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Progress Toward Safe Nanotechnology in the Workplace

A Report from the NIOSH Nanotechnology Research Center

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

NIOSH

On the cover: Transmission electron photomicrographic image of a dispersed suspension of single-walled carbon nanotubes labeled with 10-nm colloidal gold. This labeling technique allows these nanoparticles to be more easily tracked and visualized in various tissues and organs following exposure. *Image courtesy of Robert Mercer, NIOSH.*

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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. Workers are currently producing and using nanoparticles. Society requires assessment of whether these exposures present any threat to workers. 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, in collaboration with partners in other government agencies, countries, academia, industry, labor, and nongovernmental organizations, has been conducting research and developing guidance to address the occupational safety and health of workers exposed to nanomaterials. This document is a report of the progress of the NIOSH Nanotechnology Research Center (NTRC) since its inception in 2004 through 2006. Using only internally redirected resources, the NTRC has begun to make contributions to all the steps in the continuum from hazard identification to risk management.

Understanding the occupational safety and health issues of nanotechnology is a complex endeavor. The types of nanomaterials and the opportunities for workplace exposure are growing 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

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. As such, NIOSH is active in (1) identifying critical issues related to possible health hazards of nanomaterials, (2) protecting the safety and health of workers involved in this emerging technology, and (3) implementing a strategic plan to develop and disseminate methods for safely advancing the technology through workplace controls and safe handling procedures, and (4) investigating the possible applications of nanotechnology to solve workplace safety and health issues. Because of their small size and large surface area, engineered nanoparticles may have chemical, physical, and biological properties distinctly different from larger particles of similar chemical composition. Those properties may include the ability 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. NIOSH is investigating all of these properties, as it would with any new technology or material in the workplace, to provide the necessary guidance to ensure a safe and healthy workplace.

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 is taking the first steps in assessing hazards posed by various types of nanoparticles by attempting to understand the mechanisms of action of nanoparticles in living systems and assessing risks to workers. The research being conducted by the NIOSH Nanotechnology Research Center (NTRC) was funded by redirecting existing NIOSH programmatic funds: $3.0 million in FY 2005, $3.7 million in FY 2006, and $4.6 million in FY 2007. This budgetary constraint has made a more comprehensive research program specific to nanomaterials difficult to implement. Even with the budgetary constraints, NIOSH investigators have laid the foundation for an evidence-based strategy for providing safe nanotechnology in the workplace. This effort is consistent with the following guidance from the U.S. Office of Science and Technology Policy (OSTP) and the Office of Management and Budget (OMB): *to ensure that nanotechnology research leads to the responsible development of beneficial applications, high priority should be given to research on societal implications, human health, and environmental issues related to nanotechnology and to develop, where applicable, cross-agency approaches to the funding and execution of this research* [July 8, 2005 memorandum for the Heads of Executive Departments and Agencies]. Because of

its mission and the active program of research it has started, NIOSH has been identified as a lead agency in several high priority areas by the Nanotechnology Environmental and Health Implications (NEHI) Working Group within the National Nanotechnology Initiative (NNI).

Nanotechnology Research Center

NTRC was established in 2004 to coordinate and facilitate research in nanotechnology and develop guidance on the safe handling of nanomaterials in the workplace. It 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 locations. This approach has also allowed NIOSH to jump-start research and facilitate ongoing studies. The goals for NTRC are as follows:

1. Determine whether nanoparticles and nanomaterials pose risks of injuries and illnesses for workers.
2. Conduct research on applying nanotechnology to the prevention of work-related injuries and illnesses.
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 has been made toward each of these goals. The following paragraphs present highlights of each goal.

1. Determine whether nanoparticles and nanomaterials pose risks of injuries and illnesses for workers.

Since 2004, the NTRC has conducted toxicology research on the properties and characteristics of nanoparticles that are relevant for predicting whether these particles pose a risk of adverse health effects in workers (see Appendix A for the status of ongoing research and published results). These research projects have involved characterizing occupationally relevant nanoparticles—particularly the toxicity of carbon nanoparticles. Preliminary work by NTRC investigators demonstrated that exposures to specific nanotubes had harmful pulmonary effects (such as a fibrotic response) in mice soon after exposure to relatively low doses. NTRC investigators have evaluated the potential for

nanoparticles to enter the bloodstream and move to systemic tissues after being deposited in the lungs. NTRC is also assessing the impact of dermal exposure to nanoparticles. In addition, NTRC established a nanoparticle aerosol generation system and began conducting animal inhalation studies during the summer of 2006. 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 they operate. Although the results of these studies are preliminary and limited, more research is needed to predict whether they signal a health risk to humans. The data support the need to address that question and provide promising leads for strategic, ongoing studies.

NTRC investigators have evaluated exposure-response information and developed quantitative risk assessment methods for nanoscale titanium dioxide; these efforts may serve as a model for assessing the risk of other nanoparticles. To gain further knowledge about exposure and control practices, the NTRC has established a field team (see Appendix B) to conduct assessments of workplaces where exposure to engineered nanoparticles may occur. To date, this team has partnered with various companies that produce or use engineered nanoparticles to obtain useful information about potential worker exposures, control technologies, and risk management practices.

2. Conduct research on applying nanotechnology to the prevention of work-related injuries and illnesses.

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. NTRC has also conducted numerous discussions with academia and the private sector on other potential projects. Efforts are underway between NTRC, other CDC personnel, and the Georgia Institute of Technology to identify collaborative projects involving nanotechnology applications to occupational and public health problems.

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

NTRC has provided seminal guidance for workers and employers in nanotechnology through the document entitled *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. This document was posted on the NIOSH Web site in 2005 and updated in August 2006 (see Appendix H for a summary). The document concludes the following:

- Given the limited amount of information for determining with confidence whether adverse human health effects may be associated with production and use of engineered nanoparticles, interim precautionary measures should be taken to minimize worker exposures.
- For most processes and job tasks, the control of airborne exposure to nanoaerosols can be accomplished using a wide variety of engineering control techniques (e.g., exhaust ventilation, process enclosure) similar to those used in reducing exposure to other types of aerosolized particulates.
- Implementing a risk management program in workplaces where workers are exposed to nanomaterials can help to minimize the potential for exposure to nanoaerosols. Elements of such a program should include engineering control techniques and good work practices. Engineering controls such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems should be effective for capturing airborne nanoparticles. Current knowledge indicates that a well-designed exhaust ventilation system with a high-efficiency particulate air (HEPA) filter should effectively remove nanoparticles. The use of good work practices (e.g., handling and transfer practices, using wet methods, cleaning of contaminated surfaces), the education and training of workers, and the use of personal protective equipment (PPE) when needed should help reduce the potential for exposure.
- Respirators may be necessary when engineering and administrative controls do not adequately prevent exposures. Currently, there are no specific exposure limits for airborne exposures to engineered nanoparticles, although occupational exposure limits exist for larger particles of similar chemical composition. Preliminary evidence shows that for respirator filtration media, particulates as small as 2.5 nm in diameter are efficiently captured, in keeping with single fiber filtration theory. Although this evidence needs confirmation, it suggests that it is likely that NIOSH-certified respirators will be useful for protecting workers from nanoparticle inhalation when properly selected and fit tested as part of a complete respiratory protection program.

Other information products on the NIOSH Web site include the Nanotechnology topic page (with an extensive section on Frequently Asked Questions) and the Nanoparticle Information Library (NIL), which is a resource on particle information, including physical and chemical characteristics. In addition, NTRC

has convened a cross-Federal group to develop a framework document for health surveillance of workers exposed to nanomaterials. This document will also involve the business community to identify the range of issues involved in occupational health surveillance.

Nationally and internationally, NTRC has delivered a wide range of presentations on occupational safety and health issues associated with nanotechnology. These have included presentations at 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 (see Appendix A for a listing of NTRC presentations and other activities). NIOSH has cosponsored the three major international meetings on occupational safety and health involving nanomaterials. These research summits furthered the exchange of the latest information among leading scientists and promoted the application of research findings to actual workplace practice for minimizing occupational exposures. The third meeting will be held in Taiwan in 2007, and two NTRC scientists serve on the planning committee. NIOSH also cosponsored a major occupational safety and health research-to-practice (r2p) conference in Cincinnati, Ohio during December 2006, which drew more than 450 participants from 11 countries. In addition, NTRC is collaborating with the U.S. Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and other government agencies to obtain and evaluate exposure and good work practice information.

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

NTRC has established several national and international collaborations to advance understanding of occupational safety and health for nanotechnology workers. NTRC participates in the NNI and has contributed to the nanotechnology strategic plan for the Nation through the working group of NEHI. Occupational Safety and Health has been a major 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 has collaborated with the Organization for Economic Cooperation and Development (OECD) to build cooperation, coordination, and communication between the United States and 30 OECD member countries (including the European Union), and with more than 180 nonmember economies as well.

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. NTRC also works with the World Health Organization (WHO) Collaborating Centers on global projects of information dissemination and communication.

Together, the research and guidance efforts of the NTRC are expected to enhance the safe use of nanotechnology in the workplace and safe work-related handling of nanomaterials. However, until more information becomes available, it is appropriate to take precautions and apply recognized occupational exposure control measures where nanoparticle exposure may occur.

Steps to Addressing Occupational Safety and Health Implications

The NTRC research and guidance effort has been initiated to fill the knowledge gaps in prevention and control of workplace exposures to engineered nanoparticles. To accomplish this, the NTRC has focused its research program on hazard identification and characterization, exposure assessment, risk assessment, and risk management. While research continues, NIOSH partners and stakeholders have urged NIOSH to provide interim guidance for risk management until scientists understand those properties, characteristics, and behaviors of nanomaterials that may pose occupational safety and health risks. NTRC has provided such interim guidance and will continue to do so as research is being conducted.

The NTRC research program has identified 10 critical topic areas important for understanding the potential health risks and developing and disseminating recommendations. The report describes each of these critical topic areas and the research being conducted. These 10 topic areas are the core of the NTRC research program and represent the areas that are most critical to addressing occupational safety and health issues. They include toxcity and internal dose, risk assessment, epidemiology and surveillance, engineering controls and PPE, measurement methods, exposure assessment, fire and explosion safety, recommendation and guidance, communication and education, and applications. By working in these 10 critical areas, NIOSH has comprehensively begun to address the information and knowledge gaps necessary to protect workers and responsibly move nanotechnology forward so that its far-reaching benefits may be realized.

NIOSH Resource Limitations

Since its inception in 2004, the NTRC has published more than 70 papers in the peer-reviewed scientific literature (see specific research projects in the appendices) and provided a broad range of information and guidance. Publications in the area of hazard identification and characterization, exposure assessment, risk assessment, and risk management have provided a framework for beginning to address the potential hazards and risks from engineered nanoparticles. While these accomplishments have contributed significantly to our understanding of the potential health risks to nanoparticles, NIOSH research and subsequent development and dissemination of interim guidance efforts are limited by the amount of funding available. To the best of its ability in allocating limited resources to competing priorities, NIOSH has redirected funds internally over the past 3 years to build modest increases in nanotechnology research program support. 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:

1. 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 risk.

2 NIOSH field investigators have assessed exposure to engineered nanoparticles in some workplaces, but few data exist on the extent and magnitude of exposure to other types of nanoparticles in workplaces that manufacture or use nanomaterials, nanostructures, and nanodevices.

3. 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.

4. An increasing number of workers are involved with the research, development, production, and use of nanomaterials, but there is a lack of specific guidance for occupational health surveillance. NIOSH needs support to conduct research on the short- and long-term potential health risks in nanotechnology workers. This may involve the conduct of large-scale prospective epidemiologic studies and the establishment of exposure registries.

5. The utility of nanotechnology to support the 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.

In summary, the NTRC has advanced the scientific knowledge in understanding the possible health risks of engineered nanoparticles. Continuing research will help to expand this knowledge and provide opportunities for advancing the safe use of nanotechnology.

Contents

Foreword iii

Executive Summary iv

Abbreviations xiv

Acknowledgments xvii

Introduction 1

Chapter 1: Toxicity and Internal Dose 11

Chapter 2: Risk Assessment 17

Chapter 3: Epidemiology and Surveillance 23

Chapter 4: Engineering Controls and Personal Protective Equipment 27

Chapter 5: Measurement Methods 33

Chapter 6: Exposure Assessment 39

Chapter 7: Fire and Explosion Safety 43

Chapter 8: Recommendations and Guidance 47

Chapter 9: Communication and Education 53

Chapter 10: Applications 59

Appendices

A. Project-Specific Progress Reports 63

B. Field Research Team Progress Report 131

C. Occupational Health Surveillance for Nanotechnology Workers . . 137

D. Review of the NIOSH Extramural Nanotechnology Research Program: Fiscal Years 2001–2006 139

E. Nanotechnology Information Dissemination 151

F. Other NTRC Partnership Activities and Presentations 159

G. Projected Timeframe for Addressing Critical Areas 165

H. Executive Summary—*Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* 171

Abbreviations

AIHA	American Industrial Hygiene Association
AIHce	American Industrial Hygiene Conference and Exposition
ANSI	American National Standards Institute
ASSE	American Society of Safety Engineers
ASTM	American Society for Testing and Materials
BIA	Berufsgenossenschafliches Institut für Arbeitsschutz
CDC	Centers for Disease Control and Prevention
CIB	Current Intelligence Bulletin
CMPND	Center for Multifunctional Polymer Nanomaterials and Devices
CNF	carbon nanofiber
CNT	carbon nanotube
COPD	Chronic obstructive pulmonary disease
CPC	Condensation Particle Counter
CSHEMA	Campus Safety, Health and Environment Management Association
DART	Division of Applied Research and Technology
DEP	Diesel exhaust particulate
DSHEFS	Division of Surveillance Hazard Evaluation and Field Studies
DRDS	Division of Respiratory Diseases
DSR	Division of Safety Research
EHS	Environmental Health Sciences
EID	Education and Information Division
EPA	U.S. Environmental Protection Agency
EU	European Union
FAQs	Frequently Asked Questions
FMPS	Fast Mobility Particle Sizer
FY	Fiscal year
HELD	Health Effect Laboratory Division
HEPA	High-Efficiency Particulate Air Filter

HHE	Health Hazard Evaluation
HHPC	hand-held particle counter
IAPA	Industrial Accident Prevention Association
ICMAT	International Conference on Materials for Advanced Technologies
ICON	International Council on Nanotechnology
INRS	Institut National de la Recherche Scientifique
ISO	International Organization for Standardization
kW	kilowatt
LDH	lactate dehydrogenase
MCE	mixed cellulose ester
MIST	man-in-simulation test
MOU	memorandum of understanding
MOUDI	micro-orifice-uniform-deposit impactor
NASA	National Aeronautics and Space Administration
NATO	North Atlantic Treaty Organization
NCER	National Center for Environmental Research
NEHI	Nanotechnology Environmental and Health Implications
NFPA	National Fire Protection Association
NGO	non-governmental organization
NIH	National Institutes of Health
NIEHS	National Institute of Environmental Health Sciences
NIL	Nanoparticle Information Library
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
nm	nanometer(s)
NNI	National Nanotechnology Initiative
NNIN	National Nanotechnology Infrastructure Network
NORA	National Occupational Research Agenda
NPPTL	National Personal Protective Technology Laboratory
NRC	National Research Council
NSET	Nanoscale Science, Engineering, and Technology

NSF	National Science Foundation
NTRC	NIOSH Nanotechnology Research Center
OD	Office of the Director
OECD	Organization for Economic Cooperation and Development
OEP	Office of Extramural Programs
ORC	Organization Resource Council
OSH	occupational safety and health
OSHA	Occupational Safety and Health Administration
PAS	passive aerosol sampler
PPE	personal protective equipment
PRL	Pittsburgh Research Laboratory
PSLT	poorly soluble, low toxicity
QD	quantum dot
QRA	quantitative risk assessment
r2p	research to practice
REL	recommended exposure limit
RFA	request for application
RTI	Research Triangle Institute
SBIR	Small Business Innovative Research
SNORA	Small National Occupational Research Agenda on personal protective equipment
SRL	Safety Research Laboratory
SWCNT	single-walled carbon nanotube
TEM	Transmission Electron Microscopy
TEM/EDS	Transmission Electron Microscopy/ Energy Dispersive Spectroscopy
TERA	Toxicology for Excellence in Risk Assessment
TiO2	titanium dioxide
TSCA	Toxic Substances Control Act
WHO	World Health Organization

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Introduction

Background

Nanotechnology is a system of innovative methods to control and manipulate matter at near-atomic scale to produce new materials, structures, and devices. Nanoparticles are a specific class or subset of these new materials that have at least one dimension that is less than 100 nm. They exhibit unique properties because of their nanoscale dimensions. Nanotechnology offers the potential for tremendous improvement and advances in many areas that may benefit society, such as integrated sensors, semiconductors, medical imaging, drug delivery systems, structural materials, sunscreens, cosmetics, coatings, and many others. Nanotechnology is one of the most rapidly growing industries across the world. By 2015, the global market for nanotechnology-related products is predicted to reach $1 trillion and employ 1 million workers in the United States alone. The properties of nanoparticles (e.g., size, surface area, reactivity) that yield many of the far-reaching societal benefits may also pose risks. Currently, increasing numbers of workers are potentially exposed to nanomaterials in research laboratories, startup companies, production facilities, and operations where nanomaterials are processed, used, disposed of, or recycled. The challenges are to determine whether the nature of engineered nanostructured materials and devices presents new occupational safety and health risks. At the same time, the need is to realize the benefits of nanotechnology while proactively minimizing the risk.

Multiple Federal agencies are fostering the development and use of nanotechnology. The President's Council of Advisors on Science and Technology has collaborated with the interagency National Science and Technology Council to create the National Nanotechnology Initiative (NNI). This initiative supports basic and applied research and development in nanotechnology to create new nanomaterials and to disseminate new technical capabilities to industry. The purpose of NNI is to facilitate scientific breakthroughs and maintain U.S. competitiveness in nanoscience. A stated goal of this interagency program is to ensure that nanotechnology research leads to the responsible development of beneficial applications by giving high priority to research on societal implications, human health, and environmental issues related to nanotechnology.

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 a member of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council. As such, NIOSH is active in (1) identifying critical issues related to possible hazards of nanomaterials, (2) protecting

worker safety and health in this emerging technology, and (3) implementing a strategic plan for conducting research and for developing guidance documents.

Because of their small size and large surface area, engineered nanoparticles may have chemical, physical, and biological properties distinctly different from and greater than fine particles of similar chemical composition. Such properties may include a high rate of pulmonary deposition, the ability to travel from the lung to systemic sites, the ability to penetrate dermal barriers, and a high inflammatory potency per mass. At a time when materials and commercial applications are being conceived, NIOSH is well positioned to proactively identify, assess, and resolve potential safety and health issues posed by nanotechnology. NIOSH has 35 years of experience in conducting research and formulating recommendations for occupational safety and health. During this period, NIOSH has developed considerable expertise in measuring, characterizing, and evaluating new processes and new materials by conducting quantitative exposure assessments and evaluating health effects. NIOSH also has expertise in developing control systems and prevention strategies for incidental nanoparticles (for example, diesel exhaust, welding fume, smelter fume, and fire smoke particles). NIOSH is using this experience to address similar issues for engineered nanoparticles.

NIOSH has redirected programmatic funds ($3.0 million in FY 2005, $3.7 million in FY 2006, and $4.6 million in FY 2007) to resolve occupational safety and health knowledge gaps in the field of nanotechnology by conducting a broad program of research and guidance development. This report describes the progress of the NIOSH Nanotechnology Research Center (NTRC). The Center is a matrix of activities and projects consisting of and supported by more than 30 scientists from various divisions and laboratories in NIOSH who have developed and implemented a strategic plan (available at www.cdc.gov/niosh/topics/nanotech) to address occupational health issues of nanotechnology. See Appendix G for a projected timeline of activities.

The NIOSH Role in Occupational Safety and Health of Nanotechnology Workers

A complete process for managing occupational safety and health implications during the development of new technologies and materials consists of a set of progressive elements: identifying and characterizing the hazard, assessing the extent of exposure, characterizing the risk, and developing control and management procedures. As exposure assessment data become available, it can be determined whether an occupational risk exists; if so, the risk can be assessed and characterized. The risk characterization should make it possible to

determine whether workplace exposure to a given technology or material (in this case, nanoparticles) is likely to result in adverse health effects. The exposure assessment data will also provide a means to determine what controls are effective in preventing exposure that could cause adverse effects. The NTRC is involved in answering questions posed in each element in the risk management process (Figure 1). Particularly as this report illustrates, the NTRC has begun to answer questions about hazards by assessing exposures to nanoparticles in surrogate animals using well established scientific principles. Toxicological research is one element that forms the foundation for occupational safety and health. The critical routes of exposure (respiratory and skin) and their targets (lungs, cardiovascular, skin, brain, systemic) are being identified, and research is being conducted on the health effects and mechanisms of action of specific nanoparticles.

Meanwhile, research is being conducted on measuring nanoparticles in air, determining what measures are appropriate, and using this information in field assessments. Parallel efforts have been undertaken to address the control of airborne nanoparticles and the strengths and weaknesses of control approaches. Similar efforts are underway for personal protective equipment (PPE) such as respirators and gloves.

The findings of field investigations and laboratory research are continually used to update guidance for thinking about, evaluating, and managing potential nanotechnology risks. This information is being widely disseminated by NIOSH.

The problem is that it is difficult to proceed in a classic step-by-step fashion from hazard identification to risk management because each day more workers may be exposed to nanomaterials as nanotechnology permeates industrial and commercial sectors. Thus the challenge is to conduct research to address knowledge gaps while drawing on all available information to provide interim guidance. Fortunately, a body of knowledge exists on hazards, risks, and controls for particles between 100 nm and 1μm. Nanomaterials that are currently manufactured apparently have no major physical features that would make them behave differently from fine and ultrafine particles when controlling them in the workplace. However, the limits of this assumption need continued evaluation.

Despite a comprehensive approach, NIOSH research and guidance is limited by resource constraints. Workplace applications of nanotechnology are numerous and diverse. At this time, it is difficult to understand whether broad, homogenous classes of nanoparticles can be identified for testing and control purposes. The vast diversity of nanoparticles presents a challenge

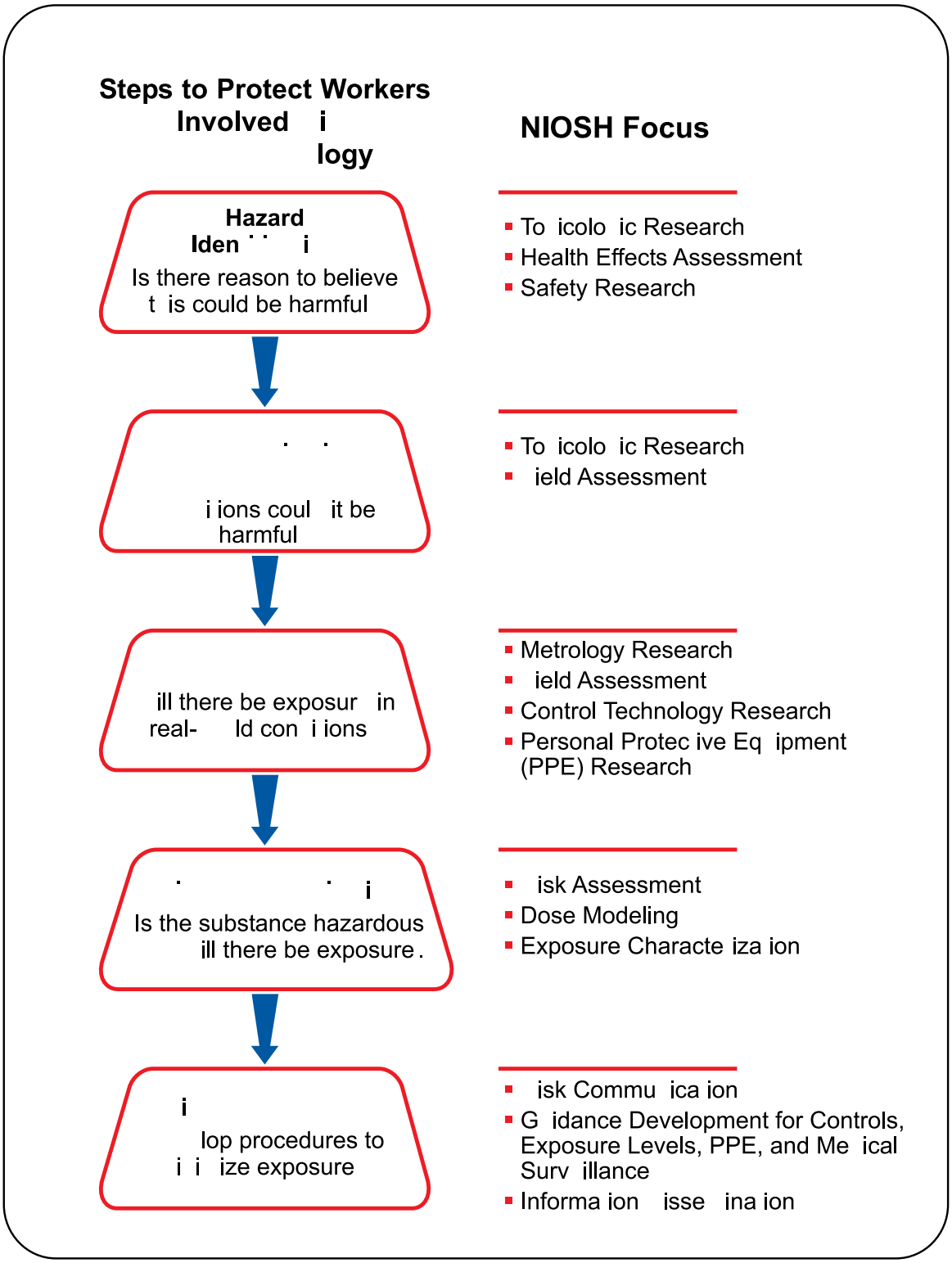


Figure 1. Steps to protect workers involved with nanotechnology. *Adapted from Gibbs, 2006.*

for determining which ones should be the focus of research. NIOSH has primarily been addressing the growing categories of carbon nanotubes, carbon nanofibers, metal oxides, and quantum dots in laboratory and field investigations. However, within each category is a broad range of combinations, surface characteristics, and physical and chemical parameters that can and are being altered by researchers and manufacturers. Although specific nanoparticles are being assessed in toxicologic research, the NTRC field team is proceeding to identify and assess the growing range of nanoparticles in the workplace.

Critical Topic Areas

NTRC has identified 10 critical topic areas (Figure 2) to (1) guide its research in areas where knowledge gaps exist, (2) develop strategies, and (3) provide recommendations. Each chapter (1–10) provides a brief description of the research that NTRC is conducting in the topic area and the applications and

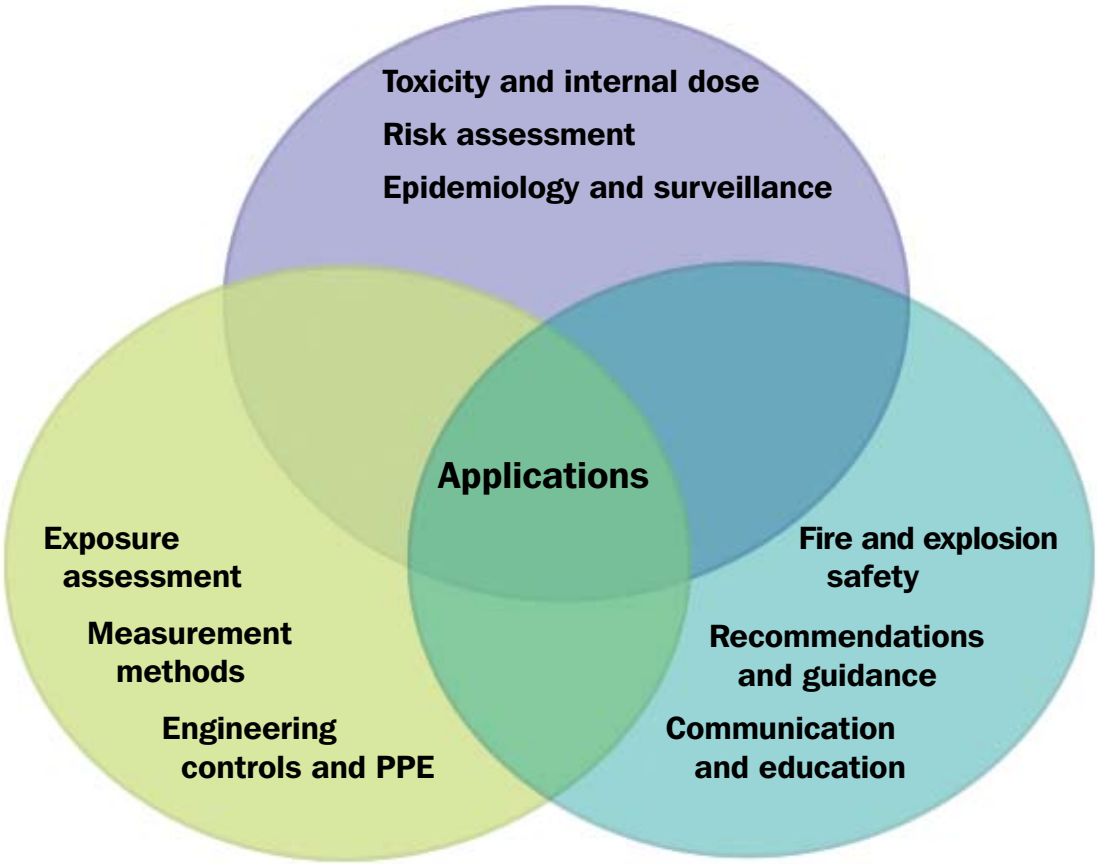


Figure 2. The 10 critical areas identified by the NTRC.

implications of nanomaterials in the workplace. Research needs for each topic area are listed as follows:

1. Toxicity and Internal Dose

- Investigating and determining the physical and chemical properties (e.g., size, shape, solubility) that influence the potential toxicity of nanoparticles
- Determining what happens to nanomaterials once they enter the body.
- Evaluating short- and long-term effects that nanomaterials may have in organ systems and tissues (e.g., lungs, brain, cardiovascular)
- Determining biological mechanisms for potential toxic effects
- Creating and integrating models to help assess hazards
- Determining whether a measure other than mass is more appropriate for determining toxicity

2. Risk Assessment

- Determining how existing exposure-response data for fine and ultrafine particles (human or animal) may be used to identify and assess occupational hazards and risks
- Developing a framework for evaluating potential hazards and predicting the occupational risk of exposure to nanoparticles

3. Epidemiology and Surveillance

- Evaluating existing epidemiological studies in the workplace where nanomaterials are used
- Identifying knowledge gaps that could be filled by epidemiological studies to advance the understanding of nanomaterials and evaluating the feasibility of conducting new studies
- Integrating nanotechnology safety and health issues into existing hazard surveillance methods and determining whether additional screening methods are needed
- Using existing systems to share data and information about nanotechnology

4. Engineering Controls and PPE

- Evaluating the effectiveness of engineering controls in reducing occupational exposures to nanoaerosols and developing new controls when needed

- Evaluating the suitability of control banding techniques when additional information is needed, and evaluating the effectiveness of alternative materials
- Evaluating and improving current PPE
- Developing recommendations to prevent or limit occupational exposures to nanomaterials (e.g., recommending respiratory protection)

5. Measurement Methods

- Evaluating methods for measuring the mass of respirable particles in the air and determining whether this measurement can be used to measure nanomaterials
- Developing and field-testing practical methods to accurately measure airborne nanomaterials in the workplace
- Developing, testing, and evaluating systems to compare and validate sampling instruments

6. Exposure Assessment

- Determining key factors that influence the production, dispersion, accumulation, and re-entry of nanomaterials into the workplace
- Determining how possible exposures to nanomaterials differ by work process
- Assessing possible exposure when nanomaterials are inhaled or settle on the skin

NIOSH monitoring of a worker during a nanomaterial powder production and collection.

7. Fire and Explosion Safety

- Identifying physical and chemical properties that contribute to dustiness, combustibility, flammability, and conductivity of nanomaterials
- Recommending alternative work practices to eliminate or reduce workplace exposures to nanomaterials

8. Recommendations and Guidance

- Using the best available science to make interim recommendations for workplace safety and health practices during the production, use, and handling of nanomaterials
- Evaluating and updating mass-based occupational exposure limits for airborne particles to ensure good, continuing precautionary practices

9. Communication and Education

- Establishing partnerships to allow for identifying and sharing research needs, approaches, and results
- Developing and disseminating training and education materials to workers, employers, and occupational safety and health professionals

10. Applications

- Identifying uses of nanotechnology for application in occupational safety and health
- Evaluating and disseminating effective applications to workers, employers, and occupational safety and health professionals

The remainder of this report provides an update describing the research and guidance efforts in each of the 10 critical topic areas of the NTRC. In addition, ongoing partnerships and collaborations are identified along with accomplishments and areas where future research is needed. The appendices provide details of each intramural project and they outline published research and presentations of the NTRC staff. Appendix D provides information regarding the nanotechnology research being funded through the NIOSH Office of Extramural Programs.

1

Toxicity and Internal Dose

Background

NIOSH has studied in great detail the toxicity of incidental exposures to nanoparticles generated from processes involving combustion, welding, or diesel engines. However, less is known about nanoparticles that are intentionally produced (engineered) with diameters smaller than 100 nm. Many uncertainties exist as to whether the unique properties of engineered nanomaterials pose occupational health risks. These uncertainties arise because of gaps in knowledge about the potential routes of exposure, movement of nanomaterials once they enter the body, and the interaction of the materials with the body's biological systems. Results from existing animal and human studies of exposure to incidental nanoscale and other respirable particles provide preliminary information about the possible adverse health effects from exposures to similar engineered nanomaterials.

The NTRC is conducting research to address the following questions:

- Is particle surface area a more appropriate measure of exposure than particle mass?
- Does a high deposition of nanoparticles in the lungs affect clearance and movement of nanoparticles from airspaces into cells, tissues, and blood vessels?
- Can nanoparticles get into various organs once they are in the bloodstream?
- By what mechanisms do nanoparticles generate reactive oxygen species?
- Do nanoparticles cause adverse health effects in workers if they penetrate the skin?
- How do shape, durability, and chemical composition of nanoparticles affect their biological activity?
- Do nanoparticles that are bound together separate into smaller, possibly more potent structures in biological fluids?
- Are in vitro assays predictive of in vivo responses to nanoparticles?

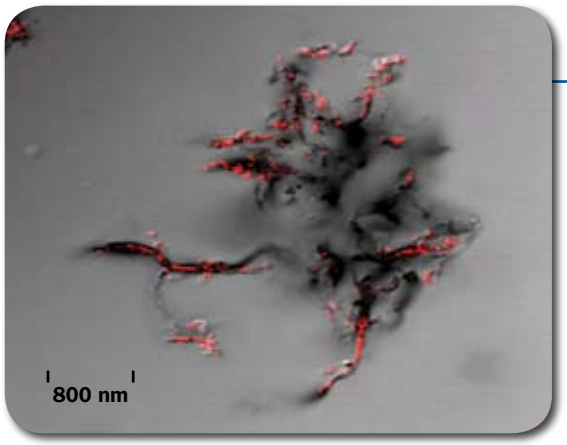
NTRC Toxicology and Internal Dose Projects

The NTRC has built a comprehensive research program focused on the question of whether nanomaterials pose occupational health risks. Currently, sev-

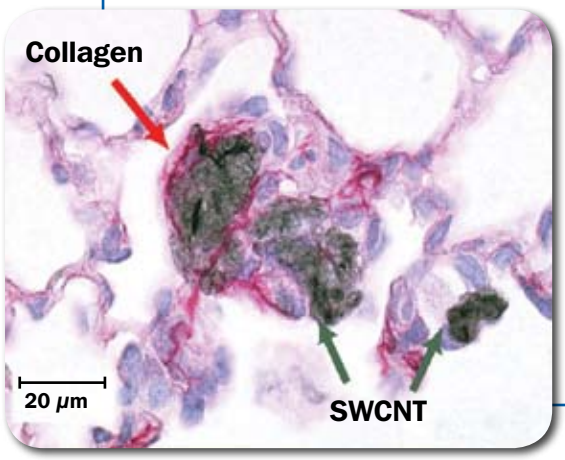
eral projects are underway and are primarily studying the effects of inhalation and dermal exposure to nanoparticles. Projects include the following:

- Measuring how nanoparticles deposit in and clear out of the lungs after intratracheal instillation, pharyngeal aspiration, or pulmonary exposure
- Monitoring how nanoparticles move from the airways into tissue and blood through the use of labeled nanoparticles
- Measuring pulmonary damage, oxidant stress, inflammation, and fibrosis after pulmonary exposure to nanoparticles of various compositions and shapes
- Measuring the cardiovascular effects of pulmonary exposure to nanoparticles of various compositions and shapes
- Measuring how nanoparticles move from the lung to brain tissue and determining whether this results in neural effects
- Determining the role of surface area in biological activity
- Determining the ability of lung lining fluid to separate nanoparticles that are bound together
- Determining whether in vitro measurement of the oxidant-generating capacity of nanoparticles predicts in vivo response
- Determining dermal effects of exposure to nanoparticles of various compositions and shapes

For more information about the NTRC nanotoxicology projects, see Appendix A, Projects 1 through 10.



Transmission electron micrograph (TEM) of dispersed multiwalled carbon nanotubes. Magnification=4,350X



Alveolar granulomas containing single-walled carbon nanotube (SWCNT) with collagen detected in granuloma, indicating a fibrotic response. The tissue sample was collected 7 days following exposure to 40 μg of SWCNT by pharyngeal aspiration in rats.

Collaborations and Partnerships

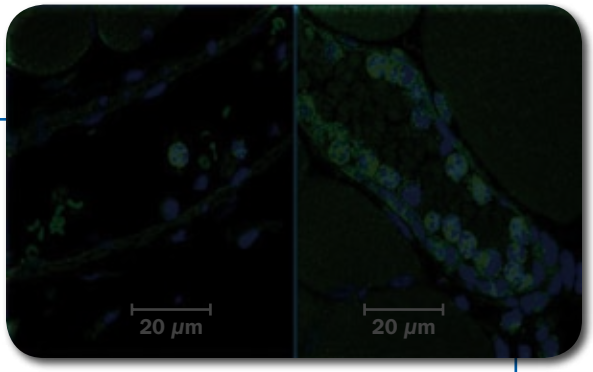
NTRC scientists working in the area of toxicity and internal dose have established external collaborations

with universities, private industries, and other government agencies. Collaborations are intended to advance knowledge and understanding of the factors that are critical for determining whether nanoparticles pose an occupational risk of harmful effects. NTRC is collaborating with organizations such as the National Aeronautics and Space Administration (NASA), the University of Pittsburgh, West Virginia University, IBM, and Mitsui Incorporated. These collaborations provide a multidisciplinary approach to addressing research needs and ensure high-quality research.

Accomplishments

The NTRC Toxicity and Internal Dose team has had significant accomplishments over the last several years to advance knowledge and understanding of exposure to nanomaterials. The team has accomplished the following:

- Developed a method for improved dispersion of nanoparticles for in vitro and in vivo exposure
- Determined the in vitro effect of single-walled carbon nanotubes or metal oxide nanoparticles on dermal cells in culture
- Determined the pulmonary effect of exposure to single-walled carbon nanotubes
- Labeled single-walled carbon nanotubes and tracked their deposition and migration in the lung in laboratory animals
- Developed systems to generate aerosolized ultrafine titanium dioxide (TiO_2) particles and single-walled carbon nanotubes (SWNCTs) at a controlled size and concentration
- Determined cardiovascular response in laboratory animals to pulmonary exposure to single-walled carbon nanotubes and TiO_2 nanoparticles



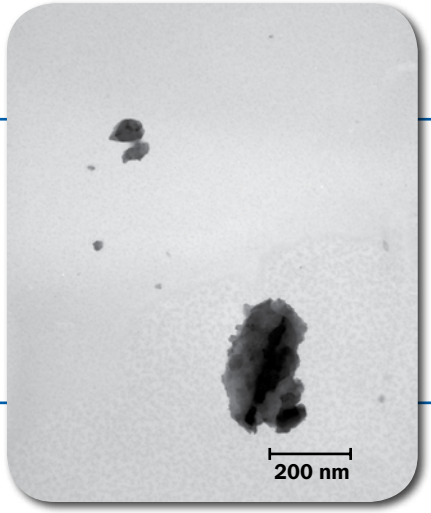
Right: Microvessel in rat muscle showing a buildup of polymorphonuclear neutrophils (PMNs) on the vessel wall 24 hours after intratracheal installation exposure to TiO_2. The vessel wall is less responsive to vasodilators and blood flow is restricted. **Left:** Microvessel from a control rat showing no buildup of PMNs and free-flowing blood cells.

For more information about the NTRC nanotoxicology accomplishments, see Appendix A, Projects 1 through 10.

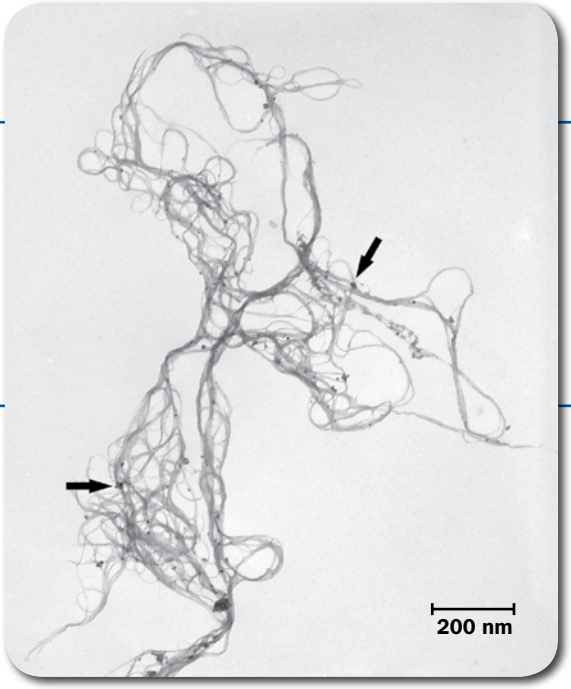
Additional Research Needs and Future Direction

Although the NTRC has made significant advancements in understanding the potential harmful effects of exposure to nanomaterials, much more research is needed. The NTRC is focusing its research efforts in the following four primary areas:

1. Determining the nature and severity of effects on the lung from inhaled nanoparticles
2. Determining whether nanoparticles can move to other parts of the body (e.g., the heart or brain) after the particles are inhaled
3. Determining whether exposure to nanoparticles has any effect on the immune system
4. Determining whether the unique physical and chemical properties of nanoparticles affect how the body responds when exposed to these particles



Fullerenes—These are TEMs of nanoparticles suspended in water and sonicated.



SWCNTs produced by the high-pressure decomposition of carbon monoxide (HiPCO) method. Arrows note iron contamination of the unpurified SWCNT.

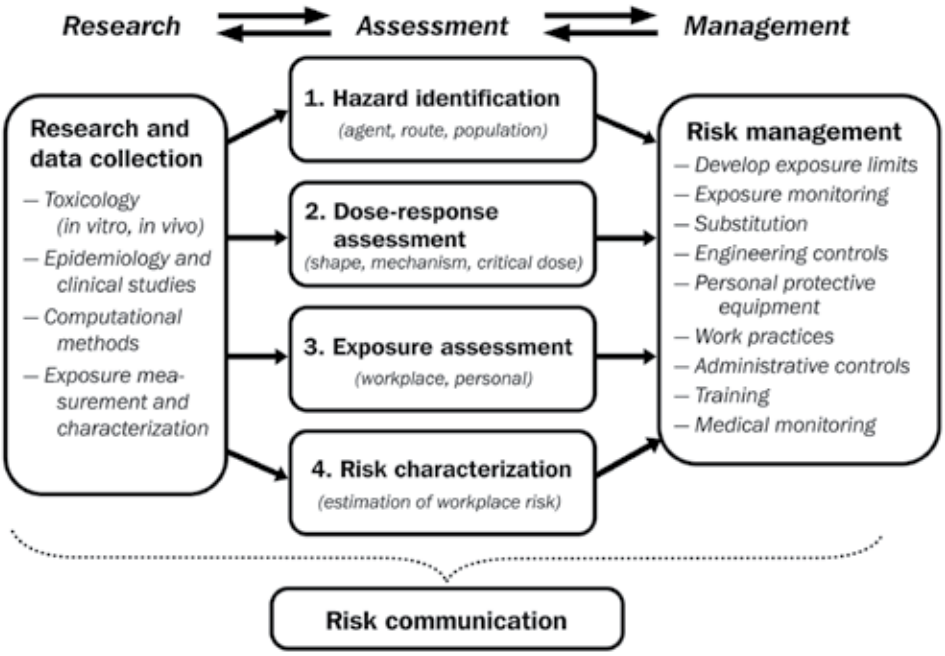
2

Risk Assessment

Background

In the context of occupational safety and health, risk assessment can be described as a scientific evaluation of the potential for adverse safety and health effects to workers exposed to hazardous substances. When assessing risk, it must be determined whether a hazard is present and the extent to which a worker is likely to be exposed to the hazard. Risk occurs only when a hazardous agent is present *and* a worker is exposed to that agent. Quantitative and qualitative risk assessment methods are used to evaluate risk.

Quantitative risk assessment methods are used when adequate data are available concerning the relationship between the *amount* of exposure received and the *reaction* to that exposure. This relationship is known as dose-response. Quantitative methods are useful to estimate exposure concentrations that are likely (or unlikely) to cause adverse health effects. The estimates are then used



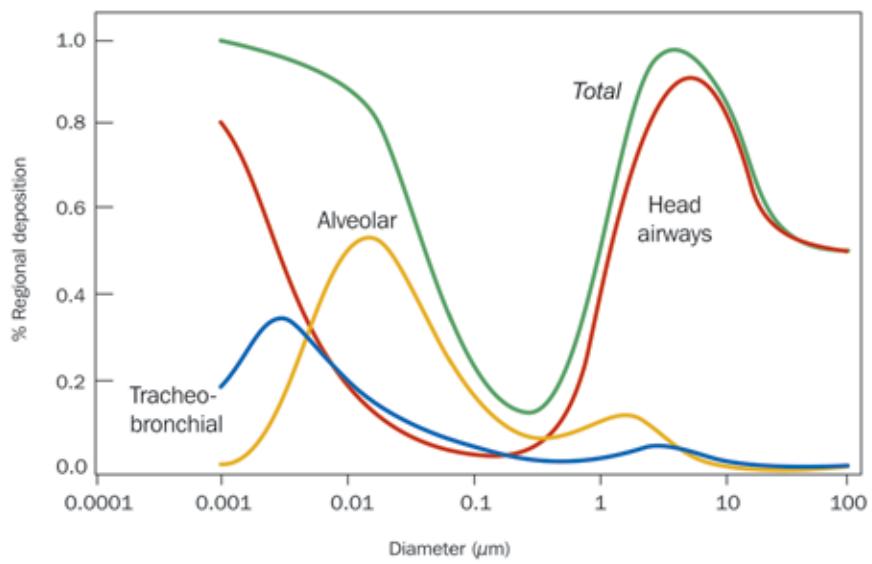
Risk assessment paradigm. (Based on National Research Council [1983]. Risk assessment in the Federal government: managing the process. Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, National Research Council. Washington, DC: National Academy Press, 191 pp.)

in conjunction with occupational exposure data (1) to characterize the health and safety risk to workers, (2) to form a basis for risk management decisions, and (3) to evaluate the effectiveness of engineering controls and other occupational safety and health measures. When adequate dose-response data are not available, qualitative risk assessment methods such as comparative or hazard-ranking approaches may be used.

To develop appropriate risk assessment models and methods, risk assessors work closely with experimental scientists to design laboratory experiments that will provide useful data for estimating risk and uncertainty. They also work with risk managers to provide the analyses needed to develop effective risk reduction strategies.

NTRC Risk Assessment Projects

The goal of occupational risk assessment is to predict conditions in the work environment that could lead to safety and health hazards for workers. This information is used by risk managers to develop appropriate preventive measures



Predicted deposition of inhaled particles in the human respiratory tract—ICRP [1994] model: light exercise, nose breathing; 0.1–5 μm, minimal inertial and diffusion deposition mechanisms. (Source: ICRP, International Commission on Radiological Protection [1994]. ICRP Publication 66: Human respiratory tract model for radiological protection. Elsevier Science, Inc. Tarrytown, NY.)

to reduce or eliminate the risk. In a new industry such as nanotechnology, human data are not yet available for estimating the risk of exposure to engineered nanoparticles. Therefore, NTRC is scientifically extrapolating existing animal data to humans to evaluate dose-response relationships and estimate the risk to workers who are producing or using nanoparticles.

To advance understanding of this risk and to provide improved scientific models and methods that assess the risk of exposure to nanoparticles, the NTRC Risk Assessment team is currently focusing its research efforts in the following three areas:

1. Extending current rodent lung models to describe the fate of inhaled nanoparticles and their increased potential for translocating to other organs in the body
2. Investigating models to describe biologically based relationships between internal dose and biological response
3. Developing state-of-the-art statistical methods to consolidate risk estimates from a number of equally plausible dose-response models

The NTRC is also investigating quantitative and qualitative risk assessment methods for occupational exposure to nanoparticles. Information currently available includes (1) toxicology and epidemiology studies of respirable airborne particles and fibers and (2) toxicology studies of in vitro and in vivo responses to nanoparticles. Existing studies provide the NTRC with a basis for developing interim occupational safety and health guidance, and for comparing the effects of well-studied materials to the effects of new nanoparticles, as data become available.

For more information about the NTRC nanotechnology risk assessment projects, see Appendix A, Project 12.

Collaborations and Partnerships

Risk assessors who are part of the NTRC have established both internal and external collaborations with other researchers and organizations. External partners include CIStems Institute of Information Technology (CIIT) Centers for Health Research, the Institute of Occupational Medicine, and Toxicology for Excellence in Risk Assessment. Research collaborations are underway in areas such as (1) study design for risk assessment of nanoparticles, (2) evaluation of dose metric, (3) translocation of labeled nanoparticles, (4) region-specific deposition of inhaled nanoparticles, and (5) biomathematical lung modeling of nanoparticle deposition and early biological responses.

Accomplishments

Between 2004 and 2006, NTRC risk assessors had significant accomplishments in their research projects. The Risk Assessment Team has accomplished the following:

- Performed quantitative risk assessment using data from existing studies of fine and ultrafine particles
- Developed partnerships with external researchers in an effort to fill data gaps and obtain the scientific information needed to achieve occupational safety and health research objectives
- Published research findings in scientific, peer-reviewed publications
- Presented research findings at scientific meetings

More specifically, a quantitative risk assessment of fine and ultrafine TiO_2 particles was used as the basis for recommended exposure limits (RELs) in a NIOSH Current Intelligence Bulletin. Modifications to a lung deposition model were completed to provide enhanced capabilities for lung dosimetry modeling and research of nanoparticles. Finally, NTRC researchers were invited to provide expert advice and consultation to national and international working groups evaluating occupational safety and health issues of nanoparticles.

Additional Research Needs and Future Direction

During FY 2007, NTRC risk assessors will initiate research efforts involving nanoparticles in two primary ways:

1. Investigating the application of risk assessment methods using existing data to provide a framework for developing preliminary risk management strategies
2. Exploring biomathematical modeling approaches to fill data gaps concerning occupational health risks of exposure to nonspherical nanoparticles (i.e., carbon nanotubes)

These research efforts, in conjunction with ongoing projects, will provide NTRC with a sound scientific basis for determining interim estimates of the potential safety and health hazards to workers exposed to engineered nanoparticles. It will also assist NTRC in providing prudent interim guidelines for using engineering controls, work practices, and other risk management strategies to protect workers responsible for producing and/or using nanomaterials. These assessments may be refined as research is finalized and new data become available.

3

Epidemiology and Surveillance

Background

Human studies of exposure and response to engineered nanomaterials are not currently available. Gaps in knowledge and understanding of nanomaterials must be filled before epidemiologic studies can be performed. For example, improvements in exposure assessment will allow researchers to identify groups of workers who are likely to be exposed to nanomaterials. In turn, health studies conducted on these worker groups can provide useful information about the health risks associated with nanomaterials. Until such studies can be conducted effectively, studies of humans exposed to other aerosols (e.g., larger respirable particles) can be used to evaluate the health risks of exposure to airborne nanomaterials.

The available health data on workplace exposure to airborne respirable particles and fibers, and the air pollution data from epidemiology literature may provide valuable insight into the hazards of nanoparticle exposure. However, applying these data to workplace exposures to nanomaterials presents a number of challenges, including the following:

- Determining the relative importance of particle size (less than 100 nm) as a cause of the observed health effect
- Determining whether nanoparticles move throughout the body and potentially affect organ systems other than the one through which they entered the body

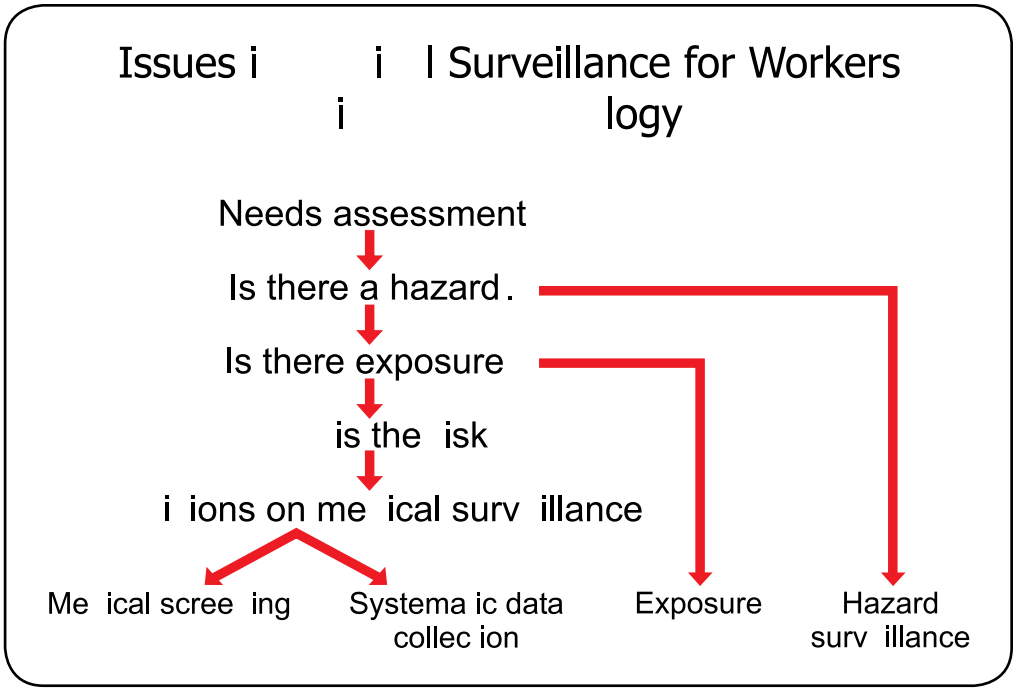
The NTRC hopes to address these and other challenges as information is gained from epidemiologic and other health studies of workers exposed to nanomaterials.

NTRC Epidemiology and Surveillance Projects

The lack of information about potential effects of workplace exposures to nanomaterials underscores the need for occupational health surveillance to be considered for nanotechnology workers. NTRC is addressing this lack of exposure and health effects data by developing guidance for employers and workers concerning the implementation of occupational health surveillance in workplaces where nanomaterials are handled.

Every workplace involved in the production, use, and/or handling of engineered nanomaterials should conduct a needs assessment to make a qualitative risk determination. The guidance being developed by NTRC will consist of a framework for approaching such a needs assessment and applying existing hazard

and medical surveillance methods in workplaces. It will provide information to improve existing occupational health surveillance programs and methods for initiating programs where none exist. As the field of nanotechnology advances, it is likely that this guidance and framework will need to be revised and updated, as will any existing occupational health surveillance programs.



Collaborations and Partnerships

The NTRC has partnered with other Federal agencies to develop guidance related to occupational health surveillance for nanotechnology workers. Partners include the following:

- U.S. Environmental Protection Agency
- U.S. Department of Energy
- U.S. Department of Defense
- Occupational Safety and Health Administration
- Lawrence Berkeley National Laboratory

Accomplishments

The NTRC has convened a cross-Federal group to develop guidance for nanotechnology employers and workers on implementing occupational health surveillance programs in the workplace. For more information about the development of an occupational health surveillance program for nanotechnology workers, please see Appendix C.

Additional Research Needs and Future Direction

A well-recognized need exists for an improved ability to assess relevant exposures to nanoparticles (e.g., we need to determine how to appropriately measure nanoparticle exposure and to assess particle size distribution and composition). Improved exposure assessment will involve a series of important first steps and will be closely tied with improvements in identifying worker cohorts likely to be exposed to nanomaterials. These gaps in our current knowledge about nanomaterials must be filled before epidemiologic studies can be effectively carried out. In addition, toxicologic and health effects research is needed to identify potential health problems to be addressed through medical surveillance programs.

4

Engineering Controls and Personal Protective Equipment

Background

Because of the current lack of exposure standards for nanomaterials, an alternative rationale is required to evaluate the need for and effectiveness of engineering controls. In addition, the success of emerging nanotechnology industries will depend on production and development costs, including the installation of new exposure controls. Minimizing occupational exposure is the most prudent approach to controlling materials of unknown toxicity such as nanomaterials. Typically, these approaches include substituting a less toxic material if possible, enclosing the hazardous process, removing workers from exposure by automating the process, isolating workers from the hazard, and/or using local exhaust ventilation where nanomaterials are handled. Improved control approaches will become more evident as the risks of exposure to nanomaterials are better understood.

When engineering controls are not feasible for reducing exposure to nanoparticles, PPE such as respirators, protective clothing, and gloves should be considered. The use of PPE should be based on a combination of professional judgment and assessment of the hazard. A concern has been raised that nanoparticles could pass through the protective barrier of PPE at a higher rate than larger particles because of their smaller size and unique properties. Therefore, NTRC is conducting research to address this concern.

NTRC Engineering Controls and PPE Projects

Engineering Controls

The published literature contains only a limited number of studies on the implementation and effectiveness of engineering controls in the nanotechnology industry. Therefore, a group of NTRC researchers is assessing multiple approaches for controlling occupational exposure to nanoparticles. As part of this assessment, standard engineering controls are being thoroughly assessed to determine how controlling nanoparticle exposure differs from controlling larger particle exposure. In addition, a group of NTRC researchers is conducting walk-through technical evaluations at a variety of facilities that handle nanomaterials. Scientists are evaluating the potential for occupational exposure to nanoparticles and the use of engineering controls at these facilities. They also provide interim recommendations on safe work practices and work with the company to evaluate the its engineering controls when applicable.

For more information about the field investigations, see Appendix A, Project 13.

Respirators and Other PPE

Scientific information is available to characterize the efficiency of respirator filtration for particles larger than 20 nm in diameter. However, less is known about smaller particles. To increase knowledge and understanding of these smaller particles, NIOSH funded a study in 2005 at the University of Minnesota's Center for Filtration Research. The purpose of this study was to measure the penetration of nanoparticles between 3 and 20 nm in size through various filter media, including glass fiber, electret, and nanofiber. The respirator filter media tested in this study effectively collected nanoparticles as small as 3 nm. There was no evidence that particles in this size range pass through filter media at a higher rate than the larger particles. The NTRC is planning studies to validate these findings using NIOSH-approved respirators and to evaluate worker exposures to nanoparticles when respirators do not fit correctly.

A flat plate test system for measuring respirator filter penetration of 3 to 20 nm silver particles

The NTRC is also developing innovative methods to measure the penetration of nanoparticles through protective clothing and ensembles. The NTRC developed a prototype passive aerosol sampler that will be used in small-scale laboratory studies and testing of human subjects. The sampler will be used to evaluate the penetration of nanoparticles through commercially available protective ensembles; iron oxide aerosols down to 20 nm will be used. Once this study is complete, the NTRC will develop a statistical model based on study results.

For more information about the NTRC PPE studies, see Appendix A, Projects 15 and 16.

Collaborations and Partnerships

Engineering Controls

NTRC engineers, scientists, and industrial hygienists have established external collaborations to evaluate the effectiveness of engineering controls. These assessments have been conducted by the NTRC Field Research team through

surveys conducted at various types of industries that handle engineered nanomaterials. One such collaboration is being used to evaluate the reduction in airborne exposure to nanomaterials after implementing engineering controls or safe work practices.

Respirators and Other PPE

NIOSH and E.I. du Pont de Nemours & Co. (DuPont) signed an agreement in June 2006 under a memorandum of understanding (MOU). The purpose of the MOU is to establish a formal partnership to conduct research and increase knowledge and understanding of nanomaterials to reduce potential occupational exposures to nanoparticles. This MOU is effective through December 2007.

Accomplishments

Engineering Controls

In December 2005, NTRC conducted a comprehensive evaluation at a research facility that incorporates carbon-based nanomaterials into composites. NTRC collected numerous airborne and surface samples and operated a set of real-time aerosol instrumentation as part of a task-based sampling approach. Engineering controls and work practices were observed and qualitatively evaluated. A report has been completed and will be made publicly available.

Checking for fiber release during destructive testing of nanofibers deposited on a substrate using optical and condensation particle counters.

In March 2006, NTRC conducted an extensive study at a primary manufacturer of nanoscale metal oxides. The purpose was to characterize potential occupational exposure to nanomaterials and evaluate use of engineering controls and safe work practices. An interim report has been prepared for the manufacturing facility that includes results of the evaluation and provides recommendations about where improvements can be made to minimize exposure. NTRC is working with this company to demonstrate the effectiveness of implementing recommended changes to engineering controls and work practices.

In July 2006, NTRC conducted a screening survey at a manufacturing facility where quantum dots are produced and encapsulated into small display units. The survey collected basic information about the types of processes employed, exposure control methods, and exposure measurement data. NTRC has drafted a report for the company that includes results from air and surface samples and provides recommendations for improving exposure controls and work practices where necessary.

Results obtained from the evaluation of engineering control practices at nanomaterial facilities will be used to update recommendations in the NIOSH draft document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* (available at www.cdc.gov/niosh/topics/nanotech/safenano/).

Enclosing hood with HEPA exhaust constructed to control possible emission of nylon nanofibers during destructive testing.

Local exhaust ventilation controlling fugitive emissions during precursor mixing at a primary nanoscale metal oxide production facility.

Respirators and Other PPE

Results of respirator and filtration research were reported in several media outlets and have been presented at national and international conferences. Findings will continue to be shared as the information becomes available.

Additional Research Needs and Future Direction

NTRC will focus its efforts on conducting in-depth field surveys and other research studies that document the effectiveness of various exposure controls and work practices for nanotechnology industries. To assist in developing sampling procedures, NTRC will continue collaborating with researchers who develop measurement protocols. NTRC will also continue its research of the potential for nanoparticles to penetrate respirators and other PPE. Findings will be used to develop standards and methods to protect workers from exposure to nanomaterials.

5

Measurement Methods

Background

Sound scientific measurement methods are essential to effectively anticipate, recognize, evaluate, and control potential occupational health risks from current and emerging nanotechnologies. Traditional measurement approaches, such as determining total and respirable dust concentrations, may not be adequate for nanomaterials because of their unique physical, chemical, and biological properties.

NTRC scientists are conducting research to identify and validate a comprehensive set of methods suitable for measuring nanomaterials. This area of research is known as nanometrology. To fill gaps in nanometrology, the Measurement Methods Team within the NTRC has identified three critical measurement goals:

1. Evaluate methods used to measure total and respirable dust concentrations to determine whether the same methods can be used to measure nanomaterials.
2. Develop and field test practical methods to evaluate their accuracy in measuring airborne nanomaterials in the workplace.
3. Develop testing and evaluation systems to compare and validate sampling instruments.

NTRC Measurement Methods Projects

The Measurement Methods team is focusing its efforts on building a knowledge base of methods suitable for measuring nanomaterials in the workplace. The team has a wide variety of research projects underway; within its projects the team is doing the following:

- Establishing a controlled laboratory environment to generate nanoparticles and evaluate the effectiveness of instruments that measure the size and morphology (structure and form) of these particles (this laboratory will allow researchers to conduct evaluations existing and new instruments using different nanomaterials)
- Evaluating instruments to monitor nanoparticle aerosols in real time
- Investigating innovative methods to estimate surface area of aerosols and demonstrating that these methods provide comparable results for nanoparticles of different shapes and sizes

- Evaluating different measurement methods to determine worker exposure to TiO_2 particles smaller than 2.5 and 0.1 µm in diameter (fine and ultrafine nanoparticles, respectively).
- Developing new direct-reading instruments to measure size distribution, surface area, and mass concentration of nanoaerosols.

In addition, the NTRC Measurement Methods Team supports the activities of the Field Research Team in characterizing exposures to nanomaterials in the workplace and evaluating the effectiveness of controls used to reduce exposures.

The above research activities will provide a better understanding of the nature and extent of potential exposure to nanoparticles in the workplace. Results from these activities will help explain how nanoparticles are generated and dispersed. In addition, the results from ongoing research will help the occupational health community develop scientifically sound health protection strategies and provide information necessary for establishing voluntary national and international standards for emerging nanotechnologies.

For more information about the NTRC measurement methods projects, see Projects 1, 5, 11, 13, 14, and 17 in Appendix A, and the Field Research Project in Appendix B.

Air sampling filter in close proximity during tear-testing of nanofiber coated cellulose.

Collaborations and Partnerships

Scientists within the NTRC Measurement Methods team are collaborating internally, as well as with external agencies and organizations, to characterize the potential for nanoparticle exposure in the workplace, evaluate sampling instruments, characterize the physical and chemical properties of nanomaterials, and evaluate methods for controlling exposure.

NTRC has established several partnerships with industries conducting research of ultrafine nanomaterials, as well as with national and international government agencies and standards organizations, academia, labor unions, and aerosol instrument manufacturers. External partnerships include the following:

- National Institute of Standards and Technology
- U.S. Environmental Protection Agency
- U.S. Department of Energy
- U.S. Department of Defense
- American National Standards Institute
- ASTM International

Comprehensive aerosols measurements conducted at different production processes within a primary nanoscale metal oxide production facility. A number of aerosol sampling methods and instruments are used simutaneously to better understand particle characteristics.

In addition, NTRC collaborates with several national and international committees and working groups, as well as with commercial instrument manufacturing companies. Additional partnerships are noted within the specific projects listed in Appendix A.

Accomplishments

Between 2004 and 2006, scientists within the NTRC Measurement Methods team made significant advancements in characterization, implementation, and evaluation of measurement tools and techniques. The Measurement Methods team has accomplished the following:

- Developed laboratory-based techniques for characterizing nanoparticles
- Evaluated innovative instrumentation for nanometrology in controlled laboratory settings
- Tested a set of measurement methods in nanotechnology workplaces
- Developed nanoparticle reference materials in collaboration with the National Institute of Standards and Technology (NIST)
- Disseminated research findings through scientific peer-reviewed publications, presentations, and the media
- Provided expert advice and consultation to stakeholders through personal interactions and the NIOSH Nanotechnology Web page
- Developed a prototype aerosol sampler that was submitted internally within NIOSH's technology transfer channels for possible patenting

For an expanded account of the accomplishments achieved within the NTRC Measurement Methods Program, see Appendix A, Projects 1, 5, 11, 13, 14, and 17.

Additional Research Needs and Future Direction

The Measurement Methods team will focus its short-term efforts on supporting the field- and laboratory-based research plans outlined in the NTRC projects listed in Appendix A. In addition, the group plans to strengthen NTRC's capabilities for characterizing nanoparticles (e.g., development of nanoaerosol samplers), ensure that research findings are incorporated into national and international consensus standards, and expand both field- and laboratory-based research plans developed through the NTRC measurement projects.

6

Exposure Assessment

Background

Exposure assessment is a critical component in determining whether nanomaterials pose occupational safety or health risks. Therefore, it is necessary to conduct exposure assessments in the workplace to identify the ways that workers may be exposed to nanomaterials, the amount of exposure that may occur, and the frequency of potential exposure. Without workplace exposure data, it is difficult to accurately characterize the work environment, identify sources that are emitting nanomaterials, or estimate the amount of nanoparticle exposure that workers may receive. In addition, exposure data can be beneficial when making decisions concerning risk management or evaluating the effectiveness of engineering controls and work practices in reducing worker exposures.

The NTRC Exposure Assessment team has initiated workplace evaluations of worker exposure to nanomaterials in industries that produce and handle different types of nanomaterials. Several exposure assessment methods are being used to characterize exposures, including methods that will identify the size, shape, structure, and chemistry of airborne nanomaterials. This information is typically gathered after a walk-through evaluation of the facility.

To the extent possible, personal breathing-zone samples are taken to ensure that each worker's exposure is measured accurately. Unfortunately, many of the instruments currently available to detect nanomaterial exposures are too large to attach to the worker to collect breathing-zone samples. Therefore, general area air samples are taken in conjunction with personal samples to estimate the magnitude of nanomaterial exposure in areas occupied by workers.

Sampling for airborne nanoparticles during a drum changing operation in a commercial nanomaterial production facility.

NTRC Exposure Assessment Projects

NTRC is currently conducting both qualitative and quantitative exposure assessment surveys in a variety of producers and end-users of nanomaterials. For more information about these activities, see Appendix B.

Collaborations and Partnerships

Scientists within the NTRC Exposure Assessment team are collaborating internally and with external agencies and organizations to develop and apply state-of-the-art methods to identify and characterize workplace exposures to nanomaterials, develop estimates of these exposures for exposure-response and risk assessment studies, and evaluate the significance of occupational exposure to nanomaterials and the effectiveness of intervention strategies.

NTRC has also established partnerships with national and international government agencies and standards organizations, aerosol instrument manufacturers, and industries conducting research on nanoscale particles. External partners include the following:

- Exposure Assessment Strategies Committee of the American Industrial Hygiene Association (AIHA)
- Nanotechnology Working Group of AIHA
- American Association for Aerosol Research and its international affiliates
- American National Standards Institute (ANSI)
- International Organization for Standardization (ISO) Technical Committee 229 on nanotechnologies

Sampling and data collection during a mixing operation.

Accomplishments

As part of the NTRC, the Exposure Assessment team has made significant recent accomplishments in characterizing workplace exposures to nanomaterials. In the past year, NTRC has completed four exposure assessment surveys with the following organizations:

- A university composite material research laboratory that integrates carbon nanofibers to strengthen plastic materials
- A manufacturer of TiO_2
- A research laboratory that handles quantum dots
- A filter manufacturer that applies nylon nanofibers to a cellulose base material to increase filtration efficiency

For more information about these exposure assessment surveys, see the Field Research Team Progress Report in Appendix B

Additional Research Needs and Future Direction

The NTRC Exposure Assessment team has identified several areas where additional research is needed. NTRC plans to continue its efforts conducting initial onsite exposure assessment surveys using handheld particle size and concentration instrumentation in various nanotechnology facilities, and investigating work processes and practices that could potentially lead to exposure to nanomaterials. Upon completion of the initial surveys, NTRC plans to conduct additional exposure characterization studies using more sophisticated instrumentation capable of measuring particle size distributions, particle surface area, and the mass of particles for various size ranges. Measurements obtained during the detailed surveys are expected to allow NTRC to determine the extent of workplace exposure to nanomaterials and estimate their potential for causing health effects.

In addition, NTRC will continue to work with partners to develop personal-sized sampling instruments that are able to measure particle size, shape, surface area, concentration, electrical charge, and other nanoparticle characteristics that may influence the conditions and potential health effects of workplace exposure. The development and validation of small sampling instruments to accomplish these characterizations are critical to the field of exposure assessment, and in understanding the health effects that exposure to nanomaterials may have on workers.

7

Fire and Explosion Safety

Background

The field of nanotechnology is relatively new, and therefore little is known about the potential occupational safety hazards that may be associated with engineered nanomaterials. However, the information that is available about the properties of nanoscale particles indicates that under given conditions, engineered nanomaterials may pose a dust explosion hazard and be spontaneously flammable when exposed to air because of their large surface area and overall small size. Until more specific data become available, NTRC is using findings from research studies involving particles smaller than 100 nm to evaluate the potential risk for fire and explosion of airborne nanoparticles.

About 20 dust explosions occur in industry settings each year and result in property damage, worker injury, and death. Dust explosions burn rapidly and with extreme intensity. During these explosions, settled surface dust may get resuspended in the air and create an environment suitable for further combustion. Processes that generate engineered nanomaterials in the gas phase or use or produce nanomaterials as powders, slurries, suspensions, or solutions, are likely to release nanoparticles into the air and therefore create the greatest risk for fire and explosion. Currently, the primary safety concerns associated with nanomaterials in the workplace are fire and explosion.

Fire and Explosion

Nanomaterials present a safety concern for potential fire and explosion because data show that decreasing the particle size of combustible materials may increase the risk for explosion. For many dust particles, the explosion risk appears to plateau at particle sizes on the order of tens of microns. However, some nanomaterials are designed specifically to generate heat through the progression of reactions at the nanoscale; this too may present a fire hazard that is unique to engineered nanomaterials.

The ability of nanomaterials to become electrostatically charged during transport, handling, and processing introduces a unique explosion hazard when dealing specifically with nanopowders. Their tendency to charge has been found to drastically increase as particle surface area increases. As a result, their large surface area may become highly charged and become their own ignition source if the powder is dispersed in the air.

Nanoparticles and nanostructured porous materials have been used for many years as effective catalysts for increasing the rate of reactions or decreasing the necessary temperature for reactions to occur in liquids and gases. Depending

on their composition and structure, some nanomaterials may initiate catalytic reactions and increase the fire and explosion potential that would not otherwise be anticipated from their chemical composition alone.

NTRC Safety Projects

NTRC has not yet begun any research projects to investigate the explosivity and risk of fire from airborne exposures to nanomaterials in the workplace. At present, NTRC has reviewed the relevant literature and has initiated the development of a research study protocol.

Collaborations and Partnerships

Collaborative efforts are underway to identify stakeholders and organizations (e.g., National Fire Protection Association [NFPA]) with expertise in areas associated with the potential safety hazards of airborne dust exposures (e.g., fire, explosion). Through established collaborations and partnerships, NTRC will develop a research plan to determine the physical and chemical characteristics of nanoscale powders that may pose the greatest risk for fire and explosion in the workplace.

Accomplishments

In the absence of data to predict the risk of fire and explosion from airborne nanoparticles, NTRC has developed and published interim guidance in a document entitled *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. This document can be obtained on the NIOSH Web site at: www.cdc.gov/niosh/topics/nanotech/safenano/.

Additional Research Needs and Future Direction

NTRC has identified several areas within the nanotechnology *fire and explosion safety* initiative where additional research is needed. These areas of research include the following:

- Understanding the chemical, physical, and reactive properties of nanomaterials
- Determining the potential for airborne nanomaterials to cause fire or explosion

- Understanding the extent to which combustible nanomaterials pose a higher risk of fire and explosion than coarser material of similar composition and quantity
- Determining any chemical and/or physical characteristics of nanomaterials that may initiate catalytic reactions and increase the potential of fire and explosion

8

Recommendations and Guidance

Background

NIOSH is responsible for (1) conducting research and making recommendations to protect the safety and health of workers, and (2) providing guidance to workers and employers on how to control potential occupational health hazards. In addition, NIOSH is dedicated to translating its research findings into recommendations and guidance that are scientifically sound and practical for the workplace.

The national and international research community has identified the development of sound scientific recommendations for nanotechnology workers and employers as a key research priority. These recommendations should help workers and employers better understand the potential risks associated with exposure to nanomaterial and provide guidance on ways to manage and eliminate these risks. NTRC has identified the following goals to ensure that workers are protected from the potential safety and health hazards from exposure to nanomaterials:

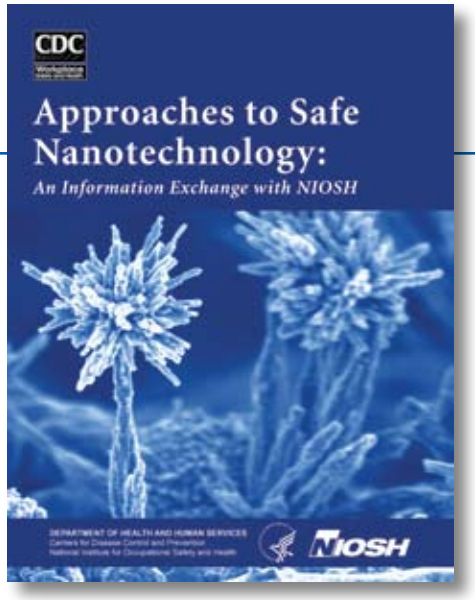
- Make interim scientific recommendations for prudent workplace safety and health practice during production and use of nanomaterials based on the best available scientific knowledge.
- Validate experience-based recommendations using scientific, field- and laboratory-based research.
- Develop partnerships with employers, workers, government agencies, and those in academia to disseminate recommendations and solicit feedback for improvement.
- Issue periodic updates and revisit interim recommendations based on new research findings.
- Evaluate Material Safety Data Sheets for informative and precautionary language that reflects current classification, toxicity data, and recommendations for working with nanomaterials.
- Evaluate and update recommended occupational exposure limits (e.g., mass-based airborne particles) to ensure that good prudent practices are used.

NTRC Recommendations and Guidance Projects

NTRC has several ongoing projects aimed at providing recommendations to employers, workers, and safety and health professionals involved or interested in the field of nanotechnology. The primary project is a document

entitled *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. This document was first issued in October 2005 and updated in July 2006. Currently, this document draws from the ongoing NTRC assessment of the potential health risks from exposure to nanomaterials and the best practices for minimizing worker exposure. This document will continue to be updated as more data become available about the potential safety and health risks, as well as measures that can be used to control workplace exposure to nanomaterials.

NTRC is also participating in the Nanotechnology Environmental and Health Implications (NEHI) effort to develop national research priorities. NTRC is participating in the following five areas: (1) instrumentation, metrology, and analytical methods; (2) nanomaterials and human health; (3) nanomaterials and the environment; (4) health and environmental surveillance; and (5) risk management methods.



NIOSH developed this document to provide an overview of what is known about nanomaterial hazards and measures that can be taken to minimize workplace exposures.

Collaborations and Partnerships

NTRC has established internal and external collaborations to gather information necessary to develop sound scientific recommendations and guidelines concerning the safe handling of nanomaterials. National and international collaborations and partnerships include the following:

- NNI through National Science and Technology Council's Subcommittee on Nanoscale Science, Engineering and Technology
- Organization for Economic Cooperation and Development (OECD)
- New England Healthcare Institute
- U.S. Environmental Protection Agency
- International Organization for Standardization
- American National Standards Institute
- ASTM International
- U.S. Department of Energy National Laboratories

In addition, the NTRC is collaborating with academic institutions, manufacturers, and employers to ensure that current recommendations on the potential safety and health hazards of nanomaterials are available to workers in the field of nanotechnology.

Accomplishments

NTRC has developed interim recommendations for workers and employers on the safe handling of nanomaterials, and it continues to publish findings from ongoing research. The Recommendations and Guidance team has accomplished the following:

- Developed and disseminated an interim guidance document for safety and health professionals entitled *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*
- Developed a draft Current Intelligence Bulletin with recommended exposure limits for workplace exposure to TiO_2 nanoparticles
- Established partnerships with national and international researchers, manufacturers, and industry leaders
- Provided expert advice and consultation as well as disseminated recommendations and guidance through invited participation in national and international working groups and expert panels
- Disseminated research findings and recommendations through peer-reviewed journal articles

Additional Research Needs and Future Direction

Currently, few quantitative data are available on occupational exposure to nanomaterials. To fill the gaps in the knowledge and understanding of nanomaterials, NTRC created the Nanotechnology Field Research Team. This team has conducted onsite investigations at facilities that produce and/or handle nanomaterials.

NTRC plans to continue its onsite field investigations in order to collect experiential data and develop a complete and accurate risk-based approach to managing nanomaterials. However, additional research is needed to fill several remaining information gaps to better understand the occupational safety and health implications of nanomaterials. Additional research and information are needed in the following areas:

- Overall characterization of nanomaterial processes
- Prudent work practices to minimize and manage exposure to nanomaterials
- Engineering controls and PPE
- Worker training that addresses potential hazards that may be associated with nanomaterials
- Evaluation of analytical instruments and methods used to measure exposure to nanomaterials
- Quantitative and qualitative measurements of exposure to nanomaterials

In addition, NTRC is developing guidance for the occupational health surveillance of workers exposed to engineered nanomaterials. This guidance will address medical and biological monitoring, health record review, and the effectiveness of exposure registries.

For more information about recommendations and guidance on the safe handling, use, manufacturing, and processing of nanomaterials, visit the NIOSH nanotechnology Web site at www.cdc.gov/niosh/topics/nanotech.

9

Communication and Education

Background

Communication and education are integral components infused throughout the NTRC research program, and they are closely related to the NIOSH research-to-practice (r2p) program, which is geared towards converting research results into safety and health information useful for workers and employers. As a result, communication and education is one of the 10 critical topic areas in addressing knowledge gaps, developing strategies, and providing recommendations concerning nanotechnology exposure.

NTRC has identified the following goals and deemed them as critical to ensuring that relevant and applicable safety and health information is available to various target audiences:

- Establish partnerships to identify and share research needs and findings
- Develop communication materials that provide the target audience with useful and appropriate scientific information

- Disseminate research findings through communication methods suitable to the target audience
- Develop effective communication and educational materials to assist in reducing occupational exposure to nanomaterials
- Develop a global collaboration with partners interested in nanotechnology communication and education

NTRC communicates with a broad range of audiences including employers, workers, safety and health professionals, researchers, congressional offices, and the media. Therefore, it is important to ensure that each audience (1) receives information in a way that is appropriate and beneficial and (2) has the potential to increase occupational safety and health within the field of nanotechnology.

NTRC Communication and Education Projects

Communication and education has a role in each of the critical topic areas. To advance knowledge and understanding of the potential impact that nanotechnology and exposure to nanomaterials has in the workplace, NTRC is doing the following:

- Developing and maintaining an in-depth Web page dedicated to nanotechnology research on the NIOSH public Web site
- Creating and disseminating a brochure that describes the NTRC research program and provides general information about nanotechnology
- Establishing and managing an online information library that contains resources about nanoparticles (Nanoparticle Information Library [NIL])
- Sponsoring international symposia on nanotechnology
- Developing documents that contain guidance and recommendations on the applications and implications of exposure to nanomaterials in the workplace
- Publishing research findings in scientific, peer-reviewed publications

For more information about communication and education as well as nanotechnology information dissemination strategies by NTRC, see Appendix E.

Collaborations and Partnerships

To leverage resources and maximize the number of employers and workers who receive information about potential safety and health effects of

nanomaterials, NTRC has built global collaborations with stakeholders and organizations. These collaborations encourage researchers, industries, government officials, and labor organizations to develop sound communication and education strategies that increase knowledge, awareness, and understanding of emerging nanotechnologies and the potential health implications of exposure to nanomaterials in the workplace. NTRC has built collaborations with groups such as the following:

- Nanoparticle Occupational Safety and Health Consortium
- Nanoscale Science, Engineering, and Technology Subcommittee of the U.S. National Science and Technology Council
- National Toxicology Program
- AIHA
- International Council on Nanotechnology
- ISO
- ASTM International
- World Health Organization (WHO)
- OECD

In addition, NTRC is a member of several national and international committees and working groups, including the Organization Resource Council (ORC) Nanomaterials Work Practices Workgroup, the ISO Technical Committee on Nanotechnology, the International Advisory Committee for the Third International Symposium on Nanotechnology in Taiwan, and the International Commission on Occupational Health Meeting Session on Nanotechnology in Milan, Italy.

Accomplishments

NTRC has developed several communication and educational products that provide workers with up-to-date information about nanotechnology and the potential safety and health risks from exposure to nanomaterials. These products include a nanotechnology topic page on the NIOSH Web site, documents and brochures, presentations, and an electronic resource that contains information about nanoparticles.

The NIOSH Nanotechnology topic page (www.cdc.gov/niosh/topics/nanotech) was updated in 2006 and currently includes the following information:

- The NIOSH role in nanotechnology
- Ten critical topic areas for NIOSH nanotechnology research
- Interim recommendations (*Approaches to Safe Nanotechnology: An Information Exchange with NIOSH)* that invite the public to provide comments
- Frequently Asked Questions about nanotechnology
- News and events
- A nanoparticle information library (NIL) developed by NTRC in partnership with national and international agencies. NIL is a searchable database that will help occupational health professionals, industry users, worker groups, and researchers organize and share information about nanomaterials.

NTRC has conducted training and education courses on occupational safety and health within nanotechnology for various national and international organizations. In addition, NTRC has participated in professional development courses with the American Society of Safety Engineers (ASSE), AIHA, the Industrial Accident Prevention Association (IAPA), and several North Atlantic Treaty Organization (NATO) countries. NTRC staff have also provided presentations and participated in expert panel discussions at numerous meetings, workshops, and conferences about nanotechnology both nationally and internationally, and published more than 70 manuscripts in scientific, peer-reviewed journals.

Additional Research Needs and Future Direction

NTRC will continue to expand and update its communication and educational products as more data become available on the exposures to nanomaterials in the workplace, and on the impact that exposure to nanomaterials has on workers. These products will be available to provide information and education to workers, companies, and educational institutions to prevent worker exposure to nanomaterials and reduce potential risk of occupational injury and illness.

10

Applications

Background

The unique properties and characteristics of nanomaterials may provide the basis for innovative new devices, products, or processes to reduce risks of work-related injuries and illnesses. Such innovations may have properties or capabilities that cannot be created or manufactured using conventional materials.

NTRC Application Projects

NIOSH has funded a number of research projects looking at applications of nanotechnology to develop advanced protective gear and sensors, both intramurally and extramurally. For more information about programs funded through the NIOSH Office of Extramural Programs, see Appendix D.

Collaborations and Partnerships

To advance the application of nanotechnology in the workplace, NTRC is building and establishing national and international partnerships. Currently, NTRC is collaborating with Carnegie Mellon University to develop a sensor that can be placed in a respirator to warn the user of inward chemical leakage through the respirator filter. NTRC is also working with the Georgia Institute of Technology to develop a thermal warning system to protect firefighters from extreme temperatures, and a sensor that can be used by emergency responders to detect biological threats.

Accomplishments

The NTRC Applications research program is in its early development stages. Research is primarily focused on improving worker safety and health by applying emerging nanotechnologies in the workplace such as sensors to warn workers of a hazardous exposure or develop better materials that can be used in making protective equipment and clothing.

Within NTRC and through partnerships and collaborations, the Applications Team has accomplished the following:

- Developed a methodology to identify emerging nanotechnologies that may pose a safety and health risk to workers
- Developed a prototype sensor that can detect organic vapors and be embedded into respirator cartridges

- Developed a noninvasive bio-monitoring capability to evaluate exposure to organophosphorus insecticides
- Developed an extremely sensitive, low-temperature, low-cost, and miniaturized sensor that can be mounted inside a respirator to warn users when toxic organic vapors are inside the respirator
- Designed, developed, and demonstrated improved sensor technology for detecting hydrogen sulfide

Additional Research Needs and Future Direction

NTRC will continue to monitor the emergence of new nanotechnologies and evaluate their implications for improving and/or harming worker safety and health. Such evaluations may lead to new recommendations to protect workers from exposure to nanomaterials.

Appendix A

Project-Specific Progress Reports

Table 1 identifies the 10 critical topic areas that are addressed within each of the research projects conducted by NTRC. Details about each project (including accomplishments, publications and presentations, and partnership activities) are also described following this table.

Table 1. Overview of the 10 critical topic areas addressed in research projects

Project number and/or category	Toxicology and internal dose	Risk assessment	Epidemiology and surveillance	Engineering controls and PPE	Measurement methods	Exposure assessment	Fire and explosion safety	Recommendations and guidance	Communication and education	Applications
Project 1	x				x					
Project 2	x									
Project 3	x									
Project 4	x									
Project 5	x				x					
Project 6	x									
Project 7	x									
Project 8	x									
Project 9	x									
Project 10	x									
Project 11					x	x			x	x
Project 12	x	x				x		x		
Project 13				x	x	x	x	x		
Project 14					x	x				
Project 15				x				x		
Project 16				x				x		
Project 17	x	x					x	x	x	
Nanotechnology information dissemination					x	x		x	x	
Office of the director partnership activities								x	x	

Research Program (Projects 1-10): Nanotechnology Safety and Health Research Program

Program Coordinator: Vincent Castranova, Ph.D., HELD/ NIOSH/CDC

Progress Report: FY 2004–FY 2006

Background

Nanotechnology is one of the fastest growing emerging technologies in the United States and across the world. Defined as the manipulation of matter at near-atomic scales to produce new materials, structures, and devices with unique properties, nanotechnology has potential applications for integrated sensors, semiconductors, medical imaging, drug delivery systems, structural materials, sunscreens, cosmetics, and coatings. By 2015, the global market for nanotechnology-related products is predicted to reach $15 trillion and to employ 1 million workers in the United States.

Engineered nanoparticles are defined as having one dimension smaller than 100 nm. Because of their small size, nanoparticles exhibit unique physical and chemical properties not associated with similar materials in the micrometer scale. These unique properties, small size, and high surface area may result in biological responses to exposure not observed with fine particles of the same composition.

To address the critical need to determine whether workers could be at risk of adverse health effects as a result of exposure to nanomaterials, NIOSH funded the Nanotechnology Safety and Health Research Program in February 2004. The original research program included the first six projects listed below:

Project 1

- Generation and Characterization of Occupationally Relevant Airborne Nanoparticles
- Principal Investigators: Bon-Ki Ku, Ph.D., and Doug Evans, Ph.D.

Project 2

- Pulmonary Toxicity of Carbon Nanotube Particles
- Principal Investigators: Anna Shvedova, Ph.D., and Paul Baron, Ph.D.

Project 3

- Role of Carbon Nanotubes in Cardiopulmonary Inflammation and COPD-Related Disease
- Principal Investigators: Michael Luster, Ph.D., and Petia Simeonova, Ph.D.

Project 4

- Particle Surface Area as a Dose Metric
- Principal Investigator: Vincent Castranova, Ph.D.

Project 5

- Ultrafine Aerosols from Diesel-Powered Equipment
- Principal Investigator: Aleksander Bugarski, Ph.D.

Project 6

- Nanotechnology Safety and Health Research Coordination
- Principal Investigator: Vincent Castranova, Ph.D.

Research activities of this program cover aerosol generation and characterization studies in the laboratory and in the field, toxicity studies investigating the significance of aerosol surface area as a dose metric, and cardiopulmonary toxicity and lung disease related to carbon nanotubes and other nanoparticles.

In October 2005, the original research program was augmented with the approval of a program expansion "Research Gaps Unaddressed in the Initial Nanotechnology Safety and Health Research Program." This expansion added the following three projects to the original program:

Project 7

- Systemic Microvascular Dysfunction: Effect of Ultrafine vs. Fine Particles
- Principal Investigator: Vincent Castranova, Ph.D.

Project 8

- Pulmonary Deposition and Translocation of Nanomaterials
- Principal Investigators: Robert Mercer, Ph.D., and James Antonini, Ph.D.

Project 9

- Dermal Effects of Nanoparticles
- Principal Investigators: Anna Shvedova, Ph.D., and Min Ding, Ph.D.

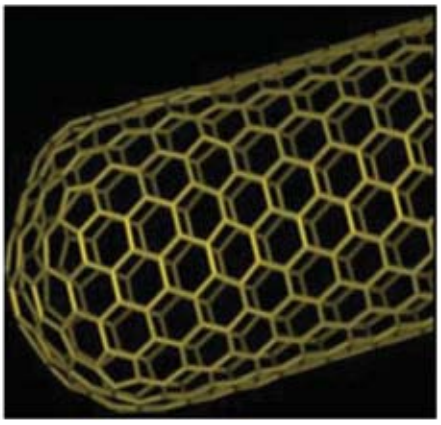
These additional three projects augment the original research program by investigating the ability of nanoparticles, once deposited in the lung, to enter the blood and translocate to systemic tissue. Effects on systemic microvascular function and resistance will be evaluated. These new projects will also evaluate effects of nanoparticles on the skin.

In FY 2006, a new project was added to investigate the pulmonary and neural effects of pulmonary exposure to an incidental nanoparticle welding fume.

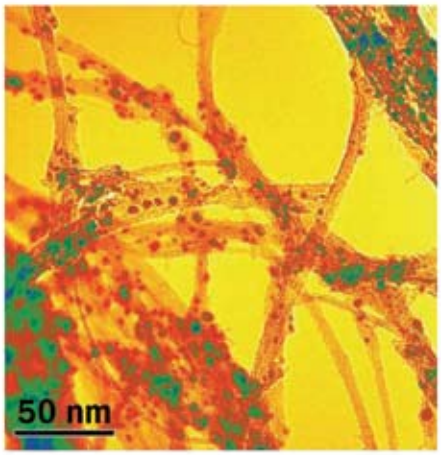
Project 10

- Neurotoxicity after Pulmonary Exposure to Welding Fumes Containing Manganese
- Principal Investigators: James Antonini, Ph.D.; Diane Miller, Ph.D.; and James O'Callaghan, Ph.D.

Unique structures and morphologies
of SWCNTs



- 1.4 nm in diameter
- Micrometers in length
- Unique physical, chemical and electronic properties



TEM

Project 1: Generation and Characterization of Occupationally Relevant Airborne Nanoparticles

Accomplishments

- Developed and fully characterized an in-situ nanoparticle generation facility for evaluating instrument response to tightly controlled particle morphology and size.
- Evaluated aerosol instrumentation for monitoring nanoparticle aerosols in real time.
- Evaluated three methods of estimating aerosol surface area (diffusion charging, transmission electron microscopy, and differential mobility analysis) and showed that these methods provide comparable measurements of aerosol surface area for particles smaller than 100 nm in diameter over a range of particle shapes.
- Characterized the morphology of SWCNTs in aqueous suspension in support of Project 2.
- Characterized the morphology of a SWCNT aerosol generated for a mouse inhalation study in support of Project 2.
- Selected and obtained various commercially available nanomaterials and performed preliminary screening of physical properties through collaboration with Project 11 and in support of Project 4.
- Developed and conducted preliminary testing of a nanomaterial redispersion system for nanoscale TiO_2 in support of Project 4. The system includes a flexible nonradioactive aerosol neutralization device.
- Constructed a flow and humidity control system for the nanomaterial redispersion system above in support of Project 4. Determined that high humidity has a serious adverse effect on redispersion of powdered nanomaterials.
- Completed preliminary testing of an electro-spray aerosol generation system to produce aerosols of nanoparticles in support of Project 4.
- Evaluated the airborne levels of SWCNTs during synthesis and handling in a laboratory setting.
- In collaboration with the University of Minnesota, used real-time new instrumentation (serial measurements of particle mobility and mass) combined with TEM analysis to obtain information about the relationship between particle morphology and particle properties of irregularly shaped nanoparticles.

- Observed anomalous behavior in state-of-the-art aerosol measurement instrumentation. These findings are anticipated to lead to the development of effective monitoring methods and new and improved instrument designs that are needed for accurate characterization of worker exposures.
- Evaluated particle sizing instrument responses to airborne carbon nanotubes and nanofibers.
- In support of a NIOSH extramural project, collaborated with University of Cincinnati researchers in the performance evaluation of a wet-electrostatic precipitator for diesel engine exhaust after-treatment.
- In collaboration with the University of Iowa:
    1. Conducted the first workplace study of ultrafine and nanoparticle mapping. Mapped ultrafine number concentration, active surface area and respirable mass concentration in an engine machining facility.
    2. Demonstrated the appropriate selection and use of mobile sampling equipment for effective monitoring of ultrafine and nanoparticles in workplaces.
    3. Demonstrated that the contribution of emissions from direct gas-fired heating systems can dominate ultrafine particle concentrations within a workplace.
    4. Mapped ultrafine number concentrations, active surface area, and respirable mass concentrations in an automotive foundry and demonstrated some limitations in mapping procedures.
    5. Conducted field research to help identify cause of high ultrafine particle concentration formation from direct gas-fired heating systems.

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- Evans D [2006]. Field measurement of nano-aerosols. International Conference on Nanotechnology. Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH, December 4–7.

Project 2: Pulmonary Toxicity of Carbon Nanotube Particles

Accomplishments

- Measured the generation of hydroxyl radicals by unpurified SWCNTs. Determined that this radical generation was due to iron contamination of the nanotubes.
- Measured oxidant stress and injury to human keratinocytes and human bronchial epithelial cells exposed to unpurified single-walled carbon nanotubes in culture.
- Determined that acid treatment removes contaminating iron from SWCNTs. Found that these purified nanotubes do not generate radicals and are not avidly phagocytized by macrophages in culture.
- Exposed mice to purified SWCNTs by pharyngeal aspiration. Observed transient inflammation and damage but a rapid and progressive fibrotic response in the lungs. Agglomerates were associated with fibrosis in granulomatous lesions; while more dispersed structures resulted in progressive diffuse interstitial fibrosis.
- In vitro exposure of macrophages to purified SWCNTs indicates that the nanotubes are not avidly phagocytized and do not stimulate an oxidative burst reaction. In vivo exposure of the lung also supports the lack of avid phagocytosis by the alveolar macrophages that correlates with the absence of persistent inflammation.
- Adsorption of phosphatidylserine (but not phosphatidylcholine) on the SWCNT surface makes them recognizable by macrophages indicating potentially promising approaches to modulating their fate in the lung.
- A generation system was developed to produce aerosols of SWCNTs for an inhalation study. Inhalation exposure studies have been taking place during the summer of 2006.

Publications and Abstracts

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- Castranova V [2005]. Pulmonary response to exposure to carbon nanotubes. Korean Society of Toxicology, Seoul, South Korea, May 13.
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- Shvedova A [2004]. Pulmonary toxicity of carbon nanotubes. International Congress on Nanotechnology, San Francisco, CA, November 7–10.
- Shvedova A [2004]. Pulmonary toxicity of SWCNT. National Nanotechnology Infrastructure Network (NNIN) meeting Nanosafe: A Workshop on Environmental Health and Safety in Nanotechnology Research, Georgia Institute of Technology, December 2.
- Shvedova A [2004]. Pulmonary toxicity of carbon nanotubes: what we know and what we do not know. National Nanotechnology Infrastructure Network (NNIN): Nanosafe: A Workshop on Environmental Health and Safety in Nanotechnology Research, Atlanta, GA, December 1–3.
- Shvedova A [2005]. Pulmonary oxidative stress, inflammation, and fibrosis induced by single wall carbon nanotubes. 2nd International Symposium on Nanotechnology and Occupational Health, Minneapolis, MN, October 3–6.

- Shvedova A [2005]. Pulmonary toxicity of carbon nanotubes. 8th International Conference on Mechanisms of Action of Inhaled Fibers, Particles, and Nanoparticles in Lung and Cardiovascular Diseases, Research Triangle Park, NC, October 25–28.
- Shvedova A [2005]. Comparative toxicity of nanomaterials in vivo and in vitro. 229th American Chemical Society Meeting. San Diego, CA, March 12–16.
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- Shvedova A [2005]. Unusual pulmonary response to carbon nanoparticles. First Annual Meeting of American Academy of Nanomedicine. John Hopkins University, MD, August 15–16.
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- Shvedova A [2005]. Pulmonary toxicity of carbon nanotubes. 8th International Conference on Mechanisms of Action of Inhaled Fibers, Particles, and Nanoparticles in Lung and Cardiovascular Disease, Research Triangle Park, NC, October 25–28.
- Shvedova A [2005]. Oxidative stress and pulmonary toxicity of carbon nanotubes. 1st International Meeting Nanotoxicology: Biomedical Aspects, Miami Beach FL, January 28–February 1.
- Shvedova A [2006]. Single-walled carbon nanotubes induced oxidative stress, acute inflammation and progressive pulmonary fibrosis. 45th Society of Toxicology Meeting, San Diego, CA, March 12–18.
- Shevedova A [2006]. Pulmonary effects of single-walled carbon nanotubes. International Conference on Nanotechnology, Occupational and Environmental Health & Safety; Research to Practice, Cincinnati, OH, December 4–7.
- Shevedova A [2006]. Pulmonary toxicity of single-walled carbon nanotubes. Karolinska Institute Nanotechnology Symposium. Stockholm, Sweden, November 15.

Project 3: Role of Carbon Nanotubes in Cardiopulmonary Inflammation and COPD-Related Diseases

Accomplishments

- Mice were exposed to purified SWCNTs by pharyngeal aspiration and cardiopulmonary responses at 1, 7, 28, 56, and 180 days post-exposure were monitored.
- At days 7, 28, 56, and 180 post-exposure to carbon nanotubes, observed mitochondrial DNA damage and increased production of reactive oxygen species in aortic tissue.
- Found that pulmonary exposure to carbon nanotubes induced similar oxidative modification in aortic tissue of ApoE-1-mice, an atherosclerosis model.
- Pulmonary exposure to carbon nanotubes induced activation of the oxidative gene, heme-oxygenase-1, in lung, heart, and aortic tissue.
- Chronic exposure of mice (four instillations of 20 µg per mouse every other week for 2 months) to purified SWCNTs induced enhanced atherosclerosis progression in ApoE-/- mice especially if the mice were fed a fat chow.
- The body weights, plasma cholesterol, glucose, and lactate dehydrogenase (LDH) levels were comparable in SWCNT- and vehicle-exposed mice under both diet regimens indicating that the enhanced progression of cardiovascular disease by SWCNTs is not due to altered lipid profiles.
- The plaque area analyzed by aortic morphometric *en face* analysis demonstrated a significant increase in the atheroma formation in SWCNT-exposed mice compared with the control-treated mice.
- Histological assessment of the lesion size in the brachiocephalic arteries of these mice confirmed that SWCNT exposure accelerated atherosclerosis progression compared with the control treatment.
- Although the plaques were larger in the SWCNT-exposed mice, the cellular composition of the plaques was similar to that of control-exposed mice.
- SWCNT-induced atherosclerosis acceleration was not associated with significant differences in the plasma levels of inflammatory cytokines including IL–6, IL–10, MCP–1, TNF–α, and IFN–*y*.
- Preliminary data demonstrated that SWCNT-induced atherogenic effects are associated with mitochondrial distress mediated endothelial

dysfunction and alterations in platelet properties (increased thrombogenic potential).

Publications and Abstracts

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Invited Presentations

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- Luster M [2005]. Nanoparticles toxicity issues. Ramazzini Collegium, Bologna, Italy, September.
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- Simeonova P [2005]. Nanoparticles—toxicological approaches. First Annual Scientific Meeting of the American Academy of Nanomedicine, Baltimore, MD, August 15–16.
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- Simeonova P [2006]. Cardiovascular effects of nanoparticles. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research on Practice, Cincinnati, OH, December 4–7.

Project 4: Particle Surface Area as a Dose Metric

Accomplishments

- Measured the particle surface area and mass of ultrafine and fine TiO_2, ultrafine and fine carbon black, and fine and coarse crystalline silica samples.
- Measured the surface area and cell numbers of primary rat alveolar macrophages and a human alveolar type II epithelial cell line in culture.
- Evaluated the toxicity of silica, TiO_2, and carbon black of different particle sizes using a mass-based and a surface-based dose metric with macrophages and type II cells. Found that silica was the most toxic of the particles tested.
- Evaluated the ability of the above particles to stimulate production of an inflammatory chemokine (IL–8 or MIP–2) by human type II cells or rat alveolar macrophages, respectively. Found that silica was the most potent stimulant of chemokine production.
- Evaluated the dose-dependent pulmonary response to intratracheal instillation of ultrafine and fine carbon black 24 hours post-exposure. Found that on an equivalent mass basis ultrafine carbon black was more inflammatory.
- Developed an improved method to disperse nanoparticles using bronchoalveolar lavage fluid for in vitro and in vivo testing.
- Demonstrated that the improved dispersal method increased the inflammatory potency of ultrafine carbon black after intratracheal instillation.

Publications and Abstracts

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Invited Presentations

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- Castranova V [2004]. Potential toxicity of nanoparticles. 2004 Northwest Occupational Health Conference, Portland, OR, October 14.
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- Castranova V [2005]. Health issues for nanoparticles and nanotubes. Australian National Council Nanotechnology Network, Canberra, Australia, July 25.
- Castranova V [2005]. Nanotechnology safety and health research in NIOSH. Korean Occupational Safety and Health Administration, Daejeon, South Korea, May 12.
- Castranova V [2005]. Toxicity of ultrafine particles. Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, Australia, July 14.

- Castranova V [2005]. Toxicity of ultrafine particles. Centre for Nanoscience and Nanotechnology, University of Melbourne, Melbourne, Australia, July 14.
- Castranova V [2005]. Toxicity of ultrafine particles. Ian Wark Research Institute, University of South Australia, Adelaide, Australia, July 26.
- Castranova V [2005]. Toxicity of ultrafine particles. NASA Scientific Group, January 19.
- Castranova V [2006]. Nanotoxicology program in NIOSH. NANOMIST Workshop. London, England, November 15.
- Castranova V [2006]. Nanotoxicology research in NIOSH. American Industrial Hygiene Conference, Chicago, IL, May 16.
- Castranova V [2006]. Nanotoxicology research in NIOSH. Nanobusiness 06, New York, May 19.
- Castranova V [2006]. Nanotechnology safety and health research in NIOSH. EPA, Research Triangle Park, NC, July 25.
- Castranova V [2006]. Pulmonary effects of exposure to single-walled carbon nanotubes. Wright Patterson Air Force Research Center. Dayton OH, October 31.
- Castranova V [2006]. Pulmonary toxicology studies with nanoparticles: experimental issues. Informa Learning's Conference on Nanotoxicology, Cambridge, MA, April 25.
- Castranova V [2006]. Toxicity of ultrafine particles. Nanotechnology Center, Ohio State University, Columbus, OH, February 24.
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- Porter D [2006]. Overview of NIOSH nanotoxicology research. Michigan Regional Chapter of the National Society of Toxicology, Augusta, MI, May 19.
- Porter D [2005]. Particulate handling in the human lung. Biological Effects of Lunar Dust Workshop, Sunnyvale, CA, March 29–31.
- Porter D [2005]. Toxicity of ultrafine particles. Nanotechnology: Occupational Safety and Health Perspectives. 21st Annual Kentucky Governor's Safety and Health Conference and Exposition, Louisville, KY, May 11.

Project 5: Ultrafine Aerosols from Diesel-Powered Equipment

Accomplishments

- Developed a diesel and nanoparticle research facility at the Lake Lynn Laboratory. Designed and built 150- and 400-kw engine/dynamometer systems; designed and built downstream, upstream, and tailpipe sampling and measurement stations; designed and built ventilation control and measurement facilities; developed and evaluated particle sampling, measurement, and analysis methodologies.
- Selected, acquired, and evaluated instrumentation for characterization of physical and chemical properties of diesel aerosols and gases.
- Conducted a field study in an underground mine using diesel mining vehicles. The Scanning Mobility Particle Sizer, Tapered Element Oscillating Microbalance, and carbon analysis were used to determine and characterize particulate matter in the mine air downstream of the tested vehicles.
- Developed protocols and conducted preliminary evaluation of the effects of emission controls, clean engines, and fuel formulations on the emission of fine and ultrafine diesel particles.
- Developed methods for sampling and analysis of in vitro mutagenic and DNA and chromosomal damage activity by surfactant dispersion or solvent extract of a diesel aerosols.

Publications and Abstracts

- Bugarski A [2004]. Characterization of diesel aerosols in an underground metal mine. Proceedings of 8th ETH-Conference on Combustion Generated Nanoparticles (CD-ROM), August 16–18.
- Bugarski A, Mischler S, Schnakenberg G [2005]. Affects of alterative fuels on concentrations of nanometer and ultrafine particles in an underground mine. In: Proceedings of 9th ETH-Conference on Combustion Generated Nanoparticles (CD-ROM), Zurich, Switzerland, August 15–17.
- Bugarski A [2006]. Characterization of combustion generated nanometer and ultrafine aerosols emitted in work environment. 10th ETH-Conference on Combustion Generated Nanoparticles (CD-ROM), Zurich, Switzerland, August 21–23.
- Bugarski AD, Schnakenberg GH Jr., Noll JD, Mischler SE, Patts LD, Hummer JA, Vanderslice SE [2006]. Effectiveness of selected diesel particulate

matter control technologies for underground mining applications: isolated zone study, 2003. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH RI 9667.

- Mischler S, Bugarski A, Schnakenberg G [2005]. Analysis of diesel particulate matter control technologies and measurements in US metal mines. Proceedings of 8th International Mine Ventilation Congress, Brisbane, Queensland, Australia, July 6–8.
- Shi, XC, Keane M, Ong T, Harrison J, Gautam M, Bugarski A, Wallace W [2006]. In vitro mutagenic and DNA and chromosomal damage activity by surfactant dispersion or solvent extract of a reference diesel exhaust particulate material. 12th Diesel Engine-Efficiency and Emission Research (DEER), August 20–24.

Project 6: Nanotechnology Safety and Health Research Coordination

Accomplishments

- Organized a retreat of NIOSH aerosol scientists August 25–27, 2004 to formulate a strategic plan and discuss research progress in nanotechnology. Dr. Lang Tran from the Institute of Occupational Medicine, Edinburgh, Scotland was the guest speaker.
- Organized a second retreat of NIOSH aerosol scientists August 23–25, 2005 to update the strategic plan and discuss research progress in nanotechnology. Dr. Pratim Biswas from Washington University in St. Louis, Missouri, was the guest speaker.
- Submitted annual reports to the Office of the Director, NIOSH.

Project 7: Systemic Microvascular Dysfunction—Effect of Ultrafine versus Fine Particles

Accomplishments

- Constructed and tested a generator of ultrafine TiO_2 for rat inhalation studies. A stable output was achieved.
- Initiated dose-response inhalation studies. Monitored the pulmonary response to the first test concentration. Monitored the systemic microvascular response to the first two test concentrations. Thus far, the systemic microvascular response to ultrafine TiO_2 is greater than to fine TiO_2.

Publications and Abstracts

- Nurkiewicz TR, Porter DW, Barger M, Hubbs AF, Millecchia L, Rao K, Chen BT, Frazer D, Castranova V, Boegehold MA [2006]. Peripheral microvascular dysfunction follows ultrafine titanium dioxide inhalation. Health Effects Institute Annual Conference, San Francisco, CA, April.
- Nurkiewicz TR, Porter DW, Barger M, Millecchia L, Rao KM, Marvar PJ, Hubbs AF, Castranova V, Boegehold MA [2007]. Systemic microvascular dysfunction and inflammation after pulmonary particulate matter exposure. Environ. Health Perspect. *114*:412–419.
- Nurkiewicz TR, Porter DW, Hubbs AF, Millecchia L, Stone S, Chen BT, Frazer D, Castranova V, Boegehold M [2007]. Inhalation of ultrafine titanium dioxide augments particle-dependent microvascular dysfunction. FASEB J 21.

Invited Presentations

- Castranova V [2005]. Microvascular dysfunction resulting from pulmonary exposure to particles. Research School of Physical Sciences and Engineering, Australian National University, Canberra, Australia, July 27.
- Castranova V [2005]. Microvascular dysfunction resulting from pulmonary exposure to particles. Asan Medical College, Seoul, Korea, May 16.
- Castranova V [2005]. Microvascular dysfunction resulting from pulmonary exposure to particulate matter. 2005 Conference on the Application of Systems Biology Methodologies to Environmental Research, Morgantown, WV, August 1.

Project 8: Pulmonary Deposition and Translocation of Nanomaterials

Accomplishments

- Developed a method to improve dispersal of SWCNTs for pharyngeal aspiration.
- Developed a method to label SWCNTs with colloidal gold or quantum dots to track their distribution and fate upon pulmonary exposure.
- Demonstrated that low doses of purified and dispersed (sub-micron) SWCNTs are capable of widely distributing in the lungs where they are incorporated into the alveolar interstitium and produce a fibrotic response.
- Demonstrated that iron-rich SWCNTs induce elevated biomarkers of oxidative stress.

Publications and Abstracts

- Kagan VE, Tyurina YY, Tyurin VA, Konduru NV, Potapovich AI, Osipov AN, Kisin ER, Schwegler-Berry D, Mercer RR, Castranova V, Shvedova AA [2006]. Direct and indirect effects of single walled carbon nanotubes on RAW 264.7 macrophages: Role of Iron. Toxicol Lett *165*:88–00.
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Invited Presentations

- Mercer R [2005]. Lung parenchymal responses to carbon nanotubes. 2nd International Symposium on Nanotechnology and Occupational Health, Minneapolis, MN, October 3–6.

- Mercer R [2006]. Distribution of SWCNT in the lungs. Nanotoxicology: Biomedical Aspects, Miami, Fl, January 28–February 1.
- Mercer R [2006]. Inhalation toxicity of single-walled carbon nanotubes. Society for Risk Assessment. Tripartite teleconference, June.
- Mercer R [2006]. SWCNT distribute and injure the lungs in a size dependent manner. New York Occupational Safety and Health Research Center, New York, April.

Project 9: Dermal Effects of Nanoparticles

Accomplishments

- Demonstrated that exposure of human keratinocytes in vitro to unpurified SWCNTs resulted in significant cytotoxicity. Purification of SWCNT to remove the iron catalyst particles resulted in less toxicity.
- Demonstrated that exposure to murine epidermal cells to unpurified SWCNT activated the transcription factor AP–1. Such activation was not seen with purified SWCNT.
- Demonstrated that exposure of mouse skin in vivo to unpurified SWCNT caused oxidant stress and inflammation.
- Demonstrated that in vitro exposure of epidermal cells to nanosized TiO_2 generated hydroxyl radicals, and activated AP–1 through phosphorylation of MAP kinase signaling pathways.

Publications and Abstracts

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- Murray AR, Kisin E, Castranova V, Kommineni C, Kagan VE, Shvedova AA [2006]. Oxidative stress and inflammatory response in dermal toxicity of single-walled carbon nanotubes. 1st International Toxicology of Nanomaterial: Biomedical Aspects Meeting, Miami Beach, FL, January 29–February 1, p. 50.
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Project 10: Neurotoxicity after Pulmonary Exposure to Welding Fumes Containing Manganese

Accomplishments

- Characterized the physical and chemical properties of generated welding aerosol.
- Compared the pulmonary, inflammatory, and immune responses after exposure to stainless steel and mild steel welding fumes.
- Designed and constructed a robotic welding fume generator and inhalation exposure system for laboratory animals.
- Initiated animal inhalation toxicity studies.
- Evaluated the translocation of welding fume metals from the lungs to other organ systems (e.g., central nervous system and cardiovascular system).
- Evaluated the potential neurotoxic effects in animals after inhalation of welding fume.

Publications and Abstracts

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- Antonini JM, Leonard SS, Robert JR, Solano-Lopez C, Young S-H, Shi X, Taylor MD [2005]. Effect of stainless steel manual metal arc welding fume on free radical production, DNA damage, and apoptosis induction. Mol Cell Biochem *279*:17–23.
- Antonini JM, Afshari AAA, Stone S, Chen B, Schwegler-Berry D, Fletcher WG, Goldsmith WT, Vandestouwe KH, McKinney W, Castranova, V, Frazer DG [2006]. Design, construction, and characterization of a novel robotic welding fume generation and inhalation exposure system for laboratory animals. J Occup Environ Hyg *3*:194–203.
- Antonini JM, Santamaria A, Jenkins NT, Albini E, Lucchini R [2006]. Fate of manganese associated with the inhalation of welding fumes: Potential neurological effects. Neurotoxicol *27*:304–310.

- Antonini JM, O'Callaghan JP, Miller DB, Miller DB [in press]. Development of an animal model to study potential neurotoxic effects associated with welding fume inhalation. Neurotoxicol.
- Santamaria AB, Cushing CA, Antonini JM, Finley BL, Mowat FS [in press]. Potential neurological effects of manganese exposure during welding: a state-of-the-science analysis. J Toxicol Environ Health.
- Solano-Lopez C, Zeidler-Erdely PC, Hubbs AF, Reynolds SH, Roberts JR, Taylor MD, Young S-H, Castranova V, Antonini JM [in press]. Welding fume exposure and associated inflammatory and hyperplastic changes in the lungs of tumor susceptible A/J Mice. Toxicol Pathol.
- Antonini JM, Roberts JR [2007]. Comparison of lung injury and inflammation after repeated treatment with welding fumes collected from different welding processes. The Toxicologist *91*(1).
- Zeidler-Erdely PC, Young S-H, Roberts JR, Antonini JM [2007]. Acute lung inflammatory response following pharyngeal aspiration of stainless steel welding fume or soluble chromium in A/J and C57Bl/6J mice. The Toxicologist *91*(1).

Invited Presentations

- Antonini J [2004]. Effect of workplace particulates on the susceptibility to bacterial infection and the suppression of lung defense responses in rats. Society of Toxicology Annual Meeting, Baltimore, MD, March.
- Antonini J [2004]. Bioavailability of manganese associated with the inhalation of welding fumes: potential neurological effects. Conference on Health Effects, Clinical Research, and Industrial Hygiene Issues in Occupational Exposure to Manganese, New Orleans, LA, April.
- Antonini J [2004]. Bioavailability of manganese associated with the inhalation of welding fumes: potential neurological effects. Conference on Welding—Industrial Hygiene and Occupational Health, American Industrial Hygiene Association, Pacific Northwest Section, Spring Meeting, Olympia, WA, April.
- Antonini J [2004]. Effect of welding fume metal composition and solubility on free radical production and lung inflammation and injury. 3rd Conference on Molecular Mechanisms of Metal toxicity and Carcinogenesis, NIOSH, September.
- Antonini J [2005]. Health effects on welding. American Industrial Hygiene Association Annual Meeting: AIHce 2005, Anaheim, CA, May.

- Antonini J [2005]. Development of an animal model to study the health effects of welding. Health Effects of Welding International Conference, sponsors: NIOSH, NIEHS, and West Virginia University, Morgantown, WV, July.
- Antonini J [2005]. Characterization of welding fumes and their neurotoxic effects. 22nd International Neurotoxicology Conference: Manganese Symposium, Research Triangle Park, NC, September.
- Antonini J [2005]. Development of an animal model to assess the effect of occupational particles on the susceptibility to bacterial lung infection. 8th International Meeting on Effects on Mineral Dusts and Nanoparticles, Research Triangle Park, NC, October.
- Antonini J [2006]. Suppression of lung defense responses after bacterial infection in rats exposed by inhalation to stainless steel welding particles. 1st International Conference on Nanotoxicology: Biomedical Aspects, Miami, FL, January.
- Antonini J [2006]. Characterization of welding fumes and their potential neurotoxic effects. International Workshop: Neurotoxic Metals—Lead, Mercury, and Manganese: From Research to Prevention: Brescia, Italy, June.

Nanotechnology Safety and Health Research Program (Projects 1–10)

National and International Activities and Conferences

- Maynard A [2004]. Co-organized the First International Conference First International Symposium on Occupational Health Implications of Nanomaterials from October 12–14 in Buxton, UK. The conference is co-sponsored by the UK Health and Safety Executive and NIOSH.
- Maynard A [2005]. Co-organized the Second International Symposium of Nanotechnology and Occupational Health, Minneapolis, MN, October 3–6.
- Castranova V [2005]. Co-organized the conference Mechanisms of Action of Inhaled Fibers, Particles, and Nanoparticles in Lung and Cardiovascular Disease, Research Triangle Park, NC, October 25–28.
- Castranova V, Maynard A [2005]. Served on an EPA Workgroup through the International Life Sciences Institute to draft a document entitled Screening Protocols for Nanomaterial Toxicity.
- Maynard A [2005]. Served as the NIOSH representative on the Nanomaterial Science Engineering and Technology Subcommittee of the National Science and Technology Council that develops guidance for the direction of Federal research in nanotechnology.
- Castranova V [2005 to present]. Serves on a scientific advisory committee for the Nanotechnology Research Institute at the University of Rochester.
- Castranova V [2006]. Served as an expert panel member: Health and Environmental Issues in Nanotechnology. Wilson Institute, Washington, DC, April 6.
- Castranova V [2006]. Served as a participant: National Nanotechnology Coordination Office Workgroup on Public Dissemination, Education, and Outreach. Arlington, VA, May 30–31.
- Shvedova A, Castranova V [2006]. Co-organized the Nanotoxicology: Biomedical Aspects Conference in Miami, FL, January 28–February 1. (The conference was co-sponsored by NIOSH and the University of Pittsburgh).
- Antonini J [2005]. Co-organized a NIOSH-sponsored international conference Health Effects of Welding, Morgantown, WV, July. The conference was co-sponsored by the National Institute of Environmental

Health Sciences (NIEHS), the Association of Occupational and Environmental Clinics, and West Virginia University.

- Antonini J [2006]. Serves as Vice Chair of the Safety and Health Committee for the American Welding Society.
- Simeonova P [2006]. Co-director of a NATO-funded Advanced Research Workshop Nanotechnology-Toxicological Issues and Environmental Security (CBP.EAP.ARW 982043), Varna, Bulgaria, August 12–17.
- Simeonova P [2006]. Co-chaired the Nanoparticles: Toxicology, Health Effects, Hazard Identification Session, Toxicology and Risk Assessment Conference, Cincinnati, OH, April 24–27.
- Simeonova P [2006]. Organized a presentation and discussions with Dr. Hussain, Air Force Laboratory on nanotoxicology risk assessment for NIOSH scientists. June 7.
- Simeonova P, Luster M [2006]. Organized a presentation and discussions on Nanomaterial Safety for NIOSH scientists with Dr. N. Walker, National Toxicology Program, July 12.

Dissemination (interviews and articles in lay press)

A. Maynard (Project 1), A. Shvedova (Project 2), and/or V. Castranova (Project 6) have been interviewed by the following press concerning NIOSH activities in Nanotechnology:

- *Nanobiotech News* 2, 20, pp. 2–3 (May 19, 2004)
- *Small Times* (May 19, 2004)
- *CN&E News* 82, 24 pp. (June 14, 2004)
- *Environmental Health Perspectives* 112, pp. A741–A749 (2004)
- *Science News:* Particular Problems: Assessing Risks of Nanotechnology, May 6, Vol. 169, pp. 280–281 (2006)
- *Science News*: How 'toxic' nanotubes were faking it. Interview with Science News writer from UK Mason Inman on June 3, 2006, published on NewScientist.com news service (June 5, 2006).

J. Antonini has been interviewed by the following press concerning the NIOSH welding project:

- *The Courier* (Louisiana), Business section (October 27, 2002)
- *Science 300*(5621):927 (May 9, 2003)

- *National Law Journal 127*(238) 3 (December 10, 2003)
- *Forbes*, p. 44 (February 2, 2004)
- *The Tennessean* (Nashville, TN), Business section, p. 1E (July 16, 2005).
- *The Synergist 16*(9):48–49 (October 2005)
- *The Plain Dealer*–Cleveland (June 2, 2006)
- *Associated Press* (June 12, 2006)

P. Simeonova was interviewed by the following press on research being conducted with SWCNTs:

- *NanoHazard, Science News* (March 19, 2005)

Partnerships and Collaborations

- J. Antonini established an interagency agreement with National Toxicology Program (NTP) to aid in the construction of a welding fume generation and animal exposure system to be used for NTP-sponsored chronic animal studies.
- J. Antonini has established a collaboration with the Manganese Health Research Program and Vanderbilt University (funded by the U.S. Department of Defense) to evaluate the effect of manganese in welding fume on neurotoxicity in laboratory animals.
- V. Castranova (Project 4) is collaborating with G. Oberdorster at the University of Rochester on the ability of nanoparticles to generate radical species.
- V. Castranova and D.W. Porter (Project 4) are collaborating with Dr. Chen at Oak Ridge Laboratory to evaluate the pulmonary toxicity of nanoparticles.
- A. Shvedova and V. Castranova (Projects 2 and 4) are collaborating with V. Kagan at the University of Pittsburgh on the toxicity of nanomaterials.
- Dr. Luster (Project 3) is collaborating with NIEHS/NIH and the Department of Defense on nanotoxicology.
- V. Castranova and D.W. Porter (Project 4) and P. Simeonova are collaborating with Mitsui Inc. and Dr. Endo (Japan) on pulmonary and cardiovascular toxicity of multi-walled carbon nanotubes.
- V. Castranova and D. Frazer are co-investigators on the extramural grant Microvascular dysfunction resulting from pulmonary exposure to fine versus ultrafine titanium dioxide funded by the Health Effects Institute, (7/05–6/08). Dr. Nurkiewicz, West Virginia University, PI.

- D. Evans collaborated with the University of Iowa on mapping measurement and characterization of airborne nanoparticles in the workplace.
- D. Evans collaborated with the University of Cincinnati for conducting a performance evaluation of a wet-electrostatic precipitator for diesel engine exhaust after-treatment.
- J. Ku and D. Evans established a partnership with the University of Minnesota on real-time measurement of nanomaterial structure.
- E. Kuempel and R. Mercer are collaborating on a model for nanoparticle deposition with Dr. Owen Price at CIIT, Research Triangle Park, NC.
- NIOSH PRL formed the Metal/Nonmetal Diesel Partnership with the National Mining Association (NMA), the National Stone Sand and Gravel Association (NSSGA), the United Steel Workers of America (USWA), the MARG Diesel Coalition and the Industrial Minerals Association—North America (IMA-NA) with the objective of reducing exposure of underground mines to diesel aerosols and gases.
- NIOSH PRL Diesel team is collaborating with the Mechanical and Aerospace Engineering Department of West Virginia University on modeling dispersion of diesel aerosol plume in underground mining environment.
- A. Shvedova (Project 2) has a MOU with NASA to evaluate the toxicity of single walled carbon nanotubes.
- A. Shvedova is collaborating with Dr. Bengt Fadeel, Karolinska University, Stockholm, Sweden; Dr. Kadiiska, NIEHS, Research Triangle Park, NC; and Dr. P. Quinn, Professor of the Department of Biochemistry, Kings College, University of London, London, UK; on oxidant generation by nanoparticles and resultant oxidant stress in exposed cells.
- A. Shvedova and V. Castranova are co-investigators on the extramural grant Oxidant stress induced by nanomaterials funded by NIOSH (7/05–6/08). Dr. Kagan, University of Pittsburgh, PA.
- P. Simeonova is collaborating with WVU, Medical School and Engineering Department, on nanomaterial toxicity and physicochemical properties.
- P. Simeonova is collaborating with the University of Rochester, Rochester, NY, Department of Environmental Medicine, with Dr. Gunter Oberdorster.

- P. Simeonova is collaborating with NIEHS/NTP, Research Triangle Park, NC, on fullerene toxicity and metal oxide nanomaterials.

NTRC Critical Research Topic Areas Addressed

1. Toxicity and Internal Dose [Projects 2–4 and 6–10]
2. Measurement Methods [Projects 1 and 5]

Research Project 11: Nanoparticles in the Workplace

Principal Investigator: Mark Hoover, Ph.D., DRDS/NIOSH/CDC

Project Duration: FY 2004–FY 2009

Background

The scope of the NIOSH Nanoparticles in the Workplace project is to foster the development of partnerships, exposure monitoring instrumentation, operational protocols, and a comprehensive and detailed database of nanoparticles and their properties. These activities are intended to provide NIOSH and the occupational safety and health community with a better understanding of the nature and extent of potential occupational exposures to nanoparticles. The results from these activities are expected to foster the development of comprehensive and scientifically sound occupational health protection strategies for emerging nanotechnologies. This work also supports NIOSH toxicology studies of nanomaterials. This project will enable NIOSH and the nanotechnology industries to better anticipate, recognize, evaluate, and control potential occupational exposures to nanoparticles during their manufacturing and use.

Accomplishments

- Partnerships were developed with nanotechnology industries, academia, government agencies, labor, and voluntary consensus standard committees to conduct joint research and develop guidelines on working safely with nanomaterials.
- Sampling protocols and safety management guidelines were developed to help characterize the extent of exposure to nanoparticles in the workplace.
- Partnerships were established with a fullerene research facility, an industrial nano-TiO_2 production facility, a cosmetics company, an industrial producer of ultrafine beryllium oxide materials, and a university research facility engaged in polymer work with carbon nanofibers to characterize occupational exposure to nanomaterials.
- Assistance was provided to the ISO in creating the new ANSI nanotechnology program, including the establishment of a nanotechnology technical committee.

- A new carbon nanotube reference material was developed and evaluated in collaboration with NIST.
- A new ultrafine beryllium oxide standard reference was developed in collaboration with NIST and the U.S. Department of Energy.
- The in-house capabilities for physico-chemical characterization of nanoparticles, especially as it relates to surface area, were established.
- The NIL Project (Web-based) was initiated to develop a database on nanomaterials.
- Partnership was established with TSI Incorporated on the characterization, under actual industrial field conditions, of the lung-deposited surface area aerosol sampling instrument.

Publications and Abstracts

- Castranova V, Hoover MD, Maynard A [2005]. NIOSH nanotechnology safety and health research program, in nanoparticles: a risk to health at work? Final Report of the First International Symposium on Occupational Health Implications of Nanomaterials, David Mark, ed., June, p. 117, http://www.hsl.gov.uk/media/1646/nanosymrep_final.pdf.
- Hoover MD [2005]. Mixed exposure issues for nanotechnology safety, in nanoparticles: a risk to health at work? Final Report of the First International Symposium on Occupational Health Implications of Nanomaterials, David Mark, ed., June, p. 115, http://www.hsl.gov.uk/media/1646/nanosymrep_final.pdf
- Hoover MD, Miller AL, Lowe NT, Stefaniak AB, Day GA, Linch KD [2005]. Information management for nanotechnology safety and health, in nanoparticles: a risk to health at work? Final Report of the First International Symposium on Occupational Health Implications of Nanomaterials, David Mark, ed., June, p. 110, http://www.hsl.gov.uk/media/1646/nanosymrep_final.pdf
- Northage C, Hoover MD [2005]. Report of workshop Group F on regulatory implications, in nanoparticles: a risk to health at work? Final Report of the First International Symposium on Occupational Health Implications of Nanomaterials, David Mark, ed., June, pp. 145–147, http://www.hsl.gov.uk/capabilities/nanosymrep_final.pdf.
- Phalen RF, Hoover MD [2006]. Aerosol dosimetry research needs. Inh Toxicol *18*(7–10):841–843.

- Stefaniak AB, Day GA, Scripsick RC, Hoover MD [2005]. Comprehensive characterization strategies for ultrafine particles: lessons from beryllium health and safety studies, in nanoparticles: a risk to health at work? Final Report of the First International Symposium on Occupational Health Implications of Nanomaterials, David Mark, ed., June, p. 118, http://www.hsl.gov.uk/media/1646/nanosymrep_final.pdf.
- Stefaniak AB, Hoover MD, Day GA, Ekechukwu AA, Whitney G, Brink CA, Scripsick RC [2005]. Characteristics of beryllium oxide and beryllium metal powders for use as reference materials. J. ASTM International, *2*(10):doi 10.1520/JAl13174.
- Watters RL, Hoover MD, Day GA, Stefaniak AB [2006]. Opportunities for development of reference materials for beryllium. J. ASTM International, *3*(1):doi 10.1520/JAl13171.

Invited Presentations

- Eshelman JC, Hoover MD, Petsonk EL, Antao VC, Trout DB, Schulte PA [2006]. Occupational Medicine Issues for Nanotechnology, American Occupational Health Conference, Los Angeles, CA, May 10.
- Hoover MD [2005]. NIOSH Nanotechnology Informatics Overview, NIOSH—Altair Nanotechnologies, Inc. Information Exchange Meeting, Reno, NV, April 19.
- Hoover MD [2004]. Mixed Exposure Issues for Nanotechnology Safety, 1st International Symposium on Nanotechnology and Occupational Health, Buxton, UK, October 11–14.
- Hoover MD [2004]. NIOSH Approaches to Safe Nanotechnology, 2006 NIST Safety Day Symposium, National Institute for Standards and Technology, Gaithersburg, MD, June 15.
- Hoover MD, Miller AL, Lowe NT, Stefaniak AB, Day GA, Linch KD [2004]. Information Management for Nanotechnology Safety and Health, 1st International Symposium on Nanotechnology and Occupational Health, Buxton, UK, October 11–14.
- Hoover MD, Hearl FA [2005]. NORA Mixed Exposures Research Agenda, Society of Toxicology Workshop on Contemporary Concepts In Toxicology Charting the Future: Building the Scientific Foundation for Mixtures Joint Toxicity and Risk Assessment, Atlanta, GA, February 16–17.

- Hoover MD [2005]. An Introduction to Nanotechnology and the Possible Hazards, Institute of Occupational and Environmental Health Lecture, West Virginia University, Morgantown, WV, March 1.
- Hoover MD [2005]. Lung Dosimetry of Boundary Fire Smoke Samples, Wildfire Symposium, Morgantown, WV, March 31.
- Hoover MD [2005]. Informatics for Nanotechnology Safety and Health, Round Table on the Role of the Occupational Safety and Health Professional in the Emerging Nanotechnology Industry, American Industrial Hygiene Conference and Exposition, Anaheim, CA, May 24.
- Hoover MD [2005]. Nanotechnology: Addressing Potential Health Impact, Council of State and Territorial Epidemiologists, Albuquerque, NM, June 6.
- Hoover MD [2005]. Planning for the Next Decade of NORA: Opportunities to translate Research into Practice through the National Occupational Research Agenda, Annual Meeting of the Health Physics Society, Spokane, WA, July 13.
- Hoover MD [2005]. Nanotechnology: Understanding and Addressing Potential Health Impacts, National Association of Scientific Materials Managers, Reno, NV, July 25.
- Hoover MD [2005]. Nanoparticles in the Workplace, NIOSH Nano-Aerosols 2005 Workshop, Oglebay, WV, August 24.
- Hoover MD [2005]. Nanotechnology: Understanding and Addressing Potential Health Impacts, Southern California Environmental Safety, Hygiene, and Health Joint Technical Symposium, Long Beach, CA, October 27.
- Hoover MD, Murashov V [2005]. National and International Standards Activities Related to Nanotechnologies, NIOSH NanoAerosols 2005 Workshop, Oglebay, WV, August 25.
- Hoover MD, Murashov V [2005]. Overview of National and International Standards Activities Related to Nanotechnologies and Draft Ideas for Discussion, U.S. Technical Advisory Group Meeting for ISO TC 229 Nanotechnologies, National Institute for Standards and Technology, Gaithersburg, MD, September 8.
- Hoover MD [2006]. Exposure Assessment for Nanotechnology, American Industrial Hygiene Conference, Chicago, IL, May 13–18.
- Hoover MD [2006]. Characterization of Nanoparticles in the Workplace, Ask the Expert session on the NIOSH Nanotechnology Research

Program, American Industrial Hygiene Conference, Chicago, IL, May 13–18.

- Hoover MD [2006]. NIOSH Approaches to Safe Nanotechnology, 2006 NIST Safety Day Symposium, National Institute of Standards and Technology, Gaithersburg, MD, June 15.
- Hoover MD [2006]. Nanoparticles in the Workplace, Campus Safety Health and Environmental Management Meeting, Anaheim, CA, July 19.
- Miller AL, Hoover MD [2006]. Building a Nanoparticle Information Library, National Occupational Research Agenda Symposium, Washington, DC, April 18–20.
- NIOSH NTRC [2006]. Approaches to Safe Nanotechnology: An Information Exchange with NIOSH. Conference on Commercialization of NanoMaterials 2006, Pittsburgh, PA, September 18–20.
- Schulte P, Geraci C, Zumwalde R, Hoover M, Castranova V, Murashov V, Howard J [2006]. Occupational Safety and Health Issues in Nanotechnology, 28th International Congress on Occupational Health, Milan, Italy, June 8–16.
- Miller AL, Hoover M [2005]. Building a Nanomaterial Information Library. Second International Symposium on Nanotechnology and Occupational Health, Minneapolis, MN, October 3–6.
- Birch ME, Evans DE, Methner MM, McCleery RE, Crouch KG, Ku B-K, Hoover MD [2006]. Workplace Assessment of Potential Exposure to Carbonaceous Nanomaterials. Second International Symposium on Nanotechnology and Occupational Health, Minneapolis, MN, October 3–6.
- Stefaniak AB, Day GA, Hoover MD [2006] Measurement Issues for Evaluating and Relating Nanoparticle Surface Properties to Bioaccessibility and Health. Workshop on Instrumentation, Metrology, and Standards for Nanomanufacturing, Gaithersburg, MD, October 17.
- Miller AL, Hoover MD [2006]. Building a Nanoparticle Information Library. Workshop on Instrumentation, Metrology, and Standards for Nanomanufacturing, Gaithersburg, MD, October 17.
- NIOSH NTRC [2006]. Approaches to Safe Nanotechnology: An Information Exchange with NIOSH. Workshop on Instrumentation, Metrology, and Standards for Nanomanufacturing, Gaithersburg, MD, October 17.

- NIOSH NTRC [2006]. NIOSH Nanotechnology Safety and Health Research Program. Workshop on Instrumentation, Metrology, and Standards for Nanomanufacturing, Gaithersburg, MD, October 17.

- NIOSH Control Banding Working Group [2006]. Potential Application of "Control Banding" for Safe Handling of Engineered Nanoparticles in the Workplace. Workshop on Instrumentation, Metrology, and Standards for Nanomanufacturing, Gaithersburg, MD, October 17.

- Hoover MD, Stefaniak AB, Methner MM, Ku BK, Geraci CL, Maher TV, Singh M [2006]. Evaluation of a Real-Time Surface Monitor in a Nanotechnology Workplace, International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

- Hoover MD [2006]. Science and Research Issues for Nanoparticle Measurements and Control, International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 7.

- Hull MS, Hoover MD, Geraci CL [2006]. Update on Understanding and Assessing an Emerging Technology in Practice: Continuation of an Innovative Industry/Government Partnership. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

- Miller AL, Hoover MD [2006]. Building a Nanoparticle Information Library. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

- Stefaniak AB, Day GA, Hoover MD [2006] Measurement Issues for Evaluating and Relating Nanoparticle Surface Properties to Bioaccessibility and Health. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

- Birch ME, Evans DE, Methner MM, McCleery RE, Crouch KG, Ku BK, Hoover MD [2006] Workplace Assessment of Potential Exposure to Carbonaceous Nanomaterials. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

- NIOSH NTRC [2006]. Approaches to Safe Nanotechnology: An Information Exchange with NIOSH. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.
- NIOSH NTRC [2006]. NIOSH Nanotechnology Safety and Health Research Program. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.
- NIOSH Control Banding Working Group [2006]. Potential Application of "Control Banding" for Safe Handling of Engineered Nanoparticles in the Workplace. International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7.

Future Presentations

- Hoover MD [2007] Characterizing and Controlling Exposures to Nanoparticles in the Workplace, American Industrial Hygiene Association Teleweb Nanoparticle Update: Measuring, Evaluating, and Managing Exposures, March 8.
- Hoover MD [2007] Measurement of Nanoparticles in the Workplace, Ask the Experts: An Update on NIOSH Research in Nanotechnology, American Industrial Hygiene Conference and Exposition, Philadelphia, PA, June 4.
- Hoover MD [2007] Exposure Assessment and Sampling Issues for Nanotoxicology and Safe Handling of Nanoparticles in the Workplace, American Industrial Hygiene Conference and Exposition, Philadelphia, PA, June 4.

National and International Activities

- Participated in the formation and activities of the ANSI Nanotechnology Standards Steering Panel, including activities resulting in the formation of the new ISO Technical Committee 229 on Nanotechnologies.
- Participating in the American Industrial Hygiene Association Nanotechnology Working Group, which is bringing together industrial hygiene expertise to develop educational programs, develop best practices, and share lessons learned.
- Participated on the organizing committee for the Frontiers in Respiratory Dosimetry meeting, which was held at the National Academies Center at the University of California, Irvine, CA, October.

- Co-organized the Nanotechnology and Health Symposium for the 2006 International Aerosol Conference in St. Paul, MN.
- Participated in the writing group to develop the new American Society of Testing and Materials (ASTM) International Committee E56 standard on Safe Handling of Unbound Nanoparticles.

Dissemination (interviews and articles in lay press)

Project participants were interviewed by the press for the following journals and articles concerning NIOSH activities in nanotechnology:

- *Inside OSHA*, *12*(16):10–11 (August 8, 2005)
- *Journal of the American Medical Association* (September 2005).
- *National Journal Technology Daily* (September 2005)
- *BNA Daily Report for Executives*, Nanotechnology: Small Nanotechnology Firms can be Leaders on Health, Safety Issues, Advisory Firm Says, *205*:A8 (October 25, 2005)
- *The Synergist*
- *Small Times*
- *Washington Post*

Partnerships and Collaborations

- Partnership with NIST to develop new standard reference materials for nanoparticles
- Partnership with Luna Innovations to characterize fullerenes in a nanotechnology research facility.
- Partnership with a primary nanoscale metal oxide manufacturer to characterize nanometal oxides in a commercial manufacturer setting.
- Partnership with a commercial cosmetics manufacturer to characterize and control exposures to nanomaterials in the production of cosmetics.

NTRC Critical Research Topic Areas Addressed

1. Exposure Assessment
2. Measurement Methods
3. Communication and Education
4. Applications

Research Project 12: Nanoparticles—Dosimetry and Risk Assessment

Principal Investigator: Eileen D. Kuempel, Ph.D., EID/NIOSH/CDC

Project Duration: FY 2004–FY 2009

Background

Risk assessment of occupational exposure to nanoparticles is needed to protect workers' health. Human data are limited on exposure, dose, and response to nanoparticles. However, data from studies in rodents are available to evaluate the dose-response relationships and estimate the exposures in workers that would be unlikely to cause adverse health effects. Using these data in risk assessment requires a scientifically reasonable approach to extrapolating the animal data to humans. One such approach is the use of biologically based lung dosimetry models. However, these models have not been fully evaluated and validated for predicting the deposition and clearance of inhaled nanoparticles. Furthermore, these models currently have limited capability to describe the translocation of nanoparticles beyond the lungs, as observed in rodent studies.

In this project, a current rat lung dosimetry model will be extended to include biologically relevant paths for the transport of nanoparticles to the blood and other organs as well as excretion. Data from the literature will be used to calibrate this model, and data from new studies at NIOSH and elsewhere will be used to validate the model. The model will be extrapolated to humans using human data where available (e.g., physiological parameters), and biologically based approaches to interspecies extrapolation will be applied to estimate from the rat model the parameter values not available in humans. These lung dosimetry models will be used in conjunction with rodent dose-response data to estimate risk of adverse health effects in workers and working lifetime exposure concentrations that are not expected to cause adverse health effects.

Specific objectives include the following:

1. Evaluate the dose-response relationships of inhaled particles by size and type and estimate the lung disease risks in workers using available data from existing studies.
2. Revise and extend a current rat lung dosimetry model to include particle size-specific clearance and translocation beyond the lungs.

3. Validate the extended rat model using in vivo and in vitro data from ongoing studies at NIOSH and elsewhere.
4. Quantify variability and uncertainty in parameter values of the human lung dosimetry models.
5. Extrapolate the validated rat model to humans.
6. Perform quantitative risk assessment for occupational exposure to nanoparticles.

Accomplishments

- Performed quantitative risk assessment (QRA) of working lifetime exposure to various poorly-soluble particles using dose-response data from chronic and subchronic inhalation studies in rats (ED Kuempel, M Wheeler, D Dankovic, AJ Bailer) (Objective 1).
  - Performed QRA for a NIOSH "Current Intelligence Bulletin: Evaluation of Health Effects Data on Occupational Exposure to Titanium Dioxide," which provided the scientific basis for developing particle size-specific RELs for fine and ultrafine TiO_2.
  - Presented findings at scientific conferences and in published papers in peer-reviewed journals. Excess risk estimates for poorly-soluble nanoparticles were greater than those for larger respirable particles of similar composition; thus lower workplace exposure concentrations were estimated to be necessary for the nanoparticles evaluated to protect workers' health.
  - Stimulated a related project to develop quantitative methods for summarizing and interpreting multiple models fit to quantal response data using Bayesian model averaging (M Wheeler and J Bailer).
- Initiated research project, *Develop and Extend a Biomathematical Model in Rats to Describe Particle Size-Specific Clearance and Translocation of Inhaled Particles and Early Biological Responses* (Objectives 2 and 3).
  - Awarded research contract in 2005 to Dr. Lang Tran, Institute of Occupational Medicine, Edinburgh, United Kingdom.
  - Designed extended rat dosimetry model for inhaled nanoparticles with clearance and translocation pathways based on biological and kinetic data from the scientific literature.
  - Currently planning the calibration and validation of the extended rat model.

- Initiated and managed research project, *Development of Specific Modifications to Multi-path Particle Deposition Model and Software Interface* (Objectives 2–5).
  - Awarded in 2005 to Drs. Bahman Asgharian and Owen Price, CIIT Centers for Health Research, Research Triangle Park.
  - Completed in 2006 the beta version of the new model, which enables batch runs, variable exposure scenarios, lung region-specific deposition estimates, and model predictions output in a format compatible with other models or software. Provides detailed deposition estimates for the rat and human lung models being developed for nanoparticles. Currently finalizing model for public release.
  - Identified need for additional region-specific deposition estimates in the nasal region and initiated follow-on research contact to extend this capability, with Drs. Julie Kimbell and Bahman Asgharian, CIIT Centers for Health Research, in 2006.
- Developed research proposal, *Development and Application of Methods to Quantify Variability and Uncertainty in Lung Dosimetry Models for Use in Risk Assessment of Nanoparticles* (Objectives 4 and 5). Awarded in 2006 to Dr. Eric Hack, Toxicology for Excellence in Risk Assessment (TERA).
- Developed research proposal, *Development of a Method for Predicting the Inhalability and Internal Dose of Airborne Carbon Nanotubes in Workers* (Objective 4). Awarded in 2006 to Dr. Bahman Asgharian, CIIT Centers for Health Research, Research Triangle Park.
- Results from research in Objectives 1–5 will be used in Specific Aim 6.

Publications and Abstracts

- Dankovic D, Kuempel E, Wheeler M [2006]. An approach to risk assessment for TiO_2. In: Proceedings of the 10th International Inhalation Symposium on Airborne Particulate Matter: Relevance of Particle Components and Size for Health Effects and Risk Assessment, held in Hannover, Germany, May 31–June 3.
- Kuempel ED, Tran CL, Castranova V, Bailer AJ [2006]. Lung dosimetry and risk assessment of nanoparticles: evaluating and extending current models in rats and humans. Inhal Toxicol *18*(10):717–724.
- Kuempel ED, Wheeler M, Smith R, Bailer AJ [2005]. Quantitative risk assessment in workers using rodent dose-response data of fine

and ultrafine titanium dioxide. [Abstract]. In: Nanomaterials: a risk to health at work? First International Symposium on Occupational Health Implications of Nanomaterials,12–14 October 2004, Buxton, Derbyshire, UK, Report of Presentations at Plenary and Workshop Sessions and Summary of Conclusions. Buxton: Health and Safety Executive, UK, p. 111.

- Kuempel ED, Aitken RJ [2005]. Regulatory implications of nanotechnology: summary of discussion and recommendations from Workshop G. In: Nanomaterials: A Risk to Health at Work? 1st International Symposium on Occupational Health Implications of Nanomaterials,12-14 October 2004, Buxton, Derbyshire, UK Report of Presentations at Plenary and Workshop Sessions and Summary of Conclusions. Buxton: Health and Safety Executive, UK, pp. 142–143.
- Maynard AM, Kuempel ED [2005]. Airborne nanostructured particles and occupational health. J Nanoparticle Res *7*(6):587–614.
- Maynard AM, Kuempel ED [2006]. Addressing the potential environmental and human health impact of engineered nanomaterials. In: The Symposium Q. Proceedings of the 3rd International Conference on Materials for Advanced Technologies (ICMAT), Singapore, July 3–8.

Invited Presentations

- Dankovic DA [2006]. An approach to risk assessment for TiO_2, by D Dankovic, E Kuempel, and M Wheeler. 10th International Inhalation Symposium on Airborne Particulate Matter: Relevance of Particle Components and Size for Health Effects and Risk Assessment. Hannover, Germany, June 3.
- Kuempel ED [2004]. Assessing the health risks of nanomaterials in workers: current knowledge and research gaps. National Research Council, Board on Environmental Science and Toxicology. Woods Hole, MA, October 12.
- Kuempel ED [2005]. Lung dosimetry and risk assessment for nanoparticles: use of *in vitro* and *in vivo* data to extend current models in rats and humans, by Kuempel E, Tran C, Bailer AJ, Castranova V. Frontiers in Aerosol Dosimetry Research Conference. Irvine, CA, October 24–25.
- Kuempel ED [2006]. Quantitative risk assessment methods for nanoparticles: strategies and data needs. Nanotoxicology: Biomedical Aspects. Miami, FL, February 1.

- Kuempel ED [2006]. Estimating nanoparticle dose in humans: issues and challenges. Overcoming obstacles to effective research design in nanotoxicology. Cambridge, MA, April 25.
- Kuempel ED [2006]. Risk assessment approaches and research needs for nanoparticles: an examination of data and information from current studies, by E Kuempel, C Geraci, P Schulte. NATO Advanced Research Workshop on Nanotechnology: Toxicological Issues and Environmental Security, Varna, Bulgaria, August 14.
- Kuempel ED [2006]. Risk assessment approaches for nanoparticles. International Conference on Nanotechnology Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH, December 6.

National and International Activities and Conferences

- Kuempel ED [2006]. Served as an invited working group participant and contributor to the IARC *Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 93: Carbon Black, Titanium Dioxide and Non-Asbestiform Talc*, Lyon, France, February 7–14. The carbon black and TiO_2 evaluated include ultrafine or nanoparticle forms.
- Kuempel ED [2006]. Served as an invited participant and presenter at the NATO Advanced Research Workshop on Nanotechnology: Toxicological Issues and Environmental Security, in Varna, Bulgaria, August 12–17. The scientific presentations, summary of workgroup discussions and recommendations will be published.

Dissemination (interviews and articles in the lay press)

ED Kuempel was interviewed for two magazine articles concerning NIOSH activities in nanotechnology:

- Parsons J [2004]. Small wonders, big questions. Am Ind Hyg Assoc J, *The Synergist 15*(10):36–39.
- Agencies publishing, generating data to protect against nanoparticle exposure [2004]. Occupational Safety and Health Reporter *34*(42):1069–1070.

Partnerships and Collaborations

- ED Kuempel is collaborating with Dr. Lang Tran at the Institute of Occupational Medicine, in Edinburgh, U.K., on a research project to

develop and extend a biomathematical lung dosimetry model in rats to describe clearance and retention of nanoparticles.

- ED Kuempel and RR Mercer are collaborating with Drs. Bahman Asgharian, Owen Price, and Julie Kimbell at the CIIT Centers for Health Research, Research Triangle Park, NC, on research projects to develop specific software modifications to the Multi-path Particle Deposition Model to enable integration of deposition estimates into the lung clearance and retention models for nanoparticles, to extend current models to include region-specific deposition of nanoparticles in the nasal region, and to explore deposition models for nonspherical nanoparticles.
- ED Kuempel is collaborating with Dr. Eric Hack at Toxicology Excellence for Risk Assessment (TERA) to develop and apply methods to quantify the variability and uncertainty in lung dosimetry models for use in risk assessment of nanoparticles.

NTRC Critical Research Topic Areas Addressed

1. Exposure Assessment
2. Toxicity and Internal Dose
3. Risk Assessment
4. Recommendations and Guidance

Research Project 13: The Measurement and Control of Workplace Nanomaterials

Principal Investigators: Doug Evans Ph.D., and Kevin Dunn M.S., CIH, DART/NIOSH/CDC

Co-investigators: Eileen Birch, Keith Crouch, Bon-ki Ku, and Paul Baron

Project Duration: FY 2006–FY 2009

Background

The current version of this project was initiated in FY 2006 to address key research gaps in the NIOSH, CDC-NORA, and NIOSH-NTRC research portfolios on engineered nanomaterials. A shift in focus of a previous NTRC-approved and funded project (*An Ultrafine Particle Intervention Study in Automotive Production Plants*, approved February 2005) was made following suggestions from the NIOSH-NTRC steering committee (the funding source of this research). This project will provide a fundamental basis for understanding how nanomaterials are released and dispersed into the workplace, demonstrate the way nanomaterials can be monitored, and the way nanomaterial exposure can be controlled. Furthermore, this work provides NIOSH with the tools for making recommendations for reducing workers' exposures to nanomaterials. Specific goals include the following:

Conduct detailed nanomaterial workplace evaluations to provide the following:

- A comprehensive workplace characterization of airborne nanomaterial release and exposure.
- A determination of nanomaterial migration within the workplace.
- A comprehensive qualitative and quantitative (where possible) assessment of engineering controls, ventilation systems, and work practices.
- Recommendations for improvements in engineering controls and work practices where applicable.
- Quantitative assessments of the efficacy of implemented engineering controls and work practices, where applicable, through workplace monitoring.

Accomplishments (FY 2006)

- A NIOSH Health Hazard Evaluation (HHE) was conducted at a nanomaterial research facility in December 2005, where carbon-based nanomaterials were incorporated into polymers and resins to produce novel nanocomposites. On the basis of extensive experience gained from previous activities supported by Project 1, the exposure characterization, engineering control, and work practice evaluation were conducted by participants supported under this project. An HHE report of the study is available at: www.cdc.gov/niosh/hhe/reports
- A large comprehensive exposure characterization, engineering control, and work practice evaluation was conducted at a primary manufacturer of nanoscale metal oxides in March 2006. An interim report has been prepared detailing observations, engineering controls, and work practice evaluations together with recommendations for improvements. A full report, detailing the comprehensive exposure characterization (size distributions, number concentrations, active surface area, mass concentrations, particle morphology, and material migration) is being prepared. Work continues with this company to demonstrate the efficacy of implemented recommended changes to engineering controls and work practices.
- A screening survey was conducted at a quantum dot manufacturing facility in July 2006, where quantum dots were produced and encapsulated into small display units. The survey involved the collection of some basic information about the types of processes employed, exposure control methods, and exposure measurement data. A limited number of samples were collected for characterizing the nanomaterials in the workplace. A report of the survey is being prepared.

Publications and Abstracts

- Birch ME, Evans DE, Methner MM, McCleery RE, Crouch KG, Ku B-K, Hoover MD [2006]. Workplace assessment of potential exposure to carbonaceous nanomaterials. Poster presentation at the International Aerosol Conference. St. Paul, MN, September.
- Dunn KH, Methner MM, Evans DE, Crouch KG, Stefaniak A, Ku B-K, Hoover MD, Curwin BD [2006]. Interim site survey report for a metal oxide and ceramic nanomaterials manufacturer.

Invited Presentations

- Dunn KH [2006]. Nanotech exposure controls and best practices. Presented at the International Conference on Nanotechnology,

Occupational and Health & Safety: Research to Practice. Cincinnati, OH, December 4–7.

- Dunn KH, Evans DE, Ku B-K, Baron PA Birch ME, Crouch KG [2006]. Overview of NIOSH research on nanomaterial characterization and control technology. Presented at the 2006 American Industrial Hygiene Conference and Exposition, Chicago, IL, May 14–18.
- Evans DE, et al. [2006]. Field measurement of aerosols at the nanoscale. Presented at the International Conference for Nanotechnology. Occupational and Environmental Health & Safety; Research to Practice. Cincinnati, OH, December 4–7.

National and International Activities and Conferences

- DE Evans is collaborating with researchers at the Health and Safety Laboratory (United Kingdom), at INRS (France) and BIA (Germany) on issues related to nanomaterial/ultrafine exposure measurement in workplaces.

Dissemination (interviews and articles in the lay press)

Washington Post Staff Writer, Rick Weiss, spoke at length with project participants during a site survey. The survey was the subject of a Post article by Mr. Weiss, which was published soon thereafter.

- The DART project *Measurement and Control of Workplace Nanomaterials* was highlighted in the March 2006 edition of *NIOSH eNews*. The summary article discussed goals of the field project and issued a request for potential collaborators.
- An article appeared in *Occupational Hazards* [2006]. This latter article covered results of related research identifying direct-fired, natural gas heating systems as sources of high concentrations of ultrafine particles in workplaces. The study was conducted with collaborators at the University of Iowa, (www.occupationalhazards.com/articles/14139).

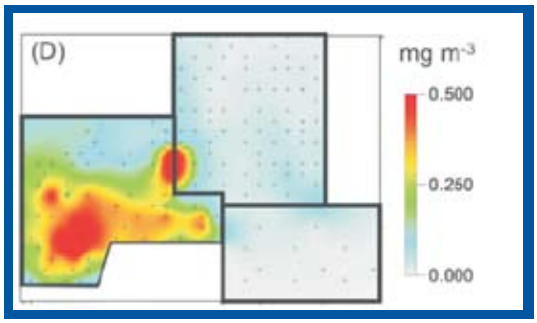
Partnerships and Collaborations

NIOSH researchers are working with the three nanomaterial manufacturers/processors mentioned above, The University of Iowa, The University of North Carolina, The Woodrow Wilson International Center for Scholars, International Truck and Engine Corporation, and the United Auto Workers Union.

NTRC Critical Research Topic Areas Addressed

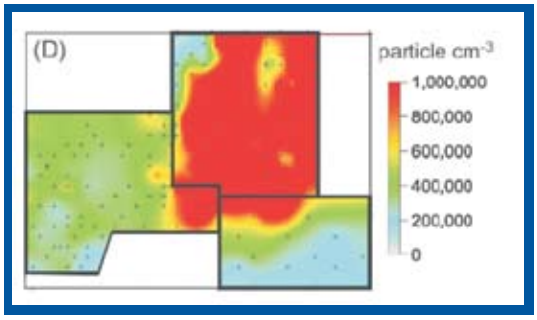
1. Exposure Assessment
2. Measurement Methods
3. Engineering Controls and Personal Protective Equipment
4. Fire and Explosion Safety
5. Recommendations and Guidance

Number versus mass concentra · · · i lant



Mass concentra ion map

High mass concentrations do not indicate high number concentrations.



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Research Project 14: TiO_2 Exposure Assessment Study

Principle Investigator: Brian Curwin, DSHEFS/NIOSH/CDC

Project Duration: FY 2006–FY 2009

Background

TiO_2, a poorly soluble, low-toxicity (PSLT) white powder, is used extensively in many commercial products, including paint, cosmetics, plastics, paper, and food as an anti-caking or whitening agent. Production in the United States was an estimated 1.43 million metric tons per year in 2004 [DOI 2005].

Ultrafine particles are hypothesized to penetrate the epithelial lining and lung interstitial spaces to a greater extent, more readily enter cells, and cause greater lung inflammation and oxidative stress compared with larger particles. Furthermore, it is hypothesized that the dose of particles, expressed as particle surface area, is associated with lung responses and this relationship is similar across PSLT particles. Persistent inflammation, tissue damage, fibrosis, and lung cancer have been observed in rats at doses of PSLT particles that impair lung clearance. Particle surface area dose has been shown to be a better predictor of lung clearance inhibition.

NIOSH has identified critical research needs for workers exposed to ultrafine and fine TiO_2, including measuring workplace airborne exposures to ultrafine TiO_2 in manufacturing and end-user facilities and evaluating the exposure response relationship between TiO_2 and human health effects. The goal of this study is to measure workplace exposure to fine and ultrafine TiO_2 in both manufacturing and end-user facilites. The specific objectives are to (1) quantify the airborne particle size distribution of TiO_2 by job or process in manufacturing and end-user facilities and (2) obtain quantitative estimates of exposure in workers to fine and ultrafine TiO_2 particle sizes in manufacturing and end-user facilities. A task-based sampling scheme consisting of various real-time and mass based area and personal aerosol sampling will be employed. In addition, each participant will be asked to provide information about their work practices and PPE use.

Accomplishments

- Protocol for TiO_2 study has been written and is undergoing review.

- Critical exposure assessment equipment has been purchased including a TSI 3007 condensation particle counter and an Ecochem DC2000 CE portable diffusion charger.
- A contract has been awarded to assist in identifying companies for study.

Publications and Abstracts

The field work has not begun and no data have been collected. Therefore, no publications or abstracts have been published.

Invited Presentations

This project is in its early stages and therefore no invitations to present results from this project have been offered.

National or International Activities and Conferences

No national or international activities have occurred or are planned at this time.

Dissemination (interviews and articles in the lay press)

This project is in its early stages. No results are available for dissemination.

Partnerships and Collaborations

- Consultations were held with Dr. Dirk Brouwer, Netherlands Organization for Applied Scientific Research (TNO), Netherlands, on study protocol development.
- Collaboration with a manufacturer and an end user of ultrafine TiO_2 has been established for conducting possible exposure characterization studies.

NTRC Critical Research Topic Areas Addressed

1. Exposure Assessment
2. Measurement Methods

Research Project 15: Evaluation of Nanoparticle Penetration Through Respirator Filter Media

Principle Investigator: Samy Rengasamy, Ph.D., NPPTL/NIOSH/CDC

Project Duration: FY 2005–FY 2008

Background

The objective of this project is to evaluate the penetration of nanoparticles through respirator filter media. Nanoparticles smaller than 100 nm in size can behave differently from larger particles of the same material. NIOSH has initiated research projects on nanoparticle exposure, health effects, and respiratory protection. For respiratory protection against various particles, particulate respirators are commonly used in different workplaces. Although NIOSH-approved respirators efficiently capture particles greater than 20 nm, few data exist on their efficiency for particles smaller than 20 nm. Some studies suggest the penetration of smaller particles through filters by a thermal rebound mechanism. The results will be confirmed by testing NIOSH-approved respirators against particles smaller than 20 nm. This study will ensure that respirators provide adequate protection for workers in the nanotechnology industries.

Accomplishments

In 2005, the research proposal was approved for a pilot project study, and a contract was awarded to the University of Minnesota. Preliminary results from the project were presented at the 2nd International Symposium on Nanotechnology and Occupational Health in Minneapolis, MN, October 2005. Silver nanoparticles of 3-20 nm in diameter were generated for testing respirator filter media. Preliminary results indicated that filtration efficiency increased with decreasing particle size as expected according to the Brownian deposition theory. No evidence for thermal rebound of nanoparticles was observed. The results of this study suggest that respirator filters may efficiently capture nanoparticles greater than 3 nm in diameter. To confirm these results, further studies with silver and/or sodium chloride aerosol particles will be used to test for penetration through particulate filtering facepieces and cartridges.

Publications and Abstracts

- Kim SC, Harrington M, Rengasamy S, Pui D [2005]. Collection efficiency of filter media for nanoscale particles. Presented at the 2nd International

Symposium on Nanotechnology and Occupational Health in Minneapolis, MN.

- Gardner P, Rengasamy S, Richardson A [2005]. Efficiency of respirator filters against nano-aerosols under high flow rate conditions. Presented at the 2nd International Symposium on Nanotechnology and Occupational Health in Minneapolis, MN, October 3–6.
- Kim SC, Harrington M, Rengasamy Samy, Pui D [2006]. Collection efficiency of filter media for nanoscale particles. Presented at the American Industrial Hygiene Conference and Exposition, Chicago, IL, May 14–18.
- Shaffer R, Gao P, Rengasamy S [2006]. Penetration of nanoparticles through protective clothing and respirator filters. Presented at the Elevated Wind Studies International Conference, Arlington, Virginia, September 25–26.
- Shaffer R, Rengasamy S, Gao P [2006]. Penetration of nanoparticles through protective clothing and respirator filter media. Presented at the International Conference on Nanotechnology, Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH December 4–7.

National and International Activities and Conferences

S. Rengasamy arranged a Round Table meeting on *Nanotechnology and PPE issues* for the 2006 AIHCE meeting in Chicago. For this session, PPE experts from academic, industrial, and nongovernmental organizations were invited. Highlights of the presentations include studies on nanoparticle penetration through filter media and respirator filters. Other presentations included developing highly adsorbent and reactive nanoparticles for protective clothing for chemical and biological warfare agents and the evaluation of protective gloves and PPE for handling nanomaterials.

Dissemination (interviews and articles in the lay press)

- S. Rengasamy and R. Shaffer had an interview with *Occupational Hazards* magazine and discussed nanoparticle filtration. An article entitled *NIOSH-funded Study Looks at Filter Efficiency for Nanoparticles* was published in September 2005 (*67*:42). The growth of nanotechnology across different industries and the effects of nanoparticles on respiratory protection and were discussed. Single fiber theory and the mechanisms of penetration of different size particles through respirator

filters were also shared. The lack of knowledge about the penetration of nanoparticles smaller than 20 nm sizes and the importance of this research were highlighted. NIOSH collaboration with the University of Minnesota to study the penetration of particles smaller than 20 nm was shared. This interview highlighted current understanding of nanoparticles, and the importance of NIOSH nanoparticle filtration research work with the University of Minnesota.

- S. Rengasamy and R. Berryann of NPPTL had an interview with the Bureau of National Affairs (BNA), Inc. in October 2005, and highlighted the current developments on respiratory protection against nanoparticles. An article entitled *NIOSH Planning More Respirator Studies after Nanoparticle Tests Find Penetration* was printed in a BNA publication, October 19, pp. 8–22.
- S. Rengasamy and R. Shaffer of NPPTL had an interview with the AIHA publication *The Synergist* in October 2005, and discussed current nanotechnology research activities in NPPTL that address worker safety and issues. An article entitled *Accelerating Research Sizes up the Implications of Nanotechnology in the Workplace* was published in *The Synergist* [2005] *17*(1):37–39.
- S. Rengasamy and R. Shaffer of NPPTL were interviewed by *Chemical and Engineering News* in April 2006. The aim of the interview was to better understand the current developments in respiratory protection against nanoparticles. An article entitled *How Well do Gloves and Respirators Block Nanoparticle* was published in the May 1 issue of *Chemical and Engineering News,* pp.14–15.
- K. Williams and A. Maynard were interviewed by *The Synergist* and highlighted the lack of complete information about nanoparticles and the performance of personal protective equipment against nanomaterials. An article titled *Small Wonders, Big Questions* was published in *The Synergist* [2004] *15*(10):37–39.

Partnerships and Collaborations

- In January 2005, K. Williams assisted the EPA by reviewing a manufacturer's application to manufacture a nanosized product that was submitted to EPA for approval under the Toxic Substances Control Act (TSCA). He provided input regarding the selection of appropriate PPE for the manufacturing process that was valuable to the EPA in the evaluation and approval of the manufacturer's application.

- Partnership with the ISEA Filter Research Task Group was established to achieve the goals of this project. ISEA Filter Research critically reviewed the proposal in January 2005. The proposal was revised taking into consideration the comments and suggestions of the ISEA Filter Research Task Group.
- S. Rengasamy, R. Shaffer, and P. Gao are actively participating in the DuPont Nanoparticle Occupational Safety and Health Consortium. The objectives of this consortium include the generation of nanoparticles, the measurement, filter penetration, and development of a portable device to measure nanoparticles in workplaces to provide safety and health to workers. An MOU between NIOSH/NPPTL and DuPont was officially executed in June 2006. This will allow NIOSH to collaborate with the DuPont Consortium and exchange information about PPE (clothing and respirators) and nanoparticles research.

NTRC Critical Research Topic Areas Addressed

1. Engineering Controls and PPE
2. Recommendations and Guidance

Research Project 16: Development of Bench and Mist Protocols for Particulate Penetration Measurements of Protective Clothing and Ensembles

Principle Investigator: Pengfei Gao, Ph.D., C.I.H., NPPTL/NIOSH/CDC

Project Duration: FY 2006–FY 2009

Background

Protective clothing and ensembles are critically important items for workers when exposed to hazardous conditions. In order to determine how well ensembles protect wearers, it is necessary to test the entire suit system while it is worn to measure potential leakage through seams, closures, areas of transition to other protective equipment, and any leakage due to movement and activities. The objective of this project is to develop innovative methodology for standardizing both bench-scale testing and man-in-simulant test (MIST) procedures for aerosol particle penetration through protective clothing and ensembles. A test method for aerosol particles including nanoparticles that does not depend on filtration will be developed. A passive aerosol sampler (PAS) using magnetic force will be developed and iron (II, III) oxide particles will be used to generate challenge aerosols. An aerosol chamber will be fabricated for evaluating the particulate penetration for particle sizes between 20 and 500 nm; a wind tunnel will be used for larger particles up to 10 µm. Iron oxide collected on the PAS will be quantified using a colorimetrical method or TEM. Performance of the PAS will be evaluated under various test conditions, including particle size, particle concentration, wind speed, exposure duration, relative humidity, and sampler orientation. A disposition velocity model will be developed to calculate sampling rates of the PAS. Penetration of nanoparticles through fabrics and protective clothing swatches will be measured with other reference samplers to compare the performance of the PAS. The research findings will be used for revised and new American Society for Testing Materials (ASTM) and NFPA standards. The project duration is proposed to last for 4 years (FY 2006–FY 2009).

Accomplishments

- A prototype passive aerosol sampler using magnetic force has been developed at NPPTL to more accurately determine aerosol particle

penetration including nanoparticle penetration through ensembles. Preliminary evaluation of the sampler performance indicates the ability to collect nanoparticles down to 20 nm by the sampler. Appropriate sampler coatings were identified to facilitate analysis of collected aerosol. Experiments to allow an improved assessment of sampler performance were completed.

- An Employee Invention Report (I–015–05) for the passive aerosol sampler was submitted to CDC Technology Transfer Office in March 2005.
- A research proposal has undergone external peer review.

Publications and Abstracts

- King WP, Gao P, Shaffer R [2006]. Review of chamber design requirements for testing of personal protective clothing ensembles. Submitted to the *Journal of Occupational and Environmental Hygiene* for publication.

Invited Presentations

- Shaffer R, Rengasamy S, Gao P [2006]. Penetration of nanoparticles through protective clothing and respirator filter media. Presented at the International Conference on Nanotechnology, Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Shaffer R, Gao P, Rengasamy S [2006]. Penetration of nanoparticles through protective clothing and respirator filters. Presented at the Elevated Wind Studies International Conference. Arlington, VA, September 25–26.
- Geraci C, Castranova V, Hoover M, Dunn K, Gao P [2006]. Ask the Expert—An update on NIOSH research in nanotechnology. Presented at a roundtable section at the American Industrial Hygiene Conference and Exposition, Chicago, IL, May 16.
- King B, Gao P [2005]. A passive aerosol sampler for evaluation of personal protective ensembles. Presented at the Advanced Personal Protective Equipment: Challenges in Protecting First Responders Conference. Blacksburg, VA, October16–18.
- King WP, Gao P [2006]. Coating evaluation for a newly developed passive aerosol sampler based on magnets for determination of particle penetration through protective ensembles. Presented at the American Industrial Hygiene Conference and Exposition, Chicago, IL, May 17.

Partnerships and Collaborations

- Efforts have been initiated to establish research collaborations between NPPTL and the Research Triangle Institute (RTI) in North Carolina, Battelle in Columbus, OH, and the Center for Health-Related Aerosol Studies at the University of Cincinnati. The project officer visited RTI in May 2006 to discuss possible collaborative efforts.
- A partnership has been arranged with the DuPont Nanoparticle Occupational Safety and Health Consortium. An MOU between NIOSH/NPPTL and DuPont was officially executed in June 2006. The MOU provides a formal mechanism for exchanging information on PPE (clothing and respirators) and nanoparticles research.

NTRC Critical Research Topic Areas Addressed

1. Engineering Controls and PPE
2. Recommendations and Guidance

Research Project 17: Web-based Nanoparticle Information Library Implementation

Principal Investigator: Arthur Miller, Ph.D., SRL/NIOSH/CDC

Project Duration: FY 2004–FY 2008

Background

The primary objective of this project is to design, build, and implement the Web-based NIL. The NIL is being developed as a global source for information concerning the properties and associated health and safety implications of the myriad nanomaterials that are being developed. This work also supports efforts ongoing in the Nanoparticles in the Workplace project. It is intended to provide NIOSH and the occupational safety and health community with access to knowledge as to the variety and extent of nanomaterials being produced worldwide, along with information concerning their physical and chemical properties, processes of origin, and possible health effects.

Accomplishments

- Collaborated with the International Council on Nanotechnology (ICON) for the development of a knowledge management hub for nanotechnology.
- Participated in the planning of the nanotechnology field team investigation effort and assisted with developing protocols.
- Provided input for redesigning the nanotechnology topic page on the NIOSH Web site.
- EIR document (patent application) titled, *A Portable Hand Held Electrostatic Precipitator for Particle Sampling.*
- Developed two protocols for analyzing workplace aerosol samples using Transmission Electron Microscopy/Energy Dispersive Spectroscopy (TEM/EDS).
- Provided consultation on the characterization of welding fume and worker exposure to the welding fume.
- Based on preliminary work conducted by participants under Project 1, developed a protocol for nano-aerosol characterization fieldwork at a metal refinery, including real time mapping of particle concentrations in the workplace.

- Developed a project to map concentrations of airborne particles in the workplace using the Fast Mobility Particle Size (FMPS) instrument. This work includes the preliminary design of a (non-GPS) spatial mapping system to be used in indoor environments.
- Built and tested an instrumentation cart for evaluating a prototype system for quasi-real-time spatial mapping of nanoparticles in the workplace.
- Incorporated a mailing interface and a newsletter interface in the design of the nanoparticle information library.
- Launched the nanoparticle information database on the NIOSH Web site. The prototype version went live in February 2006.

Publications and Abstracts

- Donggeun L, Miller A, Park K, Zachariah MR [in press]. Effects of trace metals on particulate matter formation in a diesel engine: metal contents from ferrocene and lube oil. Int J Automotive Technology.
- Lee D, Miller A, Kittelson DB, Zachariah MR [2005]. Characterization of metal-bearing diesel nanoparticles using single particle mass spectrometry. J Aerosol Sci *37*(2):88–110.
- Lee D, Miller A, Zachariah M, Kittelson DB [2004]. Single particle mass spectrometry of metal-bearing diesel nanoparticles. ACS Symposium Series No. 890–Nanotech and the Environment: Applications and Implications. Chapter 17, pp.142–151, ISBN: 0–8412–3877–4.

Papers Submitted for Publication

- Miller A, Ahlstrand G, Kittelson DB, Zachariah MR [2006]. The fate of metal (Fe) during diesel combustion: morphology, chemistry and formation pathways of nanoparticles. Unpublished. Submitted to the journal of *Combustion and Flame,* March.
- Miller AL, Habjan MC, Park K [2006]. Real-time estimation of elemental carbon emitted from a diesel engine: a preliminary study. Unpublished. Submitted to *Environmental Science and Technology*, August.
- Ng A, Miller A, Ma H, Kittelson DB [2006]. Comparing measurements of carbon in diesel exhaust aerosols using the aethalometer, NIOSH Method 5040, and SMPS. Unpublished. Submitted to the SAE journal for publication as a Technical Paper, June.

Posters

- Miller AL, Hoover M [2005]. Nanotechnology—assessing and controlling potential health impacts. Poster session for the XVIIth World Congress on Safety and Health at Work, Orlando, FL, September 19–22.
- Maher TV, Omaye ST, Geraci CL, Zumwalde RD, Miller All, Hoover MD [2006]. A case study in partnering to develop a nanotechnology occupational safety program in a nanotechnology manufacturing environment. Poster session at the 2006 NORA Symposium.
- Miller AL [2004]. Novel techniques for characterization of ultrafine metal aerosol formation: lessons from diesel combustion. Poster session at the first annual international symposium, Occupational Health Implications of Nanomaterials, co-sponsored by NIOSH, Buxton, UK, October.

Invited Presentations

- Miller AL [2005]. NIOSH's role in improving health and safety in nanotechnology workplaces. Presentation given as part of a multi-agency panel session on nanotechnology at the SAMPE–2005 conference in Seattle, WA, November 3.
- By special invitation, attended the 2006 the spring meeting of the ICON and gave two presentations:
  - Development of a Web-based NIL
  - Working Toward an Integrated Management Tool for Nanotechnology-related EHS Data
- By invitation, gave a presentation in 2006 to the NanoIGERT members at the University of Minnesota, covering the proposed NIOSH work to build a nanomaterial information library, and solicited input to same.

National and International Activities and Conferences

- Miller AL, Hoover M [2005]. Building a Nanomaterial Information Library. Presentation for the Second International Symposium on Nanotechnology and Occupational Health, co-sponsored by NIOSH, Minneapolis, MN, October 3–6.

Dissemination (interviews and articles in the lay press)

TEM images of nanoparticles prepared by Art Miller were highlighted in the TSI 2005 aerosol instrumentation catalogue, which won an award sponsored by the Society for Technical Communication in 2006.

Partnerships and Collaborations

- Sunshine Metal Refinery, WA, hosted a 2006 field study in which NIOSH staff characterized nanoparticles in the workplace.
- NIOSH is collaborating with researchers in the Atmospheric Science Division at the Desert Research Institute (DRI), regarding instrument comparisons and measurement methods for airborne carbon particulates.
- NIOSH is collaborating with EPA to study nano-fuel additives and their influence on particle generation by internal combustion engines.
- Art Miller provided instruction to engineering students at Gonzaga University on the design, building, and testing a novel hand-held electrostatic nanoparticle sampler.
- Assistance was provided by the following companies and Universities in designing the NIL:
  - Altair Nano
  - University of Minnesota
  - Washington University at St. Louis
  - Seattle University
  - Rice University/ICON consortium
  - A primary nanoscale metal oxide manufacturer

NTRC Critical Research Topic Areas Addressed

1. Toxicology and Internal Dose
2. Risk Assessment
3. Fire and Explosion Safety
4. Communication and Education
5. Recommendations and Guidance

Appendix B

Field Research Team Progress Report

Summary of Field Research Progress

Prinicpal Investigators: Mark Methner, PH.D., CIH; Charles L. Geraci, PH.D., CIH; Mark Hoover, PH.D., CIH

Evaluation of Carbon Nanofiber Composite Material at a Polymer Research Facility

Following a series of walk-through and planning visits, an in-depth survey was conducted on December 6, 2005 at a research facility evaluating the incorporation of nanomaterials into polymers. The purpose of the survey was to determine whether fugitive emissions and subsequent nanomaterial migration occurred during various laboratory processes involving both raw carbon nanofibers (CNF) and CNF bound within a composite matrix. Task-based air and surface sampling was conducted using a vacuum method. Real-time aerosol instrumentation was used to measure particle number, active surface area, mass concentration, and particle size distribution. In addition, air and surface samples were collected by NIOSH Method 5040 for subsequent total carbon analysis, as were air samples for analysis by TEM. A qualitative evaluation of engineering controls and work practices was also conducted and recommendations were made to the company. Preliminary results indicate that some release of CNF occurred during raw fiber transfer to a rotary-stirred mixing vessel. In addition, material was released during a cutting operation of CNF-laden epoxy polymer using a wet saw. A poster describing the methodology used to collect filter-based air and surface samples was presented in September 2006 at the International Aerosol Conference in St. Paul, Minnesota. Interim results have been provided to the facility. A final report has been issued (See http://www.cdc.gov/niosh/hhe/reports/pdfs/2005-0291-3025.pdf). Research activities were supported under Projects 11 and 13.

Preliminary Screening Survey Using Handheld Direct Reading Instrumentation and Air Filter/Wipe Samples at a Quantum Dot Research and Development Laboratory

A site survey was conducted on July 10, 2006, at a research and development laboratory engaged in the development of optical products with Quantum Dot (QD) coatings after several detailed conference calls. The purpose of the survey was to determine whether QD between 2 nm and 8 nm (monodisperse) were released during various laboratory treatments and processes. All processes were very well controlled by ventilation (i.e., laboratory hoods, glove boxes, Class 10,000 Clean Rooms). A total of 13 surface wipe samples were collected

using Ghostwipe® substrates and 8 high-volume air samples were collected on mixed cellulose ester (MCE) filters. The surface and air samples are currently being analyzed for elemental metals in accordance with NIOSH Method 7300. Direct reading instruments (condensation particle counter [CPC] and hand-held particle counter model HHPC-6; ART instruments) were also used to assess airborne particle concentrations in the work areas. No noticeable releases of QD were noted during any process. A final report has been submitted to the company. Research activities were supported under Project 13.

Evaluation of Nanoscale Metal Oxide Release at a Commercial Technology Development and Powder Production Facility

A comprehensive survey was conducted from March 12–17, 2005, at a commercial nanoscale metal oxide development and powder production facility following a series of walk-through and planning visits. The purpose of the survey was to assess the adequacy of engineering controls and work practices, characterize particle releases in the work area, and evaluate the performance of a range of nanoparticle characterization instruments and approaches. A series of recommendations for improved particle control and worker protection were provided to the facility. Detailed evaluation of particle size distribution, surface area, morphology, and other results are underway. Research activities were supported under Projects 11, 13, and 14.

Evaluation of Nanoscale Nylon 6 Fiber Deposition and Potential Release during Engine Filter Media Manufacturing

A recent survey (September 2006) of a filter manufacturer (electro-spinning deposition of nanoscale Nylon 6 onto cellulose substrate) has been completed. The final report is being drafted.

Preliminary Evaluation of Nanomaterial Handling Practices at a Research Facility Engaged in State-of-the-Art Materials Characterization

A series of walk-through visits have been made to a state-of-the-art materials characterization facility to assess the nature and adequacy of control practices being implemented in a newly developing nanotechnology research program at the facility. Presentations were also made to the industrial hygiene professional staff and to workers about the need for, and the nature of, good work practices for safe handling of nanomaterials. Collaborative work on documenting and improving work practices is underway.

The Many Faces of Nanotechnology

Assessment of Work Practices in a Facility Developing Specially Formulated Fullerenes for Biomedical Applications

A walk-through survey was conducted on July 28, 2005, at a research and development laboratory engaged in the development of specially formulated fullerenes for biomedical applications. Through collaboration with a local university, a detailed industrial hygiene survey was conducted and then presented at the International Aerosol Conference in September 2006, in St. Paul, MN. In addition, results of the survey and detailed observations of nanomaterial handling work practices were presented jointly by NIOSH and the company at the October 2005 International Symposium on Nanotechnology and Occupational Health in Minneapolis, MN. Frequent communication between NIOSH and the company are continuing to develop further recommendations on comprehensive management and work practice approaches to safe handling of nanomaterials. Involvement was supported under Project 11.

Assessment of Work Practices at Universities Engaged in Research on Nanomaterials

A series of walk-through investigations have been conducted at two universities engaged in materials science, aerosol science, and biomedical research on nanomaterials. The purpose of the investigations has been to learn more about the actual research and work practices underway, and to advise industrial hygiene professionals, researchers, and students about effective measures for controlling nanomaterials and preventing exposure. Opportunities for additional collaborative research are being discussed.

Evaluation of the Performance of the State-of-the-Art Nanoparticle Sampling Equipment in a Nanoparticle Aerosol Generation Laboratory

In July 2006, NIOSH and a commercial instrumentation company collaborated to evaluate the performance of a new nanoparticle real-time surface area analysis instrument under actual conditions of particle generation in an aerosol inhalation toxicology facility (supported by Project 11). Valuable lessons were learned about instrument performance, maintenance and trouble-shooting requirements, and comparison of instrument results with conventional nanoparticle characterization instrumentation. Data reduction and report writing are underway. Collaboration efforts were supported by Project 11.

Invited Presentations

- Methner MM [2006]. NIOSH nanoparticle exposure characterization and assessment. Society of Advanced Material Processing and Engineering (SAMPE). Dallas, TX.

- Methner MM [2006]. Health hazard evaluations of engineered nanoparticle exposures. Presented at the International Conference on Nanotechnology, Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Hoover MD, Stefaniak AB, Methner MM [2006]. Evaluation of a real-time surface area monitor in a nanotechnology workplace. Presented at the International Conference on Nanotechnology, Occupational and Environmental Health & Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Methner MM, Zimmer A, Baron P [2005]. Nanotechnologies: Occupational health considerations and controls. Presented at the United States Air Force Institute of Technology (AFIT), Wright-Patterson Air Force Base, Dayton, OH.

Appendix C

Occupational Health Surveillance for Nanotechnology Workers

Research Program: Occupational Health Surveillance For Nanotechnology Workers

Program Coordinator: Douglas Trout, M.D., DSHEFS/NIOSH/CDC

Program Duration: FY 2005–Present

The unique physical and chemical properties of nanomaterials, the increasing growth of nanotechnology in the workplace, and information suggesting that engineered nanomaterials may pose a safety and health hazard to workers all underscore the need for medical and hazard surveillance for nanotechnology. Every workplace dealing with engineered nanomaterials and nanotechnology should consider an occupational health surveillance program. NTRC has convened a cross-Federal group to develop a document as a framework for using existing medical and hazard surveillance mechanisms to create occupational health surveillance programs for nanotechnology workers. This guidance is not a prescriptive recommendation for a specific type of surveillance program, but rather is provided to present information that can be used to create appropriate occupational health surveillance to fit the needs of workers and organizations involved with nanotechnology. This framework presents information to help initiate occupational health surveillance where none exist. It is likely that as the field of nanotechnology changes over time modifications to any initial surveillance program will need to be considered periodically.

Appendix D

Review of the NIOSH Extramural Nanotechnology Research Program: FY 2001–FY 2006

NIOSH Nanotechnology Research Program Review for FY 2001–FY 2006

Office of Extramural Research Programs

Program Administrator: W. Allen Robison, Ph.D., NIOSH Office of Extramural Programs

Background

During 2001–2006, the Office of Extramural Programs (OEP) funded nanotechnology-related research through R01 and R43/44 mechanisms. Since FY 2005, OEP has participated in two collaborative requests for applications (RFA) for nanotechnology research grants investigating environmental and human health issues. The U.S. EPA National Center for Environmental Research (NCER) and the National Science Foundation (NSF) participated in FY 2005. NIEHS joined in FY 2006. Funding was available to support Research (R01) grants for 3 years and Exploratory (R21) grants for 2 years.

Purpose

OEP 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.

Status and Progress

From FY 2001 to FY 2004, OEP funded three R43/44 projects for a total funding commitment of almost $950K (Table 1). In FY 2005, OEP began participating in the nanotechnology-related RFAs previously mentioned. For the first RFA, 83 applications were received; 19 of these were recommended for funding. Fourteen met NIOSH criteria for relevance to occupational safety and health, five were in the competitive range for funding consideration, and two were funded by NIOSH (Table 1). In FY 2005, EPA funded 14 projects and NSF funded 2 projects under this RFA. NIOSH also funded a nanotechnology research application through the R01 Program Announcement (Table 1) in FY 2005.

In FY 2006, 81 applications were received in response to the RFA; 29 of these were recommended for funding. Six of the 29 met NIOSH criteria for relevance, three were in the competitive range for funding consideration, and one of these was funded by NIOSH (Table 1). EPA funded 21 projects, NSF funded four, and NIEHS funded three projects under this RFA. NIOSH also funded a nanotechnology research application through the Small Business Innovative Research (SBIR) Program Announcement. Summaries of projects funded by NIOSH/OEP are described below.

To date, NIOSH/OEP has committed about $3.5 million dollars to nanotechnology-related research. Projects have been funded on applications and implications of nanotechnology. Contact information for the principal investigators of the projects funded by NIOSH/OEP is provided in Table 2.

Next Steps

In FY 2007 and FY 2008, NIOSH/OEP will 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 confer with the NTRC regarding issues, knowledge gaps, and future directions.

Additional Information

Extramural investigators interested in pursuing nanotechnology studies related to occupational safety and health 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/NIL.html
- http://es.epa.gov/ncer/rfa/2005/2005_star_nano.html
- http://es.epa.gov/ncer/rfa/2004/2004_manufactured_nano.html

Information about the NIOSH goal to transfer research findings, technologies, and information into prevention practices and products in the workplace can be found at http://www.cdc.gov/niosh/r2p/. The emphasis on r2p is intended to reduce occupation-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 at the NIOSH home page (http://www.cdc.gov/niosh/homepage.html) and the program portfolio Web site (http://www.cdc.gov/niosh/programs/).

Table 1. Extramural nanotechnology research funded by NIOSH*, 2001–2006

Grant number	Investigator	Institution	Project title	Start	End	1st year funding	Total projected funding
Before FY 2004 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	Williams	Synkera Technologies Inc., Longmont, CO	Novel Hydrogen Sulfide Sensors for Portable Monitors	9/16/2003	9/15/2006	$373,430	$749,995
Pre-FY 2004 total:						$473,430	$849,995
FY 2004 Exposure assessment (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 2005 Emerging technologies (NIOSH program announcement):							
1R01OH008282–01A	Kagan	University of Pittsburgh	Lung Oxidative Stress/Inflammation by Carbon Nanotubes	7/1/2005	6/30/2009	$363,975	$1,458,862
FY 2005 Emerging technologies 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	$132,903	$392,574
1R01OH008807–01	Xiong	New York University School of Medicine	Monitoring and Characterizing Airborne Carbon Nanotube Particles	8/1/2005	7/31/2008	$158,185	$396,401
FY 2005 total:						$655,063	$2,247,837
FY 2006 Nanotechnology 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	$119,700	$359,100
FY 2006 Nanotechnology (NIOSH/SBIR):							
1R43OH008939–01	Deininger	Synkera Technologies Inc., Longmont, CO	New Nanostructured Sensor Arrays for Hydride Detection	8/1/2006	2/28/2007	$99,998	$99,998
FY 2006 total	—	—	—	—	—	$219,698	$459,098
Grand total:							$3,556,932
FY 2007 Nanotechnology (NIEHS RFA–ES–06–008):							
Release date	September 29, 2006	—	Set aside $500K; maximum project $300K; maximum length 4 years				
FY 2008 Nanotechnology RFA (EPA)—U.S./Europe:							
Anticipated release date	April 2007	—	Set aside $500K; maximum project $250K; maximum length 3 years				

*Abbreviations: EPA=Environmental Protection Agency; NIEHS=National Institue of Environmental Health Sciences; NIOSH=National Institute for Occupational Safety and Health; RFA=request for application; SBIR=small business innovative research; STAR= science to achieve results.

Extramural Nanotechnology Research Project Summaries

These brief project summaries were excerpted from the project descriptions. For additional information, please contact the identified investigator(s) for the specific project. Investigator contact information is provided in Table 2; however, information for Dr. Hooker was not available.

Hooker 7471 (R43), Williams 7471 (R44)

Novel Hydrogen Sulfide Sensors for Portable Monitors

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 literally shut off the lungs, while lower levels 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 parts per million (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 safety and health field. In addition, there are several potential spin-off opportunities in leak detection, emission monitoring, and process control. Alternative ceramic oxide materials and a unique multi-layer fabrication process to accomplish the objectives of this project will be used. 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 cannot only alert the wearer when unsafe concentrations have been encountered but also track 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 utilizing 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)

From Nanoparticles to Novel Protective Garments

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 dealing with hazardous materials released either by accident or intentionally, 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 (1) establish the feasibility of incorporating highly adsorbent and reactive nanoparticles into lightweight, permeable textiles and (2) evaluate the utility of the resultant fabric as protective clothing using standard industry testing procedures. These novel protective garments will be tailored specifically 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 adsorption 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: Establish the extent to which SWCNTs 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: Determine the potential for SWCNTs and microbial stimuli to synergistically interact to promote macrophage activation, oxidative stress, and lung inflammation.

Specific Aim 3: Reveal the extent to which SWCNTs 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 and biochemistry, cell and molecular biology of inflammation and its interactions with microbial agents, and pulmonary toxicology of nanoparticles.

Progress

Two types of SWCNTs were used (iron-rich and iron-stripped) to study their interactions with RAW 264.7 macrophages. Following ultrasonication of the SWCNTs to separate strands, neither type was able to generate intracellular production of superoxide radicals or nitric oxide by macrophages observed by flow-cytometry and fluorescence microscopy. SWCNTs with different iron content displayed different redox activity in a cell-free model system. In the presence of microbial (zymosan) stimulated macrophages, nonpurified iron-rich SWCNTs were more effective in generating hydroxyl radicals than purified SWCNTs. The presence of iron in SWCNTs may be important in determining redox-dependent responses of macrophages. Dose and time-dependence studies of inflammatory responses in mice using pharyngeal aspiration of SWCNTs demonstrated that they 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 effects of SWCNTs may exert toxic effects in the lungs of exposed animals in vivo. SWCNT-induced inflammation and exposure caused altered pulmonary function. Microbial stimulation and clearance from the lungs of SWCNT-exposed mice were compromised. An unusual and robust inflammatory and fibrogenic response was correlated with the progression of oxidative stress and apoptotic signaling. The toxic effects of SWCNTs were important to consider, and also the role of transitional metals, particularly iron, should be investigated.

O'Shaughnessy (8806)

Assessment Methods for Nanoparticles in the Workplace

Background

The primary objectives are to (1) provide the scientific community and practicing industrial hygienists with verified instruments and methods for accurately accessing airborne levels of nanoparticles and (2) assess the efficacy of respirator use for controlling nanoparticle exposures.

Objectives will be satisfied through a combination of laboratory and field studies centered on the following aims: identify and evaluate methods to measure airborne nanoparticle concentrations; characterize nanoparticles using a complementary suite of techniques to assess their surface and bulk physical and chemical properties; and 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. While the primary particle size of these powders average 20 nm, an aerosol with a median size of 120 nm 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 concentrations in two facilities; one in Minnesota and one in Texas.

Xiong (8807)

Monitoring and Characterizing Airborne Carbon Nanotube (CNT) Particles

Background

The proposed research will develop a comprehensive yet practical method for sampling, quantification, and characterization of CNT particles in air. This method will be capable of (1) classifying sampled particles into three categories:

tubes, ropes (bundles of single-walled CNT bounded by Van der Waals attraction force), and nontubular particles (soot, metal catalysts, and dust, etc.), and (2) measuring the number concentrations, size distributions for each type, and the shape characters (diameter, length, aspect ratio and curvature) of CNT.

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 (1) a validated method for sampling airborne CNT in the workplace and (2) a practical method to classify sampled CNT particles by type through quantifying and characterizing each type separately using Atomic Force Microscopy image analysis technology. These methods are needed to determine potential health risks that may result from worker exposure to the various types (CNTs, nanoropes, and nontubular nanoparticles). The results will also provide a foundation for field and personal sampling devices for CNT.

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.

Dutta (9141)

Role of Surface Chemistry in the Toxicological Properties of Manufactured Nanoparticles

Background

The objectives of this program are to verify two hypotheses: (1) the quantifiable differences in surface reactivity of nanoparticles, as measured by acidity, redox chemistry, metal ion binding and Fenton chemistry as compared with micron-sized particles of similar composition cannot be explained by the increase in surface area alone, and (2) the oxidative stress and inflammatory response induced by nanoparticles upon interaction with macrophages and epithelial cells depends on their surface reactivity. The basis of these hypotheses is that nanoparticles contain a significantly higher number 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 CNTs 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.

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 protection of 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 sensors that are substantially better than current state of the art. These improved sensors will be the basis for improved personal and permanent monitors for increased protection of workers in the semiconductor industry.

Table 2. Nanotechnology principal investigators funded by NIOSH/OEP; FY 2001–FY 2006

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Appendix E

Nanotechnology Information Dissemination

Research Project: Nanotechnology Information Dissemination

Prinicipal Investigator: Charles L. Geraci, Ph.D., C.I.H., EID/NIOSH/CDC

Project Duration: FY 2006–FY 2010

Background

Guidance and recommendations for managing and preventing occupational exposure to nanoparticles is needed to protect the health of workers. This project will produce and disseminate educational information about current best practices for minimizing occupational exposure risks during the various phases of nanomaterial research, development, production, and use. The types of communication products and vehicles to be used include the following:

- Interim recommendations on the NIOSH Web site to provide a vehicle for presenting the latest information about nanotechnology, and to provide customers a means to provide feedback, ask questions, and provide examples of work; a Nanoparticle Information Library (NIL) that contains chemical and physical properties of specific nanoparticles
- A Current Intelligence Bulletin on Working with Engineered Nanomaterials that will present NIOSH's current knowledge and recommendations on health effects, exposure limits, exposure monitoring, PPE, respiratory protection, and engineering controls
- Educational materials that will be used to teach the safety and health components of nanotechnology and nanomaterial processing at the graduate and undergraduate level
- Nano-safe training tool kits that can be used as part of an overall risk management program by nanotechnology companies or companies who incorporate nanomaterials into their products

This information will be valuable to the much larger population of secondary users of nanomaterials who may not be producing the materials, but are incorporating them into existing products. In addition to materials developed by NIOSH, partnerships with universities and businesses will be developed to incorporate their experience and share practices they have developed that have been effective. This project will allow for a direct translation of r2p by

communicating NIOSH research and field observations in training documents and tools. The time frame for this project extends into FY 2010 and will be the primary means to communicate NIOSH research results to the nanotechnology industry, and to maintain an active dialogue with that community.

Accomplishments

- Collected and assembled NTRC information and research results into the original version of Approaches *to Safe Nanotechnology: An information Exchange with NIOSH.* This document was posted on the NIOSH Web site on October 3, 2005.
- Developed a Nanotechnology Information Development and Dissemination project as part of the WHO coordinating centers portfolio.
- Developed an initial sampling protocol as part of the TiO_2 CIB to address possible contribution of nano-sized particles to workplace exposure.
- Established a working partnership with a metal oxide nanoparticle production facility to evaluate work practices and develop protocols to assess workplace exposures.
- Produced an update to *Approaches to Safe Nanotechnology* and posted it on the NIOSH Web site on June 4, 2006.
- Updated the NIOSH Nanotechnology Web topic page to highlight the ten critical research areas identified in the Strategic Research Plan.

Charles L. Geraci's activities in the NIOSH Nanotechnology Research Program

Accomplishments

- National and international promotion of NIOSH leadership in the area of nanotechnology occupational safety and health research
- Member of ISO TC 229 on Nanotechnologies, Working Group 3 in Health, Safety and Environment
- Expert reviewer to the ORC Nanotechnology Workgroup developing best practices for nanomaterial processes
- Nanotechnology expert contact for the memorandum of understanding between NIOSH and AIHA

- Project officer on the NIOSH project Nanotechnology Information Dissemination
- Developer and co-leader of the NIOSH Nanotechnology Field Research team
- Facilitated visits to three nanomaterial facilities

Invited Presentations

- Regulatory and risk overview [2006]. International Conference on Nanotechnology, Occupational and Environmental Health and Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Managing nanomaterials along the product life cycle [2006]. International Conference on Nanotechnology, Occupational and Environmental Health and Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Evaluation of a real-time surface area monitor in a nanotechnology workplace [2006]. Co-author on a poster presented at the International Conference on Nanotechnology, Occupational and Environmental Health and Safety: Research to Practice. Cincinnati, OH, December 4–7.
- Update on understanding and assessing an emerging technology in practice: continuation of an innovative industry/government partnership [2006]. Co-author on a poster presented at the International Conference on Nanotechnology, Occupational and Environmental Health & Safety; Research to Practice. Cincinnati, OH, December 4–7.
- Health issues associated with nanotechnology [2006]. Continuing Medical Education Seminar Series, College of Medicine, University of Cincinnati, November 29.
- Managing nanomaterials in the workplace: what do we know? [2006]. The American Society of Safety Engineers' Solutions in Safety Through Technology Symposium, Scottsdale, AZ, November 16–17.
- What is nanotechnology and should you be concerned? [2006]. Fall meeting of the Building Environment Council of Ohio, Columbus, OH, October 26.
- What every industrial hygienist should know about nanotechnology [2006]. Ohio Valley Section—American Industrial Hygiene Association, Cincinnati, OH, October 24.
- Risk based approach to nanoparticle management [2006]. Greater St. Louis Safety and Health Conference, St. Louis, MO, October 1.

- The NIOSH field effort to evaluate practices in nanotechnology [2006]. Commercialization of Nanomaterials, Pittsburgh, PA, September 20.
- The NIOSH nanotechnology research program: applicability to nanocomposites [2006]. Center for Multifunctional Polymer Nanomaterials and Devices, Board of Advisors Meeting, National Composites Center, Kettering, OH, August 15.
- The NIOSH nanotechnology research program: overview with emphasis on areas of industry collaboration [2006]. Joint Memorandum of Understanding Meeting: NIOSH and DuPont, NIOSH National Personal Protective Technology Laboratory (NPPTL), Pittsburgh, PA, August 3.
- Nanotechnology in the workplace: promoting innovation through better risk management [2006]. Campus Safety, Health and Environment Mangers Association Annual Conference, Anaheim, CA, July 19.
- Nanotechnology in the workplace: the NIOSH research program [2006]. NPE International Plastics Exposition, Special Educational session on Nanotechnology, Chicago, IL, June 20, 2006
- Occupational health risks of nanoparticles in the workplace [2006]. Nanocomposites 2006, Special Forum on Health Issues of Nanotechnology, Chicago, IL, June 19.
- Nanotechnology: ensuring workplace health and safety through better risk management [2006]. Nanotechnology in Food and Agriculture, Inaugural Conference by Food Chemical News, Washington, DC, June 7.
- The NIOSH nanotechnology research program: progress through industry partnerships [2006]. NanoBusiness Alliance, New York, NY, June 19.
- Nanotechnology research at NIOSH and applications to the pharmaceutical industry [2006]. AIHA Pharmaceutical Forum, American Industrial Hygiene Conference and Exposition, Chicago, IL, May 17.
- NIOSH nanotechnology program update: ask the experts—(arranged the session and presented updates): NIOSH information resources update and NIOSH Field Research Activities [2006]. American Industrial Hygiene Conference and Exposition, Chicago, IL, May 16.
- Nanotechnology: government initiatives [2006]. Special Symposium on Occupational Safety and Health Issues of Nanotechnology in the Workplace, American Industrial Hygiene Conference and Exposition, Chicago, IL, May 13.

- Nanotechnology health and safety professional development course [2006]. Health and Safety Canada, Industrial Accident Prevention Association Conference, Toronto, Canada, May 4. Delivered the following modules:
  - Physical and chemical characteristics, metrology, and exposure assessment
  - Risk management, work practices, safety, PPE
  - Information resources
- Overview of key NIOSH nanotechnology research projects: Building a nanoparticle information library, Potential application of control banding to nanotechnology, Nanotechnology information resources on the NIOSH Web, and Nanotechnology: a coordinated NIOSH research program [2006]. National Occupational Research Agenda Symposium, Washington, DC, April 18–20.
- Health and safety practices for nanotechnology [2006]. Special Panel Session, the Ohio Nanotechnology Summit 2006, Columbus OH, March 4.
- The NIOSH nanotechnology research program: an overview for Ohio [2006]. Nanotechnology Primer Session, the Ohio Nanotechnology Summit, Columbus, OH, March 4.
- A case study in partnering to develop a nanotechnology occupational safety and health program in a nanotechnology manufacturing environment [2006]. Co-author on poster presented at the Second International Symposium Nanotechnology and Occupational Health, Minneapolis, MN, October 4.

Future Presentations

- Nanotechnology: current knowledge for effective risk management [2007]. Oregon Governor's Occupational Safety & Health Conference, Salem, OR, March 12–15.
- Nanotechnology: what do we know for effective hazard communication? [2007]. Society for Chemical Hazard Communication, San Antonio, TX, April 25.
- NIOSH nanotechnology research update: ask the experts [2007]. Philadelphia, PA, June 5.

- Developing information for effective exposure evaluation and risk management in the production of nanoparticles [2007]. ASSE National Conference, Special Symposium on Developing Business Models for Managing Nanotechnology, Orlando, FL, June 2–7.

National and International Activities

- C. Geraci is a member of the ISO Technical Committee 229 on Nanotechnologies, Work Group 3 *Technical report on current safe practices in occupational settings relevant to nanotechnologies.*
- C. Geraci was the Co-Organizer of the Conference Planning Committee and Co-Chair of the Applications Session of the International Conference on Nanotechnology, Occupational and Environmental Health and Safety: Research to Practice, Cincinnati, OH, December 4–7, 2006.
- C. Geraci is the U.S. member of the International Advisory Committee Member for the U.S. for the Third International Symposium on Nanotechnology: Occupational and Environmental Health, Taipei, Taiwan, August 29 to September 1, 2007.
- C. Geraci is a member of the American Industrial Hygiene Association Nanotechnology Working Group.
- C. Geraci served as an Expert Peer Reviewer to the ORC Nanomaterials Work Practices Workgroup.

Partnerships and Collaborations

- Developed a partnership with an international cosmetic product manufacturer to evaluate exposures, work practices, and controls during the introduction of nanoparticle materials.
- Ongoing partnership with a primary metal oxide manufacturer: characterization of exposures to metal oxide nanoparticles; develop work practices and controls; evaluate effectiveness of controls; develop a return-on-investment study for controls and health safety and environmental improvements.
- Planned investigations in the nanocomposites industry through a partnership with the Center for Multifunctional Polymer Nanomaterials and Devices (CMPND) and the University of Dayton Research Institute.
- Participated in an inaugural workshop on nanotechnology with the Campus Safety, Health and Environment Management Association (CSHEMA) and developed a strategy for Web-casting workshops.

NTRC Critical Research Topic Areas Addressed

1. Exposure Assessment
2. Communication and Education
3. Recommendations and Guidance
4. Measurement Methods

Appendix F

Other NTRC Partnership Activities and Presentations

Other NTRC Staff, Activities in the NIOSH Nanotechnology Research Program

John Howard, M.D.

Presentations

- The NIOSH nanotechnology initiative: ensuring a safe and healthful workforce in a changing environment. Kansas City Safety and Health Conference, ASSE, Kansas, MO, July 14–15.
- The NIOSH nanotechnology initiative: ensuring a safe and healthful workforce in a changing environment. The Art of Safety: the 10th Anniversary Commemorative Safety & Health Congress and Expo, Isla Verde, PR. The NIOSH Nanotechnology Initiative: Ensuring a safe and healthful workforce in a changing environment, July 30–August 5.
- The NIOSH nanotechnology initiative: ensuring a safe and healthful workforce in a changing environment [2005]. OSHA Health Forum, Denver, CO, August 31.
- Perspectives on nanotechnology '[2006]. NIOSH and Nanotechnology, Woodrow Wilson International Center for Scholars, Washington, DC, February 23.
- National CleanRooms Contamination Control [2006]. Nanotechnology and Risk: The NIOSH Perspective. Technology Conference & Exposition on 15 March, Boston MA, March 15.
- Mt. Sinai annual ERC meeting on toxicity and control issues [2006]. Nanotechnology and risk: the NIOSH perspective. April 7.
- NIOSH at 5 years of NNI [2006]. International Nanotechnology Conference on Communication and Cooperation. Arlington, VA, May 15–17.
- Nanotechnology and risk: the NIOSH perspective [2006]. Congress of Nanobiotechnology and Nanomedicine (NanoBio 2006). San Francisco, CA, June 19–21.

Vladimir Murashov, Ph.D.

Publications and Abstracts

- ISO/TC 229/WG3 Summary of U.S. research and development activities on nanotechnology related to environmental health and safety [2006]. NANO TAG N 221–2006, ANSI.

- Report of the OECD workshop on the safety of manufactured nanomaterials building Co-operation, Co-ordination, and Communication [2005]. Washington DC, December 7–9. Environment Directorate, Organisation for Economic Cooperation and Development, Paris [2006].
- Murashov VV [2006]. Comments on Particle surface characteristics may play an important role in phytotoxicity of alumina nanoparticles (by Yang L and Watts, DJ, published in Toxicol Lett [2005] *158*:122–132). Toxicol Lett *164*:185–187.

Presentations

- Nanotechnology: preparing for public health assessment [2006]. George Washington University, School of Public Health. Introductory environmental and occupational health course, Washington, DC, June 5.
- Nanotechnology: research perspective/current knowledge [2006]. National Response Team Worker Safety and Health Technical Conference, Washington, DC, May 31.
- Nanotechnology: government initiatives [2006]. Nanotechnology Symposium: Nanoparticles in the Workplace, Chicago, IL, May 13.
- Safe nanotechnology [2006]. NSTI Nanotech 2006, Boston, MA, May 9.
- NIOSH nanotechnology program: funding [2006]. International Conference on Nanotechnology. Technical Association for the Pulp and Paper Industry, Atlanta, GA, April 28.
- NIOSH nanotechnology program: research [2006]. International Conference on Nanotechnology. Technical Association for the Pulp and Paper Industry, Atlanta, GA, April 26.
- NIOSH nanotechnology program [2006]. Office of Extramural Programs, NIOSH, Atlanta, GA, April 25.
- Nanotechnology and risk: NIOSH perspective [2006]. RIMS 2006 Annual Conference and Exhibition. Honolulu, HI, April 24.
- Nanotechnology: ensuring a safe and healthful workplace [2006]. PDC Piedmont Chapter of the ASSE, SC, March 16.
- NIOSH Nanotechnology Program [2006]. NanoBusiness Alliance, Washington, DC, February 17.
- NIOSH Nanotechnology Program [2006]. American Insurance Association, Washington, DC, February 8.

- NIOSH Current Intelligence Bulletin on TiO_2 [2006]. Particles and Cancer, MIT Conference, San Juan, PR, January 11.
- Nanotechnology: ensuring a safe and healthful workplace [2005]. 2005 MRS Fall Meeting, Symposium S: Nanomaterials and the Environment, Boston, MA, December 1.
- Occupational safety and health and nanotechnology: knowns and unknowns, Nanotechnology: are the health and safety concerns as small as the particles? [2005].AIHA Texas Hill Country Section 2005 Symposium, Austin, TX, November 3.
- NIOSH Nanotechnology Research Program [2005]. Nanotechnology and the Environment: Applications and Implications Progress Review Workshop III, Arlington, VA, October 26–28.
- NIOSH and National Nanotechnology Initiative [2005]. Aerospace Industries Association ES&H Fall 2005 Meeting, Redondo Beach, CA, October 12–14.
- NIOSH Nanotechnology Research Program [2005]. American Chemistry Council Nanotechnology Panel, Arlington, VA, September 20.

National and International Activities

- Member of NSET Subcommittee of the National Science and Technology Council's Committee on Technology and its working groups.
- Member of the NNI-Chemical Industry Consultative Board for Advancing Nanotechnology.
- Member of the National Electrical Manufacturers Association's Nanotechnology Advisory Council.
- Member of the external peer-review panel for EPA White Paper on Nanotechnology, June 2006.

Paul Schulte, Ph.D.

Publications

- Schulte PA, Salamanca-Buentello F [2006]. Ethical and scientific issues of nanotechnology in the workplace. *Environmental Health Perspectives*. available at http://www.ehponline.org/docs/2006/9456/abstracts.html

Invited Presentations

- Occupational Safety and Health Issues in Nanotechnology [2006]. International Commission on Occupational Health. Milan, Italy, June 12.

- NIOSH Nanotechnology Research [2005]. Nanoparticle Occupational Health and Safety Workshop sponsored by the Massachusetts Toxics Use Reduction Institute and the Center for High-Rate Nanomanufacturing. Westborough, MA. December 2.

Presentations

- Nanotechnology and Occupational Safety and Health and Ethical/Medical Issues [2006]. Presentations at the International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice. Cincinnati, OH. December 4–7.
- Nanotechnology [2006]. Health and Safety Professional Development Course, Health and Safety Canada 2006, Industrial Accident Prevention Association Conference, Toronto, Canada, May 4. Delivered the following modules:
  - Overview
  - Toxicology
  - Risk Assessment
  - Medical Surveillance
  - Ethical Issues
- Panel Member. Ethical and legal aspects of nanomaterials and environmental regulation [2005]. Materials Research Society Fall Meeting, Boston, MA, December 1.

NTRC Critical Research Topic Areas Addressed

1. Communication and Education
2. Recommendation and Guidance

Appendix G

Projected Timeframe for Addressing Critical Areas

Projected timeframe for addressing critical areas

NIOSH 10 critical areas	Calendar year				
	2005	2006	2007	2008	2009
Exposure assessment	DEP* generation and characterization studies (NORA-PRL, HELD base) Wildfire ultrafine aerosol and firefighter exposure studies (SNORA-DRDS)	Data and preliminary dosimetry for DEP (HELD base, NORA-PRL) Data and preliminary dosimetry for firefighters (SNORA-DRDS) Dosimetry lung model in rats and humans, begin phase I: structure and calibration w/ existing data (NTRC-EID) Initiate TiO_2 workplace exposure assessment (DSHEFS unfunded) Initiate field surveys of workplaces handling nanomaterials	Nanoparticle evaluations in an automotive plant (NTRC-DART) TiO2 workplace exposure assessment report (DSHEFS unfunded) Continue evaluation and characterization of nanoparticle exposures in workplaces handling nanomaterials	Dosimetry lung model in rats and humans, begin phase II: calibration and validation with translocation data (NTRC-EID pending) Continue evaluation and characterization of nanoparticle exposures in workplaces handling nanomaterials	Continue evaluation and characterization of workplaces handling nanomaterials
Toxicity and internal dose	Preliminary results from toxicity testing in laboratory animal and in vitro systems (NORA-HELD)	Hazard ID information on carbon nanotubes (NORA-HELD)	Preliminary cardiovascular endpoints (NORA-HELD pending) Surface area-mass metric results (NORA-HELD) Dose-response data for diesel exhaust particles (HELD)	Complete dose and time information on carbon nanotubes (NORA-HELD) Nanometal hazard ID (NORA-HELD) Dermal information (NORA-HELD) Neurological effects (HELD base) Translocation results in laboratory animals after pulmonary and dermal exposure to nanomaterials (NORA-HELD)	Development of firm cardiovascular endpoints (NORA-HELD) Quantification of systemic nanoparticle concentrations in laboratory animals after pulmonary exposure to nanospheres and nanofibers (NORA-HELD)

(Continued)

Projected timeframe for addressing critical areas

NIOSH 10 critical areas	Calendar year				
	2005	2006	2007	2008	2009
Epidemiology and surveillance	Phase I—baseline information gathering (NTRC-DRDS)	Survey of uses and workers (DRDS-DSHEFS unfunded) Phase I—baseline information gathering (NTRC-DRDS) Correlation of health effects with ultrafine aerosol exposures in auto workers (NTRC-DART-DSHEFS pending)	Phase I—baseline information gathering Phase II—population studies	Phase I—baseline information gathering Levels of exposure and routes	Further correlation of health effects with ultrafine aerosol exposures in auto workers
Risk assessment	Preliminary QRA on TiO_2 from existing studies (EID base) Initiate collaborative research on lung model development and nanoparticle dose estimation (NTRC-EID) External review draft of CIB developed with separate RELs for fine and ultrafine TiO_2 based on NIOSH QRA	Perform QRA on other fine and ultrafine materials from existing studies (EID base) Publish scientific papers on QRA methods for nanoparticles including TiO_2 Develop lung deposition model enhancements	Continue QRA of fine and ultrafine particles (EID) Initiate hazard/risk evaluation for nanomaterials in workplace (EID) Extend and calibrate rat lung dosimetry model for nanoparticles (NTRC-EID) Start estimation of nanoparticle deposition in nasopharyngeal region (NTRC-EID) Start evaluation and modeling of CNT inhalability and lung deposition (NTRC-EID)	QRA for nanoparticles using new NIOSH data (EID pending) Validate rat dosimetry model for nanoparticles using new NIOSH data (NTRC-EID) Human lung model variability and uncertainty results (NTRC-EID) Nasopharyngeal deposition results (NTRC-EID) CNT inhalability modeling preliminary results (NTRC-EID) Use hazard/risk evaluation in NIOSH guidance document (EID-pending)	Extend human lung dosimetry model for nanoparticle estimation (NTRC-EID) Initiate CNT human lung dosimetry model based on preliminary results (NTRC-EID pending) Preliminary QRA for CNT based on rodent data (EID pending)

(Continued)

Projected timeframe for addressing critical areas

NIOSH 10 critical areas	Calendar year				
	2005	2006	2007	2008	2009
Measurement methods	Pilot studies of nanoparticles in the workplace (DRDS) Development of techniques for online surface area measurement (DART)	Measurement studies of nanoparticles in the workplace (DRDS and others)	Established suite of instruments and protocols (NTRC-DRDS) Measurement studies of nanoparticles in the workplace (DRDS and others) Further development of online and offline nanoparticle measurement methods (DRDS-DART)	Viable and practical workplace sampling device for nanoparticles (affordable, portable, effective) (NTRC-DART-DRDS and others)	Performance results for nanoparticle measurement instruments and methods (DRDS and others)
Engineering controls and PPE	Identification of key control issues	Analyses of filter efficiency (NPPTL-DRDS) Evaluation of control banding options (NTRC-EID-DRDS-DART)	Testing controls in auto plants (DART-DSHEFS) Respirator performance evaluations (NPPTL)	Evaluation of control improvements in auto plants (DART-DSHEFS) Evaluation of clothing and other	Summary of control strategies (NTRC-DART)
Fire and explosion safety	Identification of key safety issues (DSR-NPPTL)	Initiate efforts to investigate fire and explosion hazards of nanomaterials	Good safety handling practices (NTRC-DSR-NPPTL)		Summary of nanotechnology safety experience (NTRC-DSR)
Communication and education	Basic set of FAQs (NTRC, OD base) Web site updates (NTRC-EID, OD, others base) Public presentations (NTRC and many divisions base) NIL pilot (SRL-DRDS)	Expanded set of FAQs (DART, NTRC and many divisions base) Web site updates (NTRC, EID, OD, others base) Public presentations (NTRC and many divisions base) NIL updates (SRL-DRDS)	Web site updates (NTRC, EID, OD, others base) Public presentations (NTRC and many divisions base) NIL updates (SRL-DRDS)	Web site updates (NTRC, EID, OD, others base) Public presentations (NTRC and many divisions base) NIL updates (SRL-DRDS)	Web site updates (NTRC, EID, OD, others base) Public presentations (NTRC and many divisions base) NIL updates (SRL-DRDS)

(Continued)

Projected timeframe for addressing critical areas

NIOSH 10 critical areas	Calendar year				
	2005	2006	2007	2008	2009
Recommendations and guidance	External review of NIOSH TiO_2 CIB (EID base)	Publication of TiO_2 CIB (EID base)	Good working practices guidelines (DART base) Nanomaterials document (NTRC base)	New or updated Nanomaterials document (NTRC base)	New or updated Nanomaterials document (NTRC base)
Applications	NIOSH education series	Roadmap up and running	Prioritized list of short term impact r2p	Further r2p	Further r2p

*Abbreviations: CIB=Current Intelligence Bulletin; CNT=carbon nanotube; DART=Division of Applied Research and Technology; DEP=diesel exhaust particulate; DRDS=Division of Respiratory Diseases; DSHEFS=Division of Surveillance Hazard Evaluation and Field Studies; EID=Education and Information Division; FAQs=Frequently Asked Questions; HELD=Health Effect Laboratory Division; ID=identification; NIL=Nanoparticle Information Library; NIOSH=National Institute for Occupational Safety and Health; NORA=National Occupational Research Agenda; NPPTL=National Personal Protective Technology Library; NTRC=Nanotechnology Research Center; OD=Office of the Director; PPE=personal protective equipment; PRL=Pittsburgh Research Laboratory; QRA=quantitative risk assessment; r2p=research to practice; SNORA=Small National Occupational Research Agenda (on PPE); SRL=Safety Research Laboratory; TiO_2=titanium dioxide.

Appendix H

Executive Summary

Approaches to Safe Nanotechnology: An Information Exchange with NIOSH

Approaches to Safe Nanotechnology: An Information Exchange with NIOSH

The Executive Summary is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. The draft document "Approaches to Safe Nanotechnology: An Information Exchange with NIOSH" has not been formally disseminated by CDC/NIOSH and should not be construed to represent any agency determination or policy. A copy of the draft document can be found at the NIOSH Web site: http://www.cdc.gov/niosh/topics/nanotech/

Executive Summary

Nanotechnology has the potential to dramatically improve the effectiveness of a number of existing consumer and industrial products and could have a substantial impact on the development of new applications ranging from disease diagnosis and treatment to environmental remediation. Because of the broad range of possible nanotechnology applications, continued evaluation of the potential health risks associated with exposure to nanomaterials is essential to ensure their safe handling. Nanomaterials are engineered materials having at least one dimension between 1 and 100 nanometers. Nanomaterials often exhibit unique physical and chemical properties that impart specific characteristics essential in making engineered materials, but little is known about what effect these properties may have on human health. Research has shown that the physiochemical characteristics of particles can influence their effects in biological systems. These characteristics include particle size, shape, surface area, charge, chemical properties, solubility, and degree of agglomeration. Until the results from research studies can fully elucidate the characteristics of nanoparticles that may potentially pose a health risk, precautionary measures are warranted.

NIOSH has developed this document to provide an overview of what is known about nanomaterial toxicity and measures that can be taken to minimize workplace exposures. NIOSH is seeking comments from occupational safety and health practitioners, researchers, product innovators and manufacturers, employers, workers, interest group members, and the general public so that appropriate existing safety and health guidance can be further refined and disseminated. Opportunities to provide feedback and information are available throughout the document.

The following is a summary of findings and key recommendations:

Potential Health Concerns

- The potential for nanomaterials to enter the body is among several factors that scientists examine in determining whether such materials may pose an occupational health hazard. Nanomaterials have the greatest potential to enter the body if they are in the form of nanoparticles, agglomerates of nanoparticles, and particles from nanostructured materials that become airborne or come into contact with the skin.
- Based on results from human and animal studies, airborne nanomaterials can be inhaled and deposit in the respiratory tract; and based on animal studies, nanoparticles can enter the blood stream, and translocate to other organs.
- Experimental studies in rats have shown that equivalent mass doses of insoluble ultrafine particles (smaller than 100 nm) are more potent than large particles of similar composition in causing pulmonary inflammation and lung tumors in those laboratory animals. However, toxicity may be mitigated by surface characteristics and other factors. Results from *in vitro* cell culture studies with similar materials are generally supportive of the biological responses observed in animals.
- Cytotoxicity and experimental animal studies have shown that changes in the chemical composition, structure of the molecules, or surface properties of certain nanomaterials can influence their potential toxicity.
- Studies in workers exposed to aerosols of manufactured microscopic (fine) and nanoscale (ultrafine) particles have reported lung function decrements and adverse respiratory symptoms; however, uncertainty exists about the role of ultrafine particles relative to other airborne contaminants (e.g., chemicals, fine particles) in these work environments in causing adverse health effects.
- Engineered nanoparticles whose physical and chemical characteristics are like those of ultrafine particles need to be studied to determine if they pose health risks similar to those that have been associated with the ultrafine particles.

Potential Safety Concerns

- Although insufficient information exists to predict the fire and explosion risk associated with nanoscale powders, nanoscale combustible

material could present a higher risk than coarser material with a similar mass concentration given its increased particle surface area and potentially unique properties due to the nanoscale.

- Some nanomaterials may initiate catalytic reactions depending on their composition and structure that would not otherwise be anticipated from their chemical composition alone.

Working with Engineered Nanomaterials

- Nanomaterial-enabled products such as nanocomposites and surface coatings, and materials comprised of nanostructures such as integrated circuits are unlikely to pose a risk of exposure during their handling and use. However, some of the processes (formulating and applying nanoscale coatings) used in their production may lead to exposure to nanoparticles.
- Processes generating nanomaterials in the gas phase, or using or producing nanomaterials as powders or slurries/suspensions/solutions pose the greatest risk for releasing nanoparticles. Maintenance on production systems (including cleaning and disposal of materials from dust collection systems) is likely to result in exposure to nanoparticles if it involves disturbing deposited nanomaterial.
- The following workplace tasks may increase the risk of exposure to nanoparticles:
  - Working with nanomaterials in liquid media without adequate protection (e.g., gloves) will increase the risk of skin exposure.
  - Working with nanomaterials in liquid during pouring or mixing operations, or where a high degree of agitation is involved, will lead to an increase likelihood of inhalable and respirable droplets being formed.
  - Generating nanoparticles in the gas phase in non-enclosed systems will increase the chances of aerosol release to the workplace.
  - Handling nanostructured powders will lead to the possibility of aerosolization.
  - Maintaining equipment and processes used to produce or fabricate nanomaterials or the clean-up of spills or waste material will pose a potential for exposure to workers performing these tasks.
  - Cleaning of dust collection systems used to capture nanoparticles can pose a potential for both skin and inhalation exposure.

— Machining, sanding, drilling, or other mechanical disruptions of materials containing nanoparticles can potentially lead to aerosolization of nanomaterials.

Exposure Assessment and Characterization

- Until more information becomes available about the mechanisms underlying nanoparticle toxicity, it is uncertain as to what measurement technique should be used to monitor exposures in the workplace. Current research indicates that mass and bulk chemistry may be less important than particle size and shape, surface area, and surface chemistry (or activity) for nanostructured materials.
- Many of the sampling techniques that are available for measuring airborne nanoaerosols vary in complexity but can provide useful information for evaluating occupational exposures with respect to particle size, mass, surface area, number concentration, composition, and surface. Unfortunately, relatively few of these techniques are readily applicable to routine exposure monitoring.
- Regardless of the metric or measurement method used for evaluating nanoaerosol exposures, it is critical that background nanoaerosol measurements be conducted before the production, processing, or handling of the nanomaterial/nanoparticle.
- When feasible, personal sampling is preferred to ensure an accurate representation of the worker's exposure, whereas area sampling (e.g., size-fractionated aerosol samples) and real-time (direct reading) exposure measurements may be more useful for evaluating the need for improvement of engineering controls and work practices.

Precautionary Measures

- Given the limited amount of information about the health risks associated with occupational exposure to engineered nanoparticles, it is prudent to take measures to minimize worker exposures.
- For most processes and job tasks, the control of airborne exposure to nanoaerosols can be accomplished using a wide variety of engineering control techniques similar to those used in reducing exposure to general aerosols.
- The implementation of a risk management program in workplaces where exposure to nanomaterials exists can help to minimize the potential for exposure to nanoaerosols. Elements of such a program should include the following:

- Evaluating the hazard posed by the nanomaterial based on available physical and chemical property data and toxicology or health effects data
- Assessing potential worker exposure to determine the degree of risk
- The education and training of workers in the proper handling of nanomaterials (e.g., good work practices)
- The establishment of criteria and procedures for installing and evaluating engineering controls (e.g., exhaust ventilation) at locations where exposure to nanoparticles might occur
- The development of procedures for determining the need and selection of PPE (e.g., clothing, gloves, respirators)
- The systematic evaluation of exposures to ensure that control measures are working properly and that workers are being provided the appropriate PPE

- Engineering control techniques such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems should be effective for capturing airborne nanoparticles. Current knowledge indicates that a well-designed exhaust ventilation system with a HEPA filter should effectively remove nanoparticles.
- The use of good work practices can help to minimize worker exposures to nanomaterials. Examples of good practices include; cleaning of work areas using HEPA vacuum pickup and wet wiping methods, preventing the consumption of food or beverages in workplaces where nanomaterials are handled, and providing facilities for hand-washing and showering and changing clothes.
- No guidelines are currently available on the selection of clothing or other apparel (e.g., gloves) for the prevention of dermal exposure to nanoaerosols. However, some clothing standards incorporate testing with nanoscale particles and therefore provide some indication of the effectiveness of protective clothing with regard to nanoparticles.
- Respirators may be necessary when engineering and administrative controls do not adequately prevent exposures. Currently, no specific exposure limits exist for airborne exposures to engineered nanoparticles although occupational exposure limits exist for larger particles of similar chemical composition. The decision to use respiratory protection should be based on professional judgment that takes into account

toxicity information, exposure measurement data, and the frequency and likelihood of the worker's exposure. Preliminary evidence shows that for respirator filtration media there is no deviation from the classical single-fiber theory for particulates as small as 2.5 nm in diameter. While this evidence needs confirmation, it is likely that NIOSH certified respirators will be useful for protecting workers from nanoparticle inhalation when properly selected and fit tested as part of a complete respiratory protection program.

Occupational Health Surveillance

- The unique physical and chemical properties of nanomaterials, the increasing growth of nanotechnology in the workplace, available information about biological and health effects in animals associated with exposures to some types of engineered nanoparticles in laboratory studies, and available information about the occupational health effects of incidental ultrafine particles all underscore the need for medical and hazard surveillance for nanotechnology. Every workplace dealing with nanoparticles, engineered nanomaterials, or other aspects of nanotechnology should consider the need for an occupational health surveillance program. NIOSH is in the process of formulating guidance relevant to occupational health surveillance for nanotechnology.

Delivering on the Nation's promise: Safety and health at work for all people through research and prevention

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

1–800–35–NIOSH (1–800–356–4674)
Fax: 513–533–8573
E-mail: pubstaft@cdc.gov

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