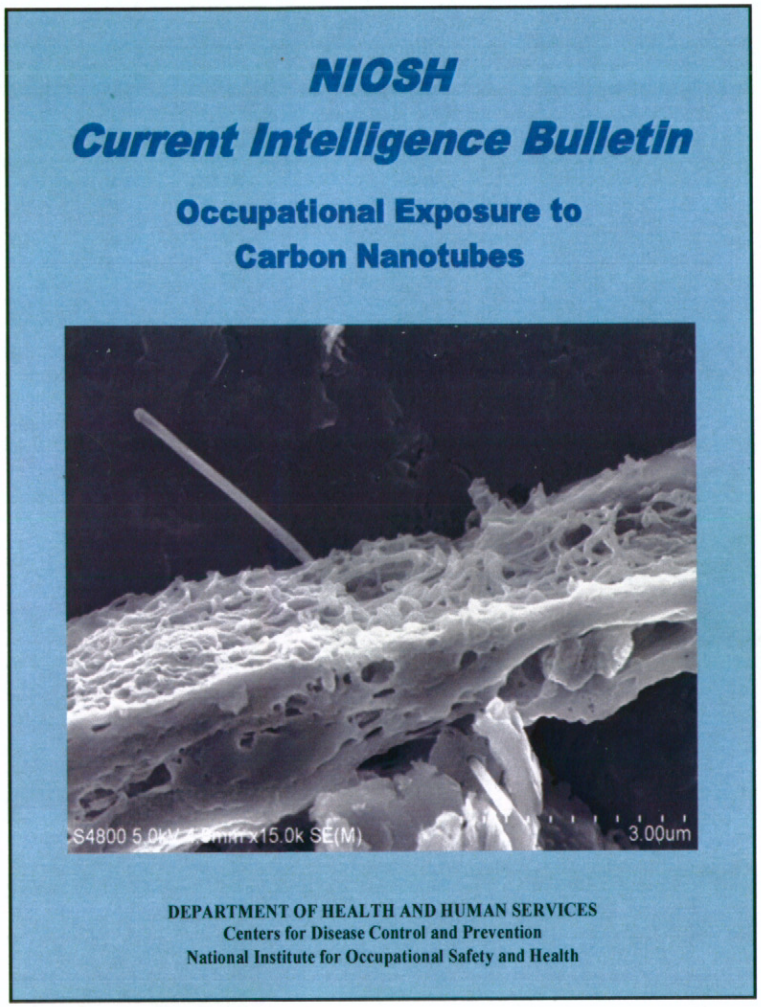

Risk Assessment of CNTs

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The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

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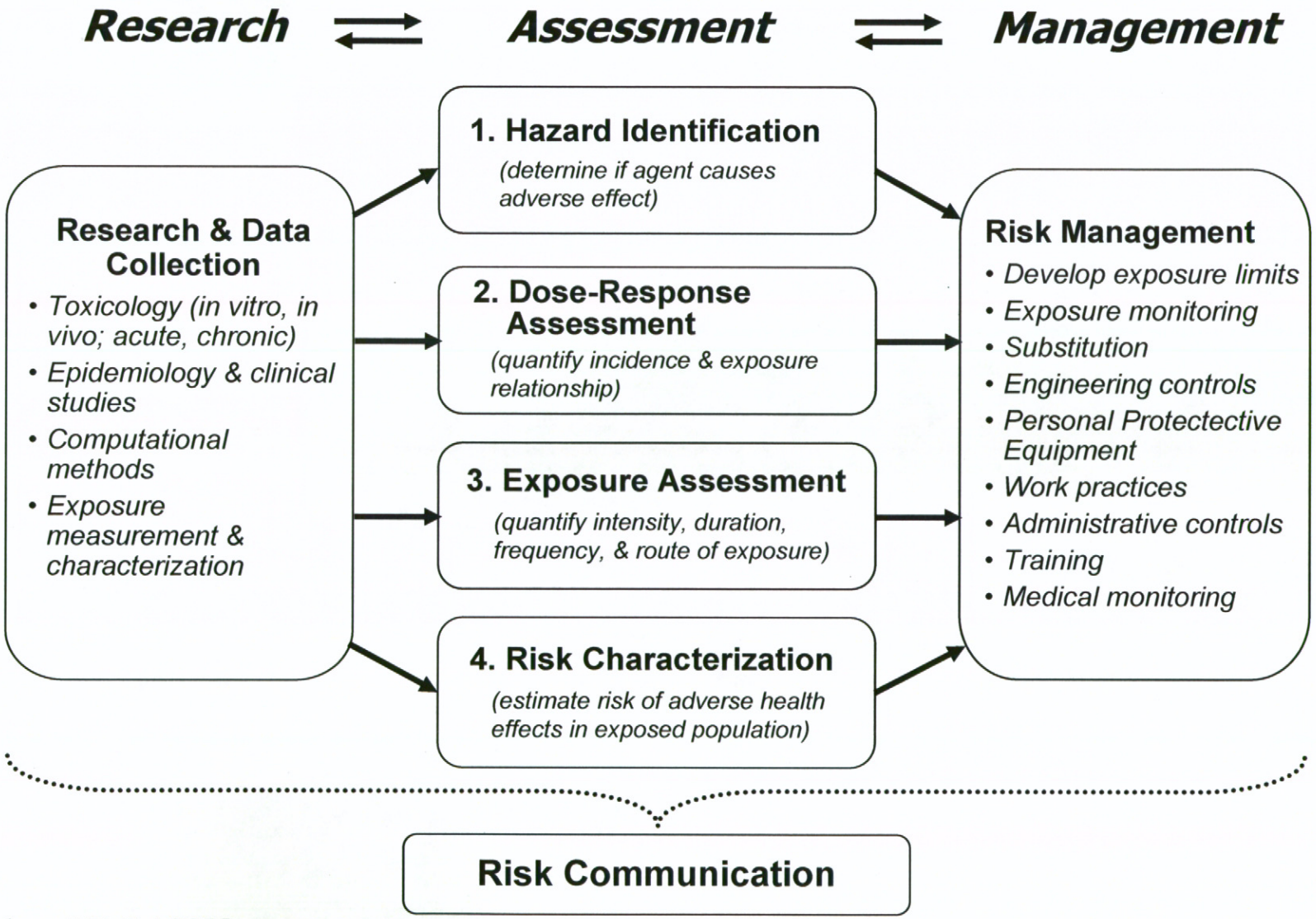
NIOSH Role

- NIOSH is authorized to develop recommended occupational safety and health standards (OSH Act of 1970)
  - Conducts toxicological research, risk assessment, exposure assessment, and health surveillance
  - Develops criteria for recommended standards
  - Forwards recommendations to OSHA

Risk Assessment Paradigm in U.S.



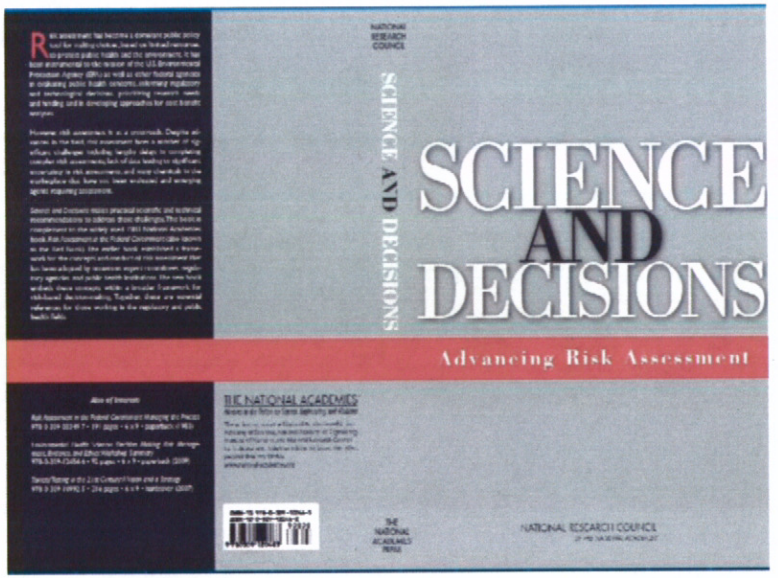
[Based on NRC 1983]

Improving the Utility of Risk Assessment:

Re-evaluating the1983 Risk Assessment Framework as Practiced

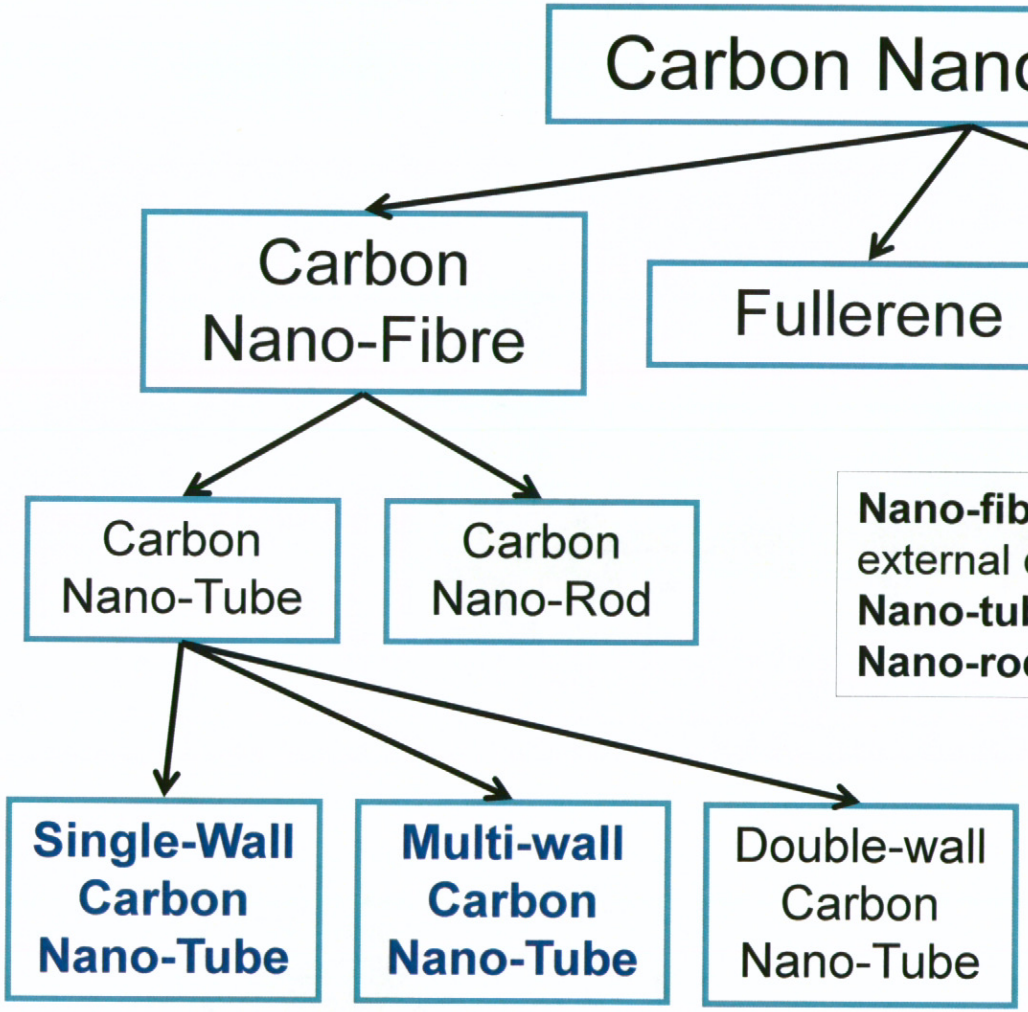
"What options are there to reduce the hazards or exposures, &

How can risk assessment be used to evaluate the merits of the various options?"



National Research Council of the National Academies (2009)

Taxonomy of Carbon Nano-Objects



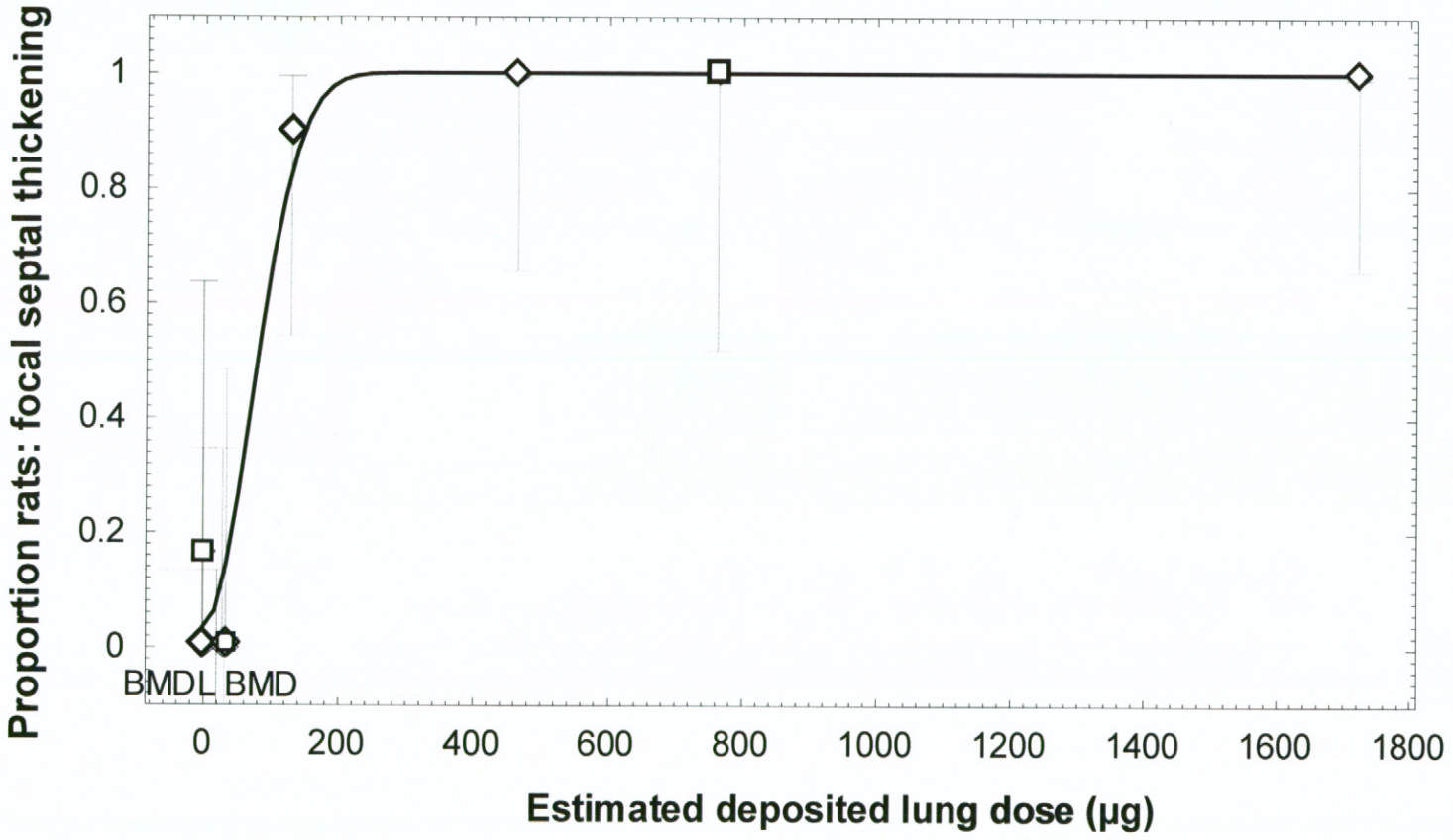
Nano-fiber: nano-object with two external dimensions at the nanoscale.
Nano-tube: *hollow* nanofiber
Nano-rod: *solid* nanofiber

[ISO TS/80004-1 2010; ISO/TS 27687 2008]

Data Evaluated for 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

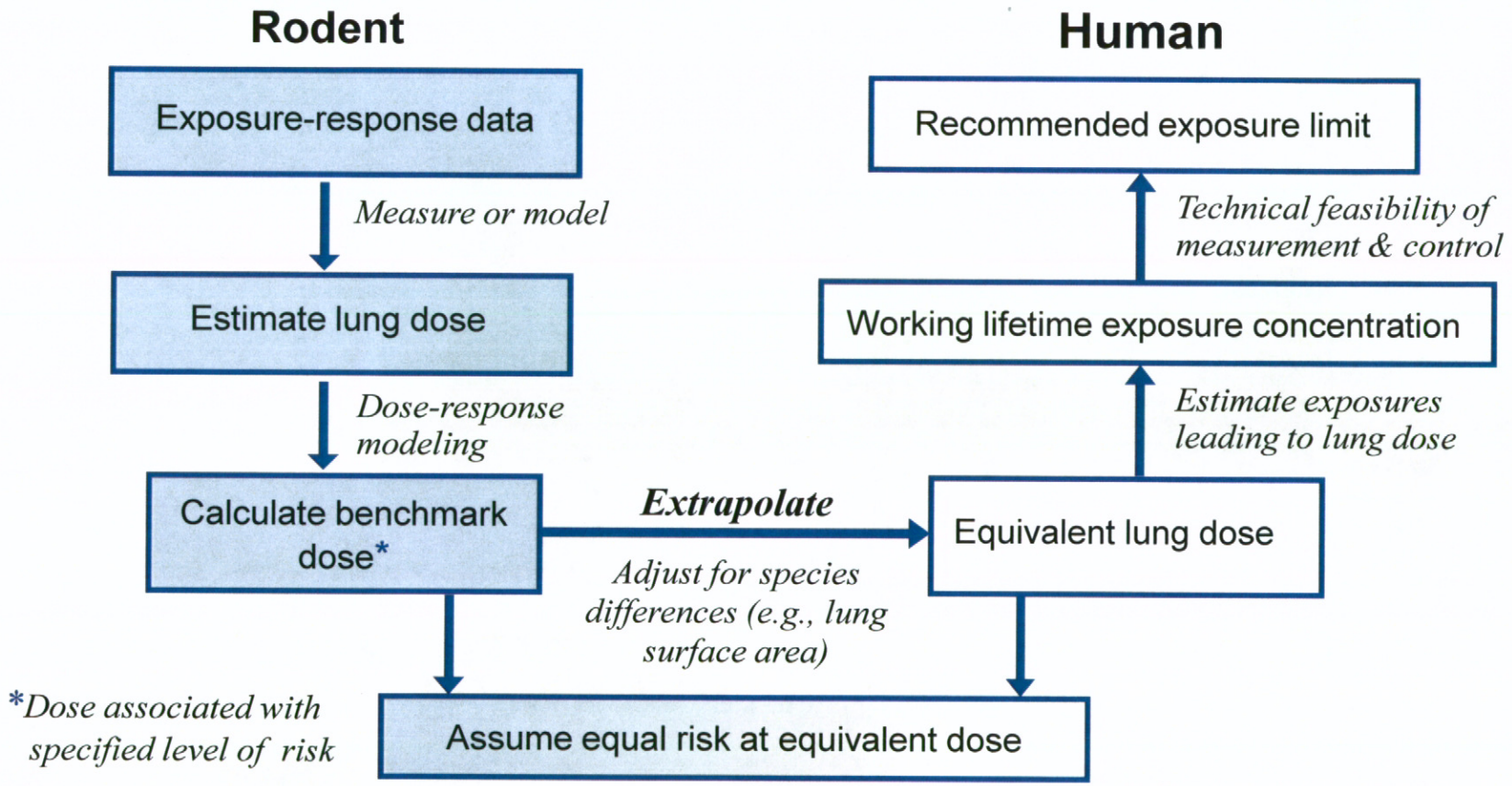
Evaluating Dose Rate & Lung Response to MWCNT



Effect Levels: BMD vs. NOAEL or LOAEL

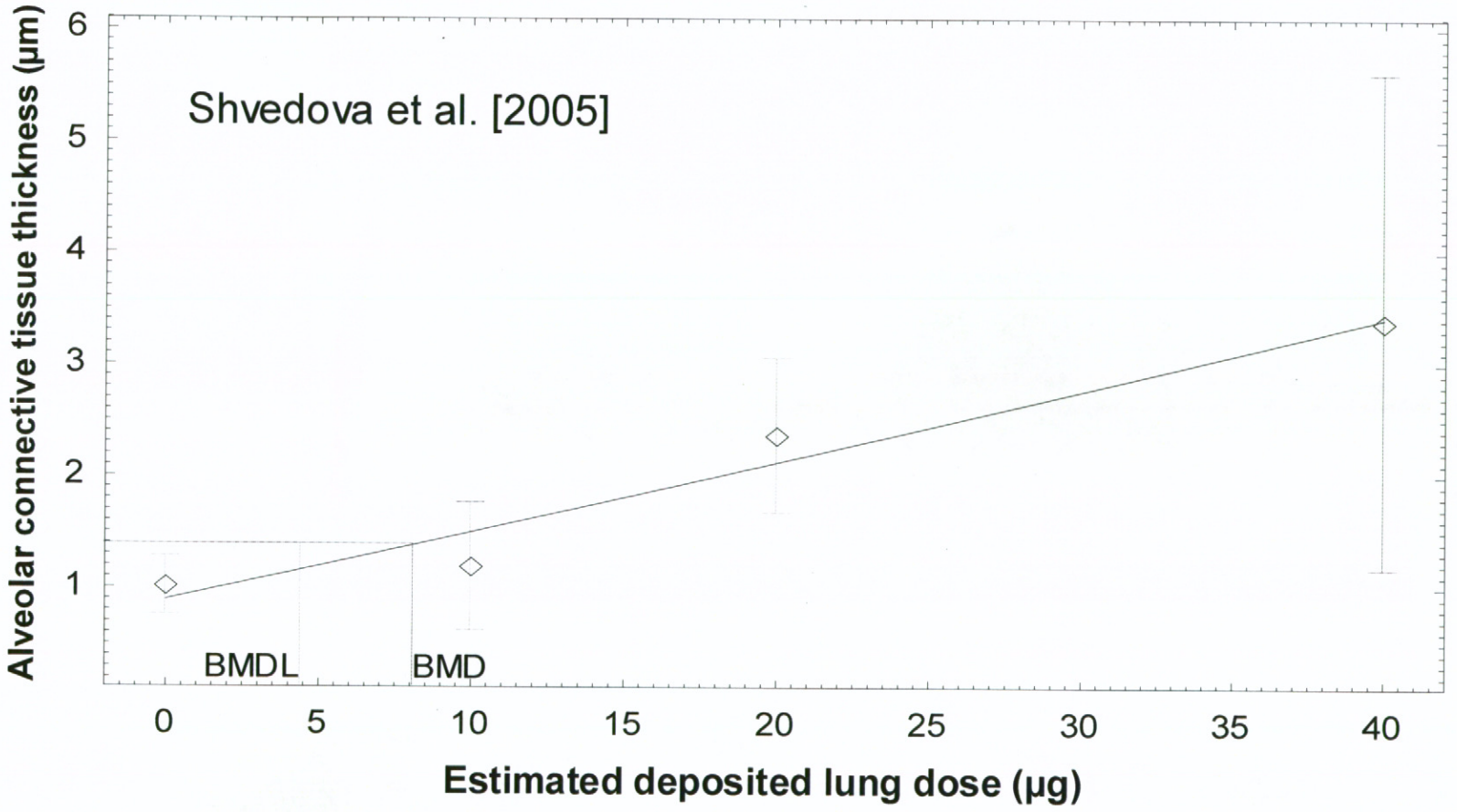
- No Observed Adverse Effect Level (NOAEL) & Lowest Observed Adverse Effect Level (LOAEL)
  - Depends on dose spacing & sample size
  - Not risk-based, extrapolation to lower doses by uncertainty factors
- Benchmark dose (BMD) estimates
  - Model uses all (or most) of the dose-response data
  - Risk estimates: maximum likelihood & confidence limits
  - Takes statistical account of sample size & variability
  - Provides standardized point of departure (e.g., 10%) for low dose extrapolation

Quantitative Risk Assessment Methods to Develop Recommended Exposure Limits for Airborne CNTs



[Based on: Kuempel et al. Inhal Toxicol 18:717–724, 2006]

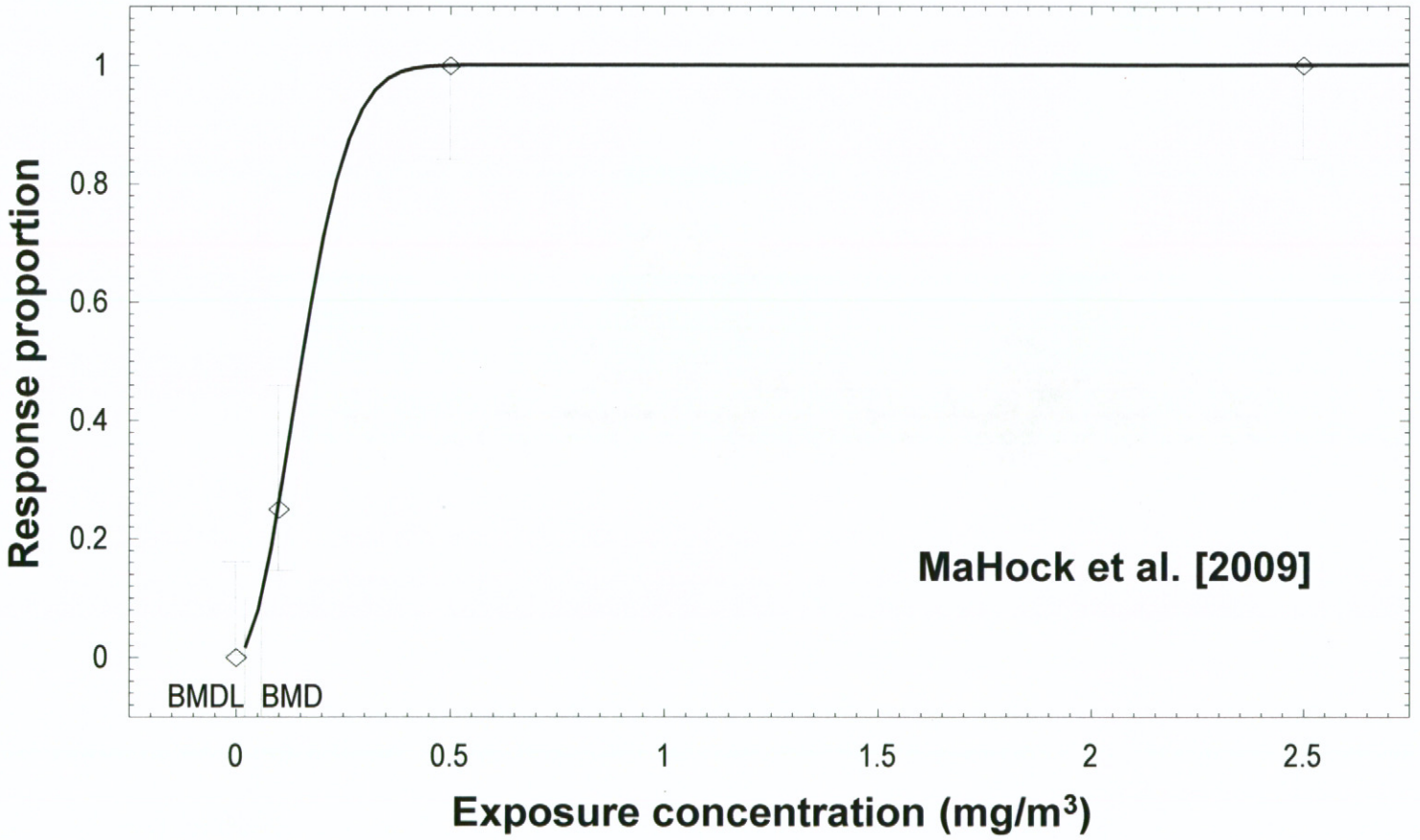
Benchmark Dose Estimation: Example of Continuous Response in Mice Exposed to SWCNT*



* Pharyngeal aspiration (single administration); examined 56 days post-exposure.

Benchmark Dose Estimation
Subchronic (13-wk) Inhalation of MWCNT in Rats

Granulomatous inflammation, minimal or greater severity

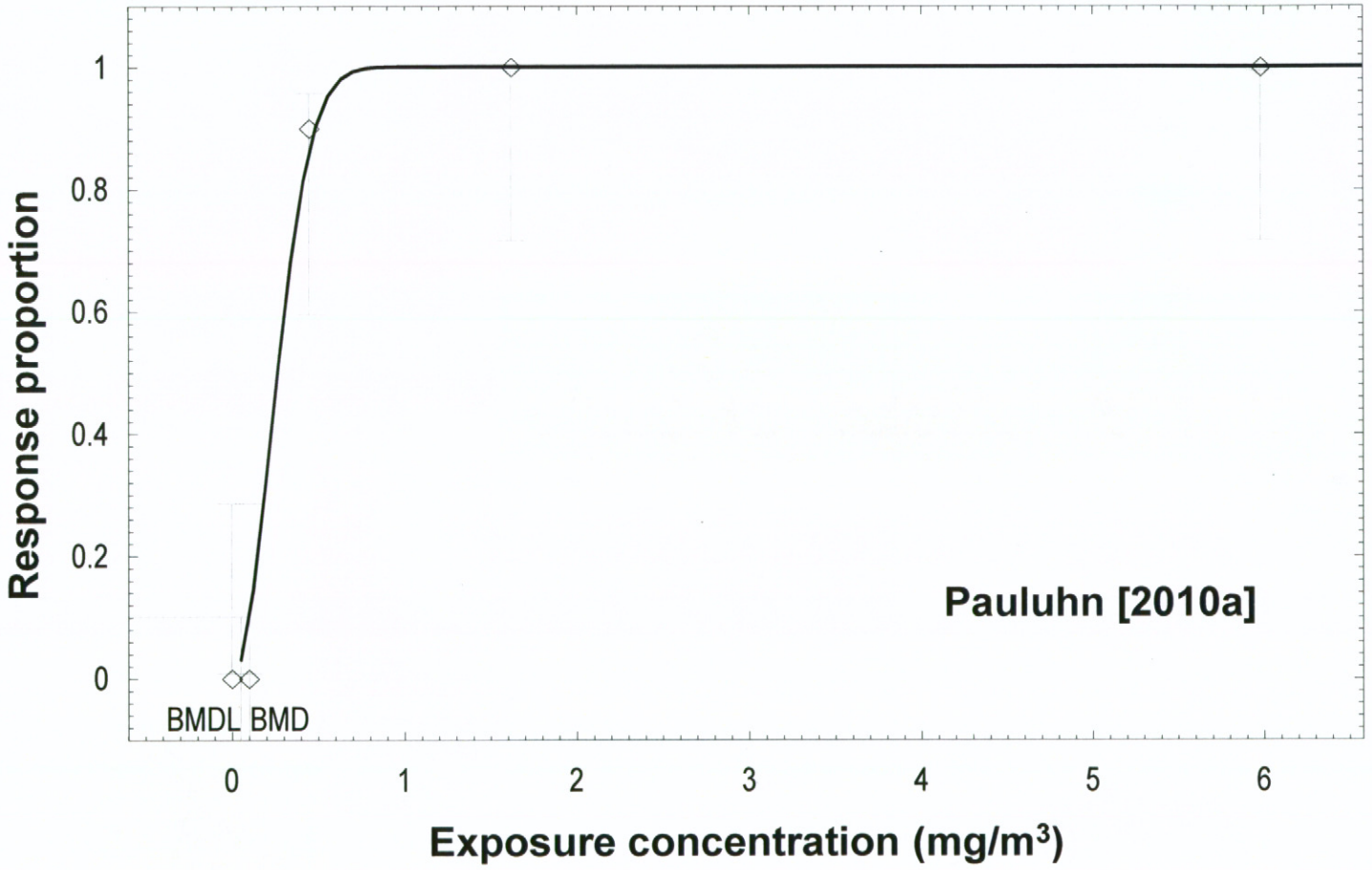


BMD(L) 10%: 0.06 (0.02) mg/m^3
LOAEL: 0.1 mg/m^3

Multistage model,
poly. degree 2
(Dichotomous response)

Benchmark Dose Estimation
Subchronic (13-wk) Inhalation of MWCNT in Rats

Alveolar interstitial thickening, minimal or greater severity



BMD(L) 10%: 0.1 (0.05) mg/m³
LOAEL (NOAEL): 0.4 (0.1) mg/m³

Multistage model,
poly. degree 2
(Dichotomous response)

Benchmark Dose* Estimates

– Continuous responses in short-term exposure studies

CNT type & metal Study description	Rodent lung burden (µg)†	Human-equivalent lung burden (mg)	Working lifetime 8-hr TWA (µg/m³)
MWCNT, 2% Al [Muller et al. 2005] Hydroxyproline amount (60d); IT in rats	760 (486)	194 (124)	**18 (12)**
SWCNT, 0.2% Fe [Shvedova et al. 2005] Alveolar connective tissue thickness (60d); PA in mice	8.1 (4.4)	15 (8.2)	**1.8 (1.0)**
SWCNT, 18% Fe [Shvedova et al. 2008] Alveolar connective tissue thickness (32d); Inhal in mice	0.48 (0.33)	0.89 (0.62)	**0.11 (0.08)**

* BMD(L): maximum likelihood (95% lower confidence limit)

† Deposited lung dose associated with pulmonary response at 1.1 SD above control mean; associated with a 10% increase in abnormal response (assumed >99th percentile of control responses)

Abbreviations: IT: intratracheal instillation; PA: pharyngeal aspiration; Inhal: Inhalation (5 d, 4 hr/d)

Benchmark Dose* Estimates

– Dichotomous responses in short-term exposure studies

CNT type & metal Study description	Rodent lung burden (µg)†	Human-equivalent lung burden (mg)	Working lifetime 8-hr TWA (µg/m^3)
SWCNT, 2% Fe [Lam et al. 2004] Granuloma (90d); IT in mice	45 (7.6)	84 (14)	**10 (1.7)**
MWCNT, 0.3% Fe [Porter et al. 2005] Fibrosis: ≥grade 4 (56d); PA in mice	3.6 (1.8)	6.6 (3.3)	**0.6 (0.3)**
MWCNT, 0.5% Co [Ellinger-Ziegelbauer & Pauluhn 2009] Focal septal thickening: minimum or greater (91d); Inhal in rats	137 (22)	35 (5.6)	**3.8 (0.6)**

* BMD(L): maximum likelihood (95% lower confidence limit)

† Deposited lung dose associated with 10% of animals having the specified response

Abbreviations: IT: intratracheal instillation; PA: pharyngeal aspiration; Inhal: Inhalation (1 d, 6 hr)

Benchmark Dose* Estimates

– Subchronic (13-wk) Inhalation of MWCNT in rats (dichotomous response)

Study	Rodent lung burden (µg)†	Human-equivalent lung burden (mg)	Working lifetime 8-hr TWA (µg/m^3)
	Estimated Deposited Lung Dose		
Ma-Hock et al. [2009]	21 (8.1)	5.4 (2.1)	**0.5 (0.2)**
Pauluhn [2010a]	28 (14)	7.2 (3.5)	**0.8 (0.4)**
	Estimated Retained Lung Dose		
Ma-Hock et al. [2009]	11 (3.8)	2.7 (0.97)	**2.7 (1.0)**
Pauluhn [2010a]	14 (6.5)	3.6 (1.7)	**4.2 (1.9)**

* BMD(L): maximum likelihood (95% lower confidence limit)

† Lung dose associated with 10% of animals having the specified response

Metal content: 9.6% Al_2O_3 [Ma-Hock et al. 2009] ;0.5% Co [Pauluhn 2010a].

Summary of Results

- Subchronic inhalation studies of two types of MWCNT in rats
  - Human-equivalent exposure to 0.2 – 2 μg/m^3 * estimated to be associated with 10% excess risk of early-stage pulmonary inflammation and fibrosis
- Short-term studies of several types of MWCNT or SWCNT in rats and mice
  - Similar estimates of 0.08 - 12 μg/m^3 *

* As 8-hr time-weighted average concentration over a 45-year working lifetime (95% lower confidence limit estimates)

Basis for the Recommended Exposure Limit (REL) of 7 µg/m^3

- **Technical feasibility of measuring airborne exposure**
  - Limit of Quantification (LOQ) of analytical method to measure exposure is ~ 7 µg/m^3 [NIOSH Method 5040].
- **NIOSH prefers lower risk levels, but excess risk of early-stage lung effects >10% at the LOQ**
  - Estimated from two subchronic and several short-term studies in rats & mice, for MWCNT & SWCNT, purified and unpurified (different metal content)
  - Qualitatively similar lung effects from CNF reported in one study of mice

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
- Generalizability of findings to non-studied types of CNT and CNF
- Comparability of physical-chemical properties of CNT used in the animals studies and the workplace

Research Needs
to Reduce Uncertainty in Risk Assessment

- Study chronic effects in animals, including cancer
- Compare biological effects among CNT/F with different physical-chemical properties
- Develop improved models to predict CNT/F deposition and retention in respiratory tract
- Characterize worker exposures
- Examine alternative exposure and dose metrics (e.g., fiber or particle number, surface area, or volume)