# 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

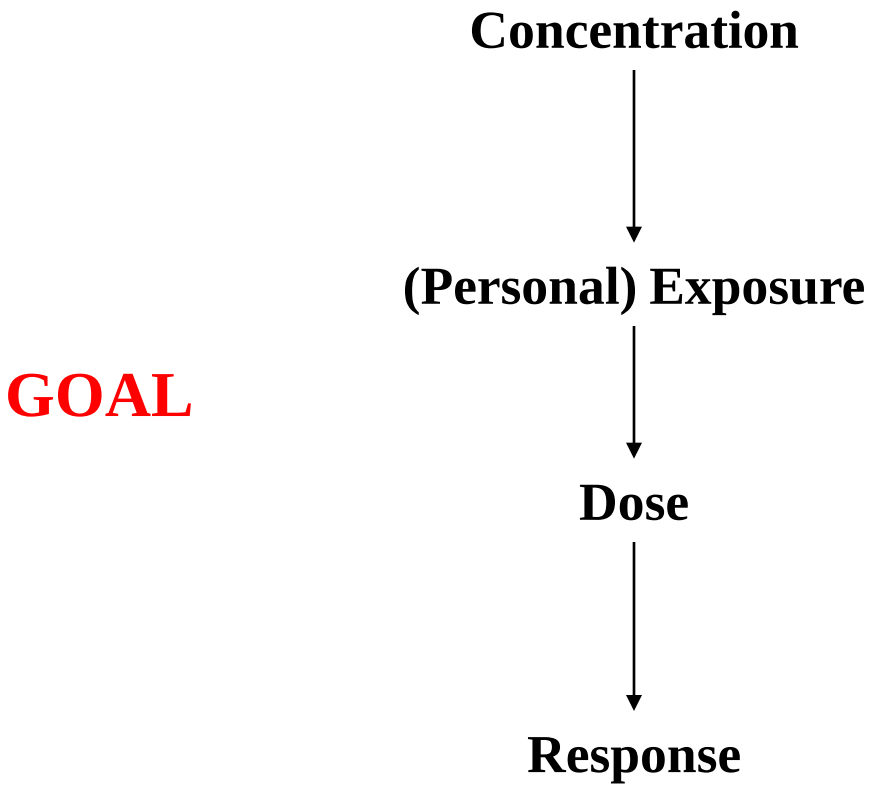
- Routes of exposure of greatest concern: inhalation and dermal
- Animal exposure-dose-response studies: acute, subchronic, chronic
- Human studies (case reports, epidemiology, carcinogenicity)
- Genotoxicity/carcinogenicity
- Reproductive/developmental toxicity
- ADME

**NOAELs for endpoints of greatest concern ($mg/m^3$)**

# 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)

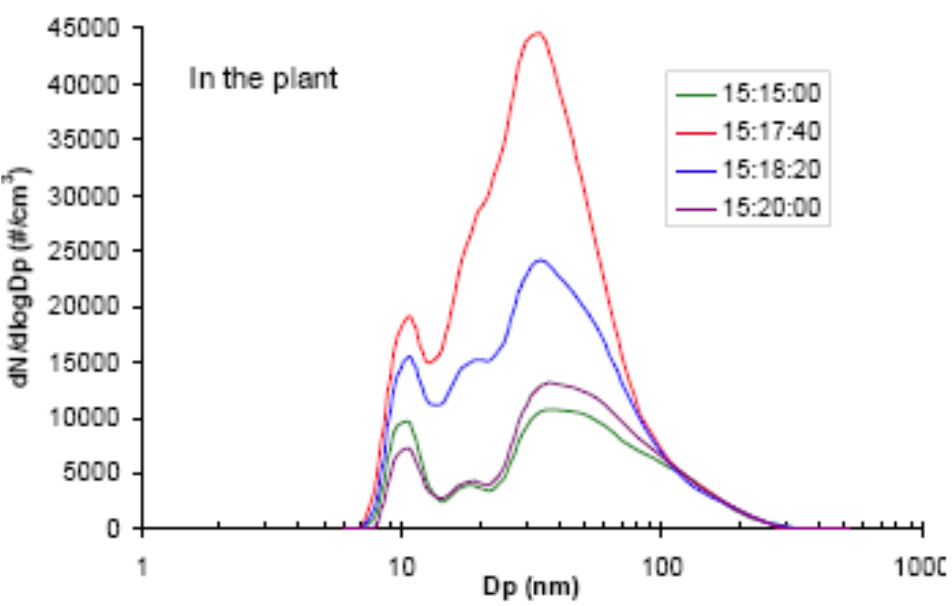
# Challenges for Implementation: Exposure Characterization

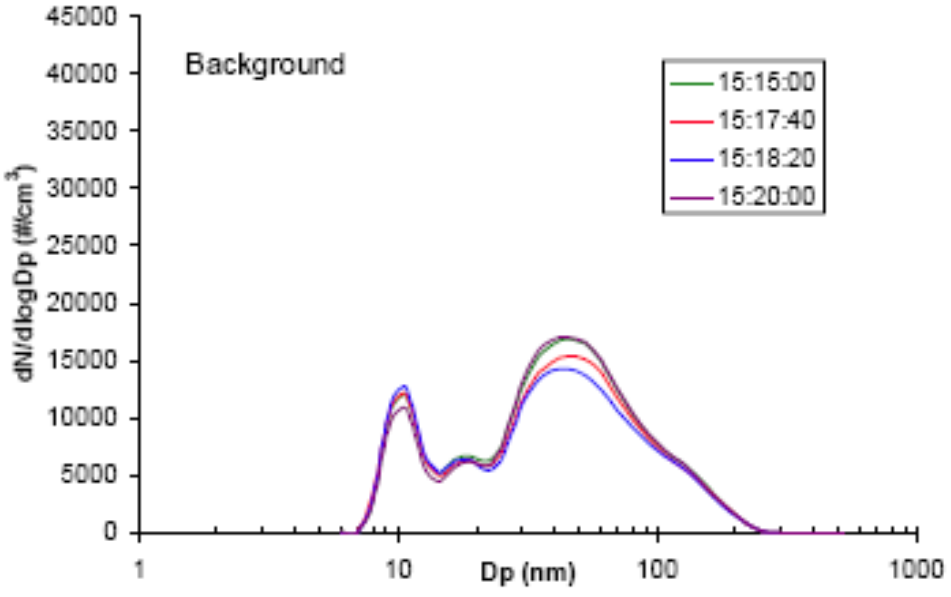


# Challenges for Implementation: Exposure Characterization

- 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

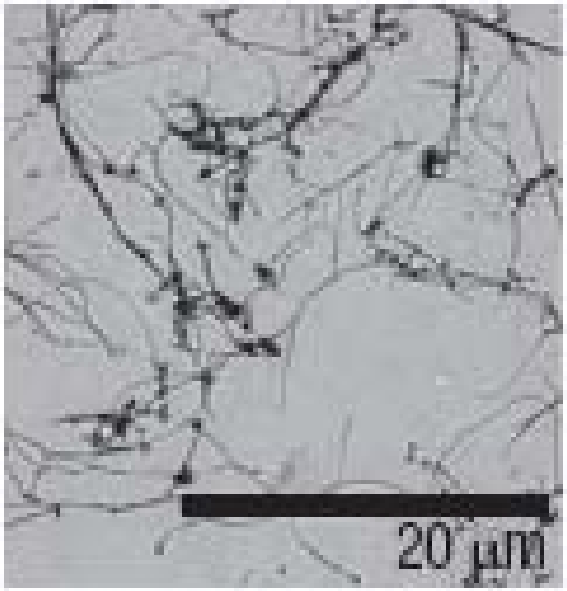


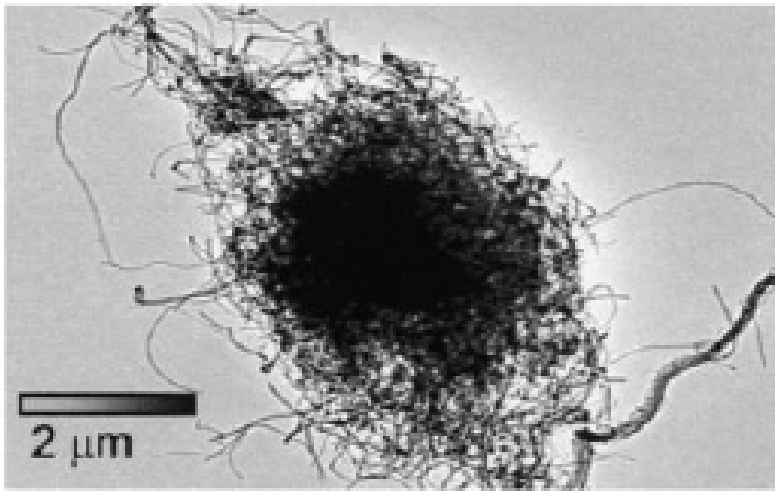




*Wang et al., 2012*

# Challenges for Implementation: Exposure Characterization

- What is being sampled or measured?



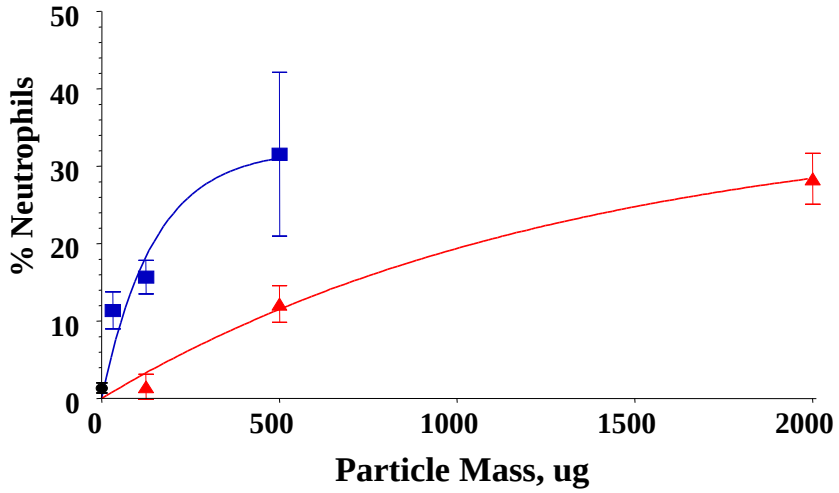

*Pauluhn et al., 2011; Poland et al., 2008*

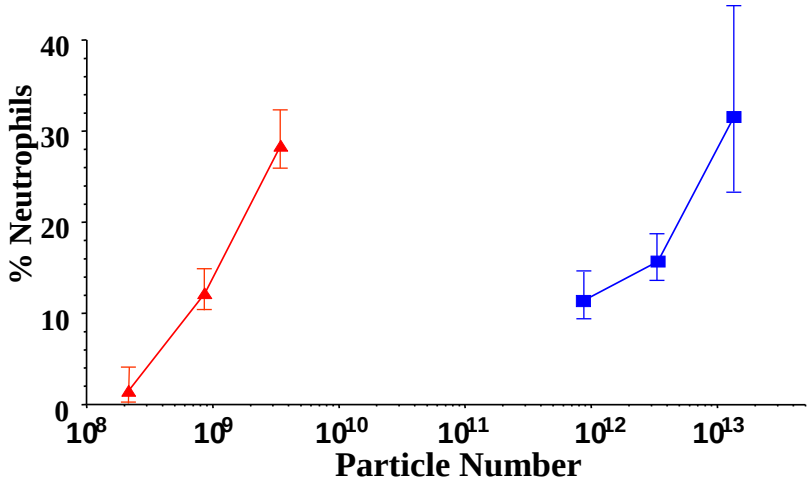
# How Do We Overcome This Problem?

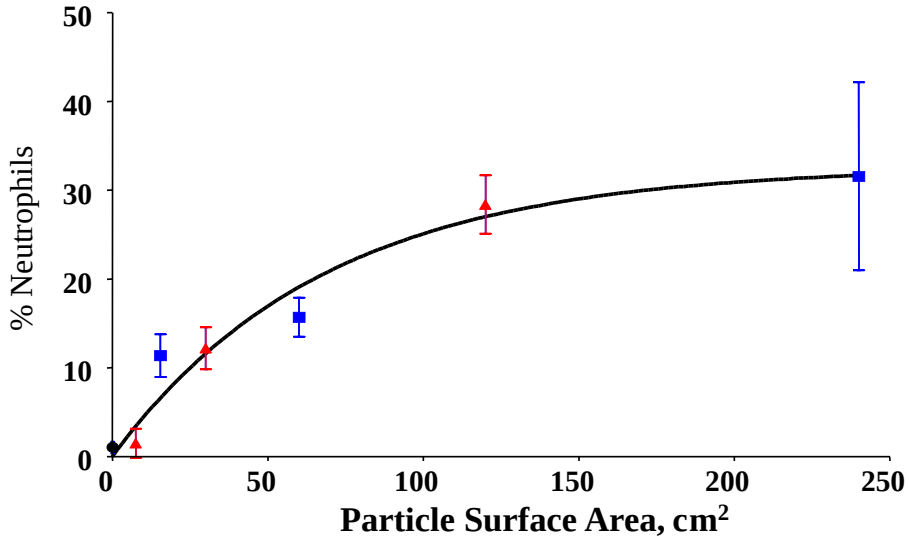
- Morphological characterization (e.g., TEM, SEM, STEM)
- Chemical characterization (e.g., AES/AAS, EDX, EELS, XRD, IR, UV/Vis)

- But … not very quantitative themselves and sampling can be inefficient

# Which Metric?: $TiO_2$-Induced Lung Inflammation following Intratracheal Instillation Exposure




▲ Fine $TiO_2$ (200 nm)
■ Ultrafine $TiO_2$ (25 nm)
● Saline

*Oberdörster et al., 2005*

# Challenges for Implementation: Exposure Characterization

| Workplace | Process | Sampling site | Sampling time (min) | Sampling volume (L) | Mass concentration ($mg/m^3$)* |
|---|---|---|---|---|---|
| Workplace A | During reactor operation | Area 4 | 298 | 595.4 | 0.50386 |
| | | SKC 1 | 185 | 1299.5 | 0.33090 |
| | | Area 5 | 296 | 585.2 | 0.63227 |
| | | SKC 2 | 292 | 2051 | 0.11702 |
| | During powder collection | Area 3 | 18 | 36.1 | 4.99251 |
| | | Area 6 | 20 | 39.7 | 3.27456 |
| | | SKC 3 (personal) | 30.9 | 216.6 | 0.55402 |
| Workplace B | During operation | Area 3 | 350 | 701.1 | 0.29955 |
| | | SKC 3 | 317 | 2222 | 0.15752 |
| | | Area 6 | 322 | 630.8 | 0.15853 |
| | | SKC 2 | 315 | 2210 | 0.09502 |
| | | Area 4 | 263 | 525.5 | 0.89443 |
| | | Cyclone 8 | 312 | 754.7 | 0.30475 |
| | | Cyclone 7 | 313 | 756.8 | 0.18498 |
| | Only during collection | SKC 1 | 47.8 | 334.6 | 0.47818 |

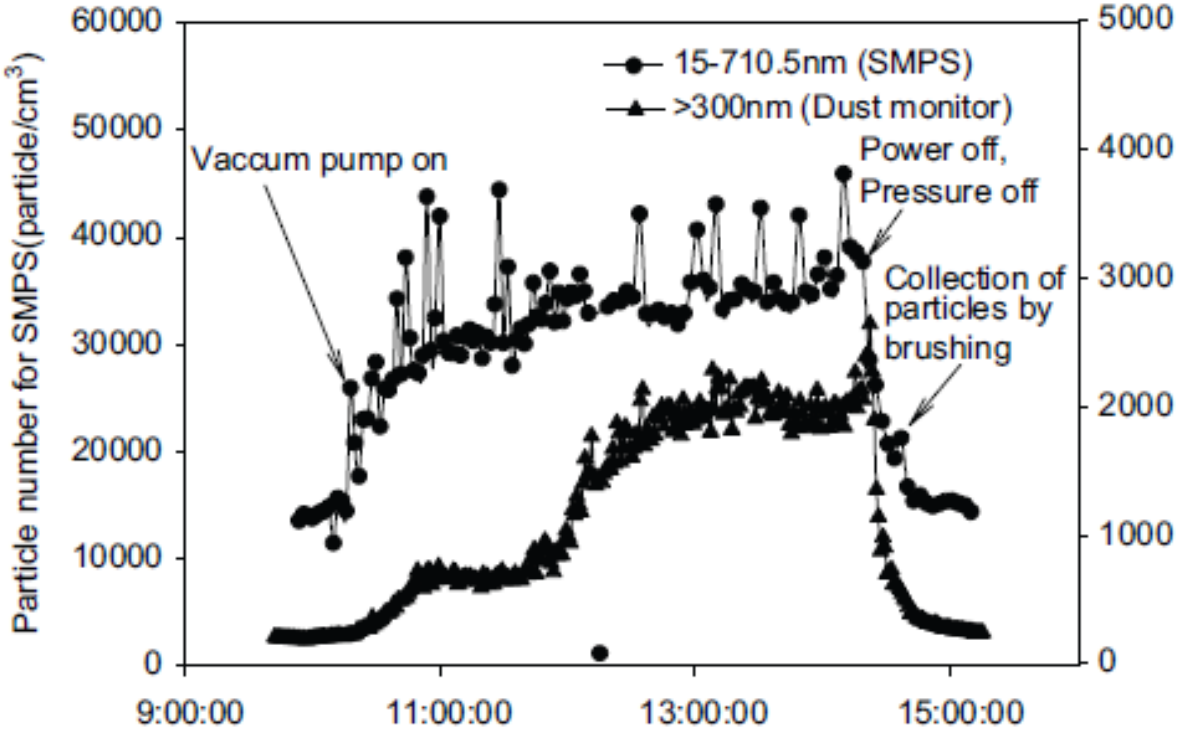
*Total suspended particulate concentrations were reported.

*Lee et al., 2011*

# Challenges for Implementation: Exposure Characterization

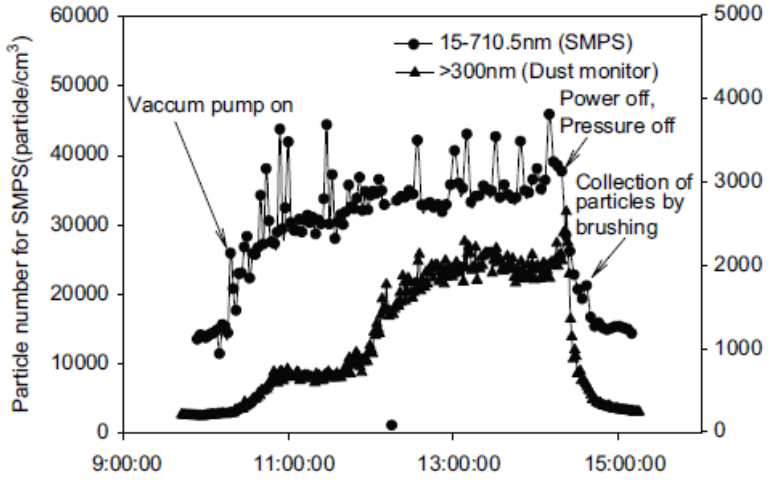
| Workplace | Process | Sampling site | Sampling time (min) | Sampling volume (L) | Mass concentration (mg/m³)* |
|---|---|---|---|---|---|
| Workplace A | During reactor operation | Area 4 | 298 | 595.4 | 0.50386 |
| | | SKC 1 | 185 | 1299.5 | 0.33090 |
| | | Area 5 | 296 | 585.2 | 0.63227 |
| | | SKC 2 | 292 | 2051 | 0.11702 |
| | During powder collection | Area 3 | | | |
| | | Area 6 | | | |
| | | SKC 3 (personal) | | | |
| Workplace B | During operation | Area 3 | | | |
| | | SKC 3 | | | |
| | | Area 6 | | | |
| | | SKC 2 | | | |
| | | Area 4 | | | |
| | | Cyclone 8 | | | |
| | | Cyclone 7 | | | |
| | Only during collection | SKC 1 | | | |

*Total suspended particulate concentrations were reported.




*Lee et al., 2011*

# Challenges for Implementation: Exposure Characterization

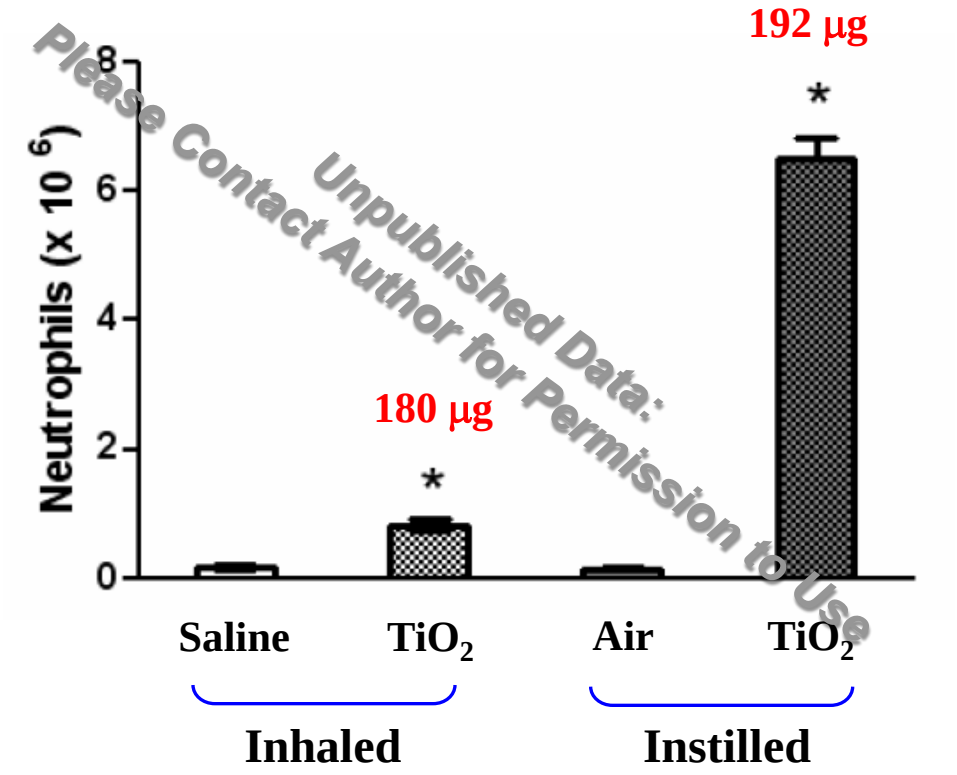



**Concentration** ~~→~~ **Exposure** ~~→~~ **Dose** → **Response**

# 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/m$^3$*)




*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 *in comparison to benchmark nanomaterials*