Progress Toward Safe Nanotechnology in the Workplace

A Report from the NIOSH Nanotechnology Research Center

Project Updates for 2007 and 2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

On the cover: Multi-walled carbon nanotubes (MWCNT) in the lungs of a mouse 56 days after exposure. The shorter fibers on the right are penetrating the lung wall from the alveolar space. The longer fibers on the upper and lower left have penetrated the outer wall of the lung into the pleural space. *Image courtesy of Robert Mercer, NIOSH.*

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DHHS (NIOSH) Publication No. 2010–104

November 2009

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Foreword

As with any new technology, the earliest and most extensive exposures to engineered nanoparticles are most likely to occur in the workplace among the workers who produce and use nanoparticles. The National Institute for Occupational Safety and Health (NIOSH) is mandated by law to conduct research and develop guidance on worker safety and health. NIOSH and its partners in other government agencies, countries, academia, industry, labor, and nongovernmental organizations have been conducting research and developing guidance to address the occupational safety and health of workers exposed to nanomaterials.

In February 2007, NIOSH issued its report on P*rogress Toward Safe Nanotechnology in the Workplace*. That report described the progress of the NIOSH Nanotechnology Research Center (NTRC) since its inception in 2004 through 2006. In this November 2009 update, we describe program accomplishments achieved in 2007 and 2008. The NTRC has, with limited resources, continued to make contributions to all the steps in the continuum from hazard identification to risk management.

Occupational safety and health issues of nanotechnology are complex. The types of nanomaterials and the opportunities for workplace exposure continue to grow rapidly. The challenge is to effectively address the safety and health issues of nanotechnology while helping society realize the far-reaching potential benefits. NIOSH will continue to respond to this challenge.

John Howard, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

Executive Summary

Occupational safety and health issues of nanomaterials are complex. Because engineered nanomaterials are small yet have a relatively large surface area, they may have chemical, physical, and biological properties distinctly different from larger particles of similar chemical composition. Those properties may affect the ability of the nanomaterials to reach the gas exchange regions of the lung, travel from the lung throughout the body, penetrate dermal barriers, cross cell membranes, and interact at the molecular level. The types of nanomaterials and the opportunities for workplace exposure to them continue to grow rapidly. The challenge is to effectively address the safety and health issues of nanotechnology while helping society realize nanotechnology's far-reaching potential benefits.

The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency responsible for conducting research and making recommendations to prevent work-related injury, illness, and death. NIOSH is mandated by the Occupational Safety and Health Act to determine whether materials in a workplace constitute any harm and to provide recommendations for preventing injury and illness.

NIOSH established the Nanotechnology Research Center (NTRC) in 2004 to coordinate and promote research in nanotechnology and to develop guidance on the safe handling of nanomaterials in the workplace. The NTRC is a virtual center in which NIOSH scientists and engineers at geographically dispersed locations are linked by shared computer networks and other technologies. This approach surmounts the logistical complications that traditionally arise when scientists and engineers collaborating on common research are not physically in the same location. In 2007 the NTRC issued *Progress Toward Safe Nanotechnology in the Workplace* (DHHS NIOSH Publication No. 2007–123). That report describes the progress of the NTRC since its inception in 2004 through 2006. This November 2009 update describes program accomplishments achieved in 2007 and 2008, and it includes summary updates from 43 intramural projects and a comprehensive extramural program. The NTRC has, with limited resources, continued to make contributions to all the steps in the continuum from hazard identification to risk management (Figure 1).

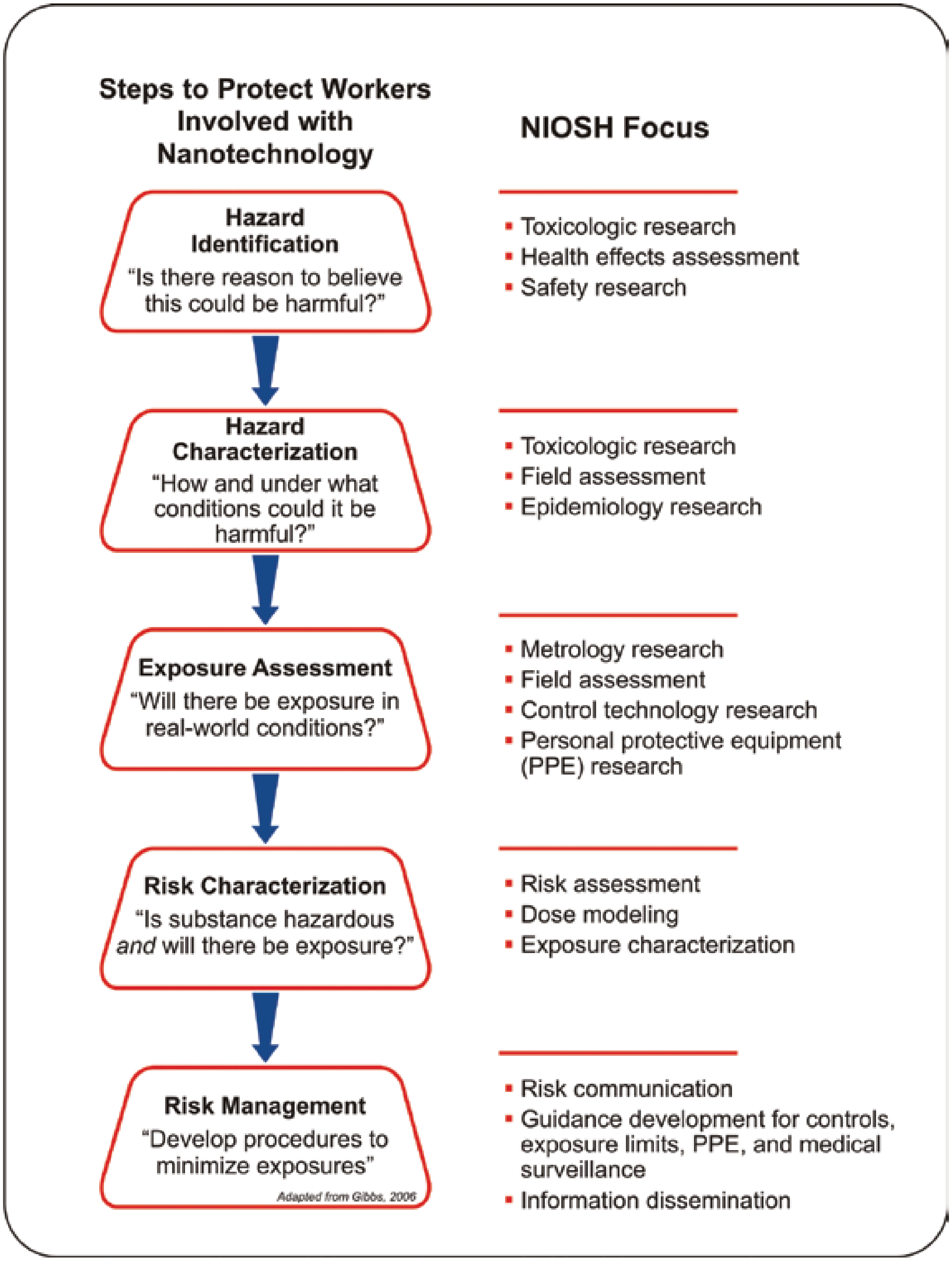

Figure 1. Steps in the continuum from hazard identification to risk management to protect workers involved with nanotechnology

The NTRC has four goals:

1. Determine whether nanoparticles and nanomaterials pose risks of work-related injuries and illnesses.
2. Conduct research to prevent work-related injuries and illnesses by applying nanotechnology products.
3. Promote healthy workplaces through interventions, recommendations, and capacity building.
4. Enhance global workplace safety and health through national and international collaborations on nanotechnology research and guidance.

As evidenced by the full report, progress continues to be made toward each of these goals. The following paragraphs present highlights of each goal.

1. Determine whether nanoparticles and nanomaterials pose risks of work-related injuries and illnesses.

Since 2004, the NTRC has pioneered research on the toxicological properties and characteristics of nanoparticles. This research is relevant for predicting whether these particles pose a risk of adverse health effects in workers. These research projects have involved characterizing occupationally relevant nanoparticles—particularly the toxicity of carbon nanoparticles. Preliminary work by the NTRC investigators demonstrated that mice exhibited harmful pulmonary effects (such as a fibrotic response) soon after low-dose aspiration exposure to specific nanotubes. The NTRC established a system for generating nanoparticle aerosol and began conducting animal inhalation studies during the summer of 2006. The inhalation studies verified the same fibrotic response seen in the aspiration studies. NTRC investigators have evaluated the potential for nanoparticles to enter the bloodstream and move to systemic tissues after being deposited in the lungs. These studies will help scientists determine whether some engineered nanomaterials pose risks to human health in the work setting. They will also help determine the mechanisms by which engineered nanomaterials operate. The results of these studies are preliminary and limited, and more research is needed to predict whether they signal a health risk to humans. The results obtained thus far support the need to address that question and provide promising leads for strategic, ongoing studies.

To gain further knowledge about exposure and control practices, the NTRC established a field team to conduct assessments of workplaces where exposure to engineered nanoparticles may occur. By partnering in 2007 and 2008 with 12 companies that produce or use engineered nanoparticles, this team collected useful information about potential worker exposures, control technologies, and risk management practices.

2. Conduct research to prevent work-related injuries and illnesses by applying nanotechnology products.

The NTRC has identified various possibilities for applying nanotechnology to occupational safety and health, including the application of this technology in fabricating more efficient filters, sensors, and protective clothing. The NTRC and the Office of Extramural Programs at NIOSH are coordinating projects with academia and the private sector.

3. Promote healthy workplaces through interventions, recommendations, and capacity building.

Nationally and internationally, the NTRC has delivered a wide range of presentations on occupational safety and health issues associated with nanotechnology. These have included presentations to scientific conferences, trade associations, and professional associations; meetings of government agencies and nongovernmental organizations (NGOs); and special panels convened by government agencies, NGOs, and professional associations. Since its inception, the NTRC has published more than 170 papers in peer-reviewed scientific literature and provided a broad range of information and guidance. In addition, the NTRC has provided seminal guidance for workers and employers in nanotechnology through the following documents:

- *Interim Guidance for Medical Screening and Hazard Surveillance for Workers Potentially Exposed to Engineered Nanoparticles*, DHHS NIOSH Publication No. 2009–116
- *Approaches to Safe Nanotechnology: Managing the Health and Safety Concerns Associated with Engineered Nanomaterials*, DHHS NIOSH Publication No. 2009–125
- *Safe Nanotechnology in the Workplace: An Introduction for Employers, Managers, and Safety and Health Professionals*, DHHS NIOSH Publication No. 2008–112
- *The Nanotechnology Field Research Team Update*, DHHS NIOSH Publication No. 2008–120
- *NIOSH Nanotechnology Field Research Effort Fact Sheet*, DHHS NIOSH Publication No. 2008–121
- *NIOSH Nanotechnology Metal Oxide Particle Exposure Assessment Study*, DHHS NIOSH Publication No. 2008–122

- Draft *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps*, published February 2008 [www.cdc.gov/niosh/topics/nanotech/strat_planA.html]

4. Enhance global workplace safety and health through national and international collaborations on nanotechnology research and guidance.

The NTRC has established several national and international collaborations to advance understanding of occupational safety and health for nanotechnology workers. The NTRC participates in the National Nanotechnology Initiative (NNI) and has contributed to the nanotechnology strategic plan for the Nation through the Nanotechnology Environmental Health Implications (NEHI) working group. Occupational safety and health has been a chief priority of the NEHI effort, and the NIOSH strategic research plan and activities are addressing most of the major issues in the NEHI plan.

The NTRC is part of the U.S. leadership on the International Organization for Standardization (ISO) TC 229, Nanotechnology Working Group on Health, Safety, and the Environment. NIOSH led the development and publication of ISO TR/12885:2008, *Health and Safety Practices in Occupational Settings Relevant to Nanotechnologies*. The NTRC also works with the World Health Organization collaborating centers on global projects of information dissemination and communication. NIOSH co-led the World Health Organization project on best practices for safe handling of nanomaterials.

The NTRC has collaborated with the Organization for Economic Cooperation and Development (OECD) to build cooperation, coordination, and communication among the United States and 30 OECD member countries (including the European Union) and with more than 180 nonmember economies. NIOSH chaired the OECD Working Party for Manufactured Nanomaterials Steering Group 8, exposure measurement and exposure mitigation.

NIOSH cosponsored the 3rd International Symposium on Nanotechnology, Occupational and Environmental Health held in Taiwan in 2007 and serves on the planning committee for the 4th international conference scheduled for August 2009 in Helsinki, Finland. In addition, the NTRC is collaborating with the U.S. Environmental Protection Agency, the Occupational Safety and Health Administration, and other government agencies to obtain and evaluate exposure and good work practice information.

Critical Topic Areas

The NTRC research program has identified 10 critical topic areas for understanding the potential health risks and developing and disseminating recommendations:

1. Toxicity and internal dose
2. Measurement methods
3. Exposure assessment
4. Epidemiology and surveillance
5. Risk assessment
6. Engineering controls and PPE
7. Fire and explosion safety
8. Recommendations and guidance
9. Communication and information
10. Applications

By working in these 10 critical areas, NIOSH has comprehensively begun addressing the information and knowledge gaps necessary to protect workers and responsibly move nanotechnology forward so that its far-reaching benefits may be realized.

Coordination with the National Nanotechnology Initiative

NIOSH participates in the NNI Strategy for Nanotechnology Environmental Health and Safety Research. Table 1 shows the alignment of the four NIOSH NTRC strategic goals and the 10 NTRC critical research areas with the NNI priority environmental health and safety research needs.

The research being conducted by the NIOSH NTRC continues to be funded by redirecting existing NIOSH programmatic funds: $4.4 million in FY 2007 and $ 5.7 million in FY 2008. A more comprehensive research program specific to nanomaterials has been difficult to implement because of this budgetary constraint. However, even with the budgetary constraints, NIOSH investigators have continued to build an evidence-based strategy for providing safe nanotechnology in the workplace.

Table 1. Alignment of the four strategic goals and ten critical research areas of the NIOSH NTRC with the priority environmental health and safety research needs of the NNI*

NIOSH NTRC strategic goals	Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses	Conduct research on applying nanotechnology to the prevention of work-related injuries and illnesses[1]	Promote healthy workplaces through interventions, recommendations, and capacity building	Enhance global workplace safety and health[1]
Toxicity and internal dose	✓[3], A2[4], B1, B2, B3, B4, B5			✓
Measurement methods	✓, A1, A2, A3, A4, A5, B2	✓	✓, E1	✓
Exposure assessment[2]	✓, A1, A2, D1, D4, D5, E1, E2		✓, E2	✓
Epidemiology and surveillance	✓, D1, D2, D3, D4, E4		✓, E4	✓
Risk assessment	✓, A2, B1, B2, D4, E3		✓, E3, E5	✓
Engineering controls and PPE	✓, D5	✓	✓, E1	✓
Fire and explosion safety	✓, A2			✓
Recommendations and guidance			✓, E1, E5	✓
Communication and information			✓, E1, E5	✓
Applications		✓		✓

[1]The NNI EHS plan does not address applications or global activities pertaining to environmental health and safety of nanomaterials. However the NIOSH efforts described herein are consistent with the overall NNI strategy which does identify international opportunities for collaboration.

[2]NIOSH is the lead agency for the NNI EHS Strategic area on human and environmental exposure assessment.

[3]A ✓ indicates that a goal is addressed by projects within the NIOSH critical research area

[4]Alpha-numeric identifications indicate alignment of the NIOSH critical research area with the specific NNI priority research needs (see Appendix A).

Contents

Abbreviations

AIHA	American Industrial Hygiene Association
ACGIH	American Conference of Governmental Industrial Hygienist
AM	alveolar macrophage
AP-1	activator protein 1
APR	air–purifying respirators
ASME	American Society of Mechanical Engineers
ASSE	American Society of Safety Engineers
ASTM	American Society for Testing and Materials
ATP	adenosine triphosphate
BAL	bronchoalveolar lavage
CARB	California Air Resources Board
CDC	Centers for Disease Control and Prevention
CNF	carbon nanofiber
CNT	carbon nanotube
COPD	Chronic obstructive pulmonary disease
CPSC	Consumer Product Safety Commission
DEP	diesel exhaust particulate
DEER	Diesel Engine– Efficiency and Emissions Research
DEPE	diesel exhaust particulate extract
DERT	Developmental Engineering Research Team
DHHS	U.S. Department of Health and Human Services
DIC	different interference confocal
DNA	dioxyribonucleic acid
DOE	U.S. Department of Energy
DPF	diesel particulate filter
EC–SOD	extracellular superoxide dismutase
EHS	Environmental Health and Safety
EPA	U.S. Environmental Protection Agency
ESD	electron spin resonance
ESLI	end-of-service life indicator
ESR	erythrocyte sedimentation rate

FASEB	Federation of American Societies for Experimental Biology
FCA–SS	flux core arc–stainless steel
FDA	U.S. Food and Drug Administration
FISH	fluorescent in situ hybridization
GMA–MS	gas metal arc–mild steel
HEI	Health Effects Institute
HEPA	high-efficiency particulate air
HHE	Health Hazard Evaluation
HPS	Health Physics Society
IANH	International Alliance for NanoEHS Harmonization
IDLH	immediately dangerous to life and health
IEC	International Electrotechnical Commission
IOM	Institute of Occupational Medicine
ILO	International Labor Organization
ILSI	International Life Sciences Institute
ISO	International Organization for Standardization
IRSST	Institut de recherché Robert–Sauvè en santé et en sécurité du travail
kW	kilowatt
LDH	lactate dehydrogenase
LLC	limited liability company
LM	Listeria monocytogenis
LNW	long nanowire
MAPKs	mitogen–activated protein kinase
MINChar	Minimum Information Needed for Characterization of Nanomaterials
MMA–HS	manual metal arc–hard surfacing
MOUDI	micro–orifice uniform deposit impactor
MPPD	multipath particle deposition
MWCNT	multi-walled carbon nanotube
NADPH	nicotinamide adenine dinucleotide phosphate
NASA	National Aeronautics and Space Administration
NATO	North Atlantic Treaty Organization

NCER	National Center for Environmental Research
NEAT	nanoparticle emission assessment technique
NEHI	Nanotechnology Environmental and Health Implications
NFkB	nuclear factor kB
NGO	non-governmental organization
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIL	Nanoparticle Information Library
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NO	nitric oxide
nm	nanometer(s)
NNI	National Nanotechnology Initiative
NORA	National Occupational Research Agenda
NS	nanosphere
NSC	National Safety Council
NSET	Nanoscale Science, Engineering, and Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
NTRC	Nanotechnology Research Center
NSC	National Safety Council
OEP	Office of Extramural Programs
OECD	Organization for Economic Cooperation and Development
OEP	Office of Extramural Programs
OPN	osteoponin
OSHA	U.S. Occupational Safety and Health Administration
PEL	permissible exposure limit
PMN	polymorphonuclear neutrophils
POSS	polyhedral oligomeric silsesquioxanes
PPE	personal protective equipment
r2p	Research to Practice
RFA	request for application
RNS	reactive nitrogen species

ROS	reactive oxygen species
SBIR	small business innovation research
SMPS	scanning mobility particle sizer
SNW	short nanowire
SRM	standard reference material
STEL	short term exposure limit
SWCNT	single-walled carbon nanotube
TC	technical committee
TEM	transmission electron microscopy
TGF–ß	transforming growth factor beta
TiO2	titanium dioxide
TR	technical report
μg/m3	microgram per cubic meter
UK	United Kingdom
USAF	U.S. Air Force
VEGF	vascular endothelial growth factor
Wc–Co	tungsten carbide
WHO	World Health Organization
WT	wild type

Acknowledgments

This report was developed by the scientists and staff of NIOSH who participate in the NTRC. Paul Schulte is the manager, and Charles Geraci is the coordinator of the NIOSH National Occupational Research Agenda (NORA), Nanotechnology cross-sector program. Special thanks go to Laura Hodson and Ralph Zumwalde for writing and organizing the report.

Others who contributed substantially to the progress report include James Antonini, Eileen Birch, Aleksandar Bugarski, Vincent Castranova, Brian Curwin, Min Ding, Douglas Evans, Pengfei Gao, Mark Hoover, Bon-Ki Ku, Eileen Kuempel, Stephen Leonard, Jane Ma, Robert Mercer, Mark Methner, Arthur Miller, Vladimir Murashov, Terri Pearce, Dale Porter, Yong Qian, Appavoo Rengasamy, Jennifer Roberts, W. Allen Robison, Liying Wang Rojanasakul, Linda Sargent, Mary Schubauer-Berigan, Ronald Shaffer, Anna Shvedova, Petia Simeonova, Jay Snyder, Krishnan Sriram, Aleksandr Stefaniak, Jennifer Topmiller, Douglas Trout, and Leonid Turkevich.

The NIOSH NTRC also acknowledges the contributions of Vanessa B. Williams, Gino Fazio, and Anne Stirnkorb for desktop publishing and graphic design and Elizabeth Fryer for editing the report.

Introduction

Background

The NIOSH Nanotechnology Research Center (NTRC) was established in 2004 to coordinate and promote research in nanotechnology and develop guidance on the safe handling of nanomaterials in the workplace. Since its inception, the NTRC has published more than 170 papers in peer-reviewed scientific literature and provided a broad range of information and guidance (see 2007 Progress Report http://www.cdc.gov/niosh/docs/2007-123/ and Table 2). Publications in the areas of hazard identification and characterization, exposure assessment, risk assessment, and risk management have provided a framework for addressing hazards and risks from engineered nanoparticles. Although NTRC has contributed significantly to the understanding of health risks to nanoparticles, further research and subsequent development and dissemination of interim guidance efforts are limited by a lack of funding. NIOSH has to the best of its ability allocated limited resources to competing priorities and redirected funds internally over the past 4 years to build modest increases in support of the NIOSH Nanotechnology Research Program. New infusions of funding beyond the current NIOSH budget, specifically directed toward the program, would be needed for significant expansion of research to address the following research gaps:

- Although NIOSH toxicology studies have provided better understanding of the ways in which some types of nanoparticles may enter the body and interact with the body's organ systems, the breadth and depth of such research efforts have been limited to a few nanoparticle types. More types of nanoparticles need to be assessed for characteristics and properties relevant for predicting potential health risks.
- NIOSH field investigators have assessed exposure to engineered nanoparticles in some workplaces, but little data exist on the extent and magnitude of exposure to other types of nanoparticles in workplaces that manufacture or use nanomaterials, nanostructures, and nanodevices.
- NIOSH guidance is a first step toward controlling nanoparticles in the workplace; however, more research is needed on the efficacy and specificity of engineering and work practice control measures. NIOSH needs support to conduct more field investigations.
- The number of workers involved with the research, development, production, and use of engineered nanomaterials is increasing, but there is a lack of specific guidance for occupational health surveillance. NIOSH needs support to conduct research on the short- and long-term

health risks in nanotechnology workers. This may involve conducting large-scale prospective epidemiologic studies and establishing exposure registries.

- The utility of nanotechnology to support development of new technologies (such as sensors, more efficient filters, and better protective materials) that can enhance the protection of workers requires further research and development and can be advanced by additional resources.

The NIOSH NTRC has advanced the scientific knowledge in understanding the possible health risks of engineered nanoparticles as demonstrated by the ongoing projects beginning on page 15. Table 2 (see Appendix B) lists the projects by number and critical topic areas researched (e.g., toxicity and internal dose, measurement methods, exposure assessment). These projects are also listed in Appendix A for each critical topic area.

Partnerships and Collaborations

Integral to completing this research are the partnerships and collaborations NIOSH has forged with countries, academia, industry, labor, other government agencies, and nongovernmental organizations. These collaborations have provided expertise and resources critical for successfully completing research and for developing and disseminating health and safety information on engineered nanoparticles. The following are some of the ongoing NIOSH NTRC partnerships and collaborations in nanotechnology research:

Universities

- The Ohio State University, evaluating workplaces, controls, and practices in the nanocomposites industry
- University of Cincinnati, translating nanotechnology research into occupational and environmental health and safety activities
- University of Dayton Research Institute, understanding and improving the control of carbon nanotubes
- University of Iowa, measuring airborne concentrations of ultrafine particles
- University of Nevada at Reno (with Altair Nano), understanding and improving the control of ultrafine metal oxides and engineered nanomaterials
- University of Massachusetts at Lowell, collaborating on the development of good practices for handling nanomaterials in research laboratories and developing exposure assessment methods
- University of Minnesota, measuring airborne concentrations of ultrafine particles
- University of Montana, evaluating the toxicity of nanowires
- University of Montreal, assessing and characterizing nanoparticles in the workplace
- University of Pittsburgh, evaluating the toxicity of nanomaterials
- University of Rochester, measuring the ability of nanoparticles to generate radical species
- University of Wisconsin, Madison, developing exposure assessment strategies and characterizing nanoparticles in friction stir welding and micromachining

- Virginia Tech University (with Luna Nano Works), understanding and improving the control of fullerines and other engineered nanoparticles
- West Virginia University Nanotechnology Center, evaluating the toxicity of metal oxide nanowires
- West Virginia University Medical School, evaluating the effects of pulmonary exposure to nanoparticles, including the influence of exposure to titanium dioxide (TiO_2) on systemic microvascular function

Safety and Health Organizations and Expert Groups

- American Industrial Hygiene Association (AIHA), participating on working group activities and information exchange and dissemination for nanoparticle characterization and control
- American Conference of Governmental Industrial Hygienists (ACGIH)
- American Society of Safety Engineers (ASSE)
- Hamner Institutes for Health Sciences, modifying software for use in lung dosimetry modeling
- Health Physics Society (HPS), participating in working group activities and information exchange and dissemination for nanoparticle characterization and control
- International Safety Equipment Association, collaborating on the respirator filter media work being conducted at the University of Minnesota to assess the filtration efficiency against nanoparticles
- International Alliance for Nanotoxicology Harmonization (IANH), establishing protocols for reproducible toxicological testing of nanomaterials in both cell cultures and animals
- National Safety Council (NSC)
- The initiative on Minimum Information Needed for Characterization of Nanomaterials (MINChar), on encouraging adoption of a minimum set of physical and chemical material characterization parameters in nanotoxicology studies
- Institute of Occupational Medicine (IOM), Edinburgh, Scotland, revising rat lung dosimetry models to account for particle size-specific clearance and retention.

Federal and Other Government Agencies

- Environmental Protection Agency (EPA)
- Occupational Safety and Health Administration (OSHA), evaluating the effectiveness of workplace control measures
- Consumer Product Safety Commission (CPSC)
- National Aeronautics and Space Administration (NASA), evaluating the toxicity of single-walled carbon nanotubes (SWCNTs)
- U.S. Air Force
- U.S. Army
- Department of Energy (DOE)
- National Institute of Environmental Health Sciences/ National Institute of Health and the Department of Defense on nanotoxicology
- National Institute of Standards and Technology (NIST), evaluating the toxicity of nanoparticles and developing nanoscale reference materials
- National Nanotechnology Initiative (NNI) through active participation in NNI's strategic and budget planning processes, and coordination of research into occupational safety and health of nanotechnology with other government agencies
- National Toxicology Program, participating in the conduct of field assessments and toxicological research
- Oak Ridge National Laboratory, evaluating the pulmonary toxicity of nanoparticles
- Institut de Recherche Robert-Sauve en Santé et en Securite du Travail (IRSST), exchanging information on approaches to safe nanotechnology
- Karolinska Institute, evaluating the effect of nanomaterials on immune cells
- U.S. Nuclear Regulatory Commission, exchanging information on emerging application and health and safety issues for nanotechnology in the nuclear arena
- World Health Organization (WHO)
- Organization for Economic Cooperation and Development (OECD), collaborating on exposure measurement and exposure mitigation

- International Labour Organization (ILO), developing information on nanotechnology for a revised edition of the Encylopaedia of Occupaitonal Health and Safety
- International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), developing international standards for terminology, characterization, and safety practices for nanotechnology

Nanotechnology Industries

- DuPont and the Nanoparticle Occupational Safety and Health industry consortium on issues related to the measurement of nanoparticles and the efficiency of filtration materials for engineered nanoparticles
- Mitsui Co. Inc., evaluating the bioactivity of multi-walled carbon nanotubes (MWCNTs).
- IBM, evaluating the bioactivity of silicon nanowires
- Luna Nano Works, understanding and improving the control of fullerines and other engineered nanoparticles
- Altair Nano, understanding and improving the control of ultrafine metal oxides and engineered nanomaterials
- Quantum Sphere, understanding and improving the control of nanoscale metals and metal oxides
- QD Vision, understanding and improving the control of quantum dots
- NanoMech LLC (Fayetteville, Arkansas), collaborating on a proposed EPA phase I SBIR project related to containment of airborne nanoparticles

Collaborative Workshops

- In FY 2005, NIOSH cosponsored the first Symposium on Occupational Health Implications of Nanomaterials in Buxton, United Kingdom
- In FY 2006, NIOSH cosponsored the second Symposium on Occupational Health Implications of Nanomaterials in Minneapolis, MN.
- In 2007,
  — NIOSH collaborated with the International Aerosol Research Assembly and the American Association for Aerosol Research to hold the Second International Symposium on Nanotechnology and

Occupational Health in conjunction with the international aerosol conference in St. Paul, MN.

- — NIOSH and the University of Cincinnati cosponsored the International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, in Cincinnati, OH.
- — NIOSH convened a collaborative workshop that included representatives from government, academia, labor, and industry in Washington, DC, to review a draft document developed by NIOSH and a cross-agency work group, titled *Interim Guidelines on Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles.*
- — NIOSH cosponsored the Third Symposium on Occupational Health Implications of Nanomaterials in Taipei, Taiwan.

- In 2008,
  - — NIOSH served as the agency lead to organize the program for the National Nanotechnology Initiative Workshop on Human and Environmental Exposure Assessment held February 2009, in Bethesda, MD.
  - — NIOSH co-sponsored a National Institute of Standards and Technology Workshop on Enabling Standards for Nanomaterial Characterization in Gaithersburg, MD.
  - — NIOSH co-sponsored The Second International Conference on Nanotechnology in Zurich, Switzerland.
  - — NIOSH co-sponsored the Organization for Economic Co-operation and Development workshop on Exposure Assessment and Exposure Mitigation in Frankfurt, Germany.
  - — NIOSH participated in the planning of the Fourth International Conference on Nanotechnology—Occupational and Environmental Health held in August 2009, in Helsinki, Finland.

NIOSH Extramural Nanotechnology Research Activities

The NIOSH Office of Extramural Programs (OEP) manages the competitive process for awarding occupational safety and health grants and cooperative agreements to the research community outside the Institute. This process includes peer review, program relevance, and priorities from the National Occupational Research Agenda (NORA), the NIOSH r2p initiative, congressional mandates, and sector, or cross-sector areas of the NIOSH Program Portfolio (http://www.cdc.gov/niosh/programs).

From 2001 to 2009, the Office of Extramural Programs (OEP) has funded nanotechnology research through Occupational Safety and Health Research Program Announcements (R01) and Small Business Innovation Research Grants (R43/44). Since FY 2005, OEP has also participated in two joint Requests for Applications (RFAs) for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. The US Environmental Protection Agency's National Center for Environmental Research (NCER) and the National Science Foundation (NSF) participated in FY 2005. The National Institute of Environmental Health Sciences (NIEHS) joined in FY 2006. Funding was available to support Research (R01) grants for three years and Exploratory (R21) grants for two year.

In FY 2007, NIOSH/OEP participated in RFA-ES-06-008 Manufactured Nanomaterials: Physico-chemical Principles of Biocompatibility and Toxicity. This RFA was jointly sponsored by NIEHS, EPA, and NIOSH.

In FY 2009, nanotechnology related research proposals submitted to standing program announcements are being considered for funding by NIOSH/OEP.

To date, NIOSH/OEP has committed about $5.3 million dollars to research on applications and implications of nanotechnology. Summaries of the projects funded by NIOSH/OEP are included in Appendix B. NIOSH/OEP plans to continue collaborative efforts with EPA/NCER, NSF, NIH/NIEHS, and other international agencies to support nanotechnology research with occupational safety and health implications. OEP will continue to confer with the NIOSH Nanotechnology Research Center regarding issues, gaps, and future directions.

Table 2. NTRC projects in the 10 critical topic areas for 2007–2008

Project number	Toxicology and Internal dose	Measurement methods	Exposure assessment	Epidemiology and surveillance	Risk assessment	Engineering controls and PPE*	Fire and explosion	Recommen-dations/ guidance	Communi-cation and information	Applications
1	X	X	X	X	X	X	X	X	X	X
2			X							
3	X									
4	X									
5	X									
6	X									
7	X									
8	X									
9	X									
10	X									
11	X									
12	X									
13	X									
14	X									
15	X									
16	X									
17	X									
18	X									
19	X									
20	X									
21	X									
22		X								
23		X	X				X			

(Continued)

Table 2 (Continued). NTRC projects in the 10 critical topic areas for 2007–2008

Project number	Toxicology and Internal dose	Measurement methods	Exposure assessment	Epidemiology and surveillance	Risk assessment	Engineering controls and PPE*	Fire and explosion	Recommen-dations/ guidance	Communi-cation and information	Applications
24		X	X							
25		X	X							
26		X								
27		X								
28		X								
29		X								
30		X								
31		X	X							
32		X								
33		X	X							
34			X							
35				X						X
36					X					
37						X				
38						X				
39						X				
40									X	
41			X						X	
42										X
43			X		X			X	X	

*PPE=personal protective equipment

Project-Specific Progress Reports

Project 1: Nanotechnology Research Center Coordination

Principal Investigator: Charles Geraci, Ph.D.

Project Duration: FY 2006–2010

Critical Topic Areas: (1) toxicity and internal dose, (2) measurement methods, (3) exposure assessment, (4) epidemiology and surveillance, (5) risk assessment, (6) engineering controls and personal protective equipment, (7) fire and explosion safety, (8) recommendations and guidance, (9) communication and information, and (10) applications

Accomplishments and Research Findings

- Coordinated the NIOSH Nanotechnology Research Program across 10 critical areas identified in the strategic research plan developed by the NTRC in 2005 to identify and prioritize nanotechnology research.
- Sponsored and provided strategic direction to the Nanotechnology Field Research Team, which conducted 14 site visits in the reporting period.
- Fostered collaboration among investigators across the entire NIOSH Nanotechnology Research Program.
- Developed and maintained successful interagency agreements with
  - — Occupational Safety and Health Administration
  - — Consumer Product Safety Commission
  - — National Toxicology Program
- Fostered collaboration in nanotechnology research with
  - — AIHA
  - — ASSE
  - — NSC
  - — U.S. Air Force
  - — U.S. Army
  - — NASA
  - — DOE

Benchtop weighing of CNT. *Image courtesy of Mark Methner, NIOSH*

  — International Alliance for NanoEHS Harmonization
  — University of Massachusetts, Lowell
  — The Ohio State University
  — University of Dayton Research Institute

- Represented NIOSH on several national and international working groups on nanotechnology, safety, and health.
- Presented overviews of the NIOSH Nanotechnology Research Program to numerous organizations.
- Provided briefings to the President's Council of Advisors on Science and Technology.

Publications and Abstracts

- Hoover MD, Stefaniak AB, Day GA, Geraci CL [2007]. Exposure assessment considerations for nanoparticles in the workplace. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 71–83.
- Kuempel ED, Geraci CL, Schulte PA [2007]. Risk assessment approaches and research needs for nanomaterials: an examination of data and information from current studies. In: Simeonova PP, Opopol N, Luster MI, eds. Nanotechnology: toxicological issues and environmental safety, NATO security through science series book. New York: Springer-Verlag, pp. 119–145.
- NIOSH [2008]. Safe nanotechnology in the workplace. An introduction for employers, managers, and safety and health professionals. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Pub No. 2008–112.
- NIOSH [2008]. The nanotechnology field research team update. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Pub No. 2008–120.
- NIOSH [2008]. NIOSH nanotechnology field research effort fact sheet. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Pub No. 2008–121.

- NIOSH [2008]. NIOSH nanotechnology metal oxide particle exposure assessment study. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Pub. No. 2008–122.
- NIOSH [2008]. Draft Strategic plan for NIOSH nanotechnology research: filling the knowledge gaps. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, February 2008 [www.cdc.gov/niosh/topics/nanotech/strat_planA.html].
- Schulte PA, Geraci CL, Zumwalde RD, Hoover MD, Kuempel ED [2008]. Occupational risk management of nanoparticles. J Occup Environ Hyg 5(4):239–249.
- Schulte PA, Trout D, Zumwalde R, Kuempel E, Geraci CL, Castranova V, Mundt D, Mundt K, Halperin W [2008]. Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: state of the science. J Occup Med *50*(5):517–526.
- Schulte PA, Geraci CL, Zumwalde R, Hoover MD, Castranova VA, Kuempel E, Murashov V, Vainio H, Savolainen K [2008]. Sharpening the focus on occupational safety and health in nanotechnology. Scand J Work Environ Health *34*(6):471–478.
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- NIOSH [2009]. Approaches to safe nanotechnology: managing the health and safety concerns with engineered nanomaterials. Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Pub. No. 2009–125.

Invited Presentations

- Geraci CL [2007]. Nanotechnology: an overview of health and safety issues "implications and applications." Ohio Safety Congress and Expo, Columbus, OH, March 20.

- Geraci CL [2007]. The NIOSH Nanotechnology Research Program: occupational implications and applications. General Electric nanotechnology summit, Miskayuna, NY, April 18.
- Geraci CL [2007]. Nanotechnology: using basic risk management concepts to address difficult questions. Society for Chemical Hazard Communication spring meeting, San Antonio, TX, April 25.
- Geraci CL [2007]. The NIOSH Nanotechnology Research Program: occupational implications and applications. Northeastern University panel on nanotechnology and policy, Boston, MA, May 1.
- Geraci CL [2007]. Nanomaterials in the workplace: applying basic risk management principles. American Society of Safety Engineers webinar, May 15.
- Geraci CL [2007]. Nanotechnology: an international perspective from NIOSH. Education Safety Association of Ontario annual conference, Ontario, Canada, May 31.
- Geraci CL, Hoover MD [2007]. Exposure assessment and sampling issues for nanotoxicology and safe handling of nanoparticles in the workplace. American Industrial Hygiene Association conference and exposition, roundtable 201: Toxicology and exposure assessment issues for nanotechnology: an update for industrial hygienists, Philadelphia, PA, June 2–7.
- Geraci CL [2007]. One year later: an update of the NIOSH Nanotechnology Research Program. American Industrial Hygiene Association conference and exposition, roundtable 218: Ask the experts: an update on the NIOSH Nanotechnology Research Program, Philadelphia, PA, June 2–7.
- Geraci CL [2007]. Building OS&H capability in nanomaterial manufacturing: an example of "research to practice." American Society of Safety Engineers conference and exposition, Orlando, FL, June 25.
- Geraci CL [2007]. Meeting the challenge: an update of the NIOSH Nanotechnology Research Program. ORC Worldwide Occupational Safety and Health joint meeting, Washington, DC, August 8.
- Geraci CL, Methner MM, Dunn KH, Coe-Sullivan S [2007]. Occupational safety and health field study of workers potentially exposed to quantum dot nanomaterials. International symposium on nanotechnology: occupational and environmental health, Taipei, Taiwan, August 29.

- Geraci CL [2007]. Occupational risk management for nanomaterials along the product life cycle. International symposium on nanotechnology: occupational and environmental health, Taipei, Taiwan, September 1.
- Geraci CL [2007]. International collaboration opportunities in nanotechnology research. International symposium on nanotechnology: occupational and environmental health, Taipei, Taiwan, September 1.
- Geraci CL [2007]. Progress in addressing the occupational safety and health concerns of nanotechnology. President's Council of Advisors on Science and Technology, briefing panel, Washington, DC, September 11.
- Geraci CL [2007]. Workplace risk management of nanomaterials: challenges and lessons learned. NanoTX'07, Dallas, TX, October 3.
- Geraci CL [2007]. Nanotechnology: the new workplace, industrial hygiene implications. Professional conference on industrial hygiene, Louisville, KY, October 17.
- Geraci CL [2007]. Nanotechnology: the new workplace, Nano 101 for the industrial hygienist. Professional conference on industrial hygiene, Louisville, KY, October 23.
- Geraci CL [2007]. The NIOSH Nanotechnology Research Program. Professional conference for industrial hygiene, Louisville, KY, October 23.
- Geraci CL [2007]. Nanotechnology: the new workplace, workplace exposure assessment challenges. American College of Occupational Medicine State-of-the-Art Conference/International Conference on Health Care Worker Health, Vancouver, British Columbia, Canada, October 27.
- Geraci CL [2007]. Safe development of nanotechnology. Massachusetts governor's panel on nanotechnology-office of technical assistance and technology, Boston, MA, November 15.
- Geraci CL, Hoover MD [2007]. A risk assessment and control approach, teleweb on nanotechnology health and safety: case studies in the occupational setting. American Conference of Governmental Industrial Hygienists, December 4.
- Hoover MD, Geraci CL [2008]. Nanotoxicology issues for assessing and managing occupational exposure risks for nanoparticles in the workplace. American Industrial Hygiene Association distance learning program, January 31.

- Geraci CL [2008]. Occupational safety and health issues and nanotechnology. Education Resource Committee program directors meeting, Galveston, TX, February 10.
- Schulte PA [2008]. Occupational safety and health issues and nanotechnology. Food and Drug Law meeting, Washington, DC, February 18 and 19.
- Geraci CL [2008]. Progress in addressing the occupational safety and health concerns of nanotechnology. Meeting with Lockheed Martin, Baltimore, MD, February 1.
- Geraci CL [2008]. Progress in addressing the occupational safety and health concerns of nanotechnology. Meeting with the New Jersey Technology Council, Rutgers University, Camden, NJ, March 4.
- Geraci CL [2008]. Nanotechnology and occupational safety and health: What do we know? SESHA annual high technology environmental health and safety symposium, Portland, OR, March 27.
- Geraci CL, Methner MM, Pearce TA, Hodson LL [2008]. Nanotechnology for industrial hygienists. American Industrial Hygiene Association—Central Ohio section meeting, Columbus, OH, April 22.
- Geraci CL, Hoover MD, Heidel DS, Pearce TA, Methner MM, Hodson LL [2008]. Nanoparticles in the workplace: assessing and managing risks. American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.
- Geraci CL [2008]. Update on NIOSH research on the measurement of nanoparticles in the workplace. American Industrial Hygiene Association conference and exposition, roundtable 218: Ask the experts: an update on NIOSH Nanotechnology Research Program, Minneapolis, MN, May 31–June 5.
- Geraci CL [2008]. NIOSH guidance on nanotechnology: protecting our workers environmental, health, and safety issues in nanomaterials workshop. Meeting sponsored by The American Ceramic Society/National Institute of Standards and Technology, Gaithersburg, MD, June 8–10.
- Geraci CL [2008]. Nanotechnology and occupational safety and health: What do we know? International conference on nanotechnology for the forest products industry, St. Louis, MO, June 25.
- Geraci CL [2008]. The NIOSH nanotechnology field research team—a brief summary and update of activities. DOE nanoscale science

research centers symposium: safe handling of engineered nanoscale materials, teleseminar to Argonne, IL, July 9.

- Geraci CL [2008]. Engineering controls: the continuum of prevention through design, control banding, and engineering controls. OECD Working Party on Manufactured Nanomaterials Workshop on Exposure Assessment and Exposure Mitigation, Frankfurt, Germany, October 20.
- Geraci CL [2008]. Nanotechnology: real world challenges for the industrial hygienist. Professional Conference on Industrial Hygiene. Tampa, FL, November 11.
- Geraci CL [2008].]. Nanotechnology: real world challenges for the industrial hygienist. California Industrial Hygiene Council, San Diego, CA, December 8.
- Methner MM, Hodson LL and Geraci CL [2008] Nanoparticle emission assessment technique (NEAT) used by NIOSH for Identifying Sources and Releases of Engineered Nanoparticles. Ohio Valley American Industrial Hygiene Association section, West Chester, OH, December 16.

Project 2: Nanotechnology Safety and Health Research Coordination

Principal Investigator: Vincent Castranova, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Coordinated the NIOSH nanotoxicology program.
- Fostered collaboration among investigators in the nanotoxicology program.
- Fostered collaboration in nanotechnology research with
  - — The Consumer Products Safety Commission
  - — International Alliance for NanoEHS Harmonization
  - — Mitsui & Co.
  - — West Virginia University
  - — NASA
  - — University of Rochester
  - — University of Montana
  - — University of Pittsburgh
  - — Karolinska Institute
- Represented NIOSH during involvement with several national and international working groups on nanotechnology safety and health.
- Represented NIOSH during involvement with the National Nanotechnology Initiative nanotechnology environmental and health implication strategic planning group.
- Presented overviews of the NIOSH nanotoxicology program to numerous organizations.

Publications and Abstracts

- Mossman BT, Borm PJ, Castranova V, Costa DL, Donaldson K, Kleeberger SR [2007]. Mechanisms of action of inhaled fibers, particles, and nanoparticles in lung and cardiovascular diseases. Part Fibre Toxicol *4*:4.

- Leonard SS, Castranova V, Chen BT, Schwegler-Berry D, Hoover M, Piacitelli C, Gaughan D [2007]. Particle size dependent generation from wildland fire smoke. Toxicol *236*:103–113.
- Balbus JM, Maynard AD, Colvin VL, Castranova V, Daston GP, Denison RA, Dreher KL, Goering PL, Goldberg AM, Kulinowski KM, Monteiro-Riviere NA, Oberdörster G, Omenn GS, Pinkerton KE, Ramos KS, Rest KM, Sass JB, Silbergeld EK, Wong BA [2007]. Meeting report: hazard assessment for nanoparticles. Environ Health Perspect *115*(11):1654–1659.
- Schulte PA, Trout D, Zumwalde R, Kuempel E, Geraci CL, Castranova V, Mundt DJ, Mundt K, Halperin WE [2008]. Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: state of the science. J Occup Environ Med *50*:517–526.
- Papp T, Schiffmann D, Weiss D, Castranova V, Vallyathan V, Rahman Q [2008]. Human health implications of nanomaterial exposure. Nanotoxicol *2*:9–27.
- Ayres JG, Borm P, Cassee F, Castranova V, Donaldson K, Ghio A, Harrison RM, Hider R, Kelly F, Kooter I, Marano F, Maynard RL, Mudway I, Nel A, Sioutas C, Smith S, Baeza-Squiban A, Cho A, Duggan S, Froines J [2008]. Evaluating the toxicity of airborne particulate matter and nanoparticles by measuring oxidative stress potential—a workshop report and consensus statement. Inhal Toxicol *20*:75–99.
- Castranova V [2008]. The Nanotoxicology Research Program in NIOSH. J Nanopart Res [www.springerlink.com/content/c302m62567162101/].
- Pacurari M, Yin XJ, Zhao J, Ding M, Leonard SS, Schwegler-Berry D, Ducatman BS, Sbarra D, Hoover MD, Castranova V, Vallyathan V [2008]. Raw single-walled carbon nanotubes induce oxidative stress and active MAPKs, AP-1, NFkB, and Akt in normal and malignant human mesothelial cells. Environ Health Perspect *116*:1211–1217.
- Pacurari M, Yin XJ, Ding M, Leonard SS, Schwegler-Berry D, Ducatman BS, Chirila M, Endo M, Castranova V, Vallyathan V [2008]. Oxidative and molecular interactions of multi-walled carbon nanotubes in normal and malignant human mesothelial cells. Nanotoxicol *2*:115–170.
- Vallyathan V, Pacurari M, Yin X, Zhao J, Ding M, Leonard S, Ducatman B, Castranova V [2008]. Alterations in molecular signaling of human

mesothelial cells exposed to raw single-walled carbon nanotubes. Respir Crit Care Med *177* Abs Issue:A219.

- Pacurari M, Robinson V, Castranova V, Leonard SS, Chen F, Vallyathan V, Bargern M [2008]. Does sandblasted metal attenuate or enhance the toxicity of freshly fractured silica? Toxicologist *102*:A300.
- Castranova V [2008]. Comparison of in vitro, pharyngeal aspiration, and inhalation results for single-walled carbon nanotubes. Toxicologist *102*:A2356.
- Hubbs AF, Mercer RR, Sriram K, Castranova V, Chen BT, McKinney W, Frazer DG, Batelli L, Willard P, Scabilloni J, Schwegler-Berry D, Porter D [2008]. Acute respiratory toxicolgic pathway of inhaled multi-walled carbon nanotubes. Vet Pathol *45*:A220.
- Schulte PA, Geraci CL, Zumwalde R, Hoover M, Castranova V, Kuempel E, Murashov V, Vainio H, Savolainen K [2008]. Sharpening the focus on occupational safety and health of nanotechnology. Scand J Work Environ Health, *34*(6):471–478.

Invited Presentations

- Castranova V [2007]. Nanotoxicology research in NIOSH. Toxicology forum, Washington, DC, January 30.
- Castranova V [2007]. Nanotechnology research in NIOSH. Meeting of the Northeastern chapter of the American Industrial Hygiene Association, Cleveland, OH, May 8.
- Castranova V [2007]. Nanotoxicology research in NIOSH. NASA Glenn Research Center, Cleveland, OH, May 8.
- Castranova V [2007]. Nanotoxicology research in NIOSH. American Industrial Hygiene Association conference and exposition, Philadelphia, PA, June 2–7.
- Castranova V [2007]. Nanotoxicology research in NIOSH. West Virginia University Cancer Center, NTRC meeting in Morgantown, WV, February 21.
- Castranova V [2007]. Critical toxicity parameters for nanoparticles vs. conventional particles. Presentation for the Department of Occupational Medicine, West Virginia University, Morgantown WV, August 28.

- Castranova V [2007]. Critical toxicity parameters for nanoparticles vs. conventional particles. Department of Physiology, West Virginia University, Morgantown, WV, August 30, 2007.
- Castranova V [2007]. What do we know about exposure and human health effects on nanoparticles. Annual scientific conference of the Occupational and Environmental Medical Association of Canada, Banff, Alberta, Canada, October 15 and 16.
- Castranova V [2007]. Critical toxicology parameters for nanoparticles vs. conventional particles. Conference on Bringing toxicology to global issues in occupational and environmental public health. Louisville, KY, October 18.
- Castranova V [2007]. Biological effects of nanoparticles. State-of-the-Art Conference/ International Conference on Health Care Worker Health, Vancouver, Canada, October 26–28.
- Castranova V [2007]. NIOSH nanomaterials research activities. International Life Sciences Institute (ILSI) nanomaterials environmental health and safety project committee, Washington, DC, November 8.
- Castranova V [2007]. Critical toxicity parameters for nanoparticles vs. conventional particles. Nanotechnology and occupational health and safety conference, Santa Barbara, CA, November 16 and 17.
- Castranova V [2007]. NIOSH nanotoxicology research. European NanOSH conference—nanotechnologies: a critical area in occupational safety and health, Helsinki, Finland, December 3–5.
- Castranova V [2008]. The Nanotoxicology Research Program in NIOSH. National Institute of Standards and Technology, Gaithersburg, MD, January 28.
- Castranova V [2008]. Nanotoxicology research in NIOSH: nanotechnology update for industrial hygienists, American Industrial Hygiene Association distance learning program January 31.
- Castranova V [2008]. Critical toxicity parameters for nanoparticles vs. conventional particles. Northern California Industrial Hygiene Society meeting, Palo Alto, CA, May 14.
- Castranova V [2008]. NIOSH nanotoxicology program. American Industrial Hygiene Association Conference and Exposition, Minneapolis, MN, May 31–June 5.
- Castranova V [2008]. NIOSH nanotoxicology research: biological activity of single-walled carbon nanotubes. American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.

Project 3: Systemic Microvascular Dysfunction: Effects of Ultrafine vs. Fine Particle

Principal Investigator Vincent Castranova, Ph.D.

Project Duration: FY 2006–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Designed, constructed, and tested a generation system to produce a stable airborne concentration of fine and ultrafine TiO_2.
- Conducted inhalation exposures evaluating the dose-independent systemic microvascular response to pulmonary deposition of fine vs. ultrafine TiO_2 and found the following:

— Inhalation of TiO_2 inhibited dilation of microvessels in the shoulder.

— Inhalation of TiO_2 resulted in inhibition of the ability of microvessels in the shoulder to respond to dilators.

— Systemic microvascular effects were demonstrated at lung burdens of TiO_2, which did not cause widespread pulmonary inflammation as judged by BAL markers.

— On an equivalent mass deposited basis, ultrafine TiO_2 was approximately 10-fold more potent in causing systemic microvascular dysfunction than fine TiO_2.

— Inhalation of TiO_2 inhibited nitric oxide production by systemic microvessels in response to dilators.

— The inhibition of nitric oxide production by microvessels is reversed by inhibitors of reactive oxygen species.

— The inhibition of microvessel dilation is partially reversed by blockade of neural input to the microvessel.

— The inhibition of microvessel dilation is partially reversed by systemic depletion of neutorphils.

— Inhalation of TiO_2 inhibited the ability of coronary vessel to dilate.

Publications and Abstracts

- Nurkiewicz TR, Porter DW, Hubbs AF, Stone S, Chen BT, Frazer D, Castranova V [2007]. Microvascular endothelium-dependent nitric oxide production is attenuated after inhalation of ultrafine particulate matter. FASEB J *21*:A846.
- Nurkiewicz TR, Porter DW, Hubbs AF, Cumpston JL, Chen BT, Frazer DG, Castranova V [2008]. Nanoparticle inhalation augments particle-dependent systemic microvascular dysfunction. Part Fibre Toxicol *5*(1).
- LeBlanc A, Hu Y, Muller-Delp J, Moseley A, Chen B, Frazer D, Castranova V, Nurkiewicz T [2008]. Particulate matter inhalation impairs coronary microvascular reactivity. Proc 25th Er Soc Microcir Conference, Budapest, Hungary, August 26–29, pp. 13–17.
- Nurkiewicz TR, Porter DW, Hubbs AF, Chen BT, Frazer DG, Castranova V [2008]. Ultrafine particulate matter inhalation attenuates microvascular endothelial nitric oxide production. Toxicologist *102*:A1255.

Invited Presentations

- Nurkiewicz TR, Porter DW, Hubbs AF, Millecchia LL, Donlin M, Chen TB, Frazer DG, Castranova V [2007]. Nanoparticle inhalation attenuates systemic microvascular endothelium-dependent nitric oxide production. World Congress for Microcirculation, Milwaukee, WI, August 15–19.
- Castranova V [2007]. Inhalation of ultrafine titanium dioxide augments particle-dependent microvascular dysfunction. Nanotoxicology conference, Venice, Italy, April 20.
- Castranova V [2007]. Cardiovascular effects of pulmonary exposure to nanoparticles. Toxicology and risk assessment conference, Cincinnati, OH, April 25.
- Castranova V [2007]. Inhalation of ultrafine titanium dioxide augments particle-dependent microvascular dysfunction. Center for Environmental Health, University of Montana, Missoula, MT, September 21.
- Castranova V [2008]. Systemic microvascular effects of pulmonary exposure to fine vs. ultrafine particles. University of Connecticut, Storrs, CT, April 7.
- Castranova V [2008]. Systemic microvascular effects of pulmonary exposure to fine vs. ultrafine particles. Meeting held at John Hopkins University, Baltimore, MD, June 10.

- Castranova V [2008]. Ambient particulates and/or nanoparticles: cardiovascular and pulmonary toxic and morphologic manifestations. International Conference on Particles: Risks and Opportunities, September 2–5.
- Chen BT, McKinney W, Schwegler-Berry D, Castranova V, Frazer D [2008]. Aerosolization and characterization of multi-walled carbon nanotubes for inhalation studies. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.
- Castranova V [2008]. Systemic microvascular effects of pulmonary exposure to particles. Presentation at the Harvard School of Public Health, Cambridge, MA, October 24.
- LeBlanc AF, Hu Y, Miller-Delp J, Chen D, Frazer BT, Castranova V, Nurkiewicz TR [2008]. Nanoparticle inhalation impairs endothelium-dependent vasoreactivity in coronary arterioles. American Heart Association conference, Washington DC, November 8–12.

Project 4: Particle Surface Area as a Dose Metric

Principal Investigator: Vincent Castranova, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Developed a method to improve dispersion of nanoparticles in biologically compatible suspension media.
- Determined that improved nanoparticle dispersion results in a greater inflammatory response after intratracheal instillation of ultrafine carbon black in rats.
- Compared ultrafine TiO_2 and carbon black to fine TiO_2 and carbon black, respectively, and determined that the ultrafine particles of both are more inflammogenic on a mass-dose basis.
- Determined that on an equivalent total particle surface area basis, the potencies of ultrafine versus fine TiO_2 or carbon black were not significantly different.
- Determined that pulmonary inflammation following intratracheal instillation of ultrafine TiO_2 was more persistent than after installation of ultrafine carbon black.
- Determined that in vitro treatment with ultrafine TiO_2 stimulates oxidant production and induction of molecular signaling events in macrophages.

Publications and Abstracts

- Shvedova A, Sager T, Murray A, Kisin E, Porter D, Leonard SS, Schwegler-Berry D, Robinson V, Castranova V [2007]. Critical issues in the evaluation of possible effects resulting from airborne nanoparticles. In: Monteiro-Riviere NA, Tran CL, eds. Nanotechnology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 221–232.

- Sager T, Porter D, Robinson V, Lindsley WG, Schwegler-Berry DE, Castranova V [2007]. An improved method to disperse nanoparticles for in vitro and in vivo investigation of toxicity. Nanotoxicol *1*:118–129.
- Sager T, Robinson V, Porter D, Schwegler-Berry DE, Lindsley W, Castranova V [2007]. An improved method to prepare suspensions of nanoparticles for treatment of lung cells in culture or in vivo exposure by pharyngeal aspiration or intratracheal instillation. Toxicologist *96*:A1120.
- Kang JL, Moon C, Lee HS, Park E-M, Kim HS, Castranova V [2008]. Comparison of the biological activity between ultrafine and fine titanium dioxide particles in RAW 264.7 cells associated with oxidative stress. J Toxicol Environ Health *71*:478–485.
- Porter DW, Sriram K, Wolfarth MG, Jefferson AM, Schwegler-Berry DE, Andrew ME, Castranova V [2008]. A biocompatible medium for nanoparticle dispersion. Nanotoxicology *2*:144–154.
- Kang JL, Moon C, Lee HS, Lee HW, Park E-M, Kim HS, Castranova V [2008]. Comparison of the biological activity between ultrafine and fine TiO_2 particles in RAW 264.7 cells associated with oxidative stress. Toxicologist *102*:A1486.
- Sager T, Porter D, Castranova V [2008]. Pulmonary response to intratracheal instillation of fine or ultrafine carbon black or titanium dioxide: role of surface area. Toxicologist *102*:A1491.
- Sager T, Kommineni C, Castranova V [2008]. Pulmonary response to intratracheal instillation of ultrafine versus fine titanium dioxide: role of surface area. Particle Fibre Toxicol *5*:17

Invited Presentations

- Castranova V [2008]. Intratracheal instillation of rats to ultrafine TiO_2 or ultrafine carbon black. Presentation at the Health and Environmental Sciences Institute, Washington, DC, May 8.

Project 5: Role of Carbon Nanotubes in Cardiovascular and COPD-Related Diseases

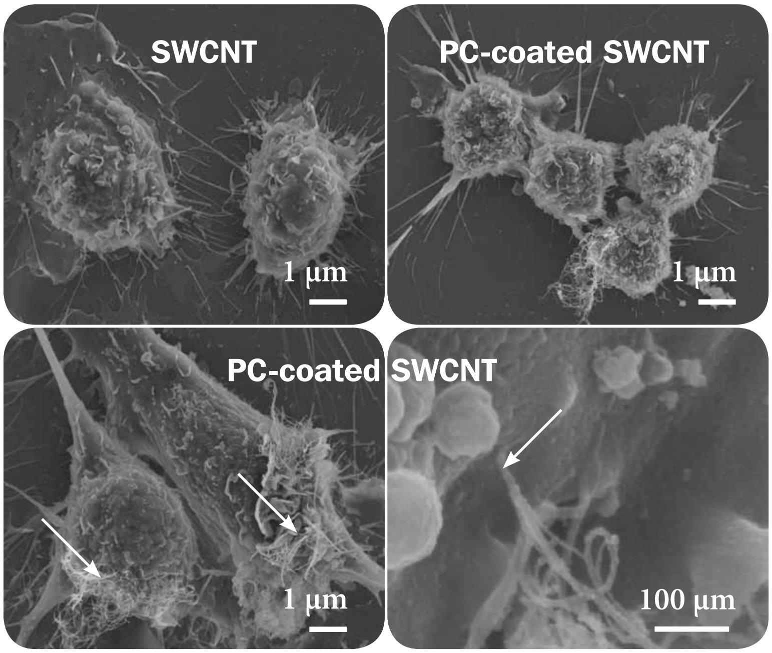
Principal Investigator: Petia Simeonova, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Evaluated cardiovascular effects resulting from respiratory exposure to purified SWCNT and MWCNT.
- A single exposure resulted in a treatment-dose dependent, distressed mitochondrial homeostasis represented by mitochondrial DNA damage, glutathione depletion, and increased protein carbonyl formation in aortic tissue. Oxidative alterations of mitochondria can trigger endothelial dysfunction, a leading mechanism in atherosclerosis progression.



SEM of macrophages treated with PC- or PS-coated SWCNT

- Multiple pulmonary exposures of apoE-/- mice, a model of human atherosclerosis, to SWCNT resulted in accelerated atherosclerosis.
- Respiratory exposure to SWCNT and MWCNT resulted in acute and chronic systemic responses related to potential cardiovascular adverse effects.
- Currently, there is no evidence for translocation of carbon nanotubes, in a measurable amount, from the lung into the systemic circulation. SWCNT and MWCNT deposited in the lung induced acute systemic inflammatory and prothrombotic responses. These effects are portrayed by a complex pattern of gene expression and protein blood analyses.
- Developed methodological approach used in the above studies for evaluating toxicity of respiratory exposure to particles. The approach will foster the development of predictive tests for estimating the toxicity of new nanomaterials based on their physiochemical characteristics and potential to induce oxidative stress, inflammation, and specific pulmonary and systemic toxicity.
- Single exposure to CNTs is associated with a chronic and persistent release of osteopontin (OPN) into the systemic circulation. Preliminary data demonstrate a differential blood OPN response between female and male mice as a result of the CNT exposure. OPN may play a role in the CNT-induced local and cardiovascular responses.
- Evaluated cardiovascular effects of subchronic inhalation exposure to C60 particles (diameter 1 and 0.05 µm) in mouse and rat models (in collaboration with the National Institute of Environmental Health and Safety).
- Found that the initial screening for cardiovascular toxicity demonstrated changes in the expression of several genes related to stress response, including c-fos, and heat shock proteins 25, 70, and 90 in the aortas of the exposed mice. Heat shock proteins are incremental in triggering many autoimmune/chronic inflammatory diseases. In this regard, it has been suggested that there is a multifaceted role for heat shock proteins in atherosclerosis. Wild type mice (not prone to develop atherosclerosis) exposed to fullerenes developed cardiovascular stress responses, which may indicate a predisposition to atherogenesis.
- Discovered that endothelial cells exposed to CNTs resulted in a direct effect. The findings of this study demonstrated actin cytoskeleton disruption, VE-cadherin disorganization, reduced tubule formation, and concomitant diminished viability of human aortic endothelial cells as a result of exposure to purified SWCNT or MWCNT. These effects were

dose dependent and most likely associated with mechanical damage of the cell membrane. The endothelial cells tolerate acute low concentrations of CNTs without changes in the viability, cytoskeleton, and function.

- Determined that study results demonstrate that the evaluation of systemic effects in parallel with pulmonary toxicity studies will provide a more complete toxicological assessment that can be used in predicting risk.

Publications and Abstracts

- Li Z, Hulderman T, Salmen R, Chapman R, Leonard SS, Shvedova A, Luster MI, Simeonova PP [2007]. Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes. Environ Health Perspect *115*(3):77–82. Nomimated for Charles C. Shepard Science Award, 2008, and was highlighted and discussed in the section “Hot-off-the-Presses Peer-Reviewed Research Article” of the EH&S Nano News [www.ehsnanonews.com/] as one of the first investigations on the potential cardiovascular effects of pulmonary exposure to SWCNT.
- Simeonava PP and Luster MI [2007]. In: Simeonova PP, Opopol N, Luster MI, eds. Nanotechnology: toxicological issues and environmental safety, NATO security through science series book. New York: Springer-Verlag, Springer-Verlag.
- NATO Security through Science Series Book *Nanotechnology-toxicological Issues and Environmental Safety* [2007]. Ed. Petia P. Simeonova, N. Opopol, MI Luster. Springer-Verlag.
- Simeonova PP [2007]. Nanoparticle exposure and cardiovascular effects—experimental data. In: Simeonova PP, Opopol N, Luster MI, eds. Nanotechnology: toxicological issues and environmental safety, NATO security through science series book. New York: Springer-Verlag. pp. 53–65.
- Simeonova PP, Erdely A, Li Z [2007]. Carbon nanotube exposure and risk for cardiovascular effects. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: charaterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 237–246.
- Simeonova PP, Li Z, Erdely A [2007]. Carbon nanotube respiratory exposure and risk from systemic effects. Toxicologist *96*(1):137.

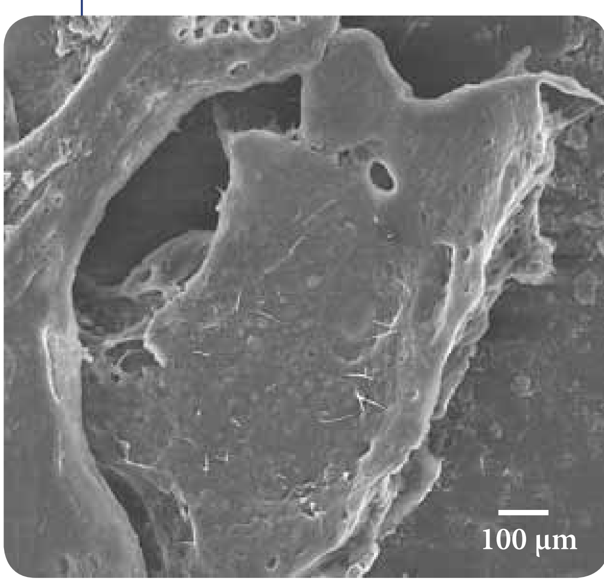
- Erdely A, Hulderman T, Salmen R, Liston A, Zeidler-Erdely PC, Simeonova PP [2008]. Carbon nanotube acute lung exposure induces plasminogen activator inhibitor 1. Toxicologist *102*(1):151.
- Simeonova PP, Erdely A, Liston A, Roycroft J, Germolec D, Walker NJ, [abstract submitted]. Potential cardiovascular effects of Fullerene C60 inhalation exposure. Society of Toxicology annual meeting, Baltimore, Maryland, March 2009.
- Erdely A, Hulderman T, Salmen R, Liston A, Zeidler-Erdely PC, Simeonova PP [abstract submitted]. Time course of systemic effects following a single exposure to carbon nanotubes. Society of Toxicology annual meeting, Baltimore, Maryland, March 2009.
- Walker VG, Hulderman T, Simeonova PP [abstract submitted]. Comparison of carbon nanotube-induced cytotoxicity in A549 and normal human bronchial epithelial (NHBE) cells. Society of Toxicology annual meeting, Baltimore, Maryland, March 2009.
- Erdely A, Hulderman T, Salmen R, Liston A, Erdely P, Schwegler-Berry D, Castranova V, Koyama S, Kim Y-A, Endo M, Simeonova PP [2009]. Cross-talk between lung and systemic circulation during carbon nanotube respiratory exposure—potential biomarkers. Nano Lett *14*:9(1), pp. 36–43.
- Simeonova PP, Erdely A [in press]. Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. Inhal Toxicol.
- Walker VG, Hulderman T, Schwegler-Berry D, Simeonova PP [in review]. Potential direct effects of carbon nanotubes on human aortic endothelial cells.

Invited Presentations

- Simeonova PP [2007]. Carbon nanotube respiratory exposure and risk from systemic effects. Society of Toxicology, Charlotte, NC, March, 25–29.
- Simeonova PP [2007]. Carbon nanotubes— toxicological evaluation. International meeting of nanotechnology, San Francisco, CA, November 5–7.
- Erdely A, Hulderman T, Salmen R, Liston A, Zeidler-Erdely PC, Simeonova PP [2008]. Crosstalk between the lung and blood following carbon nanotube exposure; potential biomarkers and implications for

cardiovascular disease. Allegheny-Erie Chapter meeting, Society of Toxicology. Best overall poster award.

- Walker VG, Hulderman T, Simeonova PP [2008]. Direct exposure to carbon nanotube induces cellular changes in primary human endothelial cells. The American Society for Cell Biology annual meeting, San Francisco, CA, December 13–17.
- Simeonova PP [2008]. Engineered nanoparticle respiratory exposure and potential risk for cardiovascular toxicity. International inhalation symposium, Hanover, Germany, June 11–15.
- Simeonova PP [2008]. Carbon nanotube pulmonary exposure—cardiovascular effects. American Association for the Advancement of Science annual meeting, Boston, MA, February 14–18.
- Simeonova PP [2008]. Air pollutants and atherosclerosis. Press briefing coordinated by the Director of the Office of Public Programs, American Association for the Advancement of Science, Boston, MA, February 14–18.
- Simeonova PP, Erdely A, Walker V [2008]. Reports on MWCNT systemic toxicity and discussions about collaborations with Dr. Endo and Japanese scientist delegation visiting NIOSH. Morgantown, WV, March 12.



Scanning electron microscopy image of mouse macrophage with engulfed CNT

Project 6: Investigations of Multi-Walled Carbon Nanotube Toxicity

Principal Investigator: Dale Porter, Ph.D.

Project Duration: FY 2007–2009

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Developed and validated a biocompatible dispersion medium for use in nanotoxicology studies.
- Investigated crystal structure of MWCNT using high resolution transmission electron microscopy.
- Determined surface chemistry of the MWCNT using x-ray photoelectron spectroscopy.
- Quantified metal contaminates and endotoxin levels preset in MWCNT.
- Evaluated dispersion status of hydrosol MWCNT using low resolution transmission electron microscopy.
- Determined zeta potential of hydrosol MWCNT.
- Determined the length and diameter of MWCNT.
- Conducted an in vivo dose-response and time-course study of MWCNT-induced toxicity after exposure by pharyngeal aspiration.
- Aspiration exposure study results indicate that MWCNT exposure induces dose- and time-dependent changes in pulmonary inflammation, damage, and fibrosis in the lung.
- Exposed mice by aspiration to gold-labeled MWCNT in order to determine MWCNT translocation. The samples have been collected and are currently being analyzed by neutron activation analyses.
- Built a MWCNT inhalation system in conjunction with the Developmental Engineering Research Team (DERT).
- Conducted a dose-response study to aerosolized MWCNT and found that inhaled MWCNT induces dose-dependent pulmonary inflammation and damage.

Publications and Abstracts

- Sager TM, Porter DW, Robinson VA, Lindsley WG, Schwegler-Berry DE, Castranova V [2007]. Improved method to disperse nanoparticles for in vitro and in vivo investigation of toxicity. Nanotoxicol *1*:118–129.
- Shvedova AA, Sager T, Murray AR, Kisin E, Porter DW, Leonard SS, Schwegler-Berry D, Robinson VA, Castranova V [2007]. Critical issues in the evaluation of possible adverse pulmonary effects resulting from airborne nanoparticles. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 225–236.
- Sriram K, Porter DW, Tsuruoka S, Endo M, Jefferson AM, Wolfarth MG, Rogers GM, Castranova V, Luster MI [2007]. Neuroinflammatory responses following exposure to engineered nanomaterials. Toxicologist *96*:A1390.
- Sager T, Robinson V, Porter DW, Schwegler-Berry D, Lindsley W, Castranova V [2007]. An improved method to prepare suspensions of nanoparticles for treatment of lung cells in culture or in vivo exposure by pharyngeal aspiration or intratracheal instillation. Toxicologist *96*:A1120.
- Porter DW, Sriram K, Wolfarth M, Jefferson A, Schwegler-Berry D, Andrew ME, Castranova V [2008]. A biocompatible medium for nanoparticle dispersion. Nanotoxicology *2*:144–154.
- Hubbs AF, Mercer RR, Sriram K, Castranova V, Chen BT, McKinney W, Frazer DG, Battelli L, Willard P, Scabilloni J, Schwegler-Berry D, Porter D [2008]. Acute respiratory toxicologic pathology of inhaled multi-walled carbon nanotubes. Vet Pathol *45*:786.
- Chen BT, McKinney W, Schwegler-Berry D, Castranova V, Frazer DG [2008]. Aerosolization and characterization of multi-walled carbon nanotubes for inhalation studies. American Association for Aerosol Research annual conference, Orlando FL, October 20–24.

Project 7: Pulmonary Toxicity of Metal Oxide Nanospheres and Nanowires

Principal Investigator: Dale Porter, Ph.D.

Project Duration: FY 2007–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Developed and validated a biocompatible dispersion medium for use in nanotoxicology studies.
- Synthesized three engineered TiO_2 nanoparticles—nanospheres, short nanowires, and long nanowires (Nianqiang Wu, West Virginia University).
- Determined crystal structure of all three anatase TiO_2 nanoparticles.
- Characterized physical characteristics (diameter, length, width) of TiO_2 nanoparticles.
- Determined surface chemistry of the TiO_2 nanoparticles using electron spin resonance spectroscopy.
- Evaluated dispersion status of hydrosol TiO_2 nanoparticles using low resolution transmission electron microscopy and dynamic light scattering.
- Conducted an in vivo dose-response and time-course study of TiO_2 nanoparticles after exposure by pharyngeal aspiration. Results from animal aspiration study indicate that exposure to TiO_2 nanoparticles induces dose- and time-dependent changes in pulmonary inflammation and damage.
- Acted as co-principal investigator on National Science Foundation (NSF) grant, Correlation among physicochemical properties, photochemical fate, and toxicity of TiO_2 nanoparticles. Funding period September 1, 2008–August 31, 2011.

Publications and Abstracts

- Sager TM, Porter DW, Robinson VA, Lindsley WG, Schwegler-Berry DE, Castranova V [2007]. Improved method to disperse nanoparticles for in vitro and in vivo investigation of toxicity. Nanotoxicology *1*:118–129.

- Sager T, Robinson V, Porter DW, Schwegler-Berry D, Lindsley WG, Castranova V [2007]. An improved method to prepare suspensions of nanoparticles for treatment of lung cells in culture or in vivo exposure by pharyngeal aspiration or intratracheal instillation. Toxicologist *96*:A1120.
- Porter DW, Sriram K, Wolfarth M, Jefferson A, Schwegler-Berry D, Andrew ME, Castranova V [2008]. A biocompatible medium for nanoparticle dispersion. Nanotoxicol *2*:144–154.
- Porter DW, Holian A, Sriram K, Wu N, Wolfarth M, Hamilton R, Buford M [2008]. Engineered titanium dioxide nanowire toxicity in vitro and in vivo. Toxicologist *102*:306.

Invited Presentations

- Hamilton R, Porter DW, Buford M, Sriram K, Wu N, Wolfarth M, Holian A [2008]. Engineered titanium dioxide nanoparticle bioactivity and toxicity are dependent on particle length and shape. Nanotoxicology—second international conference, Zurich, Switzerland. September 7–10.

Project 8: WC-Co Nanoparticles in Initiating Angiogenesis by Reactive Oxygen Species

Principal Investigator: Min Ding

Project Duration: FY 2009–2011. (Preliminary data gathering started in FY2008)

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- This project will investigate the potential pulmonary carcinogenesis in response to WC-Co particles exposure using cell culture and animal model.
- Both fine and nanoparticles of WC-Co stimulate angiogenesis using the CEM assay.
- The mechanistic investigations (gene mutation, activation of transcription factors, reactive oxygen species [ROS] generation) indicate that WC-Co nanoparticles induce ROS production, which activates AKT and ERK signaling pathways in lung epithelial cells.
- ROS production results in transcriptional activation of AP-1, NF-κB, and VEGF through AKT and ERK1/2 activation with the greater effect observed in nanoscale WC-Co when compared to fine-sized WC-Co at the same concentration.

Project 9: Evaluation of the Pulmonary Deposition and Translocation of Nanomaterials

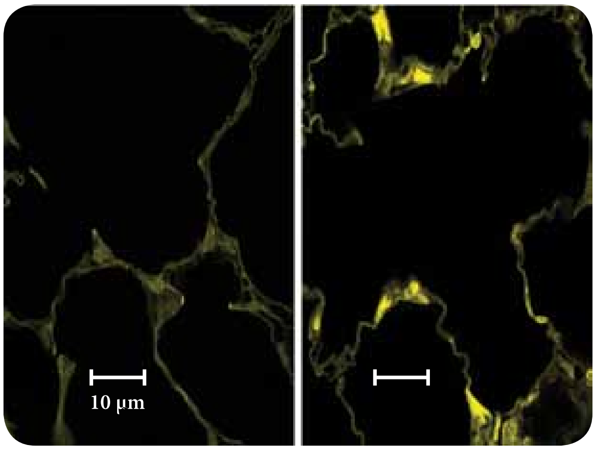
Principal Investigator: Robert R. Mercer, Ph.D.

Project Duration: FY 2006–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Found that aggregates of SWCNT disperse when deposited in the lungs.
- Demonstrated that diffuse interstitial fibrosis following exposure to SWCNT is due to a dispersed submicron form of SWCNT that had not yet been identified.
- Demonstrated that injury response (time course and resulting lesions) from the inhalation of SWCNT is similar to that produced by the aspiration of SWCNT, a less costly and more feasible delivery method.
- Received the 2008 Charles C. Shepard Science Award for outstanding scientific paper, *Alteration of Deposition Pattern and Pulmonary Response as a Result of Improved Dispersion of Aspirated Single-Walled Carbon Nanotubes in a Mouse Model.*
- Developed methods for labeling CNTs so that their potential translocation from the lungs to other organs can be studied.



The image on the left is from a normal mouse lung while the one on the right if from lungs 30 days after exposure to SWCNT indicating an increase in collagen (stained bright yellow), the key element in fibrosis.

Publications and Abstracts

- Mercer RR, Scabilloni JF, Wand L, Schwegler-Berry D, Shvedova AA, Castranova V [2007]. Dispersion significantly enhances the pulmonary toxicity of single-walled carbon nanotubes. Toxicologist *96*(231):A1115.
- Roberts JR, Mercer RR, Young S, Porter DW, Castranova V, Antonini JM [2007]. Inflammation and fate of quantum dots following pulmonary treatment of rats. Toxicologist *96*(230):A1111.
- Mercer RR, Scabilloni JF, Wang L, Battelli LA, Castranova V [2008]. Use of labeled single-walled carbon nanotubes to study acute translocation from the lungs. Toxicologist: *102*(S-1), A1399.
- Wang L, Castranova V, Rojanasakul Y, Lu Y, Scabilloni JF, Mercer RR [2008]. Direct fibrogenic effects of dispersed single-walled carbon nanotubes on human lung fibroblasts. Toxicologist: *102*(S-1), A1499.
- Wang L, Chanvorachote P, Toledo D, Stehlik C, Mercer RR, Castranova V, Rojanasakul Y [2008]. Hydrogen peroxide is a key mediator of Bcl-2 down regulation and apoptosis induction by cisplatin in human lung cancer cells. Mol Cancer Thera Mol Pharmacol *73*:119–127.
- Mercer RR, Scabilloni J, Wang L, Kisin E, Murray A, Schwegler-Berry D, Shvedova A, Castranova V [2008]. Alteration of deposition pattern and pulmonary response as a result of improved dispersion of aspirated single-walled carbon nanotubes in a mouse model. Am J Physiol Lung Cell Mol Physiol *294*:L87–97.
- Shvedova AA, Kisin E, Murray E, Johnson V, Gorelik O, Arepalli S, Hubbs AF, Mercer RR, Keohavong P, Sussman N, Jin J, Stone S, Chen BT, Deye G, Maynard A, Castranova V, Baron P, Kagan VE [2008]. Inhalation versus aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. Am J Physiol Lung Cell Mol Physiol *295*:552–565.

Invited Presentations

- Mercer RR [2007]. Inhalation toxicology of SWCNT. Society for Risk Assessment Teleseminar, June 7.
- Mercer RR [2008]. Using labeled SWCNT to determine potential acute translocation from the lungs. Society of Toxicology annual meeting, March 16–20.

Project 10: Occupational Exposures and Potential Neurological Risks

Principal Investigator: Krishnan Sriram, Ph.D.

Project Duration: FY 2008–2012

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings (Carbon nanotubes study)

- Demonstrated the efficacy of a biocompatible dispersion medium for evaluating nanoparticle neurotoxicity.
- Evaluated neuroinflammatory responses following pulmonary and inhalation exposure to MWCNT.
- Evaluated the effects of MWCNT on blood-brain barrier integrity.
- Demonstrated regional heterogeneity in the blood-brain barrier changes and neuroinflammatory responses following pulmonary and inhalation exposure to MWCNT.
- Evaluated the effects of MWCNT in eliciting Alzheimer-like pathology.
- Demonstrated that pulmonary exposure to MWCNT up-regulates key genes involved in processing of the amyloid precursor protein, accumulation of which is a pathological hallmark of Alzheimer disease.

Accomplishments and Research Findings (welding fume study)

- Investigated the neurotoxicologic potential following pulmonary exposure to diverse welding fumes. Specifically, investigated the potential of welding fumes to cause dopaminergic neurotoxicity.
- Determined the regional metal distribution in the brain following pulmonary exposure to three types of welding fumes: gas metal arc-mild steel (GMA-MS), manual metal arc-hard surfacing (MMA-HS), and flux core arc-stainless steel (FCA-SS).
- Demonstrated the accumulation of manganese from welding fumes in target-dopaminergic brain areas.

- Demonstrated that with increasing solubility of welding fumes, a greater accumulation of manganese occurred in brain areas.
- Demonstrated that the potential to oxidize dopamine was directly proportional to the solubility of the welding fumes.
- Determined changes in T1 relaxation time (as an index of manganese accumulation) in specific brain areas using magnetic resonance imaging.
- Demonstrated that pulmonary exposure to GMA-MS, MMA-HS, and FCA-SS welding fumes caused loss of tyrosine hydroxylase protein, a marker of dopaminergic neurons.
- Demonstrated that acute inhalation exposure to GMA-MS elicited neuroinflammation and gliosis in specific brain areas, including dopaminergic targets.
- Demonstrated that acute inhalation exposure to GMA-MS alters the expression of divalent metal transporters in distinct brain areas.

Accomplishments and Research Findings (titanium dioxide study)

- Investigated the influence of nanoparticle size and shape on neurotoxicologic potential, using nanosphere and nanowire TiO_2 particles.
- Evaluated neuroinflammatory responses following pulmonary exposure to TiO_2 nanosphere (NS), short TiO_2 nanowires (SNW) and long TiO_2 nanowires (LNW).
- Demonstrated that the potential of TiO_2 nanomaterials to elicit neuroinflammation was LNW>SNW>NS, indicating that particle size and shape influenced the toxicological response.

Publications and Abstracts

- Sriram K, Porter DW, Tsuruoka S, Endo M, Jefferson AM, Wolfarth MG, Rogers GM, Castranova V, Luster MI [2007]. Neuroinflammatory responses following exposure to engineered nanomaterials. Society of Toxicology annual meeting, Charlotte, NC, March 25–29, Toxicologist *96*(1):288.
- Antonini JM, Roberts JR, Sriram K, Benkovic SA, O'Callaghan JP, Miller DB [2008]. Extrapulmonary tissue distribution of metals following repeated lung exposures to welding fumes with different elemental

profiles. Society of Toxicology annual meeting, Seattle, WA, March 16–20. Toxicologist *102*(1):226.

- Porter DW, Holian A, Sriram K, Wu N, Wolfarth M, Hamilton R, Buford M [2008]. Engineered titanium dioxide nanowire toxicity in vitro and in vivo. Society of Toxicology annual meeting, Seattle, WA, March 16–20. Toxicologist *102*(1):306.
- Porter D, Sriram K, Wolfarth M, Jefferson A, Schwegler-Berry D, Andrew ME, Castranova V [2008]. A biocompatible medium for nanoparticle dispersion. Nanotoxicology *2*(3):144–154.
- Hubbs AF, Mercer RR, Sriram K, Castranova V, Chen BT, McKinney W, Frazer DG, Battelli L, Willard P, Scabilloni J, Schwegler-Berry D, Porter D [2008]. Acute respiratory toxicologic pathology of inhaled multi-walled carbon nanotubes. Vet Pathol *45*:786.

Project 11: Lung Effects of Resistance Spot Welding Using Adhesives

Principal Investigator: James Antonini, Ph.D.

Project Duration: FY 2007–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Designed a resistance spot welding generator for animal inhalation studies.
- Nearly completed construction of the resistance spot welding generator.
- Characterized the physical and chemical properties of aerosols generated after heating adhesives used in resistance spot welding.

Publications and Abstracts

- Afshari AA, Antonini JM, Castranova V, Boylstein R, Kanwal R, Frazer DG [2008]. Design of an inhalation exposure system to study resistance spot welding fume characteristics and biological effects. Society of Toxicology annual meeting, Seattle, WA, March 16–20. Toxicologist *102*:226.

Invited Presentations

- Chen BT, Stone S, Schwegler-Berry D, Frazer A, Donlin M, Cumpston J, Afshari A, Frazer D, Castranova V, Antonini JM [2007]. Characterization of welding fume particles generated from a robotic welding system. American Association for Aerosol Research annual conference, Reno, NV, September 24.
- Antonini J [2008]. Health effects of welding. American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.

Project 12: Neurotoxicity after Pulmonary Exposure to Welding Fumes

Principal Investigator: James Antonini, Ph.D.

Project Duration: FY 2007–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Characterized the physical properties of aerosol generated by welding and observed a significant number of welding particles in the nanoparticle-size range.
- Observed that, after inhalation, stainless steel particles persist in the lung and induce greater lung damage than mild steel particles.
- Observed the translocation of metals associated with welding fume (e.g., manganese and chromium) to other organ systems, including specific regions of the brain.
- Observed some alterations in inflammatory mediators in brain tissue from specific lung region.

Publications and Abstracts

- Santamaria AB, Cushing CA, Antonini JM, Finley BL, Mowat FS [2007]. Potential neurological effects of manganese exposure during welding: a state-of-the-science analysis. J Toxicol Environ Health, Part B, *10*:417–465.
- Antonini JM, Stone S, Roberts JR, Chen B, Schwegler-Berry D, Afshari AA, Frazer DG [2007]. Effect of short-term stainless steel welding fume inhalation exposure on lung inflammation, injury, and defense responses in rats. Toxicol Appl Pharmacol *223*:234–245.
- Antonini JM, Roberts JR [2007]. Comparison of lung injury and inflammation after repeated treatment with welding fumes collected from different welding processes. Society of Toxicology annual meeting, Charlotte, North Carolina, March 25–29. Toxicologist *96:*103–104.
- Antonini JM, Stone S, Roberts JR, Chen B, Frazer DG [2007]. Delayed inflammatory response after inhalation of stainless steel welding fume

in rats. American Thoracic Society international conference, San Francisco, California, May 18–23. Am J Respir Crit Care Med *175*:A429.

- Zeidler-Erdely PC, Kashon ML, Battelli LA, Young S-H, Erdely AD, Roberts JR, Reynolds SH, Antonini JM [2008]. Lung inflammation and tumor induction in lung tumor susceptible A/J and resistant C57BL/6J mice exposed to welding fume. Part Fibre Toxicol *5*:12.
- Antonini JM, Roberts JR, Sriram K, Benkovic SA, O'Callaghan JP, Miller DB [2008]. Extrapulmonary tissue distribution of metals following repeated lung exposures to welding fumes with different elemental profiles. Society of Toxicology annual meeting, Seattle, WA, March 16–20. Toxicologist *102*:226.
- Antonini JM, Stone S, Roberts JR, Schwegler-Berry D, Moseley A, Donlin M, Cumpston J, Afshari A, Frazer DG [2008]. Pulmonary effects and tissue distribution of metals after inhalation of mild steel welding fume. American Thoracic Society international conference, Toronto, Ontario, Canada, May 2008. Am J Respir Crit Care Med *177*:A910.

Invited Presentations

- Antonini J [2008]. Manganese exposure during welding. Institute of Occupational and Environmental Health, West Virginia University, Morgantown, WV, Occupational Medicine Grand Rounds Seminar, March 4.
- Antonini J [2008]. Health effects of welding. American Industrial Hygiene Association conference and exposition 2008, Minneapolis, MN, May 31–June 5.

Project 13: Potential Aneuploidy Following Exposure to Carbon Nanotubes

Principal Investigator: Linda Sargent, Ph.D.

Project Duration: FY 2007–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Primary and immortalized human small airway epithelial cells were cultured and then exposed to SWCNTs or a positive control vanadium pentoxide to investigate the potential of CNTs to induce genetic damage in normal lung cells. The nanotubes had an average diameter of 1.1 nanometer and a length of 100–1,000 nanometers. Cellular tubulin, mitotic spindle integrity, and centriole number were determined by immunofluorescence for beta-tubulin and centrin and photographed using fluorescent and confocal laser scanning microscopy. The chromosome number was examined by fluorescent in situ hybridization.
- Binucleate cells, large polyploid appearing nuclei, bundled tubulin, and fragmented centrosomes were observed following 24 hours of exposure to either SWCNT or vanadium pentoxide.
- The SWCNT-treated cells were further examined by fluorescent in situ hybridization (FISH) using large genomic probes labeled with fluorescent tags. FISH showed that the large nuclei were polyploid. The number of chromosomes per cell was not normal (aneuploid). Mitotic spindles were found to have multiple poles and many cells had anaphase bridges with fragmenting chromatin. Using different interference confocal microscopy (DIC), SWCNT were observed to be inside the cells. DIC combined with fluorescent confocal laser imaging showed that many of the cells had SWCNT in the nucleus and within the cellular and mitotic tubulin. Some of the binucleate cells appeared to be connected by SWCNT. CNTs in the mitotic spindle appear to distort the mitotic spindle apparatus. This damage was seen even at the lowest dose (24 μg/cm^3).
- The researcher contacted Dr. Jeffrey Salisbury to obtain a construct for one of the centrosome genes with a green fluorescent protein tag to allow confirmation of the centrosome fragmentation and also to follow the changes of the centrosome during the cell cycle. Dr. Salisbury

will send antibodies for the centrosome that are more specific than commercially available antibodies. These antibodies can increase the sensitivity of the detection of the centrosome. Dr. Salisbury will also participate in imaging the SWCNT treated cells by electron microscopy both in the cell and following isolation of the centrosomes by a gradient. The centrosome work will be published separately.

Invited Presentations

- Sargent L [2008]. Genetic impact of carbon nanotubes and chemically specific genetic changes in lung adenocarcinoma. Naval Health Research Center, Detachment, Environmental Health Effects Laboratory, Wright-Patterson AFB, Dayton, OH, May 28.
- Sargent L [2008]. Genetic damage following carbon nanotube exposure. Mary Babb Randolph Cancer Center-National Institute of Occupational Safety and Health scientific retreat in cancer, February 12.

Project 14: Pulmonary Toxicity of Carbon Nanotube Particles

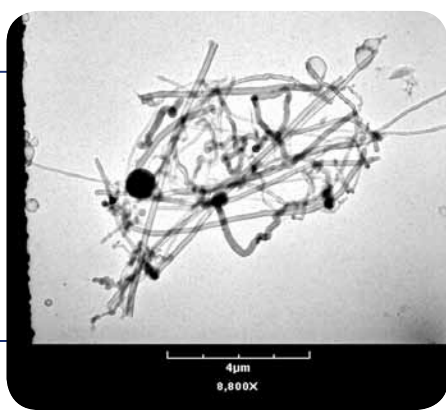
Principal Investigator: Anna Shvedova, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Low levels of antioxidants in vitamin E-deficient mice were associated with a higher sensitivity to SWCNT-induced acute inflammation, released LDH, total protein content, levels of proinflammatory cytokines, and enhanced profibrotic responses and collagen deposition.
- Exposure to SWCNTs markedly shifted the ratio of cleaved to full-length extracellular superoxide dismutase (EC-SOD) in the lungs. Found no differences in the EC-SOD responses to SWCNT-induced oxidative stress between vitamin E-deficient and vitamin E-sufficient animals.
- Sequential exposure to carbon nanotubes and bacteria enhanced pulmonary inflammation and infectivity.
- Decreased bacterial clearance in SWCNT-pre-exposed mice was associated with decreased phagocytosis of bacteria by macrophages and a decrease in nitric oxide production by these phagocytes.
- Failure of SWCNT-exposed mice to clear Lysteria led to a continued elevation in nearly all major chemokines and acute phase cytokines into the later course of infection.



Electron micrograph of carbon nanotubes at 8,800x

- An increased accumulation of neutrophils and decreased fibrosis was observed in the lungs of NADPH oxidase-deficient C57BL/6 mice exposed to CNTs. This corresponded to elevated levels of apoptotic cells in the lungs, production of proinflammatory cytokines, decreased production of the anti-inflammatory and profibrotic cytokine, TGF-beta, and reduced levels of collagen deposition.
- NADPH oxidase is an important regulator of the transition from the acute inflammation to the chronic fibrotic stage in response to SW-CNT.
- Developed a generation system that aerosolizes SWCNT for an inhalation study. The resulting aerosol was size-separated using a settling chamber and two cyclones to produce a respirable aerosol.
- The mass output efficiency of the entire system for producing a respirable aerosol from bulk material was estimated to be about 10%.
- Completed inhalation study of SWCNT in C57BL/6 mice.
- The inhalation of nonpurified SWCNT (iron content of 17.7% by weight) at 5 mg/m^3 5 hr/day for 4 days was compared with pharyngeal aspiration of varying doses (5–20 ug per mouse) of the same SWCNT.
- The chain of pathological events in both exposure routes was realized through synergized interactions of early inflammatory response and oxidative stress culminating in the development of multifocal granulomatous pneumonia and interstitial fibrosis.
- SWCNT inhalation was more effective than aspiration in causing inflammatory response, oxidative stress, collagen deposition, and fibrosis as well as mutations of K-ras gene locus in the lung of C57BL/6 mice.

Publications and Abstracts

- Shvedova AA, Sager T, Murray AR, Kisin E, Porter DW, Leonard SS, Schwegler-Berry D, Robinson VA, Castranova V [2007]. Critical issues in the evaluation of possible adverse pulmonary effects from airborne nanoparticles. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc.
- Kagan VE, Rao KMK, Kisin ER, Young S-H, Meighan T, Murray AR, Tyurina YY, Castranova V, Shvedova AA [2007]. Pulmonary effects of single-walled carbon nanotubes: inflammatory response, oxidative stress/signaling, and recognition by macrophages. In: Simeonova PP,

Opopol N, Luster MI, eds. Nanotechnology: toxicological issues and environmental safety, NATO security through science series book, New York: Springer-Verlag, pp. 65–75.

- Shvedova AA, Kisin ER, Murray AR, Gorelik O, Arepalli S, Castranova V, Young SH, Gao F, Tyurina YY, Oury TD, Kagan VE [2007]. Vitamin-E deficiency enhances pulmonary inflammatory response and oxidative stress induced by single-walled carbon nanotubes in C57BL/6 mice. Toxicol Appl Pharmacol *221*(3):339–348.
- Fadeel B, Kagan V, Krug H, Shvedova A, Svartengren M, Tran L, Wiklund L [2007]. There's plenty of room at the forum: potential risks and safety assessment of engineered nanomaterials. Nanotoxicol *1*(2):73–84.
- Kisin ER, Murray AR, Keane MJ, Shi XC, Schwegler-Berry D, Gorelik O, Arepalli S, Castranova V, Wallace WE, Kagan VE, Shvedova AA [2007]. Single-walled carbon nanotubes: geno- and cytotoxic effects in lung fibroblast V79 cells. J Tox Environ Health, Part A, *70*(24):2071–2079.
- Shvedova AA, Kisin ER, Murray AR, Gorelik O, Arepalli S, Castranova V, Young SH, Gao F, Tyurina YY, Oury T, Kagan VE [2007]. Vitamin-E deficiency enhances pulmonary inflammatory response and oxidative stress induced by single-walled carbon nanotubes in C57BL/6 mice. Toxicologist *96*(1):A179.
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- Murray AR, Kisin E, Fabisiak JP, Roberts JR, Antonini JM, Kommineni C, Reynolds J, Barchowsky A, Castranova V, Kagan V, Shvedova AA [2008]. Combined exposure to carbon nanotubes and bacteria-enhanced pulmonary inflammation and infectivity. Toxicologist *102*(1):A1494.
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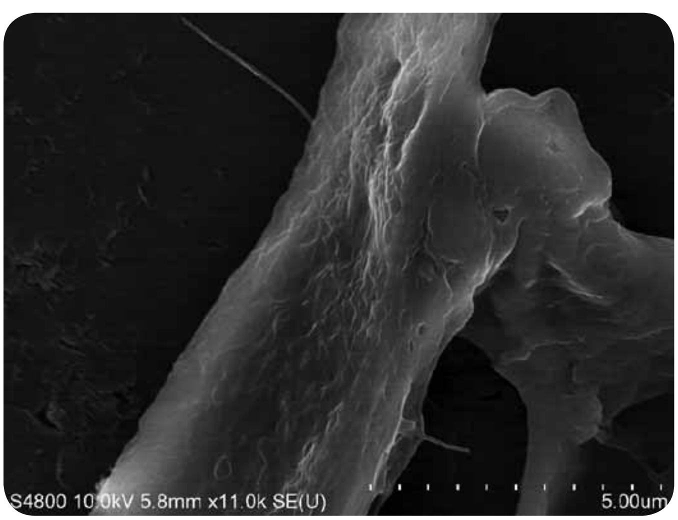


MWCNT in the lungs of a mouse 56 days after exposure. The shorter fiber on the right is penetrating the lung wall from the alveolar space. The longer fiber on the upper left has penetrated the outer wall of the lung into the pleural space.

Invited Presentations

- Shvedova AA [2007]. Pulmonary toxicity of singled-walled nanotubes. International conference on nanotoxicology, Venice, Italy, April 19 and 21.
- Shvedova AA [2007]. Pulmonary toxicity of nanoparticles. Experimental biology meeting, Washington, DC, April 30–May 3.
- Shvedova AA [2007]. Pulmonary toxicity of single-walled nanotubes in vivo: mechanisms and consequences. National Aeronautics and Space Administration/National Institute of Standards and Technology workshop on nanotube measurements. National Institute of Standards and Technology, Gaithersburg, MD, September 26–28.
- Shvedova AA [2007]. Inhalation exposure to single-walled carbon nanotubes. European NanOSH conference—nanotechnologies: a critical area in occupational safety and health, Helsinki, Finland, December 3–5.
- Shvedova AA [2008]. Single-walled carbon nanotubes: are they mutagenic? Mary Babb Randolph Cancer Center—National Institute of Occupational Safety and Health scientific retreat in cancer, Morgantown, WV, February 12.
- Shvedova AA, Kagan VE [2008]. Pulmonary toxicity of carbon nanotubes in vivo: mechanisms, regulations, and reality. Nanomaterials: environmental risks and benefits and emerging consumer products, Faro, Portugal, April 27–30.
- Shvedova AA [2008]. Carbon nanotube in the rodent lungs: recognition and modulation of toxicity. American Thoracic Society, international conference, Toronto, Canada, May 16–21.
- Shvedova AA [2008]. Relevance of animal model studies: aspiration vs. inhalation. Second international conference: nanotoxicology, Zurich, Switzerland, September 7–10.

Project 15: Dermal Toxicity of Nanotube Particles

Principal Investigator: Anna Shvedova, Ph.D.

Project Duration: FY 2005–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- SWCNTs induced geno- and cytotoxic effects in lung fibroblast V79 cells when assessed using different test systems: the comet and micronucleus assays.
- Engineered human skin exposed to unpurified SWCNT showed increased epidermal thickness and accumulation and activation of dermal fibroblasts with increased collagen level and release of proinflammatory cytokines.
- Exposure of murine epithelial JB6 P+ cells to unpurified SWCNT (30% iron) resulted in the production of ESR detectable hydroxyl radicals and caused a significant dose-dependent activation of AP-1.
- Detected no significant changes in AP-1 activation when partially purified SWCNT (0.23% iron) were introduced to JB6 P+ cells.
- NF-κB was activated in a dose-dependent fashion by exposure to both unpurified and partially purified SWCNT.
- Topical exposure of SKH-1 mice to unpurified SWCNT induced free radical generation, oxidative stress, and inflammation, thus causing dermal toxicity.

Publications and Abstracts

- Fadeel B, Kagan V, Krug H, Shvedova A, Svartengren M, Tran L, Wiklund L [2007]. There's plenty of room at the forum: potential risks and safety assessment of engineered nanomaterials. Nanotoxicol *1*(2):73–84.
- Kisin ER, Murray AR, Keane MJ, Shi XC, Schwegler-Berry D, Gorelik O, Arepalli S, Castranova V, Wallace WE, Kagan VE, Shvedova AA [2007]. Single-walled carbon nanotubes: geno- and cytotoxic effects in fibroblast V79 cells. J Tox Environ Health, Part A, *70*(24):2071–2079.

- Tyurina YY, Basova LV, Konduru NV, Tyurin VA, Potapovich AI, Cai P, Bayir H, Stoyanovsky D, Pitt BR, Shvedova AA, Fadeel B, Kagan VE [2007]. Nitrosative stress inhibits the aminophospholipid translocase resulting in phosphatidylserine externalization and macrophage engulfment: implications for the resolution of inflammation. J Biol Chem *282*(11):8498–8509.
- Kagan VE, Tyurina YY, Konduru N, Basova LV, Stolz D, Kisin ER, Murray AR, Fadeel B, Shvedova AA [2007]. Targeted delivery of phosphatidylserine coated single-walled carbon nanotubes to macrophages. Toxicologist *96*(1):233.
- Feng W, Tyurina YY, Bayir H, Shvedova AA, Kagan VE [2007]. Phosphatidlyserine enhances recognition and uptake of single-walled carbon nanotubes by rat brain microglial cells. Toxicologist *96*(1):289.
- Murray AR, Kisin E, Kommineni C, Kagan VE, Castranova V, Shvedova AA [2007]. Single-walled carbon nanotubes include oxidative stress and inflammation in skin. Toxicologist *96*:A1406.
- Ding M, Zhao J, Bowman L, Leonard S, Lu Y, Kisin E, Murray A, Vallyathan V, Castranova V, Shvedova A [2008]. Induction of AP-1-MAPKs and NF-KB signal pathways by tungsten carbide-cobalt particles. Toxicologist *102*(1):A1031.
- Feng W, Konduru NV, Tyurina YY, Clark K, Stolz DB, Bayir H, Fadeel B, Shvedova AA, Kagan VE [2008]. Involvement of endocytosis in uptake of phosphatidylserine-coated single-walled carbon nanotubes by RAW 264.7 macrophages. Toxicologist *102*(1):213.

Invited Presentations

- Shvedova AA [2008]. Single-walled carbon nanotubes: are they mutagenic? Mary Babb Randolph Cancer Center—National Institute of Occupational Safety and Health scientific retreat in cancer, Morgantown, WV, February 12.
- Murray AR, Kisin ER, Leonard SS, Kommineni C, Kagan VE, Castranova V, Shvedova AA [2008]. Induction of oxidative stress and inflammation in the skin following exposure to single-walled carbon nanotubes. Zurich, Switzerland, March 12–15.

Project 16: Specific Biomarkers for Unusual Toxicity of Nanomaterials

Principal Investigator: Liying Wang Rojanasakul, Ph.D.

Project Duration: FY 2007–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- In vitro cellular models were developed for fibrogenic and biomarker studies of CNTs, such as collagen and collagenase production from fibroblasts and TGF-β production from lung epithelial cells.
- Data from this project provided important preliminary findings used in obtaining NORA grant funding.

Publications and Abstracts

- Wang L, Castranova V, Rojanasakul Y, Lu Y, Scabilloni J, Mercer RR [2008]. Direct fibrogenic effects of dispersed single-walled carbon nanotubes on human lung fibroblasts. Society of Toxicology annual meeting, Washington, DC, March 16–20. Toxicologist *102*:A1499.
- Wang L, Castranova V, Mercer RR, Wu N, Tiao Li T, Li S, Hall J, Li M, Rojanasakul Y [abstract accepted]. Nanoparticle dispersion method using natural lung surfactant. Society of Toxicology annual meeting, Baltimore, Maryland, March 2009.

Invited Presentations

- Wang L [2007]. Carbon nanotubes exhibit tumorigenic and fibrogenic potential in vitro. West Virginia University research meeting, Morgantown, WV, September.
- Wang L [2008]. Meeting with the National Institute of Occupational Health and Poison Control on nanotoxicology research, Beijing, China, November 16 and 17.
- Castranova V [2008]. The ability of in vitro tests to predict pulmonary responses to SWCNT. John Hopkins University, Baltimore, MD, June 11.

Project 17: Pulmonary Toxicity of Diesel Exhaust Particles

Principal Investigator: Jane Ma, Ph.D.

Project Duration: FY 2003–2008

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Diesel-exhaust-particle (DEP) exposure induces lung inflammation and injury, which are mediated through reactive oxygen/nitrogen species (ROS/RNS) generation by alveolar macrophages (AM).
- C57B/6J wild type (WT) and iNOS knockout (iNOS KO) mice were exposed to saline, carbon black (35 mg/kg), or organic extract of DEP (DEPE) by aspiration and sacrificed at 1, 3, and 7 days postexposure. Carbon black, but not DEPE, significantly induced neutrophil infiltration in both WT and iNOS KO mice.
- Carbon black, but not DEPE, exposure results in inflammatory lung injury, suggesting that DEP-induced pulmonary inflammation is derived from the particulate. Nitric oxide (NO) does not play a significant role in Carbon-black-induced polymorphonuclear neutrophils (PMN) infiltration, air/capillary damage, and cytotoxicity.
- Carbon-black-exposed AM exhibited enhanced superoxide anion generation, peaking at 3 days post exposure. Carbon black exposure also induced mitochondrial damage, monitored as reduction of mitochondrial membrane potential in AM, which was not markedly affected by the NO deficiency. In contrast, DEPE did not significantly induced ROS generation or mitochondrial function in AM.
- Carbon black and DEPE did not significantly affect adenosine triphosphate (ATP) levels in either WT or iNOS KO mice, because mitochondrial oxidative phosphorylation pathway is not the major energy source for AM.
- Transmission electron microscopy analysis has shown that animals exposed to DEP or carbon black, but not DEPE, were heavily laden with particle-filled vacuoles in the lung.

- Vacuoles containing DEP from DEP-exposed animals were frequently associated with mitochondria or were in direct membrane-to-membrane contact with mitochondria, demonstrating that mitochondrial function was compromised. In contrast, carbon-black-filled vacuoles did not display functionally impaired mitochondria, and no intracellular vacuoles were found in animals exposed to DEPE.
- DEP and carbon black both induced DNA damage in AM using comet assay. DEPE did not.

Publications and Abstracts

- Ma JYC, Millecchia L, Barger MW, Ma JKH, Castranova V [2007]. Diesel exhaust particle-induced oxidant injury and cellular responses in wild type and inducible nitric oxide synthase-deficient (iNOS KO) mice: roles of particle core and adsorbed organics. Toxicologist *96*(S-1):A183.
- Yin XJ, Dong CC, JYC, Roberts JR, Antoni J, Ma JKH [2007]. Suppression of phagocytic and bactericidal functions of rat alveolar macrophages by the organic component of diesel exhaust particles. J Toxicol Environ Health, Part A, *70*(10):820–828.

Invited Presentations

- Ma JYC [2008]. Effects of exposure to diesel exhaust particles on the susceptibility of the lung to infection. The Feinstein Institute for Medical Research, Manhasset, NY, April 8.

Project 18: Induction of Lung Fibrosis by Cerium Oxide in Diesel Exhaust

Principal Investigator: Jane Ma, Ph.D.

Project Duration: FY 2009–2012 (preliminary data gathering started in FY 2008)

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

I. In vitro studies

- Cerium oxide did not induce intracellular oxidant generation or alter mitochondrial function of alveolar macrophages (AM) but significantly damaged AM membrane integrity, induced apoptosis, affected macrophage inflammatory responses, including increased TNF-α, but reduced IL-12 production. These results suggest that cerium oxide can cause direct cellular damage to AM.
- Performed tests suggest that cerium oxide, under coexposure, may elicit new cellular toxicity in addition to DEP-induced toxicity and that cerium oxide suppresses cellular defense capability.
- Previous studies have shown that nitric oxide plays an important role in the DEP-induced IL-12 production by AM. The decreased nitric oxide production in response to LPS challenge by cerium oxide is probably due to its redox characteristic, subsequently leading to the suppressed IL-12. In the coexposure cell culture, cerium oxide depressed DEP- and LPS-induced IL-12 secretion, suggesting that cerium oxide suppresses cellular defense capability.

II. In vivo studies

- Cerium oxide administered intratracheally to Sprague Dawley rats induced significant neutrophil infiltration and elevated lactate dehydrogenase activity and albumin content in the BAL fluid, suggesting that these particles induced inflammation, cytotoxicity, and epithelial damage.
- Found a direct interaction of cerium oxide with AM, resulting in elevated AM phagocytic activity as monitored using confocal microscopy.

- Cerium oxide exposure increased reactive oxygen species production in response to zymosan challenge as indicated by enhanced chemiluminescence generation.
- Cerium oxide significantly reduced nitric oxide production by AM in response to ex vivo LPS challenge, demonstrating that these particles may modify AM host defense capability.

Publications and Abstracts

- Ma JY, Hongwen Z, Barger M, Castranova V, Ma JK [2008]. Effects of cerium oxide on rat primary alveolar macrophages. Toxicologist *102*(1):A1513.
- Ma JY, Zhao H, Barger M, Murali R, Meighan T, Castranova V, Ma JK [abstract accepted]. Pulmonary responses to diesel fuel catalyst cerium oxide nanoparticles. Society of Toxicology annual meeting, Baltimore, MD, March 2009.

Project 19: Potential Effects of Silicon-based Nanowires on Lung Toxicity

Principle Investigators: Stephen S. Leonard and Jenny R. Roberts

Project Duration: FY 2008–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Completed physical characterization of silicon-based nanowires generated by IBM and titanium nanowires to be used as a control/reference material.
- Characterized and quantified nanowire-associated reactive oxygen species (ROS) using a cell-free model system and quantified nanowire-induced free radical generation in vitro in alveolar macrophages.
- Measured and evaluated pulmonary toxicity parameters in vivo using a titanium nanowire to assess the potential of the material as a control. The nanowires induced a transient, dose-dependent response in the lungs of rats that included increases in indicators of inflammation and oxidative stress.
- Evaluated the ability of pulmonary exposure to titanium nanowires to alter responses to a pulmonary infection. Only the highest dose of nanowires altered response to infection, inducing an increase in resolution of infection.
- Evaluated a potential fluorescent marker, quantum dots, for tracking distribution of nanomaterials in the lung.

Publications and Abstracts

- Roberts JR, Mercer RR, Young S-H, Porter DW, Castranova V, Antonini JM [2007]. Inflammation and fate of quantum dots following pulmonary treatment of rats. Society of Toxicology annual meeting, Charlotte, North Carolina, March 25–29. Toxicologist *96*:230.
- Leonard SS, Castranova V, Chen BT, Schwegler-Berry D, Hoover M, Piacitelli C, Gaughan D [2007]. Particle-size-dependent radical generation from wildland fire smoke. Toxicol *236*:103–113.

- Pacurari M, Yin XJ, Zhao J, Ding M, Leonard SS, Schwegler-Berry D, Ducatman BS, Sbarra D, Hoover MD, Castranova V, Vallyathan V [2008]. Raw single-wall carbon nanotubes induce oxidative stress and activate MAPKs, AP-1, NF-kB, and Akt in normal and malignant human mesothelial cells. Environ Health Perspect *116*(9):1211–1217.
- Roberts JR, Schwegler-Berry D, Leonard SS, Karim A, Tirumala V, Antonini JM, Castranova V [2008]. Pulmonary toxicity associated with nondispersed titanium dioxide nanorods. Society of Toxicology annual meeting, Seattle, Washington, March 16–20. Toxicologist *102*:308.
- Ding M, Zhao J, Bowman LL, Leonard SS, Lu Y, Vallyathan V, Castranova V, Shvedova AA [2008]. Induction of AP-1-MAPKs and NF-kB signal pathways by tungsten carbide-cobalt particles. Toxicologist *102*:212, A1031.
- Roberts JR, Antonini JM, Porter DW, Castranova V, Mercer RR [2008]. Characterization of pulmonary responses following treatment of rats with fluorescently labeled quantum dots with different surface functional groups. American Thoracic Society international conference, Toronto, Ontario, Canada, May 16–17, 2008. Am J Respir Crit Care Med *117*:A49.
- Roberts JR, Schwegler-Berry D, Chapman R, Antonini JM, Scabilloni JF, Castranova V, Mercer RR [abstract submitted]. Biodistribution of quantum dots after pulmonary exposure in rats. Society of Toxicology annual meeting, Baltimore, MD, March 2009.
- Chapman R, Roberts JR, Castranova V, Leonard SS [abstract accepted]. Generation of reactive oxygen species by silicon nanowires. Society of Toxicology annual meeting, Baltimore, MD, March 2009.
- Rushton EK, Jiang J, Leonard SS, Eberly S, Castranova V, Biswas P, Elder A, Gelein R, Finkelstein J, Oberdorster G [accepted for publication]. Predicting nanoparticle toxicity: evaluation of screening assays. Environ Health Perspect.

Project 20: Cell-Based Assessment for Iron Nanoparticle-Induced Health Risks

Principal Investigator: Yong Qian

Project Duration: FY 2008–2010

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Developed a cell-based model for assessing nanoparticle particle-induced health risks.
- Trained one post-doctoral fellow and one graduate student in nanotechnology research for advancement of their professional careers in the field.
- Data from this project provided key preliminary results for a successful Pilot Funding Grant from the Mary Babb Randolph Cancer Center in the Health Sciences Center at West Virginia University.

Publications and Abstracts

- Apopa PL, Qian Y, Guo NL, Schwegler-Berry D, Pacurari M, Porter D, Shi X, Vallyathan V, Castranova V, Flynn DC [in press]. Iron oxide nanoparticles induce human microvascular endothelial cell permeability through reactive oxygen species production and microtubule remodeling. Particle and Fibre Toxicology.
- Apopa PL, Guo NL, Schwegler-Berry D, Pacurari M, Porter D, Shi X, Vallyathan V, Castranova V, Flynn DC, Qian Y [in press]. Iron oxide nanoparticles induce human microvascular endothelial cell permeability through reactive oxygen species production and microtubule remodeling. Annual Society of Toxicology Meeting.

Project 21: Assessment of Carbonaceous Materials on Mutagenicity

Principal Investigator: Anna A. Shvedova, Ph.D., D.Sc.

Project Duration: FY 10/1/08–9/30/09

Critical Topic Area: toxicology and internal dose

Accomplishments and Research Findings

- Inhalation exposure of C57BL/6 mice (5 mg/m^3, 5 hr a day, 4 days) to respirable SWCNT caused formation of anuclear macrophages with fibrillar cytoplasm along with mitotic changes was seen in the lung interstitial cells. Pattern of anaphase bridges in macrophages was clearly detected at 7 and 28 days post inhalation. Therefore, such mitotic changes within macrophage with anaphase bridges indicated feasible spindle aberrations.
- Post-exposure findings (7-days) revealed observable foci of bronchiolar epithelial cell hypertrophy in all exposed mice. Post-exposure findings (28-days) revealed bronchiolar epithelial cell hypertrophy and hyperplasia in all exposed mice.
- Severe oxidative stress observed in the lung of mice exposed to inhalable SWCNT revealed depletion of GSH, protein thiol oxidation, accumulation of lipid peroxidation products, reduced total antioxidant reserves, and augmentation of 8-hydroxy-2'-deoxyguanosine (8-OHdG)—a marker of oxidative D damage.
- K-ras mutations were observed in the lung of C57BL/6 mice after inhalation exposure to SWCNT. The first 2 mutations in DNA samples corresponded to a change in the wild type K-ras gene codon 12 (GGT, glycine) to AGT (lane 2, serine) and GAT (lane 3, aspartate). The third mutation was a double mutation consisting of a GGT to GAT (glycine to aspartate at codon 12) and a GTG to ATG (valine to methionine at codon 8)].
- One of the mutations found in SWCNT exposed mice by inhalation route (at day 28 post exposure) consisted of a double mutation occurring at codons 12 and 8 [GGT to GAT and GTG to ATG (valine to methionine), respectively. The role of this double mutation is unknown and may be specific for SWCNT exposure.

Publications and Abstracts

- Shvedova AA, Kisin E, Murray AR, Johnson, VJ, Gorerlik O, Arepalli S, Hubbs F, Mercer RR, Keohavong P, Sussman N, Jin J, Yin J, Stone S, Chen BT, Deye G, Maynard A, Castranova V, Baron PA, Kagan VE [2008]. Inhalation versus aspiration of single walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress and mutagenesis. Am J Physiol Lung Cell Mol Physi *295*(4):L552–65.
- Elder A, Lynch I, Grieger K, Chan-Remillard S, Gatti A, Gnewuch H, Kenawy E-R, Korensten R, Kuhlbusch T, Linker F, Matias S, monteiro-Riviere N, pinto V, Rudnitsky R, Savolainen K, Shvedova A [2008]. Deposition of nanoparticles as a function of their interactions with biomolecules. In "Nanomaterials Risks and Benefits", Eds. Linkov & Steevens, Springer, The Netherland, pp. 3–29, (Proceedings of the NATO Advanced Research Workshop on Nanomaterials: Environmental Risks and Benefits Faro, Portugal, April 27–30.
- Shvedova AA, Kisin ER, Porter D, Schulte P, Kagan VE, Fadeel B, Castranova V [2008]. Mechanisms of pulmonary toxicity and medical applications of carbon nanotubes: Two faces of Janus? Pharmacol Ther December 6, PMID:19103221. [Epub ahead of print].

Invited Presentation

- Shvedova AA [2008]. Single-walled carbon nanotubes: Are they mutagenic? Mary Babb Randolph Cancer Center. National Institute of Occupational Safety and Health MBRCC, NIOSH Scientific Retreat in Cancer, Morgantown, WV, February 12.

Project 22: Generation and Characterization of Nanoparticles

Principal Investigator: Bon-Ki Ku, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Developed an electrospray generation system to produce SWCNT aerosols with well-defined morphology for the purpose of evaluation instrument response to different morphology and possibly applying them to in vitro cell culture toxicity tests.
- Field-tested size-selected nanoparticle measurement techniques and sampling methods in workplaces for physical and chemical analysis using transmission electron microscopy.
- Characterized purified SWCNTs generated by electrospraying of suspensions.
- Conducted research on the relationship among electrical mobility, mass, and size for nanodrops 1–6.5 nm in diameter.
- Demonstrated that the established relation (which is used in the scanning mobility particle sizer) between electrical mobility and mass diameter for a sphere can be applied with confidence over the whole size range down to 1.3 nm.
- Established significant partnerships with the University of Minnesota, University of Iowa, and Yale University.
- Investigated the relationship between aerodynamic and mobility diameters of SWCNTs and MWCNTs and airborne carbon nanofiber.
- In conjunction with the University of Minnesota, applied a new method to characterize the structure of airborne SWCNTs. The results obtained are expected to be used by toxicologists and other scientists to investigate and identify physical properties that may contribute to observed particle toxicity.
- Observed anomalous behavior in state-of-the-art aerosol instrumentation. This research is expected to lead to the development of effective

monitoring methods and new/improved instrument designs that are needed for accurate characterization of worker exposures.

- In conjunction with Yale University, contributed a large amount of data on mobility and mass relations for a significant number of different materials in the size range of a few nanometers. The data are valuable in giving a basis for accurate measurements of nanoparticles at very small sizes and are expected to be used in future research.
- Characterized bipolar charging characteristics of carbon nanofibers to better understand particle charging-based instrument response to different particle morphologies, such as spherical and fiber shape.

Publications and Abstracts

- Maynard AD, Ku B-K, Emery M, Stolzenburg M, McMurry P [2007]. Airborne single-walled carbon nanotube agglomerates show particle size-dependent physicochemical structure. J Nanopart Res *9*:85–92.
- Ku B-K, Maynard AD, Baron PA, Deye G [2007]. Observation and measurement of anomalous responses in a differential mobility analyzer by ultrafine fibrous carbon aerosols. J Electrostat *65*:542–548.
- Ku B-K [2008]. Nanomaterials and occupational health. Indust Health *2*:44–49 (in Korean).
- Ku B-K, Kulkarni P [in press]. Morphology of single-wall carbon nanotube aggregates generated by electrospray of aqueous suspensions. J Nanopart Res.
- Ku B-K, Fernandez de la Mora J [2009]. Relation between electrical mobility, mass, and size for nanodrops 1–6.5 nm in diameter in air. Aerosol Sci Technol *43*(3), 241–249.
- Shvedova AA, Kisin E, Murray AR, Johnson V, Gorelik O, Arepalli S, Hubbs AF, Mercer RR, Keohavong P, Sussman N, Jin J, Yin J, Stone S, Chen BT, Deye G, Maynard A, Castranova V, Baron PA, Kagan VE [in press]. Inhalation versus aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. Am J Physiol Lung Cell Mol Physiol.

Invited Presentations

- Ku B-K [2007]. Characterization of purified single-walled carbon nanotube aerosols generated by electrospraying of suspension. International symposium on nanotechnology, occupational, and environmental health, Taipei, Taiwan, August 29–September 1.

- Ku B-K, Fernandez de la Mora J, Ude S [2007]. Relation between electrical mobility, mass, and size in the nanometer range of charged nanoparticles generated by electrosprays. American Association for Aerosol Research annual conference, Reno, NV, September 24–28.
- Ku B-K [2007]. Nanoparticles and occupational health: toward safe nanotechnology conference. University of Kentucky, Lexington, KY, April 24.
- Ku B-K [2007]. Nanoparticles, occupational and environmental health: physical characterization of nanoparticles conference. Korea Institute of Machinery and Materials, Daejeon, Korea, September 3 and 4.
- Ku B-K [2007]. Contemporary issues in occupational health: nanoparticles and occupational health conference. University of Yonsei, Seoul, Korea, September 5.
- Ku B-K, Fernandez de la Mora J [2008]. Electrical mobility, mass, and size for nanodrops 1–3.5 nm in diameter. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.
- Kulkarni P, Deye GJ, Ku B-K, Baron PA [2008]. Relationship between aerodynamic and mobility diameters of single- and multi-walled carbon nanotube aerosols. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.

Project 23: Dustiness of Nanomaterials

Principle Investigator: Douglas E. Evans, Ph.D.

Project Duration: FY 2007–2009

Critical Topic Areas: measurement methods, exposure assessment, fire and explosion safety

Accomplishments and Research Findings

- Completed pilot phase of the research.
- Evaluated novel method for testing powders and found it to be suitable for testing nanomaterials. Advantages of the method include
  - — Small powder samples required (mg quantities), allowing for a potentially greater number of materials to be tested
  - — Complete enclosure of the test system so that the operator is not exposed to potentially toxic materials
  - — Relevance to the workplace
- Tested approximately 20 fine and nanoscale materials—consisting of at least three replicate tests—for total and respirable mass. Values span 2 orders of magnitude.
- Modified the testing system and protocol to investigate humidity effects on powder dispersal.
- Designed a new dispersal chamber, allowing for a greater variety of measurements to be made.
- In February 2007, visited the UK Health and Safety Laboratory in Buxton.
  - — Discussed issues related to workplace measurement of nanomaterials and dustiness testing methods.
  - — Conducted dustiness tests of the novel method in parallel with the more traditional (UK) rotating-drum method using the same materials. Technical issues were identified with both methods.
- In early 2008, submitted a full NORA/NTRC proposal for the FY 2009 solicitation to support continuing dustiness research.

Invited Presentations

- Evans DE [2007]. Working at the nanoscale: the occupational health and safety perspective. Health and Safety Laboratory, Buxton, United Kingdom, February 20.
- Mark D, Bard D, Wake D, Hoover MD, Stefaniak AB, Methner MM, Evans DE, Geraci CL [2008]. Problems and experience of measuring worker exposure to engineered nanoparticles. International inhalation symposium: benefits and risks of inhaled engineered nanoparticles, Hanover, Germany, June 11–14

Project 24: Nanoaerosol Monitoring Methods

Principle Investigators: M. Eileen Birch, Ph.D. and Douglas E. Evans, Ph.D.

Project Duration: FY 2005–2010

Critical Topic Areas: measurement methods, exposure assessment

Accomplishments and Research Findings (laboratory and field research)

- Collaborated on collection and analysis of diesel particulate samples from mines.
- Collaborated on screening survey at a major producer of carbon nanofibers. Provided analytical data and submitted report to company (screening survey completed).
- Completed walk-through at same facility.
- Completed survey on ultrafine aerosol sources at diesel engine manufacturing plant.
- Completed in-depth survey at the University of Dayton Research Institute carbon nanofiber composite facility. Prepared report to the Institute.
- Provided real-time data to Altair environmental health and safety facilitator for internal review in September 2007. Identified several areas where development of new/improved monitoring approaches is required.
- Completed construction of a novel instrument for fast measurement of nanoparticle size distribution (instrument evaluation under way).

Publications and Abstracts

- Heitbrink WA, Evans DE, Peters TM, Slavin TJ [2007]. Characterization and mapping of very fine particles in an engine machining and assembly facility. J Occup Environ Hyg *4*(5):341–351.
- Baron PA, Estill CF, Beard JK, Hein MJ, Larsen L [2007]. Bacterial endospore inactivation caused by outgassing of vaporous hydrogen peroxide from polymethyl methacrylate (Plexiglas®). Lett Appl Microbiol *45*:485–490.

- Kulkarni P, Deye G, Baron P [2008]. Bipolar diffusion chargin of carbon nanotube aerosols. J Aerosol Sci, doi:10.1016/j.jaerosci.2008.09.008.
- Wang Z, Hopke PK, Ahamadi G, Cheng Y-S, Baron PA [2008]. Fibrous particle deposition in human and nasal passage: the influence of particle length, flow rate, and geometry of nasal airway. J Aerosol Sci *39*(12):1040–1054.
- Baron P, Deye GJ, Martinez AB, Jones EN, Bennett JS [2008]. Size shifts in measurements of droplets with the aerodynamic particle sizer and the aerosizer. Aerosol Sci Technol *42*(3):201–209.
- Olfert J, Kulkarni P, Wang J [2008]. Rapid measurements of aerosol size distributions using a fast integrated mobility spectrometer. J Aerosol Sci [www.ecd.bnl.gov/pubs/BNL-79289-2007-AB.pdf].
- Evans DE, Heitbrink WA, Slavin TJ, Peters TM [2008]. Ultrafine and respirable particles in an automotive grey iron foundry. Ann Occup Hyg *52*(1):9–21.
- Baron PA, Estill CF, Deye GJ, Hein MJ, Beard JK, Larsen LD, Dahlstrom GE [2008]. Development of an aerosol system for uniformly depositing bacillus anthracis spore particles on surfaces. Aerosol Sci Technol *42*(3):159–172.
- Shvedova AA, Kisin E, Murray AR, Johnson V, Gorelik O, Arepalli S, Hubbs AF, Mercer RR, Stone S, Frazer D, Chen T, Deye G, Maynard A, Baron P, Mason R, Kadiiska M, Stadler K, Mouithys-Mickalad A, Castranova V, Kagan VE [2008]. Inhalation of carbon nanotubes induces oxidative stress and cytokine response causing respiratory impairment and pulmonary fibrosis in mice. Toxicologi *102*(1):307.
- Baron PA, Deye GJ, Chen B, Schwegler-Berry DE, Shvedova AA, Castranova V [accepted for publication]. Aerosolization of single-walled carbon nanotubes for an inhalation study. J Inhal Toxicol.
- Shvedova AA, Kisin E, Murray AR, Johnson V, Gorelik O, Arepalli S, Hubbs AF, Mercer RR, Keohavong P, Sussman N, Jin J, Stone S, Chen BT, Deye G, Maynard A, Castranova V, Baron PA, Kagan VE [in press]. Inhalation versus aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. Amer J Physiol.
- Heitbrink WA, Evans DE, Ku B-K, Maynard AD, Slavin TJ, Peters TM [2009]. Relationships between particle number, surface area, and

respirable mass concentration in automotive engine manufacturing. J Occup Environ Hyg. *6*(1):19–32.

- Kulkarni P, Deye G, Baron P [in press]. Bipolar diffusion charging characteristics of airborne carbon nanotube aerosols. J Aerosol Sci.

Invited Presentations

- Birch ME, Evans DE, Ku B-K [2007]. Occupational monitoring of carbonaceous nanomaterials. American Association for Aerosol Research annual conference, Reno, Nevada, September 24–28.
- Heitbrink WA, Evans DE, Ku B-K, Maynard AD, Peters TM, Slavin TJ [2007]. The relationship between particle surface area, number, and respirable mass concentration in an automotive foundry and engine machining facility. American Association for Aerosol Research annual conference, Reno, Nevada, September 24–28.
- Kulkarni P, Deye G, Baron P [2007]. Bipolar diffusion charging characteristics of airborne, single-walled carbon nanotubes. American Association for Aerosol Research annual conference, Reno, NV, September 24–28.
- Evans DE [2007]. Working at the Nanoscale: The occupational health and safety perspective. NANOMIST meeting, Birmingham, United Kingdom, February 19.
- Baron PA [2008]. Aerosol science enabling nanomaterial research: experience in environmental and occupational health. Inaugural meeting of the student chapter of American Association for Aerosol Research, University of Cincinnati, Cincinnati, OH, April 29.

Project 25: Measurement of Nanoscale Carbonaceous Aerosols

Principle Investigator M. Eileen Birch, Ph.D.

Project Duration FY 2007–2008

Critical Topic Areas: measurement methods, exposure assessment

Accomplishments and Research Findings (laboratory and field research)

- Completed preliminary investigations at two carbon nanofiber (CNF) facilities when this project began in June 2007. A NIOSH Health Hazard Evaluation (HHE) report on the first field study was published in 2006. A report on the second study was sent to the company in February 2007.
- Completed design and assembly of a mobile aerosol sampling unit (cart) for performing real-time aerosol measurements in workplaces. The unit is equipped with sampling ports and battery power and accommodates a laptop and multiple aerosol instruments.
- Completed in-depth field study (five site visits during FY 2007 and FY2008) at a major CNF manufacturer. Found CNF dispersion within the facility. Identified production byproducts and informed company of them. Also provided recommendations to improve air quality.
- Began work on generation of a carbon black aerosol and its collection on filter sets in July 2008. This work will continue in FY 2009 under another project.
- Participated in the American Ceramics Society Workshop, nanoparticle measurement needs for environmental health and safety in Arlington, Virginia, June 9 and 10, 2008.

Publications and Abstracts

- Methner MM, Birch ME, Evans DE, Ku B-K, Crouch KG, Hoover MD [2007]. Case study: identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations. J Occup Environ Hyg *4*(12):D125–D130.

- Noll J, Birch ME [2008]. Effects of sampling artifacts on occupational samples of diesel particulate matter. Environ Sci Technol *42*(14):5223–5228.
- Kulkarni P, Deye G, Baron P [2008]. Bipolar diffusion charging of carbon nanotube aerosols. J Aerosol Sci, doi:10.1016/j.jaerosci.2008.09.008.
- Wang Z, Hopke PK, Ahamadi G, Cheng Y-S, Baron PA [2008]. Fibrous particle deposition in human and nasal passage: the influence of particle length, flow rate, and geometry of nasal airway. J Aerosol Sci *39*(12):1040–1054.

Invited Presentations

- Birch ME, Evans DE, Ku B-K [2007]. Occupational monitoring of carbonaceous nanomaterials. American Association for Aerosol Research annual conference, Reno, NV, September 24–28.
- Evans DE, Birch ME, Ku B-K, Ruda-Eberenz T [2008]. Occupational monitoring of carbonaceous nanomaterials. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.
- Ruda-Eberenz T, Birch ME, Evans DE, Ku B-K [2008]. Occupational monitoring of carbonaceous nanomaterials. Central Regional meeting of the American Chemical Society, Columbus, OH, June 10–14.

Project 26: Nanoparticle Reference Materials for Health Protection

Principle Investigator: Aleksandr B. Stefaniak, Ph.D.

Project Duration: FY 2007–2011

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Developed a project protocol in collaboration with the National Institute of Standards and Technology (NIST) and Oak Ridge National Laboratory to develop reference materials.
- Obtained external peer-review of study protocol.
- Identified researchers at NIST who are leading nanoparticle reference material development initiatives.
- Hosted Vince Hackley (NIST) at NIOSH-Morgantown to discuss NIOSH contributions to the development and qualification of a nanoscale TiO_2 reference material.
- Identified a single-walled carbon nanohorn as an engineered nanoparticle with potential for development into reference material as a control material for toxicology studies.
- Conducted a telephone conference call of NTRC working group on engineered nanoparticle classification schemes.
- Participated in NIST-sponsored workshop on nanomaterial manufacturing, May 20–22, 2008 in Gaithersburg, MD.
  - — Participated in breakout session on separation and fractionation of nanomaterials.
  - — Reported output of workshop to the National Nanotechnology Initiative.
- Participated in the American Ceramics Society workshop on nanoparticle measurement needs for environmental health and safety, June 9 and 10, 2008 in Arlington, VA.
- Co-sponsored with American National Standards Institute, National Cancer Institute, and NIST a workshop on enabling standards for nanomaterial characterization, October 8 and 9, 2008 in Gaithersburg,

Maryland. Acted as codiscussion leader of breakout session—Reference and test materials, media and sample preparation.

- Visited Luna NanoWorks (Danville, Virginia) to discuss workplace measurement issues.

Publications and Abstracts

- Stefaniak AB, Schwegler-Berry D, Hoover MD, Goia DV, Rossner A, Postek MT, Poster DL [2007]. Development of nanoparticle size and surface area reference materials for exposure assessment. International symposium on occupational health implications of nanomaterials, Taipei, Taiwan, August.
- Mark D, Bard D, Wake D, Hoover MD, Stefaniak AB, Methner MM, Evans DE, Geraci CL [2008]. Problems and experience of measuring worker exposure to engineered nanoparticles. International inhalation symposium: benefits and risks of inhaled engineered nanoparticles, Hanover, Germany, June 11–14.

Invited Presentations

- Stefaniak AB [2008]. Methodological challenges of assessing bioavailability of emerging contaminants. University of North Carolina Superfund Basic Research Program workshop, assessing bioavailability as a determinant of pollutant exposure: building a multidisciplinary paradigm for the 21st century and beyond, Tampa, FL, February 18–20.
- Stefaniak AB [2008]. Standards needs for occupational exposure assessment of nanomaterials. National Institute of Standards and Technology workshop on enabling standards for nanomaterial characterization, Gaithersburg, MD, October 8 and 9.
- Stefaniak AB (presented by Hoover MD) [2008]. Minimal material characterization of nanomaterials. Workshop on ensuring appropriate material characterization in nanotoxicity studies, Washington, DC, October 28.

Project 27: Calm Air Chamber and Wind Tunnel Evaluation of Personal Aerosol Samplers for Nanoparticle Exposure Assessment

Principal Investigator: Terri Pearce, Ph.D.

Project Duration: FY 2008–2010

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Developed study protocol.
- Obtained external peer-review for protocol.

Invited Presentation

- Pearce T [2008]. Direct-reading nanoaerosol instrument comparison. Abstract and poster for the American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.

Project 28: Ultrafine TiO_2 Surface and Mass Concentration Sampling Method

Principle Investigator: Aleksandr B. Stefaniak, Ph.D.

Project Duration: FY 2007–2011

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Obtained external peer-review of study protocol.
- Obtained bulk ultrafine TiO_2 powder as a study material.
- Characterized bulk powder physicochemical properties (density, morphology, primary particle size, particle cluster size, total surface area by gas adsorption, purity, and crystallinity).
- Characterized intra- and inter-filter variability for three media: track-etched polycarbonate (0.4 µm pore), track-etched polycarbonate (0.8 µm pore) and Teflon (5 µm pore) including thermal integrity, pressure drop, mass stability, and collection efficiency.
- Developed a protocol for determining background surface area of blank filter media using krypton gas isotherms.
- Characterized intra- and inter-filter surface area variability for track-etched polycarbonate (0.4 µm pore), track-etched polycarbonate (0.8 µm pore) and Teflon (5 µm pore) filters.
- Developed protocol for measuring ultrafine TiO_2 surface area with specificity using bulk powder and perylene diimide dye adsorbed to particle surfaces.

Project 29: Standard Determination of Nanoparticle Size

Principle Investigator: Aleksandr B. Stefaniak, Ph.D.

Project Duration: FY 2009–2010

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Obtained external peer-review of study protocol.
- Procured three different sizes of spherical gold nanoparticle reference materials from the National Institute of Standards and Technology (NIST).
- Developed a protocol for depositing each size of gold nanoparticle reference material onto functionalized electron microscopy grids.
- Determined particle diameter for each size of gold reference material on an electron microscopy grids.
- Evaluated data to compare measurement results with certified size values. Communicated with NIST statisticians on comparison statistics.
- Cosponsored with American National Standards Institute, National Cancer Institute, and NIST a workshop on enabling standards for nanomaterial characterization, Oct 8 and 9, 2008 in Gaithersburg, Maryland. Acted as co-discussion leader of breakout session—Reference and test materials, media and sample preparation.

Project 30: Development and Evaluation of Nanoaerosol Surface Area Measurement Methods

Principal Investigator: Bon-Ki Ku, Ph.D.

Project Duration: FY 2009

Critical Topic Area: measurement methods

Planned Research:

- The objectives of this project are to (1) generate well characterized nanoaerosols with different physical and chemical properties to be used as test aerosols and (2) completely characterize diffusion charging and mobility analysis methods for nanoaerosol particles in the size range up to several microns.
- Conduct a preliminary study on diffusion charger responses to spherical particles in the range from 100 nm up to 600 nm to assess whether the diffusion charger response decreases with increasing mobility diameter.

Project 31: Workplace Monitoring of Carbon Nanofibers/Nanotubes

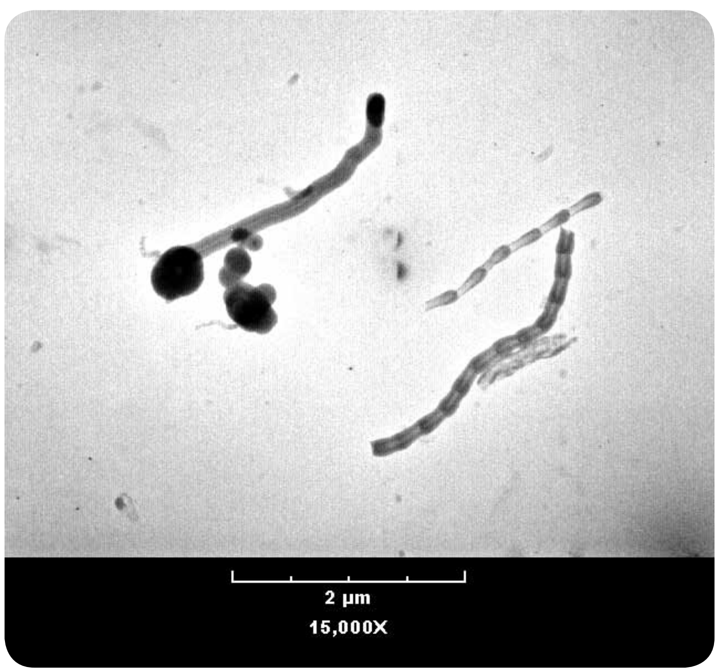
Principle Investigator: M. Eileen Birch, Ph.D.

Project Duration: FY 2009

Critical Topic Areas: measurement methods, exposure assessment

Accomplishments and Research Findings

- Contacted carbon nanotube manufacturer to discuss production processes and tentative date for field survey in FY 2009.
- Generation methods for carbon black aerosol are being investigated. The objective is collection of a matched filter set for interlaboratory comparisons.
- Initiated collaboration with NIST on an analytical reference material for carbon nanotubes.



Electron micrograph of carbon nanofibers at 15,000x

Project 32: Ultrafine Aerosols from Diesel-Powered Equipment

Principal Investigator: Aleksandar Bugarski, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: measurement methods

Accomplishments and Research Findings

- Evaluated the effects of a fuel-borne, catalyst-regenerated, sintered metal, diesel-particulate-filter (DPF) system from Mann-Hummel on size distribution and concentration of nano and ultrafine aerosols in mine air. This study conducted at NIOSH Diesel Laboratory at Lake Lynn Laboratory was used to characterize physical and chemical properties of aerosols emitted from an engine equipped with sintered metal DPF system and to assess the effects of DPF regeneration strategy (fuel-borne catalyst) on concentrations of aerosols and gases in mine air.
- Evaluated the potential of biodiesel fuels to reduce concentrations of aerosols in mine air. This study was conducted at the NIOSH Diesel Laboratory at Lake Lynn Laboratory. Compared neat and blended biodiesel fuels with ultra low sulfur petroleum diesel relating to their effects on the concentrations and size distributions of diesel aerosols in underground mine conditions. The physical and chemical properties and toxicity of diesel and biodiesel aerosols in mine air were studied.
- Evaluated the effects of an electrically regenerated, sintered metal DPF system from Rypos on size distribution and concentration of nano- and ultrafine aerosols in mine air. This study, conducted at NIOSH Diesel Laboratory at Lake Lynn Laboratory, was used to characterize physical and chemical properties of aerosols emitted from an engine equipped with sintered metal DPF system and to assess the effects of DPF-regeneration strategy (electrical current) on concentrations of aerosols and gases in mine air.
- Developed novel methodology for collection of diesel particulates for genotoxicity analysis. The samples are collected directly on lung surfactant using biosamplers and versatile aerosol concentration enrichment system developed in cooperation with University of Southern California.

- Developed the novel methodology for preparing and analyzing samples collected using aforementioned sampling system.
- Using the salmonella reversion assays, assessed genotoxic potential of the solvent extracted diesel aerosols samples collected during DPF and biodiesel studies.
- Evaluated suitability of various aerosol instrumentation, such as fast mobility particle sizer, scanning mobility particle sizer, electrical low pressure impactor, nanoparticle surface area monitor, PAS2000, and filter-sampling methodologies for measurement and sampling of diesel aerosols.
- Completed the new engine/dynamometer system with a Mercedes-Benz engine and 400 kW dynamometer. It is awaiting deployment to NIOSH Diesel Laboratory at Lake Lynn Laboratory.
- The Lake Lynn Laboratory mine has been under reconstruction since July 2008. For safety reasons, the experimental work is postponed probably until spring 2009.
- Disseminated findings in peer-review papers and at 13th and 14th Mining Diesel Emissions Council conference, 13th Diesel Engine-Efficiency and Emissions Research (DEER) conference, 12th United States/North American mine ventilation symposium.

Invited Presentations

- Bugarski AD, Schnakenberg GH Jr., Hummer JA, Cauda E, Janisko SJ, Patts LD [2007]. Examination of diesel after-treatment systems at NIOSH Lake Lynn Laboratory. Annual mining diesel emissions conference, Richmond Hill/Toronto, Ontario, Canada, October 1–5.
- Shi XC, Keane M, Ong T, Harrison J, Gautam M, Li S-Q, Bugarski A, Wallace W [2007]. Preserving diesel exhaust ultrafine (nano-) particulate structure in genotoxicity studies to support engineering development of emissions controls. Diesel engine-efficiency and emissions research (DEER) conference, Detroit, MI, August 13–16.
- Bugarski A, Schnakenberg GH Jr., Mischler S, Cauda E [2007]. Characterization of the physical and chemical properties of diesel aerosols in an underground mine diesel laboratory. ETH conference on combustion generated nanoparticles, Zurich, Switzerland, August 13–15.
- Gautam M, Wilt G, Carder D, Bugarski A [2007]. Evaluation of diesel exhaust particulate matter in a ventilated mine tunnel. ETH conference

on combustion generated nanoparticles, Zurich, Switzerland, August 13–15.

- Bugarski AD, Cauda E, Janisko S, Patts LD, Hummer JA, Mischler SE [2008]. Effects of biodiesel on aerosols in underground mine. Annual mining diesel emissions conference, Richmond Hill/Toronto, Ontario, Canada, October 5–10.
- Bugarski AD, Cauda E, Janisko S, Patts LD, Hummer JA, Mischler SE [2008]. Evaluation of an electrically regenerated sintered metal diesel particulate filter system in underground mine laboratory. Annual mining diesel emissions conference, Richmond Hill/Toronto, Ontario, Canada, October 5–10.
- Shi X-C, Keane MJ, Ong T-M, Bugarski AD, Gautam M, Wallace WE [2008]. Diesel exhaust particulate material expression of in vitro genotoxic activities when dispersed into a phospholipid component of lung surfactant. Inhaled Particles X conference, Sheffield, United Kingdom, September 23–25.
- Bugarski AD, Schnakenberg GH Jr., Cauda E [2008]. Effects of sintered metal diesel particulate filter system on diesel aerosols and nitric oxides in mine air. United States/North American mine ventilation symposium, Reno, NV, June 9–11.
- Bugarski A [2008]. Diesel particulate filtration technology in underground mines. California Air Resource Board (CARB)/Southern California Air Quality Management District, course on ultrafine particles and retrofit technologies for diesel engines, Diamond Bar, CA, November 12–14.

Project 33: Titanium Dioxide and Other Metal Oxides Exposure Assessment Study

Principle Investigator: Brian Curwin, Ph.D.

Project Duration: FY 2006–2009

Critical Topic Areas: measurement methods, exposure assessment

Accomplishments and Research Findings

- Wrote protocol for titanium dioxide study, which underwent peer review.
- Purchased critical exposure assessment equipment, including a TSI 3007 condensation particle counter, an Ecochem DC2000 CE portable diffusion charger, and a MOUDI impactor.
- Awarded a contract for support in company recruitment. Recruitment was completed in June 2008.
- Contacted 189 companies for recruitment; 10 initially agreed to participate and surveys were conducted at 7 companies. Three more companies waiting to be scheduled.
- Sent survey reports to three companies.

Project 34: Field Research Team

Principle Investigators: Mark Methner, Ph.D., and Charles Geraci, Ph.D.

Project Duration: FY 2006–2012

Critical Topic Area: exposure assessment

Accomplishments and Research Findings (field surveys)

- Performed sampling at a multi-walled carbon nanotubes manufacturer. Report issued in 2007.
- Completed two site visits at a metal oxide manufacturer to evaluate engineering controls (2007, 2008). Reports issued in 2008. Engineering case study published in the Journal of Occupational and Environmental Health in 2008.
- Conducted an observational walkthrough at a research and development laboratory that handles and compounds nanoscale polyhedral oligomeric silsesquioxanes (POSS). Subsequent air sampling was performed by facility. Future collaborations on additional air sampling and possible engineering controls are expected.

Cleaning of metal oxide reactor. Note local exhaust ventilation is in use. *Image courtesy of Mark Methner, NIOSH*.

- Performed sampling at a manufacturer of nanoenhanced, silica-iron, absorbent media. Evaluated a spray deposition of nanomaterial onto cellulose substrate inside ventilated chamber. Report issued in 2008.
- Completed two trips to evaluate chamber ventilation role in controlling releases during cleanout operations at a pilot-scale research and development facility that creates nanoscale alumina via radiofrequency plasma torch reaction. Issued two reports (2007, 2008). Future collaboration to evaluate alternative engineering controls expected.
- Performed sampling at an environmental toxicology laboratory. Facility conducts toxicology studies on invertebrates. Evaluated handling procedures during MWCNT- and fullerene-solution preparation. Report issued in 2008.
- Performed sampling at a manufacturer that compounds/blends MWCNTs and boron carbide. Company ships product to manufacturer that uses material to create body armor. Report issued in 2009. Expect future collaborations to include engineering control evaluation and potential exposure to end-user of material.
- Performed sampling at a pilot-scale, research-and-development laboratory that handles/processes MWCNTs for use in composite material production. Facility installed HEPA-filtered downdraft ventilated enclosure for use during handling operations. Air sampling conducted with and without ventilation system operating. Report issued in 2009.
- Performed sampling at a research and development laboratory that handles a variety of engineered nanomaterials (MWCNTs, metal oxides). Report issued in 2009.
- Performed sampling at a pilot-scale, research-and-development facility that synthesizes and handles MWCNTs for inclusion in composite materials. Report issued in 2009.
- Performed sampling at a Department of Defense Applied Toxicology laboratory that handles engineered nanomaterials (elemental metals and oxides) for use in animal toxicological studies. Report issued in 2009.
- Performed sampling at a research laboratory producing carbon nanotube infused fiber composites. Report issued in 2009.

Publications and Abstracts

- Methner MM, Birch ME, Evans DE, Ku B-K, Crouch K, Hoover MD, Mazzukelli LF (Ed) [2007]. Case study: identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations. J Occup Environ Hyg *4*(12):D125–D130.

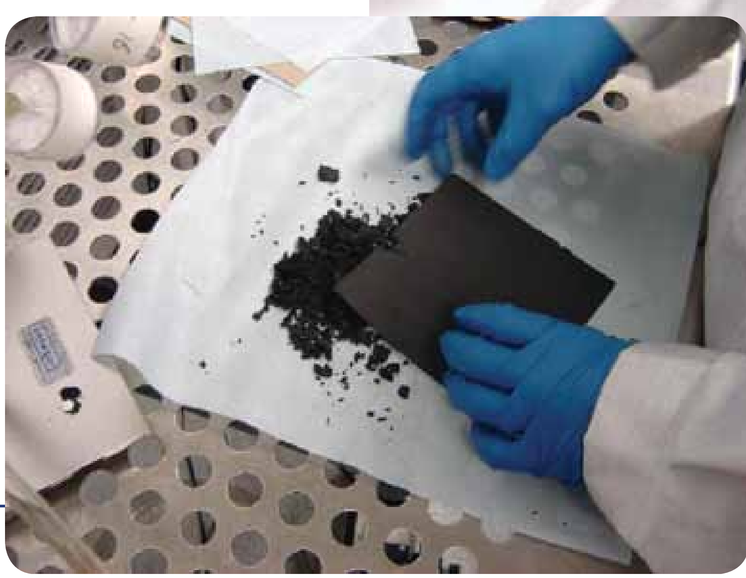
- Methner MM and Old L (Ed.) [2008]. Engineering case study: effectiveness of local exhaust ventilation in controlling engineered nanomaterial emissions during reactor cleanout operations. J Occup Environ Hyg *5*(6):D63–69.

Invited Presentations

- Hodson LL [2007]. Nanoparticles-NIOSH Nanoparticles Research Program. The Insurance Loss Control Association, Oct 31.
- Hodson, LL [2008]. Workplace exposure assessment and risk management practices for nanomaterials. The Ohio Safety Congress and Expo, Columbus, OH, April 3.
- Methner MM, Hodson LL, Geraci CL [2008]. One day workshop: Nanoparticles in the Workplace: Demonstration of the instruments used when using the nanoparticle emission assessment technique (NEAT). American Industrial Hygiene Association, Central Ohio Section, Columbus, OH, April 22.
- Hodson LL [2008]. Nanoparticles—NIOSH Nanoparticle Research Program. The Edison Electric Institute spring occupational health and safety conference, Louisville, KY, April 29.
- Methner MM [2008]. Nanotechnology: ask the expert panel discussion: results pertaining to the field use of the nanoparticle emission assessment technique (NEAT). American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.
- Methner MM, Hodson LL [2008]. Professional Development Course: Nanoparticles in the Workplace: Demonstration of the instruments used when using the nanoparticle emission assessment technique (NEAT). American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.
- Mark D, Bard D, Wake D, Hoover MD, Stefaniak AB, Methner MM, Evans DE, Geraci CL [2008]. Problems and experiences of measuring worker exposure to engineered nanoparticles. International Inhalation Symposium, Hanover, Germany, June 11–14.
- Hodson LL [2008]. The NIOSH field research team—a brief summary and update of activities. U.S. Air Force (USAF) workshop on biological interaction of engineered nanoparticles, Wright Patterson AFB, Dayton, OH, June 24.

- Hodson LL [2008]. NIOSH Nanotechnology Research Program. American Industrial Hygiene Association, Indiana section meeting, Indianapolis, IN, July 9.
- Methner MM, Hodson LL, Geraci CL [2008]. Professional Development Course: Nanoparticles in the Workplace: Demonstration of the instruments used when using the nanoparticle emission assessment technique (NEAT). American Industrial Hygiene Association, Ohio Valley Section, West Chester, OH, December 16.

Weighing CNF in an exhausted enclosure. *Image courtesy of Mark Methner, NIOSH.*



Crumbling carbon nanofiber paper. *Image courtesy of Mark Methner, NIOSH.*

Project 35: Assessing the Feasibility of Industrywide Exposure and Epidemiology Studies of Workers Exposed to Engineered Nanomaterials

Principle Investigator: Mary Schubauer-Berigan, Ph.D.

Project Duration: FY 2008–2009

Critical Topic Area: epidemiology and surveillance

Accomplishments and Research Findings

- Developed and funded a statement of work to collect and compile information on the size, characteristics, and future trends of the U.S. workforce involved in the manufacture of engineered carbonaceous nanomaterials.
- Attended the 2008 Micro Nano Breakthrough conference in Vancouver, Washington, to learn about the latest applications of engineered carbonaceous nanomaterials as well as possible timeframes and barriers for transition from startup to full-scale production for the most promising applications.
- Reviewed and compiled information on companies identified as engineered carbonaceous nanomaterials manufacturers in the Lux Report (fourth and fifth editions), supplemented with information collected from Dun and Bradstreet.
- Contacted and conducted interviews with health and safety managers at each identified company to confirm the information collected on workforce size, location, characteristics of the nanomaterials produced, and use of engineering controls and personal protective equipment.
- Developed a report on the feasibility of conducting industrywide exposure surveys and epidemiological studies among this workforce.

Project 36: Nanoparticles—Dosimetry and Risk Assessment

Principle Investigator: Eileen D. Kuempel, Ph.D.

Project Duration: FY 2005–2012

Critical Topic Area: risk assessment

Accomplishments and Research Findings

- Developed and published risk assessment methods for inhaled poorly soluble nanoparticles, including quantitative dose-response analysis in rodents, dosimetry modeling, and extrapolation of risk estimates to humans.
- Completed nanoparticle dosimetry model in rats. Dosimetry model describes clearance, retention, and translocation from lungs to systemic circulation, and early biological responses. Model calibration used dose-response data from NIOSH animal studies (IOM/NIOSH research collaboration).
- Completed olfactory deposition model of spherical nanoparticles in rats. Revised multipath particle deposition (MPPD) model to include site-specific deposition efficiency in nasal-pharyngeal region (Hamner Institute/NIOSH research collaboration).
- Initiated research with Hamner Institute to develop human olfactory deposition model of spherical nanoparticles. Will use estimates of olfactory deposition proportion in estimating dose and assessing risk of nanoaerosols.
- Developed modeling methods to predict human respiratory tract deposition model for carbon nanofibers/nanotubes structures based on fiber aerosol theory. Additional methods are being evaluated to account for diffusion diameter and to model deposition of heterogeneous nanoaerosol structures. (Hamner Institute/NIOSH research collaboration).

Publications and Abstracts

- Kuempel ED [2007]. Estimating nanoparticle dose in humans: issues and challenges. Chapter 10. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 141–152.

- Kuempel ED, Geraci CL, Schulte PA [2007]. Risk assessment approaches and research needs for nanoparticles: An examination of data and information from current studies. In: Simeonova PP, Opopol N, Luster MI, eds. Nanotechnology: toxicological issues and environmental safety, NATO security through science series book. New York: Springer-Verlag, pp. 119–145.
- Dankovic D, Kuempel E, Wheeler M [2007]. An approach to risk assessment for TiO_2. Inhal Toxicol *19*(Suppl 1):205–212.
- Tran CL, Kuempel ED [2007]. Biologically based lung dosimetry and exposure-dose-response models for poorly soluble, inhaled particles. In: Donaldson K, Borm P, eds. Particle Toxicology. Boca Raton, Florida: CRC Press, Taylor and Francis Group, Chapter 20.
- Kuempel ED, Tran CL, Castranova V, Bailer AJ [2007]. Response to letter to the editor from Dr. Peter Morfeld [re: Lung dosimetry and risk assessment of nanoparticles: evaluating and extending current models in rats and humans. Inhal Toxicol *18*(10):717–24]. Inhal Toxicol *19*(2):197–198.
- Garcia GJM, Nazridoust K, Kimbell JS [2008]. Nanoparticle deposition in the rat nasal cavity: prediction of dose to the olfactory epithelium. Toxicologist *102*(1):204.
- MacCalman L, Tran CL, Kuempel E [in press]. Development of a biomathematical model in rats to describe particle size-specific clearance and translocation of inhaled nano particles. J Physics.
- Kuempel ED, Smith RJ, Dankovic DA, Stayner LT [in press]. Rat- and human-based risk estimates of lung cancer from occupational exposure to poorly soluble particles: a quantitative evaluation. J Physics.

Invited Presentations

- Kuempel ED [2007]. Review of hazard information on nanoparticles: as relates to occupational health surveillance. Workshop on occupational health surveillance and nanotechnology workers. Washington, DC, April 17.
- Geraci CL, Schulte PA, Zumwalde R, Kuempel E, Hoover M [2007]. Occupational risk management for nanomaterials along the product life cycle. International symposium on nanotechnology, occupational, and environmental health. Taipei, Taiwan, August 29–September 1.
- Schulte PA, Murashov VV, Geraci CL, Zumwalde RD, Hoover MD, Castranova V, Kuempel ED [2007]. Current occupational safety and

health issues of nanotechnology in the USA. European NanOSH conference—Nanotechnologies: a critical area in occupational safety and health, Helsinki, Finland, December 3–5.

- MacCalman L, Tran CL, Kuempel E [2008]. Development of a biomathematical model in rats to describe the retention, clearance, and translocation of nanoparticles from the lungs. Inhaled Particles X conference, Sheffield, United Kingdom, September 23–25.
- Kuempel ED, Smith RJ, Dankovic DA, Stayner LT [2008]. Rat- and human-based risk estimates of lung cancer from occupational exposure to poorly soluble particles: a quantitative evaluation. Inhaled Particles X conference, Sheffield, United Kingdom, September 23–25.
- MacCalman L, Tran L, Kuempel E [2008]. Developing and testing a biomathematical model to describe particle size-specific clearance and translocation of nanoparticles in rats. Nanotoxicology—Second international nanotoxicology conference, Zurich, Switzerland, September 7–10.
- Schulte PA, Kuempel E, Castranova V, Trout D [2008]. Assessing the toxicological evidence base for medical surveillance of workers potentially exposed to engineered nanoparticles. Second international nanotoxicology conference, Zurich, Switzerland, September 7–10.
- Kuempel ED [2008]. Should engineered nanoparticles be considered "new chemicals"? NTRC annual meeting, Morgantown, West Virginia, January 23.

Project 37: Penetration of Nanoparticles through Respirators

Principle Investigator: Samy Rengasamy, Ph.D.

Project Duration: FY 2005–2009

Critical Topic Area: engineering controls and personal protective equipment

Accomplishments and Research Findings

- Conducted studies to measure nanoparticle penetration through the following:
  1. NIOSH-approved N95 and P100 and European-certified CE marked filtering facepiece respirators
  2. Dust masks that are available in home improvement/hardware stores
  3. FDA-approved surgical masks

Publications and Abstracts

- Rengasamy S, Verfobsky R, King W, Shaffer R [2007]. Nanoparticle penetration through NIOSH-approved N95 filtering facepiece respirators. JISRP *24*:49–59.
- Rengasamy S, Eimer B, Shaffer R [2008]. Nanoparticle filtration performance of commercially available dust masks. JISRP *25*:27–41.
- Rengasamy S, King W, Eimer B, Shaffer R [2008]. Filtration performance of NIOSH-approved N95 and P100 filtering facepiece respirators against 4–30 nanometer-size nanoparticles. J Occup Environ Hyg *5*:556–564.
- Rengasamy S, Eimer B, Shaffer R [in press]. Comparison of nanoparticle filtration performance of NIOSH-approved and CE-marked filtering facepiece respirators. Annals of Occ Hyg.
- Shaffer R, Rengasamy S [in press]. Respiratory protection against nanoparticles: A review. J Nanopart Res. Special issue on "Exposure assessment and exposure mitigation for nanomaterials in the workplace".
- Fisher E, Rengasamy S, Viscusi D, Vo E, Shaffer R [in press]. Development of a test system of apply virus containing particles to filtering

facepiece respirators for the evaluation of decontamination procedures. App Environ Microbiol.

Invited Presentations

- Shaffer R [2007]. Air purifying respirators for the nanotechnology industry. National Response Team-Worker Safety and Health Conference, Washington, DC, August 7.
- Shaffer R [2007]. An overview of NIOSH nanotechnology research and an update on the efficacy of personal protective equipment for reducing worker exposure to nanoparticles. Commercialization of nanomaterials meeting, Pittsburgh, PA, November 11–13.
- Rengasamy S, Eimer B, Shaffer R [2008]. Filtration performance of NIOSH-approved N95 and P100 filtering facepiece respirators against nanoparticles. American Industrial Hygiene Association conference, Minneapolis, MN, May 31–June 5.
- Rengasamy S, Eimer B, Shaffer R [2008]. Comparison of nanoparticle filtration performance of NIOSH-approved and European-certified filtering facepiece respirators. ISRP international conference, Dublin, Ireland, September 14–18.
- Rengasamy S, Eimer B, Shaffer R [2008]. Comparison of nanoparticle filtration performance of NIOSH-approved and European-certified filtering facepiece respirators. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.
- Rengasamy S, Shaffer R [2007]. Respiratory protection against nanoparticles. Chesapeake Area Biological Association scientific symposium, Columbia, MD, June 14.
- Shaffer R [2008]. Effectiveness of personal protective equipment and engineering controls. Safe handling of engineered nanoscale materials symposium, Argonne, IL, July 7 and 8.
- Shaffer R [2008]. Control and filtration of nanomaterials. Occupational health aspects of nanotechnology symposium. Northern California Section of the American Industrial Hygiene Association, Menlo Park, CA, May 14.
- Rengasamy S [2008]. Respiratory protection against biological and inert particles. International Society for Respiratory Protection meeting on respiratory protection issues in emergency response and healthcare, Montreal, Canada, October 6.

- Rengasamy S [2008]. Respiratory protection against nanoparticles. Institut de recherche en sante et en securite du travail, colloquium on respiratory protection: research priorities, Montreal, Canada, October 7.

Project 38: Nanoparticle Penetration through Protective Clothing

Principle Investigator: Pengfei Gao, Ph.D.

Project Duration: FY 2009–2009

Critical Topic Area: engineering controls and personal protective clothing

Planned Research

- Development of a model based on single-fiber theory to predict nanoparticle penetration through clothing materials.
- Development of a bench-scale particulate penetration test method based on a wind-driven approach.
- Measurement of particle penetration levels through various fabrics used in protective clothing ensembles.

Project 39: Development of Personal Protective Equipment Ensemble Test Methods

Principle Investigator: Pengfei Gao, Ph.D.

Project Duration: FY 2005–2009

Critical Topic Area: engineering controls and personal protective equipment

Accomplishments and Research Findings

- Developed a multidomain, magnetic passive aerosol sampler for measuring particulate penetration through protective ensembles. Submitted an employee invention report to CDC Technology Transfer Office: Ref. I–007–08 (Gao P [2007]).

Publications and Abstracts

- Gao P, King WP, Shaffer R [2007]. Review of chamber design requirements for testing of personal protective clothing ensembles. J Occup Environ Hyg *4*(8):562–571.
- Gao P, Jeffrey LB, Shaffer R [in press]. Considerations for selection of PPE to protect against nanoparticle exposure. In: Anna D, ed. Chemical protective clothing, 3rd edition. Fairfax, VA: AIHA.

Invited Presentations

- Wang ZM, Gao P [2007]. A study on magnetic passive aerosol sampler for measuring aerosol particle penetration through protective ensembles. American Association for Aerosol Research annual conference, Reno, NV, September 24–28.
- Shaffer R [2007]. An overview of NIOSH nanotechnology research and an update on the efficacy of personal protective equipment for reducing worker exposure to nanoparticles. Commercialization of nanomaterials meeting, Pittsburgh, PA, November 12.
- Shaffer R [2008]. Control and filtration of nanomaterials. Occupational health aspects of nanotechnology symposium, Northern California Section of the American Industrial Hygiene Association, Menlo Park, CA, May 14.

- Shaffer R [2008]. Effectiveness of PPE and engineering controls. Safe handling of engineered nanoscale materials symposium, Argonne, IL, July 7 and 8.
- Jaques PA, Gao P [2008]. Effect of wind velocity on particle collection using a multidomain magnetic passive aerosol sampler. American Association for Aerosol Research annual conference, Orlando, FL, October 20–24.

Project 40: Web-based Nanoparticle Information Library Implementation

Principal Investigator: Arthur Miller, Ph.D.

Project Duration: FY 2004–2008

Critical Topic Area: communication and information

Accomplishments and Research Findings

- Collaborated with Oregon State University and a Health Effects Institute (HEI) consortium toward the development of an informational hub for nanotechnology and health effects.
- Developed Web links for the NIOSH Nanoparticle Information Library to online resources at the Wilson International Center for International Scholars, the International Council on Nanotechnology bibliography on nanotechnology safety and health at Rice University and the National Science Foundation's Nanomanufacturing Network at the University of Massachusetts at Lowell.
- Continued input for redesigning the nanotechnology topic page on the NIOSH Web site.
- Developed a prototype, portable, hand-held electrostatic precipitator that would enhance development of new information for the Nanoparticle Information Library by enabling nanoparticle sampling and subsequent electron microscopy analysis.
- Developed protocols for analyzing workplace nanoaerosol samples using transmission electron microscopy/energy dispersive spectroscopy.
- Developed a protocol for nanoaerosol characterization fieldwork, including quasi-real time spatial mapping of nanoparticle concentrations in the workplace.
- Updated Nanoparticle Information Library software to meet new CDC security requirements.
- Incorporated a mailing interface and a newsletter interface in the design of the Nanoparticle Information Library.

- Developed online newsletters and disseminated them to persons on the Nanoparticle Information Library mailing list.
- Developed course curriculum entitled Nanotechnology Science and Engineering for the mechanical engineering department at Gonzaga University. The course covers the basic chemical, physical, and engineering principles governing nanomaterials, highlighting their differences from classic materials, as well as the science required to use them in nanotechnologies for real-world problem solving.
- Led a team of students in the design, building, and testing of a rapid mobility particle sizer, which has application for the Nanoparticle Information Library and nanotechnology science in general and won first place in the 2008 American Society of Mechanical Engineers (ASME) national design contest.

Publications and Abstracts

- Miller AL, Stipe C, Habjan MC, Ahlstrand G [2007]. Role of lubrication oil in particulate emissions from a hydrogen-powered internal combustion engine. Environ Sci Technol *41*:6828–6835.
- Miller AL, Hoover M D, Mitchell DM, Stapleton BP [2007]. The nanoparticle information library (NIL): a prototype for linking and sharing emerging data. J Occup Environ Hyg *4*(12):D131–D134.
- Miller A, Ahlstrand G, Kittelson DB, Zachariah MR [2007]. The fate of metal (Fe) during diesel combustion: morphology, chemistry, and formation pathways of nanoparticles. Combust Flame *149*:129–143.
- Miller AL, Habjan MC, Park K [2007]. Real-time estimation of elemental carbon emitted from a diesel engine. Environ Sci Technol *41*:5783–5788.
- Ng A, Miller A, Ma H, Kittelson DB [2007]. Comparing measurements of carbon in diesel exhaust aerosols using the aethalometer, NIOSH method 5040 and SMPS. SAE tech paper series 2007–01–0334.
- Miller AL, Habjan M, Beers-Green A, Ahlstrand G [2008]. Microscopic analysis of airborne particles and fibers, a chapter for the new American Conference of Governmental Industrial Hygienists handbook, Air sampling technologies: principles and applications [www.acgih.org/store/ProductDetail.cfm?id=2015].
- Park K, Kim J-S, Miller AL [2008]. A study on effects of size and structure on hygroscopicity of nanoparticles using a tandem differential

mobility analyzer and transmission electron microscopy. J Nanopart Res [http://dx.doi.org/10.1007/s11051-008-9462-4].

- Choo S-W, Lee D, Lee K-S, Miller AL, Park K, Zachariah M, Zhou L [2008]. Understanding nanoscale phenomena using single particle mass spectrometry and improvement of its performance—a review. Chem Physics Res J *2*(1/2):17.

Invited Presentations

- Miller A [2007]. Occupational safety and health challenges of nanotechnology: What we know and what we don't know. Oregon governor's occupational health and safety conference, Portland, OR, March 13.
- Miller A [2007]. Characterization of hazardous pollutants in the workplace. IERC workshop for sound management of hazardous chemicals and sustainable energy, sponsored by the Gwangju Institute of Science and Technology, Gwangju, Korea, October 30–November 3.
- Miller A [2008]. Spatial mapping of industrial hygiene data in the workplace. American Industrial Hygiene Association conference and exhibition, Minneapolis, MN, May 31–June 5.
- Miller A, Geraci CL, Maynard A [2008]. NIOSH's role in improving health and safety in nanotechnology workplaces. Special Libraries Association annual meeting, Seattle, WA, June 15–17.
- Miller A [2008]. NIOSH's role in improving health and safety in nanotechnology workplaces: knowledge management of nanotechnology information. Micro-nano breakthrough conference, Portland, OR, September 8–10.

Project 41: Nanoparticles in the Workplace

Principle Investigator: Mark D. Hoover, Ph.D.

Project Duration: FY 2004–2009

Critical Topic Areas: exposure assessment, communication and information

Accomplishments and Research Findings

- Summarized and published issues and approaches for exposure assessment of nanoparticles in the workplace as a chapter in a book on nanotoxicology that involved a spectrum of international contributors. The exposure assessment chapter included a comprehensive formulaic method for assessing and managing determinants of workplace exposure such as material at risk, damage ratio, airborne release fraction, respirable fraction, and control factors.
- Contributed to the development of an American Industrial Hygiene Association (AIHA) document on guidance for conducting control banding analyses. Provided leadership in activities of the AIHA control banding working group and the AIHA nanotechnology working group to develop potential nanotechnology applications of control banding approaches from pharmaceutical and other historical experiences.
- Developed a new ultrafine beryllium oxide standard reference material (SRM) through the collaborations with the National Institute of Standards and Technology (NIST), and U.S. Department of Energy (DOE). SRM 1877 was formally approved and issued for distribution and use in August 2008. This is one of the first reference materials issued in the ultrafine particle size range and will improve calibration and development of sampling and analytical methods and toxicity testing. Round-robin evaluations of analytical methods for beryllium detection in air filtration samples spiked with SRM 1877 are underway under the auspices of the Beryllium Health and Safety Committee. Results of the evaluatons are expected to have relevance for digestion and detection effeciencies of other ultrafine metal oxide particles.
- Developed partnerships with nanotechnology industries, academia, government agencies, labor, and voluntary consensus standard committees to conduct joint research and develop guidelines on working safely with nanomaterials. This included involvement in activities of the

American National Standards Institute, ASTM International, the International Standards Organization, and the International Electrotechnical Commission. This included collaboration on development of a new Web site, wiki, and other informatics and knowledge-management capabilities for sharing information, including through the NIOSH Nanoparticle Information Library and through a nanotechnology community initiative on minimum information for nanomaterial characterization.

Publications and Abstracts

- Hoover MD, Stefaniak AB, Day GA, Geraci CL [2007]. Exposure assessment considerations for nanoparticles in the workplace. In: Monteiro-Riviere NA, Tran CL, eds. Nanotoxicology: characterization, dosing, and health effects. New York: Informa Healthcare USA Inc., pp. 71–83.
- Miller AL, Hoover MD, Mitchell DM, Stapleton BP [2007]. The Nanoparticle Information Library (NIL): a prototype for linking and sharing emerging data. J Occup Environ Hyg *4*(12):D131–D134.
- American Industrial Hygiene Association [2007]. Guidance for conducting control banding analyses. Fairfax, VA: American Industrial Hygiene Association, Document 9–2007.
- Hoover MD, Poster D [2008]. Environmental, health, and safety crosscut issues for nanomanufacturing. In: Instrumentation, metrology, and standards for nanomanufacturing workshop final report. Postek MT, Lyons KW, Ouimette MS, Holdridge GM eds. National Science and Technology Council Interagency Working Group on Manufacturing Research and Development, Washington, DC

Invited Presentations

- Hoover MD [2007]. NIOSH research on applications, safety hazards, and environmental issues for nanotechnology. CSHEMA-PRIZIM regional Environmental Health and Safety seminar, University of Central Florida, Orlando, FL, April 17.
- Hoover MD [2007]. NIOSH experience in assessing practical measurement and control practices for nanoparticles. Midwest Nanotechnology Safety workshop, Madison, WI, May 21.

- Hoover MD [2007]. Case studies in assessing practical measurement and control practices for nanoparticles. American Industrial Hygiene Association aerosol technology committee symposium on nanotechnology: wonders and worries, Philadelphia, PA, June 2.
- Hoover MD [2007]. Nanotechnology health and safety issues. U.S. Department of Energy industrial hygiene and occupational safety special interest group, Philadelphia, PA, June 8.
- Hoover MD [2007]. Nanoparticle Information Library. National Nanomanufacturing Network workshop on nanoinformatics strategies, Arlington, VA, June 12.
- Hoover MD [2007]. Reference material updates and insights from the NIOSH nanotechnology and exposure assessment research programs. NIOSH-NIST information exchange meeting, National Institute of Standards and Technology, Gaithersburg, MD, June 14.
- Hoover MD [2007]. Overview of NIOSH research on environmental health and safety issues for nanotechnology session on health and safety issues associated with nanomaterials. Air and Waste Management Association annual meeting, Pittsburgh, PA, June 27.
- Hoover MD [2007]. Environmental Health and Safety overview—exposure assessment and control for nanoparticles in the workplace: insights from the NIOSH Nanotechnology Research Program. NanoScience+Engineering SPIE Optics+Photonics conference, San Diego, CA, August 30.
- Hoover MD [2007]. Materials necessary for health and occupational exposure studies, workshop on standards for environmental health and safety research needs for engineered nanoscale materials. National Institute of Standards and Technology, Gaithersburg, MD, September 12.
- Hoover MD [2008]. NanoMetrology research at NIOSH, National Institute of Standards and Technology—NIOSH scientific information exchange, National Institute of Standards and Technology, Gaithersburg, MD, January 28.
- Hoover MD [2008]. Insights from the NIOSH Nanotechnology Research Program, panel discussion on accelerators and nanoparticles, Health Physics Society midyear meeting on radiation-generating devices, Oakland, CA, January 29.
- Hoover MD [2008]. NIOSH nanotechnology initiative: remarks on exposure assessment and control and informatics opportunities. NIOSH

education and research centers industrial hygiene program directors' meeting, Galveston, TX, February 10.

- Hoover MD [2008]. The collection and characterization of nanomaterials for exposure assessment. American Industrial Hygiene Association—Northern California section technical symposium on the occupational health aspects of nanomaterials, Menlo Park, CA, May 14.
- Hoover MD [2008]. Exposure assessment data needs for emerging issues: a case study for nanotechnology risk assessment and risk management. American Industrial Hygiene Association conference and exposition, Minneapolis, MN, May 31–June 5.
- Hoover MD [2008]. Nanoparticle issues for the health physicist: insights from the NIOSH Nanotechnology Research Program. Annual meeting of the Health Physics Society, Pittsburgh, PA, July 16.
- Hoover MD [2008]. Update on the NIOSH direct-reading methods initiative. Annual meeting of the Health Physics Society, Pittsburgh, PA, July 16.
- Hoover, MD [2008]. Demonstration of the NIOSH prototype Web-based Nanoparticle Information Library. Workshop on international collaboration for nanoEHS informatics, National Institute of Standards and Technology, Gaithersburg, MD, October 10.
- Hoover MD [2008]. Nanotechnology safety issues for radioactive materials: insights from the NIOSH Nanotechnology Research Program, regional inspector counterpart seminar. U.S. Nuclear Regulatory Commission, Region 1, King of Prussia, PA, December 10.

Project 42: New Sensor Technology Development for ESLI

Principle Investigator: Jay Snyder

Project Duration: FY 2002–2010

Critical Topic Area: applications

Accomplishments and Research Findings

- Developed sensors and integrated them into APR cartridges for evaluation.
- Developed new nanomaterials for chemical sensing.

Publications and Abstracts

- King BH, Ruminski AM, Snyder JL, Sailor MJ [2007]. Optical-fiber-mounted porous silicon photonic crystals for sensing organic vapor breakthrough in activated carbon. Adv Mater *19*:4530–44.

Invited Presentations

- Snyder J [2007]. End-of-service-life sensor systems for personal protective equipment. Scientific conference on chem bio defense research, Timonium, MD, November 13–15.
- Snyder J [2007]. End-of-service life sensors and models. Technical Support Working Group, Personal Protective Equipment Conference, Fort Lauderdale, FL, November 27–29.
- Snyder J [2008]. Chemically modified porous silicon for optical sensing of organic vapor breakthrough in activated carbon filters. Nanomaterials for Defense conference, Arlington, VA, April 21–24.
- Snyder J [2008]. End-of-service life sensor development. International Isocyanate Institute (III) America analytical subcommittee meeting, Boulder, CO, June 9.
- Snyder J [2008]. Jetted nanoparticle chemical sensor circuits for respirator end-of-service-life detection. 12th International meeting on Chemical Sensors, Columbus, OH, July 13–16.

- Snyder J [2008]. A cartridge simulator for testing end-of-service life indicators. International Society for Respiratory Protection, 14th International Conference, Dublin, Ireland, September 14–18.

Project 43: Global Harmonization of Exposure Measurement and Exposure Mitigation Approaches for Nanomaterials

Principal Investigator: Vladimir Murashov, Ph.D.

Project Duration: FY 2006–2008

Critical Topic Areas: international activities in safety and health, including exposure assessment, risk assessment, recommendations and guidance, and communication and information.

Accomplishments and Research Findings

- Coordinated the international and interagency activities of the NIOSH Nanotechnology Research Program.
- Led the development and publication of ISO TR/12885:2008 Health and safety practices in occupational settings relevant to nanotechnologies.
- Provided technical expertise for several ISO TC229 projects.
- Chaired the Organization for Economic Cooperation and Development Working Party for Manufactured Nanomaterials Steering Group 8, exposure measurement and exposure mitigation.
- Co-led the WHO project on best practices for safe handling of nanomaterials.
- Fostered collaboration in nanotechnology research with the following:
  - — EPA
  - — Consumer Products Safety Commission
  - — NASA
  - — National Institute of Standards and Technology
  - — European Comission
  - — Australia
- Represented NIOSH on several national and international working groups on nanotechnology safety and health.

- Represented NIOSH on the National Nanotechnology Initiative interagency subcommittee and its working groups.
- Presented overviews of the NIOSH Nanotechnology Research Program to outside stakeholders.

Publications and Abstracts

- Murashov VV, Howard J [2007]. Biosafety, occupational health, and nanotechnology. Appl Biosafety *12*(3):158–167
- Murashov V, Howard J [2008]. The U.S. must help set international standards for nanotechnology. Nature Nanotechnol *3*:635–636.
- Schulte PA, Geraci CL, Zumwalde R, Hoover M, Castranova V, Kuempel E, Murashov V, Vainio H, Savolainen K [2008]. Sharpening the focus on occupational safety and health of nanotechnology in the workplace. Scand J Work Environ Health *34*(6):471–478.
- ISO [2008]. Health and safety practices in occupational settings relevant to nanotechnologies. Geneva, Switzerland: International Organization for Standardization, ISO/TR–12885.
- NIOSH [2008]. Nanotechnology: should carbon nanotubes be handled in the workplace like asbestos? Cincinnati, Ohio: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, NIOSH Science Blog May. [www.cdc.gov/niosh/blog/nsb052008_nano.html].
- Murashov VV [in press]. Occupational exposure to nanomedical applications. Wiley Interdisciplinary Reviews: nanomedicine.

Government Publications

- NSTC [2007]. The national nanotechnology initiative strategic plan. By Nanoscale science, engineering, and technology subcommittee, committee on technology. National Science and Technology Council, Arlington, VA. [http://www.nano.gov/NNI_Strategic_Plan_2007.pdf].
- NSTC [2007]. Prioritization of environmental, health, and safety research needs for engineered nanoscale materials. An interim document for public comment. By Nanoscale science, engineering, and technology subcommittee, committee on technology. National Science and Technology Council, Arlington, VA.
- NSTC [2008].Strategy for nanotechnology-related environmental health and safety research. Nanoscale science, engineering, and

technology subcommittee, committee on technology. National Science and Technology Council, Arlington, VA. [http://www.nano.gov/NNI_EHS_Research_Strategy.pdf].

Invited Presentations

- Murashov V [2007]. Nanotechnology health and safety concerns—NIOSH Nanotechnology Research Program. Intertech-PIRA workshop, Washington, DC, February 8.
- Murashov V [2007]. NIOSH Nanotechnology Research Program. Navy occupational health and safety preventive medicine conference, Hampton, VA, March 20.
- Murashov V [2007]. Safe handling of nanotechnology. OSHA/NIOSH Journal Club, Washington, DC, March 29.
- Murashov V [2007]. Nanotechnology health and safety concerns. Meeting of National Aeronautics and Space Administration Code 500 safety awareness campaign, Greenbelt, MD, April 18.
- Murashov V [2007]. NIOSH Nanotechnology Research Program. Conference on Nanotech 2007, Santa Clara, CA, May 21.
- Murashov V [2007]. Nanotechnology: occupational health and safety. Conference on risk assessment for nanomaterials, Cambridge, MA, May 29.
- Murashov V [2007]. Social studies at NIOSH. The Joint Wharton-CHF symposium on social studies of nanotechnology, Philadelphia, PA, June 8.
- Murashov V [2007]. NIOSH Nanotechnology Research Program. Annual environmental health and exposure assessment workshop, Washington, DC, August 17.
- Murashov V [2007]. NIOSH Nanotechnology Research Program. Interagency workshop on the environmental implications of nanotechnology, Washington, DC, September 5.
- Murashov V [2007]. Considerations for selecting standard materials for occupational safety and health. Interagency workshop on standards for environmental health and safety research needs for engineered nanoscale materials, Gaithersburg, MD, September 12.
- Murashov V [2007]. Nanotechnology health and safety concerns. American Society of Safety Engineers, Region VI PDC, Myrtle Beach, SC, September 20.

- Murashov V [2007]. Nanotechnology: occupational health and safety. Mid-Atlantic Regional conference on occupational medicine, Baltimore, MD, October 13.
- Murashov V [2007]. Nanotechnology: occupational safety and health. NanoApplications summit—CleanTech Day, Cleveland, OH, October 24.
- Murashov V [2007]. Nanotechnology: occupational safety and health. State-of-the-Art Conference/International Conference on Health Care Worker Health, Vancouver, British Columbia, Canada, October 26.
- Murashov V [2008]. Nanotechnology and risk. California State University in Northridge, Environmental and Occupational Health Nanotech symposium, Northridge, CA, February 20.
- Murashov V [2008]. International Organization for Standardization TC146/SC2. International Organization for Standardization workshop on documentary standards for measurement and characterization in nanotechnologies, Gaithersburg, MD, February 26.
- Murashov V [2008]. OECD WPMN SG8 Cooperation on exposure measurement and exposure mitigation. International Organization for Standardization workshop on documentary standards for measurement and characterization in nanotechnologies, Gaithersburg, MD, February 26.
- Murashov V [2008]. Exposure assessment and control practices for nanoparticles. University of California, San Diego, forum, San Diego, CA, March 6.
- Murashov V [2008]. Nanotechnology and risk. Joint BIONET/BSAF symposium on current topics in biosafety, La Jolla, CA, March 7.
- Murashov V [2008]. Nanotechnology and risk. 2008 Controlled Environment Testing Association conference, San Antonio, TX, April 14.
- Murashov V [2008]. Nanotechnology: exposure assessment. International symposium on risk assessment of manufactured nanomaterials, Tokyo, Japan, April 23.
- Murashov V [2008]. Nano health, safety and environment and worker protection. Second Jisso international forum, Atlanta, GA, May 22.
- Murashov V [2008]. Nanotechnology: occupational safety and health. Workshop on biological interaction of engineered nanomaterials: environmental, safety, and health issues of military concern, WPAFB, Dayton, OH, June 25.

- Murashov V [2008]. NIOSH Nanotechnology Research Program. Nanoscale Science, Engineering and Technology subcommittee meeting, Arlington, VA, July 15.
- Murashov V [2008]. NIOSH Nanotechnology Research Program. Conference on sustainable nanotechnology innovations, products, and toxicology, Fayetteville, AR, August 14.
- Murashov V [2008]. NIOSH Nanotechnology Research Program. State-of-the-Art Conference/International Conference on Health Care Worker Health, Vancouver, British Columbia, Canada, October 27.
- Murashov V [2008]. NIOSH Nanotechnology Research Program. Meeting of Chinese National Institute of Occupational Health and Poison Control, Beijing, China, November 13.
- Murashov V [2008]. NIOSH Nanotechnology Research Program. Meeting of National Center for Nanoscience and Technology of China, Beijing, China, November 14.
- Murashov V [2008]. Nanotechnology and risk. Metro Washington College of Occupational and Environmental Medicine Meeting, Bethesda, MD, December 3.
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Appendices

Appendix A | Projects by Critical Topic Area

A. Toxicology and Internal Dose

Project 1: Nanotechnology Research Center Coordination

Project 2: Nanotechnology Safety and Health Research Coordination

Project 3: Systemic Microvascular Dysfunction: Effects of Ultrafine vs. Fine Particles

Project 4: Particle Surface Area as a Dose Metric

Project 5: Role of Carbon Nanotubes in Cardiovascular and COPD-Related Diseases

Project 6: Investigations of Multi-Walled Carbon Nanotube Toxicity

Project 7: Pulmonary Toxicity of Metal Oxide Nanospheres and Nanowires

Project 8: WC-Co Nanoparticles in Initiating Angiogenesis by Reactive Oxygen Species

Project 9: Evaluation of the Pulmonary Deposition and Translocation of Nanomaterials

Project 10: Occupational Exposures and Potential Neurological Risks

Project 11: Lung Effects of Resistance Spot Welding Using Adhesives

Project 12: Neurotoxicity after Pulmonary Exposure to Welding Fumes

Project 13: Potential Aneuploidy Following Exposure to Carbon Nanotubes

Project 14: Pulmonary Toxicity of Carbon Nanotube Particles

Project 15: Dermal Toxicity of Nanotube Particles

Project 16: Specific Biomarkers for Unusual Toxicity of Nanomaterials

Project 17: Pulmonary Toxicity of Diesel Exhaust Particles

Project 18: Induction of Lung Fibrosis by Cerium Oxide in Diesel Exhaust

Project 19: Potential Effects of Silicon-based Nanowires on Lung Toxicity

Project 20: Cell-based Assessment for Iron Nanoparticle-Induced Health Risks

Project 21: Assessment of Carbonaceous Materials on Magenicity

B. Measurement Methods

Project 1: Nanotechnology Research Center Coordination

Project 22: Generation and Characterization of Nanoparticles

Project 23: Dustiness of Nanomaterials

Project 24: Nanoaerosol Monitoring Methods

Project 25: Measurement of Nanoscale Carbonaceous Aerosols

Project 26: Nanoparticle Reference Materials for Health Protection

Project 27: Calm Air Chamber and Wind Tunnel Evaluation of Personal Aerosol Samplers for Nanoparticle Exposure Assessment

Project 28: Ultrafine TiO2 Surface and Mass Concentration Sampling Method

Project 29: Standard Determination of Nanoparticle Size

Project 30: Development and Evaluation of Nanoaerosol Surface Area Measurement Methods

Project 31: Workplace Monitoring of Carbon Nanofibers/Nanotubes

Project 32: Ultrafine Aerosols from Diesel-Powered Equipment

Project 33: Titanium Dioxide and Other Metal Oxides Exposure Assessment Study

C. Exposure Assessment

Project 1: Nanotechnology Research Center Coordination

Project 23: Dustiness of Nanomaterials

Project 24: Nanoaerosol Monitoring Methods

Project 25: Measurement of Nanoscale Carbonaceous Aerosols

Project 31: Workplace Monitoring of Carbon Nanofibers/Nanotubes

Project 33: Titanium Dioxide and Other Metal Oxides Exposure Assessment Study

Project 34: Field Research Team

Project 41: Nanoparticles in the Workplace

Project 43: Global Harmonization of Exposure Measurement and Exposure Mitigation Approaches for Nanomaterials

D. Epidemiology and Surveillance

Project 1: Nanotechnology Research Center Coordination

Project 35: Assessing the Feasibility of Industrywide Exposure and Epidemiology Studies of Workers Exposed to Engineered Nanomaterials

E. Risk Assessment

Project 1: Nanotechnology Research Center Coordination

Project 36: Nanoparticles—Dosimetry and Risk Assessment

Project 43: Global Harmonization of Exposure Measurement and Exposure Mitigation Approaches for Nanomaterials

F. Engineering Controls and Personal Protective Equipment

Project 1: Nanotechnology Research Center Coordination

Project 37: Penetration of Nanoparticles through Respirators

Project 38: Nanoparticle Penetration through Protective Clothing

Project 39: Development of Personal Protective Equipment Ensemble Test Methods

G. Fire and Explosion

Project 1: Nanotechnology Research Center Coordination

Project 23: Dustiness of Nanomaterials

H. Recommendations and Guidance

Project 1: Nanotechnology Research Center Coordination

Project 43: Global Harmonization of Exposure Measurement and Exposure Mitigation Approaches for Nanomaterials

I. Communication and Information

Project 1: Nanotechnology Research Center Coordination

Project 40: Web-based Nanoparticle Information Library Implementation

Project 41: Nanoparticles in the Workplace

Project 43: Global Harmonization of Exposure Measurement and Exposure Mitigation Approaches for Nanomaterials

J. Applications

Project 1: Nanotechnology Research Center Coordination

Project 42: New Sensor Technology Development for ESLI

Appendix B | NIOSH Extramural Nanotechnology Research Activities

Background

NIOSH sponsors research and training outside the Institute through the Office of Extramural Programs (OEP). The creativity and special resources available in the extramural community make these programs an important component in achieving a national goal to have safe jobs and healthy workers. The office also serves to help NIOSH address priorities from the National Occupational Research Agenda (NORA), the NIOSH Research to Practice (r2p) initiative, congressional mandates, and the NIOSH Program Portfolio (http://www.cdc.gov/niosh/programs).

A variety of occupational safety and health-related research grants and cooperative agreements, training grants, and conference grants outside the Institute are managed by OEP. The competitive process for soliciting applications, conducting peer reviews, and for making awards is managed by OEP.

The extramural office works closely with public and private academic institutions, State and Federal agencies, and with small private businesses. Extramural program scientists also consult with intramural scientists. Extramural applicants are encouraged to collaborate with NIOSH scientists when possible; however, extramural projects are managed separately from intramural programs to ensure fair competition, maintain research integrity, and to eliminate financial and intellectual conflicts of interest.

Purpose

Extramural funding of nanotechnology-related research has been undertaken to help increase the knowledge of nanotechnology and manufactured nanomaterials as they relate to occupational safety and health. Research areas supported by NIOSH/OEP include assessment methods for nanoparticles in the workplace, toxicology of manufactured nanomaterials, and the use of nanotechnology for improved workplace monitoring. Extramural nanotechnology research adds to the overall development of new information and complements efforts undertaken within the Institute.

Overall NIOSH Extramural Nanotechnology Research Program

From 2001–2008, NIOSH/OEP has committed $5.2 million (M) to extramural nanotechnology research. Ongoing projects currently funded through 2011 account for another $1.4M (Figure 1), which brings the total to about $6.6M. This has been accomplished by the use of non-earmarked research funds, NIOSH program announcements, joint requests for applications with other Federal agencies, and Small Business Innovation Research (SBIR) funds. The office has not received additional funds for nanotechnology research.

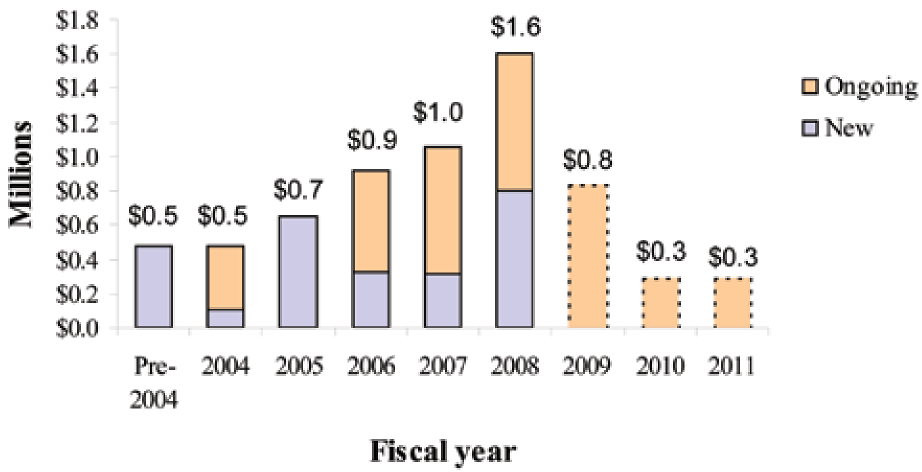

Figure 1. New and ongoing NIOSH/OEP funding in nanotechnology (Pre-2004–2008)

Funding Partnerships

OEP has partnered in two joint Requests for Applications (RFAs) for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. The U.S. Environmental Protection Agency's National Center for Environmental Research (NCER) and the National Science Foundation (NSF) participated in FY 2005. The National Institute of Environmental Health Sciences (NIEHS) joined in FY 2006. Funding was available to support Research (R01) grants for 3 years and Exploratory (R21) grants for 2 years.

Funding Mechanisms

Figure 2 summarizes the five types of funding mechanisms used by NIOSH for extramural nanotechnology research. SBIR (R43/44) and major research projects (R01) represent the major categories.

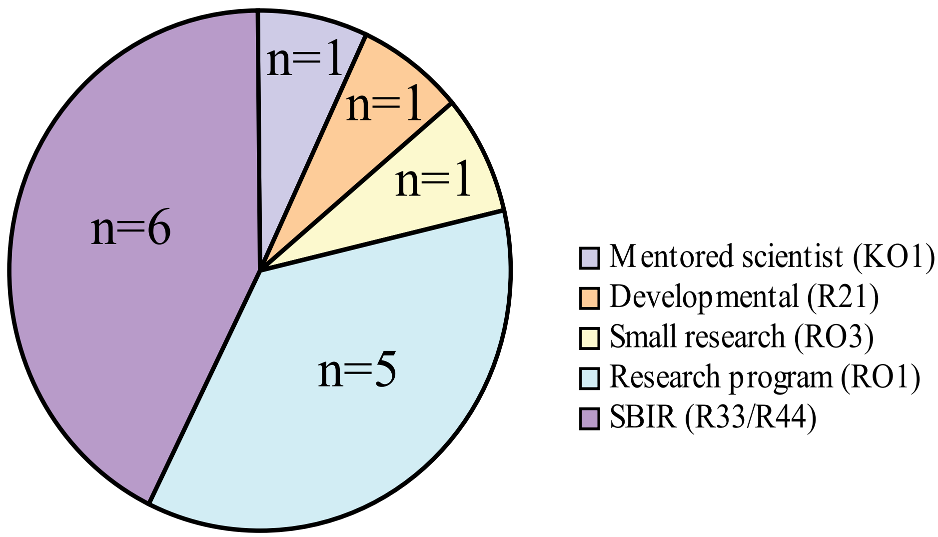

Figure 2. NIOSH/OEP funding (2001–2008) in nanotechnology by Grant Mechanism

Extramural Research Projects and NIOSH Nanotechnology Goals

The major NIOSH goals for nanotechnology research are as follows:

1. Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses.
2. Conduct research to prevent work-related injuries and illnesses by applying nanotechnology products.
3. Promote healthy workplaces through interventions, recommendations, and capacity building.
4. Enhance global workplace safety and health through national and international collaborations on nanotechnology research and guidance.

Extramural NIOSH funding for nanotechnology research has primarily been related to goals 1–3 (Figure 3). NIOSH/OEP continues to pursue partnerships in sponsoring funding opportunities that involve global collaborations between scientists in the United States and other countries.

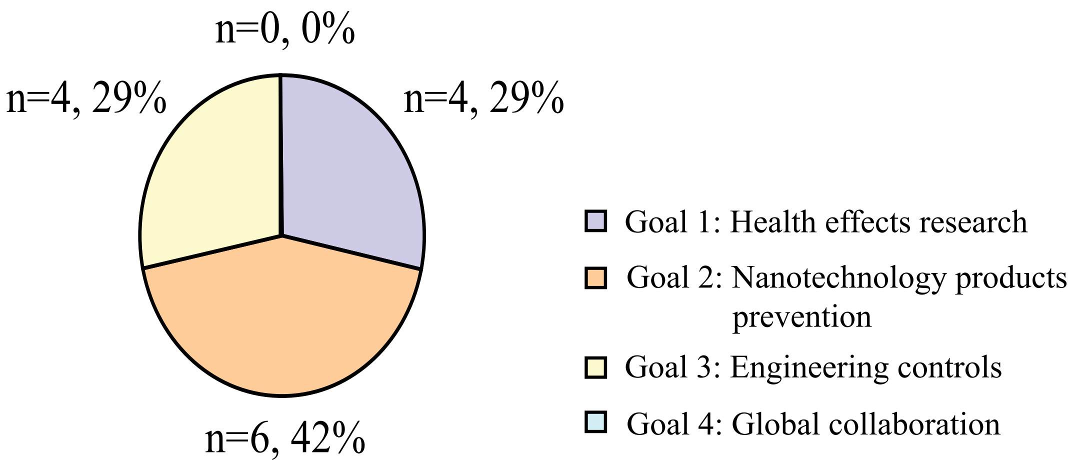

Figure 3. NIOSH/OEP nanotechnology funding by Strategic Goals

Additional Information about Extramural Portfolio

From FY 2001 to FY 2004, OEP funded three R43/44 projects for a total funding commitment of about $950K (Table 1).

In FY 2005, NIOSH funded two nanotechnology research grants through the R01 Program Announcement (Table 1). OEP also began participating in RFAs for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. For the first RFA, 83 applications were received and 19 were recommended for funding. Fourteen of these met NIOSH criteria for relevance to occupational safety and health. Five were in the competitive range for funding consideration and one was funded by NIOSH. EPA funded 14 projects and NSF funded two projects under this RFA.

In FY 2006, 81 applications were received in response to the joint RFA on environmental and human health issues. Six of these met NIOSH criteria for relevance and three were in the competitive range for funding consideration. NIOSH was able to fund one application (Table 1). EPA funded 21 projects, NSF funded four, and NIEHS funded three projects under this RFA. NIOSH also funded two SBIR grants on nanotechnology in FY 2006.

In FY 2007, NIOSH funded a 3-year career development (mentored scientist) grant involving research on personal exposure to nanoparticles at the University of Iowa. In addition, a 2-year exploratory/developmental research project was funded at Colorado State University. NIOSH also participated in RFA-ES-06-008 Manufactured Nanomaterials: Physico-chemical Principles of Biocompatibility and Toxicity, which was jointly sponsored by NIEHS, EPA, and NIOSH.

Table 1. Extramural nanotechnology research funded by NIOSH, 2001–2008

Grant Number	Investigator	Institution	Project title	Start	End	1st year funding	Total funding
Prior to FY-04 NIOSH SBIR							
1R43OH007471-01	Hooker	Nanomaterials Research LLC, Longmont, CO	Novel Hydrogen Sulfide Sensors for Portable Monitors	9/30/2001	3/31/2002	$100,000	$100,000
2R44OH007471-02	Hooker	Synkera Technologies Inc., Longmont, CO	Novel Hydrogen Sulfide Sensors for Portable Monitors	9/16/2003	9/15/2006	$373,400	$750,000
Pre-FY-04 Total						$473,400	$850,000
FY-04 NIOSH SBIR							
1R43OH007963-01A1	Rajagopalan	Nanoscale Materials, Inc., Manhattan, KS	From Nanoparticles to Novel Protective Garments	9/1/2004	5/15/2005	$100, 000	$100,000
FY-04 Total						$100,000	$100,000
FY-05 NIOSH R01 Program Announcement							
1R01OH008282-01A	Kagan	University of Pittsburgh	Lung Oxidative Stress/Inflamma-tion by Carbon Nanotubes	7/1/2005	6/30/2009	$364,000	$1,451,500
FY-05 Co-sponsored RFA (EPA STAR-2005-B1)							
1R01OH008806-01	O'Shaughnessy	University of Iowa	Assessment Methods for Nanoparticles in the Workplace	7/1/2005	6/30/2008	$133,000	$391,200
1R01OH008807-01	Xiong	New York University School of Medicine	Monitoring and Characterizing Airborne Carbon Nanotube Particles	8/1/2005	7/31/2008	$158,000	$395,200
FY-05 Total						$655,000	$2,237,900
FY-06 NIOSH SBIR							
1R43OH008739-01	Thompson	Eltron Research Boulder, CO	Antistatic Paint with Silent Dis-charge	8/30/2006	8/30/2007	$100,000	$100,000

(Continued)

Table 1. Extramural Nanotechnology research funded by NIOSH, 2001–2008

Grant Number	Investigator	Institution	Project title	Start	End	1st year funding	Total funding
1R43OH008939-01	Deininger	Synkera Technologies Inc., Longmont, CO	New Nanostructured Sensor Arrays for Hydride Detection	8/1/2006	2/28/2007	$100,000	$100,000
FY-06 Co-sponsored RFA (EPA G2006-STAR F1 to F7)							
1R01OH009141-01	Dutta	Ohio State University	Role of Surface Chemistry in the Toxicological Properties of Manufactured Nanoparticles	9/1/2006	8/31/2009	$120,000	$360,200
FY-06 Total						$320,000	$560,200
FY-07 NIOSH Exploratory/Developmental Research (R21) Program Announcement							
1R21OH009114-01	Volckens			8/1/2007	7/31/2009		
		Colorado State University	A High-Flow Personal Sampler for Inhalable Aerosol			$207,200	$421,000
FY-07 Career Development Grants (K01) Program Announcement							
1K01OH009255-01	Peters	University of Iowa	Personal Exposure to Engineered Nanoparticles	9/1/2007	8/31/2010	$106,900	$321,000
FY-07 Total						$314,100	$742,000
FY-08 Co-sponsored RFA (NIEHS RFA-ES-06-008)							
1R01OH009448-01	Grassian	University of Iowa	An Integrated Approach Toward Understanding the Toxicity of Inhaled Nanomaterials	4/1/2008	3/31/2012	$337,600	$1,222,600
FY-08 NIOSH Small Research Grant (PAR-06-551) Program Announcement							

Table 1. Extramural nanotechnology research funded by NIOSH, 2001–2008

Grant Number	Investigator	Institution	Project title	Start	End	1st year funding	Total funding
1R03OH009381	Volckens	Colorado State University	A Personal Sampler for Assessing Inhaled Nanoparticle Exposures	7/1/2008	6/30/2010	$71,500	$143,000
FY-08 NIOSH SBIR							
2R44OH007963-02	Rajagopalan	Nanoscale Materials, Inc., Manhattan, KS	From Nanoparticles to Novel Protective Garments	7/1/2008	6/30/2010	$387,700	$750,000
FY-08 Total						$796,800	$2,115,600
Grand Total							$6.6M

In FY 2008, NIOSH funded a major research grant (R01) from the joint RFA on Manufactured Nanomaterials (Physico-chemical Principles of Biocompatibility and Toxicity). This project is being conducted at the University of Iowa. NIOSH also funded a small research grant (R03) at Colorado State University and an SBIR grant at Nanoscale Materials, Inc. in Kansas.

In FY 2009, nanotechnology related research proposals submitted to standing program announcements will be considered for funding. NIOSH plans to continue collaborative efforts with EPA/NCER, NSF, NIH/NIEHS, and other international agencies to support nanotechnology research with occupational safety and health implications. OEP will continue to consult with the NIOSH Nanotechnology Research Center regarding needs and future directions for nanotechnology research.

Extramural Project Descriptions

Summaries of the extramural projects funded by NIOSH/OEP are included as part of this portfolio update. Contact information for the principal investigators of the projects is provided in Table 2 to encourage collaborative scientific efforts among researchers.

Current NIOSH Nanotechnology Related Information

Extramural investigators interested in pursuing nanotechnology studies related to occupational health and safety can learn more about the interests of NIOSH in this area by visiting the following Web pages:

http://www.cdc.gov/niosh/topics/nanotech/

http://www.cdc.gov/niosh/topics/nanotech/research.htm

NIOSH has identified 10 critical topic areas to guide in addressing knowledge gaps, developing strategies, and providing recommendations. The key role for NIOSH in conducting and partnering in research on occupational exposures to nanomaterials is noted in a new strategic plan under the National Nanotechnology Initiative.

Information about the NIOSH goal to transfer research findings, technologies, and information into prevention practices and products in the workplace is provided at the Web site http://www.cdc.gov/niosh/r2p/. This emphasis on Research to Practice (r2p) is intended to reduce occupationally-related illness and injury by increasing the use of findings from NIOSH-funded research in the workplace.

NIOSH conducts a wide range of efforts in the areas of research, guidance, information transfer, and public service. Additional information about the diverse activities of NIOSH can be found on the NIOSH home page (http://www.cdc.gov/niosh/homepage.html) and the program portfolio Web site (http://www.cdc.gov/niosh/programs/).

The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council's Committee on Technology, with support from the National Nanotechnology Coordination Office, has released a new NNI Strategic Plan as called for in the 21st Century Nanotechnology Research and Development Act (Public Law 108-153) of 2003. This plan updates and replaces the NNI Strategic Plan of December 2004 and is available at http://www.nano.gov/NNI_Strategic_Plan_2007.pdf . NIOSH participates as a member organization on this subcommittee.

Extramural Nanotechnology Research Project Summaries

The project summaries included here contain the publicly available information from the NIH CRISP database (http://crisp.cit.nih.gov/). For additional information, please contact the Office of Extramural Programs. Investigator contact information is provided in Table 2 to encourage collaborative scientific efforts between researchers. Contact information for Dr. Hooker was not available. Project summaries are listed in the order they appear in Table 1.

HOOKER 7471 (R43, R44)

Novel Hydrogen Sulfide Sensors for Portable Monitors

Background

The primary objective for this project is the design, development, and demonstration of better sensor technology for the detection of hydrogen sulfide. Hydrogen sulfide is a highly toxic, colorless, flammable gas that reacts with enzymes that inhibit cell respiration. At high concentrations, hydrogen sulfide can shut off the lungs, while lower concentrations can burn the respiratory tract and cause eye irritation.

This gas is encountered in a wide range of industries, and a number of standards have been established for occupational exposure. The OSHA permissible exposure limit (PEL) is 10 ppm, the short term exposure limit (STEL) is 15 ppm, and exposures of 300 ppm or greater are considered immediately dangerous to life and health (IDLH). Because of the potential for adverse health effects at low concentrations, the industrial hygiene community is continually seeking improved performance from hydrogen sulfide sensors. Specific requirements include reliable and accurate detection in real time, quantitative measurement capabilities, low purchase and life cycle costs, and low power consumption (for portability). Sensors meeting these requirements will find numerous applications within the health and safety field. In addition, several potential spin-off opportunities are available in leak detection, emission monitoring, and process control. We will use alternative ceramic oxide materials and a unique multi-layer fabrication process to accomplish the objectives of this project. The work plan includes optimization of the sensor materials, sensor element fabrication, sensor element packaging, in-house and external evaluation of the sensors, and establishing the foundation for new instrument development. The ultimate aim is a low-cost, low-power sensor that can be used in a new type of personal monitor. The envisioned monitor is a low profile, credit card sized "smart-card" that not only alerts the wearer when unsafe concentrations have been encountered but also tracks cumulative individual worker exposure to a particular toxic gas species.

Progress

The early portions of this project focused on developing nano-structured sensor materials and morphologies targeted toward chemiresistive-based sensors. This work resulted in a commercial sensor that is being incorporated into the fixed-system H2S detection products of multiple partnering instrument manufacturers. The middle portion of the project focused on developing solid-state electrochemical sensors using micro and nano-sized morphologies and structures. This has resulted in a working sensor currently being incorporated into an inexpensive, portable personal monitor as described above.

RAJAGOPALAN (7963-R43)

From Nanoparticles to Novel Protective Garments

Background

The overall objectives of this collaborative Phase I research between NanoScale and Gentex Corp. are to (1) investigate the use of highly adsorbent and reactive nanoparticles in protective garments and (2) create and test new materials for use in the production of protective clothing. During routine chemical use, it is not always apparent when exposure occurs. Many chemicals pose invisible hazards and offer no warnings. More importantly, terrorists and saboteurs use a variety of toxic industrial chemicals to create improvised explosives, chemical agents, and poisons. When hazardous materials are released, protective clothing is critical in guarding against the effects of toxic or corrosive products that could enter the body by inhalation or skin absorption and cause adverse effects.

This project seeks to (a) establish the feasibility of incorporating highly adsorbent and reactive nanoparticles into lightweight, permeable textiles and (b) evaluate the utility of the resultant fabric as protective clothing using standard industry testing procedures. These novel protective garments will be tailored toward personnel associated with Federal, State, or local emergency agencies as well as fire fighters and civilian first responders.

To achieve the overall objective, reactivity of selected nanoparticle formulations to various toxic industrial chemicals will be explored by use of a quartz spring balance to determine sorptive capacity. Based on the outcome of this research, a single reactive nanoparticle formulation will be chosen for use in fabrics. The selected nanoparticle formulation will then be incorporated into suitable fabrics using two established techniques. Next, fabric test swatches will be evaluated for a number of criteria using industry recognized ASTM test methods. Finally, the top four nanoparticle embedded fabrics will be tested for physical and chemical resistance against two representative toxic chemicals using a standard ASTM procedure.

KAGAN (8282)

Lung Oxidative Stress/Inflammation by Carbon Nanotubes

Background

Specific Aim 1 is to establish the extent to which SWCNT alone are pro-inflammatory to lung cells and tissue and characterize the role of iron in these effects using genetically manipulated cells and animals as well as antioxidant interventions.

Specific Aim 2 is to determine the potential for SWCNT and microbial stimuli to synergistically interact to promote macrophage activation, oxidative stress, and lung inflammation.

Specific Aim 3 is to reveal the extent to which SWCNT are effective in inducing apoptosis and whether apoptotic cells exert their macrophage-dependent anti-inflammatory potential during in vitro and in vivo SWCNT exposure. The project involves a team of interdisciplinary scientists with expertise in redox chemistry/biochemistry, cell and molecular biology of inflammation and its interactions with microbial agents, and pulmonary toxicology of nanoparticles.

Progress

Two types of single walled carbon nanotubes were used (iron-rich and iron-stripped) to study their interactions with RAW 264.7 macrophages. Following ultrasonication of the SWCNT to separate strands, neither types were able to generate intracellular production of superoxide radicals or nitric oxide macrophages observed by flow-cytometry and fluorescence microscopy. SWCNT with different iron content displayed different redox activity in a cell-free model system. In the presence of microbial (zymosan)-stimulated macrophages, non-purified, iron-rich SWCNT were more effective in generating hydroxyl radicals than purified SWCNT. The presence of iron in SWCNT may be important in determining redox-dependent responses of macrophages. Dose and time-dependence studies of inflammatory responses in mice using pharyngeal aspiration of SWCNT demonstrated that SWCNT elicited unusual pulmonary effects in C57BL/6 mice that combined a robust but acute inflammation with early onset yet progressive fibrosis and granulomas. It was demonstrated that occupationally relevant dose-dependent affects of SWCNT may exert toxic effects in the lung of exposed animals in vivo. SWCNT induced inflammation, and exposure caused altered pulmonary function and microbial stimulation. Clearance from the lungs of SWCNT exposed mice was compromised. An unusual and robust inflammatory and fibrogenic response was correlated with the progression of oxidative stress and apoptotic signaling. Not only are toxic effects of SWCNT important to consider but also the role of transitional metals, particularly iron should be investigated.

Recent Publications

Shvedova AA, Fabisiak JP, Kisin ER, Murray AR, Roberts JR, Tyurina YY, Antonini JM, Feng WH, Kommineni C, Reynolds J, Barchowsky A, Castranova V, Kagan VE [2007].Sequential Exposure to carbon nanotubes and bacteria enhances pulmonary inflammation and infectivity. Am J Respir Cell Mol Biol.

Abstract

Realistic exposures to carbon nanotubes (CNT) may occur in conjunction with other pathogenic impacts (microbial infections) and trigger enhanced responses. We evaluated interactions between pharyngeal aspiration of SWCNT and bacterial pulmonary infection of C57BL/6 mice with Listeria monocytogenes (LM). Mice were given SWCNT (0, 10, and 40 microg/mouse) and exposed to LM (10(3) bacteria/mouse) 3 days later. Sequential exposure to SWCNT/LM amplified lung inflammation and collagen formation. Despite this robust inflammatory response, SWCNT pre-exposure significantly decreased the pulmonary clearance of LM measured 3–7 days after microbial infection vs PBS/LM treated mice. Decreased bacterial clearance in SWCNT pre-exposed mice was associated with decreased phagocytosis of bacteria by macrophages and a decrease in nitric oxide production by these phagocytes. Pre-incubation of naive alveolar macrophages with SWCNT in vitro also resulted in decreased nitric oxide generation and suppressed phagocytizing activity towards LM. Failure of SWCNT-exposed mice to clear LM led to a continued elevation in nearly all major chemokines and acute phase cytokines into the later course of infection. In SWCNT/LM exposed mice, BAL PMNs, AMs, and lymphocytes as well as LDH level were increased compared to mice exposed to SWCNT or LM alone. In conclusion, enhanced acute inflammation and pulmonary injury with delayed bacterial clearance after SWCNT exposure may lead to increased susceptibility to lung infection in exposed populations.

Shvedova AA, Kisin ER, Murray AR, Gorelik O, Arepalli S, Castranova V, Young SH, Gao F, Tyurina YY, Oury TD, Kagan VE [2007].Vitamin E deficiency enhances pulmonary inflammatory response and oxidative stress induced by single-walled carbon nanotubes in C57BL/6 mice. Toxicol Appl Pharmacol *221*(3):339–348

Abstract

Exposure of mice to single-walled carbon nanotubes (SWCNTs) induces an unusually robust pulmonary inflammatory response with an early onset of fibrosis, which is

accompanied by oxidative stress and antioxidant depletion. The role of specific components of the antioxidant protective system (specifically vitamin E, the major lipid-soluble antioxidant) in the SWCNT-induced reactions has not been characterized. We used C57BL/6 mice, maintained on vitamin E-sufficient or vitamin E-deficient diets, to explore and compare the pulmonary inflammatory reactions with aspired SWCNTs. The vitamin E-deficient diet caused a 90-fold depletion of alpha-tocopherol in the lung tissue and resulted in a significant decline of other antioxidants (GSH, ascorbate) as well as accumulation of lipid peroxidation products. A greater decrease of pulmonary antioxidants was detected in SWCNT-treated vitamin E-deficient mice compared with controls. Lowered levels of antioxidants in vitamin E-deficient mice were associated with a higher sensitivity to SWCNT-induced acute inflammation (total number of inflammatory cells, number of polymorphonuclear leukocytes, released LDH, total protein content and levels of pro-inflammatory cytokines, TNF-alpha and IL-6) and enhanced profibrotic responses (elevation of TGF-beta and collagen deposition). Exposure to SWCNTs markedly shifted the ratio of cleaved to full-length extracellular superoxide dismutase (EC-SOD). Given that pulmonary levels of vitamin E can be manipulated through diet, its effects on SWCNT-induced inflammation may be of practical importance in optimizing protective strategies.

O'SHAUGHNESSY (8806)

Assessment Methods for Nanoparticles in the Workplace

Background

The primary objectives are to provide the scientific community and practicing industrial hygienists with verified instruments and methods for accurately accessing airborne concentrations of nanoparticles, and to assess the efficacy of respirator use for controlling nanoparticle exposures.

We will satisfy these objectives through a combination of laboratory and field-based studies centered on the following specific aims: (1) identify and evaluate methods to measure airborne nanoparticle concentrations, (2) characterize nanoparticles using a complementary suite of techniques to assess their surface and bulk physical and chemical properties, and (3) determine the collection efficiency of commonly-used respirator filters when challenged with nanoparticles.

Progress

Several methods were used to aerosolize nanoparticles from bulk powders in the laboratory. An apparatus was developed to inject the aerosol into a mainflow of dry, filtered air through a charged neutralizing device. The amount and size distribution of the aerosol in the chamber is sampled with a scanning mobility particle sizer; samples from the chamber are also being analyzed by TEM. Although the primary particle size of these powders average

20nm, an aerosol with a median size of 120 is generated. These findings have significance in occupational settings since agglomeration of the particles in this size range will have consequences in pulmonary deposition and respirator filtration. Nanosized particles were also found as contaminants in the water used. A variety of instruments are being compared for use in the field studies of nanoparticle exposure levels in two facilities, one in MN and one in TX.

Recent Publication

Peters TM, Elzey S, Johnson R, Park H, Grassian VH, Maher T, O'Shaughnessy P [2009]. Airborne monitoring to distinguish engineered nanomaterials from incidental particles for environmental health and safety. J Occup Environ Hyg 6:2,73–81.

Abstract

Two methods were used to distinguish airborne engineered nanomaterials from other airborne particles in a facility that produces nano-structured lithium titanate metal oxide powder. The first method involved off-line analysis of filter samples collected with conventional respirable samplers at each of seven locations (six near production processes and one outdoors). Throughout most of the facility and outdoors, respirable mass concentrations were low (<0.050 mg/m^3) and were attributed to particles other than the nanomaterial (<10% by mass titanium determined with inductively coupled plasma atomic emission spectrometry). In contrast, in a single area with extensive material handling, mass concentrations were greatest (0.118 mg/m^3) and contained up to 39% ± 11% lithium titanium, indicating the presence of airborne nanomaterial. Analysis of the filter samples collected in this area by transmission electron microscope and scanning electron microscope revealed that the airborne nanomaterial was associated only with spherical aggregates (clusters of fused 10–80 nm nanoparticles) that were larger than 200 nm. This analysis also showed that nanoparticles in this area were the smallest particles of a larger distribution of submicrometer chain agglomerates likely from welding in an adjacent area of the facility. The second method used two hand-held, direct-reading, battery-operated instruments to obtain a time series of very fine particle number (<300 nm), respirable mass, and total mass concentration, which were then related to activities within the area of extensive material handling. This activity-based monitoring showed that very fine particle number concentrations (<300 nm) had no apparent correlation to worker activities, but that sharp peaks in the respirable and total mass concentration coincided with loading a hopper and replacing nanomaterial collection bags. These findings were consistent with those from the filter-based method in that they demonstrate that (1) airborne nanoparticles in this facility are dominated by "incidental" sources (e.g., welding or grinding), and (2) the airborne "engineered" product is predominately composed of particles larger than several hundred nanometers. The methods presented here are applicable to any occupational or environmental setting in which one needs to distinguish incidental sources from engineered product.

XIONG (8807)

Monitoring and Characterizing Airborne Carbon Nanotube Particles

Background

The proposed research will develop a comprehensive yet practical method for sampling, quantification, and characterization of carbon nanotube (CNT) particles in air. This method will be capable of (1) classifying sampled particles into three categories: tubes, ropes (bundles of single-walled CNTs bounded by Van der Waals attraction force), and non-tubular particles (soot, metal catalysts, and dust, etc.) and (2) measuring the number concentrations and size distributions for each type, and the shape characters (diameter, length, aspect ratio and curvature) of CNTs.

The method will use available instrumentation to build an air monitoring system that is capable of sampling and sizing airborne CNT particles in a wide size range by using a 10-stage, micro-orifice uniform deposit impactor (MOUDI) and an integrated diffusion battery previously developed in this laboratory. Successful completion of this project will produce a validated method for sampling airborne.

CNTs in workplaces; and a practical method using atomic force microscopy image analysis technology to classify sampled CNT particles by type, and quantifying and characterizing each type separately. These methods are needed to determine health risks that may result from worker exposure to the various types: CNTs, nanoropes, and non-tubular nanoparticles. The results will also provide a foundation for field and personal sampling devices for CNTs.

Progress

Instrumentation and materials are essentially ready. Years 2 and 3 will focus on method development for sampling, quantifying, and characterizing airborne CNT aerosol particles.

THOMPSON (8739)

Antistatic Paint with Silent Discharge

Background

Proposed is an anti-static paint that can be used to alleviate danger from fires and explosions initiated by static discharge. The innovation for the proposed paint lies in its discharge mechanism, which doesn't require grounding or hydration like other products that are currently on the market. Paint can be sprayed onto surfaces of clothing or equipment, resulting in a lower capacitance or ability to build up charge on the material.

Research Design

A series of formulations will be synthesized and tested on both metallic and plastic substrates.

Relevance to Public Health

Development of the antistatic paint will lead to immediate safety improvements for persons that work with volatile solvents in the fuel, coatings, and plastic industries as well as emergency responders in haz-mat situations. The paint could be useful for protecting the general public from electrostatic initiated explosions at the gas-pump or from uncomfortable static shock. In addition, this paint could lead to substantial savings in the electronics industry, where electrostatic discharge (ESD) events cost millions of dollars each year because of lost products.

DEININGER (8939)

New Nanostructured Sensor Arrays for Hydride Detection

Background

The goal of the proposed project is to develop improved sensors for the detection of hydrides (including arsine, phosphine and diborane) for protecting worker safety and health. Current sensors suffer from severe limitations including lack of selectivity, and limited accuracy and lifetime. An electronic sensor system, capable of automatically warning workers of the presence of one of these toxic gases, would provide a substantial benefit for worker safety and health.

This project will take advantage of advances in nanotechnology, ceramic micromachining, and materials chemistry to create better sensors. These improved sensors will be the basis for improved personal and permanent monitors for increased protection of workers in the semiconductor industry.

Progress

Phase I feasibility studies have shown a significant enhancement in the sensitivity of hydride sensors fabricated from tailored nanostructured materials grown via a templated deposition process inside the pores of anodic alumina. Detection limits of less than 10 ppb were achieved, allowing application of this rugged, low-cost sensor technology to the detection of highly toxic gases (e.g. hydrides) that heretofore were not amenable to reliable detection via this sensor technology.

DUTTA (9141)

Role of Surface Chemistry in the Toxicological Properties of Manufactured Nanoparticles

Background

The objectives of this program are to verify two hypotheses. First, the quantifiable differences in surface reactivity of nanoparticles (as measured by acidity, redox chemistry, metal ion binding and Fenton chemistry) compared with micron-sized particles of similar composition cannot be explained by the increase in surface area alone. Second, the oxidative stress and inflammatory response induced by nanoparticles upon interaction with macrophages and epithelial cells depend on their surface reactivity. The basis of these hypotheses is that nanoparticles contain significantly higher numbers of "broken" bonds on the surface that provide different reactivity as compared to larger particles.

The experimental approach focuses on three classes of manufactured nanoparticles, catalysts (aluminosilicates), titania, and carbon. For the catalysts and titania samples, nanoparticles (< 100 nm) and micron-sized particles of similar bulk composition will be studied. For carbon, carbon black and single walled carbon nanotubes are chosen. Nanoparticles of aluminosilicates and titania will be synthesized, whereas the other particles will be obtained from commercial sources. Characterization will involve electron microscopy, surface area, and surface and bulk composition.

Reactivity of well-characterized particles in regards to their acidity, reaction with antioxidants simulating the lung lining fluid, coordination of iron, and Fenton chemistry will be carried out using spectroscopic methods. Particular attention will be paid to surface activation as may exist during manufacturing and processing. In vitro oxidative stress and inflammatory responses upon phagocytosis of the particles by macrophages and pulmonary epithelial cells will form the toxicological/biological end points of the study. Methods include gene array techniques, assays for reactive oxygen species and adhesion molecules on endothelial cells.

VOLCKENS (9114)

A High-Flow Personal Sampler for Inhalable Aerosol

Background

While occupational respiratory diseases inflict a severe toll on our national workforce, existing exposure assessment methods for many respiratory hazards lack sufficient detection sensitivity, preventing the practicing industrial hygienist from determining whether a hazard even exists. The goal of this research is to design a high-flow sampling device engineered to assess inhalable aerosol hazards in the workplace in a physiologically relevant fashion. This device will extend overall method detection limits by considerably increasing sampler flow rate. The design will be inexpensive and readily integrated into the commonly used 37-mm filter cassette. Because of its low cost, accuracy, ease-of-use, and adaptability, this device will have widespread application, especially in developing countries where exposure assessment resources and budgets are limited. Such widespread use was a major design goal for this technology, as increased use of an accurate exposure assessment technology will ultimately result in increased protection of worker health on a national and global scale. This project has three specific aims: (1) To design an inexpensive, modular sampling head that (a) interfaces with a standard 37-mm cassette, (b) operates at a high rate of airflow, 10 Lpm, and (c) meets the criteria for inhalable sampling set by the American Conference of Governmental Industrial Hygienists/International Standards Organization. This high-flow design will proceed from a wide body of research on existing low-flow inhalable devices. (2) Evaluate sampler performance using computational fluid dynamic modeling and to refine the prototype design based on results from these tests. (3) To validate the refined design through laboratory tests in a wind tunnel and field tests in actual occupational environments.

PETERS (9255)

Personal Exposure Monitoring to Engineered Nanoparticles

Background

Worldwide production of engineered nanoparticles is expected to grow from 2,000 metric tons to 50,000 metric tons over the next decade. New industrial processes must be introduced into the workplace to accommodate this growth. Although studies have shown some nanoparticles to be toxic, methods to assess personal exposure do not exist. Knowledge of personal exposure may be particularly important for such small particles because their concentration tends to decay rapidly with distance from a source.

Dr. Peters will conduct laboratory studies to evaluate the precision and accuracy of methods developed by his research group to assess personal exposure to nanoparticles. These methods will then be used to investigate the extent to which workers are exposed to engineered nanoparticles in a facility that produces and handles them. Mixed models will be used to identify the determinants of exposure while controlling for the between-worker (spatial) and within-worker (temporal) variability. Computer-controlled electron microscopy with energy dispersive X-ray detection will be used to further characterize the samples collected in the field study by size, composition, and morphology. These data will be used to apportion exposures to sources. The research proposed in this application is significant, because it will enable direct assessment of personal exposure to nanoparticles on time scales relevant to potential acute and chronic adverse health outcomes. As an outcome of these studies, an understanding of exposures will help to prioritize studies in toxicology, epidemiology, and engineering controls to better protect workers.

The research component will be complemented by a vigorous career development plan that will include the following: (1) formal training in responsible conduct of research, epidemiology, and electron microscopy; (2) regular meetings with the sponsors of this award; (3) participating in group meetings and departmental seminars; (4) presenting results at scientific meetings; and (5) publishing results in peer-reviewed journals. The multidisciplinary team of sponsors will play an active roll in both the research and career development component of this award.

GRASSIAN (9448)

An Integrated Approach Toward Understanding the Toxicity of Inhaled Nanomaterials

Background

Manufactured nanomaterials are found in cosmetics, lotions, and coatings, and are used in environmental remediation applications. An opportunity exists for exposure through many different routes, making it necessary to study the health implications of these materials. The primary objective of this research is to fully integrate studies of the physical and chemical properties of commercially manufactured nanoparticles with inhalation toxicological studies of these same nanoparticles to determine properties that most significantly affect nanoparticle toxicity. Our central hypothesis is that nanoparticle physico-chemical properties differ widely among particle types, and certain properties induce adverse health outcomes. Furthermore, we hypothesize that nanoparticle toxicity is influenced by the susceptibility of the individual as well as the presence of other inflammatory substances. We will address these hypotheses through a series of specific study aims designed to establish a relationship between nanoparticle physicochemical properties and health outcomes.

Specific Aim 1: Evaluate nanoparticle chemical composition (bulk and surface) on nanoparticle toxicity in acute and sub-acute exposure studies. Experiments will be designed to investigate nanoparticle composition (bulk and surface) before, during, and after inhalation exposure studies.

Specific Aim 2: Determine the impact of nanoparticle physical morphology (agglomeration size, agglomeration state, and nanoparticle shape) on nanoparticle toxicity. This study will incorporate animal inhalation studies to determine the relationship between nanoparticle agglomerate size and nanoparticle shape on toxicity.

Specific Aim 3: Determine whether (1) pulmonary clearance is impaired by inhaled nanoparticles and (2) impaired clearance increases the risk of pulmonary infection. The pulmonary clearance mechanism, especially the ability of alveolar macrophages to clear microbes or foreign particles, can be impaired by inhaled particulates. We will compare lung clearance rates after inhalation of nanoparticles of different composition.

Specific Aim 4: Compare lung inflammation produced by co-exposure of nanoparticles with other inflammatory substances and relative to the nanoparticles alone. We plan to evaluate synergistic effects with other common aerosols present in the indoor and outdoor environments including endotoxins and sulfate aerosols (e.g. ammonium sulfate).

VOLCKENS (9381)

A Personal Sampler for Assessing Inhaled Nanoparticle Exposures

Background

Elucidation of potential nanoparticle exposure-disease relationships requires the development of an adequate exposure assessment method, as exposure assessment provides key input into subsequent epidemiologic and toxicological investigation. The absence of a personal exposure assessment method for nanoparticle aerosols prevents progress towards understanding potential nanoparticle exposure-disease relationships. The goal of this work is to develop an accurate, sensitive, and specific method to assess personal exposures to engineered nanoparticles. The method will assess the inhalation route of exposure, and hence, the measurement of nanoparticle concentrations in air.

To quantify concentrations of airborne nanoparticles, a measurement must be able to segregate the aerosol by size (to capture only particles smaller than 100 nm) and count these particles following size segregation. Also, because inhaled nanoparticles enter strictly through the oral/nasal route, the method should be oriented to measure breathing zone concentrations within the vicinity of the upper torso. Finally, and perhaps most importantly, the method must be able to distinguish engineered nanoparticles from other incidental nanoparticles (i.e., ultrafine particles) that are ubiquitous in workplace and ambient air.

Successful completion of this research will establish a method to estimate human exposures to engineered nanoparticles in workplace environments. Such a method is critical to the establishment of nanoparticle dose-response relationships, as current methods lack both specificity and sensitivity. Results from this research can also be translated to the larger realm of health-related air pollution outside of the workplace (e.g., indoor air, ambient air pollution), both nationally and internationally.

RAJAGOPALAN (7963-R44)

From Nanoparticles to Novel Protective Garments

Background

The goal of this project is to develop breathable, lightweight, and disposable chemical protective clothing for use by personnel associated with law enforcement agencies, emergency medical services, medical/triage facilities, and other Federal, State, or local emergency agencies as well as by fire fighters and civilian first responders. This goal will be accomplished by producing a lightweight, chemical protective garment material. The material will have a limited number of distinct layers, that can be assembled into a breathable, protective garment. The layers impart at least one key property to the composite material. Non-breathable materials retard the human body's process of heat dissipation normally achieved through the evaporation of perspiration. Without significant transmission of water vapor or breathability, prolonged use of non-breathable materials can result in intolerable discomfort and even death to a person wearing garments made from these materials. The novelty of the proposed approach is the development of granulated reactive NanoActive(r) sorbents containing composite layered textile material. The material protects the sorbent from contact with and contamination by liquids and has good vapor permeability, thus providing for passage of air and water vapor as well as sorption of harmful and noxious vapors and gases. Based on the outcome of Phase I research, it is clear that granulated mixed metal oxide nano-formulations are required for a broad-spectrum reactivity. As a result, this Phase II project will begin by developing methodologies for granulation of mixed metal oxides based on NanoActive materials. This will be followed by performance screening of formulations against toxic industrial chemicals and chemical warfare agent simulants by a breakthrough testing procedure. The down selected formulations will then be incorporated into down selected textile materials with optimum air and water vapor permeable properties. Next, these composite fabric test swatches will be evaluated for a number of criteria using industry-recognized ASTM test methods. The top four granulated nanoparticles embedded fabrics will be tested for chemical resistance against four toxic chemicals using a standard ASTM procedure. The project will conclude by pilot studies involving scale-up of granulated nanoparticles and composite textile preparation followed by production of prototype chemical protective clothing. Relevance major deficiency of the available chemical protective garments is the failure to provide desired levels of toxic vapor sorption and still maintain sufficient transfer of heat and moisture to keep a wearer cool and comfortable. Permeable textiles containing highly reactive NanoActive(r) materials offer promise of protection and comfort. Public health relevance: major deficiency of the available chemical protective garments is the failure to provide desired levels of toxic vapor sorption and still maintain sufficient transfer of heat and moisture to keep a wearer cool and comfortable. Permeable textiles containing highly reactive NanoActive(r) materials offer promise of protection and comfort.

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DHHS (NIOSH) Publication No. 2010–104

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