

# Risk Assessment Approaches for Nanomaterials

*Eileen D. Kuempel, PhD*

Nanotechnology Research Center

Education and Information Division

National Institute for Occupational Safety and Health

*The findings and conclusions in this presentation have not been formally reviewed by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.*



# Outline

- General approaches & issues
- Specific examples
  - Carbon nanotubes
  - Titanium dioxide
- Future directions

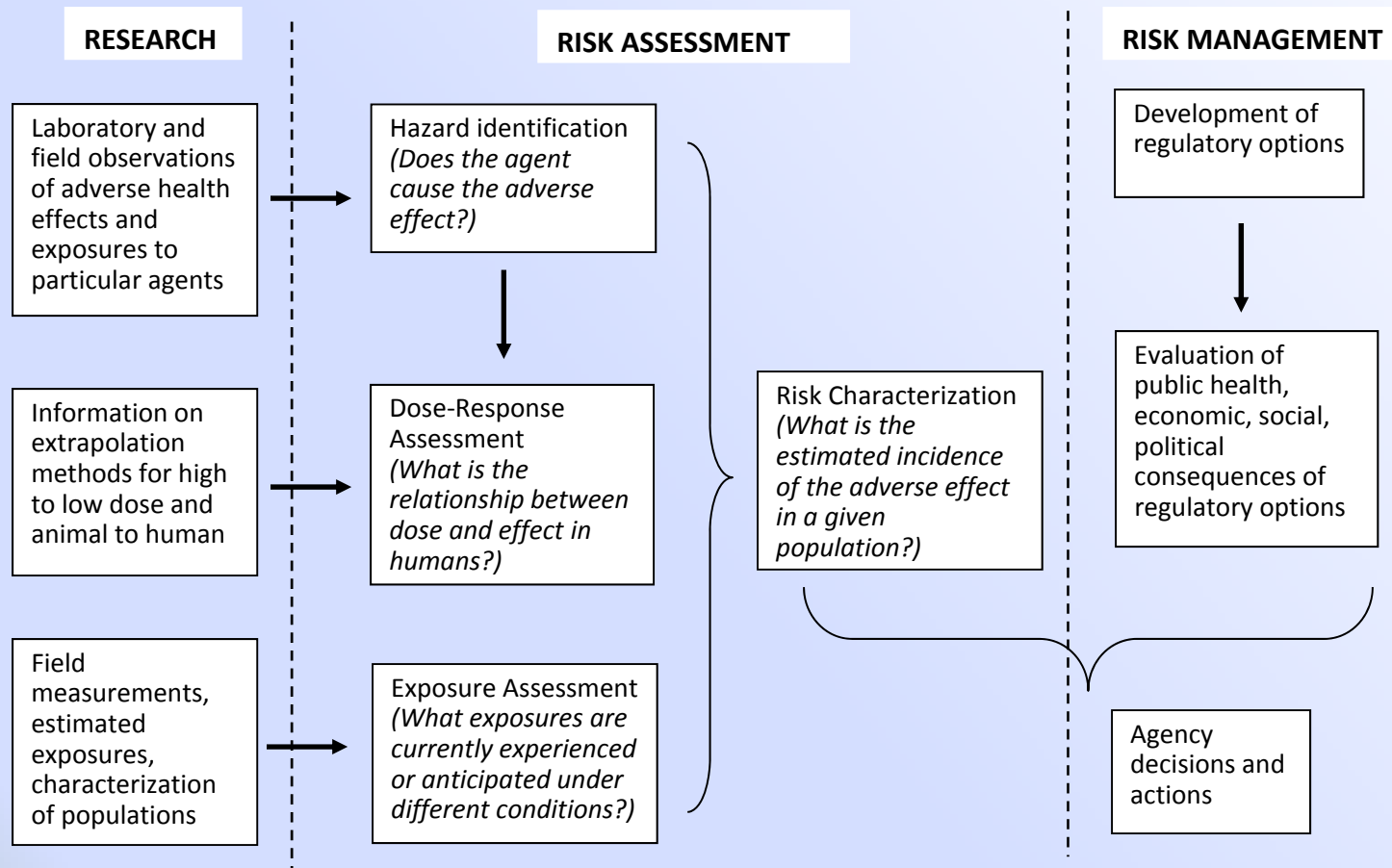
# Are Current OELs Adequately Protective for Workers Exposed to Nanomaterials?

- No data or limited data for most manufactured nanoparticles
- Animal data of poorly-soluble particles show greater toxicity of nanoparticles by mass due to greater particle number and surface area
- Most OELs are mass-based and do not account for nanoparticle size

# Possible Approaches to Nanomaterials Risk Assessment

1. No observed adverse effect level (NOAEL) or lowest (LOAEL) with uncertainty factors
2. Benchmark dose (BMD): dose associated with risk of adverse effect (e.g., 10%) with extrapolation to lower “acceptable” risk
3. Analogy or comparative toxicity to other substances with similar structure & activity and with adequate dose-response data

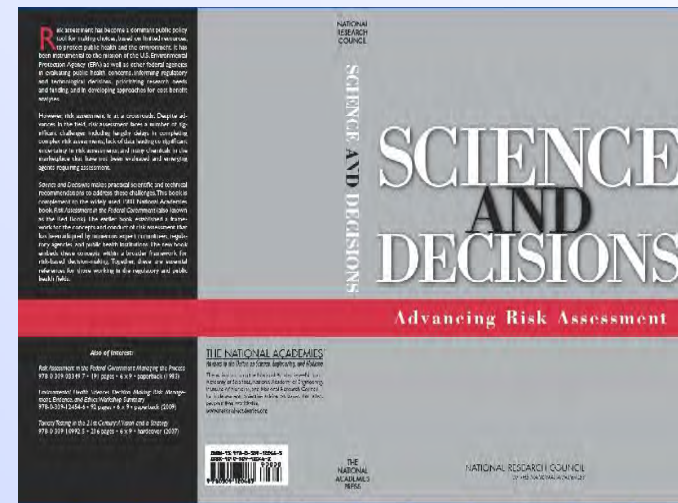
# Risk Assessment Framework in US (NRC 1983)



Source: NRC (1983) Risk Assessment in the Federal Government: Managing the Process. National Research Council, National Academy of Sciences. Washington, DC.

# Updated Risk Assessment Paradigm (NRC 2009)

- Re-evaluated the 1983 risk assessment framework as practiced
- Retained the basic four steps:
  - Hazard assessment
  - Exposure assessment
  - Dose-response assessment
  - Risk characterization
- Increased emphasis on problem formulation & risk management at beginning and end of risk assessment process.



National Research Council of the National Academies (2009)

# Quantitative Risk Assessment Steps for Inhaled Particles

1. Identify relevant animal model, dose metric, and disease response.
2. Evaluate dose-response relationship & estimate dose associated with a specified risk of adverse effect.
3. Extrapolate the animal critical dose to humans by adjusting for differences in breathing parameters & lung morphology
4. Estimate airborne exposure that would result in the human-equivalent dose.

*[Kuempel et al. Inhal Toxicol 2006]*



# Carbon Nanotube (CNT) Risk Assessment

- Focus: Preventing chronic occupational lung disease over a working lifetime
- No epidemiology studies yet in CNT workers
- Animal dose-response data available
  - Several single- or short-term exposure studies in rats & mice
  - Two subchronic (13 wk) inhalation studies in rats
  - Responses: Early-stage inflammation, granuloma, & fibrosis; persistent or progressive after the end of exposure
- Animal lung responses to CNT relevant to humans
  - Observed in workers of dusty jobs
  - Can be functionally adverse, clinically significant



# Rationale for Development of CNT CIB

- Several animal studies showed pulmonary fibrosis (early onset, persistent) and granulomatous inflammation from carbon nanotube (CNT) exposure
- Associated with both unpurified and purified CNT (raw metal contaminated)
- Effects occurring at relatively low doses
- Ability of CNT to persist and migrate to pleura
- Other adverse effects (e.g. aneuploidy)

## Adverse Effect Levels in Rats after Subchronic (13-wk) Inhalation Exposure to Carbon Nanoparticles

| Study                 | Substance                   | Effect Level in Rats       |                            |
|-----------------------|-----------------------------|----------------------------|----------------------------|
|                       |                             | NOAEL (mg/m <sup>3</sup> ) | LOAEL (mg/m <sup>3</sup> ) |
| Elder et al. [2006]   | Ultrafine carbon black      | 1                          | 7                          |
| Ma-Hock et al. [2009] | Multi-wall carbon nanotubes | --                         | 0.1                        |
| Pauluhn et al. [2010] | Multi-wall carbon nanotubes | 0.1                        | 0.4                        |

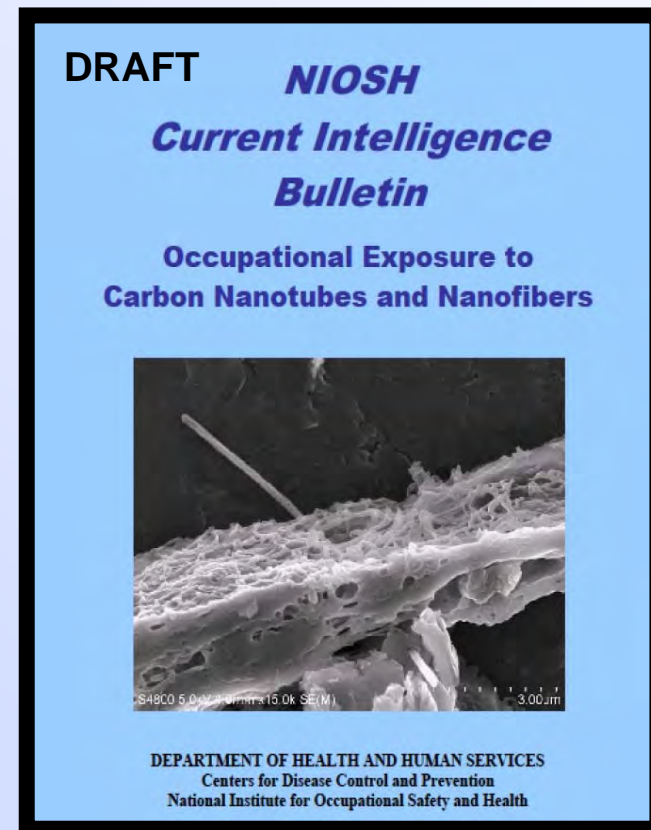
NOAEL: No observed adverse effect level LOAEL: Lowest observed adverse effect level: *pulmonary inflammation & fibrosis*

# CNT Risk Assessment Findings

- Working lifetime exposure of 0.2–2  $\mu\text{g}/\text{m}^3$  (8 hr TWA) concentration (95% lower confidence limit estimate)
  - Associated with >10% estimated excess risk of early stage lung effects (pulmonary inflammation, granulomas, fibrosis)
  - Extrapolated from subchronic inhalation studies of MWCNT
  - Similar risk estimates from other animal studies of SWCNT, MWCNT, and CNF

## NIOSH Draft Recommended Exposure Limit for CNT & CNF

- 7  $\mu\text{g}/\text{m}^3$  (8-h TWA),  
respirable fraction
- Set at the limit of  
quantification (LOQ) of the  
NIOSH analytical method to  
measure elemental carbon  
[Method 5040]



Available at: [www.cdc.gov/niosh](http://www.cdc.gov/niosh)

# Engineering Control Performance Options for Airborne Nanoparticles

| <b>Control Technology</b> | <b>Historical Performance<br/>(<math>\mu\text{g}/\text{m}^3</math>)</b> |
|---------------------------|---|
| Local exhaust ventilation | <1,000  |
| Ventilated enclosures     | 10 – 1,000  |
| Containment systems       | 1 – 10  |
| Closed systems & robotics | <1  |

# Limited CNT Occupational Exposure Data

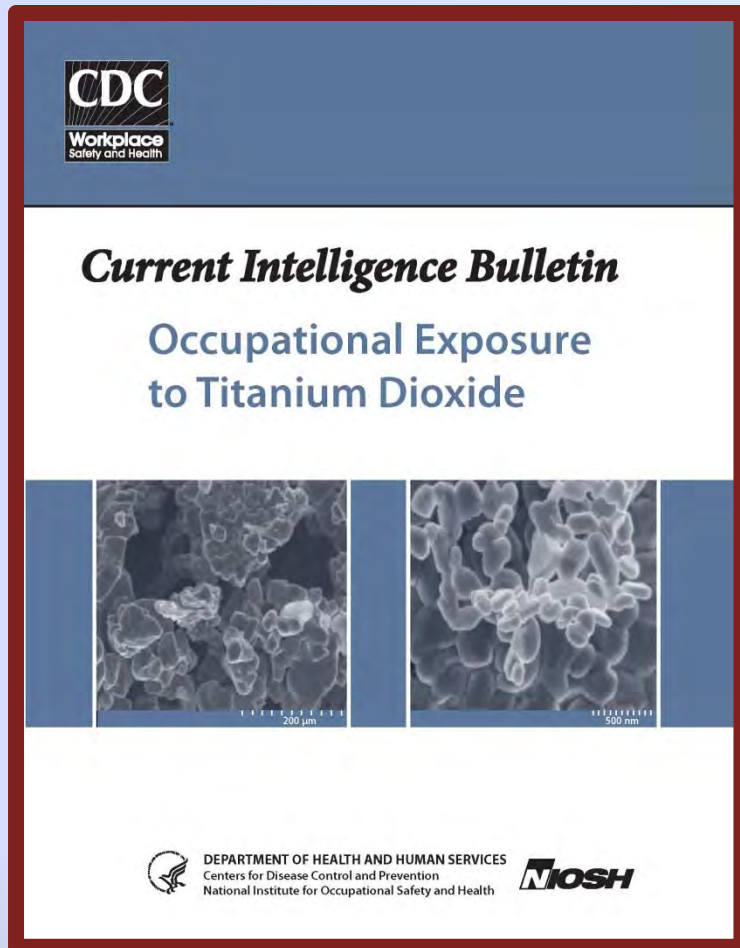
| Material & Process                                   | Concentration ( $\mu\text{g}/\text{m}^3$ )* | Reference           |
|--|---|---------------------|
| SWCNT – pilot production facility                    | 10 - 53                                     | Maynard et al. 2004 |
| MWCNT – research laboratory, before & after controls | 37- 434<br>ND - 39                          | Han et al. 2008     |
| CNF composite – weighing, mixing, cutting            | 64 - 1,094                                  | Methner et al. 2007 |
| MWCNT composite – wet or dry cutting                 | 54<br>2,110 - 8,380                         | Bello et al. 2009   |

*ND = not-detected*

\* Most are short-term (~30 min) samples of total carbon

# Uncertainties in CNT Risk Assessment

- Extrapolating short-term and subchronic data in animals to chronic exposure in humans
- Limited information on human clinical significance of the early-stage lung effects in animals
- Generalizing findings to other types of CNT and CNF
- Comparability of physical-chemical properties of CNT used in the animals studies and the workplace
- Workers' personal exposures to CNT



*Published April 2011*

*Available at: [www.cdc.gov/niosh](http://www.cdc.gov/niosh)*

▪ Separate recommended exposure limits (RELs) by particle size:

- Ultrafine TiO<sub>2</sub>: 0.3 mg/m<sup>3</sup>
- Fine TiO<sub>2</sub>: 2.4 mg/m<sup>3</sup>

<1/1,000 excess risk of lung cancer at RELs over working lifetime

▪ Ultrafine TiO<sub>2</sub> classified as potential occupational carcinogen based on rat lung tumor data and secondary genotoxic mode of action.



# Particle size fraction definitions (in TiO<sub>2</sub> CIB)

## “Fine”

- All particle sizes that are collected by respirable particle sampling (i.e., 50% collection efficiency for particles of 4 μm, with some collection of particles up to 10 μm).
- Also refers to the particle fraction between 0.1 μm and approximately 3 μm [Aitken et al. 2004], and to pigment-grade TiO<sub>2</sub> [e.g., Lee et al. 1985].
- Term has been replaced by “respirable,” which is consistent with international sampling conventions [CEN 1993; ISO 1995].

## “Ultrafine”

- The fraction of respirable particles with a primary particle diameter of <100 nm
- Includes agglomerated structures

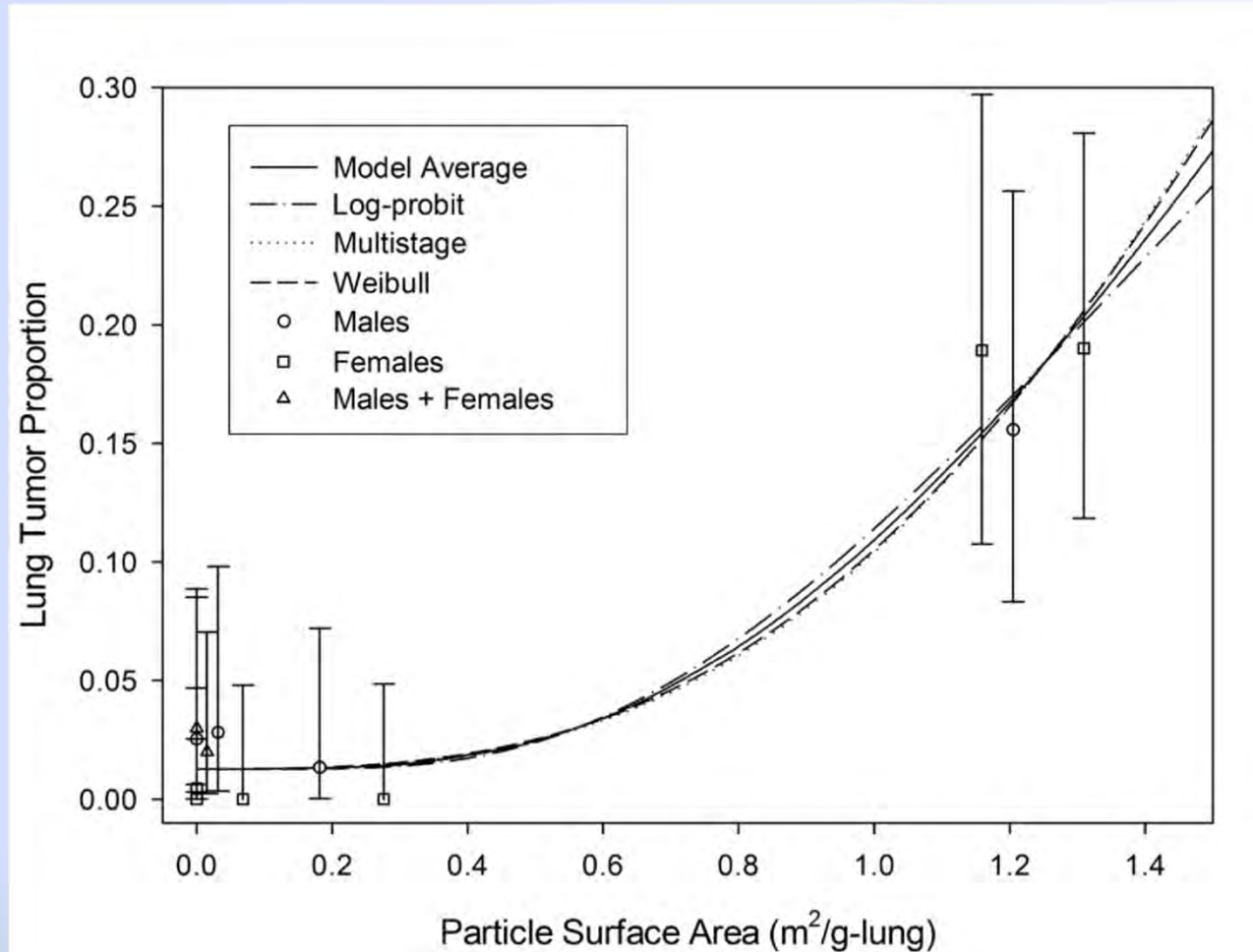
# Titanium Dioxide Risk Assessment: Data Evaluated

- Epidemiology studies
  - Elevated lung cancer mortality in one study of TiO<sub>2</sub> workers: SMR 1.23 (95% CI: 1.10-1.38)
  - No exposure-response relationship
  - Particle size exposure data limited
- Animal chronic inhalation studies (rat)
  - Fine TiO<sub>2</sub>: Elevated lung tumors (adenomas) at 250 mg/m<sup>3</sup>, but not at 10 or 50 mg/m<sup>3</sup>
  - Ultrafine TiO<sub>2</sub>: Elevated lung cancer (adenocarcinoma, squamous cell carcinoma) at 10 mg/m<sup>3</sup>
- Animal subchronic inhalation studies (rat, mouse)
  - Pulmonary inflammation greater on mass basis from ultrafine than fine TiO<sub>2</sub>

## Basis for Hazard Classification of Respirable TiO<sub>2</sub>

- *In vivo* studies indicate TiO<sub>2</sub> causes:
  - Pulmonary inflammation
  - Oxidative stress
  - Lung tissue damage
  - Epithelial cell proliferation
- These are key steps leading to lung tumor development in rats
  - Through a secondary genotoxic mechanism
  - Found for various poorly soluble low toxicity (PSLT) dusts
  - Related to total particle surface area dose

# Benchmark dose (BMD) model average fit to rat lung tumor data after chronic inhalation of fine or ultrafine TiO<sub>2</sub>



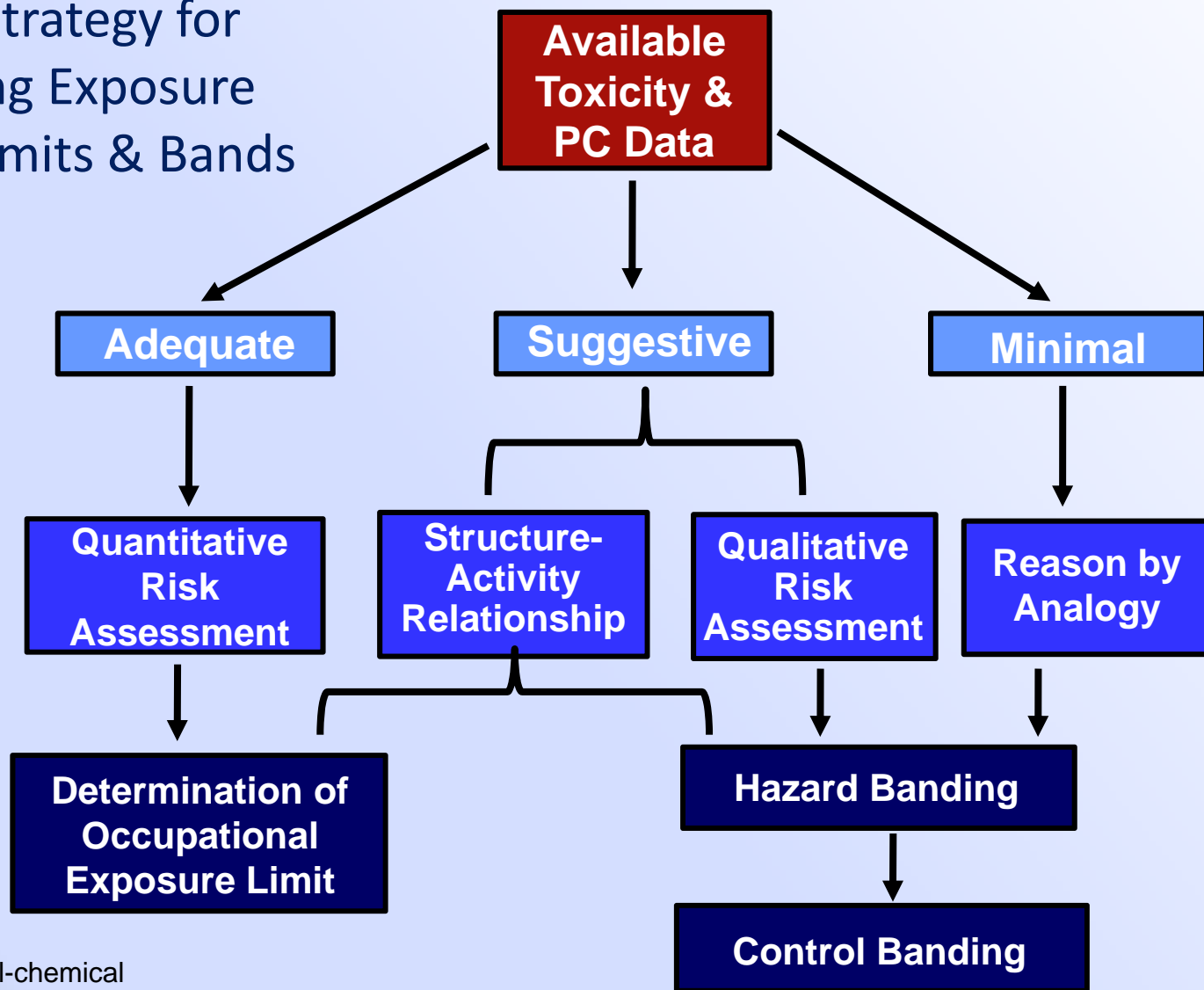
# Hazard Classification for Ultrafine (Nanoscale) $\text{TiO}_2$

- Weight of evidence suggests tumor response in ultrafine  $\text{TiO}_2$ 
  - Results from secondary genotoxic mechanism
  - Related to physical form of inhaled particle (i.e., particle surface) rather than the chemical compound itself
  - Rat tumorigenic data are sufficient and appropriate for making preventive recommendations
- Classification
  - Potential Occupational Carcinogen – inhalation exposure over a working lifetime

# Future Directions – Shifting Paradigm

- Need to address lack of OELs for most nanomaterials
- Consider developing categorical approach to OELs for nanomaterials within mode of action classes
- May provide model for occupational safety and health awareness more generally
  - Evaluate all hazards to which workers may be exposed, in addition to nanomaterials
  - Provide systematic evaluation for safer substitutes

## Possible Strategy for Developing Exposure Control Limits & Bands



PC: physical-chemical

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

# Conclusions

- Risk estimates of CNT & TiO<sub>2</sub> indicate mass-based OELs need to account for particle size & structure
- Effective exposure measurement & engineering controls are essential to protect workers
- Medical monitoring may be warranted to identify early adverse lung effects
- Standardized toxicity testing & risk assessment methods would facilitate future assessments across various types of nanomaterials

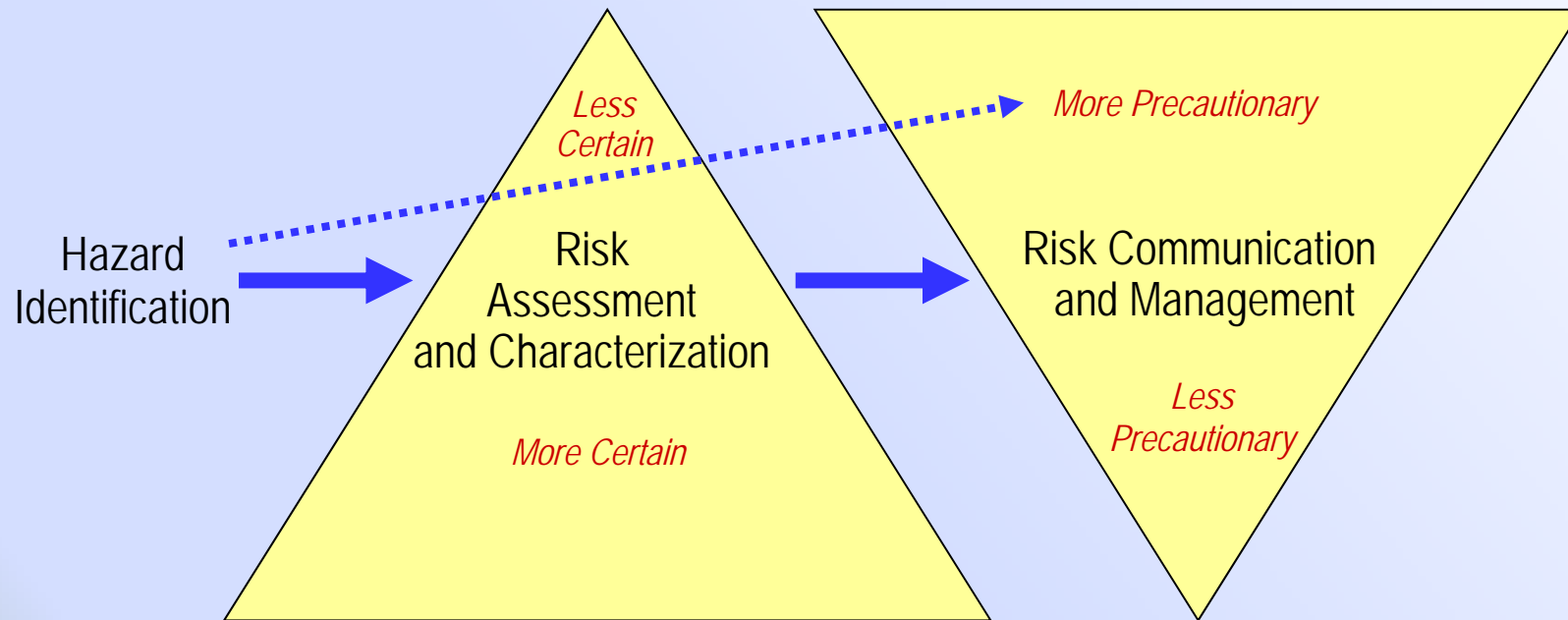


# Recent publications

- Kuempel ED, Geraci CL, Schulte PA. Risk assessment and risk management of nanomaterials in the workplace: translating research to practice. *Ann Occup Hyg.* 56(5):491-505; July 2012.
- Kuempel ED, Castranova V, Geraci CL, Schulte PA (2012). Development of risk-based nanomaterial groups for occupational exposure control. *J Nanopart Res* 14:1029. Published online: 07 August 2012.



# Hazard & Risk Balance



Source: Schulte and Salamanca-Buentello [2007]

# ***NIOSH***

**Thank you!**

**[kmartinez@cdc.gov](mailto:kmartinez@cdc.gov)**

