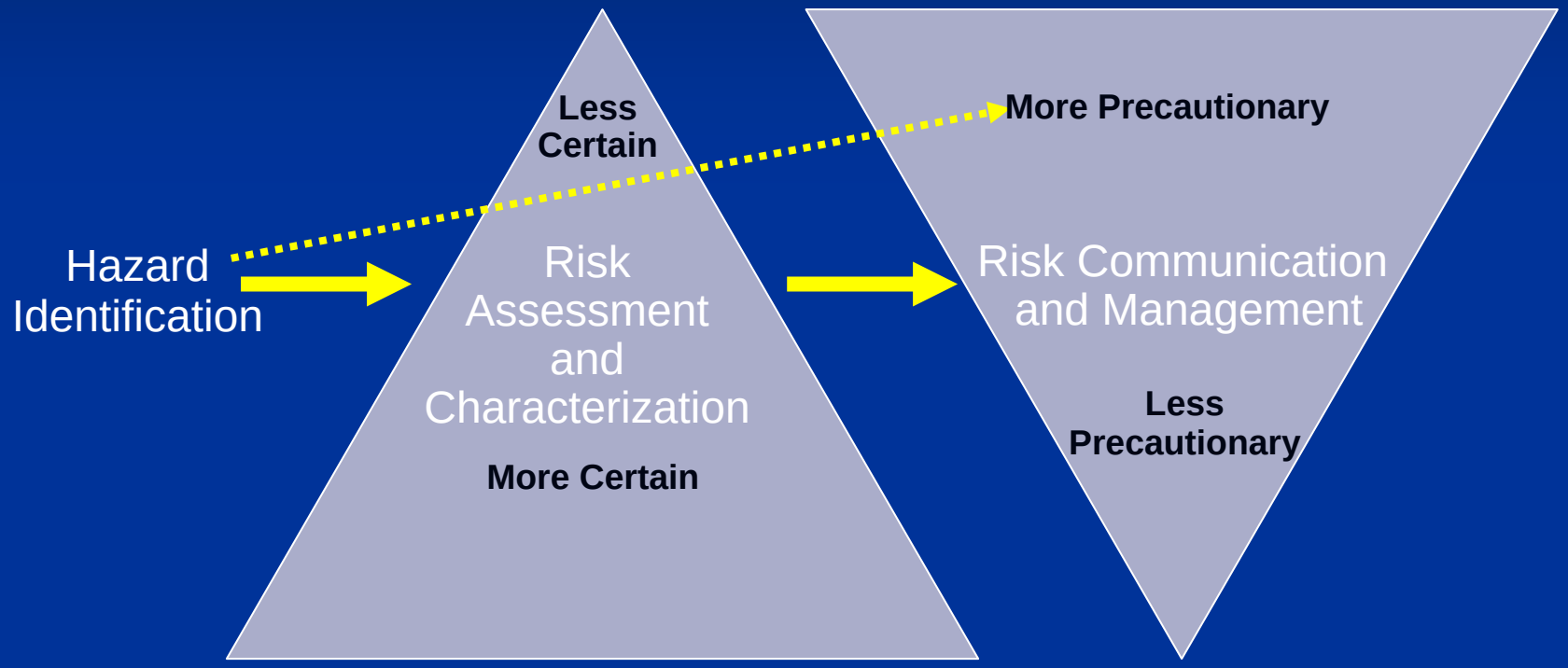


NIOSH



Safe Work
Australia

IRSST, Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail
BAuA, (German) Federal Institute for Occupational Safety and Health
HSE, Health and Safety Executive
METI, Ministry of Economy, Trade and Industry (Japan)
NIOSH, Japan National Institute for Occupational Safety and Health

Hazard and risk continuum