

Impact of Two Mechanistic Pathways on Nanomaterial Risk

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For nanoparticles, as with all chemicals, cell or organ toxicity will occur at sufficiently high tissue-specific doses. In extrapolation of these doses from inhalation exposure, the definition of particle dose is problematic. This challenge of defining dose is especially true for nanomaterials, where the traditional mass-based measurement of dose (e.g., mg/kg of lung wet-weight) may not be a specific predictor of toxic response. To establish acceptable exposure levels or to guide the design of biocompatible nanomaterials, defining the best predictors of tissue response requires additional dose and mechanistic information. In this research, the overall hypothesis to be evaluated is that nanomaterial toxicity depends on two separate and competing mechanisms: the inherent surface chemistry of the particles themselves, and the inhibition of molecular functions on the cell surface and within the cell by simple coverage of structures with particulate matter. To test the second part of this hypothesis, we propose to conduct the following experiments: measure the impact of coverage-inhibition-based mechanisms on macrophage and epithelial cell particle uptake rates, and, from these measurements, infer the importance of this pathway for toxic responses to nanoparticles compared to direct surface chemistries of the particles.

This research will be extremely relevant nanomaterials used in industry. By studying nanoparticle health effects, we provide an approach to shift the emphasis from hazard characterization to realistic prediction of the risk of nanomaterials. These studies will provide insight into mechanisms important to understanding the biological responses to inhaled nanomaterial, and will assess questions such as the following: Why singlet nanoparticles may not pose any significant health concern, yet nanoparticle-agglomerates (that disperse in lung-related fluids) may pose a significantly greater hazard.

Implications: This project has significant impact on defining the highest concentrations that can be justified reasonably in nanoparticle risk assessment extrapolations. Without studies of this kind, toxicologists could continue to use very high concentrations and produce results that become difficult to interpret in a human health context. These approaches should guide suggestions limiting maximum inhaled concentrations used in inhalation studies with nanoparticles.

Start and end date: February 2007 – December 2007

Presentation:

Moss, O. R. (2007). Toxicology of nanoparticles. Symposium on Nanotechnology: Wonders and Worries, American Industrial Hygiene Conference and Exposition (Invited presentation), Philadelphia, PA, June 2, 2007.

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Moss, O. R. (2006). Site-specific, dose-dependent transitional analysis of toxicologic mechanisms: The interplay of local metabolic and physicochemical saturation. *Toxicological Sciences* 91(2): 311-312.

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Sponsors in addition to the LRI: None.

Abstract revision date: March 2009