Health Effects of Inhaled Particles

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With particles, as with all chemicals, cell or organ toxicity is expected at sufficiently high particle dose. However, the description of dose is a challenge. For example, with nanomaterials the traditional mass-based measurement of dose (e.g., milligrams/kilogram) is not necessarily a specific predictor of toxic response. The generation of additional dosimetric and mechanistic information is essential in order to establish acceptable exposure levels or to validate the design of biocompatible materials. In this LRI-funded project the overall hypothesis was that inhaled particle biocompatibility (in particular, nanomaterial biocompatibility) depends on two mechanistic pathways: a pathway driven by chemical reactivity and a pathway driven by inhibition of biological function by coverage of cellular structures with particulate matter.

In order to test this hypothesis, we initially proposed to conduct studies with the following five specific aims (this project on health effects of inhaled particles only addressed specific aims 1, 2, and 5):

1. Measure impact of chemical-reactivity-based mechanisms on airway-smooth muscle cells;
2. Measure impact of coverage-based mechanisms on macrophage and epithelial cell particle uptake rates;
3. Determine the extent that cellular inflammation is affected by nanoparticle physical properties;
4. Match cellular-level threshold-doses with human inhalation exposure scenarios; and
5. Measure biomarkers of total lung response.

This research is extremely relevant for nanomaterials used in industry. By measuring biomarkers of total lung response, this research defined the boundaries of normal response mechanisms. Additionally, by studying nanoparticle health effects, this research provided an approach to shift the emphasis from hazard characterization to more realistic prediction of the risk of nanomaterials. These studies will provide insight into mechanisms important to understanding the risks of inhaled nanomaterial (e.g., why single particles might pose lower risks than nanoparticle-agglomerates that disperse in lung-related fluids).

Implications: Currently, nanoparticles are being proposed for many commercial uses. Toxicity of these particles is often measured in studies that use very high concentrations of these particles. We developed methods to assess response to inhaled particles in vitro and to understand conditions of overload due to high exposure concentrations. The ability to differentiate overload due to large numbers of retained particles in lungs from intrinsic particle toxicity is essential for making informed decisions about human health risk related to these novel materials.

Start and end date: January 2005 – December 2006

Presentations:


This abstract was prepared by the principal investigator for the project. Please see www.americanchemistry.com/lri for more information about the LRI.


Peer-reviewed publications:


Other publications:


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Other Private Funding: Private Industry – Non-chemical. [In this completed project we demonstrated the ability to measure breath biomarkers in a mouse model of particle-related pulmonary inflammation].

Other Private Funding: Private Industry – Non-chemical. [This currently active project is on morphometry-based cohort selection. The focus is to demonstrate proof of principle for sorting human subjects based on inhaled particle deposition efficiency].

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