Quantitative Risk Assessment: Titanium Dioxide

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Titanium Dioxide Public Meeting
Feb. 27, 2006, Cincinnati, Ohio

Animal and Human Studies

- Epidemiological Studies
  - No elevation in lung cancer mortality in 3 of 4 epidemiological studies
  - Elevated lung cancer (SMR= 1.23, CI: 1.10-1.38) in one study; no exposure-response observed
- Animal Studies: chronic inhalation in rats
  - *Fine (rutile) TiO_2:*

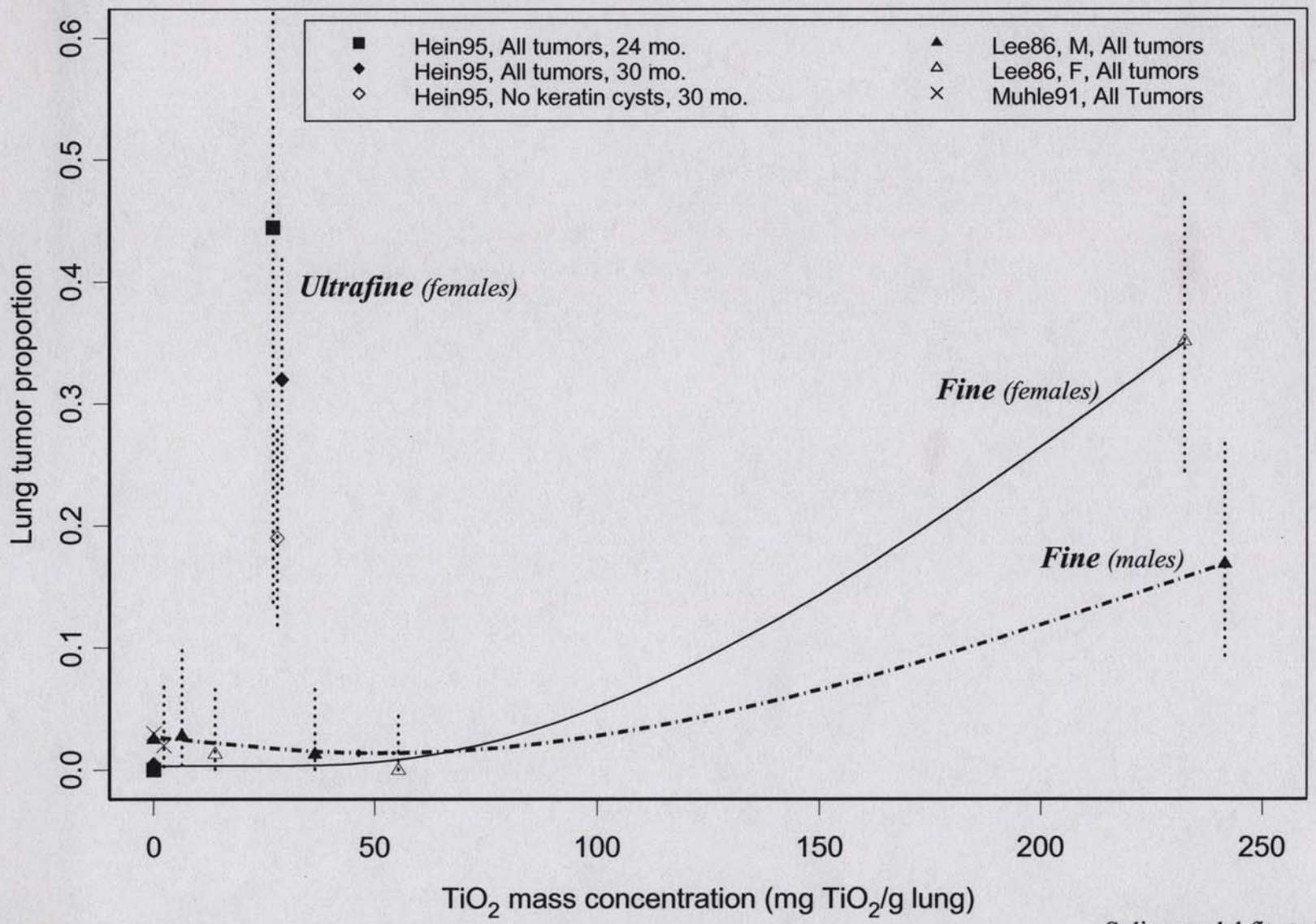
    Bronchioalveolar adenoma in male and female rats at 250 mg/m^3, but not 10 or 50 mg/m^3
  - *Ultrafine (anatase) TiO_2:*

    Adenocarcinoma, squamous cell carcinoma, and adenoma in female rats at ~10 mg/m^3

Chronic Inflammation and Lung Disease

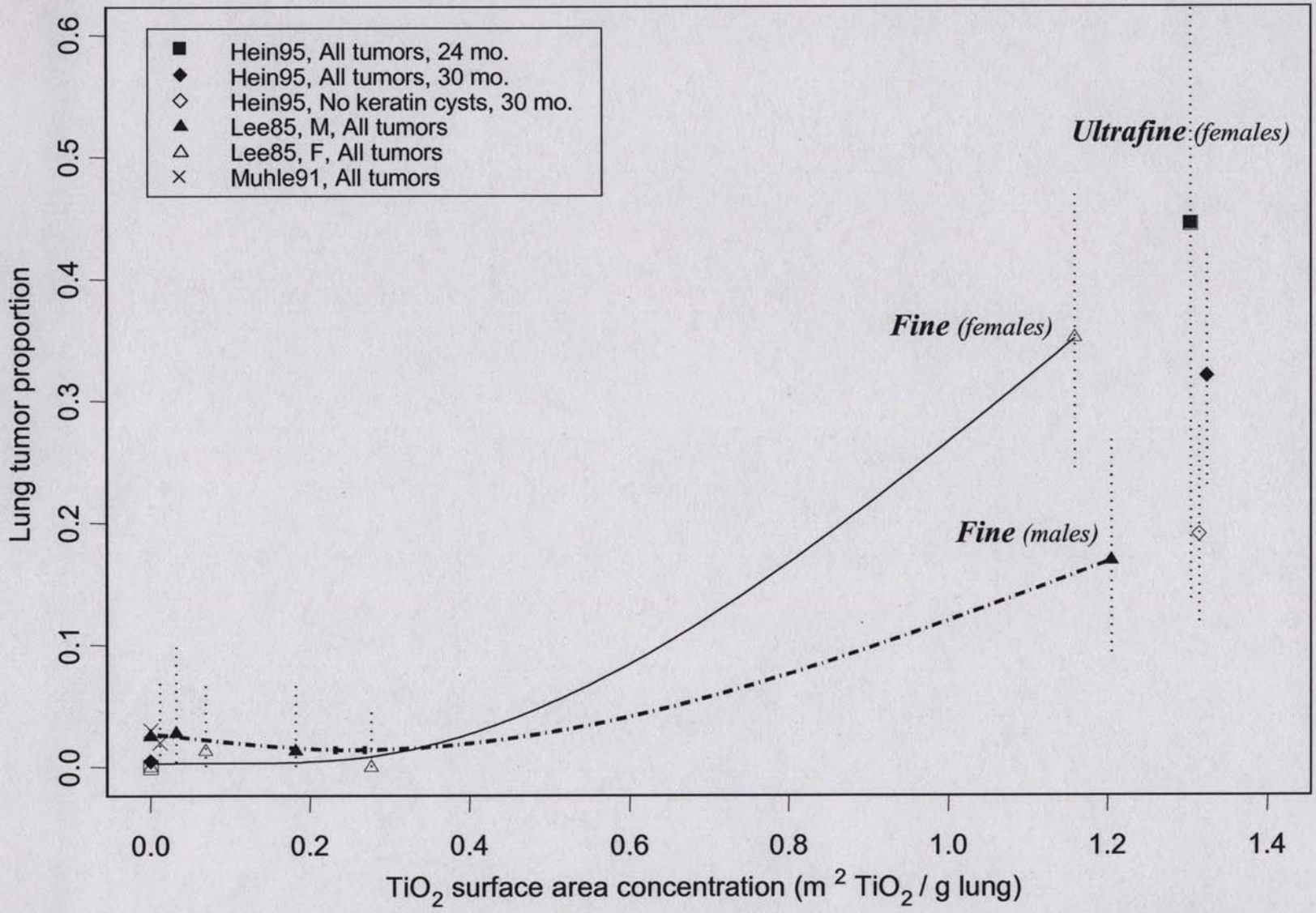
- Rats
  - *Chronic inflammation:* associated with impaired pulmonary clearance, tissue damage & repair, mutations, and lung tumors.
  - *Particle surface area dose:* better predicts pulmonary inflammation and lung tumors than mass dose for particles of similar composition.
- Humans
  - *Dusty trades workers:* Chronic inflammation, respiratory impairment, and fibrosis.
  - *Titanium dioxide worker case studies:* Alveolar proteinosis & interstitial fibrosis indicative of inflammation.
  - *Inflammation and lung cancer:* workers exposed to crystalline silica and patients with idiopathic pulmonary fibrosis.

Titanium dioxide: *Tumors* vs. *particle mass* dose in rats



Spline model fits to Lee data.
Heinrich dose data jittered.

Titanium dioxide: *Tumors* vs. *particle surface area* dose in rats



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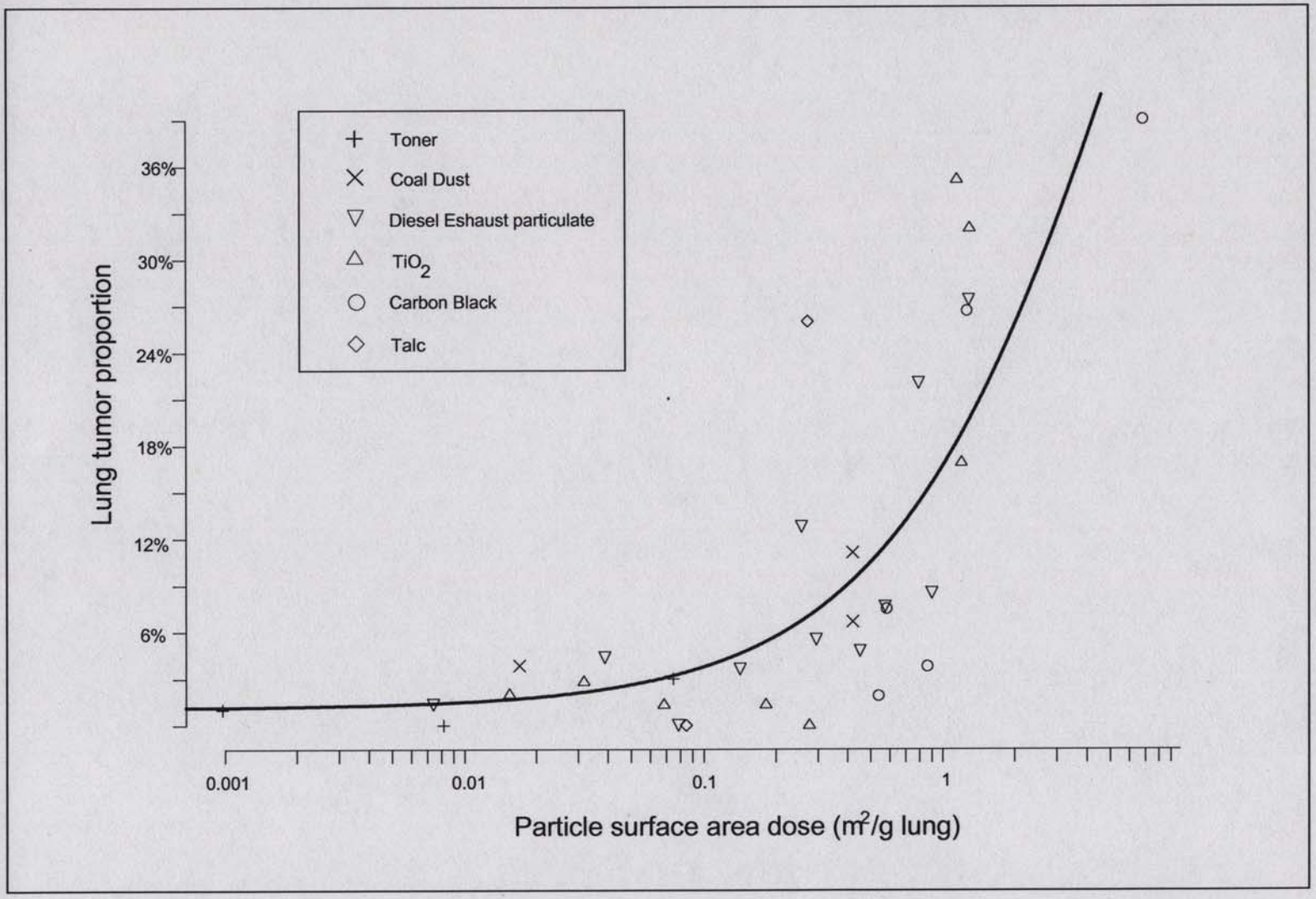
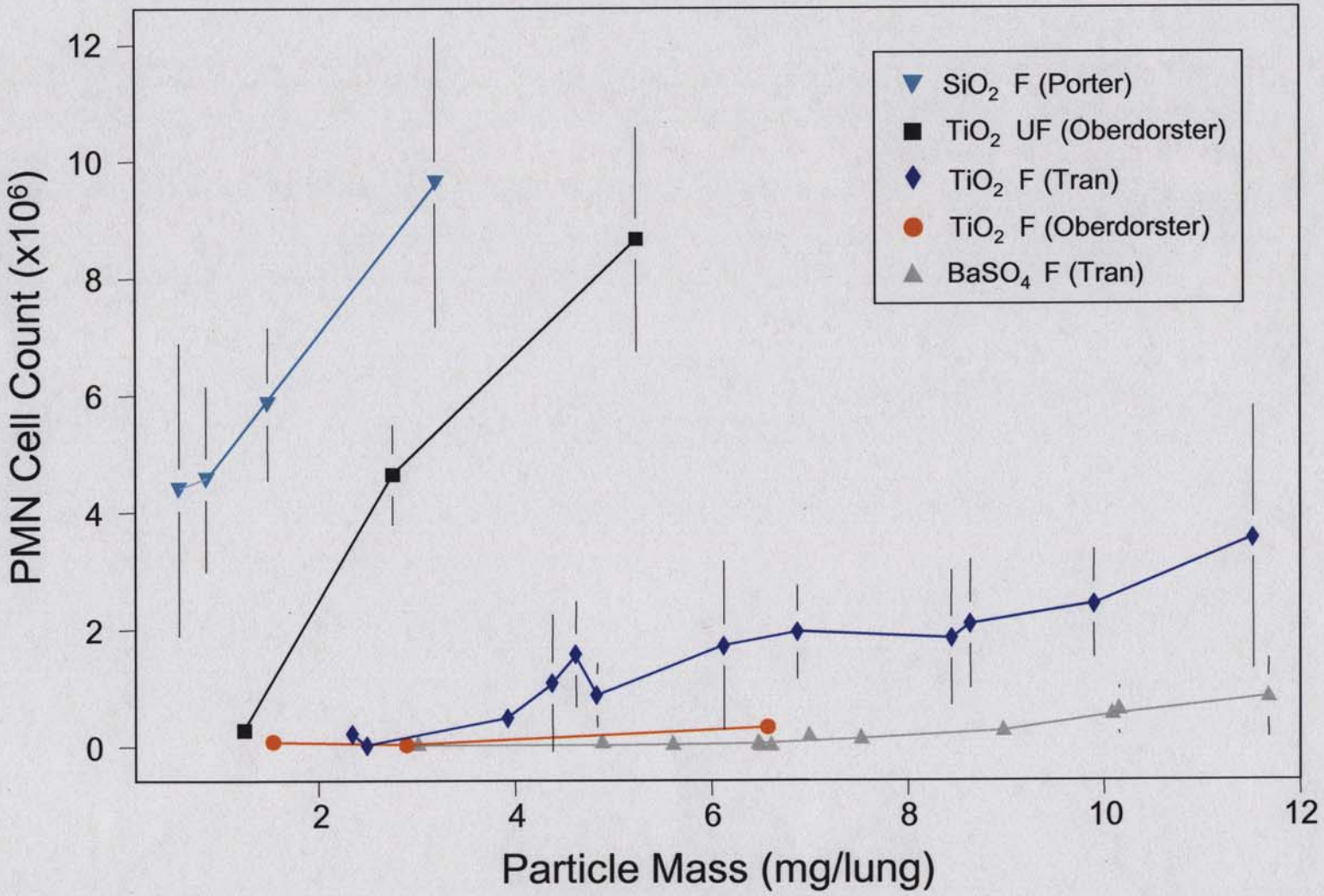
Lung tumor response associated with particle surface area dose of fine or ultrafine poorly soluble particles



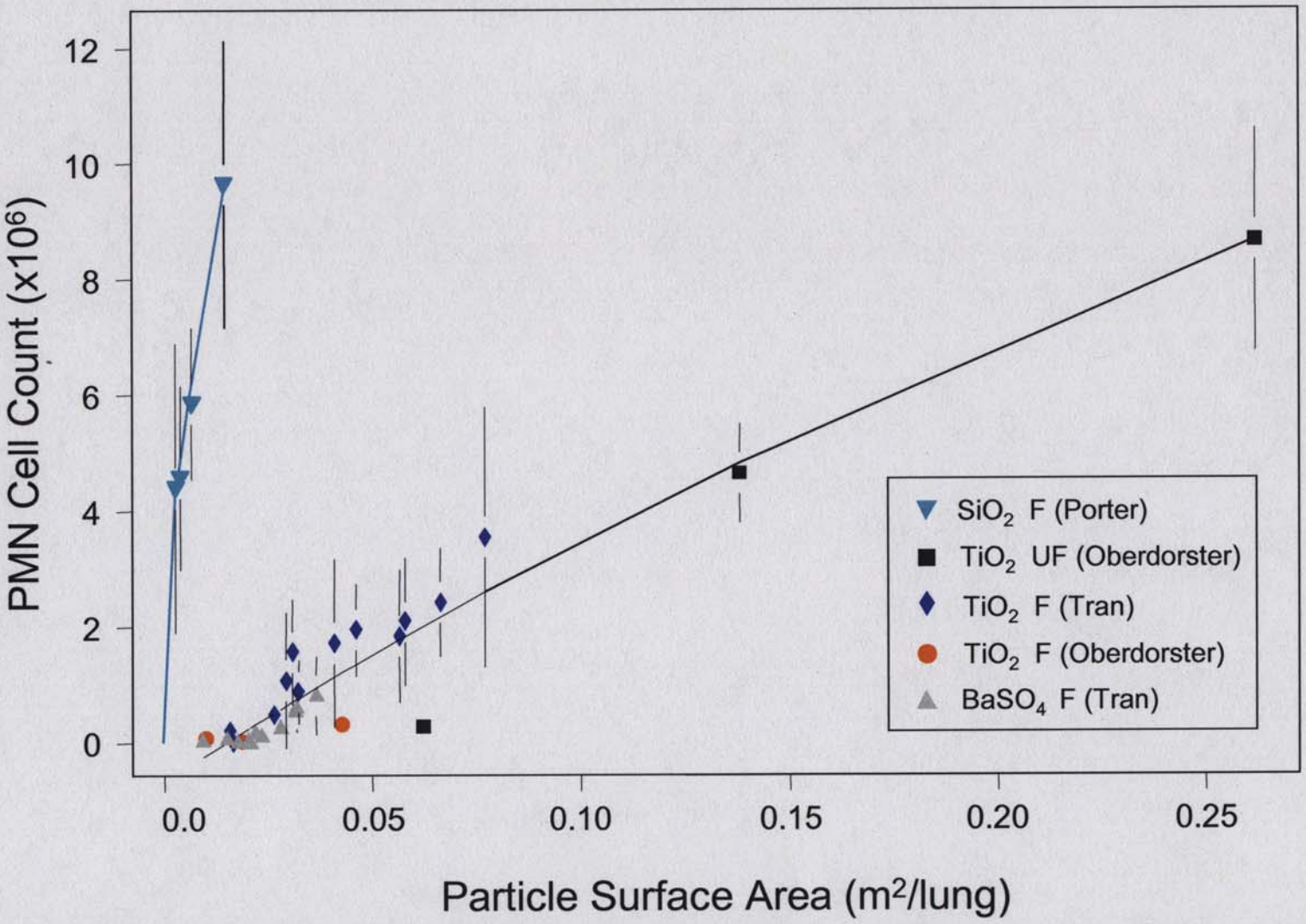
Pulmonary Inflammation in Rats: Low and High Toxicity Dust

Particle Mass Dose



Pulmonary Inflammation in Rats: Low and High Toxicity Dust

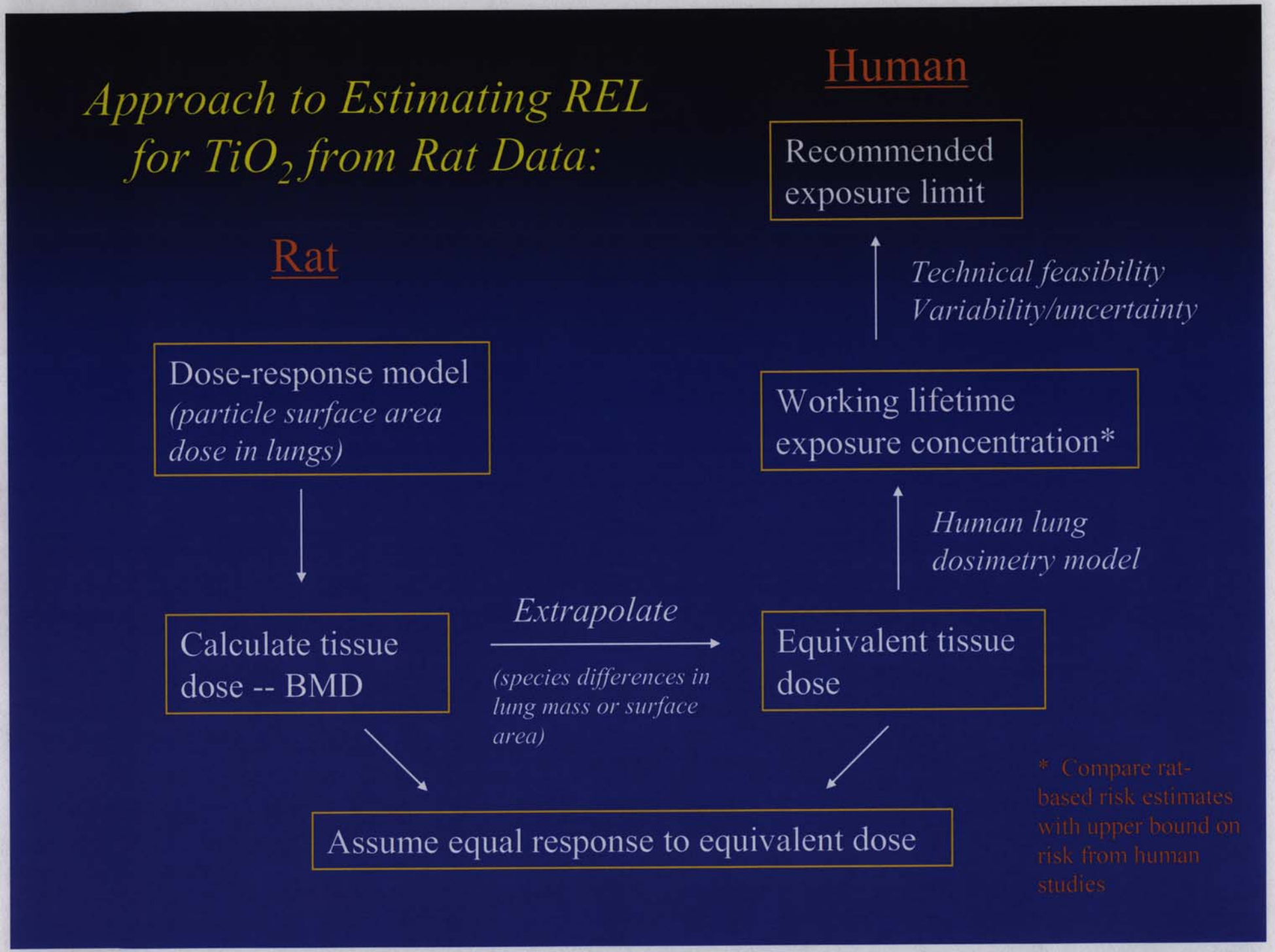
Particle Surface Area Dose



QRA Methods for Titanium Dioxide

1. Select the animal model, dose metric, and disease response.
2. Analyze dose-response relationship, and estimate dose associated with specified risk of disease.
3. Extrapolate the rat dose to humans (normalize dose by lung mass or lung surface area).
4. Determine airborne exposures associated with retained lung dose, using human lung dosimetry model.

Approach to Estimating REL for TiO_2 from Rat Data:



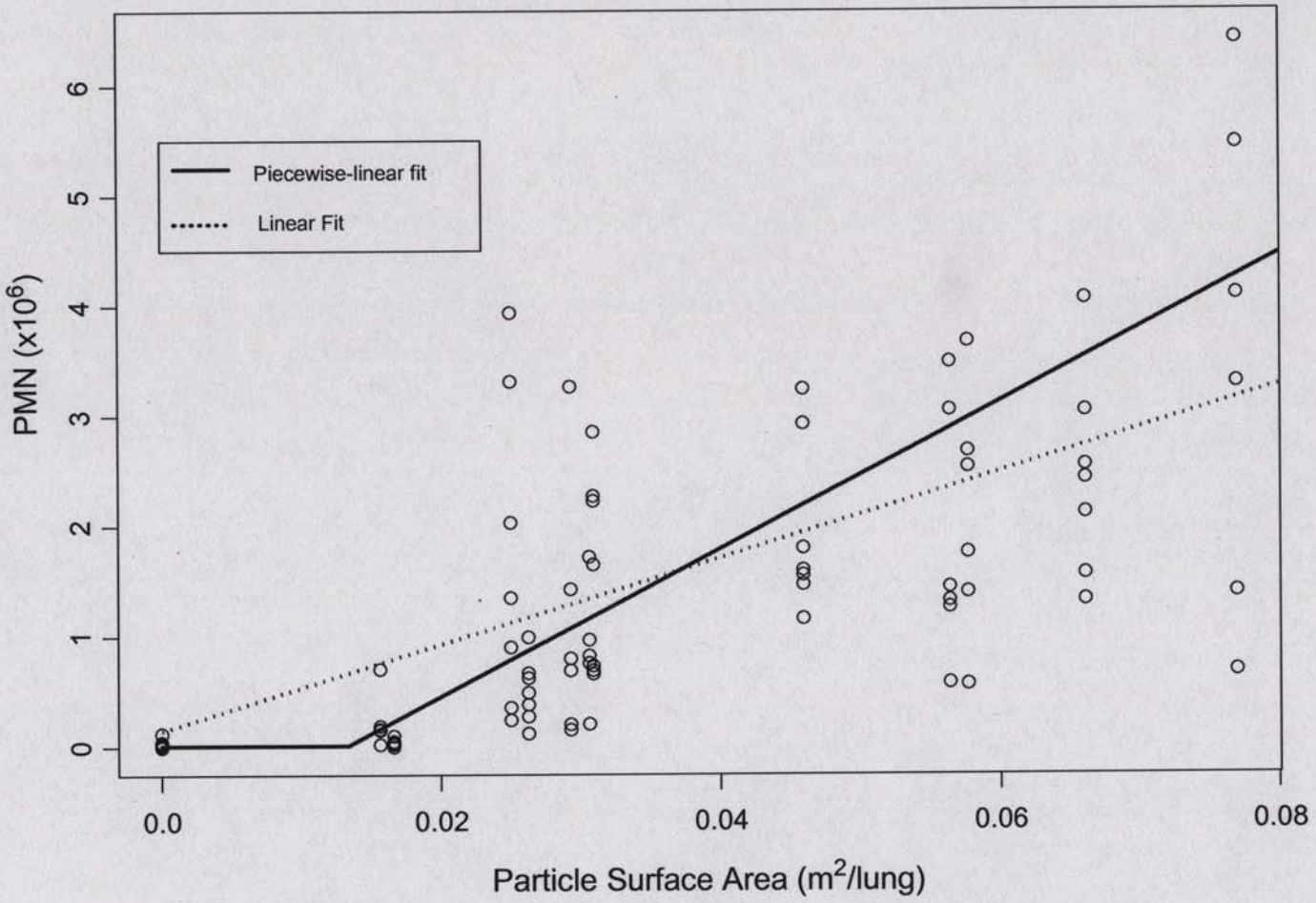


Figure 4-2. Piecewise-linear and linear model fits to rat data on pulmonary inflammation (PMN count) and particle surface area dose of titanium dioxide (data from Tran et al. [1999]).

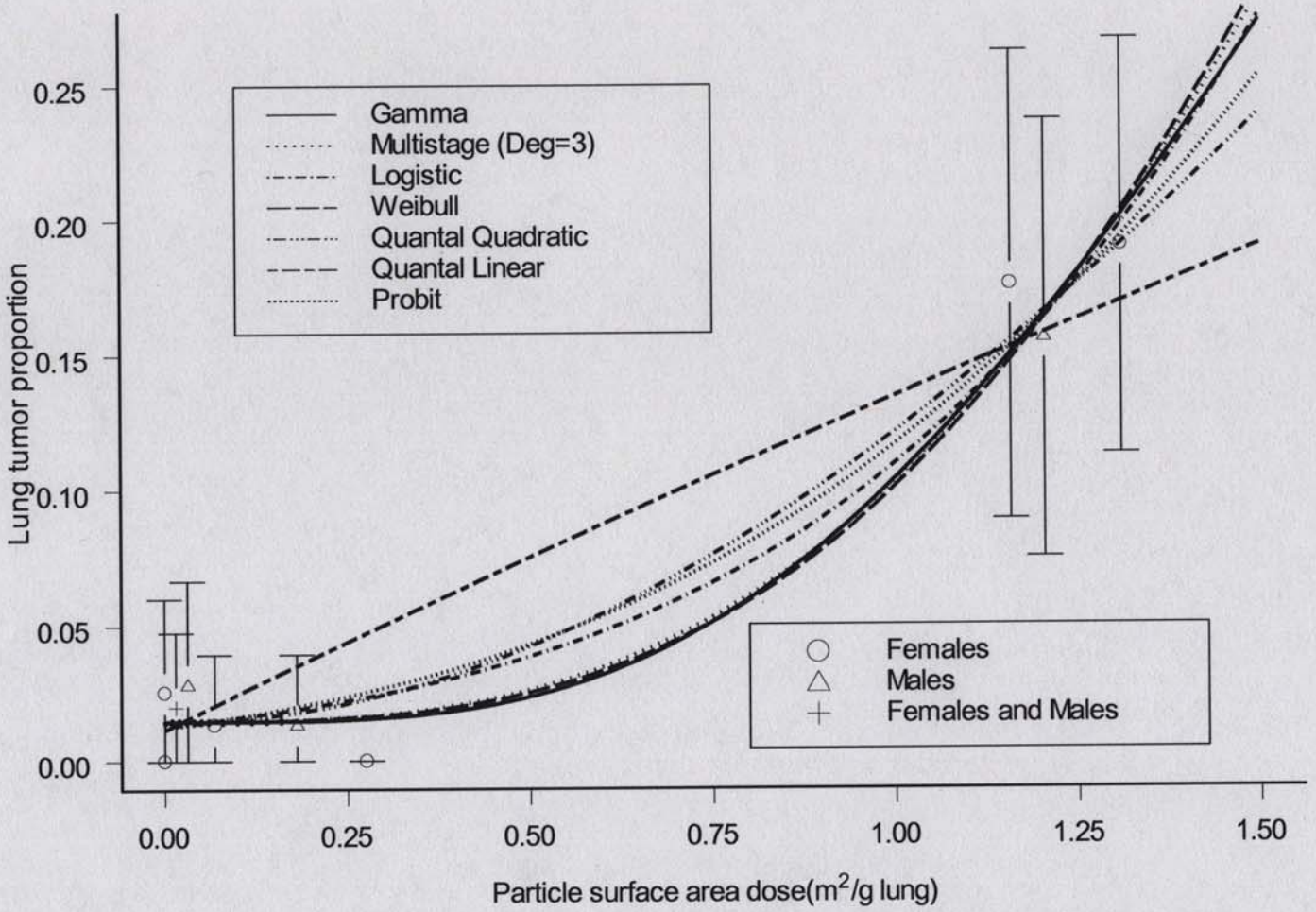


Figure 4-4. BMD models [EPA 2003] fit to the lung tumor data (without squamous cell keratinizing cysts) in male and female rats chronically exposed to fine or ultrafine TiO_2 [Lee et al. 1985; Heinrich et al. 1995] expressed as particle surface area dose. (note: confidence intervals were not constructed when the response proportion was zero).

Table 4-11. Summary of quantitative risk estimates for workers exposed to fine and ultrafine TiO_2 at various mean airborne concentrations over a 45-year working lifetime*

	Workers' mean airborne exposure (mg/m^3)	
Response	**Fine TiO_2**	**Ultrafine TiO_2**
Lung cancer excess risk ≤1/1,000 (from the BMDL)	1–5	0.05–0.5
Pulmonary inflammation (from the 95% LCL)	<2–10	<0.5–1.0

* NIOSH Current Intelligence Bulletin on Titanium Dioxide, External Review Draft (Nov. 2005)
BMDL: 95% lower confidence limit on the benchmark dose; 95% LCL: lower 95% confidence limit of the threshold dose

QRA Results

- Lung cancer response and multistage models selected to be health-protective
- Pulmonary inflammation data supportive
- Working lifetime concentration associated with <1/1000 excess risk of lung cancer:
  - *Fine TiO_2:* 1–2 mg/m^3
  - *Ultrafine TiO_2:* 0.05-0.2 mg/m^3

NIOSH proposed recommended exposure limits (RELs):

- 1.5 mg/m^3 fine TiO_2;
- 0.1 mg/m^3 ultrafine TiO_2