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Advanced Tools for NanoSafety Testing

in Vitro - in Vivo Extrapolation for Engineered NanoMaterials

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Outline

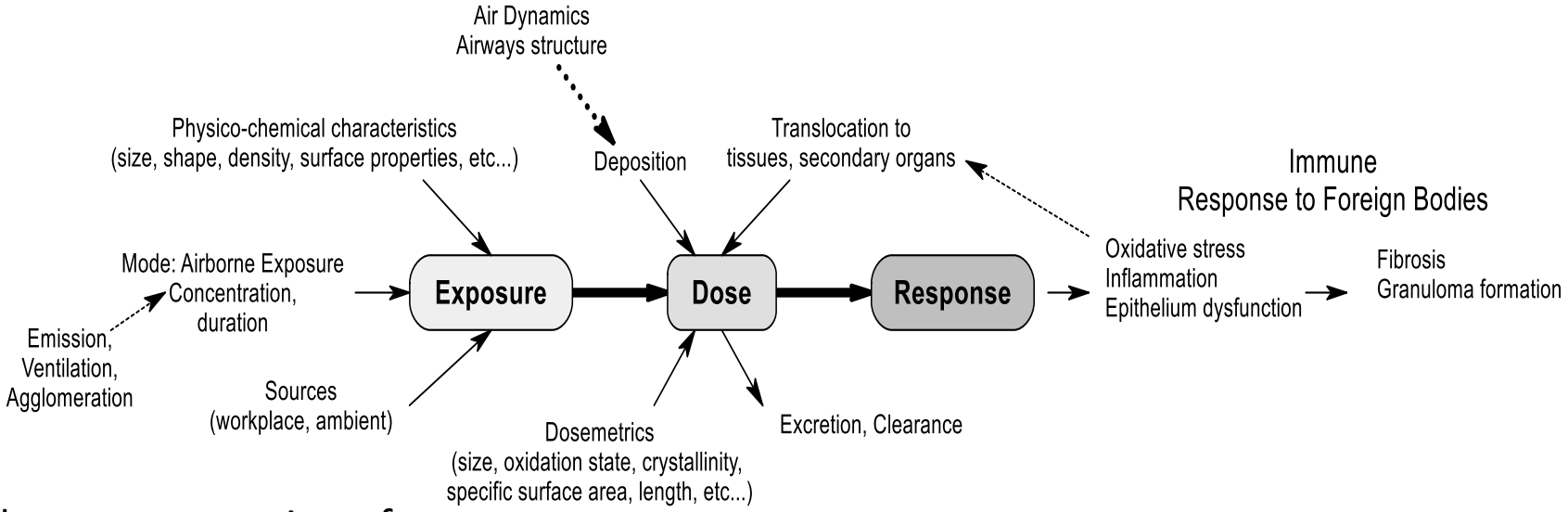
To ensure that in vitro studies are aligned with what has been done / known in vivo

How do we best align dose for in vitro studies based on our current in vivo knowledge

- For Lung – *in vitro* and *in vivo* doses have been compared for DQ12, $BaSO_4$, CeO_2, TiO_2 and MWCNT.
- Dosing strategy developed for Liver and Gut models.

Fundamental paradigm of nanotoxicology

- Fundamental to Nanotoxicology is the **Exposure-Dose-Response Relationship.**
- If a disease is caused by a nanomaterial and the disease process **follows** the Exposure-Dose-Response Relationship then it is a Nanotoxicology problem.

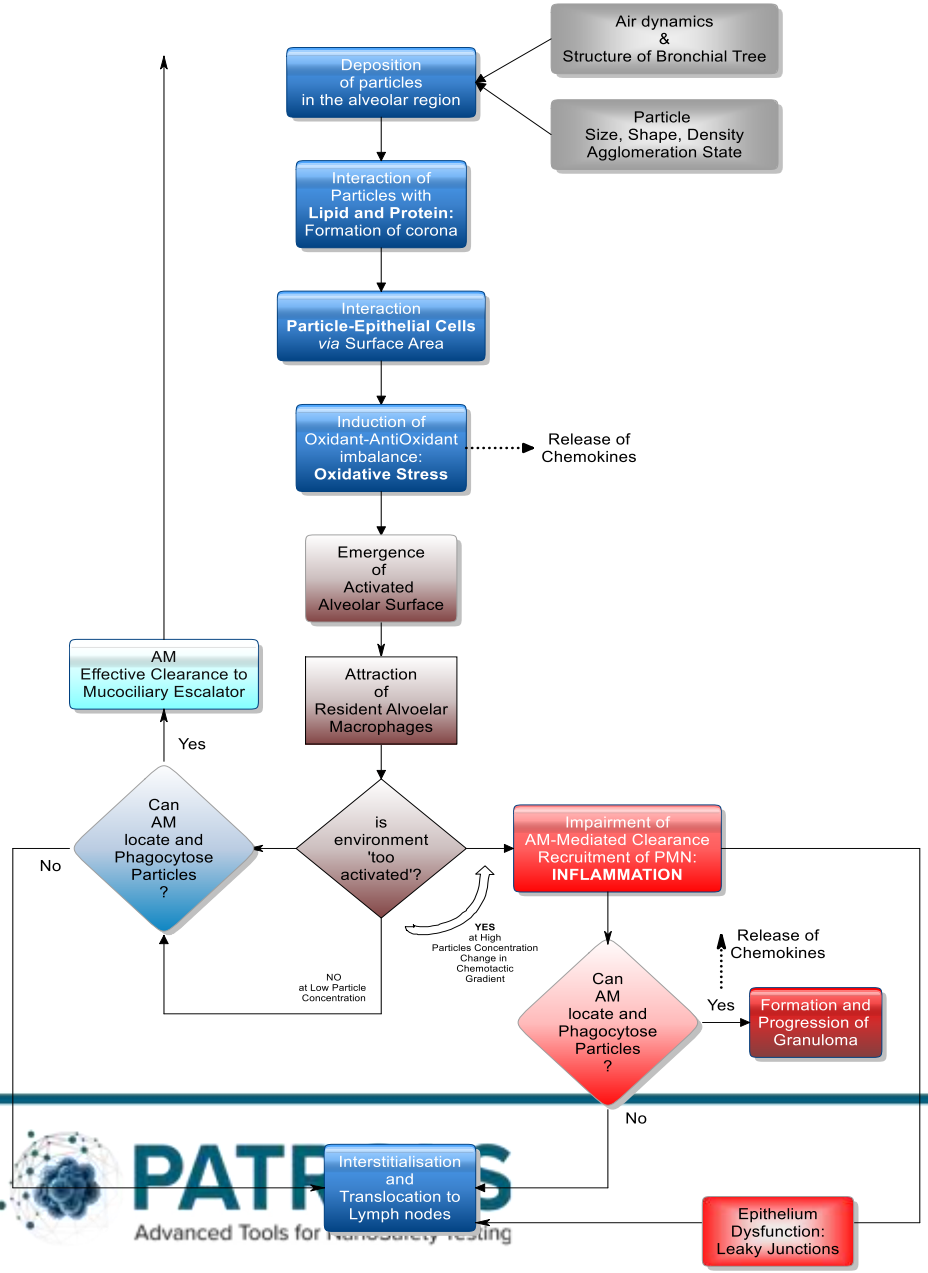


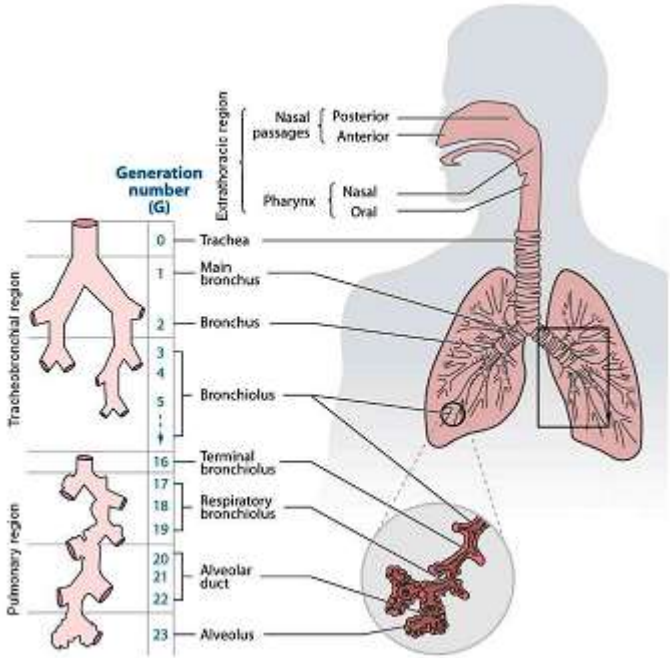
The process consists of:

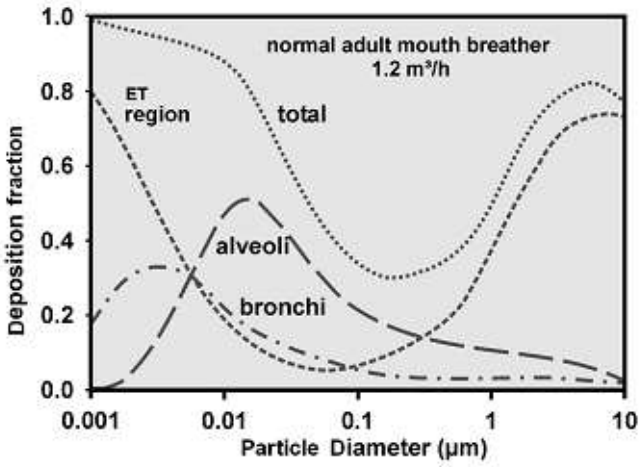
1. Deposition; 2. Translocation;3. Accumulation (retention/clearance);

4. Response

Pulmonary toxicity due to inhaled particles







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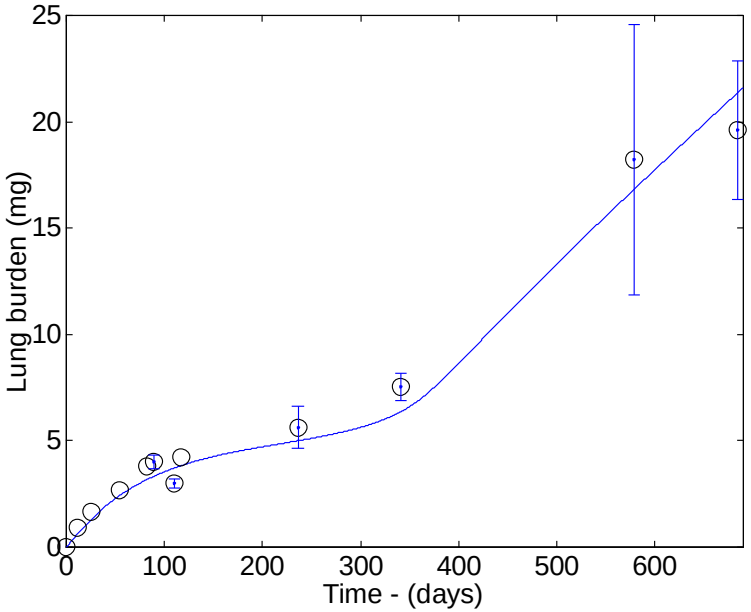
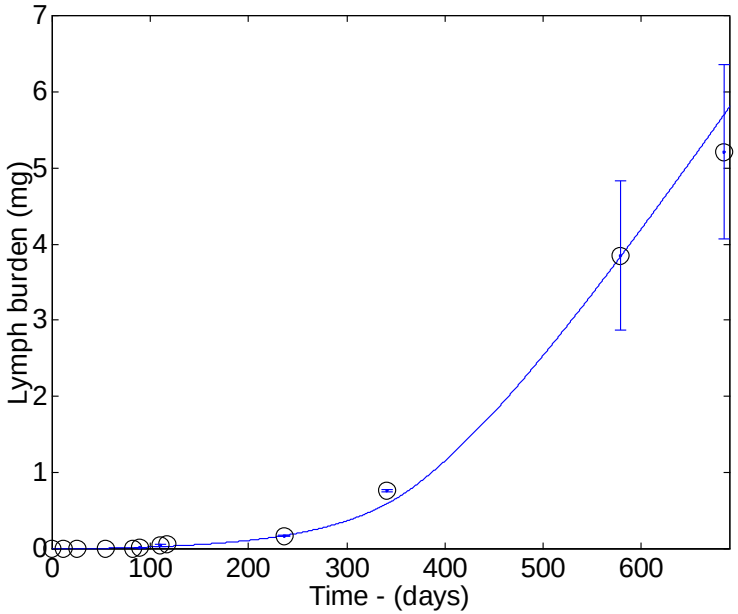
PARTICLE TOXICOLOGY



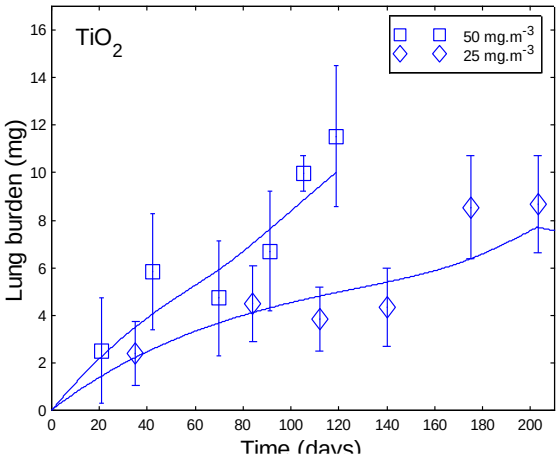


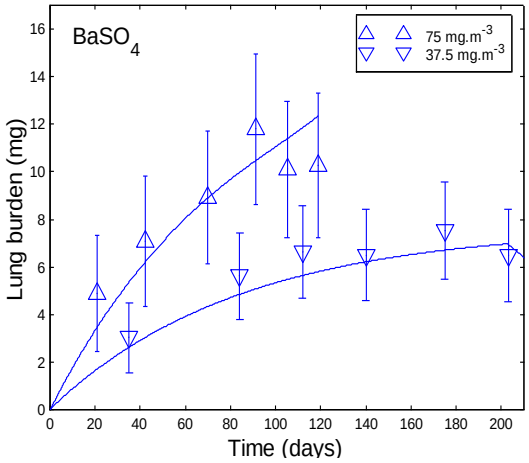
(a) Lung burden of rats exposed to titanium dioxide (TiO2) at 10 mg.m^{-3}.
(b) Lymph node burden data from the same experiment (Jones *et al.*, 1988)

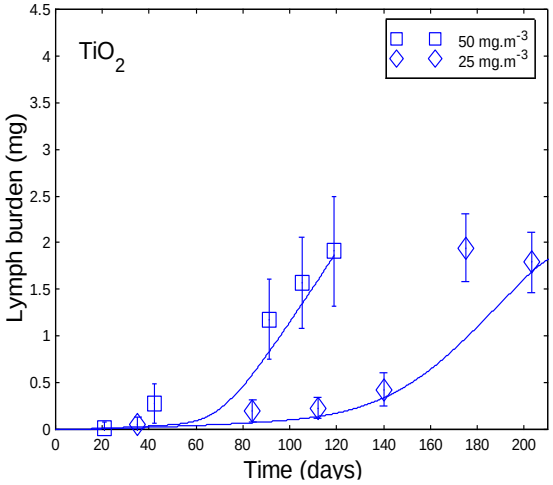
The Volumetric OVERLOAD Phenomenon

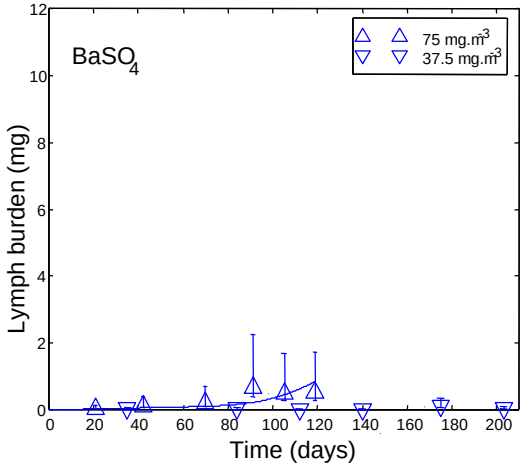
- Cessation of Alveolar Mediated Clearance
- Pulmonary Inflammation
- Translocation of Particle to Lymph nodes
- Phenomenon attributed to AM becoming overloaded
  - Retardation of clearance begins when 6% of AM volume is filled
  - Total cessation of clearance when 60% AM volume filled with particles (Morrow, 1988)
  - **Overloading is due to High Exposure and the toxicity is an artefact of 'over-dosing' of Poorly Soluble Low Toxicity Particles.**

Result 1: Lung and Lymph node Burden

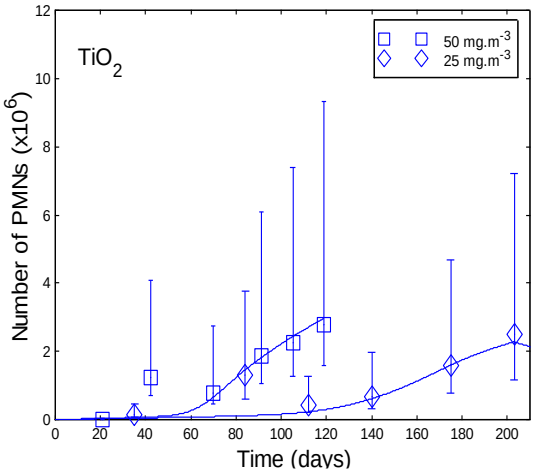


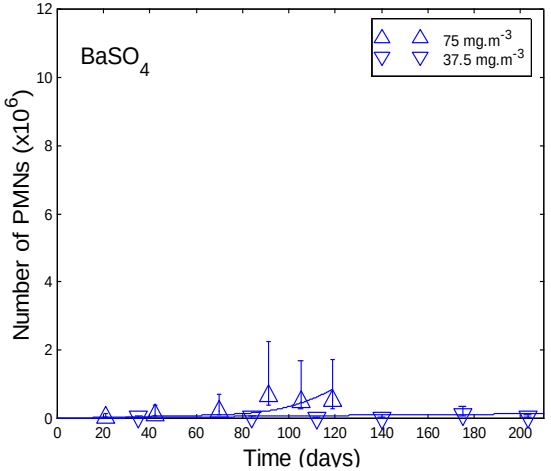


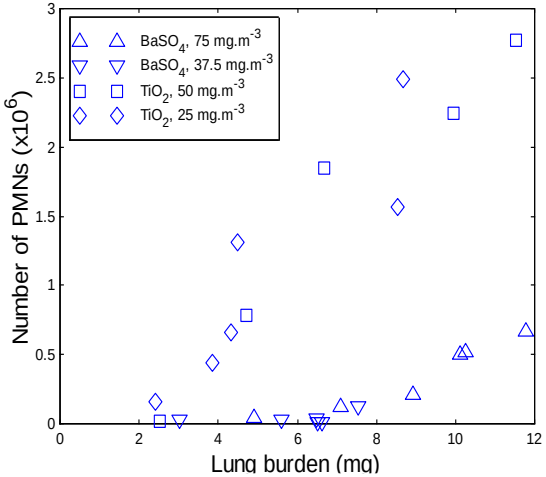


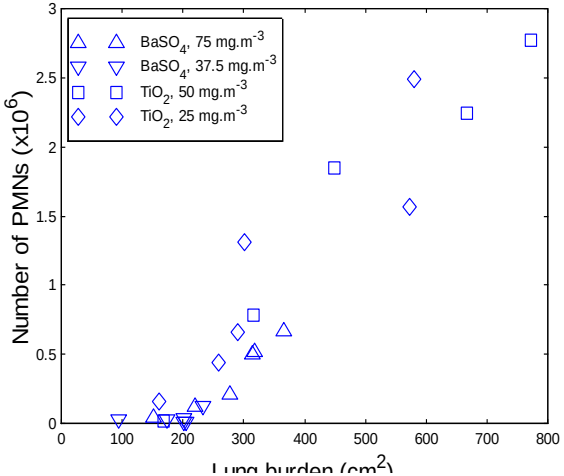


Result 2: Inflammation

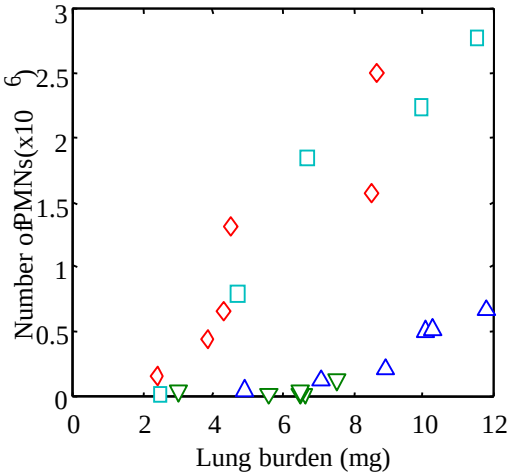


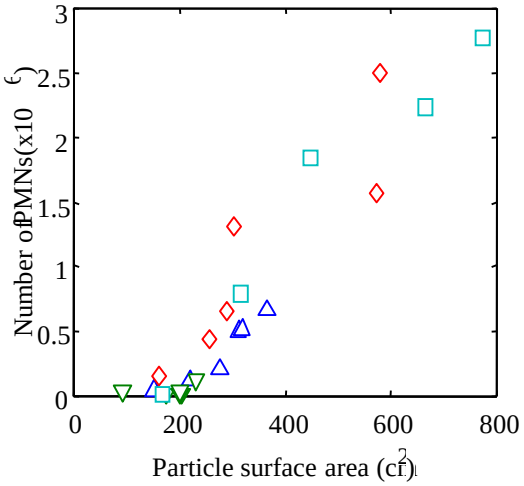


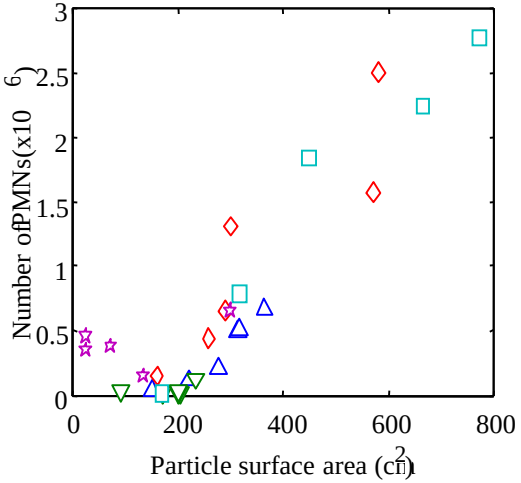


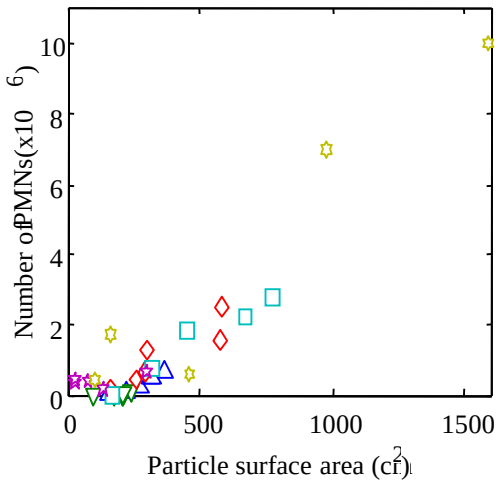


Inflammation and lung burden for TiO_2 and $BaSO_4$

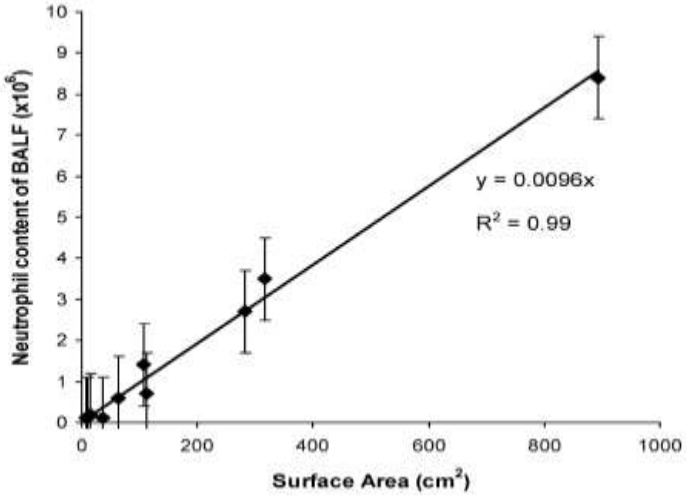


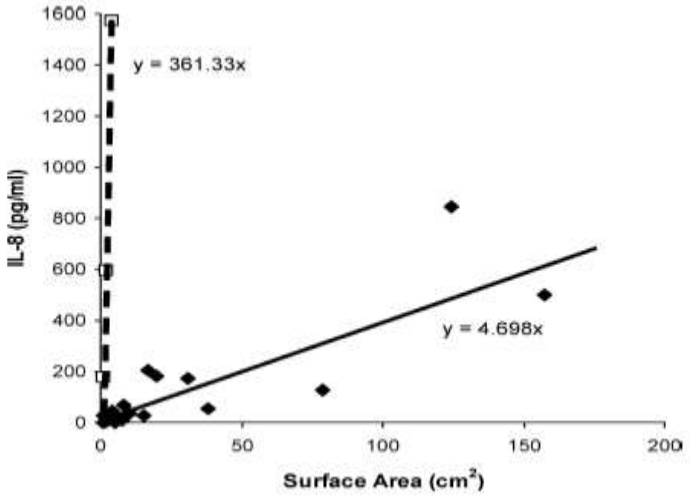


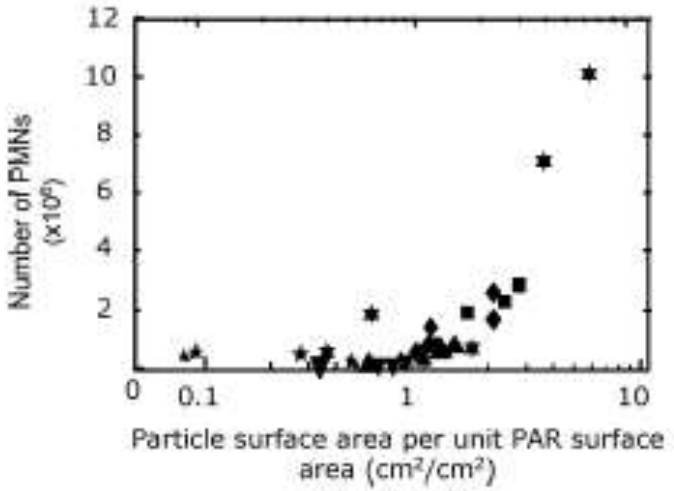


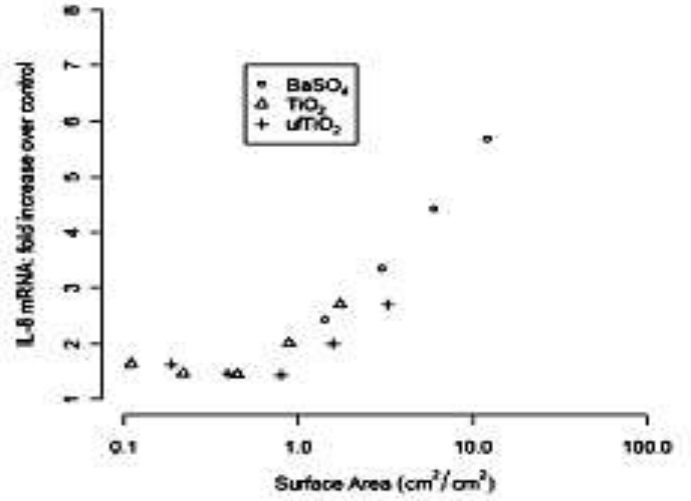


PULMONARY INFLAMMATION - DOSEMETRICS









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Strategy for Dosing Liver/Gut Model *in vitro*

Do a range finder experiment:

- Start with a High dose (ug/mL) where there is significant responses (e.g. inflammation)
- Reduce the dose incrementally to the NOAEL - So to complete a Dose-Response curve
- For liver studies –because there is no direct exposure: Use PBPK to estimate liver dose.
- For *in vivo* inhalation experiments – Data from literature on liver response for the range of inhaled NP.

Overall strategy

- Dose-Response *in vitro/in vivo* inhalation to be scaled, for a range of responses: Inflammation/fibrosis and a range of ENM (TiO2, BaSO4 etc…)
- Same approach to be used for Gut and Liver models.
- *in vitro* no-adverse effect doses to be scaled up to in vivo dose counterpart and used for risk assessment.

Conclusions

- Reduction of uncertainty in both in vitro and in vivo tests makes extrapolation more reliable. The realistic way forward is to quantify the uncertainty (e.g. inter-animal difference; extrapolation uncertainty etc…) and to understand the mechanisms behind the dose-response.
- Currently the lung model is the most promising and can be used as part of the Risk Assessment Exercise – Note that inhalation exposure is still the most likely exposure for workers and bystanders.
- The lung model is applicable to occupational and environmental sectors while Gut and Liver models are also relevant to consumer exposure.