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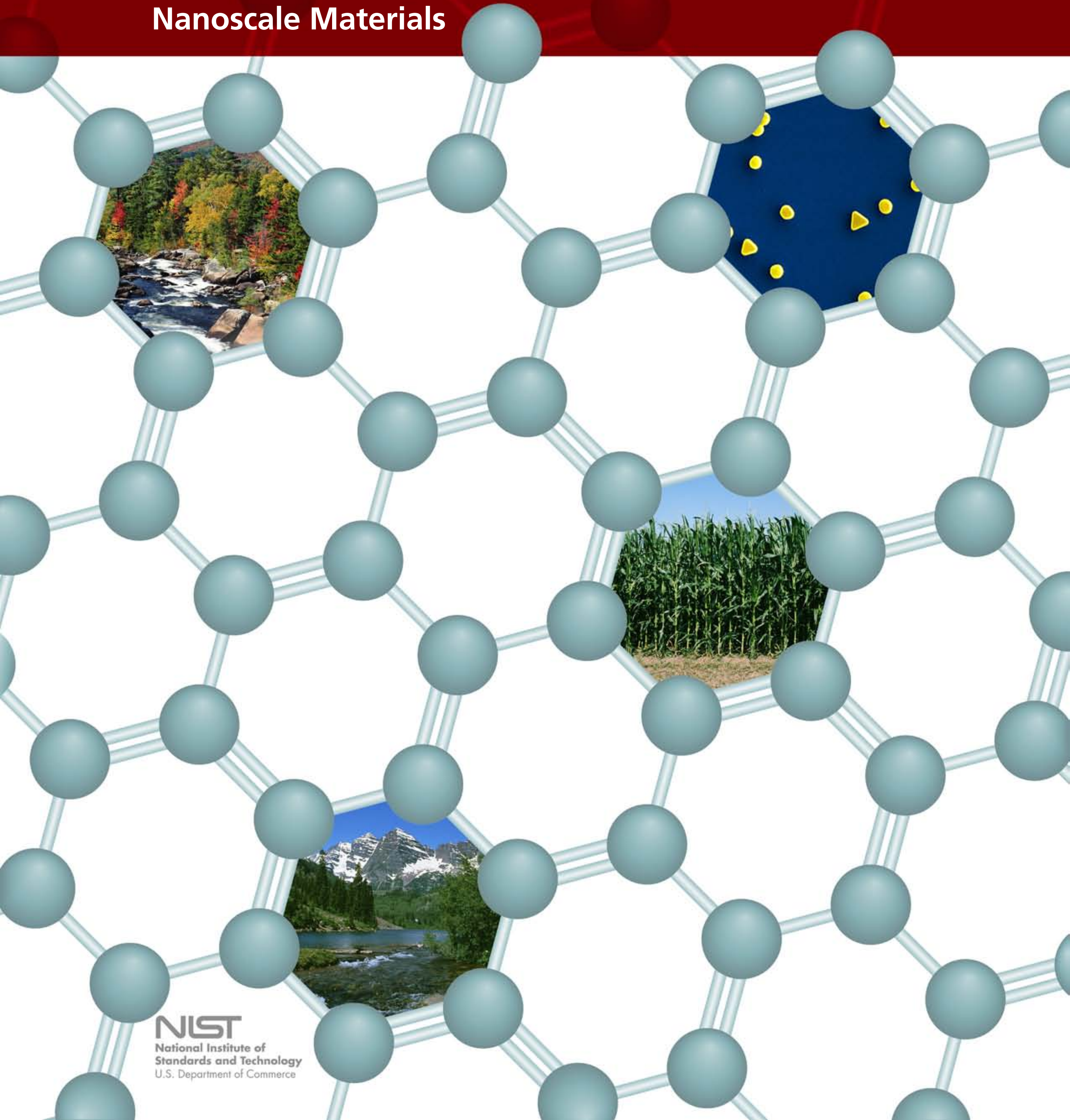
Material Standards for Environmental Health & Safety for Engineered Nanoscale Materials



NIST
National Institute of Standards and Technology
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Material Standards for Environmental Health & Safety for Engineered Nanoscale Materials

September 12–13, 2007

National Institute of Standards and Technology, Gaithersburg, MD

Workshop Co-Chairs and Principle Report Editors

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EXECUTIVE SUMMARY

The National Nanotechnology Initiative (NNI) in its 2006 document, *Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials* (available at www.nano.gov), identifies standards and standard measurement protocols as a critical, crosscutting research area needed ―to ensure full realization of the potential of nanotechnology in a safe and responsible manner." In response to this research need, the National Institute of Standards and Technology (NIST) sponsored a workshop on ―Material Standards for Environmental Health and Safety for Engineered Nanoscale Materials" at NIST in Gaithersburg, Maryland, on September 12–13, 2007.

NIST, in its capacity as the national measurement institute for the United States, identified four goals for this workshop: (1) develop approaches for identifying reference materials for critical risk assessment and risk management; (2) nominate materials specific to user and community needs; (3) identify critical materials characterization parameters required to meet the needs of specific users and communities; and (4) identify priority reference materials, characterizations, and timescales for development. To accomplish these goals, the workshop was organized around four topical areas, each of which was a breakout session topic: (1) environmental fate and transport, (2) human and ecological health, (3) occupational health and exposure, and (4) cross-cutting technology fields and scientific disciplines. Invited representatives from academia, industry, and government identified reference materials and methods needed to address toxicology and assess risks of engineered nanoscale materials for the four topical areas through participation in breakout groups.

Outputs based on discussions and recommendations put forth by the breakout groups are: (1) a set of criteria for the selection of priority reference materials; (2) a list of reference materials that meet these criteria for each topical area; and (3) a list of suggested characteristics for each material.

1) Criteria that are cross-cutting for the selection of priority reference materials include:

- exposure potential
- industrial use and commercial relevance
- hypothesis- or research-directed use
- regulatory importance

Materials suited for reference material production need to be available in variable quantities and different forms (e.g., liquids, solids, suspensions), be cost-effective, and be able to provide useful characteristics or data. Regulatory importance was a criterion that referred to materials that might be subject to regulation due to current use or potential use in future products. The breakout groups discussed current use materials such as titania due to its current use in sunscreens and paint-based products because of its reflectivity, and silver due to its use as an anti-microbial in fabrics and medical materials such as dressings.

2) Recommended materials that are suitable for reference material development and that support the needs of agencies whose representatives participated in the breakout groups include:

- Titanium dioxide (TiO_2)
- Gold (Au)
- Silicon dioxide (SiO_2), both amorphous and crystalline forms
- Fullerene (C_{60})
- Quantum dots
- Metal oxides (Cerium [Ce], Iron [Fe])
- Silver (Ag, not necessarily particulate)
- Carbon nanotubes (CNTs; single-walled [SWCNT] and multiwalled [MWCNT])

- Dendrimers
- Labeled materials (isotopic)

3) A cross-cutting set of characteristics to be determined for the reference materials are:

- Surface charge/distribution reactive oxygen species (ROS)
- Aggregation/agglomeration
- Surface area
- Chemical composition/phase/degree of crystallinity
- Standard surface coating
- Morphology/aspect ratio
- Size/polydispersity
- Reactivity
- Zeta potential

CONCLUSIONS

This workshop sought to provide recommendations for candidate materials suited to develop as reference materials to support measurements and research with respect to addressing environmental, health, and safety aspects of engineered nanomaterials. In this workshop report, candidate materials are identified for each of the topical areas, and their suitability is discussed. In addition, recommended characteristics are provided for each material. The recommendations are offered for consideration by not only NIST but also by other programs, both public and private. These other reference material programs include those that are ongoing with the Organisation for Economic and Co-operative Development (OECD), which, through the Working Party on Manufactured Nanomaterials, has identified fourteen nanomaterials and a range of endpoints to be determined for each of the fourteen materials, and with the Institute of Medicine (IOM) in the UK, which has identified a series of requirements for the further development and promulgation of reference materials for nanoparticles. The outputs from this workshop will also support efforts put forth by the International Workshop on Documentary Standards for Measurement and Characterization in Nanotechnologies held at NIST in February 2008 in conjunction with the International Organization for Standardization (ISO), the International Electrotechnical Commission (IEC), and OECD[1].

NEXT STEPS

The various recommended candidate materials, along with suggested physical and chemical properties for characterization, will be evaluated by NIST and others who support the development of reference materials for consideration in the program areas that have efforts linked to environmental health and safety (EHS) of engineered nanomaterials. NIST will continue to work with the NNI member agencies and the international community to continue efforts on the design and development of reference materials for the physical and chemical characterizations of nanomaterials that are needed for science-based EHS decisions with respect to engineered nanomaterials.

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[1] ISO, IEC, NIST and OECD International workshop on documentary standards for measurement and characterization for nanotechnologies, NIST, Gaithersburg, Maryland, USA, 26 – 28 February 2008 http://www.standardsinfo.net/info/livelink/fetch/2000/148478/7746082/assets/final_report.pdf

1. Introduction

What is Nanotechnology?

Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale.

A nanometer is one-billionth of a meter. A sheet of paper is about 100,000 nanometers thick; a single gold atom is about a third of a nanometer in diameter. Dimensions between approximately 1 and 100 nanometers are known as the nanoscale. Unusual physical, chemical, and biological properties can emerge in materials at the nanoscale. These properties may differ in important ways from the properties of bulk materials and single atoms or molecules.[1]

Currently, knowledge about the exposure levels of individuals in nanotechnology-related jobs is growing but is just beginning to be developed. Standardized methods, reference materials, protocols, and field-ready and affordable instrumentation for exposure measurements are needed to strengthen this knowledge base.[2,3] Utilizing discussions with toxicologists and stakeholders from outside the Government, the workshop described in this report provided guidance on what standards are required to support nanotechnology exposure assessments and to inform sound risk assessment and risk management of engineered nanomaterials. (Photo: Chris Gregerson, www.cgstock.com.)

Nanotechnology holds great promise for developing revolutionary new products and dramatically improving our quality of life in areas as divergent as agriculture, energy resources, consumer goods, and advanced healthcare. The grand possibilities for nanotechnology—which range from sophisticated manufacture of materials at the scale of atoms to creation of complex structures and devices—could revolutionize technology as we know it today.

Materials engineered at the nanoscale often exhibit novel or improved chemical, physical, and biological properties when compared with the same materials in bulk form. In addition, entirely new classes of materials have been created at the nanoscale, offering unique properties not otherwise achievable. Nanomaterials are already being used today in a variety of applications, such as medical imaging, catalysis, solid-state lighting, stain-resistant clothing, cosmetics, and others.

While these new materials offer many potential benefits, their use may also lead to unexpected health and environmental risks. At present, the impacts of new nanomaterials on environmental health and safety (EHS) are not well-understood, in part because the development and use of these materials is so new. To understand and manage the potential risks will require answers to some very fundamental questions. These might include, for example: How do nanomaterials interact with various physical, chemical, and biological systems? Can we accurately measure and assess their potential toxicity or biological effects? What potential routes of exposure to nanomaterials can be expected for humans and the environment, and how can exposure be measured? How do these materials behave after they are released in air, soil, or water?

These questions are made more complex by the need to understand the EHS impacts of the material or product throughout its lifecycle—from development to use and disposal. The challenge is intensified by the wide diversity of possible products and the very different and unique ways each material interacts with the environment. This complicates the management of risks that may be posed by these new materials, and these cannot be easily generalized.

To realize fully the promise of nanomaterials in technology and product innovation will require that technology developers, regulators, and consumers understand the potential impacts on EHS. There is a responsibility by the stakeholders in the nanotechnology revolution to ensure that technology innovation does not reduce the quality of human health, ecosystems, or the environment. We must begin today to understand and monitor the impacts of nanoscale materials on EHS, or we could reach a point where technology innovation arising from nanotechnology is stalled. There are already public perceptions that while nanotechnology has enormous potential to provide benefits, it is an unknown technology and gives rise to safety concerns.

1.1 ROLE OF STANDARDS AND REFERENCE MATERIALS IN EHS OF ENGINEERING NANOMATERIALS

A core requirement for assessing the impacts of new nanomaterials on EHS is the ability to make precise, accurate measurements at the nanoscale in a variety of media. Measurements such as the amount and type of material present in a given space or time are important. In addition, there may be special measurement technology challenges that must be considered that are unique to EHS, such as studying how materials interact with different environments and the ultimate fate of materials once they are discarded.

The suite of methods and technologies currently available for measuring nanomaterials are wide-ranging (see Table 1.1). However, in some cases these are pushing the limits of accuracy, resolution, and other capabilities, or are not geared toward the unique measurement priorities of EHS. In addition, some are in various stages of development and use, do not have standard protocols for how they are used, or might only provide information that is needed for one discipline or application while not addressing others. Documentary standards are under development by standard development organizations such as International Organization for Standardization (ISO) (www.iso.org), International Electrotechnical Commission (IEC) (www.iec.ch), and ASTM International (www.astm.org). A 2008 workshop at NIST focused on specifically identifying and exchanging information on existing documentary standards, standardization programs, and emerging needs in the field of measurement and characterization for nanotechnologies, including pre- and co-normative research and reference materials.[4]

Standards and, in particular, reference materials play a key role in understanding the EHS impacts of engineered nanomaterials.[2,5] Reference materials for emerging engineered nanoscale materials can provide key information about the characteristics of those materials and their chemical, physical, biological, and other properties that are consistent regardless of how they are applied. They provide researchers with a standardized, acceptable way to study, monitor, and potentially track nanomaterials as they are released into the environment and the workplace, and to assess their potential interactions with human and ecological systems. Reference materials, along with protocols for their development and use, can provide consistency in measurements of critical nanoscale materials. Nanomaterials of known composition are extremely important to meaningful EHS research.[3]

Generally, reference materials are defined as materials or substances whose property values are sufficiently homogeneous and well established to be used for calibrating an apparatus, assessing a measurement method, assigning values to materials, or for assuring quality control (e.g., product or production quality). The properties obtained from a reference material may be quantitative (e.g., amount or size of substances or species) or qualitative, (e.g., identity of substances or species). In addition, reference materials may be certified, i.e., where property values are certified as traceable in some way and the certified values are accompanied by a stated level of confidence.

Table 1.1 Methods Commonly Used for the Characterization of Nanomaterials[2]

Property	Methods and Instrumentation
Size Distribution	Microscopy Methods: • Transmission Electron Microscopy (TEM) • Scanning TEM – S(TEM) • Scanning Electron Microscopy (SEM) • Scanning Probe Microscopy (SPM) • Atomic Force Microscopy (AFM) • Scanning Tunneling Microscopy (STM) Dynamic Light Scattering (DLS), Field Flow Fractionation (FFF) with Multi Angle Laser Light Scattering (MALLS), Ultrafine Condensation Particle Counter (UCPC) by Pulse Height Analysis (PHA), Single Particle Mass Spectrometry, Scanning Mobility Particle Sizer, Full-Pattern X-ray Powder Analysis, Raman Spectroscopy, Small Angle X-ray Scattering (SAXS), Small Angle Neutron Scattering (SANS), Acoustic Methods
Agglomeration State	Centrifugation, Analytical Ultra-Centrifugation, Disk Centrifuge, Laser Diffraction Spectrometry (LDS), Ultra-Small Angle X-ray Scattering (USAXS) ,SANS, Zeta Potential (electrophoretic light scattering)
Shape	Microscopy methods (see above), DLS and MALLS, X-Ray Diffraction (XRD), Electron Holography, Surface Enhanced Raman Spectroscopy (SERS), SAXS, SANS
Crystal Structure	Electron Diffraction, XRD, SAXS, Neutron Diffraction
Surface Charge	Zeta Potential (electrophoretic light scattering), Potentiometric Titration, Electroaccoustics
Surface Area	Gas Sorption Analysis – Brunauer, Emmett and Teller (BET) Isotherm, SERS, SAXS, SANS
Surface Chemistry	Raman, Infrared, X-ray Photoelectron, Auger Electron, and Combinatorial Near Edge X-ray Absorption Fine Structure Spectroscopies, AFM
Porosity	Gas Sorption Analysis
Chemical Composition	Auger Electron, Atomic Emission, Absorption, Fluorescence, Mass, and X-ray Photoelectron Spectroscopies, NMR (Raman and IR), XRD, Near-field Scanning Optical Microscopy, AFM, SEM/Energy Dispersive X-ray Spectrometry (EDS), (S)TEM including (Selected Area Electron Diffraction (SAED), Convergent Beam Electron Diffraction (CBED), Energy Filtered TEM (EFTEM), Electron Energy-Loss Spectrometer

[2] As some of the nomenclature is unique to this field, glossary and acronym tables are provided in Appendices D and E, including definitions of reference materials and related terms.

Property	Methods and Instrumentation
	(EELS), Electron Back Scattered Diffraction (EBSD) and EDS)
Solubility	Static Light Scattering, phase equilibrium measurements using analytical methods

Reference materials may be used by researchers or product developers to evaluate and qualify the behavior or nanomaterials. For example, gold nanoparticle reference materials (RMs 8011, 8012, and 8013) developed by NIST are being used to evaluate and qualify the methodology and instrument performance related to the physical and dimensional characterization of nanoscale particles in pre-clinical biomedical research. The gold reference materials will also be useful in the development and the evaluation of *in vitro* assays designed to assess the biological response (e.g., cytotoxicity, hemolysis) of nanomaterials (See www.nist.gov/srm).

Equally important are the protocols that accompany reference materials. These provide consistency in interpreting data obtained via reference materials; ensure that the reference materials can be used in the same way across disciplines and applications; and provide a standard way to use the reference materials in different mediums (e.g., as an aerosol or in a soluble form). This consistency is vital to regulators, product developers, and researchers alike—it ensures they can publish and compare their work in a consistent manner and that there will be a common understanding and interpretation of results.

1.2 WORKSHOP OVERVIEW

To better explore the critical measurement needs related to the EHS impacts of nanomaterials, a workshop was held on September 12–13, 2007, in Gaithersburg, Maryland. The workshop was hosted and led by NIST, sponsored by NNI, and had ample participation from NNI member agencies. The workshop was attended by experts in the fields of EHS, nanotechnology, and measurement science. Representatives from government, industry, academia, national laboratories, and other institutions, including international organizations, provided their perspectives on the emerging issues related to the critical measurement needs for nanomaterial EHS, standards, and reference materials. Regulatory agencies were well represented. A list of participants and contributors to this report can be found in Appendix A. The goals for this workshop were to: (1) develop approaches for identifying reference materials for critical risk assessment and risk management; (2) nominate materials specific to user and community needs; (3) identify critical materials and characterization parameters required to meet the needs of specific users and communities; and (4) identify priority reference materials, characterizations, and timescales for development. To meet these goals, breakout groups centered on four topical areas (environmental fate and transport, human and ecological health, occupational health and exposure, and cross-cutting issues) to discuss:

- overarching challenges and considerations for reference materials and standards related to nanomaterials EHS
- the benefits of potential approaches to nominating and prioritizing candidate reference materials for evaluation and study of nanoscale EHS
- important candidate reference materials for specific user communities
- vital characterizations for each nominated material to support EHS research needs
- barriers related to development and use of identified materials

- technology barriers that would need to be addressed to overcome these challenges and enable reference material development
- timelines (near-, mid-, or long-term) for production of specific reference materials

The workshop began with a plenary presentation by Dr. Altaf Carim, co-chair of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council (NSTC). Topical technical presentations followed the plenary presentation and were interspersed with breakout sessions. Prior to the breakout sessions, general group discussions enabled all participants to provide input to the topical areas. The agenda for the workshop is provided in Appendix B.

The workshop focused on reference materials related to nanoscale EHS, not the whole spectrum of measurement science in this field. The scope included the potential impacts of nanomaterials on the environment (air, soil, water); general human and ecological health (biological systems) considerations with respect to the current science and science-based research needs; and issues unique to exposure in the workplace. The breakout topics are described in more detail in Table 1.2. In addition to the specific topics related to nanomaterials EHS, the workshop also included a session to cover some of the potentially cross-cutting issues and challenges with respect to engineered nanomaterial reference materials. Prior to the workshop, participants were provided with a list of nanomaterials to consider as possible reference material candidates. This list is provided in Appendix C.

Table 1.2 Descriptions of Workshop Breakout Topics

Materials for Environmental Fate and Transport	Materials for Human & Ecological Health	Materials for Occupational Exposure	Cross-Cut Issues in Development of Standard Materials
Reference materials for assessing environmental exposure to nanomaterials in air, water, and soil, including how these materials are transported once released, and their subsequent behavior and fate (e.g., mixing, dispersing, concentrating, agglomerating, decomposing, reacting).	Reference materials to support assessment of the biological response to engineered nanoscale materials via environmental or non-incidental exposure to humans and other living systems (terrestrial and aquatic plants and animals) including effects on sub-cellular components, cells, tissues, organs, organ systems, and whole organisms (e.g., bioaccumulation, toxicity).	Reference materials for risk assessment, risk management, and characterization of nanoparticle exposure in the workplace via inhalation, ingestion, skin absorption, or other routes; includes materials to support international consensus standards for nanoparticle exposure.	Cross-cut areas that impact multiple users and communities, including, although not limited to, challenges in universal material considerations, experimental methods, production (sources, volumes), timing, and cost. In addition, policy considerations, international cooperation, inter-laboratory comparisons, and interagency collaboration and coordination are essential cross-cutting elements for reference material development.

1.3 THE REPORT

This report is based on the discussions and recommendations resulting from the workshop held on September 12–13, 2007, and the presentations provided by plenary and other speakers. As noted, the appendices provide key background and other information.

Following this introductory chapter, an overview of the challenges and considerations related to nomination of reference materials important for investigating nanomaterial EHS is given in Chapter 2. This is based on general session discussions that followed the topical presentations. The remainder of the report is organized around the four breakout topics shown in Table 1.2, with a chapter devoted to each.

As some of the nomenclature is unique to this field, selected terms and acronym tables are provided in Appendices D and E, including definitions of reference materials and related terms.

1.4 REFERENCES

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2. Considerations and Challenges for Nanotechnology EHS

2.1 Considerations for Setting Priorities

Understanding what types of reference materials are most relevant to elements of engineered nanomaterial EHS calls for the development of a clear strategic approach due to the complexity of the issues. Reference materials are needed for all components of a nanomaterial's life cycle, from synthesis to use to disposal. Reference materials are also needed for the research components that support both human health and environmental decision making needs, from exposure assessments to biological response. Important considerations and challenges for strategic priority-setting are summarized below.

Relevance of Reference Materials

Understanding where we need to be in 5 years in terms of EHS studies at the nanoscale is critical to setting priorities today (e.g., the priorities given expected advances in development and use of nanomaterials). The process involved in developing a reference material may take years to complete, and with the rapid emergence of new materials, a reference material might not remain relevant or might need to be adapted for different purposes. Understanding future challenges for commercial products, as well as needs of other stakeholders including the regulatory community, remains a challenge for long-term reference material development plans. In other words, priorities need to be revisited every few years (or sooner) to ensure relevance and direction of efforts.

Selection Based on Critical Need

Creating an optimal list of candidate reference materials is driven by key criteria such as:

- Exposure potential. Materials that are most likely to be released into the environment would be favorable candidates for reference materials.
- Industrial-use potential and commercial relevance. This includes materials with low-volume use but with high impact, or ones with potential uses across different products.
- Priority industry or other stakeholder needs. Meeting needs of diverse stakeholders (research, government, commercial) presents unique challenges when funds for development are limited.
- Relevance of hypothesis or research-directed use versus commercial use.
- Regulatory importance. This refers to materials that might be subject to regulation due to current use or potential use in future products.
- Novelty or relevance of materials. This reflects the potential for development of challenging materials that push the edge of science as well as meeting both near- and long-term needs.

Application Dependence

Priorities can also be impacted by the nature of the application, e.g., whether it will be used in the context of establishing a library of materials versus addressing a specific critical issue. In some cases, it may not be clear whether a reference material is the right approach or how the material will be used. Questions that need to be answered include, "Is a reference material the best way to obtain useful information, given the problem?" or "Is the reference material for calibration or for other uses?" Questions such as these demonstrate how a specific reference material is chosen based on the intended use of the material.

2.2 UNIQUE ISSUES FOR DEVELOPING AND USING REFERENCE MATERIALS

In considering the nomination of materials, important considerations arise as to how useful the material will actually be in meeting the need and addressing the problem. Materials may need to be available in variable quantities and in different forms, be cost-effective, and be able to provide useful characteristics or data.

Production Issues–Volume, Format, Cost, and Consistency

Materials must be producible in large, homogeneous quantities and in useful structures and forms, and for different applications (e.g., fundamental vs. applied research, or research for commercial purposes). Materials may be needed in different formats (e.g., liquids, solids, suspensions, or all ranges of nano-sizes). Producing consistent material can be difficult since the properties of materials often vary at the nanoscale among batches. The cost of material versus the amount needed may be an issue (e.g., an *in vivo* study could require large quantities of materials depending on the scale of the study). The ready availability of sufficient amounts of material at a low cost will enable wider usage of the material. Profitability may also be an issue for commercial material vendors.

Reproducible Results

Measurements should be reproducible across labs, agencies, and the globe to the extent possible within a specified interval around a reference material measurement value, such as particle size, regardless of whether the material is designed for instrument calibration, toxicology, or other use. The use of the material needs to be clearly defined and, more importantly, protocols that may be specific for a material should accompany the reference material. For example, if a dry material needs to be suspended in solution prior to or during the measurement process that is used to obtain the measurement value, protocols that describe these procedures should be provided with the reference material. Moreover, protocols should be the same as those used to obtain the reference or information data for the reference material. This type of information ensures that reference materials can be used properly with respect to their intended functions, and that consistent, quality data will be available for science-based decision making needs. In addition, the relevancy of results to field measurements is clear.

Justification of Use

In some cases, the cost and use of a reference material in an actual operating environment might not be justified. Rather, existing materials that are available, e.g., commercially available TiO_2 or CNTs, might be sufficient proxies that generally cost less and are easily obtainable for toxicology testing. The downsides of this approach are: (a) the materials may not be pure and thus it will be unclear what caused an effect if one is noted, and (b) the materials may not be homogeneous and thus comparability of data will be difficult not only between experiments but also between different investigators. As nanoscale reference materials become more readily available and reported use begins to proliferate in the literature, such events will likely become less prevalent. Hence it is important to make available homogeneous, well-characterized materials at a reasonable cost for small businesses or manufacturers and academic investigations.

Key Characteristics—Size, Shape, and Surface

Characterization issues arise as size approaches the nanoscale because surface effects dominate. Understanding the effect of a particle’s size is an important consideration for characterization and prospects as a reference material. Toxicity, for example, has size dependency that requires a range of materials to be used, and different chemistries may be needed for different size ranges. There may be a need to make measurements in different mediums (e.g., wet, dry), where particle size varies. This is well documented for particle sizing in the micrometer regime. Particle size instruments can vary between manufacturers and even between manufacturing lots. The sensitivity of these instruments is not consistent among instruments and is a major concern. Aggregation and flocculation over time can also impact metrology of size; particle size determinations can be affected by aggregation phenomena that can occur over the timescale of preparation and storage.[1] Materials with nonspherical shapes (e.g., rod-shaped) also create characterization challenges. Shape characterization models often are based on spherical assumptions, which can be oversimplifications. Shape is thought to be one of the driving factors of nanoparticles that affect their toxicity. Overall, surface features such as surface charge, surface area, and surface contamination introduce complicating characterization issues that should be considered when nominating nanoscale materials for reference material development.

Instrumentation and Method Limitations

In theory, any analytical technique can be applied to the measurement of nanoparticles if modified correctly, and the range of techniques available is bewildering to the nonspecialist. Results may also be different between users of the same instruments with the same materials. For example, even for simple measurements such as particle diameter, the media and the technique can affect results dramatically at the nanoscale. A fundamental requirement should be detailed reporting on the measurement technique in use, as discussed above in regard to the reproducibility of results.

Stability

A reference material needs to have extended shelf life, i.e., be able to be stored for extended periods of time without reacting or changing properties. In some cases, the material medium can extend shelf life. Materials delivered as a dry powder, depending on the nature of the material, might be more stable relative to the same material in a solution. In other cases, special storage environments, such as a dark or cold environment, may be required, and these should be clearly indicated for the reference material. As homogeneity is a critical factor for a reference material, stability presents practical limits on their production.

Formulation

The unique formulations of nanoparticles in industry create challenges for identifying hazards and assessing potential impacts to human and ecological health. Attempting to meet the needs of many different stakeholders with a limited number of candidate reference materials adds to the challenges placed on reference materials.

2.3 REFERENCES

1. R.J. Aitken, S.M. Hankin, C.L. Tran, K. Donaldson, V. Stone, P. Cumpson, J. Johnstone, Q. Chaudhry, S. Cash, *REFNANO: Reference materials for engineered nanoparticle toxicology and metrology, Final report on Project CB01099*, Institute of Occupational Medicine, Edinburgh, UK (2007). www.iom-world.org/pubs/REFNANOReport.pdf

3. Environmental Fate and Transport

This breakout session addressed environmental exposure to nanomaterials in air, water, and soil, including: the determination of the fate and transport of engineered nanomaterials once they are released into the environment; the assessment of environmental exposure to nanomaterials via the atmosphere, soil, and aqueous systems such as streams, lakes, and rivers; and the understanding of their subsequent behavior and fate within and between environmental compartments via mixing, dispersing, concentrating, agglomerating, decomposing, reacting, partitioning, or transformations. The requirements for standards under this topical area indicated the materials need to be well characterized with consistent properties and quantifiable in the various environmental matrices. In addition to the physical standards, this group also stressed the need for validated protocols for dispensing the reference materials in soil, air, or water to facilitate intra- and inter-laboratory comparisons. Questions specific to the selection of candidate materials for this category included a series of questions related to performance criteria, production logistics, and projected potential for environmental exposure. Based on these criteria this group identified C_{60}*,* TiO_2*, and quantum dots as priority candidate materials for standards in environmental fate and transport.*

Complete knowledge about the environmental fate and transport of nanomaterials must account for a host of factors, including bioavailability, bioaccumulation, and persistence. Investigations may address diverse types of environmental media: air, water, soil, sediment, and plant and animal matrices. Istopically labeled nanoscale reference materials would be advantageous and practical for assessing environmental fate and transport of nanomaterials in such media. (Photo © Steve Heap/Shutterstock.)

3.1 Current Scientific and Technical Advances

Reference materials and related standards for environmental fate and transport studies are needed to assess environmental exposure to nanomaterials in air, water, and soil. Important environmental fate and transport processes include dispersion, bioaccumulation, biomagnification, agglomeration, and abiotic and biotic transformation. Each process, as well as the environmental matrix into which the material is released, gives rise to unique measurement characteristics and needs. In addition, the synergistic effects of nanomaterials combined with other contaminants or naturally occurring compounds, mobility from one media to another, and ultimate fate are important considerations. Reference materials with known properties and characteristics can help to facilitate the study of how nanomaterials behave when released into the environment. The development and testing of standard protocols to measure nanomaterials in air, water, and soil also represent a significant need.

While our understanding of the transport and fate of engineered nanomaterials in environmental matrices (e.g., soil, sediment, water, and air) is in its infancy, significant progress is underway. In the U.S., the Environmental Protection Agency (EPA) Science to Achieve Results (STAR) program is the primary funding source for much of this research, although funding levels have been limited. In 2008 the National Science Foundation (NSF) and EPA will fund a new Center for the Environmental Implications of Nanotechnology, and NSF plans to form a network around the Center in 2009 with collaboration from EPA and other agencies.[1] The European Union also has a grant program focused on the potential environmental impacts of nanomaterials. Most studies aim to understand the behavior of engineered nanomaterials upon release to air, water, or soil, including aggregation/agglomeration [2,3,4], mobility in porous media [5,6,7], and the effects of environmental constituents (e.g., natural organic matter) on these physicochemical processes.[8] More recently, the effect of biological activity on nanomaterial properties has been reported.[9] Our current understanding of these processes is based on principles of traditional colloid science through application of extended Derjaguin, Landau, Verwey, and Overbeek theory (DLVO) theory, filtration theory, and others.[10]

Existing Materials and Instrumentation

Detection and quantification of nanomaterials in the environment is extremely difficult and challenging, even with existing state-of-the-art capabilities, and often, beyond state-of-the-art capabilities are necessary. An NNI report on *Nanotechnology and the Environment* states: ―From the standpoint of environmental measurement, problems exist in measuring anthropogenic and natural nanoparticles that are present in the soil, air, and water. Particles in liquid phases present unique measurement challenges. Little is known about the diversity of chemical composition at the nanoparticle level and the transformations that occur.”[11] In fact, nanotechnology itself may provide the ways and means to better measure and detect nanomaterials in the environment through the development of new sensors or instruments that are constructed with nanomaterials.[11]

Most investigations on nanomaterials in the environment to date have investigated readily available engineered nanoparticles including C_{60}s, CNTs, metals (e.g., Fe), and metal oxides (e.g., TiO_2), since these materials are available commercially and are expected to be widely used and possibly dispersed in the environment. Most studies have used ―bare” nanoparticles, with some notable exceptions where the effects of surface modification are under investigation.[12,13] Standard instrumentation has typically been used to measure, determine, and/or monitor:

- Size distributions and aggregation/agglomeration (dynamic light scattering, electron microscopy, micro-orifice uniform deposit impactor [MOUDI], differential mobility analyzer) [14]
- Chemical composition (inductively coupled plasma mass spectrometry [ICP-MS], X-ray techniques)
- Surface chemistry and the presence and absence of coatings (X-ray photoelectron spectroscopy [XPS], Raman spectroscopy, thermogravimetric analysis [TGA])
- Crystallinity, morphology, and structure (transmission electron microscopy [TEM], electron diffraction, X-ray diffraction) [15,16]
- Specific surface area (nitrogen Brunauer, Emmett, and Teller analysis [N_2 BET])

However, nonstandard techniques have been applied to measure the production of reactive oxygen species (ROS).[17]

Ongoing R&D Advances

Ongoing research and development (R&D) generally focuses on the environmental implications of nanotechnology, particularly environmental distribution, bioavailability and ecotoxicity, transformation processes, and life cycle analysis. Both engineered (e.g., drinking water and wastewater treatment facilities) and natural environmental systems (e.g., sediments) are under investigation. Nanomaterials currently under investigation in the environment generally include carbon nanoparticles (C_{60} and CNT), metals and metal oxides, quantum dots, and dendrimers. R&D in selected areas includes:

- **Fate.** The ultimate fate of carbonaceous nanomaterials in sediments and biofilms and during drinking water and wastewater treatment is being studied.

- **Transport and physical/chemical processes affecting transport.** The transport of nanomaterials in the vadose zone and in the saturated zone is being investigated. In addition, fundamental processes affecting transport and partitioning are being investigated, including aggregation/agglomeration and air-water exchange.
- **Transformation.** Alteration of nanoparticle surface coatings by abiotic and biotic processes is being investigated, as well as the effects of such alterations on bioavailability, ecotoxicity, and transport.
- **Bioavailability and ecotoxicity.** Significant efforts are underway to evaluate the ecotoxicity, bioavailability, and trophic transfer of nanomaterials released into the environment. These studies encompass multiple levels of biological organization from subcellular to ecosystem-level effects, cover a range of organisms from bacteria to vertebrates (e.g., fish, amphibians), and include both aquatic and terrestrial ecosystems. Efforts are also underway to relate nanoparticle structure (e.g., composition, size, surface chemistry, shape) to observed toxicity.
- **Metrology.** New methods to isolate nanoparticles from environmental matrices (air, water, soil/sediment) and quantify them are under development.
- **Life Cycle Analysis (LCA).** Life cycle analyses of nanomaterials are being conducted to determine the differences in environmental effects between nanomaterials and those bulk materials they may replace.

The American Chemical Society's Division of Environmental Chemistry and the Energy & the Environment Section sponsored a special session on ―Environmental Behavior and Fate of Manufactured Nanomaterials" at the Society's Annual Spring Meeting in 2008.[18]

3.2 KEY CONSIDERATIONS AND CHALLENGES

A number of overarching challenges impede the development and effective use of standardized materials for studying and understanding the environmental fate and transport of nanomaterials. These include the following.

Identification and Nomination of Standard Materials

In general, reference materials or some form of standard test materials must be available to environmental researchers. These materials should be well characterized, consistent in their properties, and be quantifiable in different environmental matrices. In addition, standard protocols to disperse these materials in air or in water are needed to ensure that comparable results are achieved in different labs. This will allow the research community to know, with a high degree of certainty, the properties of the starting materials, and it will facilitate comparisons among studies because they begin with the same starting materials in terms of, for example, size, morphology, or surface chemistry. These direct comparisons will advance our understanding of the fate and transport of these materials in the environment.

Characterization Challenges and Limitations

The chief difficulty in selecting a reference material or a standard test material is the inability to fix all parameters (e.g., chemistry, morphology, etc.), except for the one parameter being evaluated (e.g., size). Reference materials can serve as a benchmark against which the behavior of other (similar) particles are measured, and facilitate hypothesis testing. A second overarching challenge is the current inability to isolate, detect, and quantify nanomaterials in environmental matrices. Many study results are difficult or impossible to interpret without accurate quantification. A third challenge is the lack of standard protocols for dispersing nanoparticles in environmental or exposure media. This complicates interlaboratory comparisons of even basic data such as particle size distributions. Specific characterization challenges include:

- Difficulty in obtaining nanoparticles of identical chemical composition and morphology across relatively broad size ranges using a single synthesis method.
- Ability/inability to synthesize particles with only one stable phase (e.g., TiO_2 of 100% rutile).
- Inherent instability of aqueous nanomaterial dispersions; lack of protocols to reproducibly disperse powders in solution.
- Difficulties in obtaining materials of sufficient purity and quantity with known properties.
- Difficulty accurately characterizing surface chemistry and particle behavior in situ in environmental matrices (e.g., adsorption of contaminants, aggregation/agglomeration, surface interactions in general).
- Difficulty applying idealized materials to real-world environmental situations (i.e., testing does not account for transformations of particles that may occur over time in the environment).

Because the range of nanoparticles under development is large and evolving, as are the types of surface coatings that may be applied, the dynamic nature of the field argues that periodic assessment of types of reference materials is needed.

3.3 STRATEGY FOR SELECTION OF REFERENCE MATERIALS FOR ENVIRONMENTAL FATE & TRANSPORT STUDIES

A number of factors were identified to aid in the selection of reference materials. These included possible selection criteria, questions that should be answered, and other strategic factors.

Materials Selection Criteria

In addition to expert knowledge and understanding of this area among participants, a basic set of criteria was used in the selection process for candidate materials. Since the objective is to understand how nanomaterials behave once they are released into the environment (regardless of source), the questions in Figure 3.1 were deemed important to answer.

It was also deemed important to consider issues of logistics; potential breadth of applications

Understanding How Materials Behave

- Does the material aggregate or agglomerate? Under what conditions?
- How do environmental constituents (e.g., natural organic matter) affect nanoparticle fate and transport?
- What is the material's partitioning behavior (i.e., in which environmental compartment(s) do we expect to find the materials)?
- How reactive is the surface (e.g., redox transformations, photoactivity, ability to produce ROS)?
- Does it have the ability to hydrolyze, hydroxylate, dissolve, biotransform, bioaccumulate, or biomagnify?
- Can we quantify potential releases and potential exposure concentrations?
- Do the materials alter the natural cycling of elements (e.g., carbon, nitrogen, iron)?
- Can nanomaterials reduce or enhance the transport or bioavailability of existing contaminants [e.g., polychlorinated biphenyls (PCBs), heavy metals, pesticides]?

Materials Logistics and Usability

- Can the material be produced and stored in a stable form?
- Can the material be detected in environmental matrices?
- Is the material readily available?
- Can the material fulfill multiple needs or be used to answer multiple questions?
- Is the material widely used and applied now or will it be in the near future? Is it industrially significant? Are there multiple uses?
- Do relevant benchmarks already exist for the material, and to what extent has it been studied?
- Is there a high potential for exposure to or release of the material? Is there a high potential for subsequent impacts on air, soil or water?

Figure 3.1 Essential questions relevant to reference materials for fate & transport.

given potentially constrained funding for development of these materials; and urgency (e.g., current exposures, diversity of existing use, potential for future use). From this perspective, a set of questions were formulated to serve as a basis for materials selection (see Figure 3.1).

Selection of Materials

Ideally, a strategy for developing reference materials to study nanoparticle environmental fate and transport would encompass a number of elements that maximize their utility, since only a limited number of materials may be developed. The ideal elements of this strategy are shown in Table 3.1.

Table 3.1 Essential Elements for Selecting Suitable Reference Materials for Environmental Fate & Transport Research

Availability	Ability to procure sufficient quantities of material at a reasonable cost will aid in the more widespread use of the materials by a diverse set researchers.
Range of Particle Sizes	Size ranges below which quantum effects become important and surface activity increases should be considered. This is where particles become difficult to characterize and new metrology may be required, and where new approaches may be needed to understand their fate and transport properties. The objective is to understand the effect of particle size on mobility and fate, and a range of sizes relevant to exposures or releases in the environment would be important (i.e., study of realistic conditions that simulate releases, if possible).
Staged Work on Reference Materials	Work should be staged to include materials that are feasible now. Work should be initiated for the long term as well. However, the slate of materials available and in use is continually changing. Materials that are important now may not be in use in 5 years. The process will need to be dynamic to consider emerging environmental issues.
Range of Materials	Select a set of materials that includes: • Both carbon-based and hard/soft metal nanoparticles to facilitate study of the diverse effects of different material types on the environment. • Redox active materials, because these have a greater tendency to transform and react once they are released to the environment and are therefore more likely to adversely affect living organisms; include a more benign and unreactive material to serve as a control. • Photocatalytic materials that produce ROS or are likely to readily donate electrons and therefore are likely to adversely affect living organisms.
Consistent Parameters	Select consistent parameters across the board, including those of most interest; consider that some parameters will be more difficult to measure and understand in the near-term, and that staged characterization of materials of reference might be needed (e.g., early release of material with well-known size and chemical composition; later release of material with reactive properties characterized).
Standardized Protocols	Reference nanomaterials should be supplied with standardized protocols for storage, dispersion, etc., as well as how to take consistent measurements, calibrate properly, and so forth. ASTM would be a necessary part of this protocol vetting at some stage. Example: A standard protocol to disperse a solid reference nanomaterial in water, with specific reproducible properties measurements that are well characterized after it has been dispersed.

3.4 NOMINATED MATERIALS FOR ENVIRONMENTAL FATE & TRANSPORT

Priority Materials

Table 3.2 lists all materials selected as potential reference material candidates for environmental fate and transport. The following materials were ranked as being some of the most important for studies in this area:

- Carbon 60 (C_{60}), particularly isotopically perturbed fullerenes
- Titanium dioxide (TiO_2) in both rutile and anatase forms
- Quantum dots of various compositions (cadmium selenide [CdSe], cadmium sulfide [CdS], and lead sulfide [PbS] cores are often used, but many other compositions are possible)
- Iron oxide (ferrous oxide, Fe_nO_m) in multiple phases
- Carbon nanotubes, both single-walled and multiwalled

The rationale behind the selection of these materials also is shown in Table 3.2. Materials were ranked based on strategic and other selection criteria as discussed.

As outlined above, the objectives for developing reference materials for environmental fate and transport studies are quite different than those for workforce health and safety or for manufacturing nanomaterials. The key materials nominated in Table 3.2 reflect these unique considerations, which necessarily focus on understanding how nanomaterials behave after they are released to soil, air, and water.

While not a class of nanomaterial, surface coatings are also important. These can be used on many types of nanomaterials, and are another factor that should be considered in environmental fate and transport, as they may affect how the nanomaterial behaves in certain conditions. For example, coatings often modify the surface chemistry and consequently the environmental behavior of nanoparticles. Understanding the performance and behavior of these surface coatings is important, particularly their stability.

Figures 3.2 through 3.5 summarize the key characteristics, characterization needs, performance requirements, barriers, and needed R&D activities for four of the priority materials selected. The summary figures for each priority material illustrate their unique requirements and performance characteristics. However, there are a number of overarching characterizations that are important for studying environmental fate and transport of nanomaterials and apply to all the priority materials selected. While not repeated in each material summary, they are assumed to apply to all reference materials in this area. These overarching characterizations are summarized in Table 3.3.

Table 3.2 Nominated Materials: Environmental Fate and Transport

Material	Rationale
C_{60}	• Isotopically perturbed fullerenes (e.g., ^{14}C) would be desirable to facilitate environmental fate and transport studies • Colloidal properties; has a tendency to form aggregates • Aggregates in water • Used industrially
Titanium Dioxide	• Widespread use in products today (significant potential for release) • Photocatalyst
Quantum Dots	• Easy to measure and track • Surface modification relatively easy • Well-understood optical properties • Not industrially significant, but are excellent tracers (e.g., application of dots in storm water management, biomedical applications, potential application building surfaces)
Iron Oxide	• Direct release into environment for contaminant remediation • Natural iron oxides are important constituents of soils and sediments
Carbon Nanotubes	• Isotopically perturbed carbon nanotubes would be desirable to facilitate environmental fate and transport studies • Single wall and multi-walled • Rigorous reference protocol for producing nanotubes (synthesis) needed; protocol would always be attached to material (comparable catalysts for synthesis, process, feedstocks, purification, etc.)
Fumed Silica	• Current use in products, continually emerging in new products • Universally used material
Cerium Oxide	• Potential use as diesel additive (approved in the European Union, not in the United States.) • Use in chemical/mechanical polishing
Copper Oxides	• Potentially high toxicity as a nanoparticle
Zinc Oxides	• Widespread use in sunscreens • Potential for wide release in surface waters • Photocatalyst
Dendrimers	• Potential use as markers in drug delivery
Nanoparticle Coatings	• Coatings modify surface chemistry and environmental behavior of nanoparticles • Need to understand instability/how to impart stability to coatings • Protocol for how you prepare/use the particle, how it becomes coated (e.g., salts, etc.)
Silicon Nanowires	• Emerging technology, but could potentially be widely used in various products

C_{60}

In powder form, with a protocol for dispersion in liquid; available in isotopically labeled quantities for use as a test material.

Major Applications or Problems Addressed

- Good reference material that forms highly stable aqueous dispersions
- Enables measurement in environmental matrices, where labeling is essential
- Possible benchmark material for facilitated transport (e.g., carbonaceous nanomaterials)
- Possible benchmark for ROS generation

Performance Requirements

- Ability to detect (trace) and quantify (e.g., specific activity—ability to identify how much/concentration of carbon labeled)
- Availability in gram quantities for projects

Unique Characterization Needs

- *Labeling (isotopically perturbed ^{14}C)*
- *Specific surface area in powder form*
- *Surface contamination*
- *Purity of n-C_{60} versus amorphous carbon or other impurities*

Barriers and Challenges

- *Achieving sufficient isotopic enrichment to allow measurement in environmental matrices*
- *Cost of material (enriched carbon)*
- *Potential difficulties in characterizing surface and contaminants to obtain purity*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 years)
Secure supply of fullerenes and labeled fullerenes, and validate labeling	Validate labeling of fullerenes; Determine composition and purity	Obtain particle size distribution; Establish protocol for dispersion in liquid; Determine & measure ROS generation; Deliver product in powder form

Figure 3.2 Environmental fate and transport—priority reference materials (C_{60}).

TITANIUM DIOXIDE (TiO_2)

Rutile and anatase crystalline forms; one set composition; depending on test/study requirements, also available in powder form, or powder dispersed in liquid (requires protocol)

Major Applications or Problems Addressed

- Validate metrology/laboratory measurements through instrument calibration
- Possible use as a test material for transport or other environmental studies (e.g., portioning, uptake, ROS generation, etc.)

Performance Requirements

- Reactive oxygen species
- Aggregation curves or rate of aggregation, aggregation size
- Mono-dispersed samples
- Availability in smaller quantities (e.g., grams)

Unique Characterization Needs

- *Size, shape, and surface chemistry*
- *Optoelectronic properties such as band gap, etc. (UV-sensitivity)*
- *Surface charge density*

→

Barriers and Challenges

- *Uncertainties in ROS speciation*
- *Differing synthesis methods used for different size ranges*
- *Ability to get only one phase*
- *Stability of suspensions; reproducibility of dispersing powder (adequate, robust protocols)*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 yrs)
Find supplier and determine consistency of product; Determine size, morphology, and crystallinity	Identify/characterize reactive oxygen species and stability of output; Explore/develop protocols and methods for stabilization of powders in solution (two possibilities: aqueous and in solution for producing aerosol)	Deliver powder and stable solution

Figure 3.3 Environmental fate and transport—priority reference materials (TiO_2).

QUANTUM DOTS

Surface-coated quantum dots in solution: core (semiconductor material), shell (e.g., zinc sulfide), and coating with organic functionalization (often proprietary); more environmentally benign quantum dots desirable; explore possibility of powder form

Major Applications or Problems Addressed

- Enormous potential as tracers
- Use as environmental sensors
- Can be functionalized to bind to specific targets

Performance Requirements

- Durable coatings – coating selection is critical (some degrade in environment)
- Availability of different particle sizes with the same coatings
- Many projects typically only require very small quantities

Unique Characterization Needs

- *Core size*
- *Shell thickness and completeness of coverage*
- *Surface chemistry, including good functionalization protocols*
- *Optoelectronic properties (band gap, etc.)*
- *Solubility and dissolution rate*
- *Future: Standard mixtures with dots in an environmental matrix (e.g., X quantity of dots mixed in soil)*

Barriers and Challenges

- *Very toxic when coating is lost*
- *Some functionalizations may be less stable*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 yrs)
Secure supply and validate properties; Explore approaches to diminish toxicity (e.g., modifications to core, shell, and/or coating)	Stabilize functionalization; Identify/resolve any calibration issues and determine protocol as needed (fluorescence or absorption versus particle number); Deliver product	Deliver product

Figure 3.4 Environmental fate and transport—priority reference materials (quantum dots).

IRON OXIDE (Fe_2O_3)

Multiple phases (magnetite); in powder form, with a protocol for dispersion in liquid; available in different size distributions (suggested ≤ 20 nm for metal oxide particles).

Major Applications or Problems Addressed

- Consistent identification of phases of iron oxide to enable comparisons
- Behavior and fate of engineered and naturally occurring iron oxides in the environment

Performance Requirements

- Control of aggregation (both aggregated and non-aggregated form)
- Well-characterized refractive index
- Identification of different morphologies within magnetite, or at least known morphology

Unique Characterization Needs

- *Magnetic properties and size correlations*
- *Characteristics to distinguish naturally occurring versus engineered particles*
- *Phase transformations (occurs in/mutates to multiple phases); chemistry of crystal phases*
- *Saturation magnetization*

Barriers and Challenges

- *Irreversibly aggregate in solution*
- *Exists in multiple phases*
- *Limited by inconsistent quality and control in sample supplies*

R&D Activities and Timeline

Near Term (1–2 yrs)

Select supplier and validate quality and consistency

Mid Term (3–5 yrs)

Comprehensive characterization studies (magnetic, phase, morphology, chemistry);

Produce aggregated vs. nonaggregated form;

Deliver product samples

Long Term (> 5 yrs)

Deliver product samples

Figure 3.5 Environmental fate and transport—priority reference materials (Fe_2O_3).

Table 3.3 Important Overarching Characterizations for Reference Materials

Surface characteristics	• Surface charge density and distribution • Zeta potential under well-defined conditions • Size/polydispersity/morphology/aspect ratio • Specific surface area • Surface coatings and behavior in various environments
Aggregation/agglomeration	• Aggregation/agglomeration state, fractal dimension under well-defined conditions; this will require protocols for dispersion, measuring aggregates, defining aggregates (hard) and agglomeration (soft), measuring surface area in agglomerated states (*in situ*) • Unique protocol for sedimentation/effective density, with links to fractal dimensions
Chemical	• Chemical composition/phase/degree of crystallinity
Reactivity	• Solubility, reactivity, redox activity, ROS production, adsorption/complexation of existing environmental contaminants (e.g., PCBs and heavy metals)
Other	• Hydrophobicity and partitioning behavior

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3. Environmental Fate and Transport

4. Human and Ecological Health

This breakout session addressed standards for the assessment of the biological response to engineered nanoscale materials via environmental or nonincidental exposure to humans and other living systems (terrestrial or aquatic plants and animals). In addition, this session also addressed standards for understanding effects on subcellular components, cells, tissues, organs, organ systems, and whole organisms (e.g., bioaccumulation, toxicity). Key applications that were identified by this group as critical to the selection of candidate materials included materials selected for applied toxicology/hazard identification, materials applied to fundamental research needs, materials for metrology (both instrument and assay calibrations), and materials for reference toxicants. Under each of these applications candidate materials were separated into two tiers. Tier 1 materials were those identified as most important or relevant to a specific application, and tier 2 materials were identified as relevant to specific applications but less important than tier 1 materials. Tier 1 materials were then balloted to indicate the prioritization in importance. The tier 1 materials receiving the greatest number of votes for each application are: Ag nanoparticles for applied toxicology/hazard identification, dendrimers for fundamental research, Au nanoparticles for metrology, and TiO_2 for a reference toxicant.

4.1 KEY CONSIDERATIONS AND CHALLENGES

The way nanomaterials interact within the human body and other living systems may be influenced by their key properties, such as size, shape, and surface chemistry. Nanoscale reference materials that are well characterized for both physical and chemical properties will be valuable in facilitating nanomaterial human and ecological health studies. (Photo © Elisei Shafer/Shutterstock.)

There is increasing recognition that nanomaterials may pose risks to human and ecological health. Recent toxicology studies indicate that a nanomaterial's fundamental properties can influence its toxicity, echoing concerns over consumer and environmental safety.[1] This topical area focused on nominating candidate reference materials, and on identifying characterization issues relevant to human and ecological health, specifically prioritizing:

Reference materials to support assessment of the biological response to engineered nanoscale materials via environmental or nonincidental exposure to humans and other living systems including effects on subcellular components, cells, tissues, organs, organ systems, and whole organisms (e.g., bioaccumulation, toxicity).

Numerous overarching challenges exist to developing reference materials, as discussed in Chapter 2. In addition, there are a number of considerations that are specific to understanding the potential impacts of nanomaterials on human and ecological health. To help nominate candidate reference materials for this area, criteria were considered that would apply specifically to human and ecological health from multiple perspectives. It may be necessary to suggest several materials as priority for further research to account for varying and potentially conflicting points of view from the vast spectrum of reference material users. For example, reference materials considered important from the fundamental research perspective may differ from those of interest from the metrology perspective. A general framework of key criteria to be considered was developed and subsequently binned into the four categories shown below. This framework provided guidance for the reference material recommendation process.

- **Applied Toxicology/Hazard Identification.** Materials selected for applied toxicology/hazard identification will be chosen based on their relevance and importance to human and ecological health. These materials have high potential risk of exposure. They should be produced in high volumes and may already be in commerce. The public perception must be considered; it must meet the public's need of ensuring safe nanomaterials.
- **Fundamental Research.** Fundamental research of physical and chemical properties increases the knowledge base of nanomaterials characteristics. Candidate nanomaterials for this category need to be available in several forms, including range of sizes, range of shapes, and surface modifications. They should have the potential to answer QSAR (quantitative structure-activity relationship) questions.
- **Metrology (Instrument and Assay Calibration**). Metrology reference materials need to be stable, homogenous, and available with high purity and uniformity.
- **Reference Toxicant.** Candidate reference toxicants are well studied and will enable researchers to develop a positive or negative benchmark material. Ideal reference toxicant materials have a large existing dataset with great potential to increase this knowledge. Reference toxicants can help establish translations from *in vitro* to *in vivo* studies.

4.2 APPROACH FOR MATERIALS NOMINATION FOR HUMAN AND ECOLOGICAL HEALTH

Based on information presented during the plenary sessions and input from group participants, a customized approach for identifying reference materials was developed for human and ecological health. This approach included the following steps:

1. Add to the lists of candidate materials presented in *Reference Materials for Engineered Nanoparticle Toxicology and Metrology* [2] and *Nanotechnology EH&S Research Needs Assessment Toward Nanomaterial Classes* [3], and consider these for nomination.
2. Identify critical properties, performance, or other requirements to consider when nominating materials.
3. Nominate materials within the framework of four perspectives/categories: Applied Toxicology, Fundamental Research, Metrology, and Reference Toxicant.
4. Determine which nominated materials are well-suited for each of the four categories.
5. Split the list of materials in each category into two tiers. Tier 1 indicates materials most important or relevant in each category. Tier 2 indicates a material that is well suited for each category, but less important than the tier 1 materials.
6. Vote on the tier 1 materials for each category to arrive at the ―most important" material to nominate in each category.
7. Determine key characterization requirements, scope, and time frame for conducting R&D to evaluate the nominated nanomaterials.

It was noted that the material or class of materials ultimately selected must be driven by the importance to human and ecological health and the key properties of interest identified by the group. Concerns such as characterizing surface chemistry versus size or shape should be placed in the context of a biological matrix relevant to the scope of this topical area. Determining which physical and chemical properties are most important will be difficult, and there will be no way to test all of them. In addition, one material is unlikely to satisfy all the property characterization issues. It may be necessary to nominate multiple materials based on their characterization opportunities and challenges.

4.3 NOMINATED MATERIALS FOR HUMAN AND ECOLOGICAL HEALTH

Starting with the IOM REFNANO report [1] recommendations for candidate materials and a list of materials [2,3], the group suggested additional nanoparticles types and classes that should be considered for human and ecological health (see Table 4.1). Considering the characterization challenges and the framework described above, the breakout group then evaluated the candidate list from the perspective of each category and identified nanomaterials applicable for each area. A particular nanomaterial was not restricted to apply to a single category. After these lists were compiled for each criterion, the group prioritized them into primary ―tier 1” and secondary ―tier 2” choices. The results are summarized in Table 4.2.

Participants narrowed their list of materials by selecting their top choice for the most important reference material within each tier 1 category, based on the goals and challenges that should be considered within each of the four categories. Table 4.3 presents the results of the vote. The Human and Ecological Health group nominated five nanomaterials for consideration as priority reference materials: silver, dendrimers, the C_{60} class of materials (including C_{70} and higher), Au, and TiO_2.

The complexity of nanomaterials leads to characterization issues which can vary significantly depending on the type of nanomaterial. Key issues were identified that would affect characterizations important to human and ecological health. For any reference material, the more physical and chemical properties that can be specified, the more valuable that reference material will be. Characterization can be costly, however, and it is important to highlight the characterization needs that are required rather than simply wanted.

Comments on characterization properties and key issues are presented in Table 4.4. The group did not attempt to separate the characterization needs into tiers or priority levels, but elected instead to simply define the key issues.

The possibility of producing isotopes for analysis is another key issue for researchers to consider. Varying isotopes could affect transport and other characteristics. Of the priority materials nominated in this session, dendrimers and gold are the most amenable for isotope enrichment. The method of producing the isotopes would need to be reported.

The group noted that the four categories yielded a range of materials to move forward for further research, but expressed concern that there were no carbon systems as a top choice. It was therefore decided that the C_{60} group should be included as a nominee for fundamental research, along with dendrimers, to ensure that recommendations would cover a carbon system.

Table 4.1 Initial List of Candidate Reference Materials

IOM List of Candidate Materials [3]	Additional Materials Proposed by the Group
• Carbon black	• Inorganic cage structures
• TiO_2	• C_{60}, (including C_{70} and higher order)
• ZnO	• Dendrimers
• SWCNT and MWCNT	• Liposomes
• Polystyrene (fluorescent)	• Block copolymer micelles
• Ag	• Quantum dots
• Other key metals and oxides	• Zero-valent iron
• Combustion-derived MP	• Silicon nanotubes
• Au	
• CeO_2	
• SiO_2 (amorphous)	
• Other ceramics	

Table 4.2 Primary —Tier 1” and Secondary —Tier 2”Nanomaterial Choices for Human and Ecological Health

Applied Toxicology	
Tier 1	Ag, Zero valent iron, CeO_2, TiO_2, SWCNT/MWCNT
Tier 2	ZnO, SiO_2 (amorphous), Metal & metal oxides, Au, C_{60} class of materials
Fundamental Research	
Tier 1	Au, Quantum dots, Dendrimers, C_{60} class of materials, Polystyrene (fluorescent), SiO_2 (amorphous)
Tier 2	Metal & metal oxides, Ag, CeO_2, TiO_2, SWCNT/MWCNT

Metrology	
Tier 1	Au, quantum dots, Dendrimers, Polystyrene (fluorescent)
Tier 2	SiO_2 (amorphous), C_{60} class of materials, SWCNT/MWCNT
Reference Toxicant	
Tier 1	C_{60} class of materials, TiO_2 , Carbon black
Tier 2	SiO_2, Dendrimers

[3] Not all materials from the IOM list were considered.

Table 4.3 Voting Results for Tier 1 Nanomaterials Nominations[4]

Applied Toxicology		Fundamental Research		Metrology		Reference Toxicant	
Ag	10	Dendrimers	6	Gold	12	TiO_2	10
TiO_2	4	C_{60}	4	Dendrimers	3	Carbon black	5
CeO_2	2	Gold	4	Polystyrene (fluorescent)	0	C_{60}	3
SWCNT/MWCNT	1	SiO_2 (amorphous)	3	Quantum Dot	0		
Zero-valent Iron	0	Polystyrene (fluorescent)	1				
		Quantum Dots	0				

Figures 4.1 through 4.5 summarize the key characterizations, barriers, performance requirements, and needed R&D for the priority materials selected, which are shown in red in Table 4.3. These are not all-inclusive, but provide a snapshot of the major issues and requirements.

[4] Nanomaterials in red are discussed in Figures 4.1–4.5

Table 4.4 Important Overarching Characterizations for Human and Ecological Health

Property	Characterization
Shape	Nanomaterials can have a fixed or dynamic shape. For example, C_{60} particles are more likely to flatten or change shape, while gold spheres keep a fixed shape.
Agglomeration/ Aggregation State	Knowing whether the particles will disperse or if there are soft or hard aggregates present are important characterization issues. The state of particle dispersion in the presence of other constituents such as proteins, lipids, or enzymes is also an important characterization issue. Sonication techniques can help measure the aggregation state. The source/starting material of the aggregate will need to be known as a primary aggregation mark. These issues are particularly important for TiO_2 for sedimentation/effective density, with links to fractal dimensions.
Charge/Surface Chemistry	The density of functional groups, especially for dendrimers and C_{60}, will be critical for ecological analysis. Charge and surface chemistry also affect silver's rate of dissolution and stability.
Purity of Contaminants (Compositional)	Threshold purity levels should be established, and the manufacturers should indicate levels of purity by mass. However, the expression of purity needs to change, depending on activity levels and intent. Particles available in a free or bound state need to be separately characterized. Dose metrics also influence purity. The presence of contaminant can affect level of activity, different levels of the dose metric need to be measured.
Concentration	Issues pertaining to purity also apply to characterizing nanomaterial concentration. Additionally, mass concentration and particle density concentration differ. Solubility characteristics should be reported. Researchers need to know shelf life, solubility, suspendability, and information about what to expect if the material is used in an aquatic system.
Sterility	Samples need to be sterile and free of endotoxins.
Size	Size is an important factor—a 2 nanometer difference can influence uptake and have other implications. Several sizes of particles should be defined for testing, or if one size is specified, several shapes may be needed. For TiO_2, researchers should investigate whether the number of atoms per particle, or the size of the particle is more important. For C_{60} , separate size distribution into two categories: less than 60 nm and greater than 60 nm. For each material, varying parameters will need to be defined.
Composition and Structure	For all nanomaterials, particle composition specifications should be clearly defined to ensure batch consistency.
Reactivity	There are several different assays to measure surface reactivity; determining and reporting the most appropriate assays for each material is important.
Other	Stability over time, density, synthesis/production method, solubility, and surface area.

GOLD (Au)

In aqueous format; multiple sizes (3 nm or less, one over 100nm, in addition to existing 10 nm, 30 nm, and 60 nm sizes); small aspect ratio (e.g., rod, AR = 5) and fibers/wires

Major Applications or Problems Addressed

- Primarily for metrology applications
- Also applicable to fundamental science (structure activity)

Performance Requirements

- Free of endotoxins

Unique Characterization Needs

- *Size (primary particle size), shape, surface area, agglomeration state, composition and structure, density (especially for coated particles), concentration (mass, particle number)*
- *Purity of particle, charge and surface chemistry/charge density, sterility, stability, dissolution, solubility in water and oil (like Merck index)*

Barriers and Challenges

- *Expensive*
- *Particle uniformity is dependent on production method*
- *Track record of company/source*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 yrs)
Identify and evaluate suppliers for very small spheres, very large spheres, and high aspect ratio samples; Develop intermediate sizes for spheres and rods	Develop very small spheres, very large sphere, and high aspect ratio samples	

Figure 4.1 Human and ecological health—priority research material (Au).

TITANIUM DIOXIDE (TiO_2)

In powder and different crystal forms (antase, rutile, brookite) with specified coatings; mixed crystal phases; surface areas greater than 35 m^2/g

Major Applications or Problems Addressed

- Primarily for reference toxicant applications (photoactivity reference material)
- Also applicable to applied toxicology and fundamental science

Performance Requirements

- Ensure batch-to-batch consistency
- Ample material
- Photoactivity
- Concentration – mass, particle number, surface area
- Solubility in water and oil (like Merck index)

Unique Characterization Needs

- *Size (primary particle size), shape, surface area, agglomeration state, composition and structure, overall particle density (especially for coated particles)*
- *Purity of particle, charge and surface chemistry/charge density, end toxin-free, sterility, stability, dissolution*
- *Method of manufacture*

Barriers and Challenges

- *Methods of dispersing into solution (SOP)*

R&D Activities and Timeline

Near Term (1–2 yrs)

Purchase and characterize material

(Relatively easy scope of R&D activities)

Mid Term (3–5 yrs)

Long Term(> 5 yrs)

Figure 4.2 Human and ecological health—priority research material (TiO_2).

SILVER (Ag)

In aqueous format; multiple sizes relevant to silver are used in consumer products, bactericidal (mainly 20 nm–60 nm)

Major Applications or Problems Addressed

- Primarily for applied toxicology
- Also applicable to fundamental research

Performance Requirements

- Must be relevant to silver used in consumer products, bactericidal applications
- Produce a form stable over time; can be user-activated

Unique Characterization Needs

- *Free of endotoxins*
- *Dissolution rate relative to size*
- *Size (primary particle size), shape, surface area, agglomeration state, composition and structure, density (especially for coated particles), concentration (mass, particle number)*
- *Purity of particle, charge and surface chemistry/charge density, sterility, stability, dissolution, solubility in water and oil (like Merck index)*

Barriers and Challenges

- *Stability/dissolution*
- *Producing a form stable over time; can be user-activated*
- *Need for sufficient volume and breadth of material*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 yrs)
Address stability over time; Develop breadth of material (Scope of R&D activities present medium amount of work)	Produce material in bulk quantities	

Figure 4.3 Human and ecological health—priority research material (Ag).

DENDRIMERS

Solids, but mostly solutions: Polyamidoamine [PAMAM; G4, G6) amines, carboxylic acid, neutral charge]

Major Applications or Problems Addressed

- Primarily for fundamental research applications
- Also applicable to metrology and reference toxicants

Performance Requirements

- Uniformity and size
- Branching ratio
- Integrity of generation
- Charge density

Unique Characterization Needs

- *Size (primary particle size), shape, surface area, agglomeration state, composition and structure, density (especially for coated particles), concentration (mass, particle number, surface area)*
- *Purity of particle, charge and surface chemistry/charge density, endotoxin free, sterility, stability, dissolution, solubility in water and oil (like Merck index)*

Barriers and Challenges

- *Choosing the right composition (core structure, branching, generation number, and surface function) of dendrimers to produce*
- *Not produced in mass quantities*
- *Difficulty in understanding spatial distribution of surface charge*
- *Stability*

R&D Activities and Timeline

Near Term (1–2 yrs)	Mid Term (3–5 yrs)	Long Term (> 5 yrs)
Consult with experts in the field; Research and develop dendrimers in solutions (G4, G6, amines, carboxylic acid, neutral charge)	Research and develop dendrimers with other cores and branching	

Figure 4.4 Human and ecological health—priority research material (dendrimers).

C_{60} AND RELATED STRUCTURES

In powder form; solution in a known solvent; aqueous aggregated suspension (fullerol); endohedral fullerenes

Major Applications or Problems Addressed

- Primarily for fundamental research applications
- Also applicable to applied toxicology, metrology, and reference toxicants

Performance Requirements

- Stability (e.g., light)
- Adequate volume of material

Unique Characterization Needs

- *Degree of hydroxylation for fullerol*
- *Magnetic properties, if relevant*
- *Size (primary particle size), shape, surface area, agglomeration state, composition and structure, density (especially for coated particles), concentration (mass, particle number, surface area)*
- *Purity of particle, charge and surface chemistry/charge density, endotoxin free, sterility, stability, dissolution, solubility in water and oil (like Merck index)*

Barriers and Challenges

- *Variability*
- *Easily contaminated by some organic molecules, requiring careful handling*
- *Low solubility in aqueous systems*
- *Standard Operating Procedures (SOPs) for use*
- *No commercial manufacturer for some key materials (e.g., aqueous suspensions)*

R&D Activities and Timeline

Near Term (1 – 2 yrs)

Generate standard C_{60} powder/raw powders;

Determine charge density of fullerol (could be challenging)

(Scope of R&D activities present medium amount of work)

Mid Term (3– 5 yrs)

Complete characterization and development

Long Term (> 5 yrs)

Figure 4.5 Human and ecological health—priority research material (C_{60} and related materials).

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5. MATERIALS FOR OCCUPATIONAL EXPOSURE

This breakout session addressed reference materials for risk assessment, risk management, and characterization of nanoparticle exposure in the workplace. Materials for assessing inhalation, ingestion, skin absorption, or other entry routes into the body were discussed. Materials to support international consensus standards for nanoparticle exposure as well as instrument calibrations were also discussed. The group developed a framework for the production of reference materials and identified several key performance requirements for standards in this area. Candidate materials should be easily aerosolized, produced with discreet primary particles, have predictable or controlled agglomeration characteristics, be thermally stable, be easy to mount on microscopy substrates, and cover a range of sizes from greater than 100 nm to less than 10 nm. They also identified characterization needs for this area that included physical size, surface area, density, morphology, number, mass, and physical and chemical stability. This breakout session did not identify specific materials for this topical area. Instead participants assumed that the recommendations from the other groups would be cross-cutting in nature and as such, applicable to occupational exposure. However, materials with diameters in the aerodynamic size range of 100 nm – 1500 nm that can be size fractionated for sieving and other separation approaches, such as currently significant ceramic materials like beryllium oxide, were noted as materials that would be specifically beneficial to occupational exposure assessments.

5.1 CURRENT SCIENTIFIC AND TECHNICAL ADVANCES

Relatively few measurement tools are readily applicable to routine exposure monitoring. Key instrumentation challenges exist for the determination of parameters such as particle size, surface area, number concentration, and morphology in the workplace, and reference materials are necessary to support the development of technology to meet these challenges. (Photo ©Shutterstock.)

Commercial products increasingly utilize a wide range of nanomaterials. According to the UK Institute of Occupational Medicine (IOM; www.iom-world.org), more than 60% of those applications are in the health and fitness sector, which includes cosmetics and personal care products. Other applications include paints and coatings, electronics, food, and food packaging. Of the 356 nanomaterials currently available in consumer products as listed in the inventory of the Woodrow Wilson International Center for Scholars Project on Emerging Nanotechnologies (www.nanotechproject.org/inventories/consumer/), the most commonly used nanomaterial is Au. Next are carbon nanomaterials (fullerenes and nanotubes), silica, Zn0, TiO_2, and CeO. A number of other applications are anticipated for targeted drug delivery, gene therapy, stain-resistant coatings, self-cleaning glass, agricultural chemicals, industrial lubricants, advanced tires, semiconductors, and others.

The focus of this group was primarily on worker exposure to airborne nanoparticles during the manufacturing process. Although ingestion and skin penetration could happen during handling of materials that contain nanoparticles, it was noted that little is known about possible adverse effects from these routes of exposure. The most common route of exposure to airborne particles in the workplace is by inhalation.[1]

Airborne nanoparticles may be purposely produced or may be incidental to an industrial process (e.g., from sources such as combustion, vehicle emissions, and infiltration of outside air). In general, nanomaterial exposure may occur from processes generating nanomaterials in the gas phase, or using or producing nanomaterials as powders or slurries/suspensions/solutions (i.e., liquid media). In addition, maintenance on production systems (including cleaning and disposal of materials from dust collection systems) will likely result in exposure to nanoparticles if it involves disturbing nanomaterials. Exposures associated with waste streams containing nanomaterials may also occur.

Safe Work Practices Today

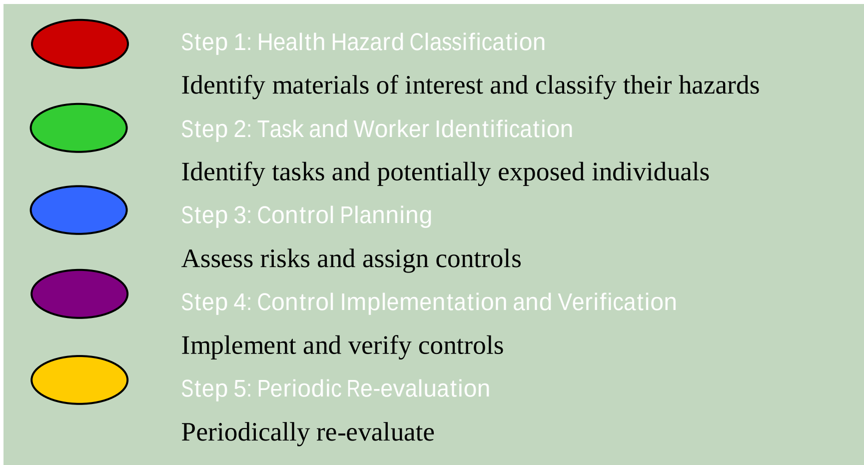

Figure 5.1 General worker protection steps.

Established safe work practices are generally based on an understanding of the hazards associated with the chemical and physical properties of a material. Because engineered nanomaterials may exhibit unique properties that are related to their physical size, shape, and structure, as well as chemical composition, considerable uncertainty exists as to whether these unique properties involve occupational health risks.

Reference materials are important to worker protection because they can support [2]:

- Development of exposure limits
- Development, validation, and calibration of commercially available sampling equipment and methods
- Development of and consensus on appropriate exposure control and medical surveillance strategies
- Development of guidance on laboratory industrial hygiene practices
- Development of guidance on appropriate personal protective equipment, including respiratory protection
- Development of employer and employee training materials on the potential health issues and measures to reduce risk

5.2 KEY CONSIDERATIONS AND CHALLENGES WITH EXISTING INSTRUMENTATION AND METHODS

Exposure assessment approaches can be performed using traditional industrial hygiene sampling methods that include the use of samplers placed at static locations (area sampling), samples collected in the breathing zone of the worker (personal sampling), or real-time measurements of exposure that can be personal or static. In general, personal sampling is preferred to ensure an accurate representation of the worker's exposure, whereas area samples (e.g., size-fractionated aerosol samples) and real-time (direct-reading) exposure measurements may be more useful for evaluating the need for improvement of engineering controls and work practices.

Many of the sampling techniques that are available for measuring airborne nanoaerosols vary in complexity but can produce useful data for evaluating occupational exposures with respect to particle size, surface area, density (e.g., particle number concentration), morphology, number, and mass. Unfortunately, relatively few of these techniques are readily applicable to routine exposure monitoring. The key considerations and challenges of these measurement techniques are described in Table 5.1.

5.3 APPROACH FOR NOMINATING MATERIALS FOR OCCUPATIONAL EXPOSURE

Developed by the Workshop Steering Committee, the approach for identifying reference materials for occupational exposure was to build on a recommended list of candidate materials [4], determine the desired properties and performance requirements of these materials, identify the challenges in developing the materials, and suggest potential applications. This approach was not an entirely suitable method for the Occupational Exposure breakout session. Rather than have the reference material drive the application, participants opted to let the application (i.e., properties) drive the material selection. Accordingly, the group took the following steps to select reference materials for occupational exposure:

1. Determine how a reference nanomaterial will be most usefully applied for characterization of nanoparticle exposure in the workplace
2. Determine the properties necessary in the application, as properties are the key drivers of material selection
3. Identify the challenges to using the reference nanomaterials in the application
4. Recommend key performance needs or other requirements of the reference nanomaterials
5. Recommend a list of potential types of materials—including one or two specific candidates—that are most likely to meet one or more of the property, performance, or other requirements of the application
6. Determine the scope and timeframe for conducting R&D to evaluate the potential candidate nanomaterials

Key Performance Requirements

The successful use of reference nanomaterials to support instrument calibration in the workplace involves the key performance requirements shown below. These, along with the considerations described above, can be used as a framework for the selection of priority reference materials.

- Ease to aerosolize
- Produce discreet primary particles
- Provide thermal stability
- Agglomerate in a predictable way
- Ease to deposit on microscopy substrates
- Range of sizes (greater than 100 nm, 100 nm, 60 nm, 30 nm, 10 nm, less than 10 nm)

Table 5.1 Key Instrumentation Challenges for Occupational Exposure

Size-Fractionated Aerosol Sampling	No commercially available personal samplers (e.g., electrostatic precipitators, thermal precipitators, and MOUDI) are designed to measure the particle number, surface area, or mass concentration of nanometer aerosols. However, several methods are available that can be used to estimate surface area, number, or mass concentration for particles smaller than 100 nm.
Real-Time Aerosol Sampling	The Scanning Mobility Particle Sizer (SMPS) is widely used as a research tool for characterizing nanometer aerosols, although its applicability for use in the workplace may be limited because of its size, cost, and use of a radioactive source. Additionally, the SMPS may take from 2 to 3 minutes to scan an entire size distribution; thus, it may be limited to use in workplaces with highly variable aerosol size distributions, such as close to a strong particle source. Fast (less than one second) mobility-based particle sizing instruments are now available commercially; however, because they have fewer channels, they lack the finer sizing resolution of the SMPS. The Electrical Low Pressure Impactor (ELPI) is an alternative instrument that combines diffusion charging and a cascade impactor with real-time measurements (less than one second aerosol charge measurements providing aerosol size distributions by aerodynamic diameter).
Surface Area Measurements	Isothermal adsorption (i.e., BET, which is a standard off-line technique used to measure the specific surface area of powders that can be adapted to measure the specific surface area of particulate material; however, the BET method requires relatively large quantities of material, and measurements are influenced by particle porosity and adsorption gas characteristics). At this time, some commercially available portable aerosol diffusion chargers provide a good estimate of aerosol surface area when airborne particles are smaller than 100 nm in diameter, but they tend to overestimate surface area when particles are larger than 100 nm in diameter.
Surface Area Estimation	Information about the relationship between different measurement metrics can be used for estimating aerosol surface area. If the size distribution of an aerosol remains consistent, the relationship between number, surface area, and mass metrics will be constant. However, in workplace environments, these estimates may be up to a factor of 10 different from actual aerosol surface area.[1] The National Institute for Occupational Safety and Health (NIOSH) is currently conducting research in this area.
Particle Number Concentration Measurements	Condensation Particle Counters (CPCs) are available as hand-held static instruments, and they are generally sensitive to particles greater than 10–20 nm in diameter. However, particle counters are generally insensitive to particle source or composition, making it difficult to differentiate between incidental and process-related nanoparticles using number concentrations alone. CPCs are capable of measuring localized aerosol concentrations, allowing the assessment of particle releases occurring at various processes and job tasks.
Morphology	Determining shape and structure with nanometer precision is a challenge using current methods and tools. Aberration-corrected analytical electron microscopy may determine nanoparticle shape. Ion mobility mass spectrometry may be an appropriate method for determining aggregation of nanomaterials. Neither of these methods has been thoroughly explored.[3]

5.4 NOMINATED MATERIALS

Discussions focused on addressing the development of reference materials to support validation and calibration of commercially available instrumentation and methods. In addition, these materials could be used in other studies of the size-dependent physical and chemical properties of nano-structured materials.

Candidate materials were selected according to the rationale described earlier. Discussions reiterated that the types of materials selected must be driven by the key properties of interest that were identified and the major issues and challenges. It may not be practical to have one material containing all of the key properties, although one or more properties may be characterized in a nominated material.

Types of Priority Reference Materials

Based on the rationale described earlier, there may be materials already available that can meet the property and performance requirements necessary for calibrating occupational exposure instruments. In addition, other areas are likely to have more stringent requirements for selecting reference nanomaterials. As a result, the materials identified by other groups are likely to be applicable for use in occupational exposure as well. For this reason, rather than nominate specific materials, the group followed the general priorities set by other areas for types of materials, since these would be cross-cutting in nature and applicable to occupational exposure as well. A summary of the priority reference material types and important characterizations, barriers, and R&D related to materials for occupational exposure is shown in Figure 5.1.

In addition, an important criterion is the consideration of 100 nm – 1500 nm physical diameter nanostructured materials that can be size-fractionated for sieving and other separation approaches and analysis. A significant ceramic material, e.g., beryllium oxide (BeO), may be considered as a beginning candidate reference material for this approach.

Properties to be Characterized

To support the development, validation, and calibration of commercially available sampling equipment and methods for occupational exposure, the key properties to be characterized were identified and are shown in Table 5.2.

Scope and Timeframe for R&D

Because materials may already be available, a reference material could be developed for use in the near-term, by 2009. Material tests should include the use of a MOUDI, nano-MOUDI, electrostatic precipitator, and thermal precipitator. The implementation strategy can make use of existing models for developing reference materials, including collaboration with the following groups:

- Instrument and material manufacturers can help develop new equipment and materials and provide the appropriate performance and protocols.
- Standards organizations can help develop the criteria for selecting reference materials and their prioritization.
- Government can help to facilitate collaboration, identify needs, and provide cost-shared funding.
- Industry can help to identify the barriers to successful application and determine priority needs for testing in the real world.

Table 5.2 Important Nanomaterial Characterizations for Occupational Exposures

Size	The deposition of discrete nanoparticles in the respiratory tract is determined by the particles' aerodynamic or thermodynamic diameters (depending on particle size). Agglomerates of nanoparticles will deposit according to the diameter of the agglomerate, not constituent nanoparticles.
Surface Area	Any material's biochemical reactivity is highly dependent upon its surface chemistry. Bioreactivity may be more pronounced in nanoscale particles, where, for a given number or mass of particles, the total surface area delivered is dramatically larger than the surface area of an equivalent number or mass of microscale particles.
Morphology	The cytotoxicity of nanoparticles may be dependent on the structure of the molecules. For example, a recent study has shown that the cytotoxicity of water-soluble fullerenes can be reduced by several orders of magnitude by modifying the structure of the fullerene molecules (e.g., by hydroxylation).[1] In addition, solubility and surface chemistry can influence the toxicity of nanoparticles.
Number	In some cases, the number of particles depositing in the respiratory system or penetrating beyond the respiratory system may be important.
Mass	Agglomerated nanomaterials may either retain or lose their emergent properties—or take on new properties—thus affecting the potential biological response. Measurements can include the mass of the individual particles (which are less than 100 nm in one dimension) or massed agglomerates (which may be larger than individual particles). The dynamics of nanomaterials agglomeration can play a critical role in determining the pulmonary deposition of respirable nanoscale material. Larger aggregates of particles tend to deposit within the airways, while dispersed nanomaterials often reach the alveoli.
Density	The importance of particle number concentration in measuring exposure and dose of nanoparticles is not clear from existing toxicity data.[3] Group discussions indicated that density may be an area of interest, and further study is needed to determine its role in occupational exposure to nanoparticles.
Stability	Stability reference materials must be able to be produced in a reproducible, homogenous, and stable manner. Due to the enhanced reactivity of nanomaterials, determining a ―shelf life" of a nanomaterial may be needed.

Materials of Interest

Materials identified by other groups, driven by properties of interest. Includes nanostructured materials of 0.1 µm–1.5 µm physical diameter that can be size-fractionated for sieving and other separation approaches and analysis; consider beginning with a currently significant ceramic material such as beryllium oxide.

Major Applications or Problems Addressed

- Instrument calibration
- Other studies of the size-dependant physical/chemical properties of nano-structured materials

Performance Requirements

- Ease to aerosolize
- Discreet primary particles
- Thermal stability
- Agglomerate in a predictable way
- Ease to deposit on microscopy substrates
- Range of sizes (>100 nm, 100 nm, 60 nm, 30 nm, 10 nm, sub-10 nm)

Unique Characterization Needs

- *Physical: size, surface area, density, morphology, number, mass*
- *Chemical/physical: stability*

Barriers and Challenges

- *Instrument measurement limitations*
- *Application-dependent*
- *Variations among instruments that measure particle size*
- *Different response from static calibration environment to real-world*

R&D Activities and Timeline

Near Term (1–2 yrs)

Include use of a MOUDI and nano-MOUDI, electrostatic precipitator, and thermal precipitator

Figure 5.2 Occupational exposure—priority reference materials.

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6. Cross-Cutting Issues and Challenges

*This breakout session addressed issues that impact multiple users and communities. The group discussed challenges in material considerations, experimental methods, production limits, time scales, cost, policy issues, international cooperation, interlaboratory comparisons, and interagency collaboration and coordination. In particular, several critical uses for which a reference material would be beneficial for assessing the environmental health and safety of nanomaterials across multiple disciplines and technologies were identified: verification of measurement methods, protocol development, and instrument calibration; toxicity testing (*in vitro *and* in vivo *testing) to enable researchers to assess the quality and comparability of results between multiple users and multiple assays; enhancement of trade venues via quality control in manufacturing and product development (e.g., purity, reliability); and communication (e.g., increased public confidence by having a standards-based, validated measurement infrastructure, including an accurate basis for trade or regulation). Materials that might possibly meet all of these needs were discussed. An area of concern was current state-of-the-art instrumentation limits with respect to our ability to determine the amount or type of a nanomaterial in a complex medium such as sediment or blood. The use of a labeled nanomaterial, e.g., iridium-tagged particles, would likely be advantageous in a reference material that consists of actual sediment. Similarly, quantum dots would likely prove to be a useful nanomaterial in a blood-based reference material.*

6.1 DESCRIPTION OF THE BREAKOUT TOPIC

Health and environmental risks of nanomaterials, both actual and perceived, can be critical roadblocks for innovation and commercialization of nanotechnology or products that contain nanomaterials and are cross-cutting to many sectors. Current data quality for measurements of nanomaterial physical and chemical properties, and the behavior of nanomaterials in biological and environmental matrices, hinders to some extent our ability to fully understand, predict, and manage potential risks of engineered nanoscale materials. This lack of certainty in nanoscale measurements ultimately impacts regulatory and policy decisions. One avenue to address measurement uncertainty at the nanoscale is to make use of reference materials that are tailored for the nanoscale regime that can meet multiple user needs.

Different groups or classes of materials will be needed by different sectors. As such, all stakeholders from industry, government, and academia are needed to identify and select specific materials for which standards will be generated and to establish the extent to which those materials will be characterized. Moreover, the key elements in identifying and nominating nanoscale reference materials, including overarching characterization challenges and limitations, are relevant to many scientific and industrial disciplines. Such reference materials have a number of key areas for use (Table 6.1). Hence, ours was a cross-cutting breakout group focused on issues that impact many users and communities. The group provided recommendations for selected materials that can be used by these sectors both for environmental health and safety research and for trade.

6.2 KEY CONSIDERATIONS AND CHALLENGES

Cross-cutting issues in the development of reference materials include (1) challenges in material considerations; (2) experimental methods, production (sources, volumes) timescales, or cost; (3) policy, international standards cooperation; and 4) interagency collaboration, coordination, and interlaboratory comparisons. Items 1 and 2 regarding material considerations and experimental methods, production, time, and costs are important for the design, planning, and preproduction of materials. Policy, cooperation, and collaborations (items 3 and 4) are important issues after materials are developed and available for distribution and use.

Table 6.1 Reference Materials Users and Key Areas for Use

Users of Reference Materials

• Research communities
  ○ Science
  ○ Occupational health
  ○ Medical
  ○ Environmental
• Product Manufacturers
• Material Suppliers
• Instrument manufacturers
• Federal sector
  ○ Regulatory
  ○ Discovery science
  ○ Basic and applied research
• NGOs and public sector

Key Areas for Reference Material Use

• Occupational health
• Public health
• Quality control
• Facilitation of trade
• Hazard identification
• Hazard screening
• Calibration of instruments
• Validation studies
• Experimental controls
  ○ Negative controls
  ○ Positive controls
  ○ Benchmarks
  ○ Tracer (detection, monitoring)
• Research areas:
  ○ Environmental fate and transport research
  ○ Source apportionment
  ○ Ecological research
  ○ Health effects research
  ○ Toxicology

Challenges in Material Considerations

Standard materials are often tailored to address specific needs of users. As such, it is important to consider uses of reference materials when considering what materials to develop. Multiple uses of reference materials include:

- Validation studies
    - Protocols for specific methods
    - Test methods
    - Normalization with controls
    - Compare benchmarks with other studies for interpretation of results
    - Battery of tests to characterize approaches under study
        - Method development

        - Analytical chemistry or physical characterizations
    - Primary measurement needs
        - Calibration of instruments
        - Controls (negative or positive)
        - Tracer (detection)
- Toxicity studies
    - *In-vivo* or *in-vitro* tests
    - Documentation of incremental realization of effects with given measurement methods
    - Instrument evaluations
    - Benchmarking with other studies
    - Assay calibration or evaluation
- Comparability of results by single or multiple users
    - Compare results from single assays
    - Compare results from different assays
    - Performance evaluation or comparisons (inter- or intralab)
- Facilitation of trade
    - Industrial references or benchmarks
    - Quality control in manufacturing
    - Performance standards
    - Extrapolation to products
- Public perception
    - Having standards in place minimizes speculation and enhances confidence
    - Needed for accurate research, trade, or regulation
        - Largely driven by industry (including biotech) and/or whether a standard is necessary
        - Examples: Au or SiO_2
    - Production volume a factor; materials with high volumes include:
        - Ag, SiO_2, TiO_2, carbon black, ZnO, nanoclays, multiwalled nanotubes
        - Impact of material on public and/or use important, examples:
            - TiO_2, Ag, SiO_2, ZnO, quantum dots
    - Materials demanded, often those in media or highlighted via industry investment:
        - Oxides (CeO_2, TiO_2, ZnO, FeO)
        - Single/multiwalled nanotubes
        - Ag
        - Nano shells (drug delivery or medical uses)

Supplier issues for reference material development include type of material needed with respect to volume or mass and homogeneity. Characterization needs for the material are a large driving factor when designing reference materials. Cross-cutting nanoscale characterization issues are summarized in Table 6.2. It is essential to document preparation methods for each parameter and the interpretation of the result (e.g., particle size: hydrodynamic or aerodynamic diameter).

Table 6.2 Important Physical Characterization Parameters for Nanoscale Reference Materials [5]

Physical or Chemical Parameters	1. Particle size 2. Primary particle size 3. Aggregate particle size 4. Particle distribution in wet/dry state 5. Rate of agglomeration 6. Agglomeration state (e.g. stability) 7. Morphology 8. Crystal structure 9. Composition and purity (elemental concentration) 10. Concentration in media (particle, mass, etc.) 11. Doping level 12. Absorption isotherm 13. Endotoxin contamination and microbes 14. Media characterization (pH, mole fraction) 15. Preparation method 16. Density 17. Chirality 18. Shell thickness 19. Surface area 20. Surface chemistry and composition 21. Surface interfacial energy 22. Solubility 23. Charge/zeta potential 24. Porosity 25. Radio label tag concentration (specific activity)
Functional Properties	26. Optical properties 27. Quantum yield 28. Magnetic properties 29. Thermal conductivity 30. Electrical conductivity 31. Mechanical properties 32. pH 33. Ligands (type, properties), surfactants (type, mole or volume fraction) or coatings (type, extent of coverage, chemistry) 34. Stability (shelf life) 35. Homogeneity 36. Heterogeneity 37. Melting point

Not every parameter identified in Table 6.2 is important to every user of a reference material. Hence, it is also essential to consider the types of appropriate characterizations that are useful for a particular community using a specific material. Generally, a minimum data set is necessary for the material to be useful. Example minimum data likely to be required for a nanoscale reference material are:

[5] Not a prioritized list; numbers correspond to those in Table 6.3.

- particle diameter
- length (for high aspect ratio)
- surface area
- number of particle per unit mass
- contaminants such as metals, soluble toxins, surfactant
- polymorphic composition

In many cases there will be multiple parameters needed, and these should be considered to some degree (where possible) in an order of priority. In addition, the degree of uncertainty needed for a specific measurement should be considered. For example, if a particle size increment of a specific material causes a specific change or effect, the uncertainty interval for the particle size of a reference material must be within this degree of cause if the material is to be useful.

International Cooperation, Interagency Collaboration, Coordination, Interlaboratory Comparisons

As the nanotechnology sector is interdisciplinary in nature, the determination of relevant data and use of definitions that meet mutual understandings among researchers from different backgrounds are necessary at the international level and among multiple bodies. Topics that are pertinent to these points include measurements of single-wall nanotubes coordinated by the ISO Technical Committee 229 and comparisons of samples by national metrology institutes. Comparisons of samples tend to:

- Involve other agencies, sectors, and the international community,
- Bring to light issues of nomenclature and details necessary for harmonization of activities or methods,
- Enhance the capabilities of the research community to conduct rigorous testing regimes as driven by demands from the public.

In some cases, comparisons of samples focus on materials for long-term (multiple year) studies. Materials developed for these types of studies are often characterized in more detail, with an emphasis on uncertainty intervals for measurements, and possibly values are presented as certified rather than as either informational or reference values. In contrast, materials developed for short-term needs often have minimal characteristics tailored to address the needs of the community for which the material is developed. Regardless, materials for either long- or short-term studies are useful for international cooperation, interagency collaboration, coordination, and interlaboratory comparisons.

Trading Zones and the Role of Reference Standards

The evolution of nanotechnology requires collaboration across disciplines and input from multiple stakeholders on the technological frontier. One way to encourage exchanges of knowledge and resources across expertise boundaries is to form trading zones around particular materials, technologies, applications, or risks. Here all the participants are motivated to solve a problem no one expertise community can handle alone.

Reference standards and materials can create the basis for such exchanges by ensuring that participants are using the same definitions and procedures. The creation of the standard can be the first step in forming a productive trading zone; it engages the participants in creating a common reference point that serves a role akin to a common language. When one research group does a study with a standard material and procedures, other research groups will understand the results, even if they disagree over interpretations and implications.

These trading zones can be greatly facilitated if one or more of the participants possess interactional expertise or the ability to carry on deep and thoughtful conversations with members of a different disciplinary culture. The interactional expert is steeped in one expertise but can speak fluently with those in one or more other expertise communities, mastering their language without being able to do their kind of research. Interactional experts are particularly qualified to help establish reference standards because they can imagine how the emerging standard will look from more than one perspective, and they also can act as translators between disciplines within a trading zone. NIST working groups like the one on cross-cutting challenges for the development of nanoscale reference materials create an atmosphere in which interactional expertise can begin to develop, but it takes repeated discussions of a common problem to develop this capability. A common problem for this group to consider was the lack of nanoscale reference materials for addressing multiple measurement needs among multiple communities. Materials identified to address cross-cutting needs are summarized in the next section.

6.3 MATERIALS FOR CONSIDERATION TO ADDRESS CROSS-CUTTING NEEDS

Key criteria for nominating cross-cutting materials as standards fell into three categories:

1. Resource Materials

These are materials that would be heavily used by key stakeholder communities like researchers, toxicologists, and manufacturers, and also address the concerns of regulators and the public. Here the reference materials would be determined not just based on which one was used most, but on whether a reference material could be useful as a standard for the use category. For example, nano silver is heavily used in a variety of products and therefore registers as a concern with the public. Gold is similar enough to silver at the nanoscale to serve as a stand-in, particularly for the determination of particle size.

2. Calibration

There are materials that would be particularly useful for calibrating instruments. In the cross-cutting group, the prime example was a lanthanide—not heavily used in the nano community, but a great calibration tool because they are so rare in nature (except in the earth's crust) that the background should be zero, and they also do not form ligands.

3. Controls

There are materials that would be particularly useful as positive and negative controls. A positive control is obviously highly toxic, and a negative has no toxic effect, so using both would determine that one's experimental setup was in fact working properly. Controls can also serve as benchmarks or tracers in experiments (Table 6.2).

An ideal material would serve several of these roles. Gold, for example, can be used as resource material and for calibration, and TiO_2 can be used for calibration and as a control. Ultimately, the identification of reference materials that can serve multiple functions will require the development and fostering of trading zones across the research, industrial, regulatory, and various consumer communities.

Candidate materials that the group described as top candidates are listed in Table 6.3. These are materials with the highest focus for the EHS community from a cross-cutting perspective. Rationale for their nomination is provided, along with a listing of parameters that would be ideal for determining the material as a reference material from both a calibration point of view as well as experimental use (control) point of view. Top candidate classes include elemental, carbon-based, and oxide materials. Interestingly, a number of ―other" materials were identified, including quantum dots and cationic dendrimers. The group recognized gold materials are available for the characterization of particle size, yet thought it would be useful to provide documentation on the anticipated extensive uses for such materials and to describe leveraging capabilities of such reference material development work. Additional candidate materials that meet cross-cutting needs are listed in Table 6.4, along with the rationale for their nomination.

Table 6.3 Top Candidate Materials that Meet Cross-Cutting Needs (not prioritized)[6]

Material	Rationale	Parameters for Calibration	Parameters for Control
Elemental			
Gold	Drug delivery applications, very stable, National Toxicology Program proposal to study gold (leverage existing work), variations on gold are under consideration, interest in developing data	1,4,7,16,25,26,30, 37	10,19,20,23,33
Carbon-based			
Single-wall nanotubes	More difficult, will take longer to develop, considered for multiple products (length and shape important)	1,4,6,7,9,15	9,15,20,25,30,31, 33,34
Oxides			
Silicon dioxide			
Amorphous	Large production volume, crystalline as a positive control, amorphous is benign	1,4,6,9,16,20,22,2 3,24,35,36	8 for both amorphous and crystalline
Crystalline		(same as amorphous plus 26	
Other Multiuse Materials			
Magnetic nano-materials (gadolinium; cobalt oxide)	Preclinical trials, possible multiple uses, convenient way to collect material, unusual property needing standard	1,6,8,9,15,20,34,3 5	1,4,28
Quantum Dots	Detectable at low concentration, attractive for imaging, functional applications, commercially applicable, built-in size standard (self-certifies), use as a cross-reference	9, 14, 18, 20, 26, 27, 33, 36	22, tracer
Rare-earth isotope	Well-defined size and shape, insoluble, relatively inert, not ubiquitous so can trace and detect at low levels, shows distinct behavior with size, useful for instrument calibration, transport properties, toxicology benchmarks, well-defined methods at NIST	1,4,6,7,9,25,34	19,20,22,25, tracer
Cationic Dendrimers (>30 microvolts)	Both positive and negative control, tightly controlled surface chemistry, inter-laboratory comparisons, tailorability, large quantities available, interest in pharmaceutical and agricultural industries	1,4	7,9,20,23,32,34,3 5

[6] Parameters found in Table 6.2

Table 6.4 Additional Candidate Materials that Meet Cross-Cutting Needs (not prioritized)

Material	Rationale
Elemental	
Silver	Available in many consumer products
Iron	Important commercial product, steers away from precious metals, cheap and ubiquitous for large-scale application, byproduct of other materials, unique properties (toxicologically, redox, catalytic), positive for water clean-up
Copper	Potency, positive control, benchmarks
Carbon-based	
Multiwalled carbon nanotubes	Large production volume, lack of knowledge of decay, in consumer goods (study in plastic/sporting goods)
Graphene	Possible future potential, 1-2 layers on top of other materials, unique shape
Fullerenes	Unique size (smaller), used in wide range of applications/products, subject of current toxicology study, impurity
Carbon black	Large production volume, multiple uses, environmental prevalence/exposure
Oxides	
Oxide nanoparticles (class)	Large production volume, multiple uses, bio-interaction, stress, therefore good as interphase, morpho toxicity
Titanium dioxide	Large production volume, multiple uses
Aluminum oxide	Large production volume, multiple uses
Iron oxide	Multiple oxidation states enable study of chemical properties, magnetic properties, diverse applications (medical, magnetic resonance images [MRIs], etc.), medical therapies
Zinc oxide	Large production volume, multiple uses
Cerium oxide	Large production volume, multiple uses
Other Multi-Use Materials	
Nanoclays	Large production volume, multiple uses
Nano-shells	Potential use in medical devices
Radio-labeled	Detection at low concentrations
Any material used as an aerosol (aerosol generation)	Formation of aerosol is critical (aerosol generation system); performance-based), way it is made is more important than chemistry—formation is critical one-way process
Protein	Biological application, defined size
Polystyrene	Well-characterized substrate for surface modification studies, NIST standards are available
Latex/acrylic latex polymer (class)	Composite industry applications
Spore, pollen, virus	Self-replicating, distinct size and shape, biological standard

Appendix A. Participants[7]

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[7] Affiliations are as of the dates of the workshop.

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APPENDIX B. WORKSHOP AGENDA

Standards for EHS Research Needs for Engineered Nanoscale Materials

Workshop Affiliated with the National Nanotechnology Initiative

National Institute of Standards & Technology, Gaithersburg, Maryland

September 12–13, 2007

AGENDA Wednesday, September 12, 2007		
Time	Activity	Speaker/Moderator
7:30 am	Continental Breakfast	
8:00 am	Welcome Introductory Remarks and Nano-EHS at NIST	Eric Steel, Director, Program Office, NIST
8:10 am	*Activities in the National Nanotechnology Initiative*	Altaf Carim, NSET Subcommittee Agency Co-chair
8:25 am	Overview of Workshop Process and Breakouts	Dianne Poster, NIST
8:35 am – 12:00 pm Session I: Approaches for Identifying Standard Materials Critical for Risk Assessment and Risk Management		
8:35 am	*Considerations for Selecting Materials for Understanding Risks of Nanomaterials - What is Necessary?*	Justin Teeguarden, Pacific Northwest National Laboratory
9:00 am	*Considerations for Selecting Standard Materials for Occupational Safety and Health*	Vladimir Murashov, National Institute for Occupational Health and Safety
9:25 am	*Considerations for Nanomaterials in Environmental Fate and Transport Assessment*	Mark Wiesner, Duke University
9:50 am	BREAK	
10:05 am	*International Council on Nanotechnology (ICON) – Nanotechnology EH&S Research Needs Assessment toward Nanomaterial Classes*	Vicki Colvin, Rice University
10:30 am	*Report of IOM Reference Materials for Engineered Nanoparticles Toxicology & Metrology (REFNANO) Project*	Steve M Hankin, Institute of Occupational Medicine (IOM), Edinburgh UK
10:50 am	Group Discussion: Approaches to identifying reference materials (key considerations, criteria)	Facilitated/Energetics Incorporated
12:00 pm	BOX LUNCH	

12:45 – 5:15 pm Session II: Nomination of Materials Specific to User and Community Needs		
12:45 pm	*Materials in Production and Products that Warrant EH&S Research*	Chris Hartshorn, Lux Research
1:10 pm	*Materials Necessary for Health and Occupational Exposure Studies*	Mark Hoover, NIOSH
1:35 pm	*Materials Necessary for Environmental Fate and Transport Studies*	Pratim Biswas, Washington University in St. Louis
2:00 pm	Group Discussion II: Key challenges to developing reference materials for nano EH&S (stability, amount, experimental methods).	Facilitated/Energetics Incorporated
2:55 pm	BREAK	
3:15 pm	Breakout Discussions (four groups): Nomination of Priority Materials	Facilitated/Energetics Incorporated
5:15 pm	ADJOURN	
5:30 pm	Bus from NIST to working dinner (reports from breakouts)	

AGENDA Thursday, September 13, 2007		
Time	Activity	Speaker/Moderator
7:30 am	Continental Breakfast	
7:55 am	Preview of Day	John Small, NIST
8:00 am – 12:15 pm Session III: Critical Materials Characterization Parameters Required to Meet Needs of Specific Users and Communities		
8:00 am	*Considerations for Characterizing the Potential Human Health Effects From Exposure to Nanomaterials*	David Warheit, DuPont
8:25 am	*Characterizations of Nanomaterials Necessary to Study Environmental Fate and Transport*	Joel Pedersen, University of Wisconsin-Madison
8:50 am	*Materials Characterization Necessary for Ecosystem Research*	Stephen J. Klaine, Clemson University
9:15 am	*Critical Lessons from the NCL Analytical Cascade Approach*	Scott McNeil, Nanotechnology Characterization Laboratory/National Cancer Institute
9:40 am	Group Discussion: Most critical characterization challenges	Facilitated/Energetics Incorporated
10:20 am	BREAK	
10:35 am	Breakout Discussions (four groups): Characterization Issues for Groups of Materials	Facilitated/Energetics Incorporated
12:15 pm	BOX LUNCH	
1:00 – 5:15 pm Session IV: Priority Reference Materials, Characterizations and Time-scales for Development		
1:00 pm	*Development and Production of Reference Materials*	Debbie Kaiser, NIST
1:20 pm	*OECD and Standard Materials*	Jim Willis, EPA
1:40 pm	BREAK	
1:55 pm	Breakout Discussions (four groups): Recommendations for Priority Reference Materials and Characterizations	Facilitated/Energetics Incorporated
3:55 pm	BREAK	
4:10 pm	Group Reports/Comments on Recommendations	Designated Technical Leads
5:15 pm	Closing Remarks	John Small, NIST
5:30 pm	ADJOURN	

Breakout Group Descriptions			
Group A: Cross-Cut Issues in Development of Standard Materials	Group B: Materials for Occupational Exposure	Group C: Materials for Environmental Fate & Transport	Group D: Materials for Human & Ecological Health
Cross-cut areas that impact multiple users and communities, such as challenges in common material considerations, experimental methods, production of materials (sources, volumes), timing and cost of materials needed, policy, international standards cooperation, interagency collaboration and coordination, inter-laboratory comparisons, and others.	Reference materials for risk assessment, risk management, and characterization of nanoparticle exposure in the workplace via inhalation, ingestion, skin absorption or other routes; includes materials to support international consensus standards for nanoparticle exposure.	Reference materials for assessing environmental exposure to nanomaterials in air, water, and soil, including how these materials are transported once released, and their subsequent behavior and fate (e.g., mixing, dispersing, concentrating, agglomerating, decomposing, reacting, etc.).	Reference materials to support assessment of the biological response to engineered nanoscale materials via environmental or non-incidental exposure to humans and other living systems (aquatic, plants, animals), including effects on subcellular components, cells, tissues, organs, organ systems, and whole organisms (e.g., bioaccumulation, toxicity).
Technical Leads	Technical Leads	Technical Leads	Technical Leads
Rick Canady (Session I), Dianne Poster (Session II/III) Mike Goreman (Session IV)	Vladimir Murashov (Session I) Mark Hoover (Sessions II/IV) David Warheit (Session III)	John Small (Session I) Greg Lowry (Session II) Joel Pedersen (Session III) Pratim Biswas (Session IV)	Justin Teeguarden (Session I) Vicki Colvin (Session II) Stephen Klaine (Session III) Nigel Walker (Session IV)

APPENDIX C. CANDIDATE MATERIALS LIST

Prepared by V. Colvin

Nanocrystalline Titanium Dioxide (Titania)

Molecular formula	• TiO_2 can exist in brookite, anatase, and rutile forms
Commercial availability and uses	• Many commercial sources of nano-titania • Used in sunscreens and other cosmetics • Future applications in solar cells and photocatalysis
Typical size and format:	• Commercial materials typically > 10 nm grain size and sold as dry powders • Laboratory materials can be size-controlled (d=3 nm–20 nm) and monodisperse
Surface coatings	• Inorganic coatings available to minimize free radical production • Rarely sold as a suspension • Laboratory materials can be coated with polymers to impart solubility
General properties	• Titania is a wide-band gap semiconductor • Materials are strong absorbers of UV-A light • With appropriate phase composition after UV excitation, materials can generate OH in water • Low solubility material
EHS publications (ICON database)	• 118 (all oxides)

Nanocrystalline Ceria

Molecular formula	• CeO_2 (common) or Ce_2O_3 (less common) often mixed or doped to increase its applications
Commercial availability and uses	• Many commercial sources of nano-ceria • Used as fuel cell electrolyte (when doped) • Used as an additive to diesel to increase efficiency (Envirox) • Abrasive in chemical mechanical polishing of IC circuits
Typical size and format:	• Commercial materials typically > 10 nm grain size and sold as dry powders • Laboratory materials can be size-controlled (d=3–20 nm) and monodisperse
Surface coatings	• Rarely sold as a suspension • Most interest in this material aimed at its use to develop fuel cell cathodes or as a dopant in gasoline
General properties	• Refractory oxide—most of unique catalytic properties arise from presence of oxygen vacancies. • Less photoactive than titania or zinc oxide. • Bulk form used in catalytic converters
EHS publications (ICON database)	• 118 (all oxides)

Nanocrystalline Zinc Oxide

Molecular formula	• ZnO
Commercial availability and uses	• Sunscreens • Much interest in its wire form for sensing applications (mainly academic)
Typical size and format:	• Commercial materials typically > 10 nm grain size and sold as dry powders • Laboratory materials can be size-controlled (d=3–20 nm) and monodisperse
Surface coatings	• Laboratory materials can be coated with polymers to impart solubility
General properties	• Zinc oxide is a wide band gap semiconductor • Materials are strong absorbers of UV-A light • Soluble in acids or alkalis
EHS publications (ICON database)	• 118 (all oxides)

Quantum Dots (primarily II-VI)

Molecular formula	• CdSe—for example • Term includes CdX (X=S, Se, Te) • ZnX (X=S, Se, Te) —often core-shell with interior material surrounded by higher bgap
Commercial availability and uses	• Commercial suppliers include Invitrogen, which sells for biomedical imaging both research and *in vivo* • Endarken sells for solar cell and Light-emitting diode (LED) applications (nascent)
Typical size and format:	• Commercial materials are monodisperse with core dimensions 2–8 nm • Overall hydrodynamic size can be up to 50 nm
Surface coatings	• Polymeric coatings are standard on quantum dots • Controlled water solubility is a goal and for electro-optical use polymer coatings facilitate charge separation
General properties	• Quantum dots are nanoscale forms of direct gap semiconductors • Their strong absorption and emission can be tuned throughout UV/visual spectrum (VIS)/ near infrared (NIR)
EHS publications (ICON database)	• 26 (all semiconductors)

C_{60} or C-sixty

Molecular formula	• C-sixty is a well-recognized molecule • It can become aggregated at sparing concentrations in water
Commercial availability and uses	• MER Corporation and Frontier Carbon are two well-known producers of high-purity C-sixty • Applications include both anti-oxidants in face creams as well as additives in fuel cells
Typical size and format:	• Sublimation techniques are used to make the material pure • Sold as black powder • Some covalent derivatives are available as well
Surface coatings	• PVP polymers can be used to stabilize in water • Surfactants may also facilitate the water solubilization of this

material

General properties	• C-sixty is considered an inorganic material, closely related to graphite. It has many unique chemical, optical, and electronic properties.
EHS publications (ICON database)	• 195 (all carbon)

Single-walled Carbon Nanotubes

Molecular formula	• Carbon nanotubes are generally pure carbon • Depending on the twist of the tube they can be metallic or semiconducting, and also can have variable length
Commercial availability and uses	• Commercial suppliers abound (greater than 5)
Typical size and format:	• Commercial materials are black powders sold with varying levels of impurities (mainly remnants of metals catalysts) • Rather extreme purification techniques must be used to generate pure materials
Surface coatings	• Polymeric coatings are becoming standard • Can also use direct covalent functionalization as well as surfactants. • The black powders as-is are not very water soluble
General properties	• Like C-sixty, SWCNT have unique electrical and optical (near-IR emission) properties. • Their chemical properties are less pronounced that spherical carbon nanostructures
EHS publications (ICON database)	• 195 (all carbon)

Iron Oxide Nanocrystals

Molecular formula	• Iron oxide can exist in a multitude of crystal phases and iron oxidation states. The most common is Fe_3O_4—magnetite.
Commercial availability and uses	• There are many suppliers for iron oxide powders • Water soluble iron oxide is used as MRI contrast agents
Typical size and format:	• Powders are generally agglomerated and polydisperse • For biomedical applications coatings are included to create isolated and water stable systems
Surface coatings	• Both polymers and surfactants are used to impart water solubility
General properties	• The magnetic properties of nanoscale iron oxides are distinctive • They can be used for MRI imaging to enhance contrast as dopants to permit rf-inductive heating of tissue • They can be used for memory storage applications.
EHS publications (ICON database)	• 118 (all oxides)

Gold Nanoparticles

Molecular formula	• Gold • Some smaller gold nanoparticles are called by the number of (e.g., Gold-55)
Commercial availability and uses	• Commercial suppliers are limited mainly to the biomedical m arena
Typical size and format:	• Most materials are sold as suspensions • The development of shape controlled materials is of great aca interest
Surface coatings	• Polymeric coatings are standard • Controlled water solubility is a goal for near-infrared imaging

General properties	• Gold nanocrystals have strong visible emission • When made as a rod, their plasmon resonance shifts to the near-II • Also used in electron microscopy labeling
EHS publications (ICON database)	• 102 (all metals)

Silver Nanoparticles

Molecular formula	• Silver
Commercial availability and uses	• Silver nanoparticles have recently received much interest for their anti-bacterial applications
Typical size and format:	• Most materials are sold as powders
Surface coatings	• Surface coatings are less available in the commercial arena where surface access is thought to be important for applications
General properties	• Silver nanoparticles have strong visible absorption and also notable anti-microbial qualities
EHS publications (ICON database)	• 102 (all metals)

APPENDIX D. SELECTED TERMS

Certified Reference Material (CRM): Reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence. (ISO International Vocabulary of Basic and General Terms in Metrology [VIM], 1993)

Reference Material (RM): Material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials. (ISO VIM, 1993)

Reference Material Certificate: Document accompanying a certified reference material stating one or more property values and their uncertainties, and confirming that the necessary procedures have been carried out to ensure their validity and traceability. (ISO Guide 30, 1992)

NIST Standard Reference Material® (SRM): A CRM issued by NIST that also meets additional NIST-specific certification criteria and is issued with a certificate or certificate of analysis that reports the results of its characterizations and provides information regarding the appropriate use(s) of the material (NIST SP 260–136). *Note*: An SRM is prepared and used for three main purposes: (1) to help develop accurate methods of analysis; (2) to calibrate measurement systems used to facilitate exchange of goods, institute quality control, determine performance characteristics, or measure a property at the state-of-the-art limit; and (3) to ensure the long-term adequacy and integrity of measurement quality assurance programs. The terms ―Standard Reference Material" and the diamond-shaped logo that contains the term ―SRM," are registered with the United States Patent and Trademark Office.

NIST Reference Material: Material issued by NIST with a report of investigation instead of a certificate to: (1) further scientific or technical research; (2) determine the efficacy of a prototype reference material; (3) provide a homogeneous and stable material so that investigators in different laboratories can be assured that they are investigating the same material; and (4) ensure availability when a material produced and certified by an organization other than NIST is defined to be in the public interest or when an alternate means of national distribution does not exist. A NIST RM meets the ISO definition for a RM and may meet the ISO definition for a CRM (depending on the organization that produced it).

NIST Traceable Reference Material® (NTRMTM): A commercially produced reference material with a well-defined traceability linkage to existing NIST standards for chemical measurements. This traceability linkage is established via criteria and protocols defined by NIST to meet the needs of the metrological community to be served (NIST SP 260–136). Reference materials producers adhering to these requirements are allowed use of the NTRM trademark. A NIST NTRM may be recognized by a regulatory authority as being equivalent to a CRM.

NIST Certified Value: A value reported on an SRM certificate or certificate of analysis for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias have been fully investigated or accounted for by NIST. (NIST SP 260–136)

NIST Reference Value: A best estimate of the true value provided on a NIST certificate, certificate of analysis, or report of investigation where all known or suspected sources of bias have not been fully investigated by NIST. (NIST SP 260–136)

NIST SRM Certificate or Certificate of Analysis: In accordance with ISO Guide 31: 2000, a NIST SRM certificate is a document containing the name, description, and intended purpose of the material, the logo of the U.S. Department of Commerce, the name of NIST as a certifying body, instructions for proper use and storage of the material, certified property value(s) with associated uncertainty(ies), method(s) used to obtain property values, the period of validity, if appropriate, and any other technical information deemed necessary for its proper use. A Certificate is issued for an SRM certified for one or more specific physical or engineering performance properties and may contain NIST reference, information, or both values in addition to certified values. A Certificate of Analysis is issued for an SRM certified for one or more specific chemical properties. Note: ISO Guide 31 is updated periodically; check with ISO for the latest version.

NIST Certificate of Traceability: Document stating the purpose, protocols, and measurement pathways that support claims by an NTRM to specific NIST standards or stated references. No NIST certified values are provided, but rather the document references a specific NIST report of analysis, bears the logo of the U.S. Department of Commerce, the name of NIST as a certifying body, and the name and title of the NIST officer authorized to accept responsibility for its contents.

NIST RM Report of Investigation: Document issued with a NIST RM that contains all the technical information necessary for proper use of the material, the logo of the U.S. Department of Commerce, and the name and title of the NIST officer authorized to issue it. There are no NIST certified values provided, and authorship of a report's contents may be by an organization other than NIST.

NIST Report of Analysis (ROA): Document containing the certification of the material and including such information as the base material used, how the SRM was manufactured, the certification method(s) and description of procedures, outside collaborators, instructions for use, special instructions for packaging, handling, and storage, and a plan for stability testing. The ROA is intended for internal NIST use only

APPENDIX E. ACRONYMS

AES	Auger electron spectroscopy
AEM	Analytic electron microscope
AFM	Atomic force microscope
AF&PA	American Forest & Paper Association
AFRL	Air Force Research Laboratory
AGM	Alternating gradient magnetometer
Ag	Silver metal
ASTM	American Society for Testing and Materials International
Au	Gold metal
BET	Burnauer, Emmett, and Teller analysis
BeO	Beryllium oxide
C_{60}	Fullerene
CBED	Convergent beam electron diffraction
CBEN	Center for Biological and Environmental Nanotechnology
CdSe	Cadmium selenide
CdS	Cadmium sulfide
CDC	U.S. Centers for Disease Control and Prevention
CEN	European Commission for Standardization
CeO_2	Cerium oxide
CNT	Carbon nanotube
CNST	Center for Nanoscale Science and Technology
CPC	Condensation particle counter
CRM	Certified Reference Material
CFSAN/FDA	U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition
CSTL	Chemical Science and Technology Laboratory
DLS	Dynamic light scattering
DNA	Deoxyribonucleic acid
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy
EDS	Energy dispersive X-ray spectrometry
EDX	Energy dispersive X-ray
EELS	Electron energy loss spectroscopy
EHS	Environmental health and safety
EM	Electron microscopy
EMI	Electro magnetic interference

EPA	U.S. Environmental Protection Agency
EPIC	Electronic and photonic integrated circuit
EPMA	Electron probe microanalyzers
eV	Electron volt
FDA	U.S. Food and Drug Administration
FDA/OC	U.S. Food and Drug Administration Office of the Commissioner
Fe	Iron metal
Fe_3O	Iron oxide
FET	Field effect transistor
FIB	Focused ion beam
FIM	Field ion microscope
FMR	Ferromagnetic resonance
FPA	Food Products Association
FTIR	Fourier transform infrared
GMA	Grocery Manufacturers Association
ICP/MS	Inductively coupled plasma mass spectrometry
IEC	International Electrotechnical Commission
IOM	Institute of Occupational Medicine
IR	Infrared
ISO	International Organization for Standardization
ISS	Ion scattering spectroscopy
ICP	Inductively coupled plasma
LEAP	Local electrode atom probe
LED	Light-emitting diode
LMMS	Laser microprobe mass spectrometry
LED	Light-emitting diode
MALLS	Multi-angle laser light scattering
MED	Mid-Continent Ecology Division
MEL	Manufacturing Engineering Laboratory
MFM	Magnetic force microscopy
MOUDI	Micro-orifice uniform deposit impactor
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MSEL	Materials Science and Engineering Laboratory
MWCNT	Multi-walled carbon nanotubes
N_2	Nitrogen gas

NASA	National Aeronautics and Space Agency
NCI	National Cancer Institute
NCL	Nanotechnology Characterization Laboratory
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NIST	National Institute of Standards and Technology
NIR	Near infrared
nm	Nanometer
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NMR	Nuclear magnetic resonance (spectroscopy)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NSF	National Science Foundation
NSET	Subcommittee on Nanoscale Science, Engineering and Technology of the Committee on Technology of the National Science and Technology Council
NSOM	Near-field scanning optical microscopy
NSTC	National Science and Technology Council
NTRMTM	NIST Traceable Reference Material Trademark
OECD	Organisation for Economic and Co-operative Development
ONAMI-SNNI	Oregon Nanoscience and Microtechnologies Institute–Safer Nanomaterials and Nanomanufacturing Initiative
ORD	Office of Research and Development
OSTP	Office of Science and Technology Policy (Executive Office of the President)
PAMAM	Polyamidoamine
PbS	Lead sulfide
PCB	Polychlorinated biphenyl
Pt	Platinum metal
PHA	Pulse height analysis
PNNL	Pacific Northwest National Laboratory
QD	Quantum dot
QSAR	Quantitative structure-activity relationship
R&D	Research and Development
RBS	Rutherford backscattering spectrometry
RM	Reference material
ROA	Report of Analysis
ROS	Reactive oxygen species

SAED	Selected area electron diffraction
SAXS	Small angle X-ray scattering
SANS	Small angle neutron scattering
SEM	Scanning electron microscope/microscopy
SEMPA	Scanning electron microscopy with polarization analysis
SERS	Surface enhance Raman spectroscopy
Si	Silicon
SiC	Silicon carbide
SiO_2	Silicon dioxide
SIMS	Secondary ion mass spectroscopy
SMPS	Scanning mobility particle sizer
SPM	Scanning probe microscopy/microscope
SRM	Standard Reference Material
STAR	Science to Achieve Results
STEM	Scanning transmission electron microscopy/microscope
STM	Scanning tunneling microscope
SWCNT	Single-walled carbon nanotubes
TiO_2	Titanium dioxide
TEM	Transmission electron microscopy/microscope
TGA	Thermogravimetric analysis
UV	Ultraviolet
VSM	Vibrating sample magnetometer
WDS	Wavelength dispersive X-ray spectrophotometer
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction
XRF	X-ray fluorescence