Strategic Plan for NIOSH Nanotechnology Research

Filling the Knowledge Gaps

Draft

September 28, 2005

Nanotechnology Research Program
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Director's Message

The National Institute for Occupational Safety and Health (NIOSH) is pleased to ask for your comments on the *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps*. The program is a part of our overall Manufacturing Sector Program of the National Occupational Research Agenda (NORA). Nanotechnology provides many opportunities and challenges for all of us in occupational safety and health. The *Strategic Plan* for the nanotechnology program is the roadmap we are using to advance knowledge about the applications and implications of nanomaterials.

I welcome your review and your comments on our plan. Please e-mail your comments to nanostratplan@cdc.gov. I also invite you to partner with NIOSH in generating new knowledge about this vitally important twenty-first century technology and in translating that knowledge into occupational safety and health practice.

Thank you.

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

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EXECUTIVE SUMMARY

Nanotechnology is the manipulation of matter on a near-atomic scale to produce new structures, materials, and devices. This technology has the ability to transform many industries and will have numerous applications to areas ranging from medicine to manufacturing. Research in nanoscale technologies is growing rapidly worldwide. By 2015, the National Science Foundation estimates that nanotechnology will have a $1 trillion impact on the global economy and employ 2 million workers, 1 million of which may be in the United States. Nanomaterials may present new challenges to understanding, predicting, and managing potential health risks to workers. Many knowledge gaps remain to be filled before we fully understand how to work safely with these materials. Through strategic planning, research, partnering with others, and making information widely available, the National Institute for Occupational Safety and Health (NIOSH) is working in parallel with the development and implementation of nanotechnology to provide national and world leadership in preventing work-related illness and injury.

NANOTECHNOLOGY AND NIOSH RESEARCH

The potential and rapid growth of nanotechnology may far outpace the knowledge about associated safety and health risks. To prevent this from happening, timely targeted research is needed to define risks and provide guidance for safe handling of nanomaterials. A concerted effort is needed by industry, academia, labor, the professions, and government to identify and address the knowledge gaps in a transparent and credible process that coincides with development of this new technology. NIOSH can play an active part in this process through scientific research in occupational safety and health and the development of strategies for worker protection. Thus NIOSH is supporting the development of a broad spectrum of research and prevention strategies related to nanotechnology.

NIOSH NANOTECHNOLOGY RESEARCH CENTER (NTRC)

Given the current and future growth of nanotechnology and the potential for wide-scale worker involvement, NIOSH established the NIOSH Nanotechnology Research Center (NTRC) in 2004 to accelerate progress in nanotechnology research across the Institute. The NTRC and its Steering Committee consist of NIOSH scientists from various disciplines who are responsible for developing and guiding NIOSH scientific and organizational plans in nanotechnology health research. Informed by a broad range of collaborations and inputs from government agencies, academia, and the private sector, NIOSH has developed a strategic plan for NIOSH nanotechnology research.

Vision of the NTRC

The vision of the NTRC is as follows:

Safe nanotechnology by delivering on the Nation's promise—safety and health at work for all people through research and prevention.

Mission of the NTRC

The mission of the NTRC is to provide national and world leadership for research into the application of nanoparticles and nanomaterials in occupational safety and health and the implications of nanoparticles and nanomaterials for work-related injury and illness.

THE STRATEGIC PLAN FOR NIOSH NANOTECHNOLOGY RESEARCH

The purpose of the strategic plan for NIOSH nanotechnology research is to provide a tool for coordinating nanotechnology research across the Institute and to provide a guide for enhancing the development of new research efforts that will respond to the challenges of working with a new technology. The strategic plan represents a cohesive, multidimensional, and timely research agenda for addressing knowledge gaps concerning possible worker exposures to nanomaterials, the health risks from such exposure, and development of control technology and prevention measures. The planning process incorporated input from collaborators and stakeholders.

GOALS FOR NIOSH NANOTECHNOLOGY RESEARCH

The goals for NIOSH nanotechnology research are as follows:

1. Understand and prevent work-related injuries and illnesses potentially caused by nanoparticles and nanomaterials.

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

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

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

The strategies for achieving these goals consist of intermediate and long-term objectives. The nature of these objectives is described for each goal:

- ► GOAL 1: Understand and prevent work-related injuries and illnesses potentially caused by nanoparticles and nanomaterials.

  To achieve this goal, researchers must determine the relative toxicity of nanoparticles and nanomaterials and identify possible health effects from the early uses of the materials. Critical to assessing risks will be the ability to measure nanoparticles in workplace air. Research will be conducted to develop and validate methods of exposure assessment. The assessment of health effects will be difficult because only a small number of workers have been exposed, and they have been exposed for relatively short periods. Innovative research will be needed to monitor the health of this emerging workforce. In addition, predictive animal models need to be developed to provide hazard identification, dose-response, and risk assessment information necessary for various nanoparticles and nanomaterials. Information and knowledge gained from this research will form the basis of recommendations and guidance on the safe handling of nanomaterials.

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

  Nanotechnology is potentially useful for studying and preventing occupational injuries and illnesses. However, such applications need to be investigated and developed. Engineered nanomaterials may support the development of high performance filter media, respirators, coatings in non-soiling/dust-repellant/self-cleaning clothes, fillers for noise absorption materials, fire retardants, protective screens for prevention of roof falls and curtains for ventilation control in mines, catalysts for emissions reduction, and cleanup of pollutants and hazardous substances. Nanotechnology-based sensors and communication devices may help in handling emergencies and in empowering workers to take preventive steps for reducing their risk of injury. The smallness of their size coupled with wireless technology may facilitate development of wearable sensors and systems for real- time occupational safety and health management. Nanotechnology-based fuel cells, lab-on-chip analyzers, and opto-electronic devices all have the potential to be useful in the safe, healthy, and efficient design of work itself.

  NIOSH intends to develop a roadmap to pursue these potential nanotechnology applications for the advancement of occupational safety and health in the workplace. Research (using partnerships with industry, academia, and labor) will focus on evaluating feasibility in the laboratory environment followed by testing in the field.

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

A critical gap in the development of nanotechnology is the lack of guidance on safe handling of nanomaterials. Two approaches will be used to accomplish this goal. First, NIOSH will develop guidance based on the review and evaluation of current best practices, available knowledge, and professional judgment. Second, NIOSH will conduct translation of research on engineering controls, protective equipment, occupational exposure limits, and administrative controls. In both approaches, the use of control banding (a hazard-based approach to risk assessment and control) will be evaluated and, where appropriate, considered for recommendation. The information developed by NIOSH will be widely disseminated and efforts will be made to incorporate it in training programs and occupational safety and health management systems.

► GOAL 4: Enhance global workplace safety and health through national and international collaborations on nanotechnology.

The growth and utilization of nanotechnology is a global phenomenon that requires a global response. The impacts of global influences on labor markets, capital investment, and scientific research are well known and will affect the development of nanotechnology. NIOSH has a history of and commitment to working with international groups to promote occupational safety and health. Use of national and international partnerships and the establishment of new partnerships will assure timely identification of research needs, development of approaches, and communication of results. This will include the development and dissemination of information and training for occupational safety and health professionals and workers.

The strategic plan is built on the integration of research, guidance, and practice. As nanotechnology grows, progresses, and is used more widely, new and expanded questions will be raised about its safety and impact on the health of workers. This developing technology calls for a dynamic planning strategy. The plan will evolve as new scientific information is obtained, questions arise, and concerns of stakeholders and partners are raised. By maintaining such a dynamic approach, NIOSH will be poised to anticipate challenges and provide useful information and knowledge for the safe handling of nanomaterials.

Strategic Plan for NIOSH Nanotechnology Research

Filling the Knowledge Gaps

I. INTRODUCTION

Background

Nanotechnology is the control and manipulation of matter at near-atomic scale to produce new materials, structures, and devices. Nanoparticles have at least one dimension that is less than 100 nanometers, and they exhibit unique properties because of their nanoscale dimensions. Nanotechnology has potential applications for integrated sensors, semiconductors, medical imaging, drug delivery systems, structural materials, sunscreens, cosmetics, coatings, and many other uses. 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.

Interagency efforts 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 nanomaterials (**Appendix A**), (2) protecting worker safety and health, and (3) developing a strategic plan to address such issues and recommend prevention strategies, methods for safe handling, and safe work practices.

Because of their small size and large surface area, engineered nanoparticles may have biological properties distinct from 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 positioned well to proactively 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. Over this period, NIOSH has developed considerable expertise in measuring, characterizing, and evaluating health effects. The Institute 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 will use this experience to address similar issues for engineered nanoparticles.

NIOSH is responding aggressively to conduct the research needed to resolve nanotechnology knowledge gaps in the field of occupational safety and health. In 2004, NIOSH funded a six-project Nanotechnology Safety and Health Research Program to address issues of exposure measurement, nanoparticle characterization, and biological effects in the pulmonary and cardiovascular systems. Also in 2004, NIOSH instituted a Nanotechnology Research Center (NTRC) to identify critical issues, create a strategic plan for investigating these issues, coordinate the NIOSH research effort, develop research partnerships, and disseminate information gained. As a result of NTRC, NIOSH has added four more projects to its nanotechnology research portfolio in the areas of surveillance, control, risk assessment, and dissemination. Four new projects are anticipated in 2006; these will focus on safe materials handling, exposure assessment and mitigation, and further toxicity testing.

NIOSH Logic Model

Like other scientific organizations, NIOSH can be described by a model of the way it functions to solve identified problems under various conditions. The overall NIOSH logic model is presented in Figure 1. It has a conventional horseshoe shape, with the operational upper branch proceeding from inputs to outcomes, and with the strategic lower branch proceeding from strategic goals to management objectives. Both branches are correlated vertically and are subject to external factors.

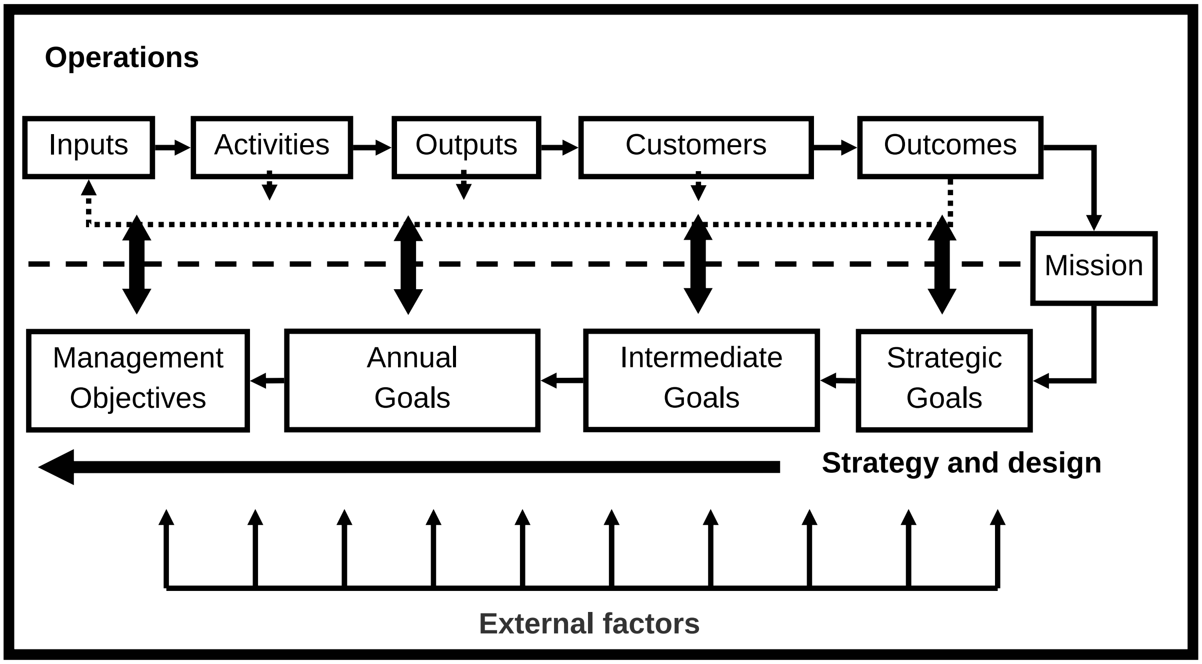

Figure 1. Schematic of the overall NIOSH logic model.

The NIOSH research program begins with an analysis of production and planning inputs (Figure 2). This analysis determines what can and should be done and thereby identifies research priorities. Intramural and extramural researchers present their project proposals, which receive appropriate internal and external review and are funded based on proposal merits. Research activities produce outputs such as published materials, oral presentations, training and educational materials, tools, methods and technologies. NIOSH research outputs are transferred directly to the final customers and partners (who implement improvements in workplace safety and health) or to intermediate customers (who transform further NIOSH outputs and produce intermediate outcomes). These intermediate outcomes such as pilot technologies, training programs, and regulations and standards are forwarded to the final customers. Since NIOSH is not a regulatory agency, it relies heavily on efforts by intermediate and final customers to achieve ultimate outcomes in the form of workplace safety and health improvements. Effectiveness in achieving these ultimate outcomes is influenced by external factors such as economic and social conditions and the regulatory environment at all stages of program operation. Results of NIOSH-funded research, intermediate feedback, and final feedback from customers contribute to the subsequent rounds of program planning.

The NIOSH Nanotechnology Research Strategic Plan will follow the NIOSH operational model (Figure 2). The strategic planning activity is being conducted by the NIOSH NTRC. The strategic goals and objectives as well as targets and performance measures are introduced in Section VII and described in more detail in Appendices B and C.

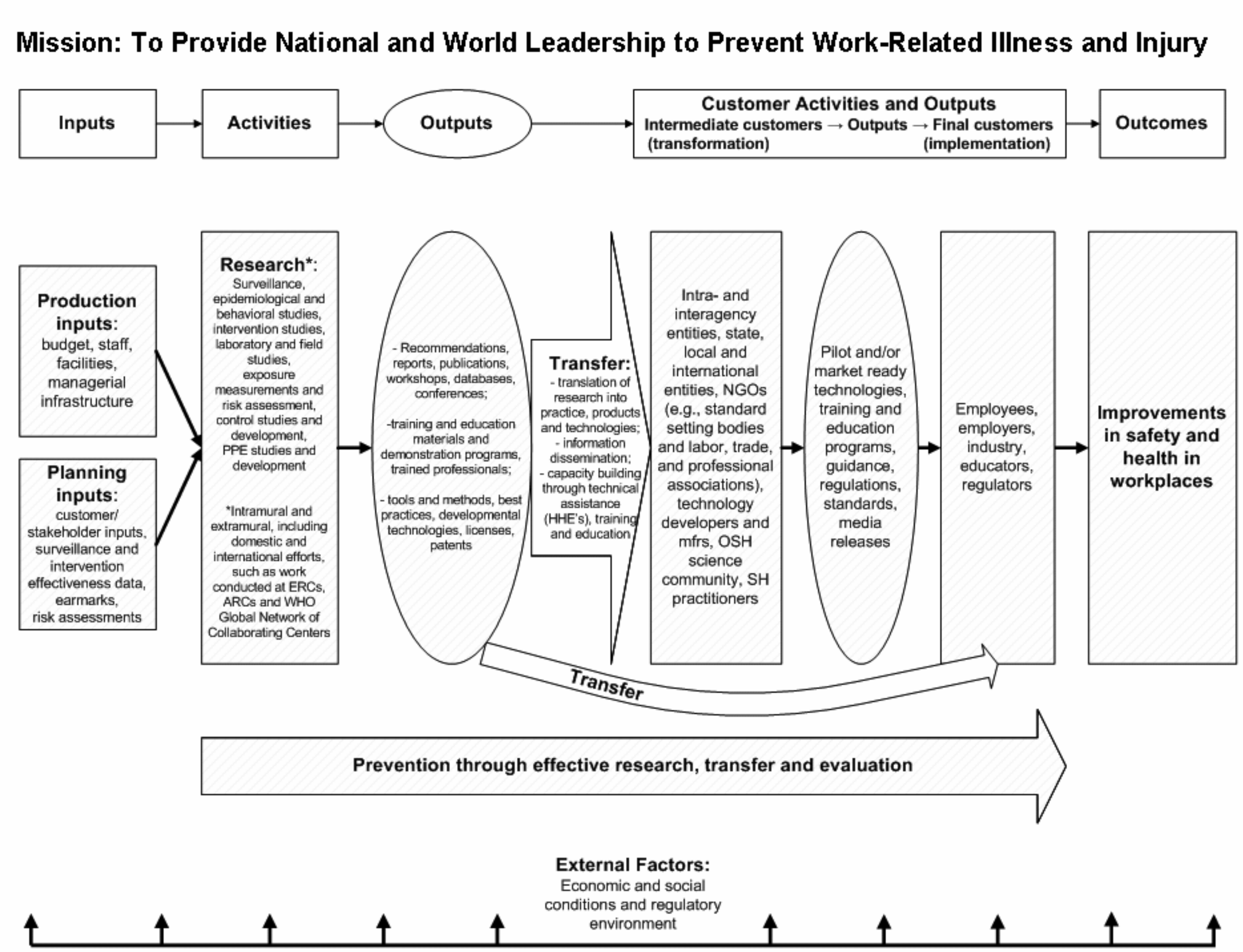

Figure 2. Schematic of the NIOSH operational model.

II. INPUTS

Congressional Mandate

In the Occupational Safety and Health Act of 1970 (OSH Act, Public Law 91-596) and the Federal Mine Safety and Health Act of 1977 (FMSH Act, Public Law 95-164), Congress declared that its purpose was to assure, insofar as possible, safe and healthful working conditions for every working man and woman to preserve our human resources. In these Acts, NIOSH is responsible for recommending occupational safety and health standards and describing exposures that are safe for various periods of employment. These include (but are not limited to) the exposures at which no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience. By means of criteria documents and other publications, NIOSH communicates these recommended standards to regulatory agencies (for example, to the Occupational Safety and Health Administration [OSHA], the Mine Safety and Health Administration [MSHA]), and others in the occupational safety and health community). Occupational safety and health research for the mining industry was part of the U.S. Bureau of Mines (Department of the Interior) until 1996, when those functions were transferred to NIOSH as the Office for Mine Safety and Health Research.

Under the OSH Act, NIOSH is charged with conducting "research, experiments, and demonstrations relating to occupational safety and health" and with developing "innovative methods, techniques, and approaches for dealing with [those] problems." The Act specifies target areas of research that include identifying criteria for setting worker exposure standards and exploring problems created by new technology in the workplace. In an amendment to the Act, NIOSH was given responsibility to conduct research on workers who are at risk for bioterrorist threats or attacks in the workplace [Section 20]. The amendment also gave NIOSH the responsibility for conducting training and education "to provide an adequate supply of qualified personnel to carry out the purposes of the Act" and for assisting employers and workers with applying methods to prevent occupational injuries and illness [Section 21].

Stakeholders' Input

As it follows from the OSH Act and the FMSH Act, the major stakeholders of NIOSH are the U.S. government (especially OSHA and MSHA), workers, employers, occupational safety and health practitioners and researchers, and the general public. NIOSH receives input through formal committees (such as the NIOSH Board of Scientific Counselors, the National Advisory Committee on Occupational Safety and Health, and the Mine Safety and Health Research Advisory Committee) and ad hoc mechanisms (such as the NIOSH Web site [www.cdc.gov/NIOSH], the NIOSH toll-free telephone line [1-800-35-NIOSH], personal professional contacts, and participation in professional conferences and interagency groups). NIOSH also provides stewardship of the National Occupational Research Agenda (NORA) (http://www2a.cdc.gov/nora/), which is a framework to guide occupational safety and health research into the new millennium—not only for NIOSH but for the entire occupational safety and health community.

The importance of occupational safety and health issues to nanotechnology has been emphasized by the interagency working group on Nanotechnology Environmental and Health Implications under the NSET Subcommittee when it invited NIOSH to join in 2004. Through an interagency effort, NIOSH received encouragement to recognize nanotechnology as one of its research priorities.

The importance of this research area and of interagency collaboration was further stressed at the March 24-25, 2005 meeting *National Academies Review of the National Nanotechnology Initiative*. Richard Denison (Environmental Defense) and Carol Henry (American Chemistry Council), in their presentations to the National Academies review panel, called for an increase in the Federal funding of 10% or $100 million in the area of environmental, safety, and health issues around nanotechnology. These calls were further reiterated in a statement by Fred Krupp (President, Environmental Defense) and Chad Holliday (Chairman and CEO, DuPont), which was published in the June 14, 2005, issue of the *Wall Street Journal*: "An early and open examination of the potential risks of a new product or technology is not just good sense—it's good business strategy. . . . [G]overnment spending on nanotechnology should be reprioritized so that approximately 10% goes to [health and environmental risk]."

E. Floyd Kvamme (Co-Chair of the President's Council of Advisors on Science and Technology), who was charged with guiding the NNI, stated in the June 24, 2005, issue of the *Wall Street Journal* "[PCAST] findings . . . indicated that the primary area for immediate concern is in the workplace, where nanomaterials are being used or manufactured and where there is the greatest likelihood for exposures."

Recognizing the importance of this research area and of interagency collaboration, John Marburger (Director of U.S. Office of Science and Technology Policy) and Joshua Bolten (Director of the Office of Management and Budget) instructed the Federal Government "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].

NIOSH Research Capabilities

The first-class research capability of NIOSH is an integral part of management inputs to the nanotechnology program. Within its research Divisions, NIOSH has world-class researchers who are trained and experienced in the full research spectrum from epidemiology and toxicology to intervention effectiveness. Sections III and IV of this document contain lists of current NIOSH research activities and publications on nanomaterials. In addition to their highly qualified research staff, NIOSH has significant laboratory capabilities in particle measurement, collection and characterization, particle surface analysis, measurement of particle surface radicals and activity, and in vitro and in vivo analysis of toxicity and pathogenesis. These laboratories are located in Spokane, Washington; Cincinnati, Ohio; Pittsburgh, Pennsylvania; and Morgantown, West Virginia. NIOSH researchers work closely with a broad range of scientists from industry, academia, and other government agencies. NIOSH involvement in national and international initiatives and programs is an important consideration when judging its capacity to address critical issues in nanotechnology.

NIOSH Partnerships

NIOSH recognizes the need to leverage activities and expertise of other research institutions, industry, federal agencies, and Nongovernmental Organizations (NGOs). Ongoing partnerships are outlined in **Appendix L**. In addition, NIOSH actively participates in committees such as the NSET Subcommittee, the NNI, the Consultative Board for Advancing Nanotechnology (CBAN), and the American National Standards Institute (ANSI) Nanotechnology Steering Committee. The Institute also partners with others through the National Toxicology Program, various industrial consortia, and other advisory groups on nanotechnology issues.

III. ACTIVITIES

NIOSH NTRC and Steering Committee

NIOSH has established the NTRC and the NTRC Steering Committee.

Vision of the NTRC

The vision of the NTRC is as follows:

Safe nanotechnology by delivering on the Nation's promise—safety and health at work for all people through research and prevention.

Mission of the NTRC

The mission of the NTRC is to provide national and world leadership for research into the application of nanoparticles and nanomaterials in occupational safety and health and the implications of nanoparticles and nanomaterials for work-related injury and illness.

Steering Committee

The Steering Committee is responsible for guiding NIOSH scientific and organizational plans in nanotechnology research (including accountable coordination for science and budget) and for developing strategic goals and objectives (**Appendix B**) and performance measures for the NTRC (**Appendix C**). To ensure the responsiveness, relevance, and impact of the Institute's nanotechnology program, appropriate representatives of its nanotechnology research program meet on an annual basis to update strategic planning for nanotechnology research. At these meetings, the Critical Occupational Safety and Health Issues Arising from Nanotechnology (**Appendix A**) are reviewed and updated as appropriate. In addition, meetings will be held with appropriate stakeholders at least every other year.

Current NIOSH Intramural Nanotechnology Research Activities

Current NIOSH research activities in nanotechnology pertain to occupational safety and health implications. Data from these studies will be used to determine nanoparticle exposure concentrations in the workplace, hazards posed by nanomaterials, and the risk of adverse health effects from occupational exposures to nanomaterials. Studies will also provide data on the characteristics of nanomaterials produced and used in the workplace, routes of exposure, work practices, and engineering controls. Findings from these studies will provide scientific data to support the development of occupational safety and health recommendations.

Several types of research activities are funded: (1) the NORA program, (2) NTRC projects, (3) Small NORA, (4) nano-related Division projects, and (5) NORA Supplemental (pending). The individual research projects in each of these areas are described in **Appendix D**, and a timeline for the program is given in **Appendix E**.

Current NIOSH Extramural Nanotechnology Research Activities

The Office of Extramural Programs leads and supports national occupational safety and health programs to reduce work-related injuries and illnesses through the support of peer-reviewed extramural research, education, and training in coordination with NIOSH intramural research goals and collaboration with worldwide partners. In FY 2004, the Office of Extramural Programs joined with the U.S. Environmental Protection Agency/National Center for Environmental Research (EPA/NCER) and the National Science Foundation (NSF) to support the nanotechnology initiative through a request for applications entitled *Nanotechnology Research Grants: Investigating Environmental and Human Health Issues*. Approximately $7 million has been committed jointly to support 15 to 20 research (R01) grants for 3 years and exploratory (R21) grants for 2 years.

The purpose of this collaborative research program is to strengthen support from EPA/NCER, NSF, and NIOSH for research on the implications of nanotechnology and manufactured nanomaterials for human health and the environment. Research areas should include (but are not limited to) the following: toxicology of manufactured nanomaterials, environmental and biological fate, transport and transformation of manufactured nanomaterials, and exposure and bioavailability of manufactured nanomaterials.

In FY 2005, a secondary review committee for programmatic relevance received and peer-reviewed 83 applications for scientific merit. Fourteen of the applications met the NIOSH criteria for relevance to occupational safety and health, and five were in the competitive range for funding. A total of 19 applications were recommended for funding, 3 of which were funded by NIOSH (see **Appendix F** for abstracts). The annual grantee meeting (*Nanotechnology and Environment: Applications and Implications Progress Review Workshop III*) will be held October 26–28, 2005, in Washington, D.C. In addition to announcements, nanotechnology research applications have been received and funded through other Office of Extramural Programs announcements, including Investigator Initiated Research (R01) and Small Business Innovation Research (SBIR).

In FY 2006, NIOSH will continue to partner with EPA/NCER and NSF. The Institute will also expand its collaboration to include the National Institute for Health/National Institute for Environmental Health Sciences and international agencies to continue supporting nanotechnology research with occupational and environmental implications.

In addition, NIOSH issued a contract for a 1-year laboratory study (ending in March 2006) to scientists at the University of Minnesota. The objective of this project is to determine whether the accepted theory of filtration remains valid for particles on the borders of nanosize and below.

IV. OUTPUTS

NIOSH Publications on Nanotechnology

- In response to public calls for information from the U.S. Government, NIOSH issued a position statement along with other agencies (**Appendix G**).

- NIOSH has prepared and posted answers to frequently asked questions (FAQs) concerning nanotechnology (http://www.cdc.gov/niosh/topics/nanotech/faq.html).

- Updates of NIOSH activities in nanotechnology research appear in *Focus on Nanotechnology* (http://www.cdc.gov/niosh/topics/nanotech/focus.html).

- A "best practice" document is under development.

- A Current Intelligence Bulletin (CIB) on titanium dioxide (TiO_2) is in review.

NIOSH Peer-Reviewed Publications

NIOSH peer-reviewed publications are listed in **Appendix H**.

Sponsored Conferences

NIOSH-sponsored conferences are listed in **Appendix I**.

Participation in Conferences

NIOSH participation in conferences and invited presentations are listed in **Appendix J**.

V. RESEARCH TO PRACTICE

Research to practice (r2p) involves the translation of research into products, practices, and usable information.

Capacity Building Through Technical Assistance

NIOSH is currently collaborating with a number of industries to develop best control and administrative practices for safe handling of nanomaterials.

Information Dissemination

In the past year, NIOSH employees have been interviewed by the press seven times concerning its activities in nanotechnology and occupational safety and health (**Appendix K**).

VI. INTERMEDIATE CUSTOMERS AND INTERMEDIATE OUTCOMES

Federal Agencies

NIOSH staff have considered the EPA request for comments (*Nanoscale Materials; Notice of Public Meeting*, published in the *Federal Register* on May 10, 2005 [70 FR 24574]). NIOSH has also provided information to the EPA effort to develop the Voluntary Pilot Program for Nanomaterials.

Dr. Andrew Maynard and Dr. Vincent Castranova served on an EPA Working Group to develop a guidance document entitled *Nanomaterials Toxicity Screening*.

Standards-Developing Organizations

NIOSH actively participates in the development of national and international standards for nanotechnology. NIOSH participates in the American National Standards Institute Nanotechnology Standards Steering Panel (ANSI-NSP), which coordinates the identification and development of critical standards in all areas of nanotechnology.

NIOSH scientists participate in the American Society for Testing and Materials (ASTM) E56 Committee on Nanotechnology, which is developing an integrated family of standards. Committee E56.03 is addressing environmental and occupational safety and health.

NIOSH scientists are also members of the U.S. Technical Advisory Group to the International Organization for Standardization (ISO) Technical Committee 229 on Nanotechnologies. ISO TC 229 will hold its opening international meeting in London on November 9−11, 2005, and NIOSH will be represented in the U.S. delegation to that meeting.

Industry

Through a number of collaborations with industry, government, and academia, NIOSH is developing "best practices" for working with nanomaterials.

Professional organizations

NIOSH is collaborating with various professional organizations to identify mutual efforts for developing training programs.

Research Collaborations

NIOSH is collaborating with several government and academic institutions on nanotechnology issues (**Appendix L**).

VII. OUTCOMES

Nanotechnology is a rapidly developing area of science and technology that promises great benefits. To realize these benefits, it is important to protect workers in nanomaterial research, production, and use from experiencing health problems or uncontrollable risks. The NIOSH strategic plan for research is designed to identify information for use in programs that will prevent and control negative impacts to worker health. In addition, research will be conducted to identify nanomaterials useful for developing more compact sensors that can produce more effective control devices.

Intermediate outcomes are needed to achieve these outcomes. These include conducting research, testing instrumentation, and developing guidance for use by employers, workers, government agencies, and organizations. The framework for reaching the outcome of safe handling and use of nanotechnology is encompassed in the strategic goals and objectives identified in **Appendix B** and in the targets and performance measures in **Appendix C**. Examples of annual metrics for these outcomes include specific scientific advancements and technological improvements, publications, citations, conferences, external funding, external collaborations, field work, technologies under commercial development, training materials, contributions to law-making and standards development, and statistical indicators of improvements in workplace safety and health.

APPENDIX A

TEN CRITICAL OCCUPATIONAL SAFETY AND HEALTH ISSUES ARISING FROM NANOTECHNOLOGY

PURPOSE AND SCOPE

This list was developed by the NIOSH NTRC to identify critical occupational safety and health issues possibly arising from nanotechnology.

1. Exposure and Dose

- **Fate of nanomaterials in the work environment.** Determine the factors influencing the generation, dispersion, deposition, and re-entrainment of nanomaterials in the workplace, including the role of mixed exposures.

- **Worker exposures.** Quantitatively assess exposures to nanomaterials in the workplace, including inhalation and dermal exposure. Determine how exposures differ by work task or process.

- **Internal dose.** Determine the fate and persistence of nanomaterials in the body (pulmonary, lymphatics, blood/systemic, brain), including possible disaggregation of nanoparticle agglomerates into primary particles.

2. Toxicity

- **Key factors and mechanisms.** Systematically investigate the physical and chemical properties of particles that influence their toxicity (e.g., size, shape, surface area, solubility, chemical properties, and trace components). Evaluate acute and chronic effects in the lungs and in other organ systems and tissues. Determine the biological mechanisms for the toxic effects, including from mixed exposures, and how the key chemical and physical factors may influence these mechanisms.

- **Predictive models for toxicity.** Integrate mechanistic models (including animal in vivo and in vitro systems) for assessing the potential toxicity of new nanomaterials and provide a basis for developing structure/function relationships and comparative toxicity analyses for risk assessment.

- **Metrics of dose.** Determine whether (1) particle number, surface area, or other measure of bioavailability or bioactivity is a more appropriate dose metric for toxicity than mass, and (2) other measures of bioavailability may be useful (e.g., an integrated measure of retention, solubility, surface area, and reactivity).

3. Epidemiology and Surveillance

- **Evaluate current knowledge.** Critically evaluate existing epidemiological studies in workplaces where nanomaterials are produced and used. Determine what is known about exposure response to existing nanomaterials, evaluate the applicability of this information to new nanomaterials, and identify data gaps and epidemiological research needs.

- **New epidemiological studies.** Evaluate the need for and feasibility of initiating new epidemiological studies in workers exposed to existing nanomaterials (e.g., carbon black) or producing and using new (engineered) nanomaterials.

- **Surveillance.** Integrate nanotechnology safety and health issues into existing health and hazard surveillance mechanisms. Determine whether these mechanisms are adequate, or whether additional medical screening or surveillance is warranted (e.g., *take home* potential and steps to avoid).

- **Nanotechnology health information systems.** Build on existing public health Geographical Information Systems and infrastructure to enable effective and economical development and sharing of nanotechnology safety and health data.

4. Risk Assessment

- **Evaluate current studies.** Determine to what extent current exposure-response data for nanoparticles in humans or animals may be used in hazard identification or quantitative risk assessment.

- **Risk assessment framework.** Develop a risk assessment framework for evaluating the hazard and predicting the risk of exposure to new nanomaterials.

5. Measurement Methods

- **Extend existing measurement methods.** Evaluate current methods for measuring airborne mass concentrations of respirable particles in the workplace. Determine whether these mass-based methods can be extended to provide a practical interim approach for measuring nanomaterials in the workplace and to maintain continuity with historical methods.

- **Develop new measurement methods.** Expand the currently available instrumentation by developing and field testing practical methods to accurately measure workplace airborne exposure concentrations of nanomaterials, using metrics associated with toxicity (e.g., particle surface area).

- **Validation of measurement methods.** Develop testing and evaluation systems for comparison and validation of sampling instruments and methods.

6. Controls

- **Engineering controls.** Evaluate the effectiveness of engineering control techniques for nano-aerosols and develop new approaches as needed.

- **Personal protective equipment (PPE).** Evaluate and improve (as needed) the effectiveness of PPE for reducing workplace exposures to nanomaterials.

- **Respirators.** Develop specific respirator recommendations for nanoaerosols, including determination of protection factors and evaluation of fit testing.

- **Work practices.** Evaluate the role of work practices and administrative controls in reducing potential exposures to nanomaterials. Make recommendations for appropriate and effective use of these approaches.

- **Control banding.** Evaluate the suitability of control banding approaches to working with engineered nanomaterials for situations in which insufficient information is available to apply traditional exposure-limit-based control strategies.

- **Substitute materials.** Evaluate the feasibility and effectiveness of substitute materials or process engineering in reducing the toxicity of nanomaterials.

7. Safety

- **Explosion and other safety hazards.** Investigate and recommend appropriate work practices to identify and mitigate other safety issues in the nanotechnology workplace, such as explosion hazards.

8. Communication and Education

- **Communication.** Develop partnerships and mechanisms for timely identification and sharing of research needs, approaches, and results.

- **Education**. Develop and disseminate effective educational and training materials for workers and occupational health professionals.

9. Recommendations

- **Occupational exposure limits (OELs).** Evaluate the current mass-based exposure limits for airborne particulates for their effectiveness in protecting workers exposed to nanomaterials. Update the OELs (as needed) to incorporate current scientific information (e.g., particle surface area versus mass as predictor of toxicity, influence of surface properties).

- **Classification.** Develop classification to support a comprehensive nanotechnology safety and health program. Implement criteria based on classification (e.g., chemical abstract system [CAS] number) to determine the need for toxicity testing and hazard and risk assessment of new, engineered, and existing nanomaterials.

- **High-production volume chemicals.** Evaluate the need to revise the existing mass-based requirements under the Toxic Substances Control Act for manufacturers to provide relevant data (e.g., toxicity testing) on high-production volume chemicals. Current scientific data indicates greater toxicity of nanomaterials by mass compared with larger particles of similar composition.

- **Material safety data sheets (MSDS).** Update the MSDS system to incorporate relevant classification, toxicity data, and safety and health recommendations for working with nanomaterials.

10. Applications

- Identify uses of nanotechnology for application in occupational safety and health.

- Evaluate and disseminate effective applications.

Projected Timeframe for Addressing Critical Issues

	Calendar Year				
	2005	**2006**	**2007**	**2008**	**2009**
Exposure and Dose	DEP[a] generation and characterization studies (NORA[b]- PRL[c], HELD[d] base) Wildfire ultrafine aerosol and firefighter exposure studies (SNORA[e] -DRDS)[f]	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[g] EID)[h] Initiate TiO_2 workplace exposure assessment (DSHEFS[i] unfunded)	Nanoparticle evaluations in an automotive plant (NTRC-DART[j]) TiO_2 workplace exposure assessment report (DSHEFS unfunded)	Translocation results in laboratory animals after pulmonary and dermal exposure to nanomaterials (NORA-HELD pending) Dosimetry lung model in rats and humans, begin phase II: calibration and validation with translocation data (NTRC-EID pending)	Quantification of systemic nanoparticle concentrations in laboratory animals after pulmonary exposure to nanospheres and nanofibers (NORA-HELD pending)
Toxicity	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)	Complete dose and time information on carbon nanotubes (NORA-HELD) Nanometal hazard ID (NORA-HELD pending) Dermal information (NORA-HELD pending) Neurological effects (HELD base)	Development of firm cardiovascular endpoints (NORA-HELD pending)

	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)	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	QRA[k] on TiO_2 from existing studies (EID base)	QRA on other fine and ultrafine materials from existing studies (EID base)	Evaluate QRA methods for nanomaterials, including rodent to human extrapolation and revised dosimetry model (NTRC-EID)	Update QRA for fine and ultrafine particles using new NIOSH data on TiO_2 and carbon black (NTRC-EID pending)	Hazard and preliminary QRA on engineering nanoparticles based on carbon nanotube and ultrafine metal oxide information (NTRC-EID pending)
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 others)	Performance results for nanoparticle measurement instruments and methods (DRDS and others)
Controls	Identification of key control issues	Analyses of filter efficiency (NPPTL-[l] 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 personal protective equipment (PPE [m])	Summary of control strategies (NTRC-DART)

	Calendar Year				
	2005	**2006**	**2007**	**2008**	**2009**
Safety	Identification of key safety issues (DSR[n]-NPPTL)		Good safety handling practices (NTRC-DSR-NPPTL)		Summary of nanotechnology safety experience (NTRC-DSR)
Communication and Education	Basic set of FAQs[o] (NTRC, OD[p] base) Web site updates (NTRC-EID, OD, others base) Public presentations (NTRC and many divisions base) NIL[q] pilot (SRL[r]-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)
Recommendations and Guidance	External review of NIOSH TiO_2 CIB[s] (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[t]	Further r2p	Further r2p

Abbreviations:

a. diesel exhaust particulate
b. National Occupational Research Agenda
c. Pittsburgh Research Laboratory
d. Health Effect Laboratory Division
e. Small National Occupational Research Agenda on personal protective equipment
f. Division of Respiratory Diseases
g. Nanotechnology Research Center
h. Education and Information Division
i. Division of Surveillance Hazard Evaluation and Field Studies
j. Division of Applied Research and Technology
k. Quantitative Risk Assessment
l. National Personal Protective Technology Laboratory
m. Personal protective equipment
n. Division of Safety Research
o. Frequently asked questions
p. Office of the Director
q. Nano information library
r. Safety Research Laboratory
s. Current intelligence bulletin
t. Research to practice

APPENDIX B

STRATEGIC GOALS AND OBJECTIVES

Building on past efforts and inputs from stakeholders and partners, the NTRC has developed the following strategic goals and objectives:

1. **Understand and prevent work-related injuries and illnesses potentially caused by nanoparticles and nanomaterials.**

    a. Conduct research on exposure and dose as related to nanomaterials including
    —determining the fate of nanomaterials in the work environment,
    —quantitatively assessing worker exposures to nanomaterials, and
    —determining the internal dose of nanomaterials.

    b. Conduct research on the toxicity of nanomaterials including
    —investigating key factors and mechanisms,
    —developing predictive models for toxicity, and
    —determining metrics of dose.

    c. Conduct research in epidemiology and surveillance in workplaces where nanomaterials are produced and used and where workers are exposed to nanomaterials.

    d. Conduct risk assessments relevant to nanomaterial.

    e. Conduct research on measuring nanomaterials in the workplace, including developing new measurement methods and validating measurement methods.

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

    a. Conduct research on work-related injury and illness prevention using engineered nanomaterials, sensing and communication nanodevices, and nanomachinery.

    b. Conduct research on work-related injury and illness prevention by developing more efficient nanotechnology-based alternative process solutions.

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

   a. Develop and evaluate engineering controls for reducing exposures to nanoparticles.

   b. Evaluate and improve personal protective equipment for reducing exposure to nanoparticles.

   c. Evaluate the suitability and role of work practices, administrative controls, and control banding and substitute materials in reducing toxicity of and exposure to nanomaterials.

   d. Identify and mitigate safety issues in the nanotechnology workplace.

   e. Develop recommendations for nanoaerosols and the nanotechnology workplace.

   f. Update occupational exposure limits (OELs) as appropriate for nanomaterials.

   g. Develop a classification system to support a comprehensive nanotechnology safety and health program.

   h. Revise the existing mass-based requirements under the Toxic Substances Control Act (TSCA) for manufacturers to provide relevant data on high-production-volume nanomaterials as appropriate.

   i. Update the Material Safety Data Sheet system to incorporate relevant classifications, toxicity data, and safety and health recommendations for working with nanomaterials.

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

   a. Develop partnerships and mechanisms for timely identification and sharing of research needs, approaches, and results.

   b. Develop and disseminate effective educational and training materials for workers and occupational health professionals.

APPENDIX C

TARGETS AND PERFORMANCE MEASURES

Achieving each strategic goal depends on meeting intermediate targets and performance measures. In this appendix, various performance measure categories are identified, but the actual performance level will depend on information gained in the review process.

STRATEGIC GOAL 1

Understand and prevent work-related injuries and illnesses potentially caused by nanoparticles and nanomaterials.

Long-Term Performance Measure 1

Progress in preventing illness and injuries possibly due to exposures to nanoscale materials.

Target and timeframe 1.0: 5- to10-year range

Successful program: Describes certain amount (percentage or number) of the following:

- PPE, respirators, and controls used in the workplace
- Reduction in occupational exposures to nanoscale materials
- Reduction of number of workers exposed to nanoscale materials
- Nanoscale materials subject to risk analysis

Minimally effective program: Describes a lower amount (percentage or number) compared with *Successful program*.

Target and timeframe 1.1: FY2010

Successful program: For work settings where respiratory protection is required, x% of workers have access to and properly use nanoeffective respirators.

Minimally effective program: For work settings where respiratory protection is required, x%–y% of workers have access to and properly use nano-effective respirators.

Annual measure 1.1: FY2005—Test effectiveness of respirator filter media

Target and timeframe 1.2: FY2010

Successful program: For work settings where the use of engineering control is required, x% of workplaces have and properly use appropriate controls.

Minimally effective program: For work settings where the use of engineering control is required, x%–y% of workplaces have and properly use appropriate controls.

Annual measure 1.2: FY2007—Evaluate effectiveness of engineering controls

Target and timeframe 1.3: FY2010

Successful program: x% reduction in workers overexposed to diesel PM.

Minimally effective program: x%–y% reduction in workers overexposed to diesel PM.

Annual measure 1.3:

FY2006—Determine the effect of exhaust filters on generation and transport of diesel nanoparticles.

FY2007—Determine the effect of fuel additives on generation and transport of diesel nanoparticles.

FY2008—Determine the comparative generation of nanoparticles by old versus new generation diesel engines.

Target and timeframe 1.4: FY2010

Successful program: x% reduction in workers overexposed to welding fumes.

Minimally effective program: x%–y% reduction in workers overexposed to welding fumes.

Annual measures 1.4:

FY2005—Develop and test an automated welding-fume generator for exposure of laboratory animals.

FY2006—Evaluate the effects of welding-fume exposures on pulmonary responses in an animal model.

FY2007—Evaluate the neural effects of welding-fume exposures on pulmonary responses in an animal model.

FY2008—Use animal data to support risk assessment.

Target and timeframe 1.5: FY2010

Successful program: Risk assessment and risk management analysis can be conducted of x% of engineered nanoscale materials produced during manufacturing.

Minimally effective program: Risk assessment and risk management analysis can be conducted of x%–y% of engineered nanoscale materials produced during manufacturing.

Annual measures 1.5:
FY2005—Develop a field method for measuring concentration (mass or surface) of nanoscale materials in the air.
FY2005—Develop a set of representative occupational environments with potential exposure to nanoscale materials.

FY2006—Develop a field method for characterizing nanoscale materials.

FY2006—Develop and characterize a set of representative nanoscale materials for biological testing.

FY2007—Conduct pulmonary toxicology tests on x representative materials.

FY2007—Conduct surveillance on x representative materials.

FY2008—Conduct dermal toxicology tests on x representative materials.

FY2008—Conduct cardiovascular toxicology tests on x representative materials.

FY2009—Conduct toxicology tests on x+y representative materials.

STRATEGIC GOAL 2

Prevent work-related injuries and illnesses by applying nanotechnology products.

Long-Term Performance Measure 2

Progress in preventing occupational illness and injuries using nano-enabled products and tools.

Target and timeframe 2.0: 5- to10-year range

Successful program: Achieves a certain amount (% or number) of the following:

- Nano-enabled PPE, respirators, controls, and sensors used in the workplace

- Reduction in occupational exposures due to applications of nano-enabled processes, controls, and PPEs
- Reduction of number of workers exposed to hazard materials due to applications of nano-enabled processes, controls, and PPEs
- Introduction of novel nano-enabled means to ensure workplace safety and health

Minimally successful program: Achieves a lower percentage or number compared with a *Successful program*.

Target and timeframe 2.1: FY2010

Successful program: x% of repirators used in occupational setting are NIOSH-certified, nano-enabled respirators.

Minimally effective program: x%–y% of repirators used in occupational setting are NIOSH-certified, nano-enabled respirators.

Annual measure 2.1: Appropriate measures to be developed.

Target and timeframe 2.2: FY2010

Successful program: x% of PPE used in occupational settings are based on NIOSH-tested nano-enabled fabrics.

Minimally effective program: x%–y% of PPE used in occupational setting are based on NIOSH-tested, nano-enabled fabrics.

Annual measure 2.2: Appropriate measures to be developed.

Target and timeframe 2.3: FY2010

Successful program: x% of worksites are equipped with real-time multi-agent ambient levels and personal exposure monitors.

Minimally effective program: x%–y% of worksites are equipped with real-time multi-agent exposure monitors.

Annual measure 2.3: Appropriate measures to be developed.

Target and timeframe 2.4: FY2010

Successful program: x% of worksites report real-time exposure data to a geospatial dynamic exposure monitoring system.

Minimally effective program: x%–y% of worksites report real-time exposure data to a geospatial dynamic exposure monitoring system.

Annual measure 2.4: Appropriate measures to be developed.

Target and timeframe 2.5: FY2010

Successful program: Two mining companies adopt wearable nanotechnology-based sensor warning devices for empowering workers to take preventative steps for reducing risks of injuries in their workplace.

Minimally effective program: One mining company adopts wearable nanotechnology-based sensor warning devices for empowering workers to take preventive steps for reducing occupational risk to injuries in their workplace.

Annual measure 2.5: Appropriate measures to be developed.

Target and timeframe 2.6: FY2010

Successful program: Field testing of nanoparticle-based advanced materials in three mining applications (noise, diesel, dust, rock safety, ergonomics, ventilation) for enhancing health and safety of workers.

Minimally effective program: Field testing of nanoparticle-based advanced materials in two mining applications for enhancing health and safety of workers.

Annual measure 2.6: Appropriate measures to be developed.

STRATEGIC GOAL 3

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

Long-Term Performance Measure 3

Progress in promoting healthful workplaces through interventions, recommendations, and capacity building.

Target and timeframe 3.0: 5- to10-year range

Successful program: Achieves a certain amount (percentage or number) of

- Criteria documents andguidelines developed by NIOSH for nano-enabled sectors of economy,

- Nano-enabled businesses using NIOSH documents,
- Educational courses on nanotechnology developed by NIOSH, and
- Outreach activities to OSH professionals;

Minimally successful program: Achieves a lower percentage or number compared with a *Successful program*.

Target and timeframe 3.1: FY2010

Successful program: x% of start-ups in nanotechnology are using NIOSH *best practices* for working with nanomaterials.

Minimally effective program: x%–y% of start-ups in nanotechnology are using NIOSH *best practices* for working with nanomaterials.

Annual Measure 3.1:

FY2006—Develop *best practices* for working with nanoscale materials.

FY2007—Update *best practices* for working with nanoscale materials.

Target and timeframe 3.2: FY2010

Successful program: x% of large- and medium-sized companies are using NIOSH *best practice* for working with nanomaterials

Minimally effective program: x-y% of large- and medium-sized companies are using NIOSH *best practices* for working with nanomaterials.

Annual Measure 3.2:

FY2006—Develop *best practices* for working with nanoscale materials.

FY2007—Update *best practices* for working with nanoscale materials.

Target and timeframe 3.3: FY2010

Successful program: x% of professional industrial hygienists are trained with NIOSH *best practices* for working with nanomaterials.

Minimally effective program: x%–y% of professional industrial hygienists are trained with NIOSH *best practices* for working with nanomaterials.

Annual Measure 3.3:

FY2006—Develop *best practices* for working with nanoscale materials.

FY2007—Update *best practices* for working with nanoscale materials.

FY2007—Sponsor a training conference for industrial hygienists

Target and timeframe 3.4: FY2010

Successful program: x% of professional industrial hygienists are aware of the nanotechnology topic page on the NIOSH Web site.

Minimally effective program: x%–y% of professional industrial hygienists are aware of the nanotechnology topic page on the NIOSH Web site.

Annual Measures 3.4:
FY2005—Develop a nanotechnology topic page.

FY2005—Develop a prototype nanoinformation library.

FY2006—Provide annual update of the NIOSH Nanotechnology Research Program.

FY2006—Beta test the nanoinformation library.

FY2007—Implement the fully interactive nanoinformation library.

STRATEGIC GOAL 4

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

Long-Term Performance Measure 4

Progress in reducing occupational injury and illness due to nanoscale materials through prevention activities and application of nanotechnology on a global scale.

Target and timeframe 4.0: 5- to 10-year range target

Successful program: Achieves a certain amount (percentage or number) of the following:

- NIOSH projects with national collaboration
- NIOSH projects with international collaboration
- NIOSH nano-documents used by international and national entities

- NIOSH participation in international standards
- International OSH specialists receiving funding/training from NIOSH
- NIOSH participation in international efforts in reducing occupational exposures to nanoscale materials

Minimally effective program: Achieves a lower percentage or number compared with a S*uccessful program*.

Target and timeframe 4.1: FY2010

Successful program: x% of national OSH agencies implement best IH practices for working with nanoscale materials.

Minimally effective program: x%–y% of national OSH agencies implement best IH practices for working with nanoscale materials.

Annual measures:
FY2006 and continuing: Review and document the metric.

Target and timeframe 4.2: FY2010

Successful program: x% of NIOSH research programs in NTRC have national and international collaborators.

Minimally effective program: x%–y% of NIOSH research programs in NTRC have national and international collaborators.

Annual measures:
FY2005 and continuing: Review and document the metric.

Target and timeframe 4.3: FY2010

Successful program: x% of ISO TC 229 working groups related to OSH issues have NIOSH experts participating in standards development.

Minimally effective program: x%–y% of ISO TC 229 working groups related to OSH issues have NIOSH experts participating in standards development.

Annual measures:
FY2006 and continuing: Review and document the metric.

Target and timeframe 4.4: FY2010

Successful program: x NIOSH researchers serve on working groups to develop protocols for testing nanomaterials and to evaluate hazards and routes of exposure.

Minimally effective program: x%–y% NIOSH researchers serve on working groups to develop protocols for testing nanomaterials and to evaluate hazards and routes of exposure.

Annual measures:
FY2005 and continuing: Review and document the metric.

APPENDIX D

INTRAMURAL NANOTECHNOLOGY RESEARCH PROJECTS

I. NORA PROGRAM

The largest current NIOSH nanotechnology research program, the Nanotechnology Safety and Health Research Program, was funded in 2004 under the National Occupational Research Agenda (NORA). This NORA program includes six research projects that are funded for 5 years.

Generation and Characterization of Occupationally Relevant Airborne Nanoparticles

Principal Investigator: Doug Evans, Ph.D., DART

Mounting evidence shows that the toxicity of some aerosols may be closely associated with the number or surface area of inhaled particles. Low-solubility ultrafine (typically smaller than 100 nm) and high-specific, surface-area particles are of particular concern. This project is part of a wider research program aimed at studying the toxicity of workplace-related aerosols in this category, including those associated with nanotechnology. Methods are being developed to generate and deliver well characterized particles to exposure systems, enabling particle characteristics responsible for specific toxic responses to be investigated in a systematic manner. The research includes the development of off-line and on-line aerosol and particle characterization techniques, including methods to measure aerosol surface area, and methods to characterize the composition and structure of nanometer-diameter particles.

Pulmonary Toxicity of Carbon Nanotube Particles

Principal Co-Investigators: Anna Shvedova, Ph.D., HELD, and Paul Baron, Ph.D., DART

This project will evaluate mechanisms of pulmonary toxicity in response to in vitro or in vivo exposure to carbon nanotubes. Aims are to (1) study mechanisms of cytotoxicity of carbon nanotubes in culture systems of bronchial epithelial cells, macrophages and alveolar type II cells; (2) determine the effect of pharyngeal aspiration of carbon nanotubes in a mouse model—determine dose-response and time course; (3) develop a generation system for carbon nanotube aerosols; and (4) conduct inhalation exposure to aerosolized carbon nanotube particles and monitor the pulmonary response in a mouse model.

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

Principal Co-Investigators: Michael Luster, Ph.D., HELD, and Petia Simeonova, Ph.D., HELD

This project will evaluate mechanisms involved in the cardiopulmonary responses to exposure to carbon nanotubes using molecular biology procedures and transgenic animal models. Specific aims are to (1) monitor changes in gene expression of lung tissue associated with intratracheal exposure to carbon nanotubes; (2) determine the role of TNF-alpha in these responses using TNF-alpha receptor knockout mice; (3) evaluate the role of carbon nanotubes in the induction of emphysema using a emphysema susceptible mouse (TSK+); and (4) characterize the cardiovascular reactions to pulmonary exposure to carbon nanotubes, using a mouse model (apo E-/-) susceptible to atherosclerosis.

Particle Surface Area as a Dose Metric

Principal Investigator: Vincent Castranova, Ph.D., HELD

This project will determine whether the high inflammatory reaction of the lung to ultrafine particles compared with an equal mass of fine particles of similar composition is due to a unique toxic property of ultrafine particles or could be explained by their high surface area, i.e., is particle surface area a more appropriate metric for exposure dose than particle mass? Specific aims are to (1) expose alveolar type II epithelial cells, bronchial epithelial cells, and alveolar macrophages to ultrafine and fine crystalline silica, titanium dioxide, or carbon black and determine toxicity on a particle surface area/cell surface area basis; (2) determine whether titanium dioxide and carbon black exhibit similar in vitro toxicity on a particle surface area basis while silica exhibits greater toxicity; (3) determine the pulmonary response to inhalation of ultrafine vs. fine titanium dioxide on an equivalent deposited particle surface area/pulmonary epithelial cell surface area basis; and (4) provide in vitro and in vivo data to EID for modeling.

Ultrafine Aerosols from Diesel-Powered Equipment

Principal Investigator: Aleksander Bugarski, Ph.D., PRL

This project will identify and evaluate the nanometer and ultrafine aerosols emitted by diesel-powered equipment and formulate control technologies to reduce the exposure of workers to these particles, thereby reducing the associated occupational health risks. The physical and chemical properties of the nanometer and ultrafine diesel aerosols will be characterized through a series of engine/dynamometer tests both at the NIOSH Lake Lynn Laboratory experimental mine and at participating active metal and coal mines. The knowledge obtained from this study will strengthen our understanding of the health implications related to exposure to diesel particulate matter and aid in assessing the potential of various control technologies for reducing this exposure.

Nanotechnology Safety and Health Research Coordination

Principal Investigator: Vincent Castranova, Ph.D., HELD

The goals of this project are to (1) increase collaboration among project investigators, (2) track progress of program projects, and (3) disseminate results and accomplishments. Thus far, this project has held an annual retreat of program scientists and other update sessions. This project has submitted an annual report for publication in the NIOSH e-NEWS, provided information for articles in the lay press, and developed partnerships with the University of Rochester, the University of Pittsburgh, the University of Minnesota, the National Toxicology Program, NASA, Oak Ridge Labs, and FDA. Over the next 6 months, NIOSH is cosponsoring symposia on nanotechnology health issues in Minneapolis, MN, (October 3–6, 2005) and Research Triangle Park, NC, (October 26–28, 2005).

II. NTRC PROJECTS

Several NIOSH research projects in nanotechnology are funded through the Nanotechnology Research Center. Four research projects were funded in FY 2005, and these may be renewed for up to 3 years. A fifth project was funded as a 1-year research contract.

Nanoparticles: Dosimetry and Risk Assessment

Principal Investigator: Eileen Kuempel, Ph.D., EID

This project will provide a unified approach for quantitative analysis of exposure, dose, and response relationships for particles of varying size and composition using rat and human in vitro and in vivo data, and evaluation of dose metric (e.g., particle surface area). Biomathematical and statistical models will be developed to estimate internal dose and disease risk in workers exposed to nanoparticles and to provide a scientific basis for developing improved occupational health recommendations to reduce the risk of lung diseases in workers. As part of this project, research contracts have been awarded to Bahman Asgharian, Ph.D., CIIT Centers for Health Research, and Lang Tran, Institute of Occupational Medicine (IOM).

Nanoparticles in the Workplace

Principal Investigator: Mark Hoover, Ph.D., DRDS

The objective of this project is to provide NIOSH and the occupational safety and health community with a better understanding of the nature and extent of current and emerging occupational exposures to nanoparticles and to foster development of a comprehensive and scientifically sound occupational health protection strategy for emerging nanotechnologies.

Web-Based Nano-Information Library Implementation
Principal Investigator: Arthur Miller, Ph.D., SRL

The primary objective of this project is to implement the Web-based programming for the Nano-Information-Library (NIL) that is being developed to support the Nanoparticles in the Workplace project. This work will 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.

An Ultrafine Particle Intervention Study in Automotive Production Plants
Principal Investigator: Keith Crouch, Ph.D., DART

Evaluate the generation and control of ultrafine particles (in terms of mass, surface area, and number) at several automotive manufacturing plants. Relate the ultrafine exposures to respiratory and other symptoms and objective measures of pulmonary inflammation while providing control recommendations linked to cost-benefit analysis.

Filter Efficiency of Typical Respirator Filters for Nanoscale Particles
Project Officer: Appavoo Rengasamy, Ph.D., NPPTL
Research contract with David Pui, Ph.D., University of Minnesota

Manufactured nanoparticles may exist as separate particles of only a few nanometers. Respirator theory predicts that as particle size decreases from 300 nm, diffusion becomes increasingly effective in capturing the particles on the filter filters. However, a recent study suggests that as particles reach sizes of a few nanometers, capture efficiency begins to decline. The goals of this project are to determine (1) whether single-fiber filtration theory is valid for engineered nanoparticles, (2) the possible boundaries of the most penetrating particle size range, and (3) the filtration boundaries of nanosized particles in the diffusional capture mechanism range. The findings from this study will enable the extension of single fiber theory beyond the traditionally described particle range. These findings will also allow NIOSH to make recommendations regarding the effectiveness of respirator filter media for engineered nanoparticles on the basis of experimental data.

III. SMALL NORA

One *small* NORA research project pertaining to nano-structured particles was funded in FY2005.

Respiratory Effects of Particulate Exposures in Wildland Firefighters
Principal Investigator: Denise Gaughan, DRDS

This project will determine the age-adjusted prevalence of airways obstruction in Federal wildland firefighters and examine predictors of decreased lung function in these workers at baseline and of short-term changes in lung function (pre-post fire), adjusting for competing and confounding factors. Predictors of airways inflammation and FEV1 and FVC as well as the relationship between these two measures will be examined. In addition, we will determine the size distribution of particulate matter in wildfire smoke and ascertain the free radical concentration in the products of combustion. Finally, we will classify by size the smoke aerosol ranging from the ultracoarse (>10 μm) through the ultrafine (<100 nm) fractions.

IV. NANO-RELATED DIVISION PROJECTS

Various projects that are directly or indirectly related to investigations of the occupational safety and health implications of nanotechnology are funded by NIOSH Divisions. These projects include the following:

A. DRDS

Emerging Issues for Occupational Respiratory Disease
Principal Investigator: Kathleen Kreiss, M.D.

This project is addressing emerging issues for respiratory disease, including agents involving very fine, ultrafine, or nanomaterials such as cobalt and tungsten carbide in the hard metal industry, vapors and particles of concentrated flavorings, and fungal fragments for indoor air quality.

Longitudinal Surveillance/Beryllium Disease Prevention
Principal Investigator: Schuler, Christine R., Ph.D.

This project is determining whether a better metric than airborne exposure exists for predicting beryllium sensitization and chronic beryllium disease. Both inhalation and dermal exposure to ultrafine beryllium particles are of concern. Particles smaller in diameter than 1 um may be able to penetrate intact skin. Experience with beryllium fume aerosols may provide insights into health risks for working with other ultrafine materials.

Direct Reading Instrument Metrology
Principal Investigator: Judith Hudnall, B.S.

Accurate measurement of indoor and industrial contaminants generated by current technology and emerging nanotechnology is an important component of occupational and environmental hygiene practice. Direct reading instruments are frequently used to determine the effectiveness of engineering controls and the quality of indoor air. The study assesses the effects of temperature, humidity, and concentration on commercially available direct-reading instruments. Other concerns are the uncertainties associated with standard factory calibrations. The results of this study are revealing limitations and opportunities for improvements in current instrumentation and will be valuable in choosing appropriate direct-reading instruments for use in field evaluation of industrial and other ventilation systems.

B. EID

NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations on Occupational Exposure to Titanium Dioxide
Project Officers: Eileen Kuempel, Ph.D. and Faye Rice, M.S.

This Current Intelligence Bulletin will provide an updated review of the scientific literature pertaining to adverse health effects in workers exposed to titanium dioxide, including epidemiology studies and experimental studies in animals. A quantitative risk assessment will be performed using both lung cancer and noncancer (pulmonary inflammation) data in rats inhaling either fine or ultrafine titanium dioxide. The rat-based estimates of internal particle surface area dose in the lungs (at specified risk levels) will be extrapolated to humans using lung dosimetry models, and the rat-based excess risk estimates for lung cancer will be compared with the confidence intervals on risk from the epidemiological studies. The recommended exposure limits will account for particle surface area differences at given mass concentrations of fine or ultrafine titanium dioxide, as well as associated differences in toxicity. The current cancer classification for titanium dioxide will be evaluated, and updated recommendations will be provided.

Assessing the Utility of Control Banding in the United States
Project Officer: T.J. Lentz, Ph.D.

In the area of innovative, efficient, and cost-effective control approaches to protect workers from materials with poorly understood toxicity, NIOSH has taken a leadership role to evaluate the potential of applying *control banding* approaches to nanotechnology handling and processing activities. NIOSH implemented a control-banding initiative in FY2004 that included coordinating and cosponsoring the 2nd International Control Banding Workshop in Cincinnati, Ohio (March 1–2, 2004). This forum emphasized the utility of control-focused strategies for addressing chemical exposures and other occupational hazards such as nanomaterials, especially in the area of pharmaceutical manufacturing where this approach has a history. Dr. Howard, Director of NIOSH, and John Henshaw, Assistant Secretary of Labor (OSHA director) were featured speakers at the

Workshop, as well as other representatives from European Union countries, the World Health Organization, and other international organizations. Nearly 200 participants, including NIOSH personnel and representatives from throughout the United States in government, industry, consulting, labor, and academia, attended the workshop. Subsequent efforts to promote discussion of control banding have included NIOSH presentations at the British Occupational Hygiene Society Meeting (Stratford-upon-Avon, U.K., April 2004), the American Industrial Hygiene Conference and Exposition (Atlanta, GA, May 2004), and Exposure 2004 (Utrecht, the Netherlands). Subsequently, the NIOSH control-banding initiative has involved continuing efforts to examine control banding applications in the United States, especially for small businesses. Towards that end, NIOSH sponsored the National Control Banding Workshop in Washington, DC (March 9–10, 2005) to bring together representatives from government, industry, academia, consulting, organized labor and others to evaluate a draft critical review of the control banding literature and consider challenges for implementing control banding strategies in the United States.

NIOSH Current Intelligence Bulletin (CIB): Health Hazards in Welders

Project officer: Ralph Zumwalde, M.S.

This CIB will provide an updated review of the scientific literature on the health hazards in workers exposed to manganese and other substances in welding fumes. Welding fumes are nano-structured aerosols. The adverse health effects observed in welders include manganese poisoning and Parkinson-like diseases. Although manganese is presumed to be a causative agent, the CIB also considers whether other toxicants present in welding fumes may contribute to the reported adverse health effects. A draft for internal review has been developed by a cross-Institute team. The intended audience includes decision-makers in government, labor, and industry.

C. HELD

Pulmonary, Immune, and Dermal Effects of Welding Fumes

Principal Investigator: James Antonini, Ph.D.

The goals of this project are to (1) design, construct, and test a generation system that would produce a consistent fume (concentration and characteristics) for inhalation exposure to rats; (2) characterize the welding fume as generated and within the inhalation chamber; (3) determine how characteristics change with distance from the generator source; (4) expose rats by inhalation to welding fume; (5) characterize pulmonary, immune, and dermal reactions to exposure; (6) determine the dose-response and time-course of these reactions; and (7) determine the effect of welding process (mild steel versus stainless steel) on pulmonary response.

Pulmonary Toxicity of Diesel Exhaust Particles

Principal Investigator: Jane Ma, Ph.D.

The objective of this project is to characterize the role of generation of reactive oxygen species in pulmonary toxicity resulting from exposure to diesel exhaust particles. Specifically, the role of reactive oxygen species will be evaluated in the induction or degradation of pulmonary P450 enzymes and the resulting effects on xenobiotic metabolism and metabolic-dependent mutagenicity. Sources of reactive oxidant production will be characterized in response to diesel exhaust particle exposure, such as reactive-oxygen species production from P450 enzymes or nitric oxide production from nitric oxide synthase.

D. NPPTL

Respirator Testing and Certification

Project Officer: Heinz Ahlers, J.D.

Although this project does not focus specifically on nanoparticles, any procedures, test protocols, and equipment for testing respirators against airborne particles will have relevance to the issue of nanotechnology. Depending on the results of future research, special respirator testing protocols may be needed for nanoparticles.

Performance Test of High APF Respirators

Project Officer: Ziqing Zhuang

The goals are to strengthen the scientific basis on which NIOSH policies and recommendations for respiratory protection depend, and to develop a validated, complete respirator performance test for high-APF respirators to be incorporated into the NIOSH certification program. The specific aims of this project are to (1) compare fit factors from six quantitative fit test methods to Freon exposure dose and (2) validate performance tests as a condition of certification.

Development of Computer-Aided Face Fit Evaluation Methods

Project Officer: Ziqing Zhuang

The goal of this project is to develop computer-aided face-fit evaluation methods. Specific aims are to (1) establish fit-test panels for today's workers and recommend changes to the NIOSH certification program; (2) determine whether mask design and face fit can be improved by using 3D data; (3) investigate the correlation between 3D parameters and face fit; and (4) develop computer-aided, face-fit evaluation methods that can be used to screen out respirators with poor face-fitting characteristics and design good-fitting respirators.

Respirator Approval: Policy and Standards Development
Project Officer: Timothy Rehak

Although this project does not focus on nanoparticles, any standards for respirators for protection against airborne particles will necessarily relate to nanotechnology. Depending on the results of future research, separate respirator standards may be necessary for nanoparticles.

End of Service Life (ESLI) Technologies
Project Officer: Jay Snyder

This project is examining various nanostructure technologies as possible sensors that can be incorporated into respirator canisters to indicate when their useful life will expire.

Degradation and Decontamination Efficacy of Chemical Protective Clothing
Project Officer: Pengfei Gao

This project is aimed at developing a suitable method for decontaminating chemical protective clothing and evaluating decon efficacy. Attempts have been made to develop new decon techniques based on physicochemical properties of material-chemical pairs, including development of self-decon structural clothing materials against chemicals.

Although the project does not have nanoparticles as a focus, it deals with decontamination methods and their effect on PPE materials. PPE decontamination will be an important consideration in reusing protective clothing to protect against skin contact with nanoparticle hazards. In addition, nanosize inorganic oxide particles such as TiO_2 and MgO can play a special role in decontaminating chemical warfare agents because of the larger surface area and greater amount of highly reactive edge and corner defect sites.

E. SPL

Reducing Diesel Particulate Exposures in Western Mines
Principal Investigator: Art Miller

This project aims at evaluating and mitigating diesel particulate matter exposures in mines. Much of the work has been done with a focus on submicron and ultrafine particles of soot and associated trace metals that are often deposited on soot particles. Part of this work focuses on the characterization of nanoparticles that increase in certain situations, including the application of new *clean-burning* diesel engines. The investigator was sent to the University of Minnesota on a long-term training assignment in assessing the formation and emission of nanoparticles by diesel engines. He submitted four journal articles in the area of nanoparticle characterization in the calendar year 2004. Research plans also include evaluating nanoparticle emissions from a variety of internal combustion engines and designing a portable sampler for collecting nanoparticle samples in the field. One task on this project entails creating a database for organizing information about nanoparticles. A prototype relational database is being constructed. The goal is to provide a Web-accessible clearing house for nanomaterial researchers. The database will contain particle images as well as information about physical and chemical properties. Available data on toxicity and health effects of nanomaterials will be attached or linked to the particle information.

Characterization and Communication of Chemical Hazards

Principal Investigator: Pam Drake

This project has three distinct goals: (1) to characterize workers' exposures to various chemical hazards; (2) to develop new analytical methods; and (3) to communicate the health effects associated with exposure to chemicals to workers. Much of the work is tailored to requests for technical assistance from industrial (mining) stakeholders. For this reason the work has naturally evolved to focus on exposures to such hazards as welding fumes, blasting fumes, and metal bearing aerosols. In some cases, the aerosols include nanomaterial and in that regard this project has become one with nanomaterial component.

Portable Monitors for Airborne Metals at Mining Sites

Principal Investigator: Pam Drake

The research focuses on evaluation of field-portable methods for measuring airborne metals. Air filter samples were collected during milling, smelting, and refining operations and analyzed, in the field, for various metals by portable anodic stripping voltammetry and X-Ray fluorescence. In some cases, the aerosols include nanoparticles and in that regard this project deals with measurement of metal derived from nanoparticles.

V. NORA SUPPLEMENTAL PROJECTS

Funding Decision Pending (review conducted June 8, 2005)

Systemic Microvascular Dysfunction: Effects of Ultrafine versus Fine Particles

Principal Investigator: Vincent Castranova, Ph.D.

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. The NIOSH Nanotechnology Research Center identifies elucidation of cardiovascular effects of airborne nanoparticles as a critical issue. This study will compare the effects of inhalation exposure to fine vs. ultrafine TiO_2 and monitor pulmonary effects and alterations in systemic microvascular function. The role of oxidant stress at the microvessels will be explored. Data will be disseminated by presentation at scientific meeting, publications in journals, summaries in the NIOSH e-News and Nanotech Web page, and meeting with partners.

Evaluation of the Pulmonary Deposition and Translocation of Nanomaterials

Principal Investigator: Robert Mercer, Ph.D.

Recent years have seen an exponential growth in the development and production of nanomaterials. These materials have unique physical, chemical, and electrical properties due to specially forged arrangements of atoms on a nanometer scale that do not occur in natural systems. Because of the unique properties and small size of nanoparticles, issues have been raised as to their potential adverse effects on the lung upon inhalation and whether they can translocate to systemic sites. This project will identify where in the lungs inhaled nanomaterials might deposit, the health risks that might arise from nanomaterial deposition, and to what extent the nanomaterials might translocate to other organs of the body after depositing in the lungs. Results of this study will address critical issues identified by the NIOSH Nanotechnology Research Center and assist in hazard identification and risk assessment.

Dermal Effects of Nanoparticles

Principal Investigator: Anna Shvedova, Ph.D.

Nanoparticles are new materials of emerging technological importance in different industries. Because dermal exposure is likely in a number of occupational settings, it is very important to assess whether nanoparticles could cause adverse effects to skin. The hypothesis is that nanoparticles are toxic to the skin and the toxicity is dependent on their penetration to skin, induction of oxidative stress, and content of transition metals. Because inflammation provides a redox environment in which transition metals can fully realize their pro-oxidant potential, a combination of inflammatory response with metal oxide particles, or iron-containing SWCNT will synergistically enhance damage to cells and tissue. Results obtained from these studies provide critical knowledge about mechanisms of dermal toxicity of nanoscale materials and will be used by regulatory agencies (OSHA and EPA) and industry to address strategies for assurance of healthful work practices and safe environments.

Pulmonary Effects of Exposure to Various Nanoparticles

Principal Investigator: Dale Porter, Ph.D.

The purpose of this project is to evaluate several types of nanoparticles for toxicity in the conducting airways and alveolar region of the lung, and to understand their mechanisms of toxicity by comparing the effects of pulmonary exposure to fine versus ultrafine metal oxide particles. The data obtained will contribute to the development of a toxicological database necessary for hazard identification and to the NIOSH Nanotechnology and Health and Safety Research Program. The project will provide data to NIOSH, OSHA, and EPA for nanoparticle exposure risk assessment and prevention.

APPENDIX E

TIMELINE FOR NIOSH NANOTECHNOLOGY RESEARCH

The following timeline broadly summarizes current and future research initiatives at NIOSH.

Current research is focused on addressing the most pressing issues such as nanoparticle toxicity, analyzing existing risk data, and gathering information that will support a long term approach to nanotechnology occupational safety and health research.

Summary of Current Research (FY2005)

• Begin toxicity testing in laboratory animal and in vitro systems
• Quantitative risk assessment on TiO_2 from existing studies • Draft a TiO_2 Current Intelligence Bulletin
• Surveillance Phase I: Identify Gather baseline information • Identify key exposure control issues • Identify key safety issues • Conduct pilot studies of nanoparticles in the workplace • Develop techniques for online surface area measurement • Conduct studies on wildfire ultrafine aerosol and firefighter exposure studies • Generate a basic set of frequently asked questions (FAQs) • Develop a pilot Nanotechnology Information Library (NIL) • Produce a NIOSH education series on nanotechnology

The next stage of NIOSH research will focus on the worker. Research will be initiated to address the immediate concerns of workers such as proper material handling and exposure mitigation. Parallel work will be done to evaluate worker exposures in some of the many new nanotechnology facilities that are emerging. Exposure models will be developed to assess worker risk. Toxicity studies will continue using key materials such as carbon nanotubes and ultrafine TiO_2, to provide the needed dose response information.

Summary of near term research plans (FY2006)

• Continue baseline surveillance information gathering • Conduct survey of uses and workers

• Conduct measurement studies of nanoparticles in the workplace • Initiate TiO_2 workplace exposure assessment • Dosimetry lung model in rats: structure and calibrate with existing data • Data and preliminary dosimetry for diesel exhaust particulate (DEP) • Data and preliminary dosimetry for firefighters • Begin correlation of health effects with ultrafine aerosol exposures in auto workers • Conduct DEP generation and characterization studies • Evaluate control banding options to reduce worker exposures • Develop an expanded set of FAQs
• Hazard ID information about carbon nanotubes • Publication of TiO_2 Current Intelligence Bulletin • Quantitative risk assessment on other fine and ultrafine materials from existing studies • Analyses of filter efficiency for nanomaterials • NIL updates • Develop a roadmap for nanomaterial applications in the field of occupational safety and health

In FY2007 we will continue work in the areas of toxicity and worker exposures, and will initiate work in the areas of population studies and applying risk assessment models to humans.

Summary of future research (FY2007)

• Define preliminary cardiovascular endpoints • Complete TiO_2 workplace exposure assessment report • Evaluate surface area-mass metric results • Complete nanoparticle evaluations in an auto plant including testing of exposure controls • Establish a suite of instruments and protocols for nanomaterial measurements • Conduct measurement studies of nanoparticles in the workplace • Further develop online and offline nanoparticle measurement methods • Develop guidelines for proper material handling and safe work practices • Conduct NIL updates
• Surveillance Phase II: Conduct population studies • Evaluate quantitative risk assessment methods for nanomaterials • Evaluate respirator performance • Draft a nanomaterials document • Develop a prioritized list of short term impact • Research to Practice (r2p)

After completion of preliminary work over the next few years, NIOSH will reassess and prioritize research to address remaining gaps. Following is a list of work that will be completed along with a list of things that represent potential new research directions being considered.

Summary of long term research planned/considered (FY2008–FY2009)

• Develop firm cardiovascular endpoints • Finish evaluation of exposure levels and routes • Develop performance results for nanoparticle measurement instruments and methods • Complete evaluation of viable and practical workplace sampling devices and methods for nanoparticles (affordable, portable, effective) • Finalize correlation of health effects with ultrafine aerosol exposures in auto workers • Finalize evaluation of control improvements in auto plants • Produce a summary of control strategies and of the nanotechnology safety experience • Complete dose and time information on carbon nanotubes • Update quantitative risk analysis for fine and ultrafine particles using data from NIOSH studies • Conduct hazard and risk assessment of engineering nanoparticles (e.g., carbon nanotube and ultrafine metal oxides) • Conduct evaluation of clothing and other personal protective equipment • Conduct NIL updates • Develop new or updated nanomaterials document
• Translocation results in laboratory animals after pulmonary and dermal exposure to nanomaterials • Dosimetry lung model in rats and humans, phase II: calibration and validation w/ translocation data • Quantification of systemic nanoparticle concentrations in laboratory animals after pulmonary exposure to nanospheres and nanofibers • Nanometal hazard ID • Dermal toxicity and penetration information • Neurological effects • Further r2p

APPENDIX F

NIOSH EXTRAMURAL NANOTECHNOLOGY PROGRAM

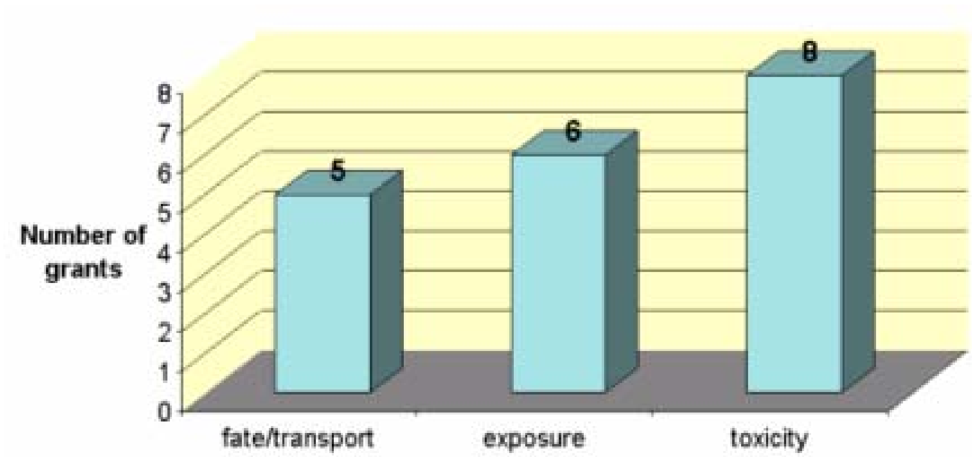

Figure F-1. Grants to be funded by EPA, NSF, and NIOSH in FY2005.

Table F-1. Grants Funded by NIOSH Extramural Research Program in FY2005.

Investigator	Funding source	Category	Institution	Title
O'Shaughnessy	NIOSH	E	U. of Iowa	Assessment Methods for Nanoparticles In the Workplace
Xiong	NIOSH	E	NYU School of Medicine	Monitoring and Characterizing Airborne Carbon Nanotube Particles
Kagan	NIOSH	T	U. of Pittsburgh	Lung Oxidative Stress/Inflammation by Carbon Nanotubes

STAR–2005–B1 (NIOSH CFDA NO. 93.262)

Assessment Methods for Nanoparticles in the Workplace, 3 yrs
R01 OH008806 O'Shaughnessy, Patrick University of Iowa
Description (Provided by Investigator)

Our primary objectives are to (1) provide the scientific community and practicing industrial hygienists with verified instruments and methods for accurately assessing airborne concentrations of nanoparticles, and (2) assess the efficacy of respirator use for controlling nanoparticle exposures. We will satisfy these objectives through a combination of laboratory and field-based studies centered on the following 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.
- Determine the collection efficiency of commonly used respirator filters when challenged with nanoparticles.

Our research approach will involve both laboratory and field work. Manufactured nanomaterials covering a range of the types available will be obtained from several sources. We will then systematically compare measurements obtained from a variety of sampling instruments, including a novel passive aerosol monitor, with measurements made by transmission electron microscopy (TEM) under controlled laboratory conditions. Field tests will involve the use of the instruments analyzed in the lab to quantify and characterize nanoparticle concentrations in workplaces that manufacture or use nanoparticles. This work will also provide the opportunity to refine an aerosol mapping technique we have developed to visualize the temporal and spatial variability of aerosol concentrations in a workplace. Laboratory testing will be conducted to determine the collection efficiency of respirator filters when challenged with a variety of nanoparticle types. We will also analyze the surface properties and chemical composition of several nanoparticle types to determine whether these qualities can help establish the cause of differences in instrument performance and filtration efficiency when challenged with different nanoparticles. The analysis will also aid in the recognition of unknown nanoparticles encountered in a workplace or in the ambient environment.

This work is an essential first step needed to accurately identify the hazards associated with a new workplace health threat. The expected results from these studies will include a greater understanding of the strengths and limitations of instruments capable of evaluating nanoparticle exposure levels. Our assessment of physical and chemical features of nanoparticles will help identify nanoparticle qualities that affect instrument performance and filtration efficiency. Moreover, this work will result in guidance on the use of respirators to protect against nanoparticle inhalation in the workplace.

Monitoring and Characterizing Airborne Carbon Nanotube Particles, 3 yrs
R01 OH008807 Xiong, Judy New York University School of Medicine
Description (Provided by Investigator)

Carbon nanotubes (CNT) are dominant among the array of nanomaterials because of their unique chemical and physical properties. Promising applications in many areas are expected to lead to industrial scale production in the near future. CNTs could become airborne during manufacturing and handling and result in inhalation and dermal exposure of workers to particles of unknown toxicity. However, knowledge is limited regarding potential exposure concentrations for workers exposed to this new type of material. Also, no adequate method exists for quantitative and qualitative monitoring of airborne CNTs because of their complexity. The proposed research will develop a comprehensive yet practical method for sampling, quantification, and characterization of CNT particles in air. The method will permit classification of sampled particles into three categories: tubes, ropes (bundles of single-walled CNTs bounded by Van der Waals attraction force), and nontubular particles (soot, metal catalysts, and dust, etc.). The method will also permit calculation of the number concentrations and size distributions for each type, and the shape characters (diameter, length, aspect ratio and curvature) of CNTs. The method will use available instrumentation to build an air monitoring system that is capable of sampling and sizing airborne CNT particles in a wide size range by using a 10-stage Micro-orifice uniform Deposit Impactor (MOUDI) and an Integrated Diffusion Battery previously developed in this laboratory. The samples of each size fraction will be collected onto Silicon-chip substrates and analyzed using Atomic Force Microscopy (AFM). Newly developed software, SIMAGIS® Nanotube Solutions, will be used for AFM image analysis and data processing, which can automatically count nanotubes, nanoropes and particles; and measure the shape characters. Other commercially available nanoparticle sampling instruments, such as an electrostatic aerosol sampler and a Nano-MOUDI will also be tested in this work. Successful completion of this project will produce a validated method for sampling airborne CNTs in the workplace and a practical method (using AFM image analysis technology) for classifying sampled CNT particles by type and for quantifying and characterizing each type separately. These methods are needed for determining 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 CNTs.

Lung Oxidative Stress/Inflammation by Carbon Nanotubes, 5 yrs
R01 OH008282 Kagan, Valerian University of Pittsburgh
Description (Provided by Investigator)

Single-Walled Carbon NanoTubes (SWCNT) are new materials of emerging technological importance. Their manufacturing requires iron resulting in its high content in SWCNT. Because iron is a catalyst of oxidative stress, iron-containing SWCNT are likely more toxic than iron-free SWCNT. Our central hypothesis is that SWCNT are toxic to the lung and the toxicity depends on their content of iron. The major toxicity mechanisms include inflammatory response synergistically enhanced by oxidative stress exacerbated by iron. SWCNT toxic effects are further augmented by microbially induced inflammation. The apoptotic/necrotic target cell death ratio dependent on the WCNT iron is also a regulator of SWCNT toxicity via production of anti-/pro-inflammatory cytokines, respectively. Aim 1 is to establish the extent to which SWCNT alone are pro-inflammatory to lung cells and tissue and characterize the role of iron in these effects using genetically manipulated cells and animals as well as antioxidant interventions. Aim 2 is to determine the potential for SWCNT and microbial stimuli to synergistically interact to promote macrophage activation, oxidative stress, and lung inflammation. Aim 3 is to reveal the extent to which SWCNT are effective in inducing apoptosis and whether apoptotic cells exert their macrophage-dependent anti-inflammatory potential during in vitro and in vivo SWCNT exposure. The project involves a team of interdisciplinary investigators with unique expertise in redox chemistry/biochemistry (V. Kagan), cell and molecular biology of inflammation (L. Ortiz) and its interactions with microbial agents (J. Fabisiak), and pulmonary toxicology of (nano)particles (V. Castranova, A. Shvedova). Based on our results, mechanism-based interventions (such as specific antioxidants) new means to control iron content (using nontoxic chelators), and biotechnological approaches (phosphatidylserine liposomes and/or apoptotic cells down-regulating inflammatory response) may be developed to decrease toxicity of (iron-containing) SWCNT.

APPENDIX G

NIOSH POSITION STATEMENT ON NANOTECHNOLOGY—ADVANCING RESEARCH ON OCCUPATIONAL HEALTH IMPLICATIONS AND APPLICATIONS

NIOSH is the Federal agency that conducts research and makes recommendations for preventing work-related injuries, illnesses, and deaths. NIOSH is part of CDC in the U.S. Department of Health and Human Services. As a member of the Nanotechnology Science, Engineering, and Technology Subcommittee (NSET) of the National Science and Technology Council Committee on Technology, NIOSH works closely with other Federal agencies and private sector organizations to plan, conduct, and facilitate research that will support the responsible development and use of nanotechnology. With the Food and Drug Administration, NIOSH co-chairs the NSET interagency working group on Nanotechnology, Environmental and Health Implications (NEHI).

At the nanoscale level, materials exhibit unique properties that affect their physical, chemical, and biological behavior. Those properties raise questions as to potential health effects that might result from occupational exposures during the manufacture and use of nanomaterials. To answer those questions, scientists need to fill significant gaps in current knowledge.

For example, do engineered nanomaterials pose unique work-related health risks? In what ways might employees be exposed to nanomaterials in manufacture and use? In what ways might nanomaterials enter the body during those exposures? Once in the body, where would the nanomaterials travel, and how would they interact physiologically and chemically with the body? Can those interactions cause acute or chronic adverse effects? What are appropriate methods for measuring and controlling exposures to nanometer-diameter particles and nanomaterials in the workplace?

NIOSH is working strategically to fill those gaps and others through an active intramural and extramural research program. NIOSH multidisciplinary research builds on the Institute's experience in defining the characteristics and properties of ultrafine particles such as welding fume and diesel particulate, which have some features in common with engineered nanomaterials. NIOSH is capable of conducting advanced health effects laboratory studies and has demonstrated historic leadership in industrial hygiene policies and practices. The NIOSH program also builds on the Institute's close partnerships with diverse stakeholders in industry, labor, the government, and academia.

NIOSH is committed to conducting and supporting studies that will improve scientists' ability to identify potential occupational health effects of nanomaterials. NIOSH will facilitate the translation of those findings into effective workplace practices. Those goals are critical for helping the United States remain strong and competitive in the dynamic nanotechnology market. In addition, NIOSH is evaluating the unique benefits that nanotechnology may bring to improving sensors and control devices in occupational safety and health.

As specific actions in support of occupational health research and nanotechnology, NIOSH has accomplished the following:

- Created an organizational NIOSH Nanotechnology Research Center to coordinate nanotechnology-related research across the Institute and to provide strategic, multiyear direction for that interdisciplinary research.
- Initiated a program under the National Occupational Research Agenda (NORA) to characterize the physical and chemical properties of nanoaerosols, study their effects on biological systems, and evaluate whether they pose work-related health risks.
- Established a new Web page to communicate its nanotechnology research program to stakeholders and the general public, and to report ongoing developments and accomplishments in a timely way.
- Joined with the Environmental Protection Agency and the National Science Foundation in 2004 to stimulate excellent extramural research through $7 million in funding of competitive grants.
- Partnered with the U.K. Health and Safety Executive to sponsor the first International Symposium on Nanotechnology and Occupational Health in October 2004. NIOSH also will sponsor a Second International Symposium in October 2005.
- Began developing documentation that will recommend effective, practical ways to control occupational exposures to nanomaterials pending research for more definitive data. At present, the limited evidence available would suggest caution when work-related exposures to nanomaterials may occur.

For more information on the nanotechnology program, visit the NIOSH Web site: http://www.cdc.gov/niosh/topics/nanotech/

APPENDIX H

NIOSH PEER-REVIEWED PUBLICATIONS

Bugarski A [2004]. Characterization of diesel aerosols in an underground metal mine. In: Proceedings of 8th ETH-Conference on Combustion Generated Nanoparticles (CD-ROM), August 16–18.

Bugarski A, Mischler S, Schnakenberg G [2005]. Effects 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), Zürich, Switzerland, August 15–17.

Kisin E, Murray AR, Johnson V, Gorelik O, Arepalli S, Gandelsman VZ, Hubbs AF, Mercer RR, Baron P, Kagan VE, Castranova V, Shvedova AA [2005]. Pulmonary toxicity of carbon nanotubes. The Toxicologist *84*:A1041.

Ku BK, Maynard AD [in press]. Generation and investigation of airborne silver nanoparticles with specific size and morphology by homogeneous nucleation, coagulation and sintering. J Aerosol Sci.

Li Z, Salmen R, Hulderman T, Kisin E, Shvedova A, Luster M, Simeonova P [2004]. Pulmonary carbon nanotube exposure and oxidative status in vascular system. Free Radical Biol Med *37*(1):S142.

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Maynard AM, Kuempel ED [forthcoming]. Airborne nanostructured particles and occupational health. J Nanoparticle Res.

Maynard AD, Baron PA, Foley M, Shvedova AA, Kisin ER, Castranova V [2004]. Exposure to carbon nanotube material during the handling of unrefined single walled carbon nanotube material. J Toxicol Environ Health, Part A *67*:87–107.

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Shvedova AA, Kisin E, Murray AR, Gorelik O, Arepalli S, Gandelsman VZ, Mercer B, Hubbs A, Kagan VE, Castranova V [2004]. Oxidative stress and pulmonary toxicity of carbonnanotubes. Free Radical Biol Med *37*(1):S55.

Shvedova AA, Kisin E, Murray A, Maynard A, Baron P, Gunther M, Keshava N, Schwegler-Berry D, Gandelsman V, Gorelik O, Aperalli S, Kagan V, Castranova V [2004]. Assessment of carbon nanotube cytotoxicity using human cells and animal models. In: Proceedings of The Toxicology Forum's 29th Toxicology Annual Winter Meeting, Washington, DC, February 2–4.

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Simeonova P, Li J, Luster MI, Shvedova A, Salmen R [in press]. Carbon nanotube exposure and cardiovascular outcomes. Second International Symposium on Nanotechnology and Occupational Health, Minneapolis, MN.

Thomas M, Peters TM, Evans, DE, Heibrink WA, Slavin TJ, Maynard AD [2005]. The mapping of fine and ultrafine particle concentrations in an engine machining and assembly facility. Ann Occ Hyg. Submitted.

APPENDIX I

NIOSH SPONSORED CONFERENCES

1. *First International Symposium on Occupational Health Implications of Nanomaterials*, October 12–14, 2004, Buxton, UK. The conference is co-sponsored by the U.K. Health and Safety Executive and NIOSH.

2. *Second International Symposium of Nanotechnology and Occupational Health*, October 3–6, 2005, Minneapolis, MN.

3. *Frontiers in Aerosol Dosimetry Research*, October 24–25, 2005, Irvine, CA.

4. *Mechanisms of Action of Inhaled Fibers, Particles, and Nanoparticles in Lung and Cardiovascular Disease*, October 25–28, 2005, Research Triangle Park, NC.

APPENDIX J

INVITED PRESENTATIONS

Castranova V. Potential toxicity of nanoparticles. 2004 Northwest Occupational Health Conference. Portland, OR, October 14, 2004.

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Maynard A. Generating and characterizing airborne nanoparticles. American Association for the Advancement of Science Conference, Washington, DC, February 20, 2005.

Maynard A. Understanding the potential impact of nanotechnology on occupational health. University of Cincinnati, Cincinnati, OH, February 23, 2005.

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Maynard A. Responsible nanotechnology and the working environment. National Research Council Review of the U.S. National Nanotechnology Initiative Meeting on Responsible Nanotechnology, Washington, DC, March 24, 2005.

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Shvedova A. 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, 2005.

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Simeonova P. Nanoparticles-systemic and vascular effects. Nanotoxicology: Biomedical Aspects, Nanotoxicology 2006, Miami, FL, January 29–February 1, 2006.

APPENDIX K

INTERVIEWS GIVEN BY NIOSH EMPLOYEES

Hoover M. *Inside OSHA* (July 2005).

Hoover M. *Journal of the American Medical Association* (September 2005).

Maynard A, Shvedova A, Castranova V. *Nanobiotech News 2*(20):2–3 (May 19, 2004).

Maynard A, Shvedova A, Castranova V. *Small Times* (May 19, 2004).

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Murashov V. *Machine Design* (August 26, 2005).

Shaffer R, Rengasamy S. *Occupational Hazards* September 2005 (August 9, 2005)

Williams K. *AIHA Synergist* October 2004 (August 10, 2004).

APPENDIX L

PARTNERSHIP

Vincent Castranova is collaborating with the University of Rochester about the ability of nanoparticles to generate radical species.

Vincent Castranova and Dale Porter are collaborating with Oak Ridge Laboratory to evaluate the pulmonary toxicity of nanoparticles.

Doug Evans is collaborating with the University of Minnesota and the University of Iowa on measurement of airborne levels of ultrafine particles.

Mark Hoover and others in the Nanoparticles in the Workplace Project are collaborating with industrial hygiene, occupational health, and industrial partners at the University of Nevada at Reno and Altairnano on understanding and improving the control of ultrafine metal oxides and engineered nanomaterials.

Mark Hoover and others in the Nanoparticles in the Workplace Project are collaborating with industrial hygiene, occupational health, and industrial partners at Virginia Tech and Luna Nanoworks on understanding and improving the control of fullerines and other engineered nanoparticles.

Eileen Kuempel is collaborating with the Chemical Industry Institute of Toxicology Centers for Health Research on software modifications for use in lung dosimetry modeling.

Eileen Kuempel is collaborating with the Institute of Occupational Medicine, Edinburgh, Scotland, on revising rat lung dosimetry models to account for particle size-specific clearance and retention.

Mike Luster is collaborating with the National Institute of Envronmental Health Sciences/ National Institute of Health and the Department of Defense on nanotoxicology.

NIOSH is collaborating with a commercial cosmetics manufacturer to understand and improve the control of ultrafine titanium dioxide and other nanoparticles in the workplace.

NIOSH has been asked by NanoMech LLC (Fayetteville, Arkansas) to collaborate on a proposed EPA Phase I SBIR project related to containment of airborne nanoparticles.

NPPTL is working with the DuPont Occupational Safety & Health consortium on the identification of test methods for protective clothing and respirators.

NPPTL (Samy Rengasamy and Ron Shaffer) are collaborating with the International Safety Equipment Association (ISEA) on the respirator filter media work being conducted at the University of Minnesota to assess the filtration efficiency against nanoparticles.

Samy Rengamsamy is organizing a roundtable discussion on nanotechnology and personal protective equipment issues at the American Industrial Hygiene Conference and Exposition— 2006, Chicago, IL, May 2006.

Anna Shvedova has a memorandum of understanding with the National Aeronautics and Space Administration to evaluate the toxicity of single walled carbon nanotubes.

Ann Shvedova and Vincent Castranova are collaborating with the University of Pittsburgh on the toxicity of nanomaterials.