Standards for Physico-Chemical Measurements of Nanomaterials

Debra L. Kaiser
Technical Program Director
Material Measurement Laboratory, NIST, US
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Outline of Presentation

• Introduction
• Key physico-chemical properties of nanomaterials
• Reference materials
• Validated protocols
• Documentary standards
• Linkages of standards
• Education standards
• Summary

Images taken at NIST
NIST’s Standards Mission

1901: House Science Committee on Coinage, Weights, and Measures passed a bill to establish the National Bureau of Standards (NBS)

A non-regulatory Agency in the Department of Commerce

Mission: Advance measurement science, standards, and technology in ways that enhance U.S. economic security and improve quality of life

- The U.S. National Metrology Institute (NMI): the organization responsible for producing standards in the U.S. that are recognized by the NMI of other countries (76 total)
- The U.S. holder of the primary standards of the seven fundamental SI units, e.g., length (m) and mass (kg)

From the U. S. Constitution, Article I, Section 8

1988: NBS becomes the National Institute of Standards and Technology (NIST)
Importance of Standardization

- Assure that manufacturers and service providers meet specifications
  - Promote trade through interoperability of products and services
  - Provide quality assurance in manufacturing
- Establish regulations
- Protect our health, safety, and the environment
- Enable scientific discoveries and advances

The Great Baltimore Fire of 1904

Fire equipment responding from regional cities were rendered useless by the incompatibility of hose and fire hydrant connections. The fire claimed 1,526 buildings in an area of seventy city blocks. An NBS study that same year revealed that there were about 600 variations in fire-hose couplings across the country. After the Baltimore fire, a national standard for fire hydrant connections was adopted.
Standards in Everyday Life

- Mass
- Time
- Current
- Temperature
- Distance
- Intensity of light
Challenges for Nanotechnology Standards

Typically, standards support mature technologies backed by an established metrological and standards systems.

Nanotechnology is an emerging area characterized by:

- Rapidly changing technical landscape
- Emergence of new fields, e.g., nanotoxicology and nanomedicine
- Evolving metrological infrastructure
- Lack of established regulatory framework
- Acute public awareness of health and safety concerns

Multi-Functional Nanoscale Platform for Cancer Detection and Drug Delivery

S. McNeil (2005)
Measurement Standards: Scope and Relationships

An object or a method used to assess and ensure that measurements yield results that are accurate, precise, and reproducible, and leading to confidence in the measurement method and results.
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Importance of Physico-Chemical Properties

2005:
“There is a strong likelihood that biological activity of nanoparticles will depend on physicochemical parameters not routinely considered in toxicity screening studies. Physicochemical properties that may be important in understanding the toxic effects of test materials include particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, and porosity.”
G. Oberdöster et al., Particle and Fiber Toxicology 2(8), 2005

2007:
“A key element of any nanomaterial toxicity screening strategy is a detailed and comprehensive physicochemical characterization of the test material being studied.”

2011:
“With the rapid rise of the field of nanotechnology and the design and production of increasingly complex nanoscale materials, it has become ever more important to understand how the physical form and chemical composition of these materials interact synergistically to determine toxicity.”
A. Maynard, D. Warheit, M. Philbert, Toxicological Sciences 120, 2011
Key Physico-Chemical Properties

18 published lists of priority properties for toxicological assessments: six most frequently listed properties

<table>
<thead>
<tr>
<th>Property or Characteristic</th>
<th>Frequency Named</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental/molecular composition (bulk)</td>
<td>16</td>
</tr>
<tr>
<td>Surface area (specific)</td>
<td>14</td>
</tr>
<tr>
<td>Particle size</td>
<td>13</td>
</tr>
<tr>
<td>Morphology/form/shape</td>
<td>13</td>
</tr>
<tr>
<td>Particle size distribution</td>
<td>12</td>
</tr>
<tr>
<td>Surface chemistry</td>
<td>12</td>
</tr>
</tbody>
</table>

agglomeration/aggregation state, crystal structure, surface charge, solubility, particle concentration...

Nanoscale reference materials for environmental, health and safety measurements: needs, gaps and opportunities.
Stefaniak et al., Nanotoxicology, 2012
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Reference Materials

Reference Material (RM)

Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process

Certified Reference Material (CRM)

RM accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated:

- Uncertainty statement
- Traceability statement (to known references)
- Metrologically valid procedures

International Vocabulary of Metrology (VIM), 2008

Organizations use different terms

<table>
<thead>
<tr>
<th>Term</th>
<th>NIST</th>
<th>Joint Research Center (JRC), EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM</td>
<td>SRM: Standard Reference Material™</td>
<td>CRM</td>
</tr>
<tr>
<td>RM</td>
<td>Many RMs meet VIM requirements for CRM</td>
<td>Quality control material</td>
</tr>
</tbody>
</table>
Importance of Reference Materials

- Increased confidence in measurement results
  - Provision of **reproducibility and accuracy**
  - Assignment of **uncertainty** values
  - Provision of **traceability** to SI units
- Conduct of **interlaboratory comparisons**
- Calibration of an apparatus or instrument
- Measurement method assessment
- Quality control / proficiency testing

http://www.nist.gov/srm/
Factors for Reference Material Selection

RMVs typically take 2-3 years to develop

- Large volume production
- Used in large number of products
- Likelihood of exposure and associated hazards
- Usefulness for an instrument calibration process
- Assignment of property values of greatest need
- Availability of appropriate materials or sources
- Potential to address a broad spectrum of needs from industry, regulatory agencies, research institutions
- Potential collaboration with external organizations (intellectual, financial support)

NIST Reference Materials

National Institute of Standards & Technology

Report of Investigation

Reference Material® 8012

Gold Nanoparticles, Nominal 30 nm Diameter

This Reference Material (RM) is intended primarily to evaluate and qualify methodology and/or instrument performance related to the physical/dimensional characterization of nanoscale particles used in pre-clinical biomedical research. The RM may also be useful in the development and evaluation of in vitro assays designed to assess the biological response (e.g., cytotoxicity, hemolysis) of nanomaterials, and for use in interlaboratory test comparisons. RM 8012 consists of nominally 5 mL of citrate-stabilized Au nanoparticles in an aqueous suspension, supplied in hermetically sealed pre-scored glass ampoules sterilized by gamma irradiation. A unit of RM 8012 consists of two 5 mL ampoules. The suspension contains primary particles (monomers) and a small percentage of clusters of primary particles.

https://www.nist.gov/srm

Search on reference number or keywords
Can read Report of Investigation without purchasing RM

Contents

• Brief description
• Expiration of value assignment
• Maintenance of RM
• Reference values
• Informational values
• Handling and storage
• Instructions for use
• Preparation and analysis
  • Material source and processing
  • Heterogeneity assessment
  • Value assignment
  • Uncertainty analysis
• Methods for reference value assignments
• References
Reference Materials from Metrology Institutes

AIST (Japan): National Inst. of Advanced Industrial Science/National Metrology Inst. of Japan
  • Titanium dioxide nanoparticles: specific surface area (3)

BAM (Germany): German Federal Inst. for Materials Research and Testing
  • Silver nanoparticles: particle size distribution

JRC (EC): European Commission Joint Research Centre
  • Silicon dioxide nanoparticles: mean diameter (3)

NIM (China): National Inst. of Metrology
  • Nano-alumina: specific surface area (3)

NIST (US): National Institute of Standards of Technology

NRC (Canada): National Research Council
  • Single wall carbon nanotube (raw soot): impurity element concentrations
  • Cellulose nanocrystals: mass fraction of trace metals
Representative Test Material

Material, which is sufficiently homogenous and stable with respect to one or more specified properties, and is implicitly assumed to be fit for its intended use in the development of measurement and test methods that target properties other than those for which homogeneity and stability have been demonstrated

ISO/Technical Specification 16195:2013, 3.1

EC/JRC Nanomaterials Repository

27 commercially sourced “representative test materials” maintained by Institute for Health and Consumer Protection (IHCP)

Some are used in the OECD testing programs


Private Sector

Producers provide nanoscale test materials of variable quality

Materials selected by OECD testing programs to provide test materials, e.g., Ag, TiO$_2$, CeO$_2$

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Validated Protocols

- Step-by-step, reproducible, and validated procedures
- Sample preparation, conduct of measurements, and data analysis
- Typically freely available on public website
- May form the basis for a documentary standard
- May be developed for a reference material

- Direct comparisons of measurements between laboratories
- Consistency in reporting results
- Harmonization of nanomaterial property measurements
NIST Validated Protocols

All protocols are freely available on the web

Sample preparation
Physico-chemical measurements
Biological measurements

• Measuring the Size of Nanoparticles in Aqueous Media Using Batch-Mode Dynamic Light Scattering
• Protocols for Accelerating Laboratory Weathering and Measurements of Degradation of Polymer-Multiwalled Carbon Nanotube Composites
• Challenges, Strategies and Opportunities for Measuring Carbon Nanotubes within a Polymer Composite by X-ray Photoelectron Spectroscopy
• Measurement of silver nanoparticle dissolution in complex biological and environmental matrices using UV/visible absorbance measurements
• Strategies for Scanning Electron Microscopy Sample Preparation and Characterization of Multiwall Carbon Nanotube Polymer Composites
• Characterization of Nanoparticle Suspensions Using Single Particle Inductively Coupled Plasma Mass Spectrometry

http://www.nist.gov/mml/nanoehs-protocols.cfm
**Other Assay Protocols**

<table>
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<th>Assay Cascade Protocols</th>
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<tr>
<td><strong>Size, Size Distribution</strong> (Questions?)</td>
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<td>PCC-1</td>
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<td>PCC-6</td>
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<td>PCC-7</td>
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<tr>
<td>PCC-10</td>
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<td>PCC-15</td>
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<tr>
<td><strong>Zeta Potential</strong> (Questions?)</td>
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<td>PCC-2</td>
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<td>PCC-12</td>
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<tr>
<td>PCC-13</td>
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<tr>
<td><strong>Chemical Composition</strong> (Questions?)</td>
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<td>PCC-9</td>
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<tr>
<td>PCC-11</td>
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<tr>
<td>PCC-14</td>
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</tbody>
</table>

Sterility & Endotoxins  
Physicochemical characterization  
*In Vitro* Characterization  
Toxicology  
Pharmacology  
*In Vivo* Characterization

All protocols are freely available on the website:  
https://ncl.cancer.gov/resources/assay-cascade-protocols
Protocol Content

Contents

1. Introduction
2. Sample Preparation and Inspection
3. AFM Imaging and Size Measurement Procedure
4. Image Analysis
5. Reporting Particle Size Data
6. References

AFM calibration grating with certified step height = 19.5 nm ± 0.8 nm
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New idea generated and presented at a Committee meeting

Vote or ballot

Rejected
Approved

New Work Item registered

Team assembled

Draft standard put to ballot for full Committee vote

Draft standard not approved

Draft standard revised to address negative comments

Draft standard approved

Standard published and sold

Requirements
- Open
- Transparent
- Consensus-driven
- Balance of participation
- Due processes
Standards Committee Structures

- Formed in 2005
- Direct participation model, organized on a country basis
- Industry, government, and academic members from each country
- 34 participating, 14 observer countries
- 4 technical subcommittees: *Terminology and Nomenclature; Measurement and Characterization; Health, Environment and Safety; Materials Specifications*
- Typically 3–5 years for entire process

ISO TC229

- Country A
- Country B
- Country C

ASTM E56

- Industry
- Government
- Academia & NGOs

- Formed in 2005
- Direct participation model
- 170 participants from 20 countries
- 5 technical subcommittees: *Informatics and Terminology; Physical and Chemical Characterization; Environment, Health and Safety; Nano-Enabled Consumer Products; Education and Workforce Development*
- Typically 1–2 years for entire process
ISO Standards Hierarchy

Normative document, *i.e.*, a document containing elements that describe the scope of the document and which set out provisions (requirements, statements and recommendations) that shall be followed

- **International Standard**
  - A normative document that is approved by the ISO Central Secretariat
  - Three published

- **Technical Specification**
  - A normative document that is approved by the Technical Committee
  - Measurement methods, terminology, and materials and product classification
  - 34 published

- **Technical Report**
  - An *informative document* that contains data or information of a different kind from that which is normally published as an International Standard
  - Results of a literature review with analysis
  - 14 published
A definitive procedure that produces a numerical test result with a precision and bias statement obtained via an interlaboratory study

- Four published

A definitive set of instructions for performing one or more specific operations that does not include a test result

- Operations include sample preparation, measurement methods, calculations
- Two published

A compendium of information or series of options that does not recommend a specific course of action

- Ten published

Interlaboratory study: conducted to develop precision and bias statements

- Precision: closeness of agreement between test results obtained under prescribed conditions; includes repeatability and reproducibility standard deviations

- Bias: systematic error that contributes to the difference between the mean of a large number of test results and an accepted reference value
<table>
<thead>
<tr>
<th>Document type</th>
<th>Number</th>
<th>Nanomaterial type</th>
<th>Measurand (property)</th>
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<td>composition (6)</td>
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<td>size (1); shape (1)</td>
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<td>surface characterization (1)</td>
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<td>quantum dots (1), cellulose nanocrystals (1)</td>
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<td></td>
<td>general (1)</td>
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<tr>
<td>Test Method</td>
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<td>surface area concentration (1)</td>
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<td>Practice</td>
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<td>mean sizes/diameters and particle size distribution (1)</td>
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<tr>
<td>Guide</td>
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<td>nanoparticles (3)</td>
<td>particle size distribution (2); particle size (1)</td>
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<td></td>
<td></td>
<td>nano-sized biological materials (1)</td>
<td>electrophoretic mobility and zeta potential (1)</td>
</tr>
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Gold NP RMs
- 1476 units sold as of 1/5/16
- 53% non-US/ 47% US
  - 46% to industry
  - 42% to government (including 12 NMIs)
  - 12% to academia
- 10 nm, 30 nm, and 60 nm nominal diameter
- 5 mL, citrate-capped in aqueous suspension
- Mean size measured by six techniques
- Extensive “informational” data included

Validated Protocols
- Size by AFM, TEM, SEM, and DLS
- Electrolytic conductivity
- pH of nanoparticle suspensions

Documentary Standards
- www.astm.org

ASTM International Committee E56 on Nanotechnology
- NIST gold nanoparticle RMs used in two interlaboratory studies
- RMs used for three Standard Test Methods: E2490-09, E2524-08, E2526-08
- RMs used to generate a precision statement for standard E2490 (DLS)
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ASTM Nanotechnology Education Standards

Basic Skill Set Standards for Education and Workforce Development

• Provide a framework for basic nanotechnology workforce education by academic institutions
• Develop or evaluate education programs in the nanotechnology field

Published Standards

E2996 Standard Guide for Workforce Education in Nanotechnology
Health and Safety

E3001 Standard Practice for Workforce Education in Nanotechnology
Characterization

E3034 Standard Guide for Workforce Education in Nanotechnology
Pattern Generation

E3059 Standard Guide for Workforce Education in Nanotechnology
Infrastructure

E3071 Standard Guide for Nano-Technology Workforce Education in
Materials Synthesis and Processing

For full course materials, contact Bob Ehrmann, rehrmann@engr.psu.edu

Framework of topics to be covered in a course

https://www.astm.org/COMMITTEE/E56Nanotechnology.htm
Summary

• Two necessary components of standardization
  • **Physical artifacts**: reference materials
  • **Methods**: validated protocols and documentary standards

• Some standards available for physico-chemical property measurements of nanomaterials
• Opportunities for participation in standards development organizations
• Opportunities for collaboration in development of all standards

Contact Information
Debbie Kaiser
debra.kaiser@nist.gov
Tel. 301-975-6759
NIST, 100 Bureau Drive, Stop 8301
Gaithersburg MD 20899

30 nm gold RM