CDC Workplace Safety and Health

Strategic Plan for NIOSH Nanotechnology Research and Guidance

Filling the Knowledge Gaps

Draft

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

NIOSH

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 and Guidance: Filling the Knowledge Gaps*. This plan updates the September 2005 strategic plan using knowledge gained from results of ongoing research as described in the 2007 report *Progress Toward Safe Nanotechnology in the Workplace: A Report from the NIOSH Nanotechnology Research Center.* The NIOSH nanotechnology research program is a cross sector program that supports 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 implications and applications of nanomaterials.

I welcome your review and your comments on our plan. Please e-mail your comments to nioshdocket@cdc.gov. Please reference docket number NIOSH-134 when providing comments. 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, 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. In June 2007, NIOSH reported its progress in conducting nanotechnology research and developing recommendations on the safe handling of nanomaterials, [see report *Progress Toward Safe Nanotechnology in the Workplace: A Report from NIOSH Nanotechnology Research Center at* http://www.cdc.gov/niosh/topics/nanotech/, DHHS (NIOSH) Publication No. 2007-123].

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 and guidance.

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 implications of nanoparticles and nanomaterials for work-related injury and illness, and the application of nanoparticles and nanomaterials in occupational safety and health.

THE STRATEGIC PLAN FOR NIOSH NANOTECHNOLOGY RESEARCH AND GUIDANCE

The purpose of the strategic plan for NIOSH nanotechnology research and guidance 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. From its inception, the strategic planning process has incorporated input from a broad range of collaborators and stakeholders.

GOALS FOR NIOSH NANOTECHNOLOGY RESEARCH AND GUIDANCE

The goals for NIOSH nanotechnology research are as follows:

1. Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses.

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

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

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

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. Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses.

To achieve this goal, NIOSH researchers will determine the relative toxicity of nanoparticles and nanomaterials and identify possible health effects from the early uses of these 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 human health effects will be difficult because only small numbers 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. Animal models need to be developed to provide hazard identification, biological reactions at the route of exposure as well as distal organs, dose-response, time course, information concerning clearance and translocation, and risk assessment information necessary for various nanoparticles and nanomaterials. In addition, in vitro screening tests predictive of in vivo response are needed to develop algorithms relating physicochemical properties to bioactivity. 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. NIOSH will continue to evaluate the potential applications. Engineered nanomaterials may support the development of high performance filter media, including those used in respirators, coatings in non-soiling/dust-repellant/self-cleaning clothes, fillers for noise absorption materials, fire retardants, protective screens for prevention of roof falls, 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 monitoring of occupational safety and health hazards. Nanotechnology-based fuel cells, lab-on-chip analyzers, and optoelectronic devices all have the potential to be useful in the safe 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.

NIOSH intends to address this goal by continuing to develop guidance based on the review of the science and evaluation of current best practices, available knowledge, and professional judgment. NIOSH provided seminal guidance for workers and employers in nanotechnology through the document entitled *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. This document was posted on the NIOSH Web site in October 2005 and updated in August 2006, and will be updated and published within the next two years. NIOSH will continue to develop guidance documents on critical occupational safety and health issues involving nanotechnology.

NIOSH will continue to evaluate engineering controls, protective equipment, occupational exposure limits, and administrative controls that have been used to reduce occupational exposures to other types of particulates to determine how they might apply to nanoparticle exposures. NIOSH will continue to evaluate medical surveillance and develop guidance for workers involved with nanotechnology. The use of control banding (a hazard-based approach to risk assessment and control) or similar qualitative risk management approaches 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 research and guidance.

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 will continue its history of and commitment to working with national and 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 NTRC identified 10 critical research areas that will be used to address the strategic goals:

- Exposure assessment
- Toxicity and internal dose
- Epidemiology and surveillance
- Risk assessment
- Measurement methods
- Engineering controls and personal protective equipment
- Fire and explosion safety
- Recommendations and guidance
- Communication and information
- Applications

The NTRC efforts are organized according to the 10 critical research areas. Targeted research in each of the critical areas is the means by which NIOSH will identify and characterize hazards, assess exposure, characterize risk and develop risk management guidance.

The strategic plan is built on the integration of basic and applied research, developing guidance, and translating results into practice. As nanotechnology grows 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 that will continue to evolve as new scientific information is obtained, questions arise, and concerns of stakeholders and partners are raised. By maintaining a dynamic approach, NIOSH will be able to anticipate challenges and provide useful information and knowledge for the safe handling of nanomaterials.

1 INTRODUCTION

1.1 Background

Nanotechnology is a system of innovative methods to control and manipulate matter at near-atomic scale to produce new materials, structures, and devices. Nanoparticles are a specific class or subset of these new materials, having at least one dimension that is less than 100 nanometers. They exhibit unique properties because of their nanoscale dimensions. Nanotechnology offers the potential for tremendous improvement and advances in many areas than may benefit society, such as 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. The properties of nanoparticles (e.g., size, surface area, reactivity) that yield many of the far reaching societal benefits may also pose risks. Currently, increasing numbers of workers are potentially exposed to nanomaterials in research laboratories, start-up companies, production facilities, and in operations where nanomaterials are processed, used, disposed or recycled. The challenges are to determine whether the nature of intentionally produced (engineered) nanostructured materials and devices presents new occupational safety and health risks. At the same time, there is a need to address how the benefits of nanotechnology can be realized while proactively minimizing the risk.

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

The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency responsible for conducting research and making recommendations to prevent work-related injury, illness, and death. NIOSH is a member of the Nanoscale Science, Engineering and Technology (NSET) Subcommittee of the National Science and Technology Council. As such, NIOSH is active in (1) identifying critical issues related to possible hazards of nanomaterials, (2) protecting worker safety and health in this emerging technology, and (3) developing a strategic plan to address such issues and recommend prevention strategies for the safe handling and use of nanomaterials.

Because of their small size and large surface area, engineered nanoparticles have chemical, physical, and biological properties distinctly different than fine particles of similar chemical composition, thus making them attractive for commercial development and application. 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 identify, assess, and resolve potential safety and health issues posed by nanotechnology. NIOSH has 38 years of experience in conducting research and formulating recommendations for occupational safety and health. During this period, NIOSH has developed considerable expertise in measuring, characterizing, and evaluating new processes and new materials by conducting quantitative exposure assessments and evaluating health effects. NIOSH also has expertise in developing control systems and prevention strategies for incidental nanoparticles (e.g., diesel exhaust, welding fume, smelter fume, and fire smoke particles). NIOSH will reapply this experience to address similar issues for engineered nanoparticles.

In 2004, NIOSH created the 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. The NTRC is comprised of nanotechnology-related activities and projects consisting of and supported by more than 30 scientists from various NIOSH divisions and laboratories. Through the NTRC, NIOSH has identified 10 critical research areas for nanotechnology research and communication. These 10 critical research areas are: (1) exposure assessment, (2) toxicity and internal dose, (3) epidemiology and surveillance, (4) risk assessment, (5) measurement methods, (6) engineering controls and personal protective equipment (PPE), (7) fire and explosion safety, (8) recommendations and guidance, (9) communication and information, and (10) applications. By working in these critical research areas, NIOSH has comprehensively begun to address the information and knowledge gaps necessary to protect workers and responsibly move nanotechnology forward so that its far-reaching benefits may be realized. A summary of research projects may be found in Appendix A. The NIOSH position statement on Nanotechnology –Advancing Research on Occupational Health Implications and Applications is presented in Appendix B. Current intramural NIOSH research activities in nanotechnology are summarized in Appendix C.

Congruent with the efforts of the NTRC are the efforts of the NIOSH Office of Extramural Programs (OEP) which are summarized in Appendix D. OEP uses several mechanisms (R01, R21, R43/44) for funding research. OEP funding of nanotechnology-related research has been undertaken to help increase the knowledge of nanotechnology and engineered nanomaterials as they relate to occupational safety and health. Research areas supported by NIOSH OEP include emission and exposure assessment methods for nanoparticles in the workplace, toxicology of engineered nanomaterials, and the use of nanotechnology for improved workplace monitoring.

NIOSH is working strategically to fill those gaps and others through active intramural and extramural research programs and collaborations (Appendix E). NIOSH is committed to conducting and supporting studies that will improve scientists' abilities to identify potential occupational health effects of nanomaterials. NIOSH will facilitate the translation of those findings into effective workplace practices.

1.2 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.

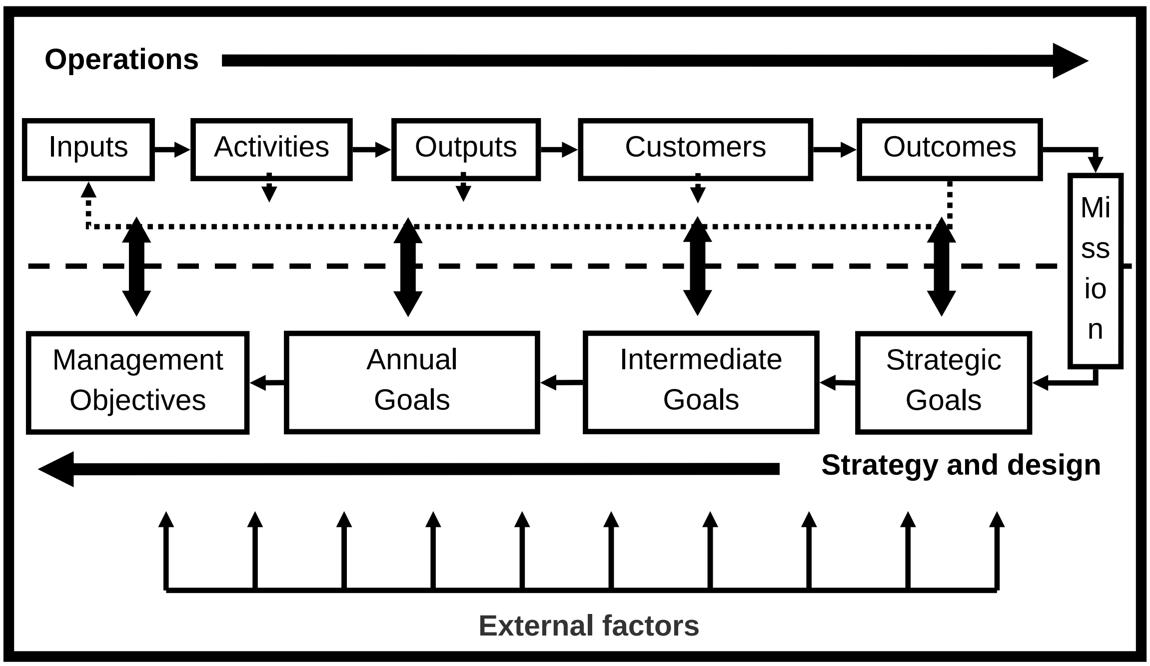

Figure 1. Schematic of the overall NIOSH logic model

The NIOSH research program begins with an analysis of production and planning inputs and follows the NIOSH operational model (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 at all stages of program operation by both external factors (such as economic and social conditions) and the regulatory environment. Results of NIOSH-funded research and customer feedback (intermediate and final) contribute to the subsequent rounds of program planning.

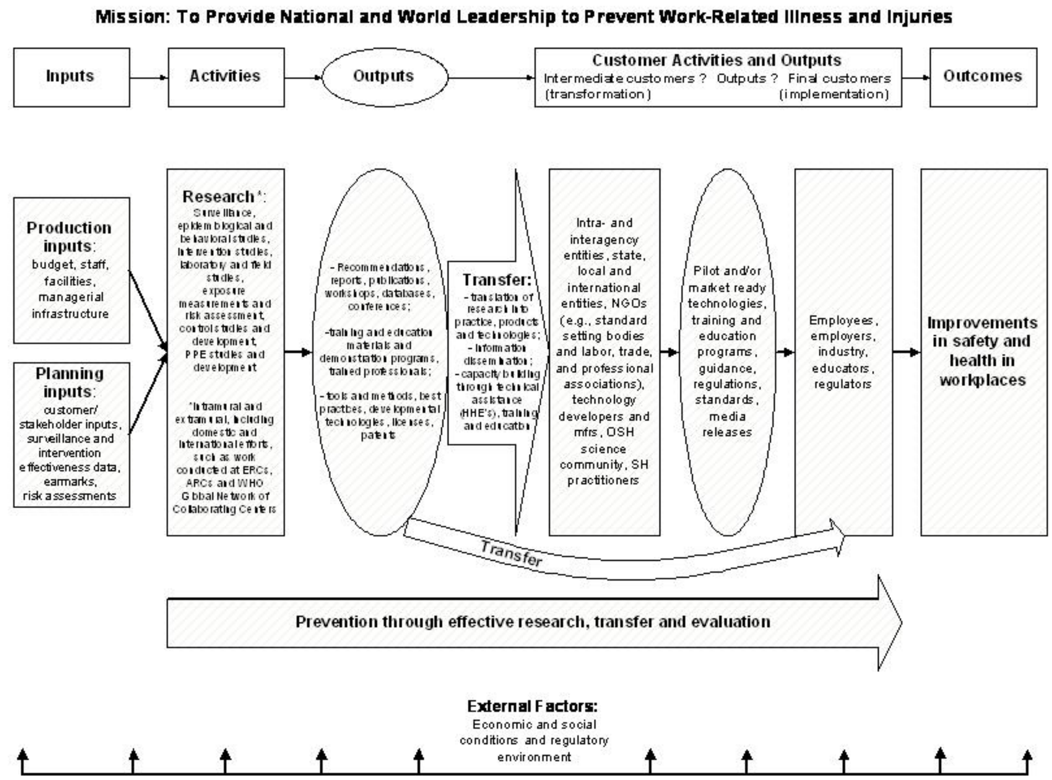

Figure 2. Schematic of the NIOSH operational model

2 INPUTS

2.1 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 given the responsibility 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 such as 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 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 of the Act).

2.2 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 through ad hoc mechanisms such as the NIOSH Web site (www.cdc.gov/niosh), the NIOSH toll-free telephone line (1-800-CDC-INFO), personal contacts with occupational safety and health professionals, and participation in professional conferences and interagency committees. NIOSH also provides stewardship of the National Occupational Research Agenda (NORA) (http://www.cdc.gov/niosh/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 (NEHI), under the NSET Subcommittee. NIOSH was formally invited to join the NEHI in 2004, and this interagency effort has consistently encouraged NIOSH to recognize nanotechnology as one of its research priorities.

The importance of research on the occupational safety and health issues for nanotechnology was further stressed at the *National Academies Review of the National Nanotechnology Initiative* held on March 24–25, 2005. Richard Denison (Environmental Defense) and Carol Henry (American Chemistry Council), in their presentations to the National Academies review panel, called for an increase in federal funding of 10%, or $100 million, to address the environmental, safety, and health issues of the nanotechnology industries. 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* that 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 the 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).

The NEHI working group 2006 publication *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* and the NNI *2008 Strategy for Nanotechnology-Related Environmental, Health and Safety Research* identified five priority environmental health and safety research needs: (1) instrumentation, metrology, and analytical methods, (2) nanomaterials and human health, (3) nanomaterials and the environment, (4) health and environmental exposure assessment, and (5) risk management methods (Appendix F). The NIOSH NTRC goals are reflective of these five priority environmental health and safety areas.

2.3 NIOSH Research Capabilities

The first-class research capability of NIOSH is an integral part of management's inputs to the nanotechnology program. Within its divisions, NIOSH has world renowned researchers who are trained and experienced in the full spectrum of necessary disciplines ranging from epidemiology to intervention effectiveness. Sections 3 and 5 of this document describe current NIOSH research activities including publications on nanomaterials and NIOSH-sponsored meetings and conferences. 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 component of its capacity to address critical occupational safety and health issues in nanotechnology.

2.4 NIOSH Partnerships

NIOSH recognizes both the practical need and the leadership obligation to extend its internal capability by leveraging activities and expertise found in other research institutions, industries, federal agencies, and nongovernmental organizations. These partnerships serve to deliver on multiple objectives; most importantly, they add to the body of knowledge on workplace health and safety issues associated with nanotechnology. Partnerships have taken several forms, ranging from formal letters or memoranda of understanding to informal working agreements on a specific topic. NIOSH will continue to pursue partnerships as a means of achieving the goals of this strategic research plan and as an effective vehicle to develop and disseminate research results that can be translated into practice that will lead to the positive impact of helping nanotechnology move forward responsibly.

NIOSH has successfully used partnerships with industry specific to nonmaterial production, to gain a better understanding of actual workplace exposures, practices, and controls that are in place. The field work that is conducted by NIOSH to assess exposures to engineered nanoparticles represents ongoing partnerships with numerous companies. NIOSH will continue to develop these partnerships in order to receive input on accomplishing its objectives of developing recommendations for the safe handling of nanoparticles; developing methods to measure exposures to nanoparticles; evaluating controls that are, or could be, used in nanomaterial processes; evaluating the need for and the effectiveness of PPEs including respiratory protection; and developing communication and information materials that will assist industry in communicating with workers and the public. Several of the industrial partnerships NIOSH has developed have provided opportunities from the beginning of the nanotechnology program to identify areas where additional research was needed.

Collaboration with other research institutes, academia, and government provides NIOSH the opportunity to combine its expertise in workplace health and safety with the capabilities of other organizations that are investigating a specific element of the research that is needed. Developing working relationships with other research institutes provides NIOSH with the information needed to guide its own research and focus its limited resources in the most effective manner. NIOSH has developed partnerships in the areas of toxicology, risk assessment modeling, exposure measurement methods, control technologies, filtration of nanoparticles, and communication of research results and safe work practices.

NIOSH broadens its activities with a wide variety of collaborators and stakeholders by its participation in a number of national and international committees and working groups. This participation provides NIOSH the opportunity to provide and receive input on the key research that is needed to address priority areas.

3 ACTIVITIES

3.1 NIOSH Nanotechnology Research Center (NTRC)

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 implications of nanoparticles and nanomaterials for work-related injury and illness, and the application of nanoparticles and nanomaterials in occupational safety and health.

3.2 NTRC Steering Committee

The NTRC Steering Committee is responsible for guiding NIOSH scientific and organizational plans in nanotechnology research (including coordination for science and budget) and for developing strategic goals and objectives and performance measures for the NTRC. To ensure the responsiveness, relevance, and impact of NIOSH's nanotechnology program, appropriate representatives of its nanotechnology research program meet in person on an annual basis to update strategic planning for nanotechnology research. At these meetings, the critical occupational safety and health issues arising from nanotechnology are reviewed and updated as appropriate. Regular updates and progress reporting is managed through weekly teleconferences conducted by the NTRC. In addition, meetings are held with appropriate stakeholders at least every other year.

3.3 Current NIOSH Intramural Nanotechnology Research Activities

Current NIOSH research activities in nanotechnology are focused on occupational safety and health implications. NIOSH has expertise in developing control systems and prevention strategies for incidental nanoparticles (e.g., diesel exhaust, welding fume, smelter fume, and fire smoke particles). NIOSH is using this experience to address similar hazard, risk, and control issues for engineered nanoparticles. It appears that nanomaterials that are presently manufactured and subsequently introduced into products have no major physical features that would make them behave differently from fine or ultrafine particles in terms of the ability to control them in the workplace. However, the limits of this assumption need continued evaluation. Data from ongoing and proposed studies with engineered nanoparticles are being 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 are also providing data on the characteristics of nanomaterials produced and used in the workplace, routes of exposure, work practices, and engineering controls. Findings from these intramural studies are providing scientific data to support the development of occupational safety and health recommendations. The timeline for conducting these research activities with individual research projects is given in Appendix A.

3.4 Current NIOSH Extramural Nanotechnology Research Activities

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

From 2001-2008 to date, the Office of Extramural Programs (OEP) has funded nanotechnology research through Occupational Safety and Health Research Program Announcements (R01) and Small Business Innovation Research Grants (R43/44). Since FY-05, OEP has also participated in two joint Requests for Applications (RFAs) for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. The US Environmental Protection Agency's National Center for Environmental Research (NCER) and the National Science Foundation (NSF) participated in FY-05. The National Institute of Environmental Health Sciences (NIEHS) joined in FY-06. Funding was available to support Research (R01) grants for three years and Exploratory (R21) grants for two years.

In FY-07, NIOSH/OEP participated in RFA-ES-06-008 Manufactured Nanomaterials: Physicochemical Principles of Biocompatibility and Toxicity. This RFA was jointly sponsored by NIEHS, EPA and NIOSH.

In FY-08, nanotechnology related research proposals submitted to standing program announcements are being considered for funding by NIOSH/OEP.

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

3.5 Collaborative Workshops

In FY05, NIOSH co-sponsored the 1st International Symposium on Nanotechnology and Occupational Health in Buxton, United Kingdom, and in FY06, NIOSH co-sponsored the 2nd International Symposium on Nanotechnology and Health in Minneapolis, MN. In FY07, NIOSH collaborated with the International Aerosol Research Assembly and the American Association for Aerosol Research to hold an International Symposium on Nanotechnology and Health in conjunction with the International Aerosol Conference in St. Paul, Minnesota. In FY07, NIOSH and the University of Cincinnati cosponsored the International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice, in Cincinnati, OH. In FY07 NIOSH convened a collaborative workshop including representatives from government, academia, labor, and industry in Washington, DC, to review a draft document developed by NIOSH and a cross agency work group, titled "Interim Guidelines on Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles." In FY07 NIOSH cosponsored the 3rd International Symposium on Nanotechnology Safety & Health in Taipei, Taiwan. In FY08 NIOSH began to participate in the planning of the 4th International Congress on Nanotechnology Safety and Health planned for August 2009, in Helsinki, Finland.

4. GOALS

The NIOSH Nanotechnology Research Center (NTRC) has developed the following strategic goals based on inputs from stakeholders and partners:

Strategic Goal 1. Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses.

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

b. Conduct research on the toxicity of nanomaterials including investigating key factors for bioactivity; identify pulmonary, systemic, and dermal response; and elucidate mechanisms. Develop screening tests and predictive models for toxicity, and determine the 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 research on measuring nanomaterials in the workplace, including developing new measurement methods and validating measurement methods.

e. Conduct risk assessments relevant to nanomaterials. Evaluate the role of nanoparticle properties in exposure-dose-response relationships, develop and validate models for nanoparticle risk assessment, and determine risk estimates of occupational exposures.

Strategic Goal 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.

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

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

b. Evaluate and develop guidance on the proper selection and use of personal protective equipment (e.g., respirators, clothing, gloves) for reducing exposure to nanoparticles.

c. Evaluate the suitability and role of work practices, administrative controls, 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 controlling nanoaerosols in 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. Act as a resource in evaluating adequacy of the existing mass-based safety and health criteria of nanomaterials to a broad range of government and non-governmental stakeholders.

i. Act as a resource to manufacturers to update the Material Safety Data Sheet system to incorporate relevant classifications, toxicity data, and safety and health recommendations for working with nanomaterials.

j. Develop guidance based on the review of the science and evaluation of current best practices, available knowledge, and professional judgment.

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

a. Develop partnerships for identifying research and for the sharing of research needs, approaches, and results.

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

4.1 Risk Management Process

A complete process for managing occupational safety and health implications during the development of new technologies and materials consists of a set of progressive elements: identifying and characterizing the hazard, assessing the extent of exposure, characterizing the risk, and developing control and management procedures. As exposure assessment data become available, a determination can be made whether or not an occupational risk exists, and if so, the risk can be assessed and characterized. A goal of the risk characterization is to determine whether exposure to a given technology or type of material (in this case, nanoparticles) is likely to result in adverse health effects. Exposure assessment data also provide a means to determine what controls are effective in preventing exposure that could cause adverse health effects. The NIOSH NTRC is involved in answering questions posed in each element in the risk management process. Figure 3 provides a visual representation of the risk management process and the NIOSH research associated with each step.

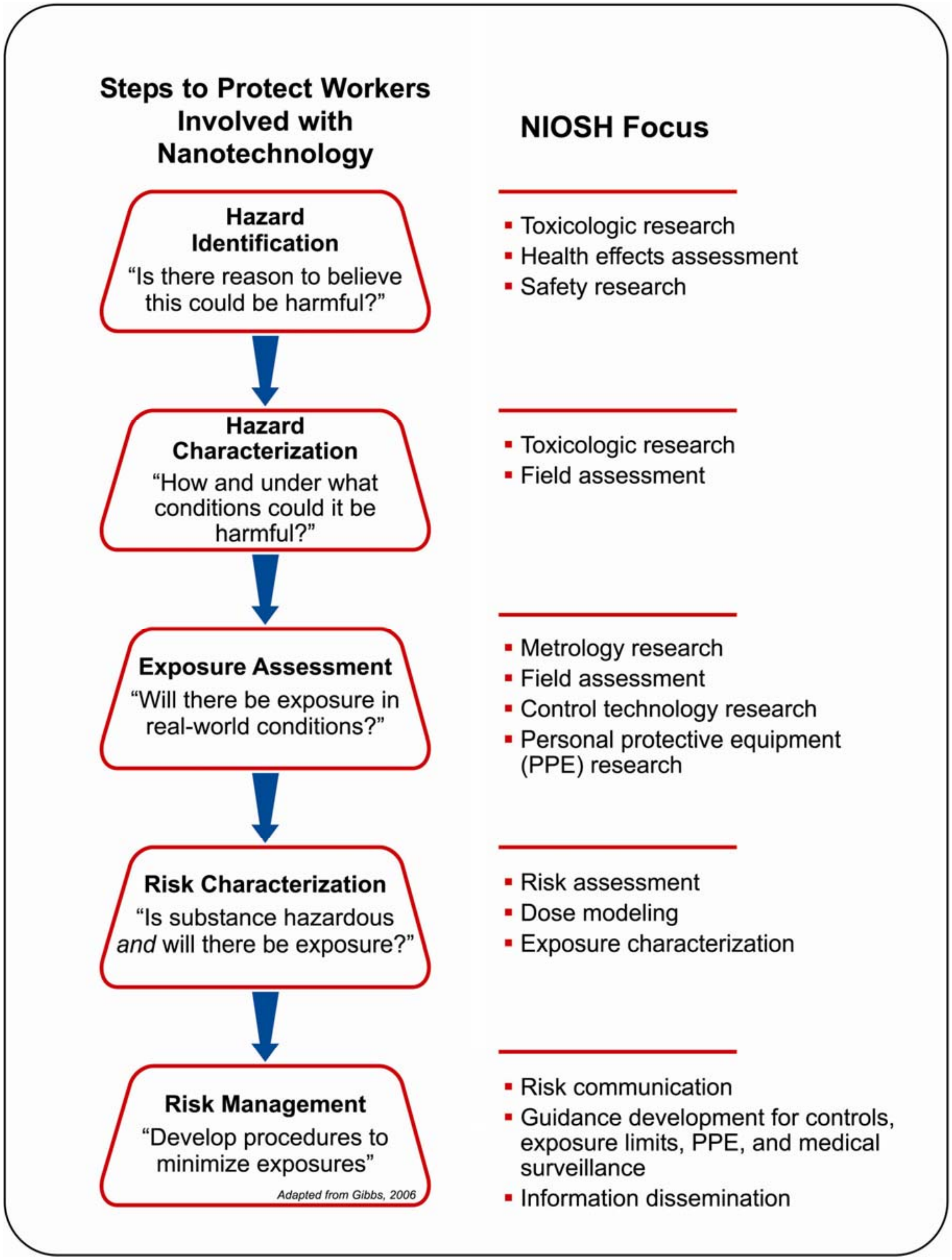

Figure 3. Steps to protect workers involved with nanotechnology

4.2 10 Critical Research Areas

NIOSH has comprehensively begun to address its NTRC strategic goals by identifying the knowledge necessary to step through the risk management process to protect workers and responsibly move nanotechnology forward. The NIOSH NTRC strategic goals are being addressed by identification of intermediate goals and performance measures in 10 critical research areas: (1) exposure assessment (2) toxicity and internal dose, (3) epidemiology and surveillance, (4) risk assessment, (5) measurement methods, (6), engineering controls and personal protective equipment (PPE), (7) fire and explosion safety, (8) recommendations and guidance, (9) communication and information, and (10) applications. Additionally, since the fourth strategic goal of enhancing global workplace safety and health through national and international collaborations on nanotechnology research and guidance cross-cuts all 10 critical research areas, intermediate goals were developed for this area. Section 4.3 lists the intermediate goals and performance measures for each of the NIOSH NTRC critical research areas and the global collaboration efforts.

NIOSH participates in the National Nanotechnology Initiative's (NNI) "Strategy for Nanotechnology Environmental Health and Safety Research." Figure 4 shows the alignment of the four NIOSH NTRC strategic goals and the 10 NTRC critical research areas with the NNI environmental health and safety (EHS) priority research needs (see Appendix F). Planned projects within each of the 10 NIOSH critical research areas may meet one or more of the four NIOSH Strategic Goals. A check mark (✓) means that a goal is addressed by projects within the critical research area. Alpha-numerical identifications indicate alignment of the NIOSH critical research goals with the NNI EHS priority environmental health and safety areas.

	Critical Research Areas									
NIOSH NTRC Strategic Goals	Exposure Assessment[2]	Toxicity and Internal Dose	Epidemiology and Surveillance	Risk Assessment	Measurement Methods	Engineering Controls and PPE	Fire & Explosion Safety	Recommendations & Guidance	Communication and Information	Applications
1 Determine if nanoparticles and nanomaterials pose risks for work-related injuries and illnesses	✓ A1 A2 D1 D4 D5 E1 E2	✓ A2 B1 B2 B3 B4 B5	✓ D1 D2 D3 D4 E4	✓ A2 B1 B2 D4 E3	✓ A1 A2 A3 A4 A5 B2	✓ D5	✓ A2			
2 Conduct research on applying nanotechnology to the prevention of work-related injuries and illnesses[1]					✓	✓				✓
3 Promote healthy workplaces through interventions, recommendations, and capacity building	✓ E2		✓ E4	✓ E3 E5	✓ E1	✓ E1		✓ E1 E5	✓ E1 E5	
4 Enhance global workplace safety and health[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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

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

Figure 4. Alignment of Critical Research Areas with the four Strategic Goals of the NIOSH NTRC and the NNI EHS priority environmental health and safety areas

4.3 Intermediate Goals and Performance Measures

4.3.1 Exposure Assessment

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

> **Intermediate Goal 1.1 Fate of nanomaterials in the work environment.** Determine the key factors influencing the generation, dispersion, deposition, and re-entrainment of nanomaterials in the workplace, including the role of mixed exposures.
>
> Performance Measure 1.1 Support at least 12 research projects (field trips) over the next three years to assess the fate of nanomaterials in the work environment.
>
> **Intermediate Goal 1.2 Worker exposures.** Quantitatively assess exposures to nanomaterials in the workplace including inhalation and dermal exposure. Determine how exposures differ by work task or process.
>
> Performance Measure 1.2 Within three years develop a baseline worker exposure assessment that identifies how exposures differ by work task or process.

4.3.2 Toxicity and Internal Dose

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

Intermediate Goal 2.1. 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 rates of clearance of nanoparticles after pulmonary exposure and translocation to systemic organs; characterize systemic effects. Determine dermal response to exposure to skin and quantitative penetration of nanoparticles into skin. Determine the biological mechanisms for toxic effects (e.g., role of oxidant stress), including from mixed exposures, and how the key chemical and physical factors may influence these mechanisms. Determine if nanoparticles are genotoxic/carcinogenic.

Performance Measure 2.1. Determine the pulmonary response (dose dependence and time course) to single-walled carbon nanotubes (SWCNT) within the next two years and multi-walled carbon nanotubes (MWCNT) within the next three years. Determine the cardiovascular response to pulmonary exposure to SWCNT and ultrafine titanium dioxide within the next two years. Determine the pulmonary deposition and fate of SWCNT within the next two years and MWCNT and ultrafine titanium dioxide within the next three years. Determine the in vitro effects of SWCNT and metal oxide nanoparticles on skin cells within the next two years and the in vivo effects of topical exposure within the next three years. Determine the genotoxic and carcinogenic effects of SWCNT within the next four years. Determine the central nervous system effects of pulmonary exposure to nanoparticles within the next four years. Determine the pulmonary and systemic effects of other nanoparticles with the next five years. These results will elucidate toxicological mechanisms over the next five years.

Intermediate Goal 2.2. Predictive models for toxicity. Integrate mechanistic models (including animal *models* and *in vitro* screening tests) for assessing the potential toxicity of new nanomaterials and provide a basis for developing predictive algorithms for structure/function relationships and comparative toxicity analyses for risk assessment. Evaluate the relationship between in vitro and in vivo responses, the relevance of instillation or aspiration exposure to inhalation, and the relevance of animal studies to human response.

Performance Measure 2.2. Determine the role of oxidant-generating potential in bioactivity of metal oxide nanoparticles and carbon nanotubes over the next three years. Determine the role of shape (nanospheres vs. nanowires) in bioactivity over the next three years. Determine the role of carbon nanotube diameter and length in bioactivity over the next four years. Develop in vitro assays for oxidant generation, fibrogenic potential, and ability to cause endothelial dysfunction over the next four years. These results will address the development of predictive algorithms for toxicity over the next five years.

Intermediate Goal 2.3. 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 or (2) other measures of bioavailability may be useful (e.g., an integrated measure of retention, solubility, oxidant-generating potential, surface area, and binding reactivity for proteins/lipids).

Performance Measure 2.3. Determine the pulmonary response to exposure to fine vs. ultrafine particles using both mass and surface area as the dose metric. Determine the role of oxidant generation in the bioactivity of metal oxide nanoparticles and carbon nanotubes. These results will address issues of most appropriate dose metric over the next three years.

Intermediate Goal 2.4. Internal dose. Determine the fate, clearance, and persistence of nanomaterials in the body (i.e., pulmonary, lymphatics, blood/systemic, brain) including possible de-agglomeration of nanoparticle agglomerates into primary particles and translocation of nanomaterials from the lung to systemic organs.

Performance Measure 2.4. Develop methods to label carbon nanotubes and track their pulmonary deposition and fate (i.e., clearance, interstitialization, and translocation) with time post-exposure. Use chemical analysis to track the deposition and fate of metal oxide nanoparticles. These results will address issues of internal dose over the next five years.

4.3.3. Epidemiology and Surveillance

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

Intermediate Goal 3.1. Evaluate current knowledge. Critically evaluate existing exposure and health data for workers employed 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.

Performance Measure 3.1. Over the next three years, seek input from a collaborative working group made up of representatives from industry, government, academia, and labor concerning the value and utility of establishing exposure registries for workers potentially exposed to engineered nanoparticles.

Intermediate Goal 3.2. New epidemiological studies. Evaluate the need for and feasibility of initiating epidemiological or other health studies in workers exposed to existing nanomaterials (e.g., carbon black) or producing and using new (engineered) nanomaterials.

Performance Measure 3.2. Over the next three years assess the feasibility of industry-wide exposure and epidemiological studies of workers exposed to engineered nanomaterials.

Intermediate Goal 3.3. Surveillance. Integrate nanotechnology safety and health issues into existing hazard surveillance mechanisms. Determine whether these mechanisms are adequate or whether additional screening or surveillance methods are needed.

Performance Measure 3.3. Finalize the "Interim Guidance for the Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles" within the next year, followed by an update within the following three years. Investigate the feasibility of establishing a registry of workers exposed to engineered nanoparticles.

Intermediate Goal 3.4. Nanotechnology health information systems. Build on existing public health geographical information systems (GIS) and infrastructure to enable effective and economical development and sharing of nanotechnology safety and health data.

Performance Measure 3.4. By 2012 create a GIS infrastructure populated with nanotechnology exposure data.

4.3.4. Risk Assessment

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

Intermediate Goal 4.1. Evaluate current studies. Determine to what extent current exposure-response data (human or animal) for fine and ultrafine particles may be used to identify and assess potential occupational hazards and risks to nanomaterials.

Performance Measure 4.1. Within three years complete a quantitative risk assessment (QRA) on ultrafine and fine materials from existing studies. Evaluate QRA methods for nanomaterials. Start QRA for nanoparticles using new NIOSH data. Use NIOSH nanoparticle data to calibrate and validate dosimetry models for nanoparticles.

Intermediate Goal 4.2. Risk assessment framework. Develop a risk assessment framework for evaluating the hazard and predicting the risk of exposure to nanoparticles.

Performance Measure 4.2 Within five years develop a risk assessment framework to rank hazard and estimate risk from exposure to selected nanoparticles in the workplace.

4.3.5. Measurement Methods

Scientifically credible measurement methods are essential in order to effectively anticipate, recognize, evaluate, and control potential occupational health risks from current and emerging nanotechnologies. Traditional measurement approaches, such as determining total and respirable dust concentrations, may not be adequate for analyzing nanomaterials due to their unique physical, chemical, and biological properties. A summary of capabilities and gaps for nanotechnology measurement methods at NIOSH may be found in Appendix G.

Intermediate Goal 5.1. Extend existing measurement methods. Evaluate current methods for measuring airborne mass concentrations of respirable particles in the workplace and determine whether these mass-based methods can be used as an interim approach for measuring nanomaterials in the workplace and to maintain continuity with historical methods.

Performance Measure 5.1. Within three years evaluate the correlation between particle number, surface area, mass, and particle size distribution airborne measurement results and provide guidance for sampler selection based on the nanomaterial of interest. Continue to conduct measurement studies of nanoparticles in the workplace over the next five years and establish a suite of instruments and protocols for nanoparticle measurement in the workplace. Continue with refining the NIOSH method 5040 specifications for the collection of elemental and organic carbon for application to the collection of carbon nanotubes and nanofibers.

Intermediate Goal 5.2. Develop new measurement methods. Expand the currently available instrumentation by developing and field testing methods that can accurately measure workplace airborne exposure concentrations of nanomaterials using metrics associated with toxicity (e.g., particle surface area, particle number).

Performance Measure 5.2. Support at least three research projects over the next three years with the goal of creating a measurement method that can be correlated with the metrics associated with toxicity. Within five years develop a handheld fast-response nanoparticle monitor and software for spatial mapping of nanoparticles.

Intermediate Goal 5.3. Validation of measurement methods. Develop testing and evaluation systems for comparison and validation of nanoparticle sampling instruments and methods.

Performance Measure 5.3. Within three years publish procedures for validation of nanoparticle sampling instruments and methods.

Intermediate Goal 5.4. Standard reference materials. Identify and qualify scientifically credible, nanoscale certified reference materials (RMs) with assigned physical and/or chemical values for use in evaluating measurement tools, instruments, and methods.

Performance Measure 5.4. Within three years strengthen interactions with the National Institute of Standards and Technology to identify commercially available RMs and perform coherent research to identify, develop, and qualify nanoscale RMs and benchmark materials for evaluating measurement tools, instruments, and methods.

4.3.6. Engineering Controls and Personal Protective Equipment (PPE)

Currently there are no exposure standards specific to engineered nanomaterials. Therefore, to evaluate the need for and effectiveness of engineering controls an alternative rationale is required. In addition, the success of emerging nanotechnology industries will depend on production and development costs, including the installation of new exposure controls. Minimizing occupational exposure to the lowest possible level is the most prudent approach for controlling materials of unknown toxicity, such as nanomaterials. Typically, these approaches include substituting a less toxic material if possible, enclosing the hazardous process, removing workers from the exposure by automating the process, isolating workers from the hazard, and/or utilizing local exhaust ventilation where nanomaterials are handled. Improved control approaches will become more evident as the risks of exposure to nanomaterials are better understood.

Intermediate Goal 6.1. Engineering controls. Evaluate the effectiveness of engineering control techniques for nanoaerosols and develop new approaches as needed.

Performance Measure 6.1. Conduct field investigations of workplaces where nanoparticles are manufactured and used and evaluate existing engineering controls. Within three years publish updated engineering control guidance.

Intermediate Goal 6.2. Personal protective equipment (PPE). Evaluate and improve the effectiveness of PPE for reducing worker exposures to nanomaterials.

Performance Measure 6.2. Within five years publish updated guidance on the effectiveness of PPE for reducing worker exposures to nanoparticles.

Intermediate Goal 6.3. Respirators. Evaluate the effectiveness of NIOSH-approved air purifying respirators to determine whether existing respirator guidelines would still apply for workers exposed to nanoaerosols.

Performance Measure 6.3. Within five years publish updated respiratory protection guidance.

Intermediate Goal 6.4. 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.

Performance Measure 6.4. Within five years publish updated work practice and administrative control guidance.

Intermediate Goal 6.5. Control banding. Evaluate the suitability of a qualitative risk management approach similar to control banding to develop guidance for working with engineered nanomaterials due to insufficient information available to apply traditional exposure-limit–based control strategies.

Performance Measure 6.5. Within three years publish a document on the suitability of control banding approaches for nanomaterials.

Intermediate Goal 6.6. Substitute materials. Evaluate the feasibility and effectiveness of substitute materials or modification of the engineered nanoparticle in reducing the toxicity of nanomaterials.

Performance Measure 6.6. Support at least three projects over the next five years to evaluate substitute and modified nanoparticles with toxicological studies.

4.3.7. Fire and Explosion Safety

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

Intermediate Goal 7.1. Explosion and fire hazards. Identify physical and chemical properties that contribute to dustiness, combustibility, flammability, and conductivity of nanomaterials. Investigate and recommend appropriate work practices to eliminate or reduce the risk to explosions and fires.

Performance Measure 7.1. Support at least two projects to evaluate explosion and fire hazards. Within three years publish guidance to eliminate or reduce explosion and fire hazards.

4.3.8. Recommendations and Guidance

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

Intermediate Goal 8.1. Guidance documents. Translate research findings into useable guidance documents for nanotechnology owners and workers.

Performance Measure 8.1. Within two years, update the document, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. Within two years, produce brochures and fact sheets to provide guidance to owners, workers, and laboratory staff. Continue to look for opportunities to translate research from the critical research areas into practice.

Intermediate Goal 8.2. 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, shape, influence of surface properties). Consider development of an OEL for selected carbon nanotubes.

Performance Measure 8.2. By 2008, complete the current intelligence bulletin (CIB), *Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide*, with the OEL for ultrafine titanium dioxide. Support a project over the next three years to evaluate other ultrafine or nanoparticle OELs. Develop a CIB on carbon nanotubes by 2011.

Intermediate Goal 8.3. Classification. Develop a nanoparticle classification system 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.

Performance Measure 8.3. Initiate a project that will develop a classification scheme based on chemical and physical properties. Release this classification scheme within the next three years.

Intermediate Goal 8.4 High-production volume (HPV) nanomaterials. Evaluate adequacy of mass-based safety and health criteria developed for bulk chemicals for nanomaterials. Current scientific data indicates greater toxicity of nanomaterials by mass compared to an equal mass of larger particles of similar composition.

Performance Measure 8.4. Support a project to evaluate the toxicity of HPV nanoscale materials.

Intermediate Goal 8.5. Material safety data sheets (MSDS). Work with partners to update the MSDS system to incorporate relevant classification, toxicity data, and health and safety recommendations for working with nanomaterials.

Performance Measure 8.5. Within three years, increase awareness of the need for specific nanomaterial information on MSDS among the target audience by 33% over baseline.

4.3.9. Communication and Information

Communication and information are integral components infused throughout the research activities of the NIOSH NTRC and are closely related to the NIOSH Research-to-Practice (r2p) initiative. Research-to-Practice is geared towards translating research results into useful health and safety information tailored to various audiences including workers and employers. As a result, communication and information is one of the 10 critical research areas identified to address knowledge gaps, develop strategies, and provide recommendations concerning workplace exposure to engineered nanomaterials/nanoparticles.

Intermediate Goal 9.1. Nanoinformatics. Develop a roadmap to create a nanoinformatics database management tool relevant to nanomaterial environmental health and safety information.

Performance Measure 9.1. Creation of a roadmap that aligns new nanoinformatics with the NIOSH Nanoparticle Information Library (NIL) within the next three years.

Intermediate Goal 9.2. Communication. Establish and maintain national and international partnerships with whom knowledge gaps, research needs and priorities, approaches, and results can be shared openly and collaboratively.

Performance Measure 9.2. Within one year, identify and initiate/establish contact with at least one potential partner from each of the following areas: government, industry, academia, and labor.

Intermediate Goal 9.3. Information. Develop and disseminate effective information, education, and training materials to various target audiences such as nanotechnology workers and employers, occupational safety and health professionals, policy-makers, decision-makers, and/or the scientific community.

Performance Measures 9.3. Within one year, develop at least one informational document tailored to a target audience identified above. Evaluate/assess the reach and effectiveness of the above tailored informational piece within two years. Update progress report on the NIOSH nanotechnology research and communication efforts within two years. Within two years, update the document, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*.

4.3.10. Applications for Occupational Safety and Health

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

Intermediate Goal 10.1. New devices and uses. Identify uses of nanotechnology in occupational safety and health.

Performance Measure 10.1. Support at least three projects over the next three years to evaluate the application of nanotechnology in the manufacture of filters, respirators, and respirator cartridge end-of-service indicator.

Intermediate Goal 10.2. Dissemination. Evaluate and disseminate effective nanotechnology research findings that may have applications to new sensors, PPE or other nanotechnology health and safety applications.

Performance Measure 10.2. Within five years publish application findings and disseminate findings to workers, employers, and occupational safety and health professionals.

4.4 International Activities

The international component of NIOSH nanotechnology research aims at achieving the fourth program goal—Enhance global workplace safety and health through national and international collaborations on nanotechnology research and guidance—with two objectives:

1. Develop partnerships for identifying research and for the sharing of research needs, approaches, and results.
2. Develop and disseminate effective educational and training materials for workers and occupational health professionals.

NIOSH international activities crosscut all 10 critical research areas by developing partnerships (first objective) to address critical research gaps and by developing and disseminating occupational safety and health (OSH) documents (second objective). In order to achieve these objectives, NIOSH will continue to engage with a number of international entities at all levels—principle investigator, as well as national, regional, and global organizations.

At the national organization levels, NIOSH has been communicating and collaborating with the United Kingdom Institute of Medicine and Health and Safety Laboratory, the Netherlands Organization for Applied Scientific Research (TNO), the Finnish Institute of Occupational Health, and the Australian Safety and Compensation Council.

An example of regional level interactions is NIOSH participation in interagency discussions with European communities about establishing a joint U.S./European Union solicitation to fund research looking at nanotechnology health and safety implications. This international solicitation would provide an important venue for leveraging research resources and, as such, is aimed at addressing the first objective.

At the global organization level, NIOSH will continue to be actively engaged with the Organization for Economic Co-operation and Development (OECD), the World Health Organization (WHO), the International Organization for Standardization (ISO), and the International Council on Nanotechnology (ICON).

OECD. NIOSH participation in OECD Working Party on Manufactured Nanomaterials (WPMN) and Working Party on Nanotechnology (WPN) aims at addressing both global objectives by developing international government-level instruments, decisions and recommendations to improve occupational safety and health of nanotechnology globally, and by building cooperation, coordination, and communication between the United States and 30 OECD-member countries including the European Union, and more than 70 nonmember economies.

OECD is government-level organization which is especially effective at conducting economic evaluations, harmonizing test guidelines, exchanging information and data, and facilitating adoption of globally-harmonized voluntary and regulatory programs by governments around the world. It can also provide a mechanism for leveraging research resources by facilitating international government program coordination.

Presently, NIOSH engagement with OECD includes (a) leading an OECD project on Co-Operation on Exposure Measurement and Exposure Mitigation established under the Environmental Directorate, (b) providing expertise in other OECD projects, and (c) exchanging occupational safety and health information through the OECD Working party on Manufactured Nanomaterials and the Working Party on Nanotechnology. NIOSH Nanoparticle Information Library (NIL) is cross-linked with an OECD database of nanotechnology research projects which are currently under development.

A project on “The analyses and recommendations for exposure measurement and exposure mitigation in nanotechnology occupational settings” has been initiated in 2007. The project will deliver a report in 2008 followed by additional reports for specific areas of interest to WPMN.

WHO. NIOSH was instrumental in establishing a 2006–2010 work plan for the World Health Organization Global Network of Collaborating Centers in Occupational Health, and NIOSH’s participation in this activity addresses both global objectives. WHO is the directing and coordinating authority for health within the United Nations system, and the “Network” is comprised of key institutions with expertise in occupational safety and health distributed throughout the world.

Since 2006 NIOSH has been leading a nanotechnology project on “Best practices globally for working with nanomaterials” in collaboration with occupational safety and health institutions in Switzerland, the United Kingdom, and Germany.

ISO. NIOSH scientists are actively involved with the International Organization for Standardization Technical Committee 229 on Nanotechnologies (ISO TC 229) by providing expertise to and leading the development of individual standards and through membership in the U.S. Technical Advisory Group to TC 229. The International Organization for Standardization provides a mechanism for international expertise within the global community to develop the highest quality standards of which are globally accepted. ISO can also serve as a vehicle for global dissemination of NIOSH products.

Since 2006, NIOSH has been leading the development of an ISO TC 229 technical report on safety and health practices in occupational settings relevant to nanotechnologies which is based on *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*. It is expected that the technical report will be published in 2008.

ICON. The International Council on Nanotechnology is an international multistakeholder organization whose mission is to assess, communicate, and reduce the environmental and health risks of nanotechnology while maximizing its societal benefit. NIOSH experts have been involved in ICON projects related to occupational safety and health since 2006.

Since 2006 ICON has been hosting the development of an internet site on occupational practices for the safe handling of nanomaterials utilizing a wiki software platform “GoodWiki: Good Occupational Practices for the Nanotechnology Industry.” NIOSH is a member of a multistakeholder international steering group designing a plan for launching such a novel mechanism for creating and maintaining global occupational safety and health guidance.

Intermediate Goal 11.1. Improve resource leveraging for research globally.

Performance Measure 11.1.1. Strengthen coordination of research through government-level organizations (OECD and WHO).

Performance Measure 11.1.2. Expand collaborations to developing nations and emerging powers (Asia-Pacific, Eastern Europe).

Intermediate Goal 11.2. Improve sharing critical data globally.

Performance Measure 11.2.1. Develop global portal for information on nanomaterials relevant to occupational safety and health.

Performance Measure 11.2.2. Develop global exposure registry database: European countries, ECHA, Asian countries, OECD.

Performance Measure 11.2.3. Participate in OECD Nanomaterial Safety Testing Program by sponsoring nanomaterial testing and by data exchange.

Intermediate Goal 11.3. Produce highest quality products.

Performance Measure 11.3.1. Facilitate development of government-level exposure mitigation guidance (OECD).

Performance Measure 11.3.2. Increase utilization of web-based tools for document development (such as wiki-based platforms).

Intermediate Goal 11.4. Enhance global dissemination.

Performance Measure 11.4.1. Increase utilization of emerging information technology mechanisms (e.g., NIOSH science blog, web-based social networks, virtual reality).

Performance Measure 11.4.2. Establish partnerships for translation of NIOSH publications to other languages.

Intermediate Goal 11.5. Increase global acceptance.

Performance Measure 11.5.1. Strengthen participation in globally recognized organizations.

Performance Measure 11.5.2. Expand partnerships to international bodies with economic instruments to implement OSH measures such as financial institutions (Inter-American Development Bank, World Bank) and insurance companies (Swiss Re, Munich Re, Lloyds).

5 OUTPUTS

5.1. 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 describing the lack of information on the potential health risks to workers who are exposed to nanomaterials and the types of research needed to address those concerns (see Appendix B).

- NIOSH has posted a safety and health topic page, "Nanotechnology," containing accessible information on the safety and health implications of nanotechnology and the related research activities that NIOSH is conducting. http://www.cdc.gov/niosh/topics/nanotech/

- NIOSH has prepared and posted answers to frequently asked questions (FAQs) concerning nanotechnology and NIOSH's involvement with the occupational safety and health research in the field of nanotechnology. http://www.cdc.gov/niosh/topics/nanotech/faq.html

- Updates of NIOSH activities in nanotechnology research appear on the NIOSH Safety and Health Topic Page, "Nanotechnology." http://www.cdc.gov/niosh/topics/nanotech/

- Audience-specific documents (e.g., worker, employer, safety professional) are under development describing the potential for nanoparticle exposure and steps that can be taken to minimize exposure.

- A NIOSH current intelligence bulletin (CIB), *Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide*, on fine and ultrafine titanium dioxide (TiO_2) has undergone stakeholder and peer review and is being finalized for publication. http://www.cdc.gov/niosh/review/public/TiO2/default.html

- NIOSH has prepared a draft document, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*, for public comment. http://www.cdc.gov/niosh/topics/nanotech/safenano/

- NIOSH has developed a web-based Nanoparticle Information Library (NIL) which is a resource on particle information including physical and chemical characteristics. http://www2a.cdc.gov/niosh-nil/index.asp

- NIOSH has published *Progress Toward Safe Nanotechnology in the Workplace: A Report from the NIOSH Nanotechnology Research Center* [DHHS (NIOSH) Publication No. 2007-123], a progress report on the status of nanotechnology research conducted by the NIOSH NTRC through 2006. http://www.cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf

- NIOSH has prepared a draft document *Interim Guidelines on Medical Screening of Workers Potentially Exposed to Engineered Nanoparticles* for public comment. http://www.cdc.gov/niosh/review/public/115/

5.2. NIOSH Peer-Reviewed Publications

NIOSH scientists will publish results of research as the data become available. More than 85 peer-reviewed articles were published through 2007 addressing scientific and technical issues in the field of nanotechnology. For a listing of publications, see *Progress Toward Safe Nanotechnology in the Workplace: A Report from NIOSH Nanotechnology Research Center* [DHHS (NIOSH) Publication No. 2007-123 http://www.cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf].

5.3 Sponsored Conferences

NIOSH will continue to partner with others in sponsoring and conducting conferences on nanotechnology. To date, NIOSH has cosponsored three international meetings on occupational safety and health involving nanomaterials and has cosponsored a major occupational safety and health research-to-practice (r2p) conference in Cincinnati, OH, in 2006 which drew over 450 participants from 11 countries. NIOSH staff also participated on several scientific and technical panels convened by government agencies, nongovernmental agencies, and professional associations. For a listing of meetings, panels, and conferences, see *Progress Toward Safe Nanotechnology in the Workplace: A Report from NIOSH Nanotechnology Research Center* [DHHS (NIOSH) Publication No. 2007-123 http://www.cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf].

5.4 Presentations

NIOSH staff will deliver presentations nationally and internationally concerning occupational safety and health issues associated with nanotechnology, including presentations at scientific conferences, and trade and professional associations. For a listing of presentations, see *Progress Toward Safe Nanotechnology in the Workplace: A Report from NIOSH Nanotechnology Research Center* [DHHS (NIOSH) Publication No. 2007-123 http://www.cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf]. NIOSH staff will continue to provide presentations at major conferences, meetings, and workshops on the occupational safety and health implications of nanomaterials.

6 RESEARCH TO PRACTICE (r2p)

Research to practice (r2p) involves the translation of research into products, practices, and usable information. The NIOSH nanotechnology research strategic plan reflects the r2p vision to work with partners and stakeholders (see Section 7 and Appendices D and E) to translate research findings into NIOSH products (e.g., guidance documents, instrumentation, filtration) that will be used to reduce or prevent worker injury and illness from nanotechnology.

6.1 Capacity Building Through Technical Assistance

NIOSH is currently collaborating with a number of industries to develop appropriate engineering controls and effective administrative practices for the safe handling of nanomaterials. NIOSH will work with industry in evaluating workplace exposures to nanoparticles and provide recommendations that will minimize worker exposures. For information on the workplace assessments conducted by NIOSH, see *Progress Toward Safe Nanotechnology in the Workplace: A Report from NIOSH Nanotechnology Research Center* [DHHS (NIOSH) Publication No. 2007-123 http://www.cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf].

NIOSH will continue to make recommendations and provide information based on its research and the published scientific literature. The recommendations will pertain to all areas of the risk management continuum shown in Section 4.1

7 INTERMEDIATE CUSTOMERS AND INTERMEDIATE OUTCOMES

7.1. Federal Government Agencies

NIOSH will conduct and coordinate research with other agencies to foster the responsible development and safe use of nanotechnology as identified by the National Nanotechnology Initiative (NNI).

7.2. Standards Development Organizations

NIOSH actively participates in the development of national and international standards for promoting the health and safety of workers in the nanotechnology industries. NIOSH participates in the American National Standards Institute Nanotechnology Standards Steering Panel, 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 will continue as members of the U.S. Technical Advisory Group to the International Organization for Standardization (ISO) Technical Committee 229 on Nanotechnologies (ISO TC 229).

7.3. Industry, Labor, and Academia

NIOSH is coordinating input from industry, labor, academics, and a wide range of government agencies in creating guidance for occupational health surveillance. Additionally, NIOSH plans to coordinate input from those same groups of partners and stakeholders with the goal of providing options for the development of standardized data systems for epidemiological research based in workplaces producing and using nanomaterials. Through collaborations with industry, government, and academia, NIOSH developed a "best practices" document, *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* (http://www.cdc.gov/niosh/topics/nanotech/), and other communication materials on the safe handling of nanomaterials are in progress. NIOSH is working with industry to characterize occupational exposure to nanoparticles and how to implement effective risk management practices to minimize worker exposure to nanoparticles. In June 2006, NIOSH and E.I. du Pont de Nemours & Co signed an agreement to collaborate on work to evaluate current product performance, test methods, and research gaps related to personal protective equipment used to reduce occupational exposures to nanoparticles.

7.4. Professional Organizations

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

7.5. Research Collaborations

NIOSH has established several national and international collaborations to advance research into the safe use of nanotechnology. NIOSH participates in the National Nanotechnology Initiative (NNI) and has contributed to the nanotechnology strategic plan for the Nation through the working group of Nanotechnology Environmental and Health Implications (NEHI). Occupational Safety and Health is a major priority of the NEHI effort, and NIOSH's strategic research plan and activities have been developed to address most of the major issues in the NEHI plan. NIOSH is also collaborating with the Organization for Economic Cooperation and Development (OECD) to build cooperation, coordination, and communication between the United States and 30 OECD member countries, including the European Union (EU), and more than 180 nonmember economies as well. NIOSH is also working with the World Health Organization Collaborating Centers on global projects of information dissemination and communication.

8. 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 resulting in the handling of nanomaterials. The NIOSH strategic plan for research is designed to identify and develop information for use in risk management programs that will prevent and control negative impacts to worker health. In addition, research will be conducted to advance the use of nanomaterials in the development of sensors (e.g., detection of harmful chemicals) that can be used in the workplace to ensure an effective control of exposure.

Outcomes of the NIOSH strategic plan include translating research results into products that can be used by the nanotechnology community to advance the technology responsibly and with minimal risk. Specific areas of improvement include sampling/analytical instrumentation and guidance documents. NIOSH will conduct ongoing assessments of the extent to which NIOSH research is used and cited by scientists; scientific, professional, and government agencies; trade associations; unions; nongovernmental organizations; and international communities. NIOSH also will evaluate how research and guidance developed by NIOSH influences others to take action to prevent or control hazards related to nanomaterials.

APPENDIX A

Timeline for NIOSH Nanotechnology Research

Summary of Ongoing or Initiated Research Projects in FY05

Critical Research Area	**Projects**
Exposure Assessment	• Conduct exposure assessment pilot studies of nanoparticles in the workplace.
Toxicity and Internal Dose	• Begin toxicity testing in laboratory animal and in vitro systems.
Epidemiology and Surveillance	• Surveillance Phase I: Identify and gather information relevant for determining need for worker surveillance. • Conduct studies on wildfire ultrafine aerosol and firefighter exposure studies.
Risk Assessment	• Quantitative risk assessment on ultrafine and fine TiO_2. • Initiate collaborative research on lung model development and nanoparticle dose estimation.
Measurement Methods	• Develop techniques for particle surface area measurement. • Generation and characterization of nanomaterials. • Nanoaerosol monitoring methods. • Ultrafine/respirable particle mapping in automotive manufacturing facilities.
Engineering Controls and PPE	• Identify key exposure control issues. • Initiate research on the filtration efficiency of typical respirator filter media for nanoscale particles. • Initiate research on automobile ultrafines.
Fire and Explosion Safety	• Identify key safety issues.
Recommendations and Guidance	• Develop a draft document on working safely with nanomaterials. • Draft a titanium dioxide (TiO_2) current intelligence bulletin.
Communication and Information	• Develop a pilot Nanotechnology Information Library (NIL). • Generate a basic set of frequently asked questions (FAQs).
Applications	• Initiate pilot project on nanofiber-based filter media. • Continue a study to investigate nanomaterials for improving sensor technology needed in respirator cartridge end-of-service indicators.
Global Activities	• Co-sponsor the 1st International Symposium on Occupational Health Implications of Nanomaterials in Buxton, UK • Contribute to development of ISO technical report on nanoparticle exposure, assessment and characterization in workplace atmospheres.

Summary of Ongoing or Initiated Research Projects in FY06

Critical Research Area	**Projects**
Exposure Assessment	• Conduct survey of nanomaterial uses and workers exposed. • Conduct exposure assessment pilot studies of nanoparticles in the workplace. • Develop study protocol for conducting TiO2 workplace exposure assessments. • Conduct studies to gather hazard ID information about carbon nanotubes.
Toxicity and Internal Dose	• Pulmonary toxicity of carbon nanotube particles. -determine the oxidant generating potency and cytotoxicity of SWCNT in vitro. -determine the pulmonary response to aspiration of SWCNT in the mouse model; time course and dose-response. • Pulmonary toxicity of diesel exhaust particles (DEP). -determine the effects of exposure to DEP on the generation of oxidants in the lung. -determine the role of oxidant generation by DEP on genotoxicity. • Nanotechnology safety and health research coordination. -disseminate results of the NIOSH nanotoxicology program through invited presentations. • Dermal effects of nanoparticles. -determine the effects of SWCNT on skin cells in vitro.
Epidemiology and Surveillance	• Surveillance Phase I: Continue to ascertain the need for worker surveillance information (e.g., exposure, medical). • Conduct studies on wildfire ultrafine aerosol and firefighter exposure studies.
Risk Assessment	• Perform QRA on ultrafine particles from scientific literature. • Develop lung deposition model software enhancements.
Measurement Methods	• Develop techniques for particle surface area measurement. • Analyze filter efficiency for collecting nanoparticles. • Conduct exposure assessment pilot studies of nanoparticles in the workplace with various measurement methods.
Engineering Controls and PPE	• Identify key exposure control issues. • Evaluate control banding options to reduce worker exposures. • Release contract final report on the “Penetration of Nanoparticles through Respirator Filter Media.” • Initiate intramural research project on “Respiratory Protection Against Nanoparticles” to measure the effectiveness of air purifying respirators against nanoparticles.

	• Initiate intramural research on the "Development of PPE Ensemble Test Methods" to better understand the barrier effectiveness of protective clothing and ensembles. • Evaluate existing exposure controls and provide recommendations. • Continue research on automobile ultrafines.
Fire & Explosion Safety	• Identify key safety issues.
Recommendations and Guidance	• Update recommendations on the safe handling of nanomaterials (ongoing). • Initiate investigation of qualitative risk assessment and management methods for nanomaterials. • Host occupational safety and health research-to-practice (r2p) conference on nanotechnology. • Hold public meeting and address external review comments on draft TiO_2 current intelligence bulletin.
Communication and Information	• Update the NIL (ongoing). • Develop an expanded set of frequently asked questions (FAQs). • Develop a topic page specific to nanotechnology.
Applications	• Complete pilot project on nanofiber-based filter media. • Continue to investigate nanomaterials for improving sensor technology needed in respirator cartridge end of service life indicators.
Global Activities	• Join OECD and begin development of international government-level instruments, decisions, and recommendations to improve occupational safety and health of nanotechnology. • Join ISO and develop international consensus-based standards. ISO tech report TC229 initiated. • Join WHO work group to develop and disseminate best practices globally. • Join ICON to develop and disseminate best practices globally. • Co-sponsor the 2nd International Symposium on Occupational Health Implications of Nanomaterials in Minneapolis, MN

Summary of Ongoing or Initiated Research Projects in FY07

Critical Research Area	**Projects**
Exposure Assessment	• Conduct market surveys of nanomaterial uses and workers exposed. • Conduct exposure assessment studies of nanoparticles in the workplace. • Initiate ultrafine and fine TiO_2 and metal oxides workplace exposure assessments. • Conduct studies to gather hazard ID information about carbon nanotubes.
Toxicity and Internal Dose	• Define preliminary cardiovascular endpoints. • Gather data and develop preliminary dosimetry for diesel exhaust particulate (DEP); determine the role of DEP-induced nitric oxide production on genotoxicity. • Determine pulmonary toxicity of carbon nanotube particles. -determine the role of lung antioxidants on the pulmonary response to SWCNT. -determine the effect of exposure to SWCNT on susceptibility of the lung to infection. • Develop particle surface area as a dose metric. -develop a method to disperse nanoparticles for in vitro and in vivo toxicity testing. -determine if degree to dispersion of a nanoparticle suspension affects bioactivity. • Evaluate systemic microvascular dysfunction effects of ultrafine vs. fine particles. -construct an inhalation exposure system for fine and ultrafine T_iO_2. -determine the effects of pulmonary exposure to ultrafine T_iO_2 on systemic arteriole function. • Evaluate the pulmonary deposition and translocation of nanomaterials. -determine the effect of dispersion on the pulmonary fibrogenic potency of SWCNT. • Determine role of carbon nanotubes in cardiovascular inflammation. -determine if pulmonary exposure to SWCNT causes oxidant stress in cardiovascular tissue. -determine if pulmonary exposure to SWCNT causes arterial plaque formation. • Disseminate results of the NIOSH nanotoxicology program through invited presentations.
Epidemiology and Surveillance	• Draft guidelines on occupational health surveillance for nanotechnology workers with assistance from a cross-governmental work group as well as

	representatives from industry, government, academia, and labor. • Conduct studies on wildfire ultrafine aerosol and firefighter exposure studies.
Risk Assessment	• Extend and calibrate rat lung exposure-dose model for nanoparticles. • Develop nanoparticle deposition model in rat nasopharyngeal region. • Begin model for of CNT inhalability and lung deposition in humans.
Measurement Methods	• Evaluate surface area–mass metric airborne measurement results. • Establish a suite of instruments and protocols for nanomaterial measurements. • Continue to conduct exposure assessment/measurement studies of nanoparticles in the workplace. • Continue to develop offline and online nanoparticle measurement methods. • Evaluate a high flow personal sampler. • Evaluate candidate nanomaterials for use in studies of nanoparticle surface area measurement. • Evaluate dustiness testing methods for powdered nanomaterials.
Engineering Controls and PPE	• Identify key exposure control issues. • Evaluate control banding options to reduce worker exposures. • Continue developing intramural research project on "Respiratory Protection Against Nanoparticles" with an initial focus on filtration efficiency of commercially available respirators. • Continue intramural research on the "Development of PPE Ensemble Test Methods."
Fire & Explosion Safety	• Identify key safety issues.
Recommendations and Guidance	• Continue updating recommendations on the safe handling of nanomaterials (ongoing). • Prepare final draft of TiO_2 document. • Develop worker and employer guidelines for safe work practices and proper nanomaterial handling. • Draft guidelines on occupational health surveillance for nanotechnology workers with assistance from a cross-governmental work group as well as representatives from industry, government, academia, and labor. • Draft interim guidance on the medical screening of workers potentially exposed to engineered nanoparticles.
Communication and Information	• Continue updating the Nanotechnology Information Library (NIL) (ongoing). • Develop a progress report on NIOSH nanotechnology research and communication efforts. • Cosponsor training courses in safe handling of nanoparticles. • Conduct research-to-practice (r2p) activities (ongoing) such as the development of brochures, fact sheets, updating the topic page, etc.

	• Disseminate results of the NIOSH nanotoxicology program through invited presentations.
Applications	• Develop a method to identify significant emerging nanotechnology products. • Research monolayer-protected gold nanoparticles conducted to study whether these nanoparticles can be used in sensors for respirator cartridge end of service life indication. • Initiate proposal for FY09 NORA on antibacterial HVAC air filters.
Global Activities	• Continue OECD development of international government level instruments, decisions, and recommendations to improve occupational safety and health of nanotechnology. • Continue ISO development of international consensus-based standards; ISO tech report TC229 initiated. • Continue with WHO work group to develop and disseminate best practices globally. • Continue with ICON to develop and disseminate best practices globally. • Establish NIOSH-UK HSL collaboration concerning dustiness testing for nanomaterials and detailed workplace measurements.

Summary of Ongoing or Initiated Research Projects in FY08

Critical Research Area	**Projects**
Exposure Assessment	• Continue with exposure assessments of nanoparticles in the workplace. • Continue ultrafine and fine metal oxides workplace exposure assessments. • Conduct studies to characterize size, concentration, and morphology of nanoparticles emitted by various processes. •Evalute the dustiness potential for powdered nanomaterials..
Toxicity and Internal Dose	• Determine potential aneuploidy following exposure to carbon nanotubes. -determine the effect of in vitro exposure to SWCNT on the mitotic process. • Evaluate pulmonary toxicity of carbon nanotubes. -construct an inhalation exposure system for SWCNT. -compare the fibrotic response to inhalation vs. aspiration of SWCNT. • Establish particle surface area as a dose metric. -determine the pulmonary response to fine vs. ultrafine T_iO_2 and carbon black using mass and surface area dose metrics. -evaluate oxidant generation potential as a predictive in vitro screening test for metal oxide nanoparticles. • Evaluate systemic microvascular dysfunction effects of ultrafine vs. fine particles -determine the role of oxidant stress in the microvascular response to pulmonary exposure to ultrafine T_iO_2. • Evaluate the pulmonary deposition and translocation of nanomaterials. -determine the rate of translocation of SWCNT from the lung to systemic organs. • Evaluate dermal effects of nanoparticles. -determine oxidant generation and cytotoxicity of metal oxide nanoparticles with skin cells in vitro. • Determine role of carbon nanotubes in cardiovascular inflammation. -measure blood cytokine levels in response to pulmonary exposure to SWCNT. • Evaluate occupational exposures and potential neurological risks. -evaluate markers of brain inflammation and blood/brain barrier damage following pulmonary exposure to MWCNT.

	• Determine neurotoxicity after pulmonary exposure to welding fumes. -determine the pulmonary inflammatory response to inhalation of welding fumes. -determine the effect of welding fumes on the susceptibility of the lung to infection. • Conduct nanotechnology safety and health research coordination. -disseminate results of the NIOSH nanotoxicology program through invited presentations.
Epidemiology and Surveillance	• Finalize interim guidelines on medical screening for nanotechnology workers. • Assess the feasibility of industry wide exposure and epidemiology studies of workers exposed to engineered nanomaterials. • Seek input from a collaborative working group made up of representatives from industry, government, academia, and labor concerning the value and utility of establishing an exposure registry for workers potentially exposed to engineered nanoparticles.
Risk Assessment	• Begin hazard and risk estimates of carbon and metal nanoparticles using new NIOSH toxicity data. • Calibrate rat dose-response model for nanoparticles using NIOSH toxicity data. • Complete nasopharyngeal deposition model in rats.
Measurement Methods	• Evaluate surface area–mass metric airborne measurement results. • Establish a suite of instruments and protocols for nanomaterial measurements. • Continue to conduct exposure assessment/measurement studies of nanoparticles in the workplace. • Continue to develop offline and online nanoparticle measurement methods. • Develop a hand held fast response nanoparticle monitor. • Develop software for spatial mapping of nanoparticles. • Evaluate collection efficiency of personal mass based aerosol samplers. • Identify, qualify, and develop nanoscale reference materials for measurement quality control.
Engineering Controls and PPE	• Continue to evaluate the effectiveness of controls to reduce workplace exposures to nanoparticles and metal oxides. • Continued research on “Respiratory Protection against Nanoparticles” with a focus on face seal leakage.

	• Continued research on the "Development of PPE Ensemble Test Methods." • Evaluate existing exposure control and provide recommendations as part of the exposure assessment/measurement studies in the workplace.
Fire & Explosion Safety	• Evaluate the dustiness potential for powdered nanomaterials.
Recommendations and Guidance	• Continue updating recommendations on the safe handling of nanomaterials (ongoing); specifically, information on the field protocol. • Continue preparing final TiO_2 document that incorporates peer review comments (ongoing). • Develop worker and employer guidelines (brochures) for proper nanomaterial handling and safe work practices. • Evaluate control banding options to reduce worker exposures. • Conduct a public meeting to discuss interim guidance on the medical screening of workers potentially exposed to engineered nanoparticles.
Communication and Information	• Continue updating the NIL (ongoing). • Continue conducting r2p activities (ongoing), such as the development of brochures, fact sheets, updating the topic page etc. • Develop a web site highlighting the nanotechnology coordinated emphasis program as part of the NIOSH National Occupational Research Agenda (NORA). • Draft supplemental strategic plan specific to nanoinformatics and the programs projected communication efforts.
Applications	• Research monolayer-protected gold nanoparticles used in prototype respirator cartridge end of service indicator (ESLI). • Prepare full proposal for NORA on antibacterial HVAC air filters.
Global Activities	• Continue participation with ISO, ICON, OECD, and WHO. • Initiate GoodWiki for good occupational practices for the nanotechnology industry. • Participate in nanotech symposium at World Congress on Safety and Health at Work, Seoul, Korea. • Participate in 2nd international conf. on nanotoxicology, Zurich, Switzerland.

Summary Research Planned for FY09-FY10

Critical Research Area	**Projects**
Exposure Assessment	• Continue evaluation of workplace exposures to nanomaterials and their potential routes of exposure. • Continue evaluation of size, concentration and morphology of nanoparticles emitted by various processes. • Focus on collecting personal exposure data for engineered nanoparticles. • Develop task-based exposure profiles for engineered nanoparticle processes.
Toxicity and Internal Dose	• Determine the dermal toxicity and penetration potential to the most used nanomaterials. • Identify specific biomarkers for unusual toxicity of nanomaterials. Develop an in vitro screening test for fibrogenic potential of nanomaterials. • Conduct in vivo investigations of MWCNT; determine time and dose dependence of pulmonary response; compare response to aspirated vs. inhaled MWCNT. • Complete studies of nanoparticle translocation in laboratory animals after pulmonary exposure to nanoparticles. • Determine the potential for neurological effects following transport of metal oxide nanoparticles to the brain (e.g., transport by olfactory nerve). • Evaluate the potential effect of silicon-based nanowires on lung toxicity; determine the oxidant generating potency and cytotoxicity in vitro. • Evaluate systemic microvascular dysfunction effects of ultrafine vs. fine particle pulmonary exposure. • Construct and test an inhalation exposure system for spot welding fume; determine lung effects of resistance spot welding using adhesives. • Determine effects of inhalation of welding fume on markers of brain inflammation and blood/brain barrier damage in a rat model. • Conduct cell-based assessment for iron nanoparticle in vitro effects on endothelial cells and the role of ROS. • Determine the role of carbonaceous materials on mutagenic and or carcinogenic response in vitro and in vivo. • Elucidate mechanisms by which pulmonary exposures to nanoparticles causes brain inflammation; determine dose-response and time course.
Epidemiology and Surveillance	• Update interim guidelines on medical screening for nanotechnology workers based on input from published literature and collaborative input from representatives of industry, government, academia, and labor. • Initiate industry wide exposure studies of workers exposed to engineered nanomaterials.

	• Assess the feasibility of establishing exposure registries for nanotechnology workers for the purposes of occupational health surveillance and future epidemiologic study.
Risk Assessment	• Continue hazard and risk assessment of engineering nanoparticles. • Complete model of CNT inhalability and deposition in humans. • Initiate human nanopharyngeal deposition model. • Initiate integrated revision to human dosimetry models.
Measurement Methods	• Evaluate surface area–mass metric airborne measurement results. • Establish a suite of instruments and protocols for nanomaterial measurements. • Continue to conduct exposure assessment/measurement studies of nanoparticles in the workplace. • Continue to develop offline and online nanoparticle measurement methods. • Develop performance results for current nanoparticle measurement instruments and methods. • Complete evaluation of viable and practical workplace sampling devices and methods for nanoparticles (affordable, portable, effective). • Continue to develop a handheld, fast response nanoparticle monitor. • Continue development software for spatial mapping of nanoparticles. • Develop a standardized aerosol test method using magnetic passive aerosol samplers. • Identify, qualify, and develop nanoscale reference materials for measurement quality control.
Engineering Controls and PPE	• Continue evaluation of respirator filtration performance and continue to evaluate the effectiveness of controls to reduce workplace exposures to nanoparticles. • Produce a summary of control strategies. • Initiate and conduct research on "Nanoparticle penetration through protective clothing" to investigate penetration through non-woven materials used in protective clothing and develop predictive models that can be used to improve and/or develop guidance documents, performance requirements, and test methods.
Fire & Explosion Safety	• Produce a summary of key safety issues and recommendations. • Evaluate the dustiness potential for powdered nanomaterials.
Recommendations and Guidance	• Develop new or updated recommendations for the safe handling of nanomaterials.

	• Continue conducting r2p activities (ongoing), such as the development of brochures, fact sheets, updating the topic page, etc. • Publish respirator selection guide for workers handling nanoparticles.
Communication and Information	• Publish an updated progress report on NIOSH nanotechnology research and communication efforts. • Continue conducting r2p activities (ongoing), such as the development of brochures, fact sheets, updating the topic page, etc. • Update the web site highlighting the nanotechnology coordinated emphasis program as part of the NIOSH NORA program portfolio (ongoing). • Continue updating the NIL (ongoing).
Applications	• Evaluate application of nanotechnology for improving antibacterial effect of HVAC filters. • Further develop and refine end-of-service indicators using nanomaterials.
Global Activities	• Continue participation with ICON, ISO, OECD and WHO. • Continue with development of GoodWiki for good occupational practices for the nanotechnology industry. • Participate in ICOH International congress on occupational health in Cape Town, South Africa (2009). • Participate in 4th international congress on nanotechnology, Helsinki, Finland (2009). • Expand collaborations to developing nations and emerging powers (Asia-Pacific, Eastern Europe). • Develop partnerships for translation of NIOSH publications to other languages.

Summary Research Planned for FY11-FY12 (pending)

Critical Research Area	**Projects**
Exposure Assessment	• Complete evaluation of workplace exposures to nanomaterials and their potential routes of exposure. • Complete evaluation of size, concentration, and morphology of nanoparticles emitted by various processes.
Toxicity and Internal Dose	• Evaluate induction of lung fibrosis by cerium oxide and diesel exhaust. • Evaluate the potential pulmonary reaction to inhalation of commercial spray containing ultrafine TiO2. • Develop predictive algorithms for nanoparticle bioactivity. • Evaluate the predictive value of in vitro screening tests for the fibrogenic potential of carbon nanotubes. • Elucidate mechanisms by which carbon nanotubes induce lung fibrosis.
Epidemiology and Surveillance	• Assess the feasibility of industry wide health effects studies of workers exposed to engineered nanomaterials. • Evaluate occupational exposures and potential neurological risks.
Risk Assessment	• Evaluate/validate nanoparticle exposure-dose-response models. • Investigate models with additional routes of exposure. • Develop risk estimates using models of kinetic and biological activity of nanoparticles. • Characterize risk of nanoparticle exposure in the workplace. • Contribute to OSH recommendation development.
Measurement Methods	• Develop instruments capable of distinguishing process from background nanoparticles. • Develop techniques to characterize agglomeration state of nanoparticles.
Engineering Controls and PPE	• Finalize development of a standardized aerosol test method using magnetic passive aerosol samplers for PPE ensemble testing. • Expand particulate penetration project to include different types of fabrics, electrostatic charges, cylindrical fabric swatches, wind tunnel, and bellows effects. • PPE workplace protection factor studies of nanotechnology workers. • Laboratory performance of filter media against carbon nanotubes and/or other key nanoparticle classes.
Fire & Explosion Safety	• Update pertinent safety issues and recommendations.

Recommendations and Guidance	• Continue conducting r2p activities (ongoing), such as the development of brochures, fact sheets, updating the topic page, etc. • Publish protective clothing selection guide for workers handling nanoparticles.
Communication and Information	• Publish an updated progress report on NIOSH nanotechnology research and communication efforts. • Continue conducting r2p activities (ongoing), such as the development of brochures, fact sheets, updating the topic page, etc. • Update the Web site highlighting the nanotechnology coordinated emphasis program as part of the NIOSH NORA program portfolio (ongoing). • Continue updating the NIL (ongoing).
Applications	• Evaluate application of nanotechnology for improving antibacterial effect of HVAC filters and PPE. • Further development and refinement of end-of-service indicators using nanomaterials.
Global Activities	• Strengthen participation with globally recognized organizations ICON, ISO, OECD and WHO. • Continue refinement of GoodWiki for good occupational practices for the nanotechnology industry.

APPENDIX B

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 co-sponsor the Second International Symposium in October 2005.
- Co-sponsored a major occupational safety and health research-to-practice conference held in Cincinnati, OH in December of 2006.
- Developed the document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* in 2005 and updated in 2006 to describe the potential health risks to nanoparticles and 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 C

Intramural Nanotechnology Research Projects

The following projects pertaining to ultrafine or nanoparticles have been funded as NIOSH intramural research projects and demonstrate the breadth of research activities ongoing at NIOSH since 2005. Results obtained from projects listed in this appendix will be used to further NIOSH's understanding of the behavior of engineered nanoparticles.

Generation and Characterization of Occupationally Relevant Airborne Nanoparticles

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

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, and Paul Baron, Ph.D.

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, and Petia Simeonova, Ph.D

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.

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.

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.

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. NIOSH cosponsored symposia on nanotechnology health issues in Minneapolis, MN, (October 3–6, 2005) and Research Triangle Park, NC, (October 26–28, 2005).

Nanoparticles: Dosimetry and Risk Assessment

Principal Investigator: Eileen Kuempel, Ph.D.

This project will develop quantitative methods to describe exposure, dose, and response relationships for inhaled particles of varying size and composition including evaluation of dose metric (e.g., particle mass or surface area). Biomathematical and statistical models will be developed to estimate internal dose and disease risk in workers exposed to nanoparticles and to support the development of occupational safety and health recommendations and guidance. As part of this project, research contracts have been awarded to the Hamner Institutes for Health Sciences and the Institute of Occupational Medicine.

Nanoparticles in the Workplace

Principal Investigator: Mark Hoover, Ph.D.

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. This project was initially funded to identify areas of research for NIOSH and will be replaced by a portfolio of projects.

Web-Based Nano-Information Library Implementation

Principal Investigator: Arthur Miller, Ph.D.

The primary objective of this project is to implement and maintain the Web-based programming for the NIOSH Nanoparticle 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.

Filter Efficiency of Typical Respirator Filters for Nanoscale Particles

Principal Investigator: Appavoo Rengasamy, Ph.D.

[conducted in 2006 by a 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. To increase knowledge and understanding of these smaller particles, NIOSH funded a study in 2005 at the University of Minnesota's Center for Filtration Research. The purpose of the study was to measure the penetration of nanoparticles between 3nm and 20nm in size through various filter media, including glass fiber, electret, and nanofiber. The respirator filter media tested in this study effectively collected nanoparticles down to 3nm in size. There was no evidence that particles in this size range pass through filter media at a higher rate than the larger particles. NIOSH is planning studies to validate these findings using NIOSH-approved respirators, and to evaluate the likelihood of worker exposure to nanoparticles when the respirator does not fit the person correctly. 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.

Respiratory Effects of Particulate Exposures in Wildland Firefighters

Principal Investigator: Denise Gaughan

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, the size distribution of the smoke aerosol (<100 nm – 10 um) will be determined to ascertain the free radical concentration in the products of combustion.

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.

Direct Reading Instrument Metrology

Principal Investigator: Terri Pearce, PhD, and 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.

NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations on Occupational Exposure to Titanium Dioxide

Principal Investigators: Faye Rice, M.S. and David Dankovic, Ph.D.

A Current Intelligence Bulletin (CIB) was developed to 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 was 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) were extrapolated to humans using lung dosimetry models, and the rat-based excess risk estimates for lung cancer were compared with the confidence intervals on risk from the epidemiological studies. Recommended exposure limits were derived based on 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 was evaluated, and updated recommendations were provided. The CIB has undergone external peer review in 2006 and is currently being revised to address peer review comments.

NIOSH Current Intelligence Bulletin (CIB): Risk of Parkinsonism in Welders

Principal Investigator: Ralph Zumwalde, M.S.

A Current Intelligence Bulletin (CIB) was drafted in 2006 to provide a critical scientific review of the potential risk to welders for developing neurobehavioral effects. Welding fumes are nano-structured aerosols that can deposit in the respiratory tract and systemically transfer to other organ sites. Neurobehavioral effects, including a type of parkinsonism, has been observed in welders and is thought to be associated with environmental factors including exposure to manganese found in the fume at certain welding processes. The CIB also considers whether other toxicants present in welding fumes may contribute to the reported signs and symptoms of neurotoxicity. A draft for internal review has been developed by a cross-Institute team; external peer review of the document is expected in 2008.

Neurotoxicity After Pulmonary Exposure to Welding Fumes Containing Manganese

Principal Investigator: James Antonini, Ph.D.

Millions of workers worldwide are exposed to welding aerosols daily. It has been suggested that welders are at an increased risk for the development of neurodegenerative diseases due to the presence of manganese in welding fumes. Epidemiology studies regarding the neurological health of welders are inconclusive. An experimental model is needed that will examine the potential neurotoxic effects after inhalation to welding fumes. A completely automated, computer-controlled welding fume generation and inhalation exposure system for laboratory animals has been developed. This project will assess the pulmonary and neurotoxic effects of animals exposed by inhalation to welding fumes that are composed of varying concentrations of manganese. Results will provide mechanistic information concerning welding fume exposure and be useful for risk assessment and the development of prevention strategies to protect exposed workers.

Pulmonary Toxicity of Metal Oxide Nanospheres and Nanowires

Principal Investigator: Dale Porter, Ph.D.

The objective of this project is to study the pulmonary effects of occupationally relevant engineered metal oxide nanospheres and nanowires. The project objectives will be accomplished as a result of both *in vitro* and *in vivo* studies. We expect that engineered nanomaterials of the same chemical composition, but different shapes, i.e., nanospheres versus nanowires, will exhibit different toxicities. The toxicological data obtained will dramatically increase our understanding of the potential exposure hazard passed by TiO_2 and SnO_2 nanospheres and nanowires. This knowledge will provide some of the initial, critical data needed for hazard identification and would also aid in the design of future experiments. Such data would contribute to risk assessment studies which may ultimately establish exposure standards and recommended handling practices to avert significant human health risks in the futures.

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.

Respirator Testing and Certification

Principal Investigator: Heinz Ahlers, J.D.

This project addresses the implementation of NIOSH's mandated respirator certification responsibilities through the testing, approval, and audit of respirators and manufacturing site quality systems in accordance with federal standards. The project develops the processes needed to provide certification of respirator protection in a manner to address contemporary hazards and new technologies. Although this project does not currently focus on nanoparticles or nano-enabled respirators, depending on the results of future research, special respirator testing protocols may be implemented in this project. As new nano-enabled technologies for respiratory protection become commercially available, new test methods, policies, and performance standards may also be required if NIOSH certification is needed.

End of Service Life (ESLI) Technologies

Principal Investigator: Jay Snyder

This project is examining sensor technologies that can be incorporated into respirator canisters to indicate when their useful life will expire. Prototype chemiresistor-based ESLI devices have been developed using monolayer-protected nanoclusters to detect trace levels of organic vapors inside a carbon bed to simulate a respirator cartridge. Collaborations with respirator manufacturers have been initiated to integrated prototype devices into actual respirator cartridges.

Respiratory Protection Against Nanoparticles

Principal Investigator: Samy Rengasamy, PhD.

Recent advances in nanotechnology have increased the amount of airborne engineered nanoparticles in industrial workplaces. NIOSH approved respirators are used for protection against particulates in workplaces. Previous studies show that NIOSH-approved particulate respirators efficiently capture particles down to the size of 20 nm diameter, while the penetration of particles smaller than 20 nm size is not as well understood. This project will investigate the penetration of particles ranging from 4 to 400 nm through NIOSH approved particulate respirators. Smaller size nanoparticles have high mobility. Little data on face/mask interface leakage for smaller size nanoparticles is available. This issue will be addressed by investigating the effect of face/mask interface leakage of various size particles. The research data from this project will enhance our understanding of the performance of respiratory protection devices against a wide range of nanoparticles to ensure worker safety and health. The research findings of this project will be incorporated into NIOSH nanotechnology guidance documents and international standards including ASTM and ISO.

Development of Protocols for Particulate Penetration Measurements of Protective Clothing and Ensembles

Principal Investigator: Pengfei Gao, PhD.

Protective clothing and ensembles are critically important items for workers when exposed to hazardous conditions. In order to determine how well ensembles protect wearers, it is necessary to test the entire suit system while it is worn to measure potential leakage through seams, closures, areas of transition to other protective equipment, and any leakage due to movement and activities. The objective of this project is to develop innovative methodology for measurement of aerosol particle penetration through protective clothing and ensembles. A test method for aerosol particles including nanoparticles that does not depend on filtration will be developed. A passive aerosol sampler (PAS) using magnetic force will be developed and iron (II, III) oxide particles will be used to generate challenge aerosols. An aerosol chamber will be fabricated for evaluating the particulate penetration for particle sizes between 60 and 500 nm; a wind tunnel will be used for larger particles up to 10 µm. Iron oxide collected on the PAS will be quantified using a colorimetrical method or transmission electron microscopy. Performance of the PAS will be evaluated under various test conditions, including particle size, particle concentration, wind speed, exposure duration, relative humidity, and sampler orientation. A deposition velocity model will be developed to calculate sampling rates of the PAS.

Penetration of nanoparticles through fabrics and protective clothing swatches will be measured with other reference samplers to compare the performance of the PAS. The research findings will be used for revised and new ASTM and NFPA standards.

Evaluating Real Time Monitors for Diesel Particulate in Mines

Principal Investigator: Art Miller, PhD.

This project aims at evaluating real time monitors for measuring diesel particulate matter in mines. Much of the work has been done with a focus on providing a method for estimating tailpipe emissions during maintenance. Part of this work focuses on the characterization of nanoparticles that increase in certain situations, including the application of new *clean-burning* diesel engines. 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.

Characterization and Communication of Chemical Hazards

Principal Investigator: Art Miller, PhD.

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 refinery fumes, welding fumes, blasting fumes, and metal bearing aerosols. In some cases, the aerosols are nanoscale particles and this project often deals with determining the origin and fate of metal-bearing nanoparticles.

Titanium Dioxide and other Metal Oxide Exposures Assessment Study

Principal Investigator: Brian Curwin, PhD.

NIOSH has identified critical research needs for workers exposed to ultrafine and fine TiO_2, including the measurement and characterization of workplace airborne exposures to TiO_2 in manufacturing and end-user facilities and evaluation of the exposure response relationship between TiO_2 and human health effects. The goal of this study is to measure and characterize workplace exposure to fine and ultrafine TiO_2 in both manufacturing and end-user facilities. The specific objectives are threefold: 1) characterize airborne TiO_2 exposure metrics by job or process, 2) obtain quantitative estimates of exposure in workers to fine and ultrafine TiO_2 particle sizes by relating the measured exposure metrics to worker exposure, and 3) evaluate a strategy for measuring workplace exposure to fine and ultrafine TiO_2.

A full shift combined with a task based sampling scheme consisting of various real-time and mass based area and personal aerosol sampling will be employed. In addition, information will be collected on the use of personal protective equipment (PPE) and the types of controls and work practices used to minimize worker exposures to TiO_2.

Monitoring Methods for Nanoaerosols

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

This project is an umbrella project in the DART aerosol group that supports multiple, nano-related pilot research projects. Current focus areas include: development/evaluation of off-line and on-line (real-time) nanoaerosol characterization methods for use in toxicology studies and for workplace monitoring. A fast, real-time instrument for measurement of nanoparticle size distributions are under development. In addition, nanoaerosol generation methods, nanoparticle transport, and novel approaches for surface area measurement are being investigated. This project also supports detailed field screening surveys of workplaces that use nanomaterials. Previous field studies have employed a suite of real-time instruments for characterization of nanomaterial releases, and collection of air and surface samples for laboratory analyses.

Dustiness of Nanomaterials

Principal Investigators: Douglas Evans, Ph.D.

This project is aimed at investigating the relative dustiness of nanomaterial powders. Dustiness is a relative measure of the propensity of a bulk powder to aerosolize through handling. It is an important property of powders if dust inhalation is of concern. This project will aid nanomaterial manufacturers, by targeting their exposure control efforts most effectively.

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.

Measurement of Nanoscale Carbonaceous Materials

Principal Investigator: Eileen Birch, Ph.D.

This project has two specific aims: 1) Apply multiple methods to characterize carbon nanofiber/nanotube materials in bulk, surface, and air samples. Metrics include: particulate carbon; metals; adsorbed organic fraction; particle size, shape, and elemental composition. 2) Generate filter samples of carbonaceous aerosols with known organic and elemental carbon (OC-

EC) content. Evaluate suitability of filter sets for quality assurance measurements on nanoscale carbonaceous aerosols.

Nanoaerosol Surface Area Measurement Methods

Principal Investigator: Bon-Kiu Ku, PhD.

The overall objective of this project is development and evaluation of methods to measure the surface area of airborne nanomaterials with different physicochemical properties over a wide size range of interest. One objective of this project is to investigate the differences between instrument responses to spherical and nonspherical particles, as well as between sub-100nm and super-100 nm particles. This work may permit extension of the existing theory of diffusion charging and of the instrument to surface area measurements on non-spherical particles. Overall, the complete characterization of surface area instruments and methods, and their application to determining the toxicity of nanomaterials, will provide a basis for understanding whether surface area is a more appropriate measure than mass for evaluating toxicity.

Nanoscale Reference Materials for Respiratory Disease Prevention

Principal Investigator: Aleks Stefaniak, PhD.

The purpose of this project is to provide a scientific basis for development of methods to ensure accurate measurement of engineered nanomaterials (EN) size and surface area in industrial hygiene samples. It is hypothesized that nanoscale colloidal gold nanospheres can be used as reference materials for nanoparticle size and surface area. This project aims are to develop nanoscale reference materials for use in quantifying EN particle size and particle surface area. In this project, various sizes of electro statically stabilized gold nanospheres will be will be generated and particle size characterized using multiple complimentary analytical techniques (microscopy, x-ray diffraction, liquid suspension counter, etc.). Knowing particle size, it will be possible to characterize particle porosity then particle surface area using complimentary techniques (gas adsorption, microscopy, etc.). It is anticipated that results from these studies will contribute towards qualifying these gold nanospheres as Respirable Masses (RMs)

Ultrafine TiO2 Surface and Mass Concentration Analysis

Principal Investigator: Aleks Stefaniak, PhD.

The purpose of this project is to test the hypothesis that ultrafine titanium dioxide (µTiO2) surface area can be measured with specificity on heterogeneous particle-laden filter samples using surfactant isotherms and/or fluorescence labeling. This project aims are to: develop a model for quantifying bulk ultrafine TiO2 powder specific surface area using lung surfactant and/or

fluorescent labeling; extend the model to evaluate surface area of aerosolized TiO2 particles collected on filter media in a laboratory chamber; and test the proposed model in a ultrafine TiO2 primary production workplace.

Exposure Assessment in Tungsten Refining and Manufacturing

Principal Investigator: John McKernan, PhD.

The proposed 3-year research project will determine if airborne tungsten oxide (WOX) fiber concentrations and physicochemical properties vary with production and manufacturing processes in the tungsten industry, and other down-stream industries that consume and incorporate tungsten in their products. The study design is an observational IH exposure assessment of approximately four similarly exposed groups, consisting of 20 workers. The research will identify groups at elevated risk of exposure, document exposure patterns among occupational cohorts, and characterize airborne particle morphology in domestic tungsten production and use among six facilities.

Investigations of Multi-Walled Carbon Nanotube Toxicity

Principal Investigator: Dale Porter, PhD.

Carbon nanotubes are in commercial use, and thus the possibility that persons will be exposed to carbon nanotubes is a reasonable expectation via occupational settings or from attrition of materials that contain carbon nanotubes. Thus, we are investigating multi-walled carbon nanotube-induced toxicity in both the lung and brain. Mice will be exposed to multi-walled carbon nanotubes (0, 10, 20, 40 and 80 μg/mouse) by pharyngeal aspiration. At 1, 7, 28 and 56 days post-exposure, multi-walled carbon nanotube-induced toxicity will be evaluated in the lung and brain. Translocation of multi-walled carbon nanotubes from the lung and deposition in other major organs will also be determined. The results of this study will be used in hazard and risk analyses, and will contribute to the development of occupational health and safety recommendations.

Potential Aneuploidy Following Exposure to Carbon Nanotubes

Principal Investigator: Linda Sargent, PhD

The data from the in vivo and in vitro studies indicate that SWCNT are capable of inducing progenitor cell proliferation, DNA damage, increased inflammation and oxidant stress as well as multinucleate cells and dysplasia in the mouse lung. In vivo exposure to SWCNT and MWCNT resulted in anaphase bridges and multinucleate cells indicating the possibility of spindle aberrations. Preliminary in vitro data demonstrated the induction of DNA damage in established A549 lung cancer cells, however, the response in normal mouse and human respiratory epithelial cells has not been determined. We therefore will analyze the spindle apparatus and chromosome number in normal mouse and human respiratory epithelial cells after exposure to equal weight doses of MWCNT and SWCNT.

Specific Biomarkers for Unusual Toxicity of Nanomaterials

Principal Investigator: Liying Rojanasakul, PhD.

Nanomaterials are potentially toxic to humans. Unfortunately, critical understanding of the adverse health effects has not been achieved. A key factor to this limited success is the lack of appropriate in vitro tests which are predictive of in vivo response to nanomaterials. Recent studies have shown that single-walled carbon nanotubes can induce lung fibrosis in animal models. The proposed studies will investigate the potential fibrogenicity of diverse nanomaterials using newly developed in vitro models. It is expected that the results of these studies will provide key information on risk assessment and development of preventive and intervention strategies for nanomaterial-induced lung fibrosis. The proposal addresses NIOSH Nanotechnology research Center goal to evaluate toxicity of nanoparticles and conduct studies supportive of risk assessment of carbon nanotubes.

Determination of Diameter Distribution for Carbon Nanotubes by Raman Spectroscopy

Principal Investigator: Madalina Chirila, PhD.

The goal of this proposal is to develop a method to determine the diameter distribution and the dispersion of carbon nanotubes (CNT) in various forms: powder, air samples, suspended in aqueous solution, and mixture of CNT and surfactant. Based on these measurements, we will quantify the amount of CNT in a sample. This study seeks to provide a methodology to qualitatively and quantitatively determine a biologically-relevant metric of exposure associated with CNT material. We will address this issue by using Raman spectroscopy combined with photoluminescence (PL).

Lung Effects of Resistance Spot Welding Using Adhesives

Principal Investigator: James Antonini

Aerosols formed during resistance spot welding may cause respiratory irritation in exposed workers. Information about the composition of substances generated during resistance spot welding is lacking. A robotic welding arm in the NIOSH lab will be configured and programmed to perform resistance spot welding to expose laboratory animals using process parameters common in the automotive industry. By using an animal model to mimic workplace exposures, the goal is to determine which component of the aerosols generated during resistant spot welding may be potentially toxic to exposed workers.

Occupational Exposures and Potential Neurological Risks

Principal Investigator: Krishnan Sriram, Ph.D.

Occupational exposure to aerosolized nanoparticles, ultrafine and fine particles or chemical agents can result in translocation of these materials to the brain and elicit transient, irreversible, or progressive damage to the nervous system. Currently there is little information on the adverse neurotoxicological effects of industrial materials, especially nanomaterials and new chemical agents. To predict and reduce the risk of occupational illnesses, it is important to establish their neurotoxicity. This project will evaluate neurological effects of industrial materials, particularly nanomaterials and new chemical agents. A 3-tiered approach to evaluate neurotoxicity will be implemented. Results from this study will be used to develop hazard and risk assessment paradigms emphasizing mechanisms of causation and significantly contribute to occupational safety standards.

Cell-based Assessment for Iron Nanoparticles Induced Health Effects.

Principal Investigator: Yang Qian, Ph.D.

This project is to develop an *in vitro* screening model for assessing the potential vascular toxicity of nanoparticles and to provide a basis for recommendations and guidance on the safe handling of nanoparticles. Specifically the project will identify the molecular mechanisms by which iron nanoparticle induces production of reactive oxygen species (ROS) in endothelial cells and study the regulatory roles of ROS in iron nanoparticle induced endothelial cell barrier damage, which can lead to cardiovascular dysfunction. The research strategies applied within this project may provide a rapid inexpensive *in vitro* alternative to the use of animal models to study the cardiovascular health risks of occupational exposure to various nanoparticles.

Mutagenicity Assessment of Carbonaceous Nanomaterials

Principal Investigator: Anna Shvedova, Ph.D.

Exposure to ultrafine particles has been linked to respiratory diseases, cardiovascular diseases and lung cancer. Lung cancer is currently the leading cause of cancer mortality in the United States. A preliminary study revealed potential mutagenicity of SWCNT and some hyperplasia in the lung of tumor-resistant mice exposed to SWCNT. Therefore, a more complete study is required to determine the mutagenic/carcinogenic potential of carbonaceous nanomaterial in the lung. Elucidation of mechanisms involved in lung cancer development may lead to the strategies for early detection in susceptible workers. Data obtained from these studies will be used for hazards identification, risk assessment, and management of carbonaceous engineered nanomaterial with respect to occupational exposures and will be used by regulatory agencies and industry to address strategies for assurance of healthy work practices and safe environments.

APPENDIX D
NIOSH Extramural Research
Nanotechnology Portfolio Summary
FY 2001-2008

Background

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

From 2001-2008 to date, the Office of Extramural Programs (OEP) has funded nanotechnology research through Occupational Safety and Health Research Program Announcements (R01) and Small Business Innovation Research Grants (R43/44). Since FY-05, OEP has also participated in two joint Requests for Applications (RFAs) for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. The US Environmental Protection Agency's National Center for Environmental Research (NCER) and the National Science Foundation (NSF) participated in FY-05. The National Institute of Environmental Health Sciences (NIEHS) joined in FY-06. Funding was available to support Research (R01) grants for three years and Exploratory (R21) grants for two years.

In FY-07, NIOSH/OEP participated in RFA-ES-06-008 Manufactured Nanomaterials: Physico-chemical Principles of Biocompatibility and Toxicity. This RFA was jointly sponsored by NIEHS, EPA and NIOSH.

In FY-08, nanotechnology related research proposals submitted to standing program announcements are being considered for funding by NIOSH/OEP.

Purpose

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

Extramural nanotechnology research is important to NIOSH because it adds to the overall development of new information and complement efforts undertaken within the Institute. The creativity and special resources available in the extramural community make it an important component in achieving a National goal to have safe jobs and healthy workers.

Status/Progress

From FY-01 to FY-04, OEP funded three R43/44 projects for a total funding commitment of about $950K (Table 1). In FY-05, OEP began participating RFAs for Nanotechnology Research Grants Investigating Environmental and Human Health Issues. For the first RFA, 83 applications were received and 19 were recommended for funding. Fourteen of these met NIOSH criteria for relevance to occupational safety and health. Five of these were in the competitive range for funding consideration and two were funded by NIOSH. In FY-05, EPA funded 14 projects and NSF funded two projects under this RFA. NIOSH also funded one nanotechnology research grant through the R01 Program Announcement in FY-05 (Table 1).

In FY-06, 81 applications were received in response to the RFA and 29 of these were recommended for funding. Six of these met NIOSH criteria for relevance and three of these were in the competitive range for funding consideration. NIOSH was able to fund one of these (Table 1). EPA funded 21 projects, NSF funded four and NIEHS funded three projects under this RFA. In FY-06, NIOSH also funded two Small Business Innovative Research grants on nanotechnology.

In FY-07, a career development grant involving research on personal exposure to nanoparticles was funded. This is a three year project at the University of Iowa.

To date in FY-08, NIOSH has funded a grant from the joint RFA on Manufactured Nanomaterials (Physico-chemical Principles of Biocompatibility and Toxicity). This project will be conducted at the University of Iowa. During the remainder of FY-08, nanotechnology related research proposals submitted to standing program announcements will be considered for funding by NIOSH/OEP. It is anticipated that at least two additional nanotechnology-related projects will be funded in FY-2008.

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

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

Additional Information

Extramural investigators interested in pursuing nanotechnology studies related to occupational health and safety can learn more about the interests of NIOSH in this area by visiting the following web pages:
http://www.cdc.gov/niosh/topics/nanotech/
http://www.cdc.gov/niosh/topics/nanotech/research.html
http://www2a.cdc.gov/niosh-nil/

Table D-1. Extramural Nanotechnology Research Funded by NIOSH, 2001-2008.

Grant Number	Investigator	Institution	Project Title	Start	End	1st year Funding	Total Funding
Prior to FY-04 NIOSH/SBIR							
1R43OH007471-01	Hooker	Nanomaterials Research LLC, Longmont, CO	Novel Hydrogen Sulfide Sensors for Portable Monitors	9/30/2001	3/31/2002	$100,000	$100,000
2R44OH007471-02	Williams	Synkera Technologies Inc., Longmont, CO	Novel Hydrogen Sulfide Sensors for Portable Monitors	9/16/2003	9/15/2006	$373,430	$749,995
					Pre-FY-04 Total		$849,995
FY-04 Exposure Assessment (NIOSH/SBIR)							
1R43OH007963-01A1	Rajagopalan	Nanoscale Materials, Inc., Manhattan, KS	From Nanoparticles to Novel Protective Garments	9/1/2004	5/15/2005	$100, 000	$100,000
					FY-04 Total	$100,000	$100,000
FY-05 Emerging Technologies (NIOSH Program Announcement)							
1R01OH008282-01A	Kagan	University of Pittsburgh	Lung Oxidative Stress/Inflammation by Carbon Nanotubes	7/1/2005	6/30/2009	$363,975	$1,458,862
FY-05 Emerging Technologies RFA (EPA STAR-2005-B1)							
1R01OH008806-01	O'Shaughnessy	University of Iowa	Assessment Methods for Nanoparticles in the Workplace	7/1/2005	6/30/2008	$132,903	$392,574
1R01OH008807-01	Xiong	New York University School of Medicine	Monitoring and Characterizing Airborne Carbon Nanotube Particles	8/1/2005	7/31/2008	$158,185	$396,401
					FY-05 Total	$655,063	$2,247,837
FY-06 Nanotechnology (NIOSH/SBIR)							
1R43OH008739-01	Thompson	Eltron Research Boulder, CO	Antistatic Paint with Silent Discharge	8/30/2006	8/30/2007	$93,452	$93,452
1R43OH008939-01	Deininger	Synkera Technologies Inc., Longmont, CO	New Nanostructured Sensor Arrays for Hydride Detection	8/1/2006	2/28/2007	$99,998	$99,998
FY-06 Nanotechnology RFA (EPA G2006-STAR F1 to F7)							
1R01OH009141-01	Dutta	Ohio State University	Role of Surface Chem in the Toxicological Properties of Manufactured Nanoparticles	9/1/2006	8/31/2009	$119,700	$359,100
					FY-06 Total	$313,150	$552,550
FY-07 Career Development Grant							
1K01OH009255-01	Peters	University of Iowa	Personal Exposure to Engineered Nanoparticles	9/1/2007	8/31/2010	$106,962	$320,864
					FY-07 Total	$106,962	$320,864
FY-08 Nanotechnology (NIEHS RFA-ES-06-008)							
1R01OH009448-01	Grassian	University of Iowa	An Integrated Approach Toward Understanding the Tox of Inhaled Nanomatl	4/1/2008*	4/1/2012*	$337,000	$1,200,000
					FY-08 Total	$337,000	$1,200,000
					Grand Total		$5,271,246

* Tentative start and end dates; approximate funding amounts. Funded in FY-2008.

Extramural Nanotechnology Research Project Summaries

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

HOOKER 7471 (R43), WILLIAMS 7471 (R44)

Novel Hydrogen Sulfide Sensors for Portable Monitors

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

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

Progress

The early portions of this project focused on developing nano-structured sensor materials and morphologies targeted toward chemiresistive-based sensors. This work resulted in a commercial sensor which is being incorporated into the fixed-system H_2S detection products of multiple partnering instrument manufacturers. The middle portion of the project focused on developing solid-state electrochemical sensors utilizing micro and nano-sized morphologies and structures. This has resulted in a working sensor currently being incorporated into an inexpensive, portable personal monitor as described above. Development of this monitor is wrapping up as the project is coming to an end during September 2006.

RAJAGOPALAN (7963) From Nanoparticles to Novel Protective Garments

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

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

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

KAGAN (8282) Lung Oxidative Stress/Inflammation by Carbon Nanotubes

<u>Background</u>

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

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

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

Progress

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

O'SHAUGHNESSY (8806) Assessment Methods for Nanoparticles in the Workplace

Background

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

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

Progress

Several methods were used to aerosolize nanoparticles from bulk powders in the laboratory. An apparatus was developed to inject the aerosol into a mainflow of dry, filtered air through a charged neutralizing device. The amount and size distribution of the aerosol in the chamber is sampled with a scanning mobility particle sizer, samples from the chamber are also being analyzed by TEM. While the primary particle size of these powders average 20nm, an aerosol with a median size of 120 is generated. These findings have significance in occupational settings since agglomeration of the particles in this size range will have consequences in pulmonary deposition and respirator filtration. Nanosized particles were also found as contaminants in the water used. A variety of instruments are being compared for use in the field studies of nanoparticle exposure levels in two facilities, one in MN and one in TX.

XIONG (8807) Monitoring and Characterizing Airborne Carbon Nanotube Particles

Background

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

The method will utilize available instrumentation to build an air monitoring system that is capable of sampling and sizing airborne CNT particles in a wide size range by using a 10-stage Micro-orifice uniform Deposit Impactor (MOUDI) and an Integrated Diffusion Battery previously developed in this laboratory.

Successful completion of this project will produce a validated method for sampling airborne

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

Progress

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

THOMPSON (8739)

Antistatic Paint with Silent Discharge

Long term Objectives

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

Research Design

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

Relevance to Public Health

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

DEININGER (8939) New Nanostructured Sensor Arrays for Hydride Detection

Background

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

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

DUTTA (9141)

Role of Surface Chemistry in the Toxicological Properties of Manufactured Nanoparticles

Background

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

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

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

PETERS (9255)
Personal Exposure Monitoring to Engineered Nanoparticles
Worldwide production of engineered nanoparticles is expected to grow from 2,000 metric tons to 50,000 metric tons over the next decade. New industrial processes must be introduced into the workplace to accommodate this growth. Although studies have shown some nanoparticles to be toxic, methods to assess personal exposure do not exist. Knowledge of personal exposure may be particularly important for such small particles because their concentration tends to decay rapidly with distance from a source.

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

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

GRASSIAN (9448)

An Integrated Approach Toward Understanding the Toxicity of Inhaled Nanomaterials

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

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

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

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

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

Table D-2. Nanotechnology Principal Investigators Funded by NIOSH/OEP, 2001-2008.

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APPENDIX E

Research Partnerships and Collaborations

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

The following are some of the ongoing NTRC partnerships and collaborations in nanotechnology research:

- Collaboration with the University of Rochester about the ability of nanoparticles to generate radical species.
- Oak Ridge Laboratory to evaluate the pulmonary toxicity of nanoparticles.
- University of Minnesota and the University of Iowa on measurement of airborne levels of ultrafine particles.
- Industrial hygiene, occupational health, and industrial partners at the University of Nevada at Reno and Altairnano, Reno, Nevada on understanding and improving the control of ultrafine metal oxides and engineered nanomaterials.
- 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.
- Industrial hygiene, occupational health, and industrial partners at Quantum Sphere on understanding and improving the control of nanoscale metals and metal oxides.
- Industrial hygiene, occupational health, and industrial partners at QD Vision on understanding

and improving the control of quantum dots.

- Hamner Institutes for Health Sciences on software modifications for use in lung dosimetry modeling.

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

- National Institute of Environmental Health Sciences/ National Institute of Health and the Department of Defense on nanotoxicology.

- NanoMech LLC (Fayetteville, Arkansas) to collaborate on a proposed EPA Phase I SBIR project related to containment of airborne nanoparticles.

- 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.

- National Aeronautics and Space Administration to evaluate the toxicity of single walled carbon nanotubes.

- University of Pittsburgh on the toxicity of nanomaterials.

- Dupont and the Nanoparticle Occupational Safety and Health (NOSH) industry consortium on issues related to the measurement of nanoparticles and the efficiency of filtration materials for engineered nanoparticles.

- Mitsui Co. Inc. on evaluating the bioactivity of MWCNT.

- NASA on evaluating the toxicity of SWCNT.

- IBM on evaluating the bioactivity of silicon nanowires.

- West Virginia University Nanotechnology Center on evaluating the toxicity of metal oxide nanowires.

- Karolinska Institute on evaluating the effect of nanomaterials on immune cells.

- University of Montana on evaluating the toxicity of nanowires.

- NIST on evaluating the toxicity of nanoparticles.

- West Virginia University Medical School on evaluating the effects of pulmonary exposure to nano TiO_2 on systemic microvascular function.

APPENDIX F

NNI Priority Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

Research Category	Research Needs

A. Instrumentation, Metrology, and Analytical Methods

1. Develop methods to detect nanomaterials in biological matrices, the environment, and the workplace
2. Understand how chemical and physical modifications affect the properties of nanomaterials
3. Develop methods for standardizing assessment of particle size, size distribution, shape, structure, and surface area
4. Develop certified reference materials for chemical and physical characterization of nanomaterials
5. Develop methods to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity

B. Nanomaterials and Human Health

Overarching Research Priority: Understand generalizable characteristics of nanomaterials in relation to toxicity in biological systems.

1. Understand the absorption and transport of nanomaterials throughout the human body
2. Develop methods to quantify and characterize exposure to nanomaterials and characterize nanomaterials in biological matrices
3. Identify or develop appropriate in vitro and in vivo assays/models to predict in vivo human responses to nanomaterials exposure
4. Establish the relationship between the properties of nanomaterials and uptake via the respiratory or digestive tracts or through the eyes or skin, and assess body burden
5. Determine the mechanisms of interaction between nanomaterials and the body at the molecular, cellular, and tissular levels

C. Nanomaterials and the Environment

1. Understand the effects of engineered nanomaterials in individuals of a species and the applicability of testing schemes to measure effects
2. Understand environmental exposures through identification of principle sources of exposure and exposure routes
3. Evaluate abiotic and ecosystem-wide effects
4. Determine factors affecting the environmental transport of nanomaterials
5. Understand the transformation of nanomaterials under different environmental conditions

D. Humans and Environmental Exposure Assessment

1. Characterize exposures among workers
2. Identify population groups and environments exposed to engineered nanoscale materials
3. Characterize exposure to the general population from industrial processes and industrial and consumer products containing nanomaterials
4. Characterize health of exposed populations and environments
5. Understand workplace processes and factors that determine exposure to nanomaterials

E. Risk Management Methods

Overarching Research Priority: Evaluate risk management approaches for identifying and addressing risks from nanomaterials,

1. Understand and develop best workplace practices, processes, and environmental exposure controls
2. Examine product or material life cycle to inform risk reduction decisions
3. Develop risk characterization information to determine and classify nanomaterials based on physical or chemical properties
4. Develop nanomaterial-use and safety-incident trend information to help focus risk management efforts
5. Develop specific two-way risk communication approaches and materials

From The National Nanotechnology Initiative, Strategy for Nanotechnology-Related Environmental, Health, and Safety Research, 2008.

APPENDIX G

Summary of Capabilities and Gaps for Nanotechnology Measurement Methods at NIOSH

Measurement Methods is a critical topic area in the NIOSH Nanotechnology Research Center (NTRC) Strategic Plan. This reflects the fact that effective and scientifically justified measurement methods are essential to understanding, predicting, and quantifying the chemical and physical properties and the behavior and toxicity of nanomaterials. The overarching Measurement Methods goals identified in the NTRC Strategic Plan are:

1. **Extend existing measurement methods.** Evaluate current methods for measuring airborne mass concentrations of respirable particles in the workplace and determine whether these mass-based methods can be used as an interim approach for measuring nanomaterials in the workplace and to maintain continuity with historical methods.
2. **Develop new measurement methods.** Expand the currently available instrumentation by developing and field testing methods that can accurately measure workplace airborne exposure concentrations of nanomaterials using metrics associated with toxicity (e.g., particle surface area).
3. **Validation of measurement methods.** Develop testing and evaluation systems for comparison and validation of sampling instruments and methods.

Meeting these goals supports success in the other nine critical topic areas of the NTRC Strategic Plan: Toxicity and Internal Dose, Risk Assessment, Epidemiology and Surveillance, Engineering Controls and Personal Protective Equipment, Exposure Assessment, Fire and Explosion Safety, Recommendations and Guidance, Communication and Education, and Applications.

In addition, the key components of the NTRC Strategic research plan have been incorporated into the five critical Environmental, Health and Safety (EHS) research areas identified by the Nanotechnology Environmental and Health Implications (NEHI) Working Group: Instrumentation, Metrology, and Analytical Methods; Nanomaterials and Human Health; Nanomaterials and the Environment; Health and Environmental Exposure Assessment; and Risk Management Methods.

Similar to NIOSH goals in the NTRC Strategic Plan, the NEHI goals in the research category of “Instrumentation, Metrology, and Analytical Methods” are:

1. Develop methods to detect nanomaterials in biological matrices, the environment, and the workplace.
2. Understand how chemical and physical modifications affect the properties of nanomaterials.
3. Develop methods for standardizing assessment of particle size, size distribution, shape, structure, and surface area.
4. Develop certified reference materials for chemical and physical characterization of nanomaterials.

5. Develop methods to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity.

Success in the Measurement Methods activities at NIOSH will foster success in overall national program. The following sections summarize NIOSH capabilities and critical gaps in Measurement Methods as they apply to the ten NTRC critical topic areas:

Toxicity and Internal Dose: NIOSH has developed and is using a suite of biological measurement techniques to assess mechanisms of damage and health endpoints such as oxidative stress, inflammation, and fibrosis. (See attached Table 1.) The ability to relate those endpoints to physical and chemical properties of the administered nanoparticles cannot rely on simple measures such as particle mass. The recent purchase and installation of a field-emission electron microscope to the NIOSH HELD facility in Morgantown has improved the capability to image nanoparticles such as gold-labeled carbon nanotubes in biological tissues. I addition, this instrument is being used to determine the size of nanoparticles sampled from an aerosol or a suspension. Evaluations of the capabilities of the new microscope are underway, including examination of reference materials obtained in collaboration with NIST. NIOSH/HELD is also determining the size of nanoparticles in suspension using a Dynamic Light Scattering Analyzer. The NIOSH field team needs similar improvements their microscopy capabilities to characterize workplace aerosols. Completion of the purchase and delivery of a new TEM/STEM to the NIOSH DART laboratories in Cincinnati will provide an improve linkage between measurement studies for toxicity and measurement studies for field team and exposure assessment studies.

Development of a graded suite of nano-reference materials is needed to support improved understanding of the mechanisms of toxicity of mixed materials. NIOSH/HELD is studing well characterized SWCNT (NASA), MWCNT (Mitsui), SnO2 and TiO2 nanospheres and nanowires (WVU), and silicon nanowires (IBM). They are also working with NIST to obtain other nanoparticles types. Recent in vitro toxicity testing at NIOSH of a raw single-walled carbon nanotube material obtained from NIST has demonstrated the uncertainties associated with assessing toxicity of a “real-world” complex mixture material. The joint NIOSH-NIST-DOE certified reference material for 200-nm diameter primary particle size beryllium oxide will be issued in early 2008.

Risk Assessment: Because occupational exposure limits have not been, and are not soon expected to be developed for nanoscale particles and nanoparticle-containing materials, NIOSH is developing proactive guidance for risk assessment and risk management that incorporates successful pharmaceutical industry approaches to the use of performance-based occupational exposure limits. Current measurement gaps to bringing together the key risk assessment factors of risk identification, exposure assessment, dose-response relationships, and human dosimetry are two-fold: lack of real-time instruments that can discriminate nanomaterials of interest and lack of actual field measurements of actual workplace conditions. Progress is unlikely on the real-time discrimination front, but there is promise in NIOSH work on an improved method to discriminate between types of carbon materials. As noted in the toxicity section, evaluation of nanomaterial properties is likely to require retrospective analyses such as microscopy. In the risk assessment area, as well as for all critical areas in the NTRC strategic plan, the opportunity to develop and validate improved measurement methods will be ongoing.

Epidemiology and Surveillance: "Who is exposed to what" is the key measurement question for epidemiology and surveillance that may be filled in part by the NIOSH study of industrial exposures to nano-metal-oxides. Based on available technologies for measuring airborne nanoparticles, the metrics of exposure are currently limited to particle number concentration, and particle size distributions based on total particle mass or number, or retrospective analysis of collected material. This gap is not soon likely to be filled. Collecting and archiving airborne total and size-selected dust samples from representative workplaces may provide a resource for future analysis.

Engineering Controls and Personal Protective Equipment: Recent experimental confirmation at NIOSH and at other research centers that nanoparticles are efficiently collected on filter media by diffusion has filled a critical gap in the understanding area of respiratory protection. These studies were enabled by aerosol generation and measurement methods for nanoscale aerosols including silver and sodium chloride. Measurement methods are being developed to assess penetration of nanoparticles through protective clothing.

Exposure Assessment: The NIOSH nanotechnology field team protocol for baseline exposure assessment involves condensation particle counting, optical particle counting, and electron microscope for particles collected on 37-mm diameter filter cassettes. (See Table 2.) This protocol is currently the state of the art. The expanded field team assessment protocol involves research-grade instruments that are larger in size, heavier in weight, more susceptible to damage, more expensive, and more labor-intensive. These include scanning mobility particle sizing, lung-deposited surface area sampling, and electrical and low-pressure cascade impaction. A challenging gap to be addressed my instrument manufacturers is to improve the portability of research grade instruments. A key gap that NIOSH can address is to determine the extent to which basic measurements and research measurements can be related.

Fire and Explosion Safety: The essential measurement methods gap for fire explosion safety is the need to assemble the currently available body of information about the state of the art for assessing fire and explosion safety, both for conventional materials and for nanomaterials. NIOSH can provide a valuable contribution by bringing this information together and making it accessible to the industrial hygiene community.

Recommendations and Guidance: The key measurement methods gaps for providing recommendations and guidance are the lack of validated tools to conduct a comprehensive set of risk assessment and risk management steps. The best that can currently be done is to establish an approach that can function with limited information, and grow with improved measurement methods in the future. The draft approach under development involves a combination of proactive qualitative risk assessment and control, performance-based occupational exposure limits, and verification of the efficacy of control.

Communication and Information: An alternate way to view measurement methods goes beyond measuring properties of nanomaterials and focuses on measuring the need for an effectiveness of communication and education for nanotechnology health and safety. One view of measuring effectiveness is that it can best be done in conjunction with existing safety initiatives that begin with the similarities of concerns for nanomaterials as a subset of chemical hazards in the workplace.

Applications: Although a number of nanotechnology-enabled improvements of occupational safety and health practice have been proposed, a critical gap is that few have been catalogued and critically evaluated. An example question is whether nanosilver impregnated filters actually involve nanoparticles, and whether such filters are actually more efficacious for collection and neutralization of bioaerosols than conventional filter media.

Table G- 1: Status Summary for the NIOSH Suite of Measurement Methods to Characterize the Biologically Relevant Properties of Nanoparticles in Health Hazard Evaluations

Parameters to be Measured	Instrumentation, Method or Procedure for the Measurement	Status at NIOSH / comments
1. Generation of reactive species in vitro by the nanoparticles of interest	a. Electron spin resonance (ESR) spectroscopy of nanoparticles suspended in phosphate-buffered saline plus H_2O_2.	Available and in use
	b. ESR of lung or dermal cells exposed in vitro to nanoparticles.	Available and in use
	c. Oxygen consumption, superoxide anion release, H_2O_2 production, or chemiluminescence from alveolar macrophages exposed in vitro to nanoparticles.	Available and in use
2. Cytotoxicity of nanoparticles in vitro	a. Release of lactate dehydrogenase from cell exposed to nanoparticles in vitro	Available and in use
	b. Oxidative metabolism (MMT assay) of cells exposed to nanoparticles in vitro.	Available and in use
3. Oxidant stress from exposures to nanoparticles in vitro	a. Depletion of total antioxidants in cell exposed to nanoparticles in vitro.	Available and in use
	b. Decrease of total thiols in cells exposed to nanoparticles in vitro.	Available and in use
	c. Oxidative DNA damage in cells exposed to nanoparticles in vitro.	Available and in use
4. In vivo exposure methods for controlled delivery of nanoparticles	a. Intratracheal instillation of a suspension of nanoparticles.	Available and in use Agglomeration can result in non-uniform delivery of particles to the lung. Suspension of nanoparticles in alveolar lining fluid greatly improves delivery and increased the magnitude of pulmonary response.
	b. Pharyngeal aspiration of a suspension of nanoparticles.	Available and in use Provides less intrusive, more reproducible, and better characterized delivery efficiency than instillation Is faster and more economical than inhalation Suspension in alveolar lining fluid reduces nanoparticle clumping and improves the dispersion and delivery of individual nanoparticles

Parameters to be Measured	Instrumentation, Method or Procedure for the Measurement	Status at NIOSH / comments
	c. Inhalation of an aerosol of nanoparticles.	Available and in use for SWCNT, MWCNT, and ultrafine TiO_2
	d. Dermal application of a suspension of nanoparticles.	Available and in use
5. In vivo response to nanoparticles	a. Pulmonary responses: cell damage (lavage LDH), air/blood barrier damage (lavage albumin), inflammation (lavage PMN, lavage cytokines, alveolitis by histopathology),	Available and in use
	b. oxidant stress (lung antioxidant levels, lung lipid peroxidation), fibrosis (collagen staining histopathology).	Available and in use
	c. fibrosis (collegen staining histopathy).	Available and in use.
	d. Cardiovascular responses: microvascular response to vasodilators, microvascular oxidant stress, adhesion of PMN to the microvessel wall, aortic oxidant stress (HO-1 production, oxidative, mitochondrial DNA damage), aortic plaque formation (histopathology).	Available and in use
	e. Neuro responses: cytokine production in various regions of the brain, markers of blood/brain barrier damage.	Available and in use
	f. Dermal responses: inflammation (histopathology), oxidant stress (lipid peroxidation, antioxidant depletion).	Available and in use
6. Translocation of nanoparticles	a. Label nanoparticles with gold or quantum dots and track their movement to systemic organs by neutron activation or fluorescence, respectively.	Available and in use. Substantially enhanced by 2007-09 acquisition of the new field emission microscope Addition of gold may alter nanoparticle characteristics Not all nanoparticles can be labeled

Table G-2: Summary of the Instruments and Nanoparticle Measurement Methods being used and evaluated in the NIOSH Nanotechnology Research Program

Instrument or Method	Purpose	Status at NIOSH / Comments
Condensation Particle Counter (CPC), TSI model 3007	Measures total particles in the 10 nm - 1000 nm range	Used in nano field team baseline assessments Cannot discriminate nanoparticles of interest from other airborne particles (This inherent problem applies to all air sampling instruments in this table.) There is a general lack of validation of how this and other air sampling instruments respond to the full spectrum of nanoparticles that may be found in the workplace, including varieties of primary particles, agglomerates or aggregates, and other physical forms and varieties of chemical forms. A suite of nanoparticle reference materials are needed to perform the needed validations.
Condensation Particle Counter (CPC) TSI Model 8525 P-Trak Ultrafine Particle Counter	Measures total particles in the 20 nm – 1000 nm range through a hand-held probe that enables extractive sampling from ducts or enclosures	Procured in October 2007 for use in nano field team baseline assessments Enables extractive sampling from ducts or enclosures Limitations include lack of definitive data on particle-size-dependent losses in the probe and sampling line
Optical Particle Counter, ARTI model HHPC-6	Measures particles in the 300 nm – 50,000 nm range	Used in nano field team baseline assessments Enables assessment of agglomerates and aggregates of nanoparticles and larger diameter particles of nanostructured materials

Indoor Air Quality Monitor, TSI Model Q-Trak Plus	Provides ambient temperature, RH, CO_2, and CO measurements	Used in nano field team expanded assessments, or when it has been demonstrated that environmental conditions need to documented Questions about the importance of environmental conditions are being addressed in the DRDS instrument chamber tests
Optical Particle Counter, Grimm model 1108	Measures particles in the 300 nm – 20,000 nm range	Used in nano field team expanded assessments
Diffusion charger, Eco-Chem Analytics Model DC 2000-CE	Measures active particle surface area up to 1000 nm particle diameter	Used in nano field team expanded assessments
Aerosol photometer, Dustrak model 8520	Measures particle mass from 300 nm to 2500 nm	Used in nano field team expanded assessments Could be used in the baseline studies
Electrical Low Pressure Impactor (ELPI), Dekati	Measures number of particles/size cut-point from 7 nm to 10000 nm in 12 stages	Used in nano field team expanded assessments
Scanning Mobility Particle Sizer, TSI model 3034	Measures number of particles as a function of mobility diameter in the range of 10 nm to 487 nm in 54 size channels	Used in nano field team expanded assessments
Airway deposited particle surface area analyzer, TSI Model 3550	Purports to estimate the surface area of particles deposited in the lung relative to ICRP standard reference man.	Used in nano field team expanded assessments Surface area measurements include more than the nanoparticles of interest. Reported values are estimates of the external particle surface area, whereas total particle surface area (e.g., of all primary particles in agglomerate or aggregate clusters) may be the more biologically relevant metric.
Wide-Range Particle Spectrometer, MSP Corp.	Measures number of particles as a function of mobility diameter in the range of 10 nm to 10,000 nm	Used in nano field team expanded assessments
Micro-Orifice Uniform Deposit Impactor (MOUDI) sampler, MSP Corp.	Collects particles in the range from 5 nm to 18000 nm as a function of aerodynamic diameter by cascade impaction on 12 or more stages plus a back up filter at a flow rate of 30 lpm.	Used in nano field team expanded assessments

Sioutas Cascade Impactor	Collects particles in the range from 250 nm to 2500 nm as a function of aerodynamic diameter by cascade impaction on 4 stages (cut points of 2.5 um, 1.0 um, 0.5um , and 0.25) plus a back up filter at a flow rate of 9 lpm. This personal cascade impactor unit may be worn by a worker.	Used in nano field team expanded assessments Could be used in baseline assessments
Point-to-plane electrostatic precipitator (ESP), InTox Products	Collects particles on 3-mm-diameter grids for transmission electron microscopy (TEM).	Used in nano field team expanded assessments Has promise for routine inclusion in baseline assessments when NIOSH development of a rugged, hand-held version of the ESP is fully developed
Impactor-based collection on TEM grid	Collects particles on 3-mm grids mounted onto MOUDI substrates for TEM.	Used in nano field team expanded assessments
37-mm plastic cassette with mixed-cellulose-ester (MCE) filters	Collects particles from the personal breathing zone of workers or from the general area for analytical chemistry or for scanning electron microscopy (SEM) or for TEM if the filter is clarified.	Used in nano field team baseline assessments
Cascade aerosol cyclone, SRI-type, InTox Products	Collects particles as a function of aerodynamic diameter for particle size distribution and for subsequent evaluation of particle properties as a function of size	Has been used in other NIOSH research programs (e.g., beryllium) Could be used in nano field team expanded assessments
Collection of bulk powder samples	Collection of bulk process powder materials for retrospective physicochemical analyses, including microscopy, surface area analysis, density determination, etc.	Used in nano field team expanded assessments Occasionally used in intermediate assessment studies to allow access to a greater variety of feedstock materials than may be currently in use during a baseline assessment
Helium gas pycnometry, Quantachrome Multipycnometer	Measures the particle material density of bulk samples	Used in nano field team expanded assessments
Nitrogen adsorption specific surface area measurement, Quantasorb BET system	Measures particle specific surface area of bulk samples	Used in nano field team expanded assessments Limitations include possible material alterations during sample heating to removed adsorbed water