Traditional Quantitative Substance-by-Substance Methods for Establishing Occupational Exposure Guidelines

Nano OEL Workshop
The George Washington University
Washington, D.C.
September 10-11, 2012

Alison Elder
Department of Environmental Medicine
University of Rochester
Exposure Guidelines for Airborne Chemicals Encountered in the Workplace

- Threshold Limit Values (TLVs®)
- Workplace Environmental Exposure Levels (WEELs)
- Permissible Exposure Limits (PELs)
- Recommended Exposure Limits (RELs)
- MAKs (Germany, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)
- Industry-specific exposure limits
Quantitative Approach for Protecting Occupational Health: Threshold Limit Values

- TLVs® are derived through a weight-of-evidence approach by a committee of industrial hygienists, occupational physicians, epidemiologists, and toxicologists.
- TLVs® are recommended levels at which nearly all workers can be exposed without experiencing adverse effects.
Quantitative Approach for Protecting Occupational Health: Threshold Limit Values

- TLVs® are derived through a weight-of-evidence approach by a committee of industrial hygienists, occupational physicians, epidemiologists, and toxicologists.
- TLVs® are recommended levels at which nearly all workers can be exposed without experiencing adverse effects.
- TLVs® are not derived through a consensus process or with reference to a legal framework.
- TLVs® are not enforceable exposure limits and should not be used as such.
Quantitative Approach for Protecting Occupational Health: Threshold Limit Values

- Routes of exposure of greatest concern: inhalation and dermal
- Animal exposure-dose-response studies: acute, subchronic, chronic
- Human studies (case reports, epidemiology, carcinogenicity)
- Genotoxicity/carcinogenicity
- Reproductive/developmental toxicity
- ADME

NOAELs for endpoints of greatest concern (mg/m³)
But … There Are Challenges to Implementing this Approach with Engineered Nanomaterials

- Exposure characterization
- Utility of existing database for the same physicochemical form with a bigger size, i.e. ‘bulk’ material
- Quality of existing studies regarding nanoscale materials (difficult to establish dose-response relationships)
Challenges for Implementation: Exposure Characterization

GOAL

Concentration

(Personal) Exposure

Dose

Response
Challenges for Implementation: Exposure Characterization

- Exposure ‘identity’ (what is sampled?)
- Exposure concentration ... which metric to use?
- Need area and personal sampling data for mass and number concentrations
  - and finer detail regarding size distributions for both metrics
Silicon Nanoparticle Exposure Characterization in a Pilot Facility

Wang et al., 2012
Challenges for Implementation: Exposure Characterization

- What is being sampled or measured?

Pauluhn et al., 2011; Poland et al., 2008
How Do We Overcome This Problem?

- Morphological characterization (e.g., TEM, SEM, STEM)
- Chemical characterization (e.g., AES/AAS, EDX, EELS, XRD, IR, UV/Vis)

But … not very quantitative themselves and sampling can be inefficient
Which Metric?: TiO$_2$-Induced Lung Inflammation following Intratracheal Instillation Exposure

Oberdörster et al., 2005
Challenges for Implementation: Exposure Characterization

<table>
<thead>
<tr>
<th>Workplace</th>
<th>Process</th>
<th>Sampling site</th>
<th>Sampling time (min)</th>
<th>Sampling volume (L)</th>
<th>Mass concentration (mg/m³)*</th>
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*Total suspended particulate concentrations were reported.

Lee et al., 2011
Challenges for Implementation: Exposure Characterization

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Lee et al., 2011
Challenges for Implementation: Exposure Characterization

Concentration → Exposure → Dose → Response
Challenges for Implementation: Quality of existing studies

- Animal studies are often conducted using high dose rate, bolus delivery instead of inhalation
Percent PMN Response:
Instillation vs. Inhalation Exposure
(inhalation: 4 hrs at 33 mg/m³)

Baisch et al., unpublished data
Challenges for Implementation: Quality of existing studies

- Animal studies are often conducted using high dose rate, bolus delivery instead of inhalation
- Many reports are from short-term exposures
- Many reports are from single-dose experiments
So, What Should Be Done?
(if we accept that traditional methods will fail us)

- Develop provisional mass-based TLVs (substance specific or by groups?) that account for:
  - Intended use and anticipated exposures
  - Available data about morphology, surface chemistry/reactivity, solubility, surface area
  - Available short-term in vivo and in vitro toxicity data

- Validate and refine approach through prioritized and targeted research to:
  - Develop confidence in exposure measurement and characterization techniques
  - Develop short-, intermediate-, and long-term exposure-response relationships and biokinetics data with acellular and in vitro testing complementarity for unknown nanomaterials \textit{in comparison to benchmark nanomaterials}