

Olfactory Transport and Systemic Delivery of Inhaled Nanoparticles

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There is still very limited knowledge of the fate of inhaled nanomaterials. Delivery of inhaled materials can reach the central nervous system (CNS) by systemic delivery or via direct transport of materials from the nasal cavity to the brain via the olfactory nerve (olfactory transport). There is a critical need to determine whether inhaled nanoparticles are delivered to the CNS via either of these routes. Studies with commercially available nanoparticles will examine mechanisms involved in the initial uptake of these materials by the olfactory epithelium. An initial phase of the project will examine the uptake of nanomaterials by cells lining the respiratory tract (e.g., alveolar macrophages, respiratory epithelial cells, olfactory neurons). These studies will use appropriate *in vitro* systems, including primary cells, cell lines, or explant cultures, and a variety of nanomaterials with different diameters. Other experiments will compare and contrast CNS delivery of materials following nasal or intratracheal (pulmonary) instillation or intravenous injection to explore the potential of a select group of nanomaterials to undergo olfactory transport and/or systemic delivery to the CNS (and other tissues). Nanomaterials to be used in this phase of the project will be chosen in part based upon their commercial availability, results of our *in vitro* studies, and our ability to use the materials in inhalation studies. Research products will include a more quantitative understanding of delivery and retention of particles in tissues. In this manner, real data on particle uptake and clearance will displace vague concerns that lead to conservative, default decisions. Data derived from these studies will also be used by CIIT scientists that have developed dosimetry models that describe nasal and lung deposition of particles and olfactory transport of inhaled materials, as well as other models developed to describe the fate of inhaled materials by laboratory animals. Our research will improve our understanding of the dosimetry and toxic potential of nanoparticles.

Implications: A limited number of particles can be deposited on tissues within the nose and taken up into the CNS along nerves of the olfactory system. Without a more quantitative measure of uptake rates and sites of accumulation of different particles, it will be difficult to confirm or refute the importance of this pathway for possible toxicity. This study provides approaches to measure CNS uptake from nasal epithelium and place this pathway in perspective compared to other routes of administrations and other possible target tissues.

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Presentations:

Dorman, D. C. (2005). Particle delivery and the brain. European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) Workshop on Testing Strategies to Establish the Safety of Nanomaterials, Barcelona, Spain, November 7–8, 2005.

Dorman, D. C. (2006). Risk assessment implications of direct nose-to-brain transport of inhaled xenobiotics. 45th Annual Meeting Society of Toxicology, San Diego, CA, March 5–9, 2006.

Dorman, D. C. (2006). An overview of nose-to-brain transport of inhaled metals. 45th Annual Meeting Society of Toxicology, San Diego, CA, March 5–9, 2006.

Dorman, D. C. (2006). Olfactory transport of inhaled metals. Naval Health Research Center, Wright Patterson Air Force Base, Dayton, OH.

Dorman, D. C. (2006). Nanoparticle research at CIIT Centers for Health Research. Naval Health Research

Center, Wright Patterson Air Force Base, Dayton, OH.

Moss, O. R. (2006). Toxicity of nanoparticles. Invited presentation at Nanotechnology Symposium: Nanoparticles in the Workplace, American Industrial Hygiene Conference and Exposition, McCormick Place Convention Center, Chicago, IL, May 13, 2006.

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

Moss, O. R. and Wong, B. A. (2006). Effective research in nanotoxicology requires five essential measurements; measurements to separate cell overload from covering of cells with particles. Presentation at 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. Poster presentation at American Association of Aerosol Research/International Society of Aerosols in Medicine International Meeting, Special Symposium on Nanoparticle Dosimetry Toxicology and Cellular Interactions, 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, November 13, 2006.

Radcliffe, P. M., Wong, V. A., Moss, O. R., and Dorman, D. C. (2008). Uptake of fine and ultra-fine polystyrene latex beads in Af549 cells. *The Toxicologist* 102 (S–1), 310. (Abstract 1511).

Peer-reviewed publications:

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

Radcliffe, P. M., Wong, V. A., Moss, O. R., and Dorman, D. C. (2008). Uptake of fine and ultra-fine polystyrene latex beads by human lung epithelial-like (A549) cells. *Nanotoxicology*. (Submitted).

Other publications:

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

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