NIST Special Publication 1233

NIST Nanotechnology Environmental, Health, and Safety Research Program: 2009–2016

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https://doi.org/10.6028/NIST.SP.1233

National Institute of
Standards and Technology
U.S. Department of Commerce

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November 2018

U.S. Department of Commerce
Wilbur L. Ross, Jr., Secretary

National Institute of Standards and Technology
Walter Copan, NIST Director and Under Secretary of Commerce for Standards and Technology

National Institute of Standards and Technology Special Publication 1233
Natl. Inst. Stand. Technol. Spec. Publ. 1233, 55 pages (November 2018)
CODEN: NSPUE2

This publication is available free of charge from:
https://doi.org/10.6028/NIST.SP.1233

Abstract

In response to needs of a government-wide initiative in nanotechnology led by a subcommittee within the White House's Office of Science and Technology Policy, NIST established a nanotechnology environmental, health, and safety (nano-EHS) research program in 2009 that remained active through 2016. This document summarizes the NIST Nano-EHS Program goals, projects, outputs, and impacts. The program was designed to address, in collaboration with other agencies, the research needs for a comprehensive U.S. measurement infrastructure for nano-EHS as identified by federal agencies participating in the National Nanotechnology Initiative. Such an infrastructure included a suite of measurement tools—methods, protocols, standards (reference materials and documentary), instruments, models, and benchmark (validated) data. The NIST Nano-EHS Program made substantial progress in developing the required infrastructure, producing 9 reference materials, 24 web-accessible protocols, and 212 archival journal articles, 59% of which have been published in journals with impact factors greater than 3. In addition, program team members held leadership positions in the nanotechnology committees of major standards development organizations and led and contributed to the development of standards in these committees.

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1. Introduction

1.1. What is Nano-EHS?

Nano-EHS is a shorthand term for nanotechnology-related environmental, health, and safety issues, which may determine the potential risks of engineered nanomaterials (ENMs)[1] and nanotechnology-enabled products (NEPs)[2] to the environment and to humans. Nanotechnology has already led to new and improved products and remains poised to further "transform production processes and consumer products for everything from traditionally high-tech products like computers to less obvious sources of innovation and growth like sunscreen and paint" [1]. Potential nano-EHS risks must be identified, assessed, and managed to enable widespread commercialization and adoption of ENMs and NEPs. Knowledge of such risks to workers, the public, and the environment will enable appropriate regulatory measures to be established, thus alleviating consumer concerns and spurring development and manufacturing of ENMs and NEPs. To perform science-based assessment and management of nano-EHS risks, industry and regulatory agencies need access to and the means to generate accurate and reproducible data on properties, exposure, and hazards of ENMs and NEPs.

1.2. The National Nanotechnology Initiative and Nano-EHS

The use of nanomaterials in art dates to the 4th century BC [2] and there are numerous examples of nanotechnology innovations dating from the mid-to-late 1900's, such as the scanning tunneling microscope that enabled single atom imaging, the semiconductor transistor that is the basis of integrated circuits, and the discovery of novel nanomaterials including carbon nanotubes and quantum dots. In 2000, President Clinton launched the National Nanotechnology Initiative (NNI) to coordinate Federal agency nanotechnology efforts and to spur U.S competitiveness in nanotechnology, which led to the rapid promulgation of the term 'nanotechnology'. Three years later, Congress enacted the 21st Century Nanotechnology Research and Development Act [3], which established the statutory foundation for the NNI. The first NNI Strategic Plan [4], written by NNI Federal agency representatives to the Nanoscale Science, Engineering, and Technology Subcommittee (NSET) of the National Science and Technology Council's Committee on Technology, was published in 2004. One of the Plan's four goals was to *Support the Responsible Development of Nanotechnology*, which largely concerned nano-EHS issues. In addition, the formation of a Nanotechnology Environmental and Health Implications (NEHI) Working Group consisting of Federal agency representatives was mandated in this Strategic Plan. The criticality of addressing EHS issues led to the 2006 publication of a document addressing nano-EHS research needs [5]. Subsequently, strategies for nano-EHS research in the Federal government were published in 2008 [6] and 2011 [7]. The NEHI Working Group developed all three of these documents, and NIST staff members have played an active and leading role in the NEHI Working Group since its inception. In addition, NIST led the development of a 2014 report [8] documenting the

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[1] Engineered nanomaterials (ENMs) are materials that have been purposely synthesized or manufactured to have at least one external dimension of approximately 1 to 100 nanometers (nm)—at the nanoscale—and that exhibit unique properties determined by this size. [7]

[2] Nanotechnology-enabled products (NEPs) are intermediate engineered nanoscale products, including ENMs embedded in a matrix material, that exist during manufacture and in final products. [7]

accomplishments and coordination of the NNI-NEHI agencies in response to the needs called out in the 2011 strategy document.

1.3. The NIST Role in Federal Nano-EHS Efforts

Figure 1 illustrates the inter-relationships and synergies of the six core research categories in the 2011 nano-EHS research strategy. The product of exposure and hazard is a measure of the risks of ENMs to humans and the environment. Quantifying risk requires accurate and reproducible measurements, which are central to the *Nanomaterial Measurement Infrastructure* (NMI) research category. The NMI consists of a "suite of complementary tools for accurate, precise, and reproducible measurements [that] is critical for reliable assessment of exposure and hazards for humans and the environment across all life cycle stages of…ENMs and…NEPs" [1]. The NMI is foundational because of the role "measurement tools play in supporting and enabling the research needs in the other research categories" [1]. Measurement tools are defined as methods, protocols, standards (reference material and documentary), instruments, models, and benchmark (validated) data. The goals of the NMI core research area are two-fold:

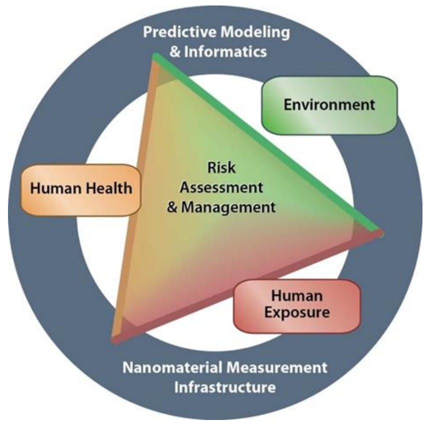

Fig 1. Interrelationships of the six core research areas

(1) Develop measurement tools to detect and identify engineered nanoscale materials in products and relevant matrices and determine their physico-chemical properties throughout all stages of their life cycles

(2) Develop measurement tools for determination of biological response, and to enable assessment of hazards and exposure for humans and the environment from ENMs and NEPs throughout all stages of their life cycles.

NIST is the lead agency for the NMI research category. As described in subsequent sections of this report, the NIST Nano-EHS Program was well-aligned with the NMI goals.

2. History of the NIST Nano-EHS Program

2.1. Biomedical Applications

Four years prior to the establishment of the NIST Nano-EHS Program, a NIST-wide effort in nanomaterial metrology and standards was initiated, with a focus on nanoparticles for cancer therapeutics. In 2005, the National Cancer Institute (NCI) established the Nanotechnology Characterization Laboratory (NCL) [9], the activities of which represent a formal scientific partnership between the NCI, the Food and Drug Administration (FDA), and NIST. The NCL's mission is to "perform and standardize the pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics…and facilitate the development and translation of nanoscale particles and devices for clinical applications" [9]. The NCI awarded NIST $1.0 M/y for three years to develop quantitative, reproducible measurement methods and protocols for nanoparticle characterization and to collaborate with NCI and FDA researchers to determine the best measurement tools, protocols, and analysis methods for physically characterizing nanoparticles. One key output of the partnership was the production of three gold nanoparticle reference materials (RMs) with nominal diameters of 10 nm [10], 30 nm [11], and 60 nm [12]. These nanoscale RMs, formally requested by the Office of the Director of NCI, were the first of their kind appropriate for biomedical-related studies and applications. As a direct result of the gold nanoparticle RM project, NIST gained critical expertise and established core capabilities across a broad range of ENM property measurements, including quantitative analysis of nanomaterial size using six independent measurement techniques. This expertise and associated capabilities provided the initial foundation on which the NIST Nano-EHS Program was built, and established NIST internationally as a leader in nanomaterial metrology.

2.2. Nano-EHS Funding

Formal NIST-wide programs are typically established with new, federally appropriated "Initiative" funds that are designated for a specific topic. Such funds are a common means of increasing the NIST Scientific and Technical Research and Services (STRS) budget. After five years, Initiative funds become general undesignated STRS funds. The Program received funds from two Initiatives: *Nano-EHS* in 2009 and *Nanomanufacturing* in 2012. Additional one-year funds were received from the NIST Director in 2010 and 2011. These designated funds are summarized in Table 1. Many of the Divisions involved in the Program supplemented their nano-EHS activities with their own STRS funds; these funds are not included in Table 1.

Table 1. Designated Nano-EHS funds

	Funds by Fiscal Year, $ M							
Source of Funds	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Nano-EHS Initiative	1.8	1.8	1.8	1.8	1.8			
NIST Director		1.0	1.0					
Nanomanufacturing Initiative				2.0	2.0	2.0	2.0	2.0
Total funds	**1.8**	**2.8**	**2.8**	**3.8**	**3.8**	**2.0**	**2.0**	**2.0**

Table 2. Nano-EHS investments reported to the NNI

Investments by Fiscal Year, $ M							
2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
3.5	3.4	3.2	7.2	6.2	5.1	6.7	5.9

Annually, each Federal agency participating in the NNI is required to report its investments by topic, known as Principal Component Areas (PCAs). These investments are included in the annual *NNI Supplement to the President's Budget;* the figures that NIST reported for the EHS PCA for years 2009-2016 [13-20] are shown in Table 2. The funding levels in Table 2 were obtained by directly querying the NIST Operating Units and include both designated and division funds.

2.3. Nano-EHS Program Researchers

Since its inception in 2009, the nano-EHS Program has involved researchers from at least seven Divisions and three Laboratories (Operating Units) within NIST. From 2012-2016, the participating Labs and Divisions were:

- Engineering Laboratory
  - *Materials and Structural Systems Division, 731*
- Material Measurement Laboratory
  - *Materials Science and Engineering Division, 642*
  - *Materials Measurement Science Division, 643*
  - *Biosystems and Biomaterials Division, 644*
  - *Chemical Sciences Division, 646*
  - *Applied Chemicals and Materials Division, 647*
- Physical Measurement Laboratory
  - *Engineering Physics Division, 682*

More than 90 researchers have worked on the Program over its eight-year span. The researchers, listed in Appendix A, are grouped into five categories: (1) NIST principal investigators; (2) NIST contributing staff members; (3) NRC postdoctoral fellows; (4) Postdoctoral research associates; and (5) Student research associates.

3. NIST Nano-EHS Program Goals and Projects

Throughout the tenure of the Program, the overarching focus has been on the development of measurement tools, defined here as methods, instrumentation, protocols and assays, and RMs. In developing measurement tools, studies on specific ENMs produced validated data that were published. The term "validated" implies that the data were reproducible and generated by metrologically valid methods to ensure the greatest accuracy and "quality" of the data.

From the outset, the Program focused on ENMs of greatest regulatory concern based on production volume, widespread use in NEPs, and likely hazards—namely, silver (Ag) and titanium dioxide (TiO_2) nanoparticles, and carbon nanotubes (CNTs), both single-wall (SW) and multi-wall (MW). Gold (Au) nanoparticles are a key benchmark material for physico-chemical and toxicological measurements and are important in advanced biomedical applications such as cancer treatment. As the Program progressed, the media in which measurements were performed transitioned from simple media (*e.g.*, air, vacuum, water) to complex media, including both environmental (*e.g.*, sediment, soil) and biological (*e.g.*, blood, tissue) media. From 2012–2016, a portion of the Program was devoted to the application of measurement tools to specific ENM-NEP systems. Throughout the Program, many researchers led or contributed to the development of documentary standards and guidance documents in three standards-related organizations, namely ASTM International, the Organization for Economic Cooperation and Development (OECD), and the Organization for International Standardization (ISO).

3.1. 2009–2011

In 2009, a Steering Committee was formed whose function was to distribute the Nano-EHS Initiative and NIST Director's funds. In 2009 and 2010, the funds were used to support single principal investigator research activities on the order of $25 K–$150 K. These activities focused on the development of methods to measure physico-chemical and biological properties of ENMs and on the development of ENM RMs. Examples of activities included the development of single-wall carbon nanotube and titanium dioxide RMs, methods for stabilizing silver nanoparticles in environmental and biological media, and protocols for assessing DNA damage in plants and organisms due to the presence of ENMs. These activities were not centrally coordinated, though some involved informal interactions between researchers at NIST and researchers from other government agencies, industry, and academia.

In 2011, the Steering Committee defined three Program focus areas: (1) the determination of surface attributes and transformations involving molecular adsorbents on ENM surfaces; (2) measurement of the concentrations of nano-silver and silver ions in various media; and (3) toxicological measurements. Although the activities within the focus areas were not centrally coordinated, the collaborations among NIST staff members increased substantially and channels for information sharing became well established.

3.2. 2012–2014

Beginning with the award of the Nanomanufacturing Initiative in 2012, a Technical Program Director was appointed to coordinate the Nano-EHS Program and the Steering Committee was disbanded. Three-year (2102–2014) Program and Spend Plans were developed by this Director and approved by the NIST Director's Office. The Plans were closely aligned with the research needs in the Nanomaterial Measurement Infrastructure (NMI) research category of the 2011 Nano-EHS Research Strategy [1]. Coordination with other NNI-NEHI agencies was strengthened and collaborations among various agencies were initiated and expanded, some continuing through 2016. Funds were allocated for specified research activities by designated researchers in the Divisions. The goals of the Program were two-fold:

(1) Enable other organizations to perform accurate and reproducible measurements by providing validated measurement tools
(2) Enable other organizations to detect and quantitatively characterize ENMs in NEPs using broadly available, commercial instruments

Specific deliverables by year for 2012-2014 are presented in the Program Plan document in Appendix B.

3.2.1. Goal 1

There is an endless combination of ENMs subjected to various media during their lifecycles; thus, it was clear that NIST could not determine the properties of *all* ENMs of interest to multiple stakeholder groups under *all* possible scenarios. To maximize the impact of its investment, NIST focused on the provision of measurement tools to enable other organizations to perform reproducible and accurate measurements on their own materials. This necessitated that the Program focus, to the extent possible, on common, affordable, and widely used instruments for which access was readily available to many organizations.

The objectives of Goal 1 were to conduct the following activities of high-priority as determined by interactions with NNI-NEHI agency and industrial representatives:

a) Develop and release RMs
b) Develop and broadly disseminate validated measurement methods and protocols
c) Lead and provide strong technical contributions to documentary and pre-documentary standards development activities

3.2.2 Goal 2

For the duration of the Program, the number of NEPs on the market has continually increased [21]. Two prevalent NEPs are fabrics (textiles) containing nano-scale Ag, and NEPs manufactured from MWCNT-polymer composites. These two NEPs are the focus of the two objectives for Goal 2:

a) Develop methods to detect and quantitatively characterize key properties[3] of Ag nanoparticles in fabrics
b) Develop methods to detect and quantitatively characterize key properties[4] of MWCNTs in polymer matrix-based NEPs

Teams were established among NIST Program participants to address the objectives for Goals 1 and 2. Team members also worked closely with other key agency partners, notably two of the five US regulatory agencies, i.e., the Consumer Product Safety Commission (CPSC) and the FDA, as well as other National Metrology Institutes (NMIs), including NRC Canada and BAM in Germany, and the European Commission Institute for Reference Materials and Methods (now the Joint Research Centre).

3.3. 2015–2016

In 2015, four new project areas were defined by the Program Director in collaboration with several principal investigators in the Program. Funds were distributed to the seven participating Divisions for specific activities in these new projects and in an overarching measurement tool project that is a continuation of the work in Goal 1 above. These projects continued through 2016, when the NIST Nano-EHS Program formally ended.

The five project areas were:

1) Measurement Tools
2) Release of MWCNTs from Polymer Composites
3) Graphene in Microelectronic Devices
4) Engineered Nanomaterials in Heterogeneous Matrices
5) Lifecycle Speciation of Nano-silver

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[3] For example, number concentration and size and size distribution of Ag NPs; distribution and chemical form of Ag in fabrics.

[4] For example, size and size distribution, morphology, and number concentration of MWCNTs; distribution of MWCNTs in matrix.

Plans for each project were developed that included a team leader, team members, project goal, objectives, and deliverables by objective.

4. NIST Nano-EHS Program Outputs

During its eight-year tenure, the NIST Nano-EHS Program was prolific by any objective measure, producing a substantial number of publications, protocols, and RMs. Each output type will be described separately below.

4.1. Publications

The publications associated with the Program, presented in Appendix C, are organized by type and year published (2009-2018). The type and total number of each are as follows:

1) Archival journal publications: 212
2) Conference proceedings: 25
3) NIST Technical Notes: 3
4) Book chapters: 14

In addition, two team members are co-editors of the book *Metrology and Standardization of Nanomaterials - Protocols and Industrial Innovations*, which has 31 chapters.

One commonly used metric of a publication's impact is the *Journal Impact Factor* (JIF). JIF is a measure that reflects the yearly average number of citations to recent articles published in that journal. 126 of the 212 archival journal publications had JIF values greater than 3. Table 3 shows the number of publications for several ranges of JIF values. JIF values of 5 or above are generally considered representative of "high impact" journals.

Table 3. Number of publications per JIF range.

JIF range	Number of publications
3-5	46
5-10	63
10-15	17

The journals with the greatest number of publications are:

- *Analytical and Bioanalytical Chemistry*: 23
- *Environmental Science and Technology*: 21
- *Journal of Nanoparticle Research*:13
- *ACS Nano*: 11
- *Nanotoxicology*: 9

These journals demonstrate the breadth of the NIST Nano-EHS Program, encompassing physico-chemical, environmental, and toxicological measurement research. As noted in Appendix C, several articles received special recognition from the journals in which they were published.

4.2. Protocols and Assays

Protocols and assays, defined here as step-by-step, reproducible, and validated procedures (methods), are an essential first step in the harmonization of ENM/NEP property measurements by enabling direct comparisons of data between laboratories and greater consistency in reporting data. Protocols may address, either separately or conjointly, sample preparation, conduct of measurements, and data analysis. The need for and importance of protocols are called out in the 2011 Nano-EHS Research Strategy [1], by agencies that regulate ENMs and NEPs, and by industry. Protocols can form the basis for the development of documentary standards published by ISO, ASTM International, and other standards-related organizations.

The list of nanomaterial measurement protocols and assays relevant to nano-EHS that NIST published from 2012–2018 is presented in Appendix D. NIST has a dedicated web site containing 24 publicly available nanomaterial measurement protocols; see https://www.nist.gov/mml/nano-measurement-protocols. These protocols have been published in the 1200 series of NIST Special Publications (SPs) with citable DOI names to provide persistent identification. Five of these protocols were developed in conjunction with the *Center for the Environmental Implications of NanoTechnology*, a multi-university entity led by Duke University with funding from the National Science Foundation and the Environmental Protection Agency. In addition, NIST team members have led the development of 11 assays that are publicly available on NCL's Assay Cascade Protocol web site https://ncl.cancer.gov/resources/assay-cascade-protocols.

4.3. Reference Materials

Reference materials (RMs) is a generic term used here to include NIST Reference Materials, NIST Traceable Reference Materials™ and NIST Standard Reference Materials™ [22]. Definitions of these three types of RMs are provided on the NIST web site [23].

The RMs of relevance to the Nano-EHS Program are listed in Appendix E, which includes technical and sales information. As mentioned previously, the NIST Nano-EHS Program focused on ENMs of greatest regulatory concern based on production volume, widespread use in NEPs, and potential hazards—namely, silver (Ag) and titanium dioxide (TiO_2) nanoparticles and carbon nanotubes (CNTs), both single-wall (SW) and multi-wall (MW). From 2011-2018, NIST produced RMs for each of these ENMs. The three gold nanoparticle RMs, though released in 2008, are included in Appendix E because the large majority of the sales of these RMs occurred post-2008. To date, more than 2050 units of the nine RMs listed in Appendix E have been delivered to stakeholders world-wide.

4.4. Documentary Standards

ISO Technical Committee (TC) 229 on Nanotechnologies and ASTM International Committee E56 on Nanotechnology are arguably the two prevalent standards development organizations (SDOs) in nanotechnology. NIST researchers have played prominent leadership roles in these SDOs, both at the committee level and for specific technical standards.
Committee-level leadership positions include:

- Chair, US Technical Advisory Group (TAG) to ISO TC229 (2005–2010 and 2015–2016)
- Chair, US TAG to ISO TC229 Joint Working Group 2 (JWG2). *Measurement and Characterization* (2005–2016)
- Convener, ISO TC229 WG 3, *Health, Safety and the Environment* (2006–2013)

- Chair, ASTM Committee E56 (2009–2015)
- Vice-Chair, ASTM Committee E56 (2015–2016)
- Co-Chair, ASTM Subcommittee E56.02, *Physical and Chemical Characterization* (2015–2016)
- Chair, ASTM Subcommittee E56.05, *Liaison and International Cooperation* (2012–2016)
- Chair, ASTM Subcommittee E56.07, Education and Workforce Development (2014–2016)

NIST researchers have also led or co-led the writing nearly 20 ISO and ASTM standards, including those currently under development. NIST researchers have also participated substantially in the development of other standards as approved experts serving on the US delegation to ISO 229 and as subject matter experts within ASTM E56. Another international effort in which NIST researchers have been involved is the Organization for Economic Co-operation and Development (OECD), which has produced guidelines pertinent to nano-EHS.

5. NIST Nano-EHS Program Impacts

The number, quality, and breadth of outputs are indicative of the significant impacts of the NIST Nano-EHS Program. Two case studies presented below illustrate the magnitude of specific impacts.

5.1. Case Study I: Gold Nanoparticle Reference Materials

In 2008, NIST released a series of three gold nanoparticle RMs: 8011, nominal diameter = 10 nm; 8012, nominal diameter = 30 nm; and 8013, nominal diameter = 60 nm (Fig. 2). Nanoparticle sizes were determined by six independent techniques, five of which use commonly available commercial instruments. While the RMs were originally intended to support pre-clinical biomedical efforts, they have found great utility in nano-EHS research and metrology development. Though anticipated to be used primarily to evaluate and qualify methodology and instrument performance for dimensional measurements, the RMs have been employed to develop and evaluate *in vitro* assays designed to assess biological response (*e.g.*, cytotoxicity and hemolysis) of ENMs. Further, the RMs have been used in interlaboratory test comparisons for the development or uncertainty analysis of three ASTM E56 and one ISO TC 229 standard. RMs 8012 and 8013 have been widely adopted as calibration standards for single particle inductively coupled plasma mass spectrometry, an important and rapidly emerging measurement technology. Collectively and as of April 2018, 1783 units of the gold RMs have been sold in nearly equal numbers to US and foreign organizations.

Fig. 2. Units of RMs 8011, 8012, and 8013.

A detailed impact study was performed on RM 8012 [11], with information collected and analyzed as of July 10, 2015. Sales statistics for RM 8012 are presented in Table 4. It is notable that, of the 479 units sold, nearly 90 % were purchased by industry and government agencies, including National Metrology Institutes world-wide.

Table 4. Purchasers of RM 8012 as of September 2015

Purchasers of RM 8012	Units, number or % of total sold
Total number	479
Domestic organizations	47%
Foreign organizations	53%
Industry	46%
Government	42%
Academia	12%
NMIs (part of government)	12

As of August 2016, there were more than 90 peer-reviewed publications and 8 non-peer reviewed documents (application notes, documentary standards, white papers, and notes) that utilize one or more of the three gold RMs (8011, 8012, and 8013) for a variety of purposes, or in which the gold RMs are a significant focus of discussion. A graph of the publications related to the gold RMs as of September 2015 is shown in Fig. 3. The principal uses of the gold RMs, from both published and anecdotal sources, include:

- Quality control and quality assurance (especially in analytical services labs and pharmaceutical companies)
- Method and instrument calibration
- Interlaboratory studies and comparisons
- Basic research
- Metrology research
- Method and technique comparisons
- Toxicological and environmental investigations

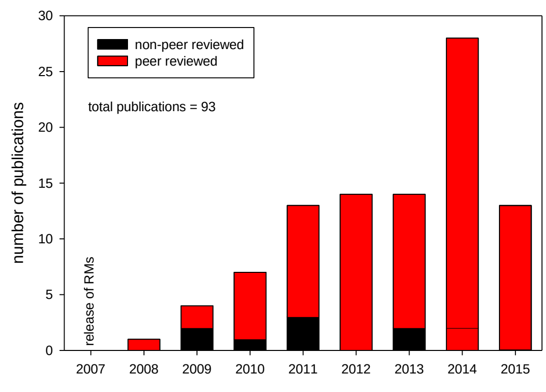

Fig 3. Number of publications by year.

In summary, the NIST gold nanoparticle RMs have been used across the world, with significant impacts on nano-EHS, biomedical applications and nanometrology as demonstrated by sales and documented uses.

5.2. Case Study II: Measurement Assurance for a Nanotoxicity Assay

Cell-based toxicity assays (*i.e.*, cytotoxicity assays) are commonly employed as screening tools to identify potential hazards associated with new chemicals and materials used in manufacturing. These assays are also used to evaluate biological effects associated with ENMs. Significant variability in such assays due to various sources have led to conflicting hazard data. For ENMs, some sources may include nanometer dimensions, large surface-to-volume ratios, wide ranges of composition and coatings, and the introduction of ENMs into living cell culture systems. The need to improve cell-based assays for nano-cytotoxicity has been demonstrated in interlaboratory studies coordinated by the International Alliance for Nano-EHS Harmonization wherein large variabilities in measurements were obtained.

In response to this need, researchers in the Cell Systems Science group developed an approach to determine sources of variability that uses a novel measurement system to assess quality metrics for nano-cytotoxicity assay performance. The system is a 96-well plate based on the well-known MTS assay and uses protocols for cell line identification testing, dosing preparation, and pipetting procedures. Seven in-line quality assessment controls include reagent quality, cell seeding quality, cell function, and nanoparticle interference (Fig. 4). Measurements using the well plate and associated protocols yield a nano-cytotoxicity value and six additional results that characterize the measurement system. The system enables intermediate measurements pertinent to the assay that could be used to validate comparability of measurements between different laboratories and different nanomaterials.

The validity of the measurement system was assessed by an interlaboratory study including EMPA (Switzerland), NanoTEC (Thailand), Joint Research Centre (European Commission) and KRISS (Korea). The results of this study indicated several sources of variability associated with: (1) cell line identification; (2) rinsing attached cell layers; and (3) nanoparticle dispersion techniques. The large number of data sets from the different laboratories resulted in performance specifications for each of the in-line process controls and provided criteria that can be used to ensure comparability between data sets.

This work culminated in three publications [24-26] and the development of an ISO International standard (ISO/DIS 19007: Nanotechnologies – *In vitro MTS assay for measuring the cytotoxic effect of nanoparticles*) using the MTS assay in nano-cytotoxicity testing [14-16]. This work serves as an exemplar for developing high-quality assays and translating measurement science into a documentary standard.

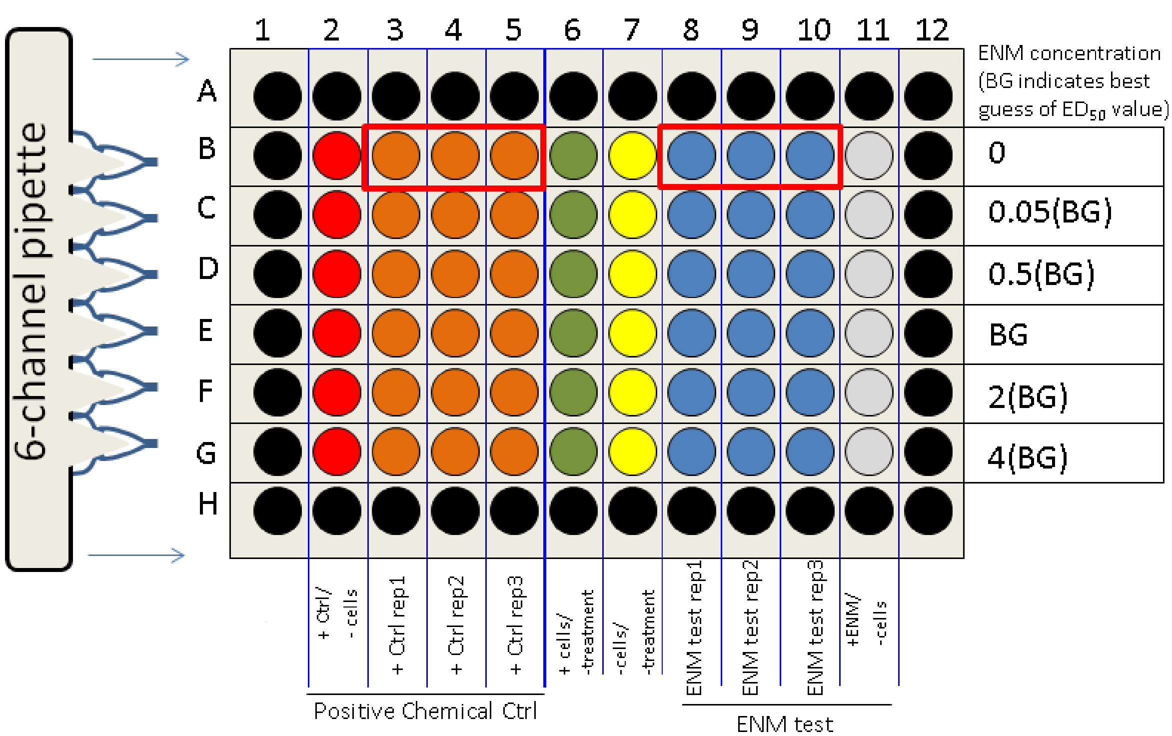

Fig. 4. 96-well plate layout for cytotoxicity assays on ENMs

6. Conclusions

The eight-year NIST Nano-EHS Program has been successful by several objective measures. Outputs from the Program—publications, protocols, and RMs—are diverse and large in number. The significant impact of the Program has been demonstrated here through two case studies: the NIST gold nanoparticle RMs and the toxicity assay measurement assurance. Beginning in 2012, the teamwork demonstrated by all the researchers has been profound. The measurement infrastructure and knowledge base established through the NIST Nano-EHS Program will be beneficial in other innovative application areas of importance to commerce and healthcare, such as biomedical devices, energy generation, and water purification. The combined experience, expertise, and facilities resulting principally from the Program represent new core competencies at NIST, which can be further exploited to address a wide range of nanotechnology measurement issues of importance to a broad range of stakeholders, including industry and regulatory bodies. Finally, the interdivisional and interdisciplinary network of scientists, established in large part due to the Program, will have a lasting legacy that reaches beyond nano-EHS and nanotechnology.

Acknowledgements

The authors would like to thank John Elliott and Elijah Petersen of NIST for contributing Case Study II: Measurement Assurance for a Nanotoxicity Assay.

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Appendix A: Nano-EHS Program Researchers

(most recent position held)

NIST Staff: Principal Investigators

John Elliott
Jeffrey Fagan
Jeffrey Gilman
Justin Gorham
Vincent Hackley
Angela Hight-Walker
R. David Holbrook
Robert MacCuspie*
Elisabeth Mansfield
Karen Murphy
Bryant Nelson
Elijah Petersen
John Pettibone
Vytas Reipa
Keana Scott
LiPiin Sung
Andras Vlàdàr
Michael Winchester

NIST Staff: Contributing Members

Donald Atha
T. J. Cho
Miral Dizdaroglu
Shannon Hanna*
Deborah Stanley Jacobs
Pawel Jaruga
Monique Johnson
Peter Krommenhoek*
Stephen Long
Rabia Oflaz
Alex Peterson
Savelas Rabb
Marc Salit
Blaza Toman
Wyatt Vreeland
Stephanie Watson
Jeremiah Woodcock
Lee Yu
Rolf Zeisler
Justin Zook

NRC Postdoctoral Fellows

Mark Bailey
Michelle Blickley
Christopher Brown
Danielle Cleveland
Chelsea Davis
Sherrie Elzey
John Heddleston
Constantine Khripin
Stephanie Lam
Christian Long
Stacey Louie
Bryce Marquis
Grant Myers
Nathan Orloff
Fatima Sequeira
Christopher Sims

*the researcher is no longer at NIST

NIST Associates: Post-docs

Jens Breffke
Bryan Calderon Jimenez
Ning Chen
Guangun Cheng
Hsiang Chun Hsueh
Hind El Hadri
Julien Gigault
Preshagar Kavuri
Sung Kim
Thomas Lam
Jingyu Liu
Arnab Mukherjee
Antonio R. Montoro Bustos
Bharath Natarajan
Liz Nguyen
Tinh Nguyen
Yongyan Pang
Yanmei Piao
Vinayak Rastogi
Carlos Silvera Batista
Julian Taurozzi
Vipin Tondare
De-Hao Tsai
Ji Yeon Huh
Minhua Zhao

NIST Associates: Students

George Caceres
Yu-Lun Cheng
Yu-Fang Chuang
Anne Galyean
Carly Geronimo
James Ging
Sin-Ru Huang
Samuel Norris
Bastien Pellegrin
Cristina Rios Valdez
Brian Stock
Jiaojie Tan
Chun-Chieh Tien
Chen-Hsiang Tsai

Appendix B: Nano-EHS Initiative Program Plan, FY12-14

Excerpts from the Program Plan are given below.

Program Goals, Objectives, and Deliverables
The technical work described below will significantly advance the establishment of a nanomaterial measurement infrastructure consisting of critical tools—standards, measurement methods, and validated data and models. The technical scope of the work will encompass four of the five Research Needs identified in the Nanomaterial Measurement Infrastructure Research Chapter of the NNI 2011 Nano-EHS Research Strategy: (1) determination of the physico-chemical properties of ENMs, a necessary first step in exposure and hazard evaluation; (2) detection of ENMs and NEPs; (3) evaluation of transformations of ENMs; and (4) evaluation of biological responses to ENMs and NEPs. The Program will provide the metrological foundation and measurement tools essential to the fifth Research Need, evaluation of release mechanisms of ENMs from NEPs. To maximize the relevance and impact of NIST work, FY12-FY14 priorities in Research Needs (1) and (2) are MWNCTs in polymer matrix-based NEPs such as sporting goods, and Ag NPs in NEPs such as fabrics. These ENM-NEP priorities are also consistent with those of the NanoRelease Project, a group of international representatives and technical experts from government agencies, industry, non-governmental organizations, and universities focused on the identification and development of methods to detect and characterize ENMs released from NEPs.

Goal 1: *Enable other organizations to perform accurate, precise, and reproducible measurements by providing measurement tools*

A. **Objective**: Develop and release standard reference materials (SRMs) and reference materials (RMs)

Task		FY	Deliverable
i	Develop methods for next-generation SRMs and RMs, *i.e.*, zeta potential measurement, positive toxicity controls	12	Progress reports
ii	Complete SRMs and RMs for key ENMs (TiO_2 and Ag NPs and single-wall CNTs) certified for specific surface area and dimensions	12	SRMs and RMs
iii	Demonstrate the applicability of new hyphenated instruments to next generation SRMs and RMs, *i.e.*, ENMs in complex matrices and Ag NPs in aqueous media	12-13	Progress reports

iv	Design and produce prototype SRMs and RMs for zeta potential measurement and positive toxicity controls	12-13	Progress reports, prototype SRMs and RMs
v	Design and produce prototype SRMs and RMs for determination of chirality in purified SWCNTs	12-13	Progress reports, SRMs and RMs
vi	Develop methods and produce prototype SRMs and RMs for ENMs in complex matrices such as soil	13-14	Progress reports, prototype SRMs and RMs
vii	Develop methods and produce prototype SRMs and RMs for determination of concentration of total Ag, Ag ions, and Ag NPs in relevant media	13-14	Progress reports, prototype SRMs and RMs
viii	Evaluate potential for RMs on other key ENMs, *i.e.*, MWCNTs, CeO NPs, and nanoclays	13-14	Progress reports
ix	Initiate production of SRMs and RMs for zeta potential measurement, positive toxicity controls, and determination of chirality in purified SWCNTs	14	WCF proposals, progress reports

B. **Objective**: Develop and broadly disseminate validated measurement protocols and assays

Task		**FY**	**Deliverable**
i	Prepare manuscripts on three NIST protocols for dispersion of TiO_2 in various media	12	NIST Special Publications (SPs) NIST website postings
ii	Demonstrate the adequacy and extensibility of at least two existing *in vitro* and *in vivo* toxicity assays to ENMs	12	Progress reports, publications
iii	Complete a VAMAS interlaboratory study (ILS) on chirality measurements of single wall CNT mixtures and develop a protocol	12-13	Report on ILS results NIST SP on protocol NIST website posting
iv	Develop protocols to stabilize soluble NPs such as Ag	12-13	NIST Special Publication (SP) NIST website posting

v	Develop *in vitro* and *in vivo* toxicity assays, based on existing or new assays	13-14	Progress reports, publications
vi	Evaluate and initiate development of sample preparation and measurement protocols for other key ENMs, i.e., MWCNTs, and CeO NPs, and nanoclays	13-14	Reports by study groups (internal and external) and on ILS's initiated in VAMAS and ASTM E56
vii	Develop draft protocols for the use of hyphenated instruments, *e.g.*, DMA/AFFF/ICP-MS	14	Progress reports

C. **Objective**: Lead and provide strong technical contributions to documentary and pre-documentary standards development activities

Task		**FY**	**Deliverable**
i	Increase staff leadership and participation in nano-EHS-related SDOs and pre-standardization organizations	12-14	Listing of leadership positions and active staff members
ii	Lead and participate in the completion and publication of ongoing work items	12-13	Listing of published standards with noted NIST leadership role
iii	Lead and participate in the development of new work items	12-14	Listing of new work items with noted NIST leadership role Progress reports
iv	Co-organize workshops that enable the prioritization and increased use and value of documentary standards	12-14	Workshop reports
v	Facilitate communication, cooperation, and coordination of activities among SDOs	12-14	Reports describing actions taken

Goal 2: *Enable other organizations to detect and quantitatively characterize ENMs in NEPs using broadly available, commercial instruments*

A. **Objective**: Develop methods to detect and quantitatively characterize Ag NPs in fabrics

Task		**FY**	**Deliverable**
i	Evaluate the applicability, advantages, and limitations of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS for the detection of Ag NPs; develop sample preparation approaches for each method	12	Progress reports, publications
ii	Evaluate the applicability, advantages, and limitations of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS for quantitative measurements of Ag NPs; identify specific properties that can be determined with each method	12-13	Progress reports, publications
iii	Generate data and associated measurement uncertainties using FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS	13-14	Progress reports, publications
iv	Evaluate the feasibility of extending the capabilities of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS, (*e.g.*, high throughput and three-dimensional measurements) for the detection and characterization of Ag NPs	14	Progress reports, publications

B. **Objective**: Develop methods to detect and quantitatively characterize MWCNTs in polymer matrix-based NEPs

Task		**FY**	**Deliverable**
i	Evaluate the applicability, advantages, and limitations of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS for the detection of MWCNTs; develop sample preparation approaches for each method	12	Progress reports, publications
ii	Evaluate the applicability, advantages, and limitations of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS for quantitative measurements of MWCNTs; identify specific properties that can be determined with each method	12-13	Progress reports, publications
iii	Generate data and associated measurement uncertainties using FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS	13-14	Progress reports, publications
iv	Evaluate the feasibility of extending the capabilities of FE-SEM, TEM, AFM, ICP-MS, SEC, and XPS, (*e.g.*, high throughput and three-dimensional measurements) for the detection and characterization of MWCNTs	14	Progress reports, publications

Appendix C: Nano-EHS Program Publications

(in increasing chronological order by type of publication)

Archival Journal Articles

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Raman spectroscopy. *Carbon* 47: 3238-3241. https://doi.org/10.1016/j.carbon.2009.07.037

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15. Wu C, et al. (2010) Effect of nanoparticle clustering on the effective thermal conductivity of concentrated silica colloids. *Physical Review E* 81:011406-1-7. https://doi.org/10.1103/PhysRevE.81.011406
16. Dair BJ, et al. (2010). The effect of substrate material on silver nanoparticle antimicrobial efficacy. *Journal of Nanoscience and Nanotechnology* 10:1-7. https://doi.org/10.1166/jnn.2010.3566
17. Cleveland D, et al. (2010) Chromatographic methods for the quantification of free and chelated gadolinium species in MRI contrast agent formulations. *Analytical and Bioanalytical Chemistry* 398(7-8):2987-2995. https://doi.org/10.1007/s00216-010-4226-2
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28. Xiao Y, et al. (2010). Dynamics and mechanisms of quantum dot nanoparticle cellular uptake. *Journal of Nanobiotechnology* 8:13-1-9.

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30. MacCuspie RI, Allen AJ, Hackley VA (2011) Dispersion stabilization of silver nanoparticles in synthetic lung fluid studied under in situ conditions. *Nanotoxicology* 5(2):140-156. https://doi.org/10.3109/17435390.2010.504311

31. Taurozzi JS, Hackley VA, Wiesner MR (2011) Ultrasonic dispersion of nanoparticles for environmental, health and safety assessment – issues and recommendations. *Nanotoxicology* 5(4):711-729. https://doi.org/10.3109/17435390.2010.528846

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using UV-Visible absorbance. *Analytical and Bioanalytical Chemistry* 401(6):1993-2002. https://doi.org/10.1007/s00216-011-5266-y

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Appendix D: Nano-EHS Program Protocols and Assays

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Appendix E: Nanoscale Reference Materials

RM: Reference Material; SRM: Standard Reference Material; NP: nanoparticle; CNT: carbon nanotube

Material Type	Identifier(s)	Form	Reference Property	Nominal Value	Release Date	Total # Units Sold*
gold NPs	RM 8011	in aqueous suspension	mean diameter	30 nm	12/17/07	555
	RM 8012			60 nm	12/17/07	615
	RM 8013			100 nm	12/17/07	613
TiO_2 NPs	SRM 1898	dry powder	specific surface area	55 m^2/g	6/14/12	118
silver NPs	RM 8017	freeze-dried	mean diameter	75 nm	12/6/14	67
silicon NPs	RM 8027	in toluene suspension	mean diameter	2 nm	2/4/14	9
single-wall CNTs	SRM 2483	dry soot	mass fraction	impurity elements	11/14/11	62
	RM 8281	in aqueous suspension	length	"long", "medium", "short"	7/9/13	15
multiwall CNTs	SRM 2484	dry soot	mass fraction	impurity elements	6/1/17	0

*As of July 2018