

# Risk Assessment Approaches for Nanomaterials

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# Outline

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

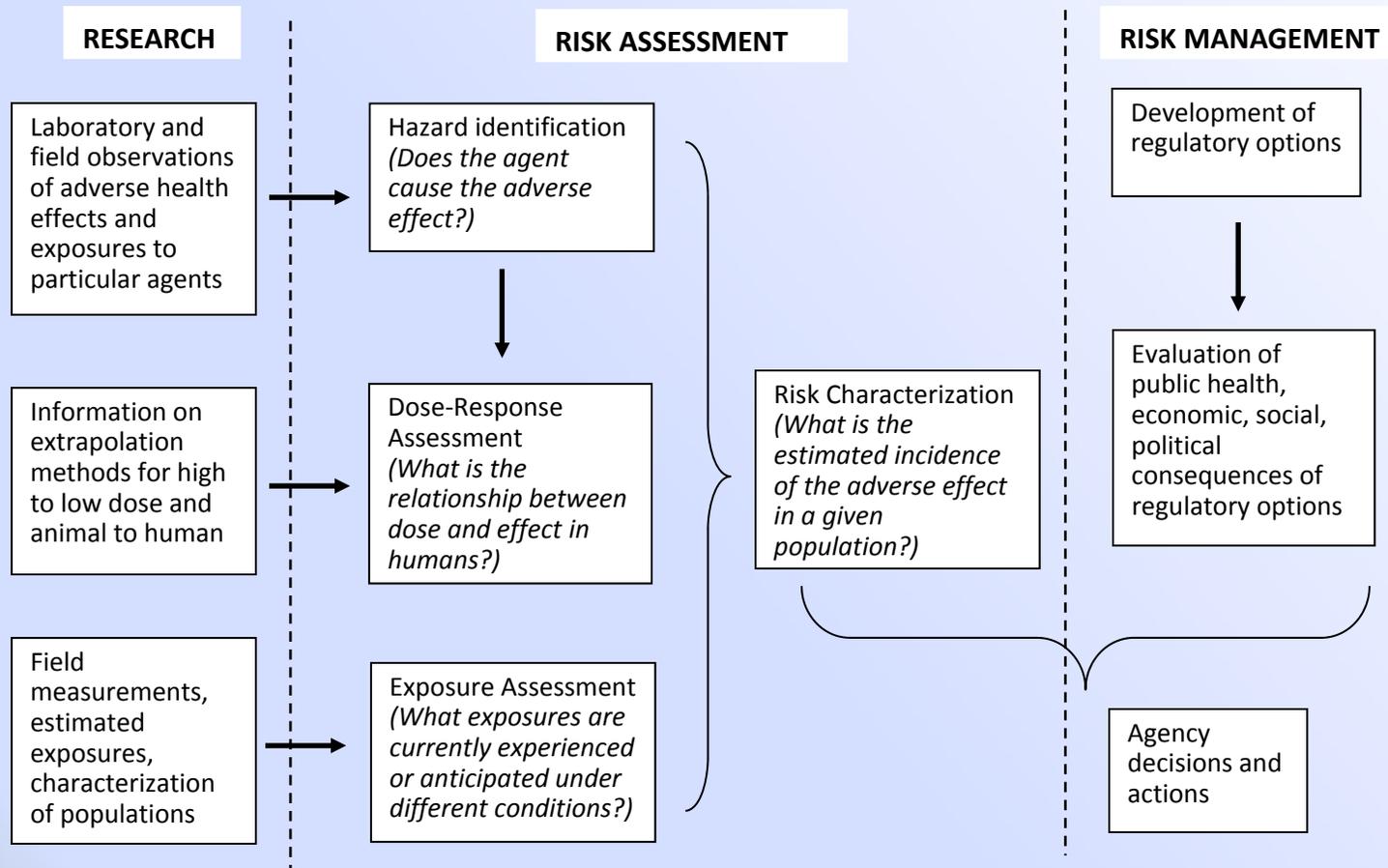
# Are Current OELs Adequately Protective for Workers Exposed to Nanomaterials?

- 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

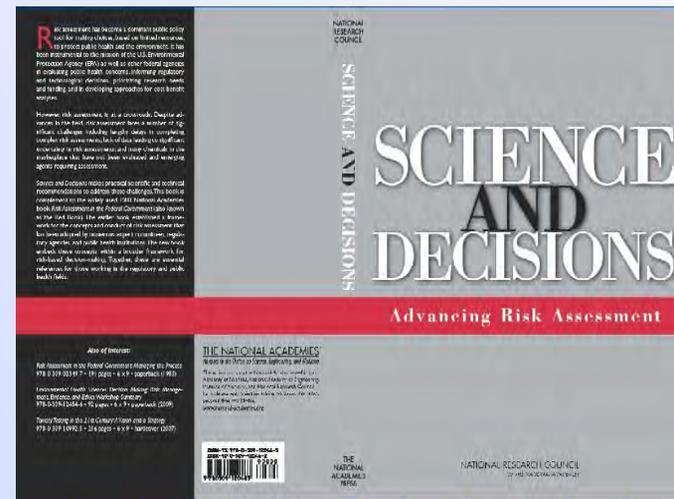
# Risk Assessment Framework in US (NRC 1983)



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

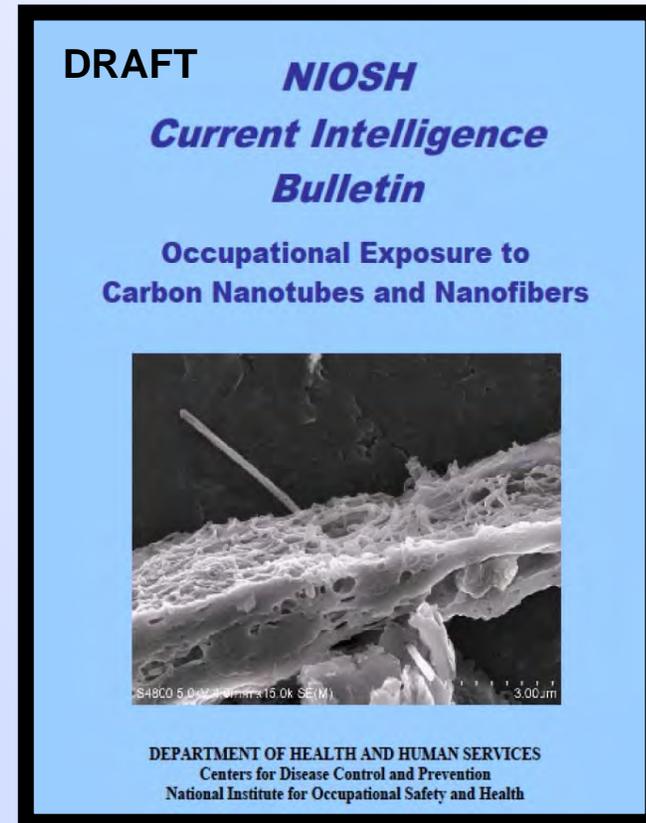
NOAEL: No observed adverse effect level LOAEL: Lowest observed adverse effect level: *pulmonary inflammation & fibrosis*

# 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 (<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

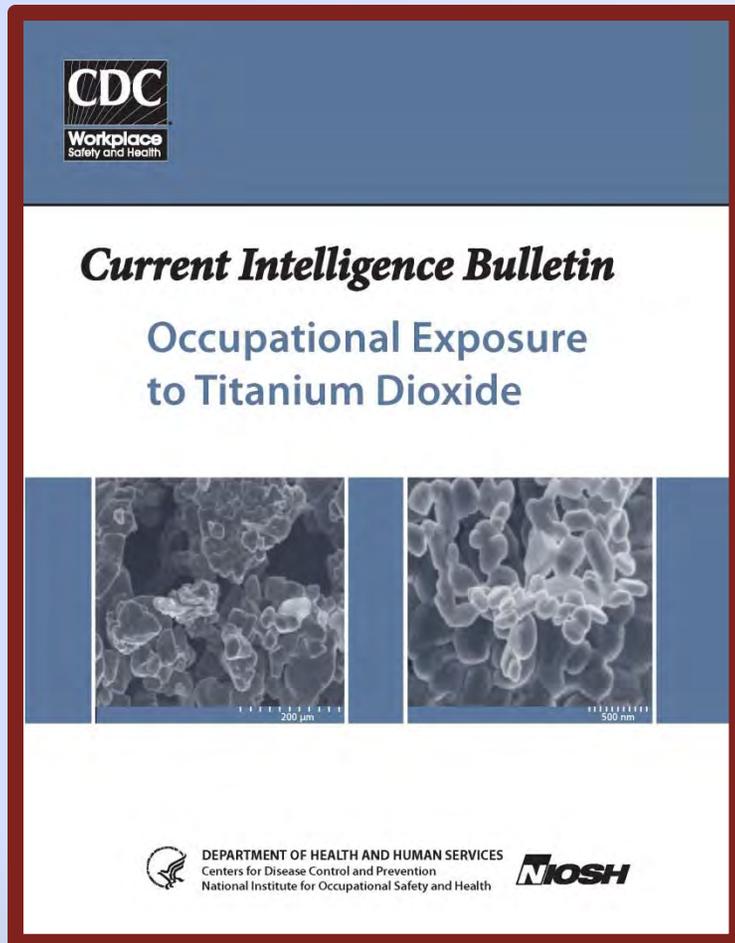
Material & Process	Concentration ( $\mu\text{g}/\text{m}^3$ )*	Reference
SWCNT – pilot production facility	10 - 53	Maynard et al. 2004
MWCNT – research laboratory, before & after controls	37- 434 ND - 39	Han et al. 2008
CNF composite – weighing, mixing, cutting	64 - 1,094	Methner et al. 2007
MWCNT composite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



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*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

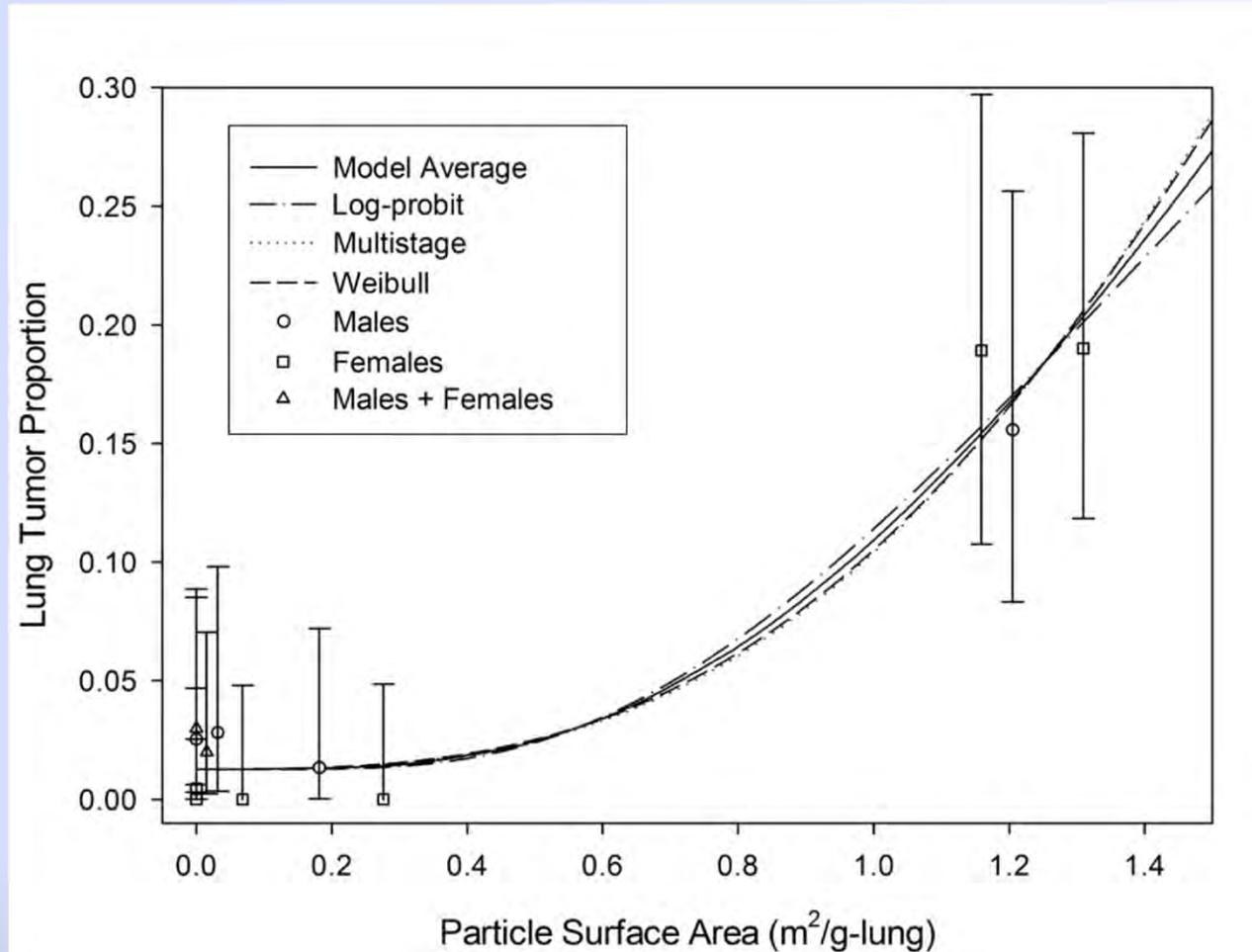
# Titanium Dioxide Risk Assessment: Data Evaluated

- 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>



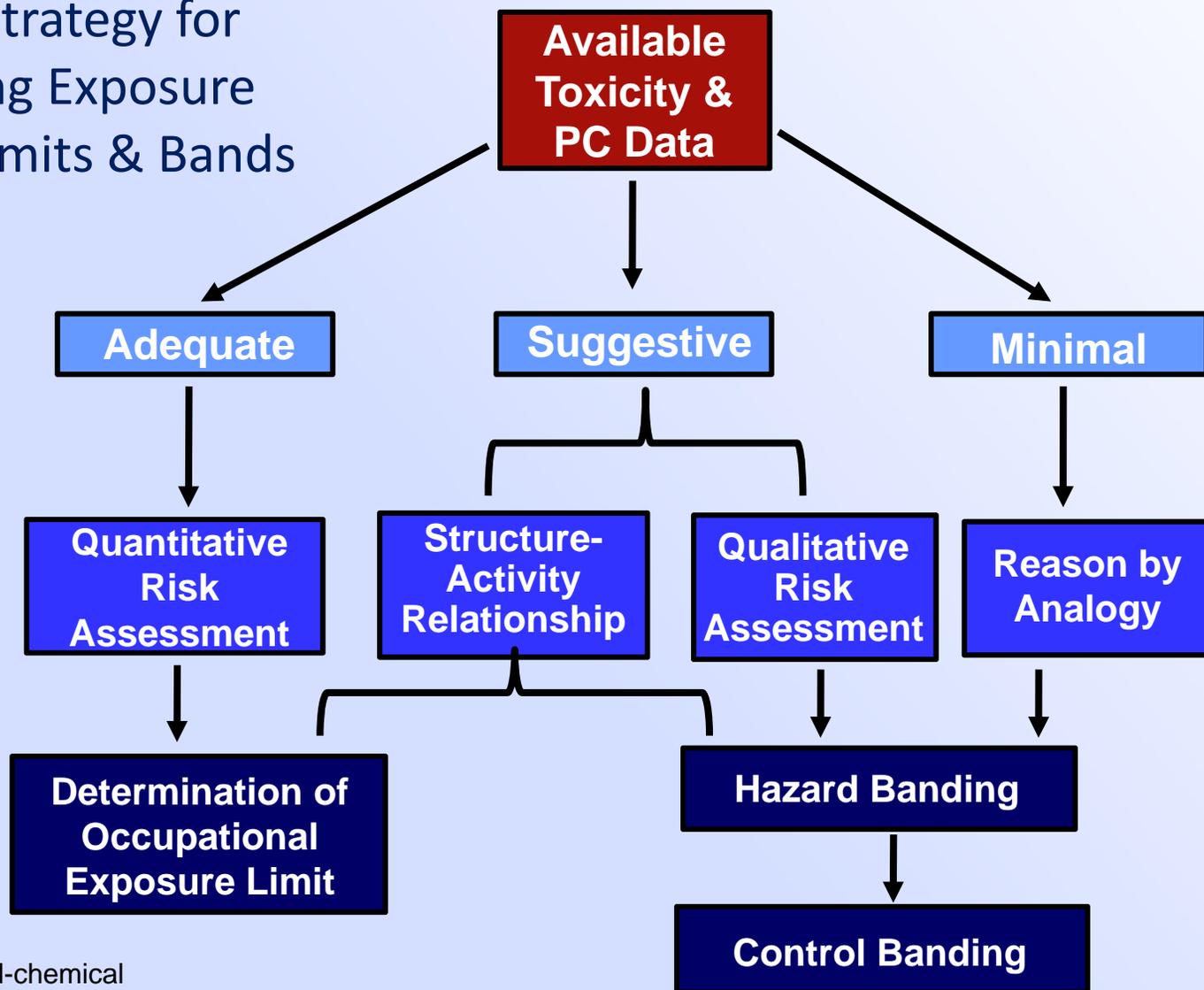
# Hazard Classification for Ultrafine (Nanoscale) $\text{TiO}_2$

- 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

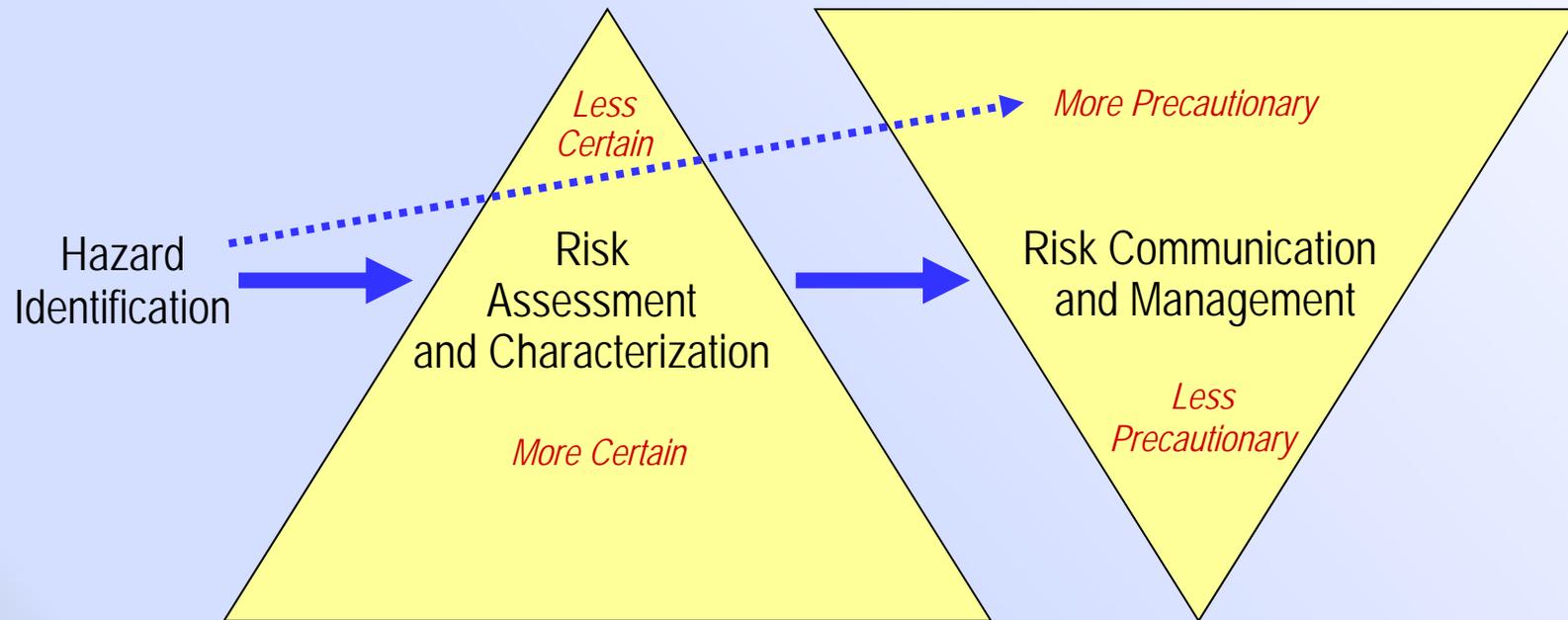
- Risk estimates of CNT & TiO<sub>2</sub> indicate mass-based OELs need to account for particle size & structure
- Effective exposure measurement & engineering controls are essential to protect workers
- Medical monitoring may be warranted to identify early adverse lung effects
- Standardized toxicity 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!**

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