

Biology and Dosimetry of Nanoparticles

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Compared to reliance on airborne levels of particles as a measure of dose, human health risk assessments are enhanced by calculation of deposition of airborne pollutants at specific sites in the lungs. Description of physical and physiological processes that lead to the transport and deposition of airborne material in the lung involves developing a mathematical model. Detailed models that include major aspects of these processes have been developed to support prediction of site-specific tissue dosimetry of fine and coarse particles. Models of particle deposition in the human lung covering a range of particle sizes, including nanoparticles (less than 100 nanometers) were developed. An existing computational lung-dosimetry model was modified to account for nanoparticles dosimetry. Modification of the existing lung-dosimetry model is a sequential process involving computation of particle transport and deposition in the human central airways, incorporation of lobar ventilation, particle axial diffusion and dispersion, and enhancement of the computational dosimetry model to include a graphical user interface format. The results of this research will support estimation of tissue dosimetry in several ongoing Long-Range Research Initiative (LRI) research projects on nanoparticle toxicology/kinetics and provide a user-friendly computer model that can be used to improve risk assessments with particles of various sizes.

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Presentations:

Asgharian, B. and Gudi, S. (2006). Calculations of airflow and particle deposition in an expanding-contracting lung geometry. Poster presentation at American Thoracic Society International Conference, San Diego, CA, May 19–24, 2006.

Asgharian, B., Gudi, S., and Wong, B. A. (2006). Particle deposition in the lung central airways. *The Toxicologist* 90(S-1): 434. (Abstract 2119).

Moss, O. R. (2006). Dosimetry can change mechanistic models: The challenge of scrutinizing dose calculations before building a response model. Teleconference presentation at Risk Assessment Specialty Section, Society of Toxicology, February 8, 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 1679).

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

Asgharian, B. (2005). Modeling airflow and particle deposition in the lung. Platform presentation at Department of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, April 19, 2005.

Asgharian, B., Price, O., Jarabek, A., and Miller, F. J. (2005). Improved dosimetric adjustment factors for interspecies extrapolation of inhaled, poorly soluble particles. *The Toxicologist* 84(S1): 432. (Abstract 2110).

Asgharian, B. and Price, O. T. (2005). The effect of body orientation on deposition of particles in the human lung. Proceedings of annual conference of the American Association for Aerosol Research, Houston, TX, October 17–21, 2005, p. 37. (Abstract 1PF5).

Asgharian, B. and Price, O. T. (2005). Calculated particle deposition in the human lung using various ventilation models. Platform presentation at Frontiers in Aerosol Dosimetry Research Conference, The Beckman Center for the National Academies, Irvine, CA, October 24–25, 2005.

Jarabek, A. M. (2005). Evaluation and prediction of dosimetry in children: Empirical and mechanistic approaches. *The Toxicologist* 84(S-1): 275. (Abstract 1342).

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., 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 International Society for Aerosols in Medicine, Perth, Australia, March 14–18, 2005.

Schroeter, J. D., Asgharian, B., and Kimbell, J. S. (2005). Effect of particle inertia on regional deposition of inhaled aerosols in a computational fluid dynamics model of human nasal airways. Poster presentation at International Society for Aerosols in Medicine 15th International Congress, Perth, Australia, March 14–18, 2005.

White, D. C., Beacock, A. D., Chang, Y.-J., Jo, S.-C., Cantu, J., Biggerstaff, J. P., Lepuil, M., Sublette, K. L., Moss, O. R., and Bermudez, E. (2005). Biomarkers to define interactions in the environment and health. Plenary lecture at International Conference on Environmental, Industrial, and Applied Microbiology, BioMicro World, Badajoz, Spain, March 15–18, 2005.

Wong, B. A., Kelly, J. T., Kimbell, J. S., and Asgharian, B. (2005). Nanoparticle deposition efficiency in human nasal airway replicas. *The Toxicologist* 84(S-1): 212. (Abstract 1039).

Asgharian, B. (2004). Deposition of hygroscopic particles in the lung and its application to aerosol drug delivery. Poster presentation at Respiratory Drug Deliver IX, Palm Springs, CA, April 25–29, 2004.

Asgharian, B. (2004). Dosimetry of inhaled particles in humans. Poster presentation at annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Miami, FL, May 5–6, 2004.

Asgharian, B. (2004). Models of airflow transport in the human lung. Platform presentation at American Society of Mechanical Engineers International Mechanical Engineering Congress and Research, Development, & Design Expo, Anaheim, CA, November 19, 2004.

Asgharian, B. and Price, O. (2004). Airflow and particle deposition in the human lung. Presentation at 23rd annual conference of the American Association for Aerosol Research, Atlanta, GA, October 4–8, 2004.

Asgharian, B. and Price, O. (2004). Airflow and particle deposition in the lung at microgravity and hypergravity environments. Presentation at 23rd annual conference of the American Association for Aerosol Research, Atlanta, GA, October 4–8, 2004.

Asgharian, B. and Price, O. (2004). Airflow distribution and particle deposition in different lobes of the lung. *The Toxicologist* 78(S-1): 435. (Abstract 2109).

Kimbell, J. S. (2004). Applications of computational fluid dynamics to studies of nasal uptake and deposition. Invited presentation at Biomathematics Program, Department of Statistics, North Carolina State University, Raleigh, NC, February 10, 2004.

Kimbell, J. S. (2004). Correlation of nasal surface-area-to-volume ratio with predicted inhaled gas uptake efficiency in humans. Poster presentation at annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Miami, FL, May 5–6, 2004.

Miller, F. J. (2004). Microdosimetric comparisons for particles in animals and humans: An overview of current knowledge and future needs. Invited platform presentation for 23rd annual conference of the American Association for Aerosol Research, October 5, 2004.

Moss, O. R. (2004). Microdosimetry of methacholine reveals interplay of morphology and physiology in pulmonary hypersensitivity. Invited presentation at Visiting Pulmonary Scholar Program, Durham, NC, November 3, 2004.

Moss, O. R., Tewksbury, E. W., and DeLorme, M. P. (2004). Microdosimetry of methacholine reveal interplay of morphology and physiology in pulmonary hypersensitivity. Platform presentation at 23rd annual conference of the American Association for Aerosol Research, October 5, 2004.

Segal, R., Kepler, G. M., Kalisak, D. L., Richardson, R. B., and Kimbell, J. S. (2004). Correlation of nasal surface-area-to-volume ratio with predicted inhaled gas uptake efficiency in humans. *The Toxicologist* 78(S-1): 434. (Abstract 2107).

Wong, B. A., Kelly, J. T., Asgharian, B., and Kimbell, J. S. (2004). Comparison of experimental measurements with model calculations of particle deposition efficiencies in the monkey and rat nasal airways. *The Toxicologist* 78(S-1): 435. (Abstract 2110).

Asgharian, B. (2003). The effect of particle growth on deposition in lung airways. Poster presentation at American Association for Aerosol Research annual conference, Anaheim, CA, October 20–24, 2003.

Asgharian, B. and Miller, F. J. (2003). Equivalent human exposure concentrations from rat inhalation studies. Poster presentation at American Association for Aerosol Science PM Meeting, Pittsburgh, PA, March 31, 2003.

Asgharian, B., Kimbell, J. S., Wong, B. A., and Moss, O. R. (2003). Compound independent dosimetry of inhaled material. Poster presentation at first annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Herndon, VA, June 24–25, 2003.

Gross, E. A., Kelly, J. T., Joyner, D. R., Dunn, C. S., Kimbell, J. S., and Asgharian, B. (2003) Generation of life-like rodent nasal models. *The Toxicologist* 72(1): 296. (Abstract 1437).

Kimbell, J. S. (2003). Considerations of dosimetry in the upper respiratory tract in animals and humans. Invited seminar at U.S. Environmental Protection Agency Workshop on Inhalation Risk Assessment: A Superfund Focus, Washington, DC, September 10, 2003.

Kimbell, J. S. (2003). Nasal dosimetry of inhaled gases and particles: Where do inhaled agents go in the nose? A multidisciplinary approach to assess nasal injury caused by the inhalation of complex mixtures in the rodent, a Society of Toxicologic Pathologists Symposium. Invited speaker at annual meeting of the American College of Toxicology, Washington, DC, November 4, 2003.

Kimbell, J. S., Segal, R. A., Kalisak, D. L., Richardson, R. B., and Kepler, G. M. (2003). Effects of interindividual differences in human nasal anatomy on upper respiratory tract airflow and inhaled gas uptake. Poster presentation at first annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Herndon, VA, June 24–25, 2003.

Kimbell, J. S., Segal, R. A., and Wexler, D. (2003). Three-dimensional computer modeling of the human upper respiratory tract. Poster presentation at 10th Congress of the International Rhinologic Society, 22nd International Symposium on Infection and Allergy of the Nose, Seoul, Korea, October 23–26, 2003.

Miller, F. J. (2003). Dosimetry of gases and particles: Issues related to the September 11 World Trade Center disaster. Invited platform presentation at annual Experimental Biology Meeting, San Diego, CA, April 15, 2003.

Miller, F. J. (2003). Dose to the target: The critical linkage between human exposure and response. Plenary session presentation at first annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Herndon, VA, June 24–25, 2003.

Moss, O. R. and DeLorme, M. P. (2003). Inhalation dosimetry differences in BALB/c and B6C3F1 mice influence airway responsiveness to methacholine challenge. *The Toxicologist* 72(1): 122. (Abstract 594).

Segal, R. A. and Kimbell, J. S. (2003). Three-dimensional computer modeling of the human upper respiratory tract. Platform presentation at 10th Congress of International Rhinologic Society, 22nd International Symposium on Infection and Allergy of the Nose, 26th Congress of the Korean Rhinologic Society, Seoul, South Korea, October 23, 2003.

Wong, B. A., Tewksbury, E. W., Kelly, J. T., and Asgharian, B. (2003). Regional and lobar deposition of fine and coarse particles in the lungs of rats and mice. *The Toxicologist* 72(1): 39. (Abstract 189).

Peer-reviewed publications:

Asgharian, B. and Price, O. (2006). Airflow distribution in the human lung and its influence on particle deposition. *Inhal. Toxicol.* 18: 795–801.

Asgharian, B., Price, O., and Oberdörster, G. (2006). The effect of gravity on airflow distribution and particle deposition in the lung. *Inhal. Toxicol.* 18: 473–481.

Kimbell, J. S. (2006). Nasal dosimetry of inhaled gases and particles: Where do inhaled agents go in the nose? *Toxicol. Pathol.* 34: 270–273.

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

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

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. *Inhal. Toxicol.* 18: 45–51.

Schroeter, J. D., Kimbell, J. S., and Asgharian, B. (2006). Analysis of particle deposition in the turbinate and olfactory regions using a human nasal computational fluid dynamics model. *J. Aerosol Med.* 19: 301–313.

Ménache, M. G., Hoffman, W., Asgharian, B., and Miller, F. J. (2006). Airway geometry models of children's lungs for use in dosimetry modeling. *Clin. Anat.* (Accepted).

Jarabek, A. M., Asgharian, B., and Miller, F. J. (2005). Dosimetric adjustments for interspecies extrapolation of inhaled poorly soluble particles (PSP). *Inhal. Toxicol.* 17: 317–334.

Kelly, J. T., Asgharian, B., and Wong, B. A. (2005). Inertial particle deposition in a monkey nasal mold compared with that in human nasal replicas. *Inhal. Toxicol.* 17: 823–830.

Asgharian, B. (2004). A model of deposition of hygroscopic particles in the human lung. *Aerosol Sci. Technol.* 38: 938–947.

Kelly, J. T., Asgharian, B., Kimbell, J. S., and Wong, B. A. (2004). Particle deposition in human nasal airway replicas manufactured by different methods. Part I: Inertial regime particles. *Aerosol Sci. Technol.* 38: 1063–1071.

Kelly, J. T., Asgharian, B., Kimbell, J. S., and Wong, B. A. (2004). Particle deposition in human nasal airway replicas manufactured by different methods. Part II: Ultrafine particles. *Aerosol Sci. Technol.* 38: 1072–1079.

Asgharian, B., Kelly, J. T., and Tewksbury, E. W. (2003). Respiratory deposition and inhalability of monodisperse aerosols in Long-Evans rats. *Toxicol. Sci.* 71: 104–111.

Hoffman, W. and Asgharian, B. (2003). The effect of lung structure on mucociliary clearance and particle retention in human and rat lungs. *Toxicol. Sci.* 73: 448–456.

Price, P. S., Conolly, R. B., Chaisson, C. F., Gross, E. A., Young, J. S., Mathis, E. T., and Tedder, D. R. (2003). Modeling interindividual variation in physiological factors used in PBPK models of humans. *Crit. Rev. Toxicol.* 33(5): 469–503.

Other publication(s):

Asgharian, B. (2004). Deposition of hygroscopic particles in the lung and its application to aerosol drug delivery. In *Respiratory Drug Delivery IX*, Vol. 2, Dalby, R. N., Byron, P. R., Peart, J., Suman, J. D., and Farr, S. J., editors), pp. 449–451. Virginia Commonwealth University, Richmond, VA.

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