The use of nanotechnology in consumer and industrial applications will likely have a profound impact on a number of products from a variety of industrial sectors. Nanomaterials exhibit unique physical/chemical properties and impart enhancements to engineered materials, including better magnetic properties, improved electrical activity, and increased optical properties. The United States, Europe, and Japan have each initiated comprehensive programs to promote and expand the utility of nanotechnology for commercial applications. An important component of these programs is the development of reliable risk and safety evaluations for these materials to ensure their safety for human health and the environment. The scope of each of these programs includes efforts to assess the hazards posed by nanomaterials in realistic exposure conditions.

**Key Words:** nanotechnology; nanomaterial risk evaluation; nanoscale material risk assessment.

Research efforts are being funded and/or conducted by the governments of several countries to develop priorities for risk-based safety evaluations for nanomaterials. Each of these efforts is intended to provide better data for evaluating the environmental and human health effects of nanomaterials or to objectively evaluate the utility of nanomaterials for applications such as enhanced monitoring, detection, and analysis for environmental pollutants and environmental remediation. The purpose of this paper is to highlight selected efforts that are being funded or conducted by governments in the United States, Europe, and Japan to develop a better fundamental understanding of the behavior of nanomaterials to facilitate an improvement in the scientific basis for evaluating the environmental and human health risks associated with nanomaterials. In addition, this paper also seeks to summarize research needs that have been identified by governmental organizations, which are viewed as important for advancing the science associated with nanomaterial risk assessment.

**U.S. EFFORTS TO DEVELOP IMPROVED DATA FOR NANOMATERIAL RISK ASSESSMENTS**

In the United States, government research efforts on nanotechnology are part of the National Nanotechnology Initiative (NNI) that is coordinated under the National Science and Technology Council (see http://www.nano.gov for more information on the NNI). In concert with promoting the development of nanotechnology, the NNI has also supported environmental health and safety (EHS) research since its inception. However, as more nanotechnology products have moved into the marketplace, there is a growing need for a more coordinated approach to developing the information required to assess the potential risks to human health and the environment from exposure to nanomaterials. The Nanoscale Science, Engineering and Technology (NSET) subcommittee, which includes members from agencies across the government, is now the coordinating body for U.S. government efforts associated with evaluating the human health and environmental impacts of nanotechnology.

Several U.S. agencies have research programs to evaluate the human health and environmental impacts of nanomaterials. These efforts are being coordinated through the NSET Nanotechnology Environmental and Health Implications Workgroup (NEHI). Currently, NEHI is preparing a document that will outline a strategy for prioritizing the research and other
information needs related to assessing the human health and environmental risks from exposure to nanomaterials. This document will present a path forward for U.S. EHS research for nanotechnology involving a staged approach which will incorporate research underway within government, industry, and academia.

Since 2001, various federal agencies have sponsored extramural and intramural research to evaluate the potential applications of nanotechnology and the associated human health and environmental implications. These agencies include the U.S. Environmental Protection Agency (EPA), the National Institutes of Health, the National Science Foundation, the National Institute for Occupational Safety and Health, and the Departments of Agriculture, Defense, and Energy. More recently, the National Toxicology Program has engaged in research to evaluate the ecological and human health impacts of specific engineered nanomaterials including quantum dots, fullerenes carbon nanotubes (CNTs), and titanium dioxide. For more information on the specific activities of these agencies, visit the agency links from the site http://www.nano.gov. Among those U.S. agencies that will have a role in the development of risk assessments for nanomaterials, the U.S. EPA will be very important.

U.S. EPA Research Efforts to Develop Improved Data for Nanomaterial Risk Assessments

EPA is taking a holistic approach to studying nanotechnology, targeting research toward the identification of the beneficial applications of nanotechnology, seeking additional exposure and fate/transport data, developing appropriate risk assessment/management strategies, pursuing novel pollution prevention and environmentally benign techniques for the technology, and assisting in the development of novel treatment and remediation technologies using nanotechnology. Many efforts have shown promise for using nanomaterials to remediate environmental pollutants (Chen et al., 2000; Tungtiplakorn et al., 2004, 2005; Zhang et al., 2003).

The unique properties that make nanomaterials useful and novel are also likely to be the properties that could impact humans and the environment under specific conditions. Consequently, it will be necessary to consider these unique properties and their potential impacts on fate, exposure, and toxicity in developing risk assessments for nanomaterials (Dreher, 2004; European Commission, 2004; European NanoSafe Report, 2004; HSE, 2004; Swiss Report Reinsurance Company, 2004; U.K. Royal Society, 2004).

EPA and other federal agencies are also identifying critical research needs for the development of comprehensive risk assessments for nanomaterials. A brief summary of these research needs is listed below. A more comprehensive description of EPA's draft nanotechnology research needs can be found in EPA's draft Nanotechnology White Paper. The White Paper, currently undergoing external peer review, may be found at http://www.epa.gov/osa.

Characterization

It is currently unclear whether existing physicochemical property testing methods are adequate to sufficiently characterize nanomaterials. Research needs in this area include compiling data on the unique chemical and physical characteristics of nanomaterials, particularly the impact of size, morphology, charge, and surface coatings on reactivity, toxicity, and mobility. In addition, there is also a need to develop ways to distinguish engineered nanomaterials from incidental (anthropogenic) and natural nanoparticles and to better understand differences in terms of human health and environmental impact from exposure to these varying types of nanomaterials.

Transformation and Interaction

Data concerning the transformation of specific compounds—individually and in complexes with other compounds—and the interactions that may occur between the compound and its surroundings are critical to developing environmental protection policies. While there are historical data and models for conventional pollutants, such data and models may not be sufficient for engineered nanomaterials. Consequently, research is needed to fully understand how nanomaterials may differ from their bulk counterparts in terms of the extent to which they react with other compounds and with environmental media and the mechanisms by which these interactions occur. Nanomaterial transformation and interaction research needs include determining the physiochemical properties that affect stability and persistence in the environment, understanding the degradation processes of these materials, determining how physiochemical properties may be altered in environmental media consisting of a complex array of compounds and materials, and determining differences between engineered nanomaterials and bulk materials in the environment.

Environmental Fate and Transport

The fundamental properties that influence the environmental fate of nanomaterials are not well understood (European Commission, 2004). Consequently, it is essential to determine the fate of nanomaterials in the environment and the availability of these materials to living organisms. Accordingly, more research is needed on the transport and potential transformation of nanomaterials in soil, subsurface, surface waters, water treatment systems, and the atmosphere. Evaluation and modification of existing methods or the development of new test methods to support these investigations must also be carried out, as well as the development of properties estimation techniques. Environmental fate research needs include determining the factors that influence the fate, transport, and transformation of engineered nanomaterials in ecosystems, determining under what circumstances nanomaterials bound to products are released or leached into surrounding

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environmental media, understanding mobility characteristics of engineered nanomaterials, and determining by what mechanisms and in what form engineered nanomaterials transition from one environmental media to another. In addition, determining the dissolution characteristics for nanomaterials is essential for developing a comprehensive understanding of the behavior of these materials. Understanding the potential for these materials to bind or complex with solid, aqueous, or gaseous matter is also important.

**Exposure Assessment**

Some of the potential exposures to nanomaterials include workers exposed during the production and use of these materials, general population exposure from releases to the environment during the manufacture, use, or disposal/recycling of these materials, and ecosystem exposure during the manufacture, use, or disposal/recycling of nanomaterials or products containing nanomaterials (Aitken et al., 2004). Exposure research needs include determining the adequacy and accuracy of current exposure assessment techniques for nanomaterials, determining those nanomaterial properties that have relevance for hazard (size, surface characteristic, charge, morphology, etc.), determining potential exposure scenarios for sensitive populations (such as children, the elderly, and people with health conditions such as asthma), and understanding the impacts of varying physical and chemical properties of nanomaterials on exposure outcomes. In addition, there is also a need to determine the adequacy of personal protective equipment (PPE). Also important is the development of techniques to accurately detect nano-sized materials in indoor and ambient environments.

**Ecological Effects**

Ecosystems may be affected through inadvertent or intentional releases of engineered nanomaterials. Drug and gene delivery systems, e.g., are not likely to be used directly in the environment but may contaminate soils or surface waters through wastewater treatment plants (from human use and excretion), as runoff from concentrated, animal-feeding operations or from aquaculture applications. Direct applications to the environment may include nanoscale monitoring systems, control or clean-up systems for conventional pollutants, and desalination or other chemical modifications of soil or water. Nanoscale particles may affect aquatic or terrestrial organisms differently than larger particles due to their potential to cross and/or damage cell membranes and differences in other chemical and physical properties (U.S. EPA, 2003). Furthermore, use of nanomaterials in the environment may result in novel by-products or metabolites that also may pose significant risks. Ecological effects research needs include determining whether current testing methods (organisms, end points, exposure regimens, media, analytical methods) are applicable for testing nanomaterials in standardized toxicity tests; determining the distribution of nanomaterials in ecosystems; determining adsorption, distribution, metabolism, and excretion (ADME) parameters of various nanomaterials for ecological receptors; and examining the interaction of nanomaterials with model ecosystems.

**Human Health Effects Assessment**

The potential for adverse health effects from exposure to engineered nanomaterials may result from inadvertent release of the materials during manufacture, use, disposal, or recycling, through the generation of unintentional by-products during environmental application, or through the intentional introduction of these materials for cosmetic, health, or other purposes. Little data exist on the deposition and fate or specific susceptibility from exposure to engineered nanomaterials or their associated by-products. Although standard toxicological test methods were designed to detect a broad array of structural (histopathological) and functional end points, it is also unclear whether standard test methods can be used to identify toxicities associated with the unique physicochemical properties of intentionally produced nanomaterials (ILSI, 2005).

The studies conducted to date suggest that the toxicological assessment of specific engineered nanomaterials may be difficult to extrapolate from existing databases (Lam et al., 2004; Warheit et al., 2004). While the human physiologic relevance of these studies is a topic of considerable debate, the hazards identified in these studies should be examined more closely. Although the toxic effects of engineered nanomaterials have not been fully characterized or understood, it is known that these materials differ from their bulk counterparts in their physical-chemical properties. There is a critical need to develop methodologies for characterizing and testing nanomaterials in a systematic and comparable way such that research results can be appropriately evaluated and compared.

As a result of their size, nanoparticles may pass into cells directly through cell membranes or via cellular transport mechanisms and may penetrate the skin and distribute throughout the body. Recent research has shown that multi-walled CNTs which have not been derivatized or optimized for biological applications are capable of localizing within human epidermal keratinocytes and have demonstrated inflammatory responses (Monteiro-Riviere et al., 2005). There is also a concern for systemic effects (e.g., migration to target organs and the cardiovascular and neurological systems) in addition to portal of entry (e.g., inhalation, dermal, and oral) toxicity.

Human health effects research needs include determining the adequacy of current testing methods for nanomaterials, identifying the properties of nanomaterials that are most predictive of toxicity to receptors, assessing which nanomaterials have high commercial potential for dispersive applications in order to establish priority for toxicity testing, and determining the potential health effects (local and systemic; acute and chronic) resulting from direct exposure to either nanomaterials or their by-products.
Life-Cycle Analysis

Life-cycle analysis (LCA) is an approach to evaluating the environmental consequences of a product through all stages along the life cycle of a compound, including production, use, recycling, and disposal.

Adequate information on the use of nanomaterials is a critical data need in applying LCA. The processes that are involved in the production of nanomaterials and their incorporation into consumer products are not centrally reported. Exposure to nanomaterials from a specific product may vary considerably based on the stage of life of the material. For example, during consumer use, exposure pathways/routes may be present (e.g., mouthing of products by children) that would not be expected in occupational settings.

LCA research needs include the following: evaluating the adequacy of current LCA tools and models for application to nanomaterials; compiling data sets for engineered nanomaterials; developing standardized methodologies for LCA that provide consistent, comparable techniques; determining process data and defining specific nanomaterial emission information through the use of the currently available, broad database for bulk compounds; developing an impact comparison for conventional versus nanomaterial compounds; and formulating an assessment of the broad potential environmental impacts of engineered nanomaterials throughout product life cycles.

EUROPEAN COMMISSION RESEARCH EFFORTS TO DEVELOP IMPROVED DATA FOR NANOMATERIAL RISK ASSESSMENTS

Products based on Nanosciences and Nanotechnologies (N&N) are already in use, and analysts expect markets to grow by billions of euros during this decade. The risk assessment of these nanoengineered materials has become the focus of increasing international attention. Although a number of institutions have published reports discussing the potential environmental and health risks associated with the manufacture, use, distribution, and disposal of nanomaterials, to date the widely accepted view is that there are still a number of unanswered questions. Some dedicated European Union (EU)–funded research within the previous Framework Program (FP5) and the present (FP6) in the field of nanotechnology are underway to assess these potential risks.

On 12 May 2004, the European Commission (EC) adopted the communication Towards a European Strategy for Nanotechnology in which a safe, integrated, and responsible strategy was proposed. The purpose of this strategy is to reinforce the Union’s leading position in N&N research, development, and innovation, while addressing any environmental, health, safety, and societal concerns.

On 7 June 2005, the EC prepared the communication Nanosciences and Nanotechnologies: An Action Plan for Europe 2005–2009. This action plan defines a series of articulated and interconnected actions for the immediate implementation of the EU strategy based on the priority areas identified in the above-mentioned communication. The action plan and strategy can be found at http://cordis.europa.eu.int/nanotechnology/actionplan.htm.

To achieve a high level of public health and environmental protection, the EC highlighted the need to identify and address safety concerns (real or perceived) at the earliest possible stage, reinforce the integration of human health and environmental protection into research and development (R&D) activities, and to support the generation of data on toxicology and ecotoxicology (including dose-response data), and evaluate potential human and environmental exposure.

The EC also called upon the Member States to promote the adjustment, if necessary, of risk assessment procedures to fully consider the particular issues associated with nanotechnology and the integration of human health (both workplace and consumer) and environmental risk assessment at all stages of the life cycle for nanotechnology (including conception, R&D, manufacturing, distribution, use, and disposal).

More research is also needed to determine the most appropriate basis for developing a science-based regulatory program for these materials. This research should consider the impacts of nanotechnology throughout their full life cycle. Because the impacts for some nanomaterials would not have geographical boundaries, it would be advantageous to systematically pool knowledge at the international level.

Addressing the potential risks of nanotechnology to human health and the environment will also require evaluating the possible reuse of existing data and generating new, material-specific toxicology and ecotoxicology data (including dose-response and exposure data) certain nanomaterials. This also will also require examining and, potentially, revising existing risk assessment methods. In practice, addressing the potential risks associated with nanomaterials necessitates that risk assessment be integrated into every step of the life cycle of nanotechnology-based products. The Scientific Committee in Emerging and Newly Identified Health Risks has issued in 2005 a scientific opinion on “the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies.” This opinion was opened on the Internet for public consultation and debate. The replies, which have been duly analyzed and elaborated, have been included in the final document for publication.

The EC has also highlighted international cooperation as a key asset to advance nanomaterial research. The European research programs are open to the world, and they allow research teams from virtually all countries to participate in projects. This is particularly important for nanotechnology, where a large amount of basic knowledge is still needed, and many scientific and technical challenges remain. International cooperation can accelerate research by overcoming knowledge gaps more rapidly and encouraging the introduction of
solutions from a broad array of stakeholders. In particular, the EC believes there is an urgent need to share knowledge in the health, safety, and environmental aspects of nanotechnology for the benefit of all citizens.

Common, shared principles for nanomaterial research could be embodied in a voluntary framework which could be made available to the public, such as a “code of good conduct” or a declaration or a common press release done by research ministers of the main concerned nations. Following the EC “Strategy” communication of 2004 (European Commission, 2004), an international dialog on responsible nanotechnology has been initiated.

Completed and Ongoing EU Nanomaterial EHS Projects

The current portfolio of projects addressing risk assessment and in particular nanomaterial toxicology and ecotoxicology includes projects for almost € 25 million in grants. Both engineered and nonengineered nanoparticles were addressed. A list of the projects is presented below. This information does not include other EU-funded projects where risk assessment and safety issues in relation to nanoparticles may be addressed but are not the main objective of the project.

It should also be noted that EU Member States are also funding research on risk assessment such as the German Federal Ministry of Education and Research (the project NanoCare started on 1 March, 2006, and has an overall budget of € 7.6 million) and two studies funded by the U.K. Department for Environment, Food, and Rural Affairs. These include a scoping study to identify hazard data needs for addressing the risks presented by nanoparticles and nanotubes and another scoping study to identify exposure data needs for addressing the risks presented by nanoparticles and nanotubes.

The following EU projects have been completed. The total value of these grants was approximately € 2.5 million.

- Nanosafe: This project assessed the risks associated with the production, handling, and use of nanoparticles in industrial processes that produce commercial and consumer products. The objectives of the project were to collect available hazard information for nanomaterials, to evaluate consumer and workplace risks, and to recommend regulatory measures and codes of practice for reducing risk.
- Nanoderm: The objectives of this project were to apply and develop methods for evaluating the effectiveness of skin as a barrier to nanoparticles and to assess the biological activity of nanoparticles in skin.
- Nanopathology: The goal for this project was to identify innovative diagnostic methods for micro- and nanoscale particles, to investigate the pathological mechanisms of possible particle-included diseases, and to determine the pathological significance of the nanoparticles.
- MAAPHRi (Multidisciplinary Approach to Airborne Pollutant Health Related Issues): The objectives of this project were to develop new screening tools to assess environmentally related health issues associated with exposure to airborne pollutants and to investigate hazardous engine exhaust components and their relative contribution to toxicity.

The following EU Nanomaterial EHS projects are ongoing. The total value of these grants is approximately € 10.6 million.

- Nanotox: The objective of this project is to produce guidelines and recommendations for the development of European standards, legislation, ethics, policies, and codes of practice for nanomaterials.
- Impart (Improving the Understanding of the Impact of Nanoparticles on Human Health and the Environment): The objective of this project is to improve the fundamental understanding of the impact of nanoparticles on human health and the environment by fostering communication between different initiatives and facilitating cooperation.
- Nanosafe2: This project seeks to develop an integrated system for addressing the potential hazards related to nanoparticle technology, in particular workplace and consumer health and safety, and environmental protection. The system will be based on detection and characterization techniques, hazard assessment, and safe production processes with a particular emphasis on the societal and environmental implications of nanotechnology.
- Particle-Risk: This project will assemble a bank of five particles and assess the health risks from exposure to these materials via respiratory and oral exposure, using in vitro and in vivo techniques.
- Polysoa (Polymers in Secondary Organic Aerosols): The goal of this project is to achieve a basis to assess the risk of nanoscale contaminants to human health and to evaluate the importance of aerosol polymerization for air quality and climate change.
- Antistorm (Anthropogenic Aerosols Triggering and Invigorating Severe Storms): This project will seek to understand the role of anthropogenic influences in the incidence of severe storms and to provide a scientific basis for improving the prediction models for these storms.

Future EU Nanomaterial EHS Research Projects

In addition to the ongoing research projects, a thematic call in the area of “Nanotechnologies and nanosciences, knowledge-based multifunctional materials and new production processes and devices” was launched in December 2004 under the topic “Interaction of engineered nanoparticles with the environment and the living world”, requesting proposals for projects that addressed interdisciplinary toxicological and ecotoxicological research on as many aspects as possible of the interaction of nanoparticles with the environment and the living world.

Four out of 21 proposals were selected during the evaluation in October 2005 and are currently under negotiation. The total budget for new projects is approximately € 11 million.

N&N will have an important role in FP7. The advances enabled through R&D in N&N are intended to address the needs of citizens and contribute to the EU’s competitiveness and sustainable development objectives and many of its policies including public health, employment and occupational safety and health, information society, energy, transport, security, and space. FP7 will be the main initiative for implementing the action plan on N&N.

In the EC’s proposal for a Council Decision (located at http://europa.eu.int/comm/research/future/pdf/specific_programmes/fp7sp_cooperation_en.pdf), the Specific Programme “Cooperation” that implements the FP7 (thematic area “Nanosciences, Nanotechnologies, Materials and New Production Technologies”) research on risk assessment (e.g., nanotoxicology and ecotoxicology), as well as safety, nomenclature, metrology and standards, was identified as a priority.

Additional topics for nanomaterial research in the EU will be identified through open calls for proposals. The first call in FP7 is expected to be launched at the end of 2006; however, both the FP7 and the Specific Programmes have still to be approved (by a codecision by the European Parliament and the Council for FP7 and by the Council following opinion by the European Parliament for the Specific Programmes).

Consistent with the statement “risk assessment related to human health, the environment, consumer and workers should be responsibly integrated at all stages of the life cycle of the technology, starting at the point of conception and including R&D, manufacturing, distribution, use and disposal or recycling. Appropriate assessments should be carried out and risk management procedures elaborated” the EC seeks to identify and address safety concerns associated with applications and use of N&N at the earliest possible stage.

All documents cited as well as additional information on EU-funded research projects (completed and ongoing) are available at the EC Nanotechnology home page http://cordis.europa.eu.int/nanotechnology/.

**RESEARCH STRATEGIES FOR RISK ASSESSMENT OF ENGINEERED NANOMATERIALS IN JAPAN**

Research on the toxicity of engineered nanomaterials was initiated in the early 1990’s in Japan. Research projects were conducted individually using government research funds from the then Ministry of Education, Science, and Culture and the then Ministry of Health and Welfare (MHW). One study examined scale-specific biological responses by injecting “standard-scale” (average diameter of 5 μm) and “ultrafine-scale” (average diameter of 20 nm) metal particles (Ni and Co) in physiological saline into the trachea of rats and reported that the nanoparticles were more toxic than the micrometer-sized particles in terms of pulmonary inflammation induction (Zhang et al., 1998, 2000, 2003). MHW sponsored a research project on carbon clusters between 1992 and 1994, in which mutagenicity (Sera et al., 1996), antagonistic effects on agonist-induced responses in the isolated intestinal tract and trachea of various test animals (Satoh et al., 1995), and the phototoxicity (Nakajima et al., 1996) of fullerenes were investigated. “Studies of Tissue Responses and Applications to Biotechnology of Nanotubes, Nanoparticles, Microparticles”’ is another research project (2002–2004) sponsored by the Ministry of Health, Labor and Welfare (MHLW). The main objective of the project was to study the medical applications of nanomaterials such as titanium oxide and CNTs in dental implants and to examine the biocompatibility of such materials. The histological responses of CNTs implanted sc and their in vitro stimulatory effects on macrophages to produce proinflammatory cytokines such as the tumor necrosis factor were also examined (Sato et al., 2005a,b).

**Scope of Current Government-Funded Research in Japan**

The advisory council for formulating nanotechnology policy was established and operated by the Ministry of Economics, International Trade and Industry (METI) from January to March in 2005. The following four topics formed the basis of nanotechnology priorities: (1) the national goal of promoting nanotechnology, (2) feasible application of nanotechnology, (3) industrial nanotechnology policy, and (4) the social impact of nanotechnology. An interim report was officially published in March 2005. The safety of nanotechnology was addressed by the working group of “the Societal Impact of Nanotechnology.” It was reported that nanotechnology is not yet at the stage in which definite toxicity inherent to nanomaterials could be determined but that it is crucial that continuous effort should be devoted to evaluating the safety of nanomaterials. Specifically, the report stated, “it is crucial to accumulate scientific knowledge regarding the safety of nanotechnology to promote the development of nanotechnology.” The report also stated, “The nation itself should conduct studies on test assessment methods and collect and provide various relevant data while collecting overseas and domestic information regarding the safety of nanotechnology. It is desired that the nation play a proactive role in such projects that have large external effects.”

In response to the above proposal, a project on the “Facilitation of Public Acceptance of Nanotechnology” funded by the Ministry of Education, Sports, Culture, Science, and Technology (MEXT) was formed to conduct a preliminary investigation of public acceptance and the safety of nanomaterials in 2005. The following four themes comprised the focus of the project: (1)...
RESEARCH STRATEGIES FOR SAFETY EVALUATION OF NANOMATERIALS

preliminary research and surveys on the risk assessment of nanomaterials, (2) environmental issues involving nanomaterials, (3) ethics and social issues, and (4) technology assessment to promote the public acceptance of nanotechnology and to determine its socioeconomic effects. Individuals from representative national institutions (i.e., the National Institute of Health and Science under the jurisdiction of MHLW, the National Institute for Material Science under the jurisdiction of MEXT, the National Institute for Environmental Studies under the jurisdiction of the Ministry of Environment [ME], and the National Institute of Advanced Industrial Science and Technology [AIST] under the jurisdiction of METI) are involved in the project in collaboration with many universities and colleges.

“Research on the Development and Standardization of In Vitro Toxicity Testing Methods for Nanomaterials” is a project that was started in 2005 as one of the research projects for developing industrial standards (funded by METI). AIST was charged with developing convenient in vitro testing methods for evaluating the toxicity of nanomaterials. The goal for this research was the development of convenient in vitro testing methods for evaluating the toxicity of nanomaterials on the basis of possible toxicity mechanisms attributable to nanomaterials within 3 years. The rationales for such a high priority being given to the development of in vitro testing methods include the following. (1) It will take a long time to validate existing toxicity test systems using experimental animals for nanomaterials. (2) It must be much easier to verify the presumed nanoscale-specific biological effects. (3) In vitro test systems can be used for preliminary but effective toxicity screening purposes for nanomaterials.

AIST started a research project on nanomaterial risk assessment using its own funds (approximately ¥ 100 million in 2005) in 2005. This is an unprecedented comprehensive project in which major nanotechnology-related research branches in AIST, such as the Nanomaterial Production Department, Metrology Department, Environmental Management Department, and Chemical Risk Management Department, conduct joint studies on the standardization and risk assessment of nanomaterials. In this project, many research resources have been invested on not only nanomaterial toxicity research but also the development of nanomaterial measurement and characterization techniques, the evaluation of exposure to nanomaterials in the workplace and research laboratory, and the assessment of exposure due to products made of nanomaterials during the life cycle of products. The rationale for this investment comes from the understanding that the development of techniques for the accurate measurement of nanoscale materials in testing systems such as aqueous media or body fluids is urgently required.

**Future Course of Research Projects and Tasks in Japan**

The New Energy and Industrial Technology Development Organization, which is one of the funding agency under the control of METI, starts a 5-year plan for a comprehensive research project on the safety and risk assessment/management of nanomaterials in FY 2006. The estimated budget is ¥ 420 million in 2006 for a total of approximately ¥ 2 billion over 5 years. The goal of this research project is to establish methods for the human health risk assessment of nanomaterials, to carry out risk assessments for typical nanomaterials, and to propose risk management methods on the basis of the assessment results. The objectives include the following four themes: (1) the development of hazard assessment measures; (2) the development of preparation and measurement methods for samples subjected to toxicity testing; (3) the development of assessment methods to evaluate human exposure levels and risks posed by nanomaterials; and (4) the proposal of a risk management framework of nanomaterials. The results of this research are expected to provide a scientific rationale, based on which entities (i.e., regulatory agencies, academic communities, businesses, and consumers) will be able to make appropriate decisions about the risk management of nanomaterials. Moreover, it is expected that protocols for sample preparation and characterization in toxicity tests and the framework for the hazard assessment of nanomaterials will be established by FY 2008, as shown in the time schedule or road map (see Fig. 1) for this project.

The nanomaterials used in this research project include metals, metal oxides, silica, latex, fullerene, and CNTs. Regarding the framework of hazard assessment, the tiered approach is expected to be adopted, and the following three stages are considered: tier 1, in vitro test; tier 2, simplified in vivo test in the inhalation pathway such as intratracheal ingestion; and tier 3, animal inhalation toxicity test. Thus, the highest priority is given to the inhalation pathway, and this reflects the special circumstances in which Japan finds itself. Since health hazards caused by asbestos used in large quantities in the 1970’s–1980’s became apparent in 2005, the Japanese society as a whole is very critical about the harmful effects of microparticles on health via exposure to the respiratory pathway.

Theme (2), i.e., the development of preparation and measurement methods for samples subjected to toxicity testing, is based on the premise that toxicity tests should be conducted with well-characterized and sufficiently deagglomerated test samples. Nanomaterials are generally aggregated or agglomerated; thus, it is hard to deagglomerate them using ordinary dispersion methods such as ultrasonic treatment. It is undeniable, however, that people may be exposed to dispersed nanoparticles somewhere during the processes from production to consumption, disposal, and recycling. Because nanocarbon materials bind strongly to biomolecules such as DNA (Zheng et al., 2003a,b) and proteins, aggregated nanocarbon materials tend to be dispersed or dissolved by these biomolecules under certain circumstances.

One of the important aims of the project is to assess the toxicity of nanomaterials in the deagglomerated state and to develop methods of nanomaterial deagglomeration.
The project’s objectives also include the development of measurement techniques not only for the distributions of particle size, shape, and the specific surface area of nanomaterial samples subjected to toxicity tests but also for the nanomaterials in vitro and in animal systems. Furthermore, measurement techniques must be developed for nanomaterials whose diameter is on the order of 1 nm both in the aqueous media and in the atmosphere.

In theme (3), i.e., exposure assessment, the initial tasks are monitoring workplaces and the development of technologies for this monitoring. At the same time, fate studies in the environment and the prediction of parameters and the environmental kinetics of nanomaterials using computational chemistry are also included. Risks associated with exposure to nanomaterials will be analyzed using results obtained in these studies, and proposals for risk management will be made. Theme (4), i.e., research on social impact, will be started later, in 2007.

There are several research subjects that have not been initiated. First, in the assessment of toxic effects associated with nanomaterials, priority has been placed on the hazards of exposure via inhalation, but hazards posed by exposure via other pathways such as skin exposure should also be assessed in the future. Accordingly, the Japan Cosmetic Industry Association has started working on cutaneous permeability tests of cosmetics containing nanomaterials. Second, biokinetics studies such as ADME (absorption, distribution, metabolism and excretion) are not yet firmly scheduled in the project because there are so many technical difficulties in tracing nanomaterials in the body.

The management of the risk due to nanotechnology is one of the general issues among Japanese Ministries such as MEXT, ME, and MHLW, in addition to METI. The Council for Science and Technology Policy, a cabinet office, is generally involved in drafting plans and coordinating research projects among various offices and ministries. It is expected that other research plans would be developed in cooperation with competent ministries under the authority of the Council for Science and Technology Policy in the future. The outcome of research on nanomaterials in Japan will be reflected in the standardization activities conducted by ISO/TC229 (nanotechnology) as well as in discussions at Organization for Economic Cooperation and Development. It is desirable that, with further enhancement of such international cooperation, a system capable of promoting efficient research by sharing research funds, research goals, and research results should be developed.

**SUMMARY AND CONCLUSIONS**

The United States, Europe, and Japan have devoted substantial resources to promoting nanotechnology for economic, commercial, and societal benefit by allocating significant resources to identifying and developing promising applications...
of the technology. In addition, substantial research efforts are underway in the United States, Europe, and Japan to develop data to facilitate the development of comprehensive risk assessments for nanomaterials in an effort to assess the safety of these materials. There are many common elements to this research. In particular, each has developed extensive programs to evaluate the human health and environmental impacts from exposure to nanomaterials. With regard to human exposure, each of these programs seeks to identify the risks associated with workplace and consumer exposure to nanomaterials and to develop dose-response models for engineered nanomaterials. The United States, Europe, and Japan are also interested in the development of monitoring techniques to assess workplace and environmental concentrations of nanomaterials. Each is also interested in the development of techniques for measuring nanomaterials in a variety of media, including biological fluids and tissues.

International cooperation for standardization of assessment methods and harmonization of risk evaluation techniques will be critical for the development of scientifically rational standards for public health decision making. Given the similarities of the goals associated with the human health and environmental research underway in the United States, Europe, and Japan, the development of formal collaborations and consortiums could facilitate the generation of data for risk assessments in a more efficient manner and minimize duplication of effort. Government agencies in the United States, Europe, and Japan should encourage these collaborations in a way that is transparent and that allow input from a broad spectrum of stakeholders.

There is also a strong interest among government research organizations in the United States, Europe, and Japan to evaluate the utility of existing testing and measurement methods for evaluating nanomaterials. This was identified as a priority for developing strategies for appropriately characterizing nanomaterials. The United States, Europe, and Japan also believe that evaluating the production, use, and disposal of products containing nanomaterials from a life-cycle perspective is important. It does not appear that sufficient data exist currently to accommodate a life-cycle evaluation of nanomaterials. Development of a multidisciplinary, international collaboration to identify and prioritize the critical elements for developing life-cycle assessments for nanomaterials is the requisite initial step for evaluating the full impact of these materials.

There also appear to be research needs that could benefit from additional attention from government research organizations. Specifically, a coordinated effort to determine the most appropriate PPE and handling considerations (e.g., laboratory hood requirements) for those nanomaterials that are the focus of current research efforts would be especially helpful to those conducting research in academic laboratories, industry, and government research institutions. In addition, much of the current research focuses on inhalation exposure. While this route is certainly important, particularly given what is known about the systemic hazards associated exposure to fine-sized particles, it is also important to develop comprehensive programs to address dermal and oral exposure to nanomaterials. While there is considerable activity in these areas underway in the private sector, government, and academia, it is not clear that information generated from these efforts is being communicated or coordinated internationally.

REFERENCES


