Categorical Approaches to Developing OELs

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The Motivation

- Workers worldwide are potentially exposed to nanomaterials during production and use
- Few occupational exposure limits (OELs) have been developed for specific nanomaterials
- Adequacy of existing OELs is often not known
- Categorical OELs approaches may facilitate hazard and risk evaluation for wide variety of nanomaterials

Benefits of Categorical Approach

- More efficient use of data
- Reduced costs and animal use
- Increased sample size
- Greater robustness of results
- Increased biological plausibility for other materials in same mode of action (MOA) category

[OECD, Env/JM/MONO(2007)28]

Categories of Nanomaterials in OECD Toxicity Testing Sponsorship Program

- **Carbon-based**
  - SWCNT, MWCNT, C60
- **Metal oxides**
  - Titanium, aluminum, silicon, cerium, zinc
- **Metals**
  - Iron, silver, gold
- **Dendrimers**
- **Nanoclays**

http://www.oecd.org/dataoecd/33/4/45910320.pdf

Data & Analysis Needs for Categorical OELs

- Determine the relevant MOA categories, physical-chemical properties, & dose metrics influencing bioactivity of nanomaterials
- Identify benchmark (reference) particles* within each category

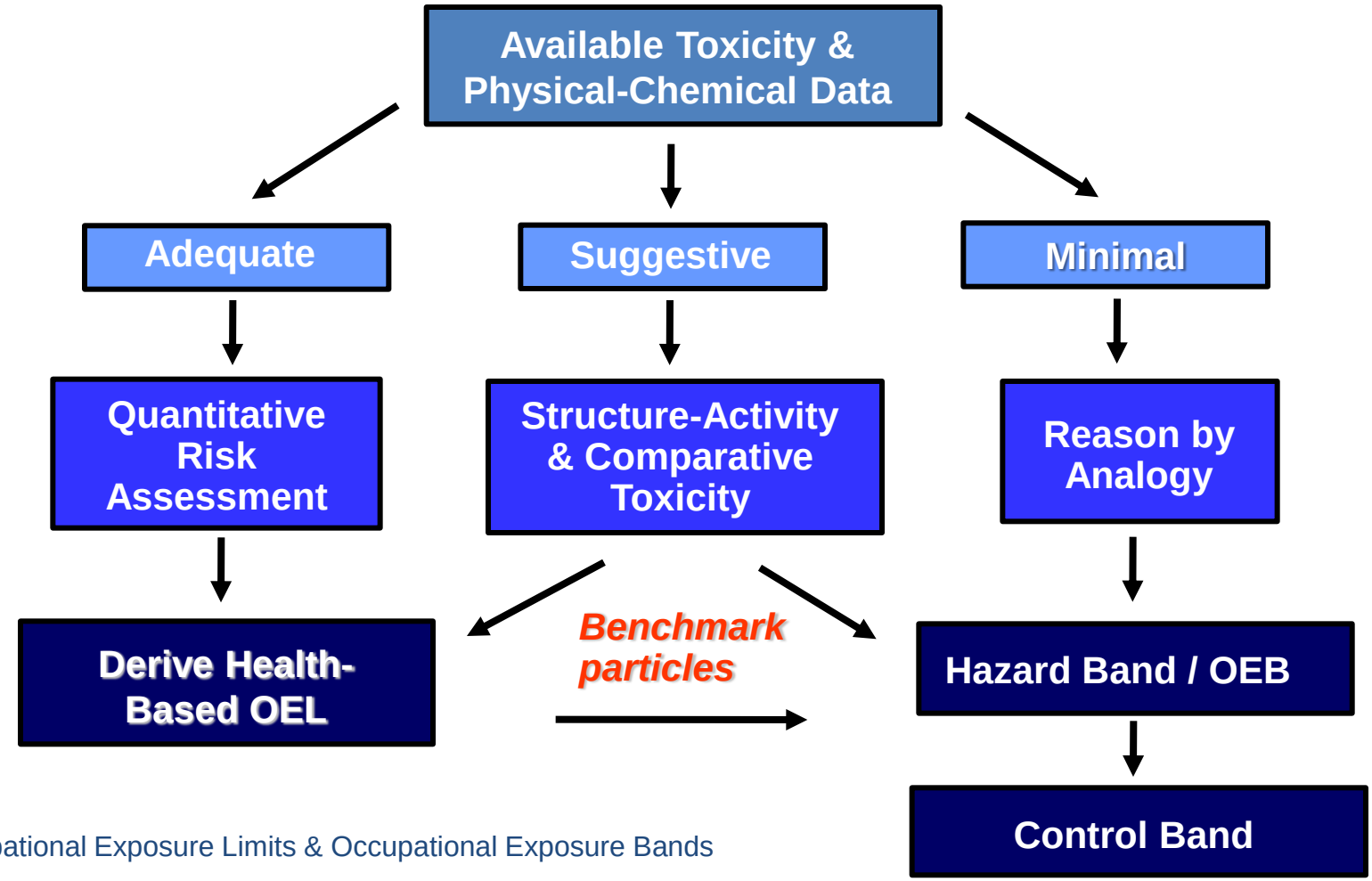
  * i.e., well-characterized materials for which the occupational health risk has been (or could be) quantified & OELs developed
- Develop toxicological & statistical criteria for category assignments

Possible Mode of Action Categories for Nanomaterials*

Parameter	Higher solubility particles	Poorly-soluble, low toxicity particles	Poorly-soluble, high toxicity particles	Fibrous particles
Benchmark particle example	Zinc oxide Copper oxide I	Titanium dioxide Carbon black	Crystalline silica Nickel oxide III Chromium oxide III	Carbon nanotubes & nanofibers
Adverse effects, selected	Acute lung effects Systemic toxicity	Lung inflammation, fibrosis, cancer (rats)	Lung inflammation, fibrosis, cancer	Lung fibrosis, cancer, mesothelioma
Mode of action example	Toxic ions reach systemic tissues	Surface area dose of respirable particles	Reactive surface area dose of respirable particles	Biopersistence Migration to pleural Genotoxicity

[Kuempel et al., JNR 14:1029; 2012]

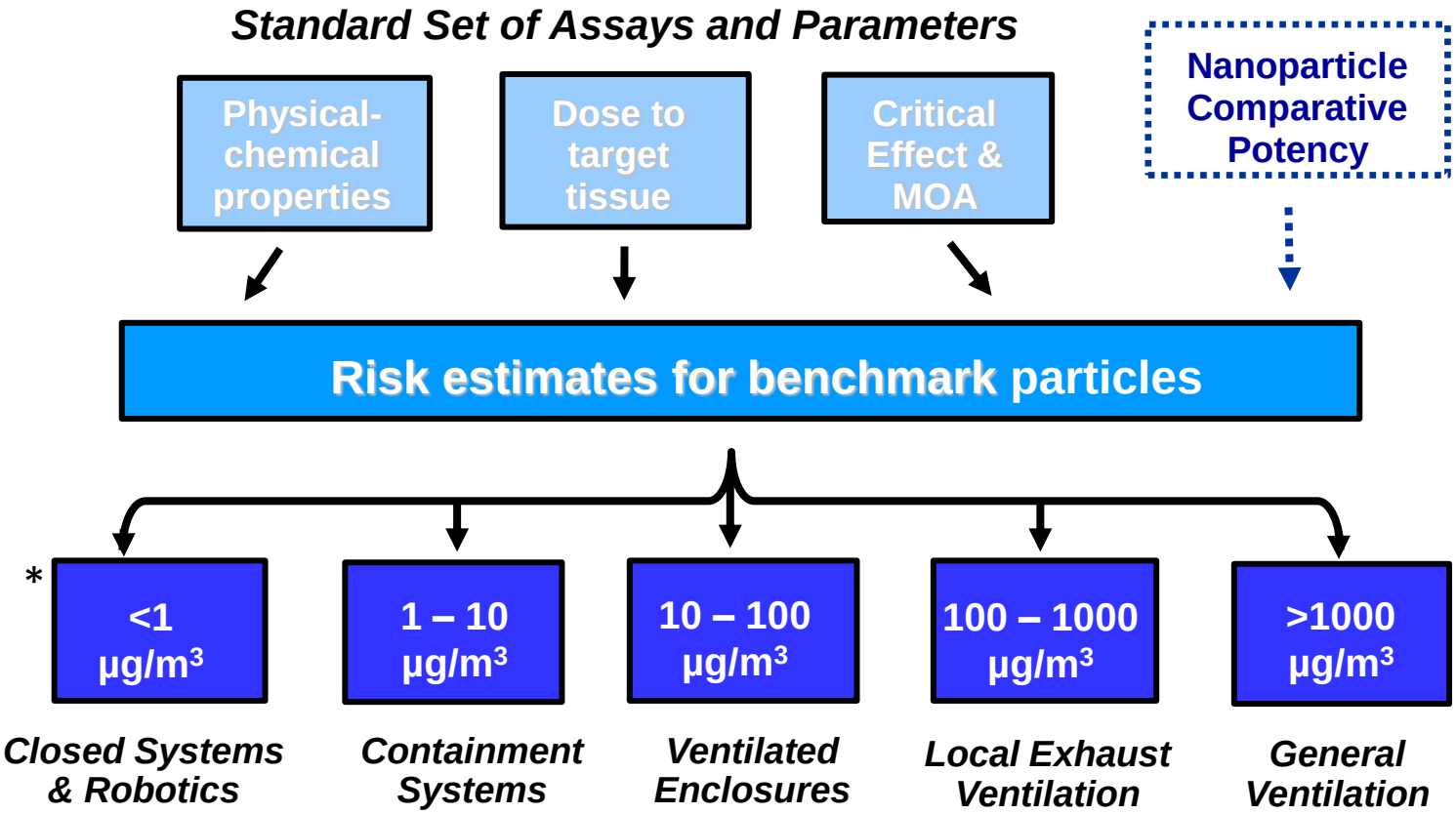
Evidence-based Strategy to Develop OELs & OEBs*



*Occupational Exposure Limits & Occupational Exposure Bands

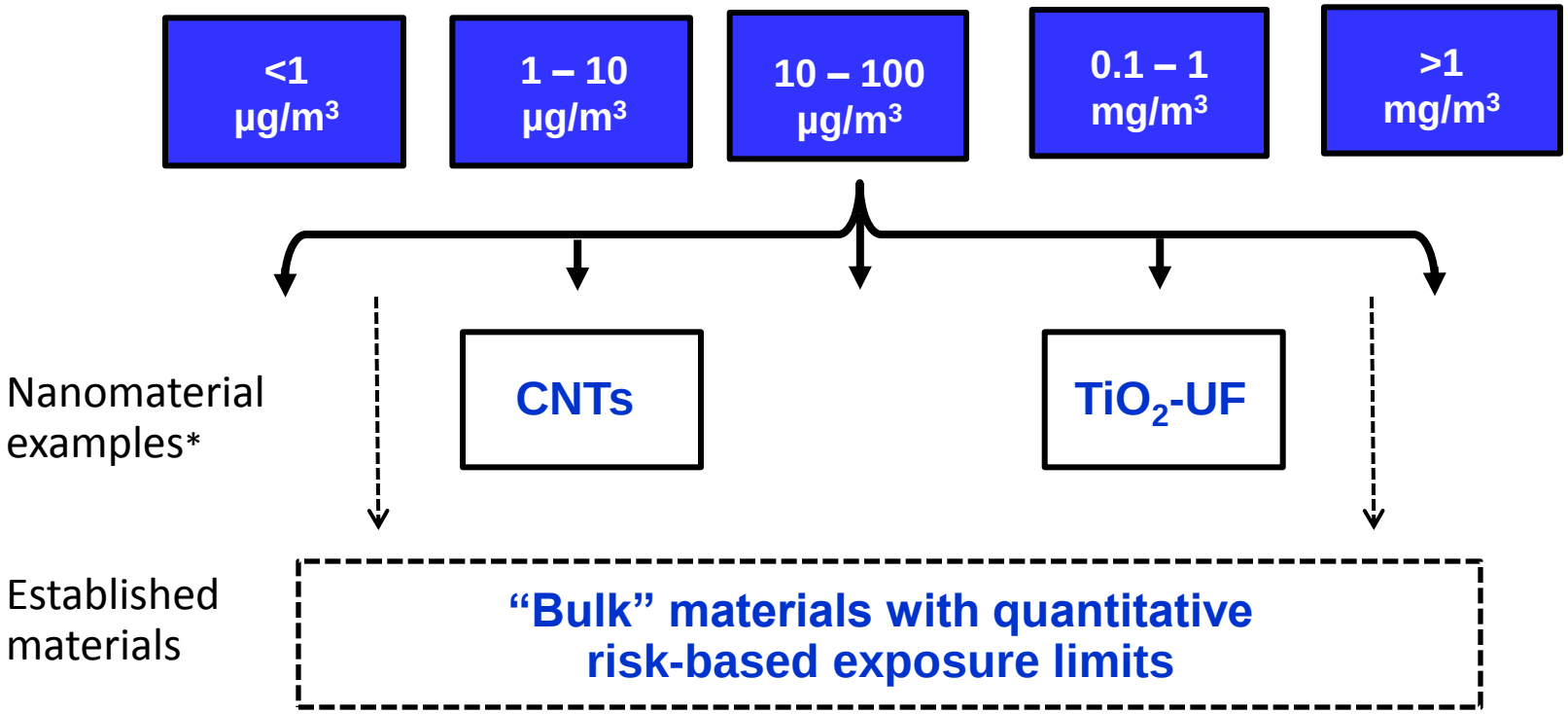
[Schulte et al. 2010; Kuempel et al. 2007, 2012]

Risk Assessment in Hazard & Control Banding



** Exposure control bins based on: Naumann et al. 1996; Ader et al. 2005; Zaik & Nelson 2008; 8-hr TWA concentrations*

Possible Benchmark Particles for Comparative Potency Analyses



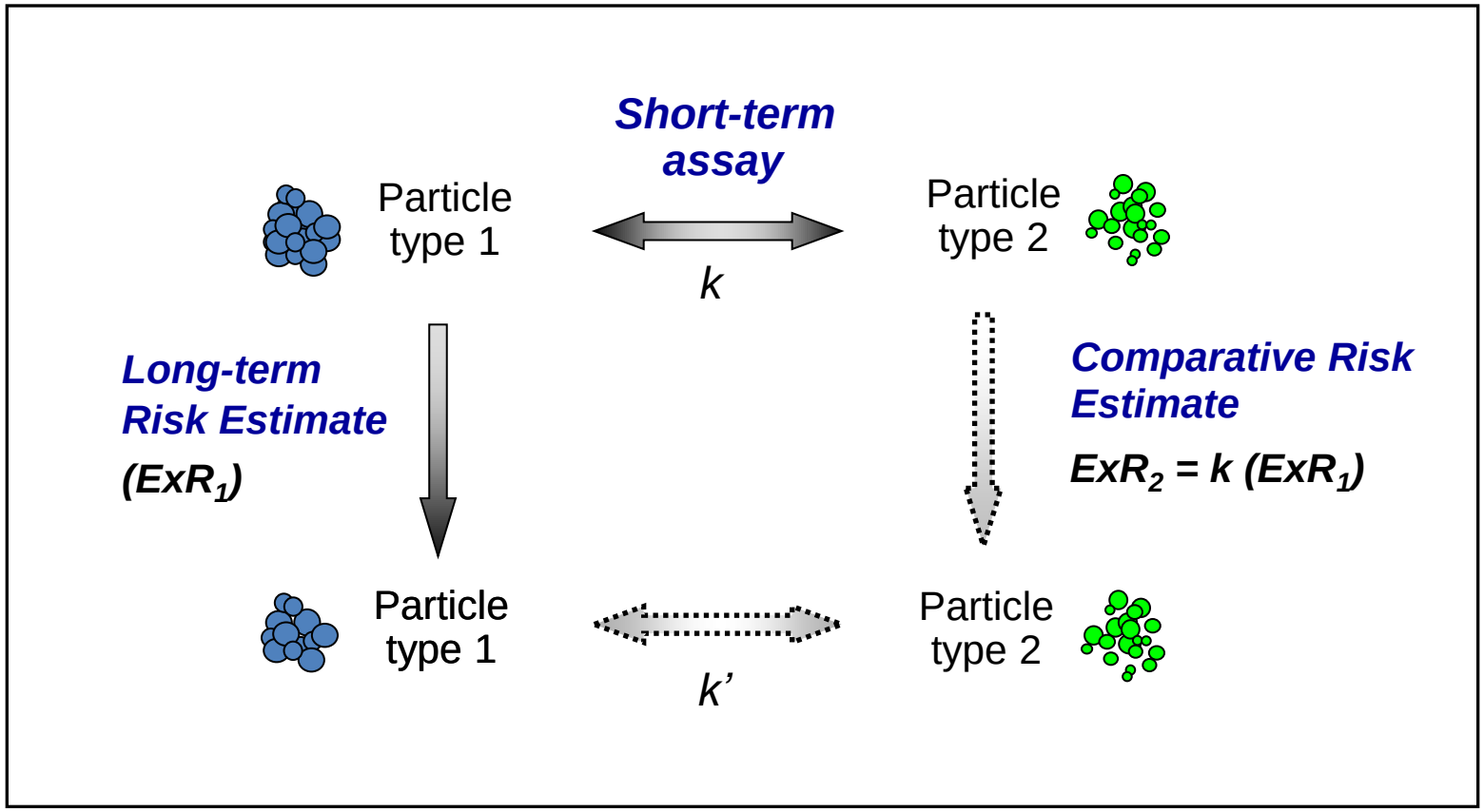
*Categories assigned based on NIOSH recommended exposure limit (REL) of 7 µg/m^3 (draft) for carbon nanotubes (CNTs) and 0.3 mg/m^3 for ultrafine titanium dioxide (TiO_2-UF). Adverse lung effects in animals include pulmonary inflammation & fibrosis (CNT), and lung tumors (TiO_2-UF).

Example OELs for Nanomaterials and Associated Exposure Control Category

Nanomaterial	OEL ($\mu g/m^3$)	Reference	Exposure control bin ($\mu g/m^3$)
TiO_2 – ultrafine	610*	Gamo (2011) Nakanishi (2011)	100 – 1,000
TiO_2 – ultrafine	300	NIOSH (2011)	
Fullerene (C_{60})	390*	Shinohara (2011) Nakanishi (2011)	
MWCNT	50	Pauluhn (2010)	10 – 100
CNT	30*	Nakanishi (2011)	
CNT & CNF	7 (draft)	NIOSH (2010)	1 – 10
MWCNT	1-2	Aschberger et al. (2010)	

* Period-limited (15-yr) OEL.

Comparative Potency Analysis



[Based on: Schoeny & Margosches 1989 ; Sobels 1993; Sutter 1995]

Steps in Developing OELs

- Identify adverse health effects of relevance to humans
- Determine effect level (NOAEL, LOAEL, BMDL) level in animal studies
- Extrapolate to lower (acceptable or feasible) risk level
- Estimate human-equivalent concentration (HEC) in the workplace
- Consider technical feasibility of measuring or controlling exposures (NIOSH RELs)

Effect Levels (in animal study)

- No Observed Adverse Effect Level (NOAEL) & Lowest Observed Adverse Effect Level (LOAEL)
  - Depends on dose spacing & sample size
  - Considers multiple responses
  - Not risk-based, extrapolation to lower doses by uncertainty factors
- Benchmark dose (BMD) estimates
  - Model estimate of dose associated with benchmark response
  - Evaluates shape of dose-response relationship
  - Takes statistical account of sample size & variability
  - Provides standardized, risk-based point of departure (e.g., 10%) for low dose extrapolation

Basic parameters needed for risk assessment of inhaled particles

Parameter	Purpose
• Particle size, shape, density	• Estimate inhalation & lung region-specific deposition fraction
• Particle surface area, reactivity, solubility, etc.	• Evaluate mode of action & effects
• Multiple exposure or dose groups	• Describe dose-response relationship; estimate benchmark dose
• Biological significance of response	• Evaluate severity and relevance to humans
• Body and lung weights; target lung region	• Normalize dose from animals to humans

Utility of Categorical Approach

- Evidence-based strategy to develop initial OELs or OEBs for nanomaterials
- Facilitates development and adoption of standard risk assessment methods
- Provides framework for characterizing relative hazard among nanomaterials and benchmark materials
- Enables systematic evaluation to design safer materials
- Links with existing approaches (e.g., hazard and control banding)

Research Needs

- Standard set of particle descriptors, dose metrics, and response parameters in order to compare mode of action & potency across studies.
- Further development of predictive models, *incl.* short-term to long-term *in vivo* response and multivariate comparisons.
- Chronic dose-response data and validation or refinement of the initial occupational exposure bands.