NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

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Risk Assessment Approaches for Nanomaterials

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CDC Workplace Safety and Health

NIOSH

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

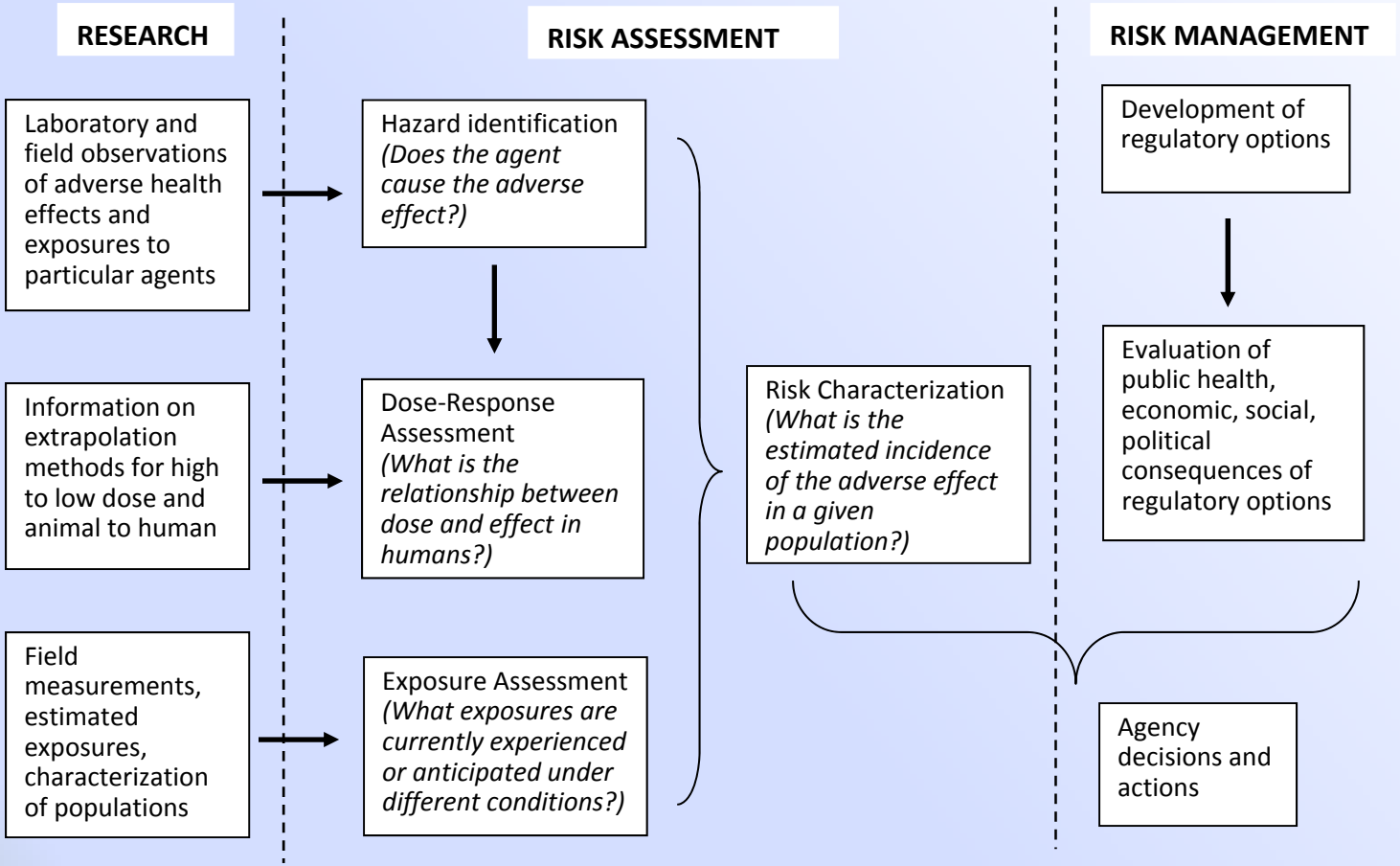
Possible Approaches to Nanomaterials Risk Assessment

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

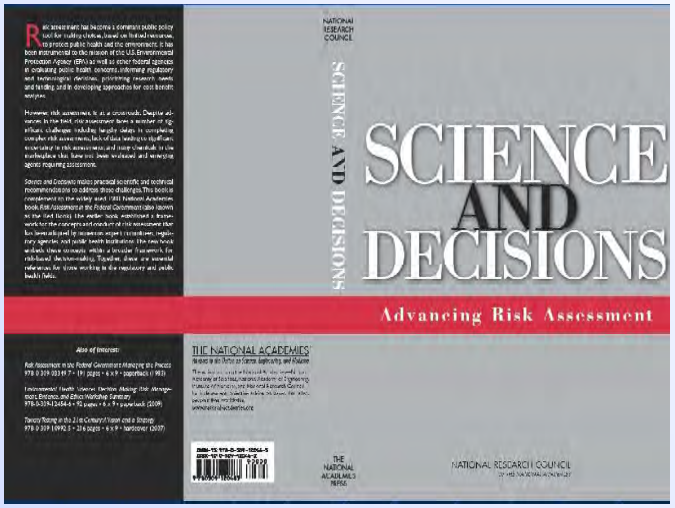
Risk Assessment Framework in US (NRC 1983)



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^3)	LOAEL (mg/m^3)
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*

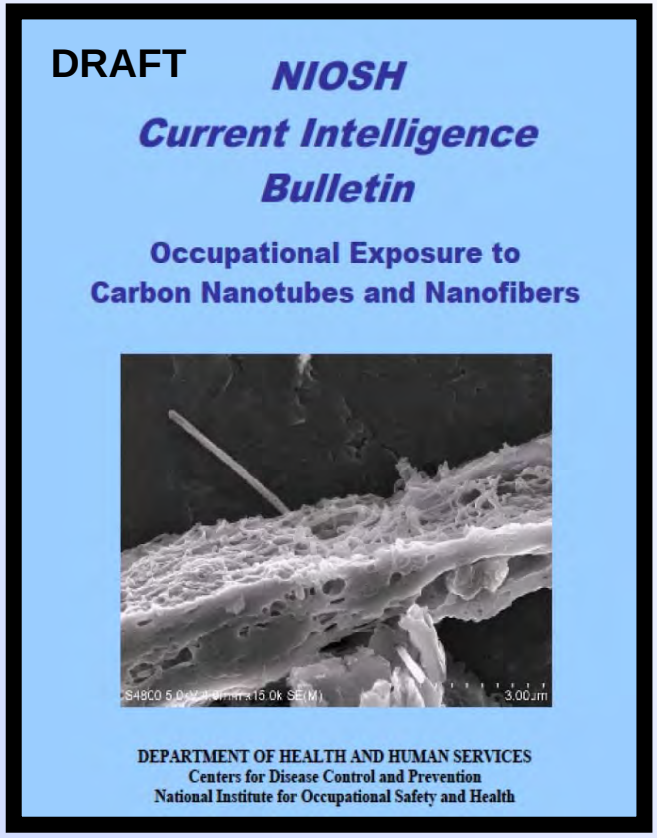
CNT Risk Assessment Findings

- Working lifetime exposure of 0.2–2 µg/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 µg/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]



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Engineering Control Performance Options for Airborne Nanoparticles

Control Technology	Historical Performance ($\mu g/m^3$)
Local exhaust ventilation	<1,000
Ventilated enclosures	10 – 1,000
Containment systems	1 – 10
Closed systems & robotics	<1

Limited CNT Occupational Exposure Data

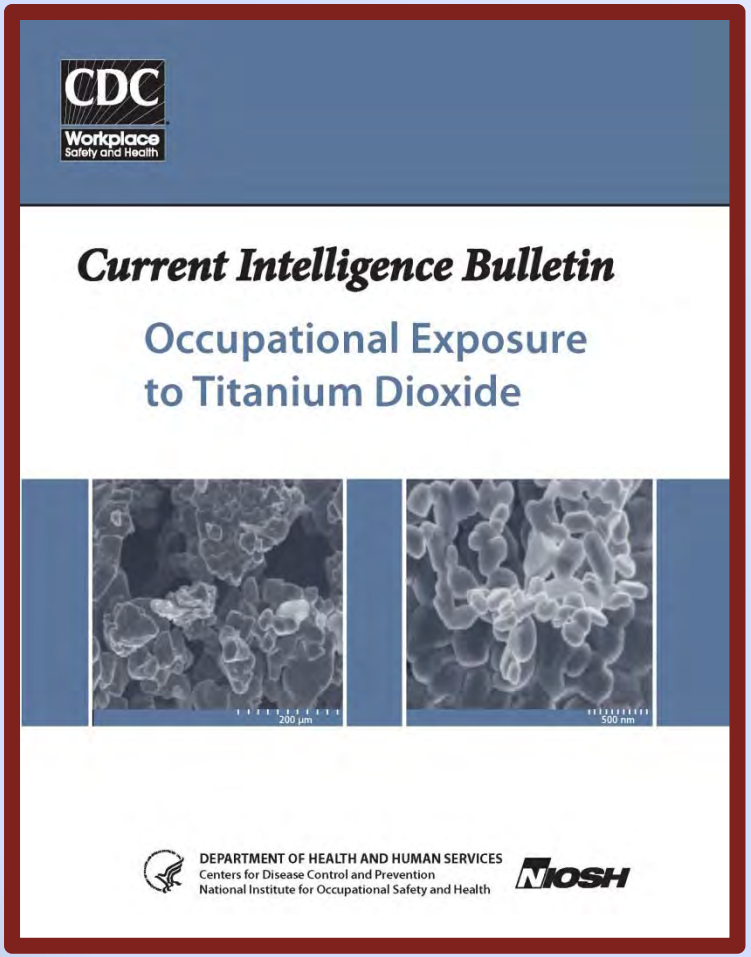
Material & Process	Concentration ($\mu g/m^3$)*	Reference
SWCNT – pilot production facility	10 - 53	Maynard et al. 2004
MWCNT – research laboratory, before & after controls	37- 434 ND - 39	Han et al. 2008
CNF composite – weighing, mixing, cutting	64 - 1,094	Methner et al. 2007
MWCNT composite – wet or 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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- Separate recommended exposure limits (RELs) by particle size:
  - Ultrafine TiO_2: 0.3 mg/m^3
  - Fine TiO_2: 2.4 mg/m^3

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

- Ultrafine TiO_2 classified as potential occupational carcinogen based on rat lung tumor data and secondary genotoxic mode of action.

Particle size fraction definitions (in TiO_2 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 TiO2 [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

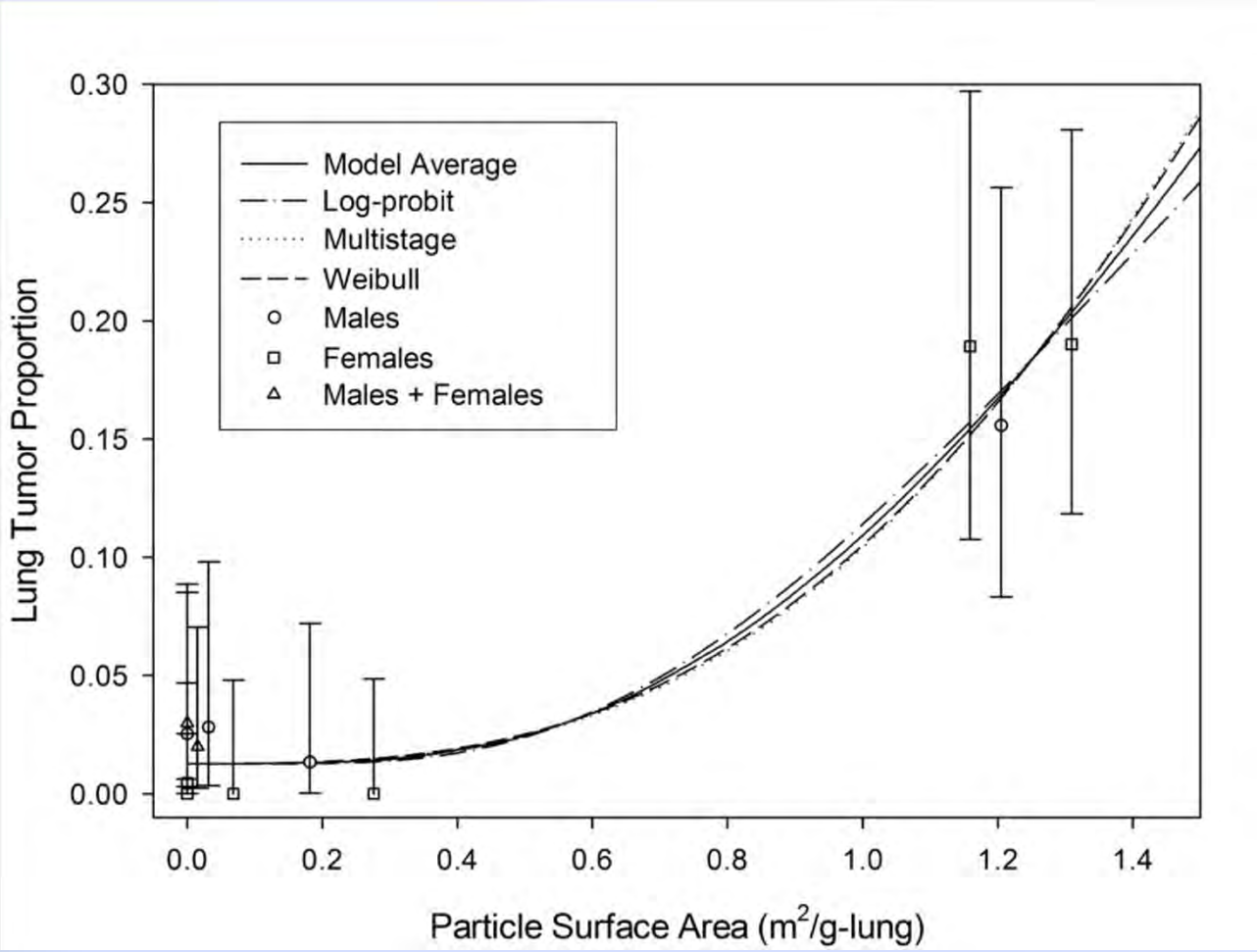
Titanium Dioxide Risk Assessment: Data Evaluated

- Epidemiology studies
  - Elevated lung cancer mortality in one study of TiO_2 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_2: Elevated lung tumors (adenomas) at 250 mg/m^3, but not at 10 or 50 mg/m^3
  - Ultrafine TiO_2: Elevated lung cancer (adenocarcinoma, squamous cell carcinoma) at 10 mg/m^3
- Animal subchronic inhalation studies (rat, mouse)
  - Pulmonary inflammation greater on mass basis from ultrafine than fine TiO_2

Basis for Hazard Classification of Respirable TiO_2

- *In vivo* studies indicate TiO_2 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_2



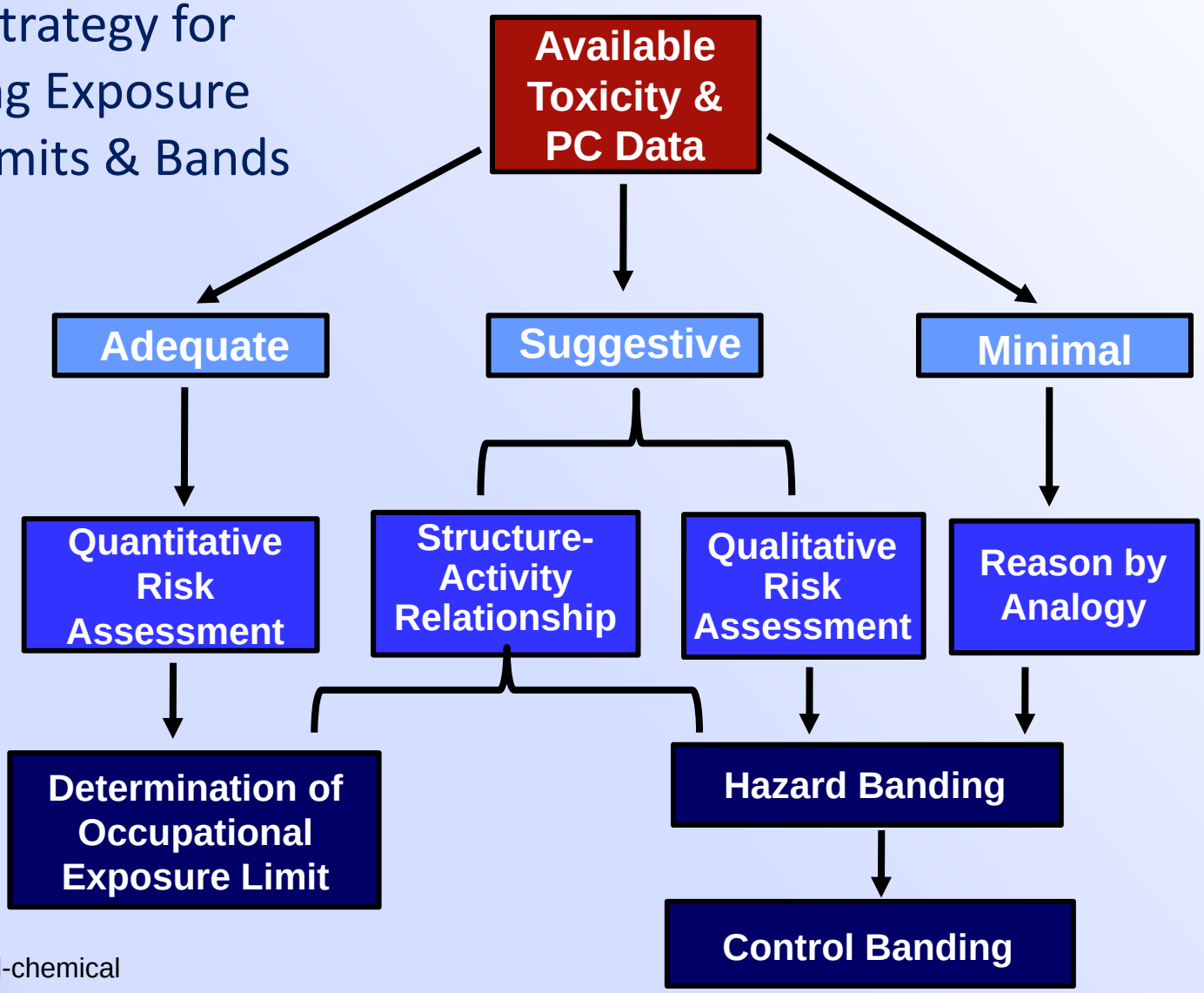
Hazard Classification for Ultrafine (Nanoscale) TiO_2

- Weight of evidence suggests tumor response in ultrafine 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

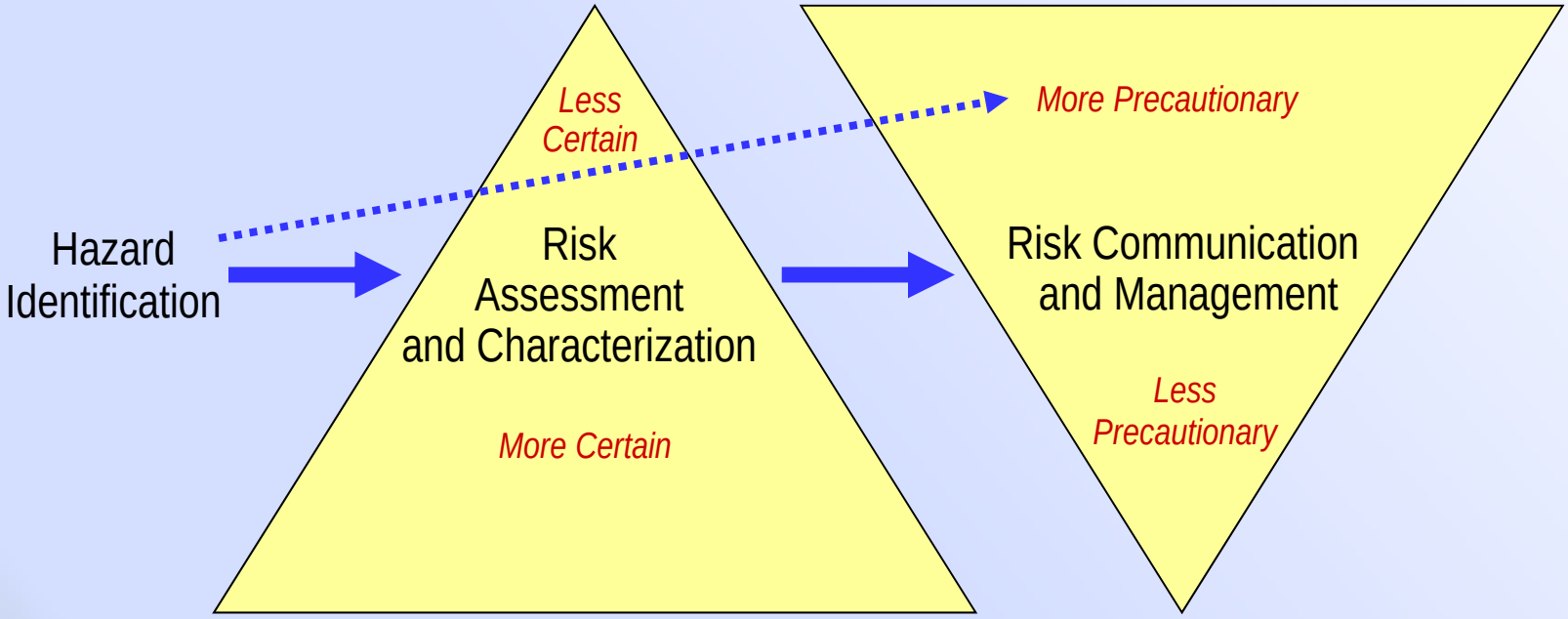
- Risk estimates of CNT & TiO_2 indicate mass-based OELs need to account for particle size & structure
- Effective exposure measurement & engineering controls are essential to protect workers
- Medical monitoring may be warranted to identify early adverse lung effects
- Standardized toxicity testing & 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]

Thank you!

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