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Benchmark Approaches to Classifying Nanomaterials

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Key question

How do we translate nanotoxicology research to risk management practice in the workplace?

… through benchmark (reference) materials and standardized bioassays and risk assessment methods.

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Risk Assessment Roles in PtD

- Characterize material hazard using standardized criteria
- Estimate health risk to workers given exposure
- Support PtD in engineering controls
- Evaluate evidence for safer nanomaterials
- Prioritize materials for further testing

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What data are available to assess hazard and risk of nanomaterials?

- Recent *in vivo* and *in vitro* studies reported in the literature (provide relative ranking)
- Existing studies of lung effects from inhaled particles and fibers
  - Animal subchronic and chronic inhalation studies
  - Occupational lung disease data in workers
- Provides benchmark (reference) materials from which to evaluate new nanomaterials

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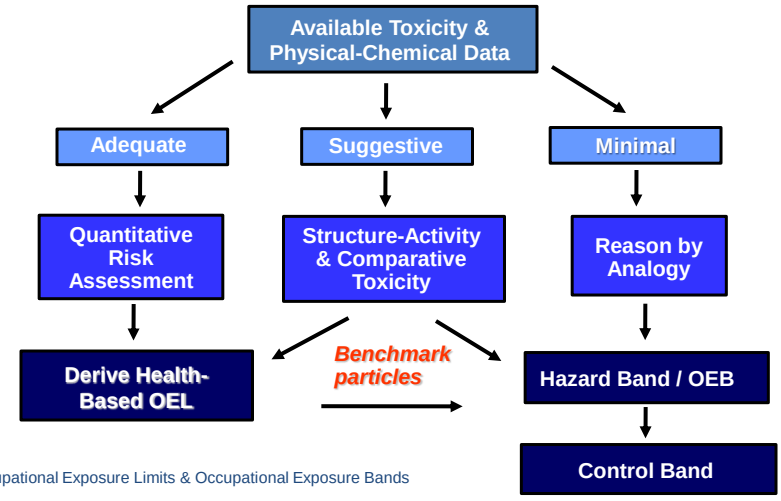
Evidence-based Strategy to Develop OELs & OEBs*



*Occupational Exposure Limits & Occupational Exposure Bands

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

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Example OELs for Nanomaterials and Associated Exposure Control Category

Nanomaterial	OEL (µg/m³)	Reference	Exposure control bin (µg/m³)
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.

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Factors Influencing OELs

- Differences in toxicity of materials
- Differences in risk assessment methods and assumptions, including:
  - Dose adjustment from animals to humans
  - Uncertainty factor selection
- Consideration of feasibility (e.g., limitations in exposure measurement)

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Example 1: Carbonaceous nanoparticles

Effect Levels in Rats after Subchronic (13-wk) inhalation

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 (MWCNT)	--	0.1
Pauluhn et al. [2010a]	Multi-wall carbon nanotubes	**0.1**	0.4

NOAEL: No observed adverse effect level
LOAEL: Lowest observed adverse effect level: *lung inflammation, granuloma, alveolar septal thickening*

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Estimating Human Equivalent Concentration

A human-equivalent concentration (HEC) to an animal effect level or point of departure (POD) (e.g., NOAEL) can be estimated as:*

$$HEC\_POD = POD_{ANIMAL} / DAF$$

where DAF is the dosimetric adjustment factor:

$$DAF = (VE_H/VE_A) \times (DF_H/DF_A) \times (RT_H/RT_A) \times (NF_A/NF_H)$$

and where

VE: Ventilation rate (e.g., total volume of air inhaled per exposure day, m^3/d) in humans (H) or animals (A);
DF: Deposition fraction (e.g., alveolar region of the respiratory tract);
RT: Retention half-time of particles in the lungs; and
NF: Normalization factor for inter-species dose.

* Similar to methods used in EPA [1994] and Pauluhn [2010b]

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Estimates of Human-Equivalent Concentration to the Rat MWCNT NOAEL

$HEC\_POD = 100\ \mu g/m^3 / 2$
$= 50\ \mu g/m^3$ *Pauluhn [2010b]*

$HEC\_POD = 100\ \mu g/m^3 / 27$
$= 4\ \mu g/m^3$ *NIOSH [2010 & ff]*

Differences in dose adjustment factor due to different models used to estimate long-term particle retention in human lungs and interspecies dose normalization.

NOTE: No uncertainty factors have been applied to these estimates

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Example 2: Nickel hydroxide, $Ni(OH)_2$[a]

Acute & subchronic inhalation in mice [Gillespie et al. 2009]

Inhalation exposure duration	Effect level[b]	Animal Ni exposure concentration (µg/m³)	Human equivalent concentration (HEC) (µg/m³)[c]	Ratio HEC/REL[d]	Ratio HEC/PEL[e]
1 d, 4 hr	NOAEL	65	48	0.3	~20
	LOAEL	358	337	0.04	3
3 mo, 5 hr/d	AEL	82	90	0.2	~10

[a] 40 nm count median diameter
[b] NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level; AEL: adverse effect level
[c] 8-hr time-weighted average (TWA), estimated in following slide.
[e] **NIOSH REL (nickel metal and other compounds, as Ni) (8-hr TWA) (Ca): 0.015 mg/m³**
[e] **OSHA PEL (8-hr TWA): 1 mg/ m³**

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Human equivalent concentration (HEC) estimate of nickel hydroxide

HEC (µg/m³) = animal exposure (µg/m³)
x air inhaled per exposure day (A/H)
x alveolar deposition fraction (A/H)
x alveolar surface area (H/A)

90 µg/m³ = 82 µg/m³
x (0.0013 m³/hr x 5 hr) / 9.6 m³/d
x (0.2/0.25)
x (102 m²/0.05 m²)

Animal (A); Human (H). Mouse body weight: 22.5g; Minute ventilation: 0.022 L/min = 0.0013 m³/hr [Raabe et al. 1988]. Mouse alveolar deposition fraction reported in Gillespie et al. [2009]. Human alveolar deposition fraction estimated from MPPD 2.1 [ARA 2011]. Alveolar epithelial surface area from Stone et al. [1992].

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Observations on nickel hydroxide

- OSHA PEL is too high based on this study
  - Several times higher than estimated HEC, which caused acute or subchronic pulmonary inflammation in mice.
- NIOSH REL is more health protective
  - ~3x lower than the rat acute NOAEL and ~5x lower than AEL at 3 months, but is this a sufficient margin of safety?
- Uncertainty factors applied to the POD typically on the order of 100 -1000
  - e.g., 3-10 times each for animal to human extrapolation, subchronic to chronic exposure, human inter-individual variability, and (LO)AEL vs. NOAEL.

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Observations on nickel hydroxide *(contd.)*

- $Ni(OH)_2$ is highly soluble
  - by 24 hr, 86% and 96% of the starting material was dissolved at pH 7.4 and 4.5, respectively.[a]
- Yet the retained lung dose increased with exposure
  - At 1 wk, 3 mo, or 5 mo: 148, 559, 925 ng Ni/g lung tissue, respectively.[a]
- Lung retention kinetics were not considered in this example, but should be for chronic risk estimation

[a] Gillespie et al. [2009]

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Research ⟹ Guidance ⟹ Practice

- Workers are currently producing and using nanomaterials, yet most do not have specific OELs.
- Industrial hygienists use OELs to evaluate the efficacy of exposure controls.
- Toxicology data translation to worker health risk requires standardized assays & methods.
- Relative ranking as well as absolute risk estimates (e.g., based on benchmark particles) are needed.

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