

Human Health-Relevant Effects of ENMs: Priorities for Addressing Knowledge Gaps

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Conceptual framework: Ambient PM-to-ENM knowledge transfer



What have we learned and what can focus our future research efforts?

- Continued improvements with in vitro and in vivo dosimetry models
- Persistence and disposition of ENM in primary and secondary target tissues is largely unknown, as well as the impact of repeated/chronic exposures
- Keep innovating the methods for characterizing, detecting, and quantitating ENMs in media, cells, and tissues
- Have to deal with the complexity of exposure
- Leverage mechanistic knowledge from air pollution health effects database to identify vulnerable or susceptible populations

Risk = Hazard x Exposure

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Dosimetric models for particle delivery in vitro

ISDD: A computational model of particle sedimentation, diffusion and target cell dosimetry for *in vitro* toxicity studies

Paul M Hinderliter¹, Kevin R Minard^{1,3}, Galya Orr^{2,3}, William B Chrisler¹, Brian D Thrall^{1,3}, Joel G Pounds¹, Justin G Teeguarden^{1,3*}

Interactions of engineered nanomaterials in physiological media and implications for *in vitro* dosimetry

Joel Cohen, Glen DeLoid, Georgios Pyrgiotakis, & Philip Demokritou

An integrated approach for the in vitro dosimetry of engineered nanomaterials

Joel M Cohen¹, Justin G Teeguarden² and Philip Demokritou^{1*}

ISD3: a particokinetic model for predicting the combined effects of particle sedimentation, diffusion and dissolution on cellular dosimetry for in vitro systems

Dennis G. Thomas^{1*}, Jordan N. Smith², Brian D. Thrall², Donald R. Baer³, Hadley Jolley², Prabhakaran Munusamy³, Vamsi Kodali², Philip Demokritou⁴, Joel Cohen⁴ and Justin G. Teeguarden^{2,5*}

Nanotoxicol. (2013); Part. Fibre Toxicol. (2010, 2014, 2018)

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Dissolution and intracellular disposition of Cubased NPs (A549_{luc} cells)



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Particle distribution: Relationship to dissolution

Non-Calcined Mn_xO_v NP



What physicochemical changes do nanoparticles undergo in tissues? SiO₂ NP processing in lung tissue

(4 hr/day, 5 d/wk, 4 weeks; 27 d post-exposure; high dose)



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 - □ What is the 'identity' of the proximal toxicant: particle, solute, secondary particle, mixture??

Biodistribution of SiO_2 slurry NPs following inhalation exposure



18.1 mg/m³ SiO₂ Single 4-hr inhalation exposure Tissues harvested 7 days PE

Guttenberg et al., 2016

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No identification

Guttenberg et al., 2016

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Exposure to MWCNTs exacerbates allergen-induced airway inflammation and mucous secretion





Implications for individuals with asthma/allergic airways disease?

Thompson et al., 2015

Needs for future research efforts : broad themes

- Dosimetry
- Exposure 'identity'
- Model (toxicological) validation
- Embrace the chronicity of exposure
- Vulnerability/susceptibility

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