

Particulate-Induced Pulmonary Pathobiology in Compromised Animals

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Research to elucidate the uncertainty of the health effects posed by inhalation of particulate matter (PM) is a high priority area. Concern about airborne particulate matter in recent years has been driven largely by epidemiological surveys that have reported relatively consistent associations between ambient PM levels and adverse health effects of both acute and chronic nature. To date, there has been limited toxicological evidence to suggest biological mechanisms to explain the toxic effects attributed to PM in epidemiological studies. Despite this, the U.S. Environmental Protection Agency recently added PM_{2.5} to the PM regulatory strategy. The U.S. Court of Appeals (DC Circuit) recently remanded the newly promulgated PM and Ozone standards to the EPA raising legal issues and calling for the Agency to clarify the “intelligible principles” used in setting the standards. The evolving body of evidence, in conjunction with the uncertainty posed by the PM issues in epidemiological studies, has suggested interspecies differences in the pathobiological response to inhaled particulates and the uncertainty of how humans are similar or dissimilar to well utilized animal models. The CIIT research team is primarily interested in addressing the issue of “individual susceptibility.” Examining the contribution of inhaled fine and ultrafine particulates on the genesis of lung disease in juvenile animals and in subjects having pre-existing pulmonary dysfunction is the focus of the project. Studies are being conducted to develop mouse models of pulmonary inflammation involving either allergy or viral infection for assessing responses to inhaled particles.

Start and end date: January 1998 – December 2002.

Presentation(s):

Floyd, H. S., Tichelaar, J. W., Dance, S. T., Everitt, J., Whitsett, J. A., and Miller, M. S. (2003). Expression of mutant human KI-ras induces lung tumors in bitransgenic mice. *Toxicol. Sci.* 72, 85. Supplement–*The Toxicologist*. (Abstract 413).

Lambert, A. L., Mangum, J. B., DeLorme, M. P., and Everitt, J. I. (2003). Exacerbation of respiratory syncytial virus infection by ultrafine carbon black particle exposure. *Toxicol. Sci.* 72 (1), 375. Supplement–*The Toxicologist*. (Abstract 1823).

DeLorme, M. P. and Moss, O. R. (2002). Interstrain differences in airway responsiveness to methacholine challenge observed in unrestrained, but not in restrained, plethysmography of mice. *Toxicol. Sci.* 66 (1), 98–99. Supplement–*The Toxicologist*. (Abstract 481).

Floyd, H. M., Tichelaar, J. W., Mizesko, M. C., Dance, S. T., Everitt, J., Whitsett, J. A., and Miller, M. S. (2002). Doxycyclin (dox)-regulated, lung-specific expression of mutant human Ki-ras I bitransgenic mice: alterations in lung morphology. *Toxicol. Sci.* 66(1), 310. Supplement–*The Toxicologist*. (Abstract 1519).

Lambert, A. L., DeLorme, M. P., Trasti, F. D., Mangum, J. M., and Everitt, J. I. (2002). Effect of ultrafine carbon black exposure on respiratory syncytial virus infection in mice. Presented at North Carolina Society of Toxicology Annual Meeting, Research Triangle Park, NC, March 2.

Lambert, A. L., DeLorme, M. P., Trasti, F. S., Mangum, J. B., and Everitt, J. I. (2002). Effect of ultrafine carbon black exposure on respiratory syncytial virus infection in mice. *Toxicol. Sci.* 166 (1), 360. Supplement—*The Toxicologist*. (Abstract 1765).

DeLorme, M. P. (2001). Thinking like a scientist. Invited presentation at Hillburn Elementary School, Raleigh, NC, January 1.

DeLorme, M. P. (2001). Effect of titanium dioxide exposure in BALB/c mice with endotoxin-induced pulmonary inflammation. Poster presentation at Annual Meeting of the Society of Toxicology, San Francisco, CA, March 27.

DeLorme, M. P. (2001). Effect of particulate matter exposure in the inflamed lung. Invited presentation at Johns Hopkins University Applied Physics Laboratory, Laurel, MD, May 9.

DeLorme, M. P. (2001). Tox-in-a-Box toxicology in the classroom. Invited presentation at St. Mary Magdalene School, Apex, NC, June 6.

DeLorme, M., Reverdy, E., Everitt, J., and Moss, O. (2001). Effect of titanium dioxide exposure in BALB/C mice with an endotoxin-induced pulmonary inflammation. Poster presentation at North Carolina Society of Toxicology Annual Meeting, Research Triangle Park, NC, March 3.

Everitt, J. I. (2001). Interspecies comparison of pulmonary responses to inhaled TiO₂. Presentation at Laboratory of Experimental Pathology, National Institute of Environmental Health Sciences, Research Triangle Park, NC, March 14.

Asgharian, B., Wong, B. A., Bermudez, E., and Everitt, J. I. (2000). A model of clearance of titanium dioxide from the rat lung. *Toxicol. Sci.* 60 (1), 195. Supplement—*The Toxicologist*. (Abstract 928).

Bermudez, E. (2000). Comparison of the pulmonary responses of rats, mice and hamsters to inhaled pigmentary titanium dioxide particles. Presentation at CIIT, Research Triangle Park, NC February 23.

Bermudez, E., Mangum, J. B., Reverdy, E. E., Wong, B. A., Asgharian, B., Hext, P. M., Warheit, D. B., and Everitt, J. I. (2000). Pulmonary responses of rats, mice, and hamsters to inhaled titanium dioxide (TiO₂). *Toxicol. Sci.* 54 (1), 314–315. Supplement—*The Toxicologist*. (Abstract 1476).

Bermudez, E., Mangum, J. B., Wong, B. A., Asgharian, B., Hext, P. M., Warheit, D. B., and Everitt, J. I. (2000). Pulmonary responses of rats, mice, and hamsters to inhaled ultrafine titanium dioxide (UTiO₂). *Toxicol. Sci.* 60 (1), 195. Supplement—*The Toxicologist*. (Abstract 929).

DeLorme, M. P., Reverdy, E. E., Everitt, J. I., and Moss, O. R. (2000). Effect of titanium dioxide exposure in BALB/c mice with endotoxin-induced pulmonary inflammation. *Toxicol. Sci.* 60 (1), 195. Supplement—*The Toxicologist*. (Abstract 926).

Reverdy, E. E., Bermudez, E., Mangum, J. B., Asgharian, B., and Everitt, J. I. (2000). The relationship of protein carbonyl levels to inflammatory responses in bronchoalveolar lavage fluid in rats, mice, and hamsters following inhaled pigmentary titanium dioxide. *Toxicol. Sci.* 54 (1), 13. Supplement—*The Toxicologist*. (Abstract 64).

Reverdy, E. E., Bermudez, E., Mangum, J. B., Asgharian, B., and Everitt, J. I. (2000). The relationship of protein carbonyl levels to inflammatory responses in bronchoalveolar lavage fluids in rats, mice, and hamsters following inhaled pigmentary titanium dioxide. Poster presentation at Annual Meeting of the Society of Toxicology, Philadelphia, PA, March 20. (Also presented at North Carolina Society of Toxicology Annual Meeting, Research Triangle Park, NC, February 26.)

Asgharian, B. (1999). An automated, tuned system for generating and delivering ultrafine titanium dioxide particles to three exposure chambers at different concentrations. Poster presentation at meeting of American Association for Aerosol Research, Tacoma, WA, October 10–15.

Everitt, J. I., Bermudez, E., Mangum, J. B., Asgharian, B., Reverdy, E., Wong, B., and Moss, O. R. (1999). Comparison of the pulmonary responses of female rats, mice, and Syrian golden hamsters to inhaled pigmentary titanium dioxide. Invited presentation at 7th International Symposium on Particle Toxicology, Maastricht, The Netherlands, October 14.

Reverdy, E. E., Everitt, J. I., Bermudez, E., Mangum, J. B., Asgharian, B., Wong, B., and Moss, O. R. (1999). Protein carbonyls in bronchoalveolar lavage fluid are a biomarker of pulmonary oxidative damage in mice, rats, and hamsters following inhalation of pigmentary titanium dioxide particles. Poster presentation at 7th Symposium on Particle Toxicology, Maastricht, The Netherlands, October 12–16.

Reverdy, E. E. (1999). Protein carbonyls in BALF, a biomarker of oxidant damage in lungs of rodents after TiO₂ inhalation. Young Investigator's Award for poster presentation at 6th Annual Meeting of the Oxygen Society, New Orleans, LA, November 18–22.

Peer-reviewed publication(s):

White, D. C., Geyer, R., Cantu, J., Jo, S., Peacock, A. D., Saxton, A. M., Mani, S., Jett, M., and Moss, O. R. (2005). Feasibility of assessment of regulatory lipids in breath condensate as potential presymptomatic harbingers of pulmonary pathobiology. *J. Microbiol. Methods* 62, 293–302.

Bermudez, E., Mangum, J. B., Moss, O. R., Wong, B. A., and Everitt, J. I. (2003). Pleural dosimetry and pathobiological responses in rats and hamsters exposed subchronically to MMVF 10a fiberglass. *Toxicological. Sci.* 74, 165–173.

Lambert, A. L., Mangum, J. B., DeLorme, M. P., and Everitt, J. I. (2003). Ultrafine carbon black particles enhance respiratory syncytial virus-induced airway reactivity, pulmonary inflammation, and chemokine expression. *Toxicol. Sci.* 72, 339–346.

Lambert, A. L., Trasti, F. S., Mangum, J. B., and Everitt, J. I. (2003). Effect of preexposure to ultrafine carbon black on respiratory syncytial virus infection in mice. *Toxicol. Sci.* 72, 331–338.

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Dye, J. A., Lehmann, J. R., McGee, J. K., Winsett, D. W., Ledbetter, A. D., Everitt, J. I., Ghio, A. J., and Costa, D. L. (2001). Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiologic studies in Utah Valley residents. *Environ. Health Perspect.* 109 (Suppl 3), 395–403.

Everitt, J. I., Mangum, J. B., Bermudez, E., Wong, B. A., Asgharian, B., Reverdy, E. E., Hext, P. M., and Warheit, D. B. (2000). Comparison of selected pulmonary responses of rats, mice, and Syrian golden hamsters to inhaled pigmentary titanium dioxide. *Inhal Toxicol.* 12 (Supplement 3), 275–282.

Reverdy, E. E., Bermudez, E., Mangum, J. B., Asgharian, B., Wong, B., and Everitt, J. I. (2000). Protein carbonyls in bronchoalveolar lavage fluid in mice, rats, and hamsters following inhalation to pigmentary titanium dioxide particles. *Inhal. Toxicol.* 12 (Supplement 3), 283–289.

Other publication(s):

CIIT Centers for Health Research (2001). Subchronic inhalation toxicity study of pigmentary titanium dioxide in female B6C3F1 mice, Fischer 344 rats, and Syrian golden hamsters. CIIT Centers for Health Research, Research Triangle Park, NC, 2001. (9 vol.)
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