

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 these novel materials.

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Presentations:

Bermudez, E. and Moss, O. R. (2005). Exhalation of cytokines by laboratory rodents. *The Toxicologist* 84 (S-1): 105. (Abstract 517).

Moss, O. R. (2005). When nanoparticles get in the way: Impact of projected area on *in vivo* macrophage function. Platform presentation, Frontiers in Aerosol Dosimetry Research Conference, The Beckman Center of the National Academies, Irvine, CA, October 24–25, 2005.

Moss, O. R., DeLorme, M. P., and Oldham, M. A. (2005). Morphometric and microdosimetric measurements, in methacholine-exposed A/J, Balb/c, and B6C3F1 mice, identify differences that have implications in detection of asthma susceptibility. Poster Presentation at the International Society for Aerosols in Medicine, Perth, Australia, March 14–18, 2005.

Moss, O. R., James, R. A., Parkinson, C. U., and Wong, B. A. (2005). Impact of low flow operation in three nose-only exposure systems. *The Toxicologist* 84 (S–1): 298. (Abstract 1463).

Moss, O. R., Tewksbury, E. W., Boggs, J., and Jackman, J. (2005). Use of aerosols to increase recovery of exhaled breath protein from unanesthetized pigs. Poster presentation at the 14th annual conference of the American Association for Aerosol Science, Austin, TX, October 17–21, 2005.

Bermudez, E. and Moss, O. R. (2006). Expression of osteopontin by rat alveolar macrophages in vitro. *The Toxicologist* 90 (S–1): 38. (Abstract 184).

Moss, O. R. (2006). Dosimetry can change mechanistic models: The challenge of scrutinizing dose calculations before building a response model. Presentation to Product Evaluation Division, R. J. Reynolds Tobacco Company, Winston-Salem, NC, February 6, 2006.

Moss, O. R. (2006). Dosimetry can change mechanistic models: The challenge of scrutinizing dose calculations before building a response model. Presentation by teleconference to Risk Assessment Specialty Section, Society of Toxicology, February 8, 2006.

Moss, O. R. (2006). Nanotechnology Symposium: Nanoparticles in the workplace. Invited platform presentation at American Hygiene Conference and Exposition, Chicago, IL, May 13, 2006.

Moss, O. R. (2006). Insights into nanoparticle toxicity. Invited platform presentation at National Institute for Occupational Safety and Health, Division of Applied Research and Technology, Cincinnati, OH, October 20, 2006.

Moss, O. R., Bermudez, E., and Tewksbury, E. W. (2006). Murine models of exhaled breath. Presentation to Product Evaluation Division, R. J. Reynolds Tobacco Co., Bowman Gray Technical Center, Winston-Salem, NC, February 6, 2006.

Moss, O. R., Bermudez, E., and Tewksbury, E. (2006). Murine models of exhaled breath. Presentation at Chlorine Research Project Group, U.S. EPA, Pulmonary Toxicology Branch, Research Triangle Park, NC, February 15, 2006.

Moss, O. R. and Tewksbury, E. W. (2006). Three minute inhalation of methacholine by B6C3F1 or Balb/c female mice produces no change in pressure drop across the isolated upper respiratory tract. *The Toxicologist* 90(S–1): 347. (Abstract 1697).

Moss, O. R. and Wong, B. A. (2006). Overcoming obstacles to effective research design in nanotoxicology. Poster presentation at Informa Learning's Conference on Overcoming Obstacles to Effective Research Design in Nanotoxicology, Cambridge, MA, April 24–25, 2006.

Moss, O. R. and Wong, V. A. (2006). Measuring the avalanche scenario in alveolar macrophages: Application of the confocal LSM in semi-automated counting of *in vitro* macrophage uptake of nanoparticles. Special Symposium on Nanoparticle Dosimetry Toxicology and Cellular Interactions at

American Association of Aerosol Research / International Society of Aerosols in Medicine International Meeting,, St. Paul, MN, September 10–15, 2006.

Moss, O. R. and Wong, V. A. (2006). Measuring the avalanche scenario in alveolar macrophages: Application of the confocal LSM in semi-automated counting of *in vitro* macrophage uptake of nanoparticles. Poster session at Symposium on Cancer Nanotechnology, Carolina Center of Cancer Nanotechnology Excellence, University of North Carolina, Chapel Hill, NC, November 13, 2006.

Moss, O. R. and Oldham, M. J. (2007). Impact of pulmonary morphometry in estimating regions of sensitivity to inhaled smooth-muscle agonists. Presentation at annual meeting of the International Society of Aerosols in Medicine, Vinci Congress Center, Tours, France, June 16–20, 2007.

Moss, O. R. and Wong, V. A. (2007). Accumulation rates of 26nm diameter particles by macrophages and epithelial cells. *The Toxicologist* 96 (S-1): 233. (Abstract 1124).

Moss, O. R., Tewksbury, E. W., and Nash, D. G. (2007). Capturing the exhaled protein aerosol: Evaluation of rodent-based systems. Poster presentation at annual meeting of the American Association for Aerosol Research, Reno, NV, September 24–28, 2007.

Peer-reviewed publications:

Mangum, J. B., Bermudez, E., Sar, M., and Everitt, J. I. (2004). Osteopontin expression in particle-induced lung disease. *Experimental Lung Research* 30: 585–598.

White, D. C., Geyer, R., Cantu, J., Jo, S.-C., Peacock, A. D., Saxton, A. M., Mani, S., Jeff, M., and Moss, O. R. (2004). Feasibility of assessment of regulatory lipids in breath condensate as potential presymptomatic harbingers of pulmonary pathobiology. *Journal of Microbiological Methods* 62: 293–302.

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.

Moss, O. R. and Oldham, M. J. (2006). Dosimetry counts: Molecular hypersensitivity may not drive pulmonary hyperresponsiveness. *Journal of Aerosol Medicine* 19(4): 555–564.

Moss, O. and Wong, V. (2006). When nanoparticles get in the way: Impact of projected area on *in vivo* and *in vitro* macrophage function. *Inhalation Toxicology* 18: 711–716.

Moss, O. R., James, R. A., and Asgharian, B. (2006). Influence of exhaled air on inhalation exposure delivered through a directed flow nose only exposure system. *Inhalation Toxicology* 18(1): 45–51.

Moss, O. R. (2008). Insights into the health effects of nanoparticles: Why numbers matter. *International Journal of Nanotechnology* 5(1): 3–14.

Other publications:

Jackman, J. and Moss, O. R. (2004). Mass spectrometry of breath for the diagnosis of infection and exposure. *Johns Hopkins Applied Physics Laboratory Technical Digest* 25: 6–13.

Moss, O. R. (2006). Insights into the health effects of nanoparticles: Why numbers matter. *CIIT Activities* 26(2): 1–7.

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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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