Developing Nano-Measurements and Standards

The NIST Role

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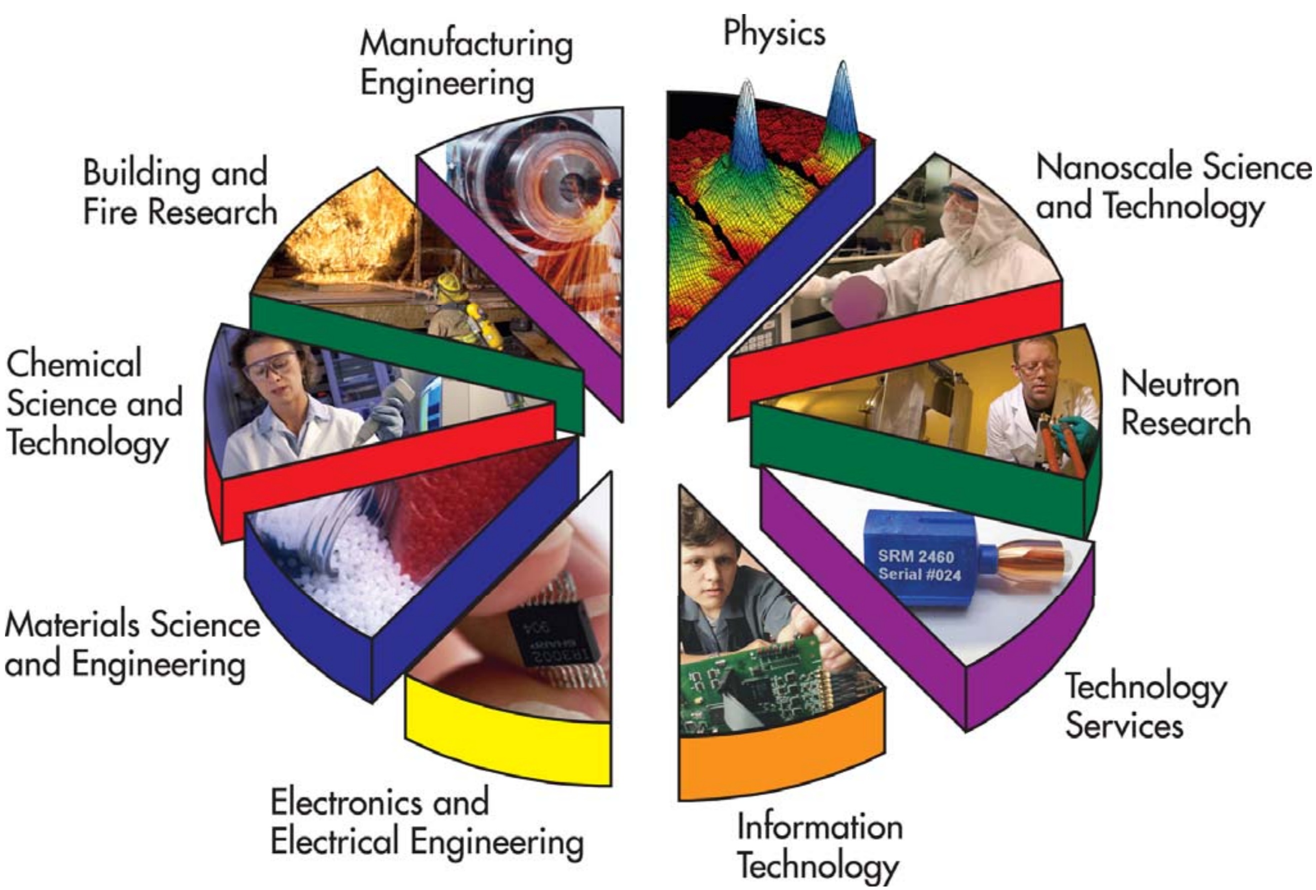
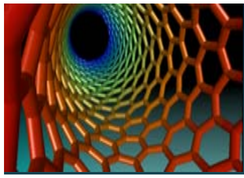
NIST: The National Measurement Institute for the USA

To promote U.S. innovation and industrial competitiveness by advancing *measurement science*, *standards*, and *technology* in ways that enhance economic security and improve our quality of life



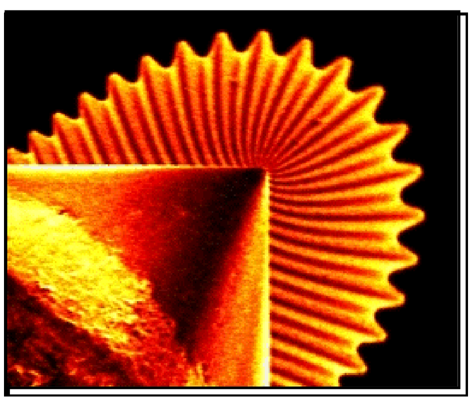


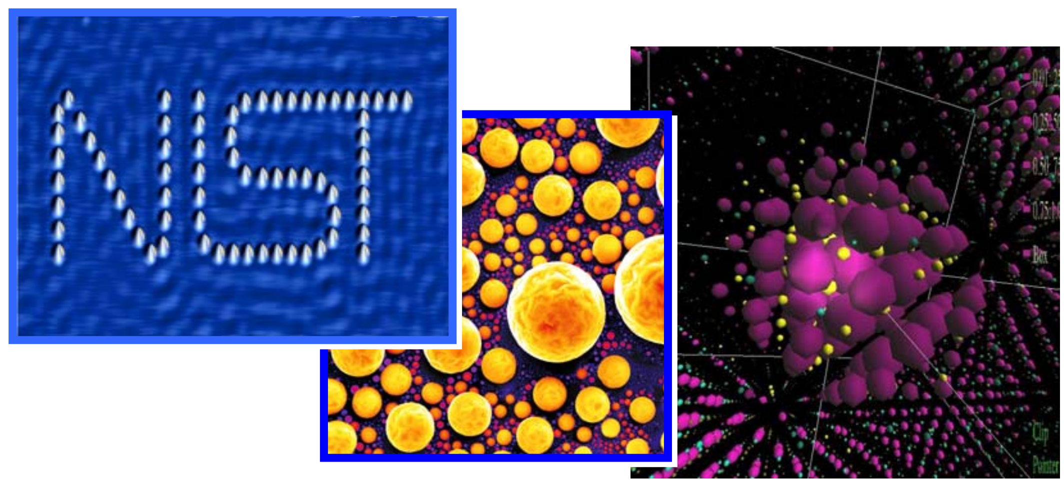
NIST Nano EHS Program Goals

In consultation and collaboration with our stakeholders, academia, government agencies and industry, we will:

- Provide a scientific basis to discover the health and environmental effects of nanotechnology

- Enable US industry to safely develop, exploit, commercialize nanotechnologies



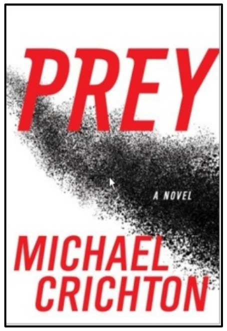


NIST Motivation

- Health and environmental risks of nanomaterials (real and perceived) are roadblocks for innovation and commercialization of nanotechnology.

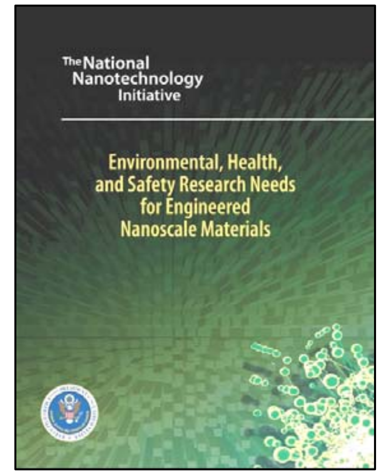
- Data quality inhibits the ability to understand, predict, and manage potential risks of engineered nanoscale materials.

- Lack of certainty in nanoscale measurements impacts regulatory and policy decisions.



NIST: Key Part of the Federal Plan

NNI strategy addressing priority research on the environment, health, and safety (EHS) aspects of nanomaterials that have been identified in previous reports.



NIST identified as the lead agency for:

Instrumentation, Metrology and Analytical Methods

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

Proposed NIST Workplan for NanoEHS

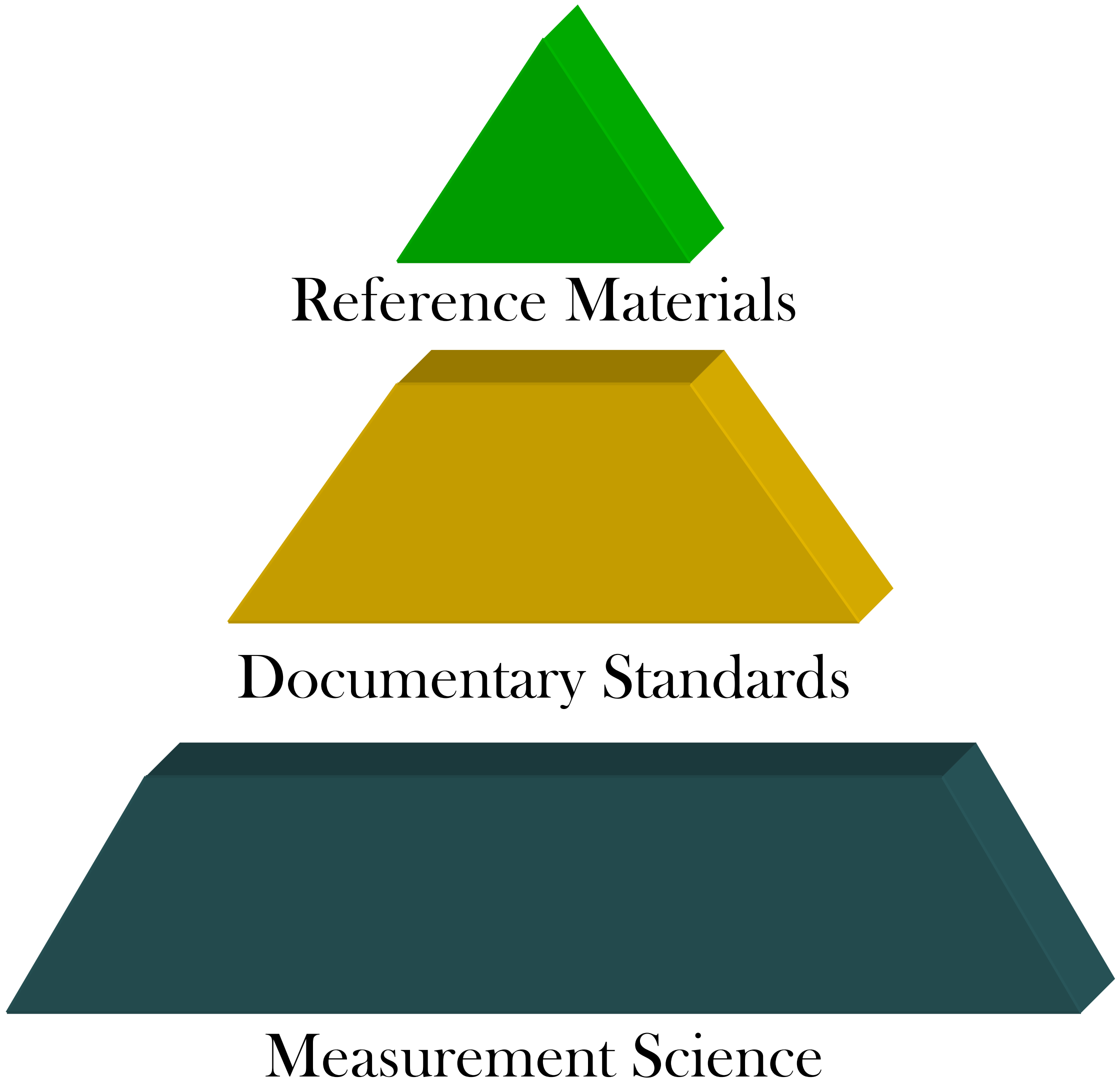
**under development*

1. **Research and Innovation,**

2. **Nanomaterial Characterization**, and
   - Materials and measurement protocols for quantifying the type and amount of nanomaterials in biological matrices, the environment, and the workplace
   - Methods to understand the effect of modifications on the properties of nanomaterials
   - Measurement science for standardizing assessment of nanoparticle size and size distribution, shape, structure, and surface area
   - Innovative technology to characterize a nanomaterial's spatio-chemical composition, purity, and heterogeneity

3. **Validation of Toxicological Methods.**

NIST Approach



Definitions

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): *(SRM NIST)*
Reference materials characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability. Property values are certified as traceable to an accurate realization of the unit in which the property values are expressed.

Definition from the international organization for Standards (ISO)

Procedure for NIST (S)RM Development

Research

- Customer needs and market assessment indicate an (S)RM is required to address barriers to innovation
- Underpinning measurement science and technology

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Development

- Select materials and source, define property values, select measurement methods, establish testing plan
- Develop a prototype whose reference values are not necessarily traceable

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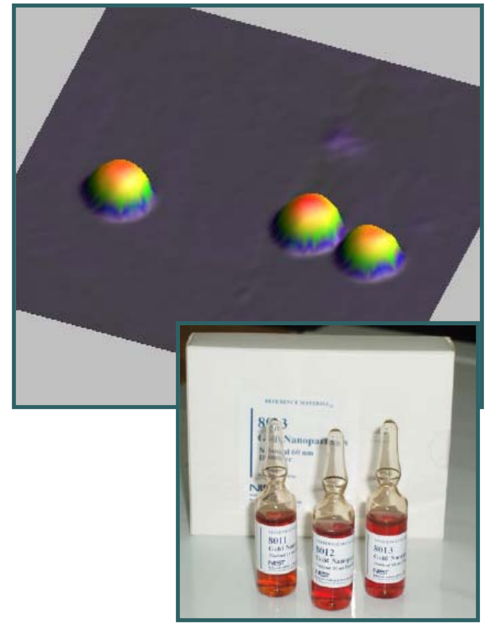
Production

- Process and package material, heterogeneity testing, generate certified, references and information values, perform statistical analyses
- Generate COA or ROI and release (S)RM

Development and production stages typically take 2 years

NIST Nano Reference Materials



Presently Available:

Polystyrene (down to 60 nm)

Dimensional features on substrates

Most Recent Addition:

Gold nanopartciles

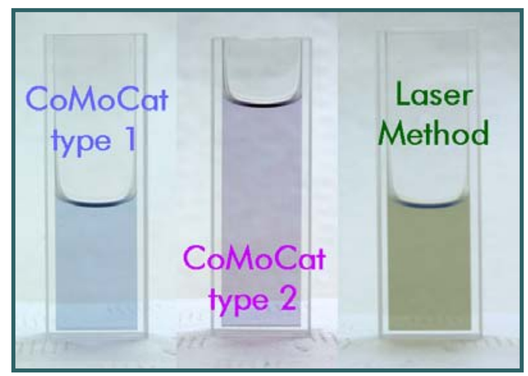
three sizes; 10 nm, 30 nm, 60 nm

Near Future:

Single-walled carbon nanotubes (SWCNTs)

likely three types; powder, pellet, liquid

TiO_2

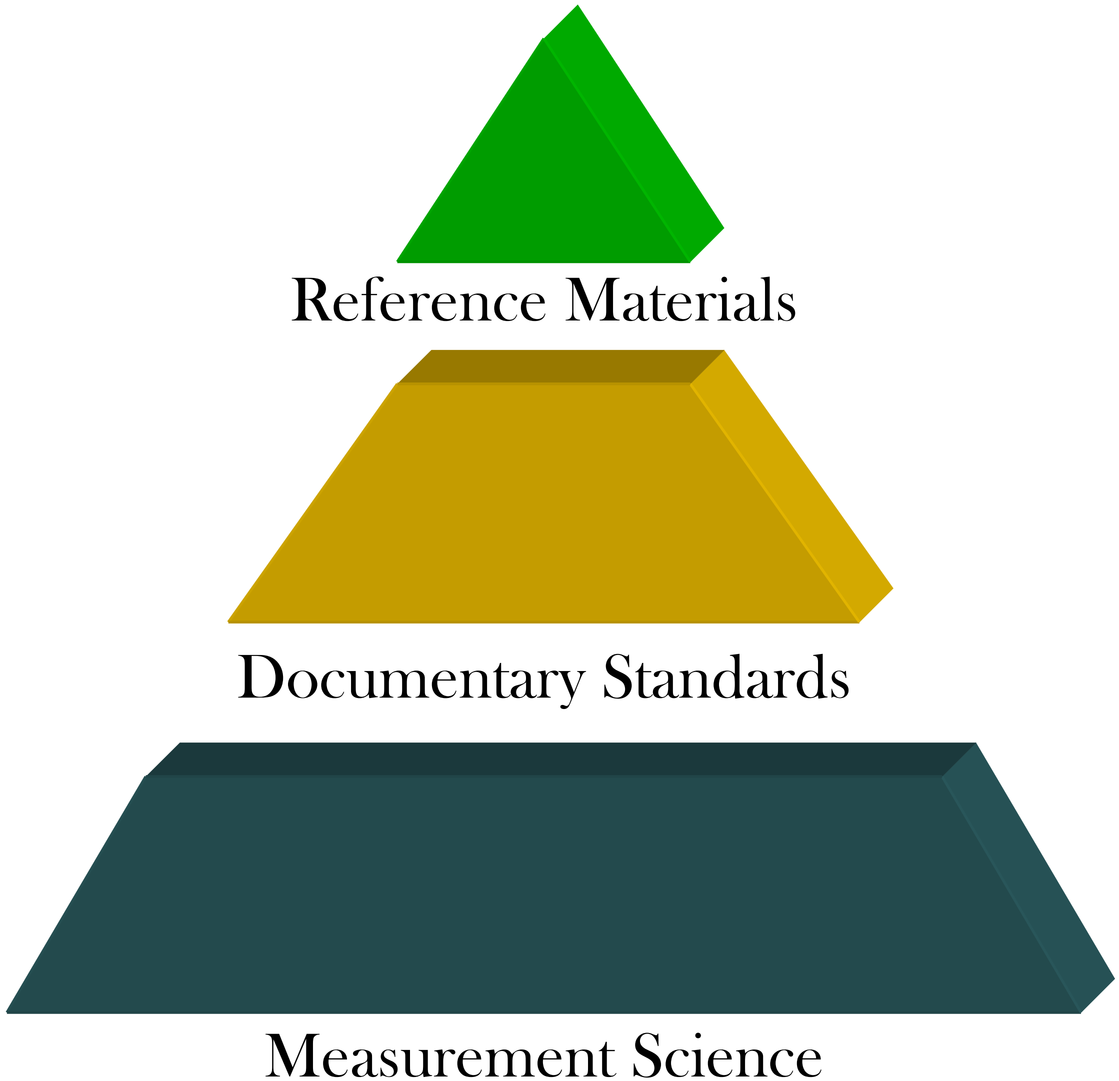


Future:

Many under consideration

**Co-funded by NCI*

NIST Approach



International Standards Landscape

Different tools for different market needs:

- National participation models
  - Treaty organizations; ISO, IEC
  - Formality in process
  - One country, one vote

- Direct participation models
  - ASTM International, SAE, IEEE, etc.
  - Direct link between technical experts and SDOs

- Corporate participation models
  - Consortia and fora
  - Wide range of processes and procedures allows flexibility

The Alphabet Soup of Nano Standards

NIST hosted a workshop in February 2008 to coordinate documentary standards development relevant to nanotechnology as well as identify immediate and medium-term standards needs.

- ASTM International: E42, E56
- IEC: TC113
- IEEE-SA
- ISO TCs: 24/SC4, 146, 194, 201, 209, 213, 229
- OECD–WPMN: Steering Groups 3, 6, 7 and 8
- National Metrology Institutes (NMIs)
- SEMI
- Versailles Project on Advanced Materials and Standards (VAMAS)

Nanotechnologies
International Workshop
26-28 February 2008

Workshop Outcomes

- Greater communication and coordination within and between the various standards development organizations and with interested metrology laboratories;
- The development of a centralized, maintained, searchable and freely accessible repository of information on existing standards and standardization projects in the field;
- The development and introduction of a freely accessible and searchable terminology and definitions database;
- Wider participation of stakeholders in identifying and verifying standards needs;
- Consideration of all available standardization instruments from Workshop Agreements through to full consensus standards and their equivalents in order to provide stakeholders with relevant documents in a timely manner;
- Urgent and detailed consideration of the instruments needed to address current concerns and challenges in investigating the implications for human health and environmental safety of manufactured nanomaterials.

ISO IEC NIST OECD

Nanotechnologies
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Nanotechnology Documentary Standards

ISO TC 229: Nanotechnologies – established 2004

Chair and Secretariat with UK

Three working groups:

WG 1: Terminology and nomenclature (Canada- Chair)

WG 2: Measurement and characterization (Japan- Chair)

WG 3: Health, Safety and Environmental Aspects of Nanotechnologies (USA/NIST – Chair)

IEC TC 113: Nanotechnology standardization for *electrical and electronics products and systems* – established 2006

Secretariat: Germany, and Chair: US

US TAG recently formed

Emphasis on strong liaison with ISO TC 229

Nanotechnology Documentary Standards

ASTM E56: Standards and guidance for nanotechnology and nanomaterials - established 2004

Six sub-committees:

- E56.01 Terminology & Nomenclature
- E56.02 Characterization: Physical, Chemical, and Toxicological Properties
- E56.03 Environment, Health, and Safety
- E56.04 International Law & Intellectual Property
- E56.05 Liaison & International Cooperation
- E56.90 Executive
- E56.91 Strategic Planning and Review

IEEE: Standards activities under IEEE Nanotechnology Council addressing materials, devices and system-level interoperability

Part of IEEE Nanoelectronics Standards Roadmap initiative – March 2006

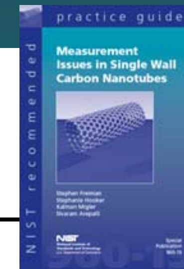
Anticipatory standards philosophy

Standards for nanoelectronics:

- IEEE P1650 standard test method for measurement of electrical properties of CNTs- standard approved and adopted in 2005
- Work underway on development of standard method for characterization of CNTs used as additives in bulk materials (IEEE P1690)

Nanotechnology Standards Examples 1

ISO TC 229/WG2



Matrix: Purity & Structural Properties, SWCNTs

Category \ Property	Method: SEM/EDX (Lead:USA)	TEM (Lead:USA, Co-lead:Japan)	Raman Spectroscopy (Lead:USA)	UV-Vis-NIR Absorption (Lead:Japan)	NIR-PL/ Fluorescence (Lead:Japan)	TGA (Lead:USA, Co-lead:Korea)	TG-MS (Lead:Japan)
Morphology	Tube structure, bundle thickness, orientation	Wall structure, amorphous carbon, metal catalyst coatings					
Purity	Non-carbon impurities	Tube surface cleanliness	Nanotube and non-nanotube carbon	Carbonaceous content (Quantitative) (Lead:USA)		Non-carbon content (Quantitative) Non-CNT content (Quantitative)	Non-carbon content (Quantitative)
Length and Diameter	Length and diameter	Tube diameter, metal cluster size	Diameter (Lead:Japan)	Diameter (Lead:Japan)	Diameter		
Tube Type			Metallic/ Semiconducting	Metallic/ Semiconducting (Lead: USA, Colead: Korea)	Chirality (Semi conducting tubes)		
Dispersability/ Solubility	Tube bundling			Tub bundling or separation (solution)	Tube bundling		
Additional						Oxidation/transition temparatures	Oxidation/transition temparatures
Other Participants	China	China, Korea	Korea	Korea	USA	China	

TBD:Canada and Germany

Nanotechnology Standards Examples 2

ISO TC 229/WG3

TABLE 2. Focused List of Physico-Chemical Characteristics of Engineered Nano-Objects for Toxicological Assessment

May 28, 2008 version

- Agglomeration state / Aggregation
- Composition (e.g., chemical composition and structure)
- Particle size / size distribution
- Purity/impurity
- Shape
- Solubility (hydrophobicity, lipo solubility, water solubility)
- Stability
- Surface area
- Surface chemistry
- Surface Charge

Nanotechnology Standards Examples 2

ISO TC 229/WG3

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OECD

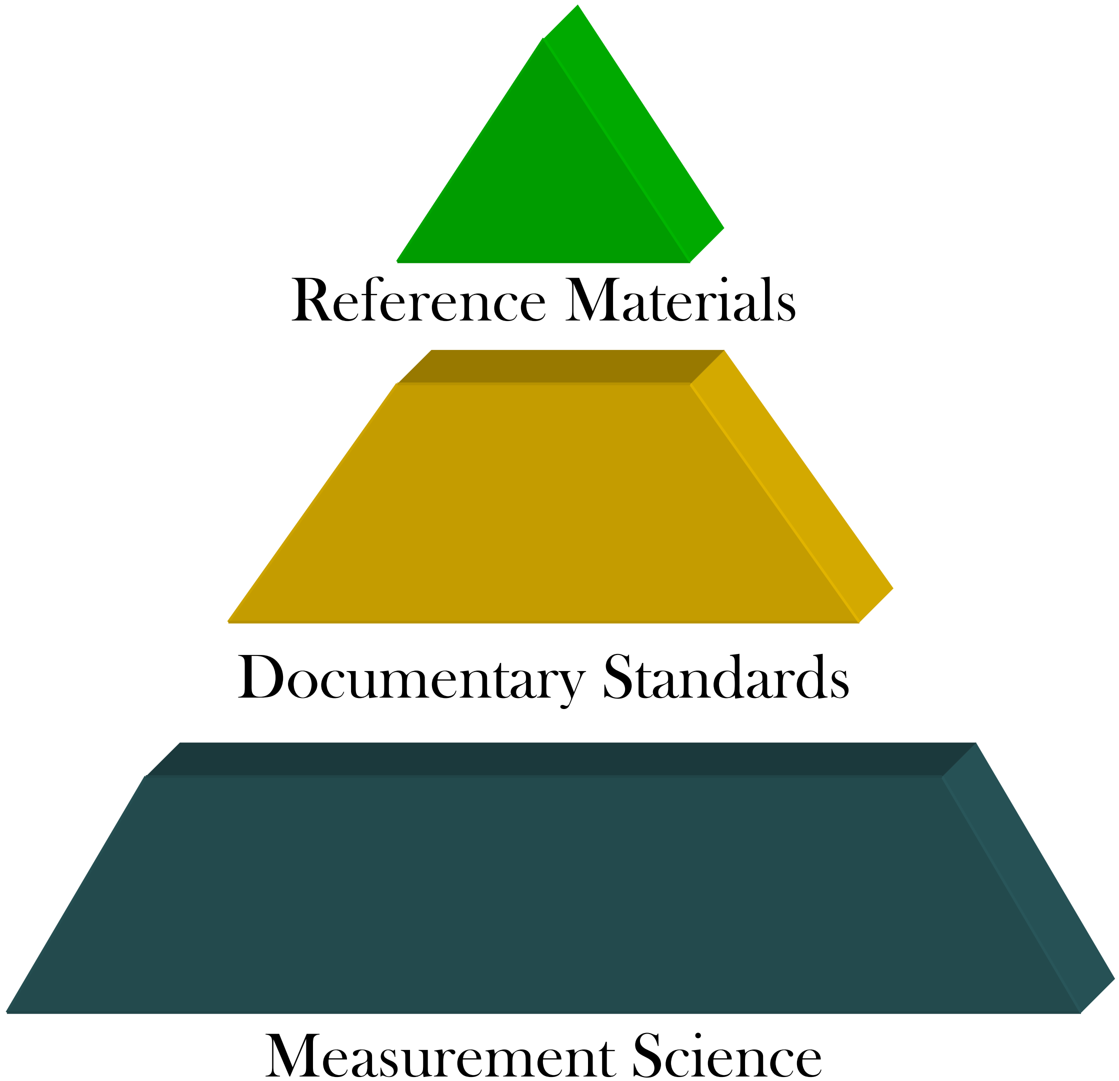
Project 4
Physical Chemical properties

- **necessary pre-requisite properties – review existing non-OECD Testing methods (national testing methods, ISO, CEN, ASTM, JIS etc.**

• **Agglomeration/ aggregation**	• Length
• **Catalytic properties**	• Purity
• Composition	• Shape
• **Concentration** (needs to be defined)	• Specific surface area
• Crystalline phase	• **Surface charge**
• Dustiness	• Surface chemistry
• Fat solubility/ oleophilicity	• Water solubility/ hydrophilicity
• Grain size	• ***Zeta potential***
• Hydrodynamic size/particle size measurement/ distribution	

2008 May @ISO TC229 WG3 for Official Use Only

NIST Approach



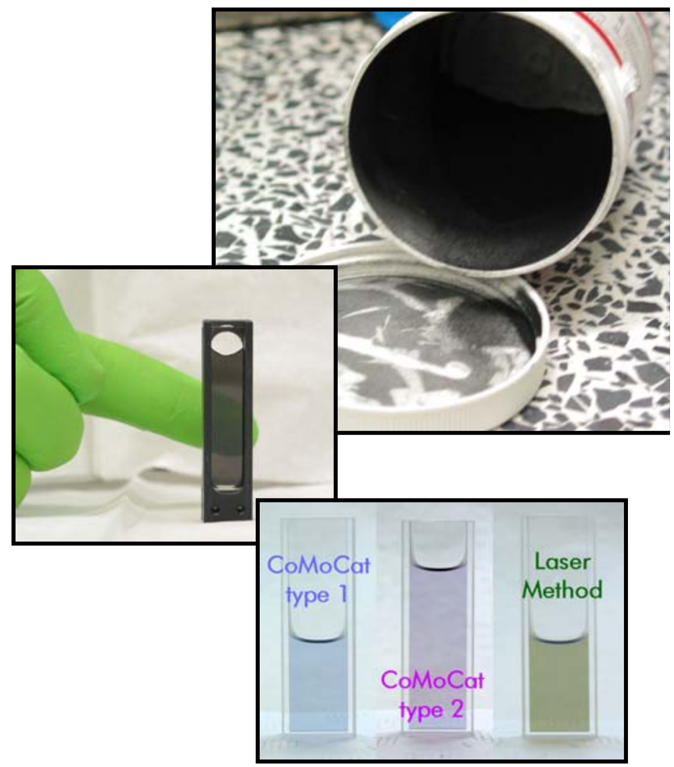
Nanomaterial Characterization

Environment Matters!
More than ONE measurement is necessary!

Characterization along the entire nanoparticle pathway is critical for scientific understanding toxicology response

What is it?
How much of "it" is there?

- As received
- As dispersed
- As inhaled
- In matrix
- In cells
- In organs
- In bodies



Nanomaterial Characterization

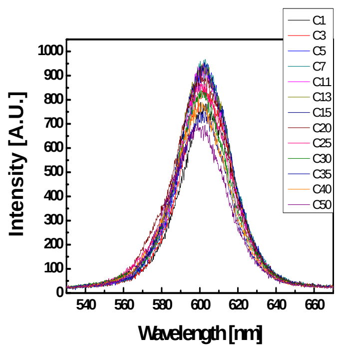
Identify the fundamental properties of the nanomaterials

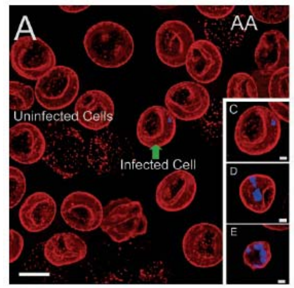
Isolate the nanomaterial for study

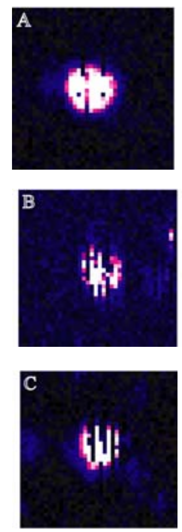
Intrinsic Properties

Quantum Dots

Clustering and coatings change PL

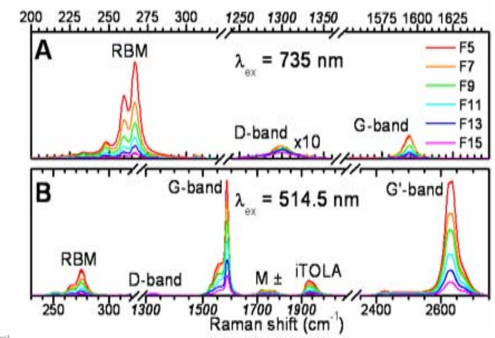


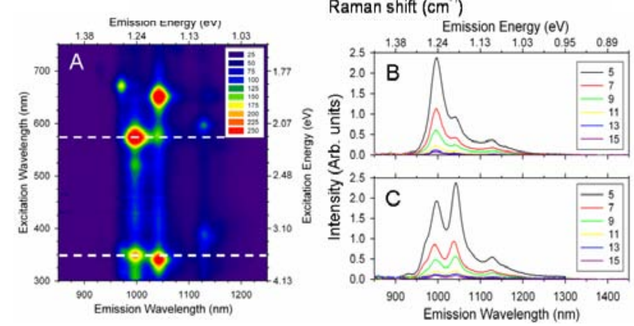




Carbon Nanotubes

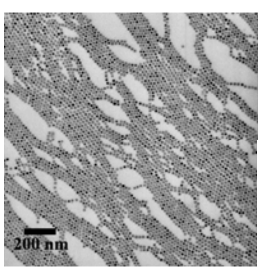
Length matters

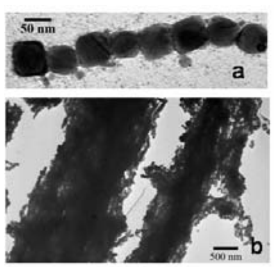


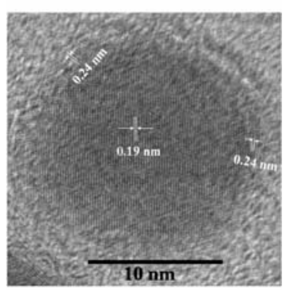


Magnetic Nanopartciles

Cooperative behavior and stability

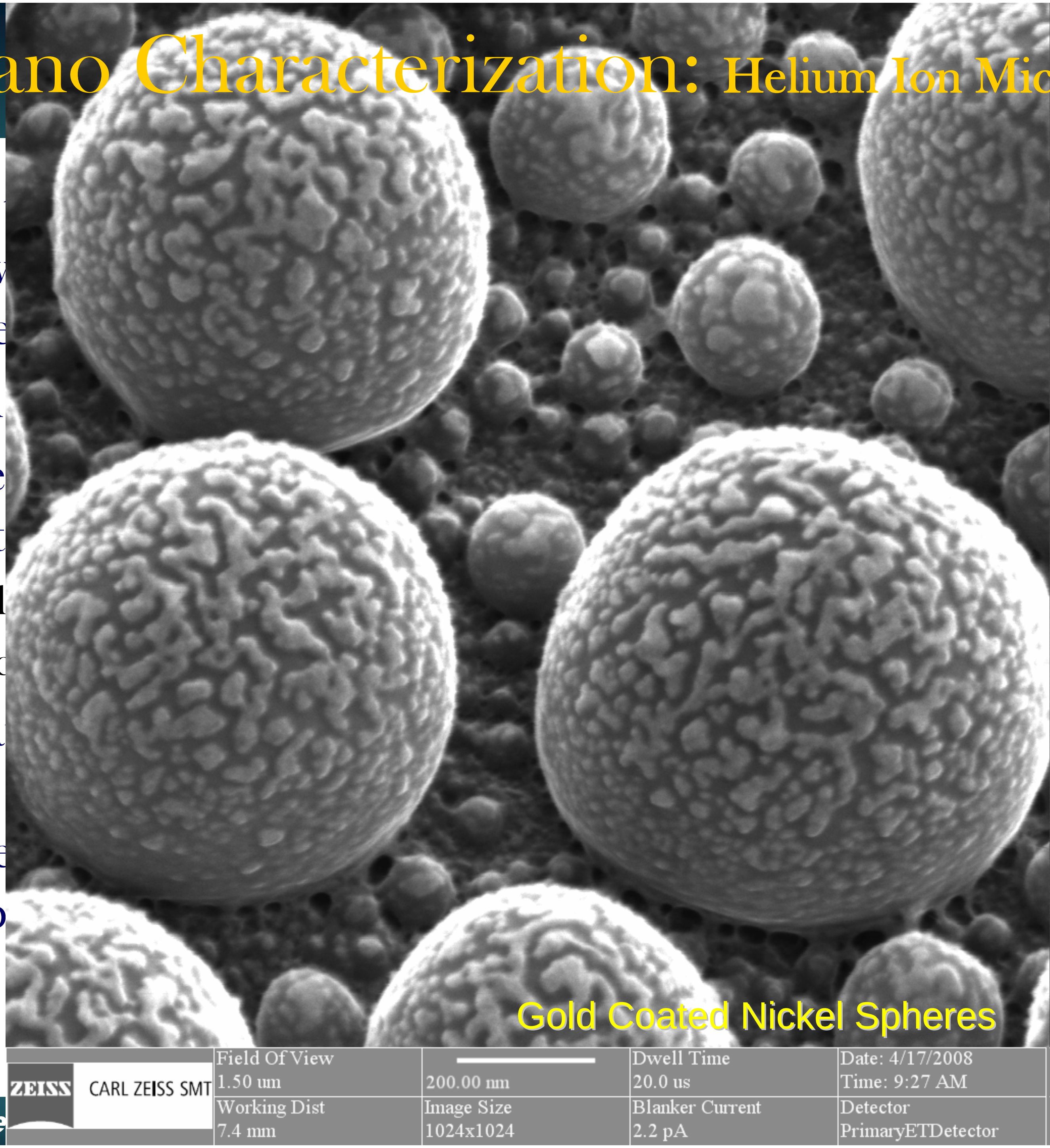






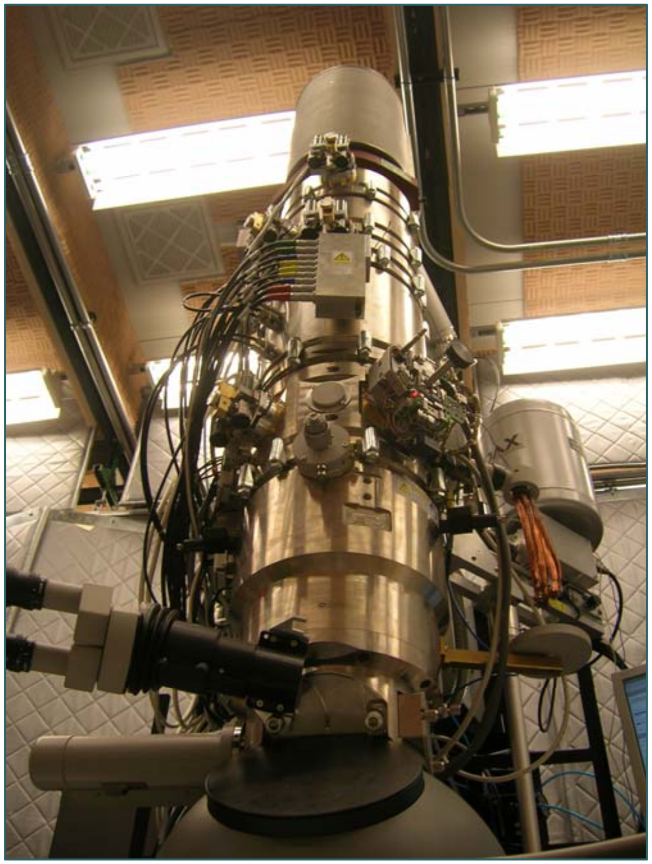
Nano Characterization: Helium Ion Microscope

- First of ... d at NIST w... ecision Enginee...
- Helium ...
- HIM re... r than the best ...
  - Detail...
  - Surfac... tion
- Applica... science ... facilitate... develop...



Nano Characterization: Advanced Imaging

3D Chemical Imaging with aberration-corrected monochromated AEM to improve resolution



Analytical Electron Microscope

Delivered to NIST March 2006

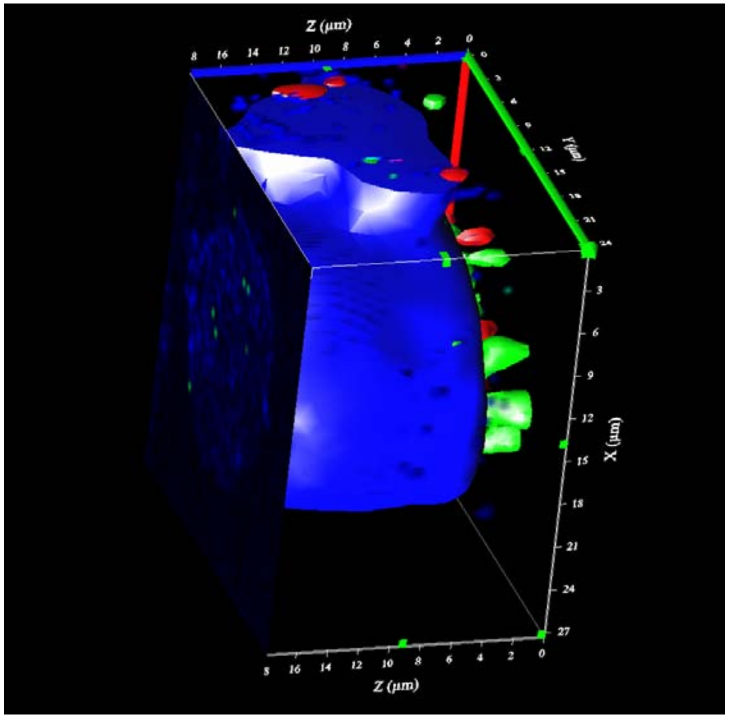
Capable of sub-Angstrom imaging in both transmission and scanning mode technique development:

3D spectroscopic identification of location and elemental identities of all atoms in a small nanostructure

Nanobiosensing: 3D Imaging

OPTICAL PROBES of NANOPARTICLES

- 3D imaging of nanoparticle interactions with biological systems to further understand nanoparticle drug delivery and toxicity
- 3D reconstruction of a human cancer cell (blue) cultured with two different types of quantum dots
- reconstruction/surface-modeling, images can distinguish and locate nanoparticles inside and outside
- with sufficient computer memory and speed, multiple cells can be evaluated at once (skin tissue studies)



streptavidin-conjugated quantum dots

Reconstructed cell (blue) showing two types of quantum dots (red and green). The dots on the cell exterior are represented by balloons.

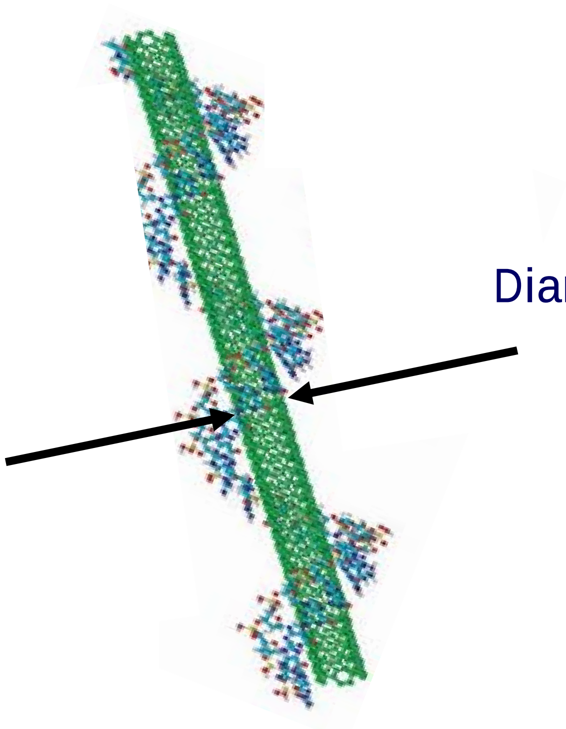
FOV~ 25 x25 x 6 μm^3.

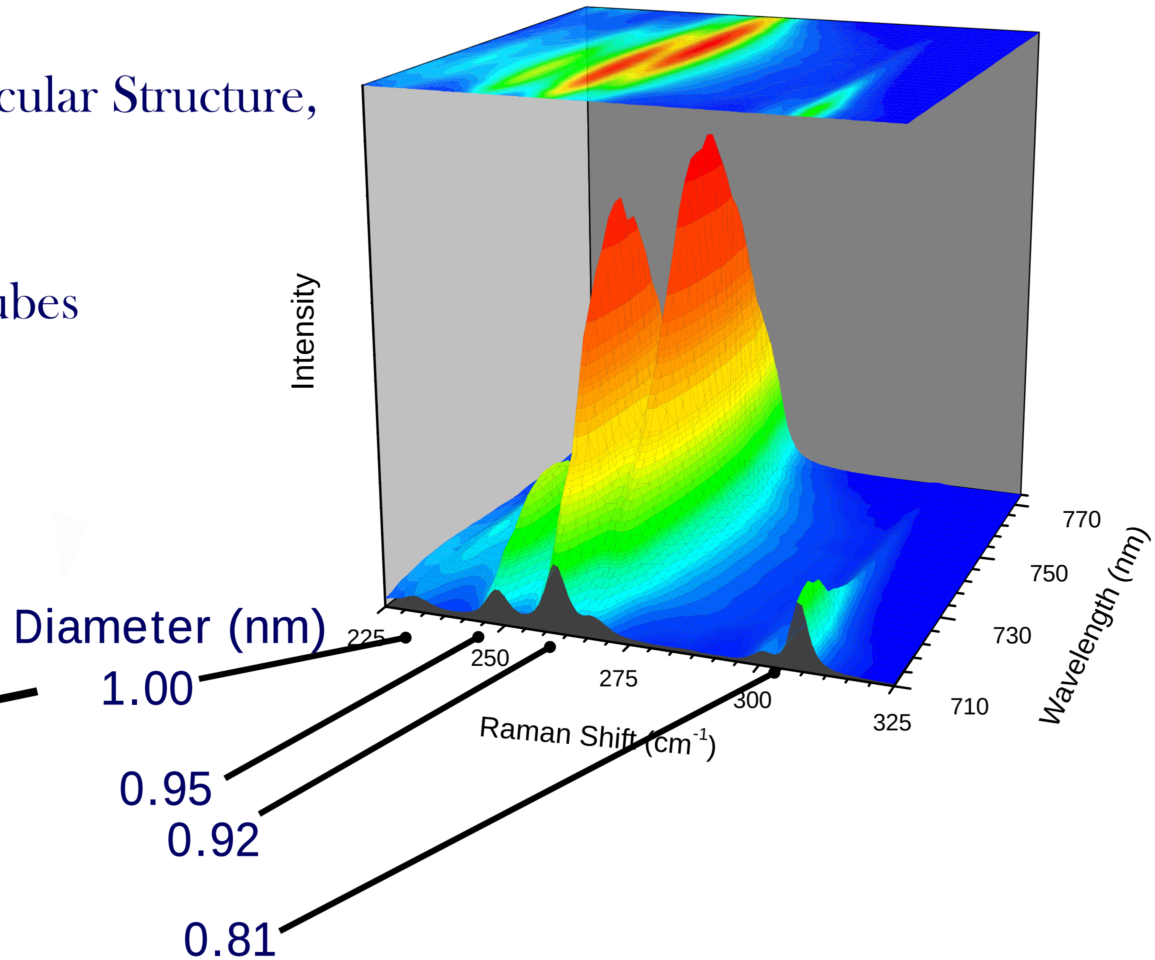
Nano Characterization: Raman Spectroscopy

Raman Spectroscopy

Chemical Composition, Molecular Structure, Crystal Structure, etc…

DNA-Wrapped Carbon Nanotubes

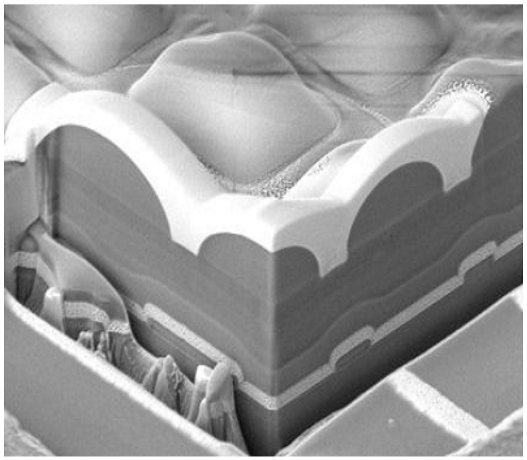




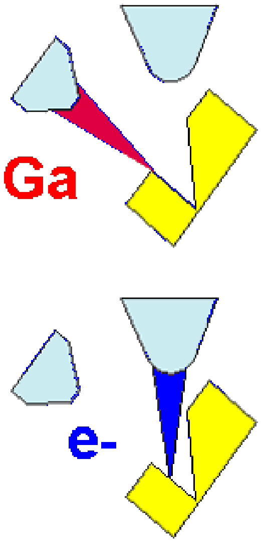
Nano Characterization: Advanced Imaging

3-D Chemical Imaging

FIB cross section



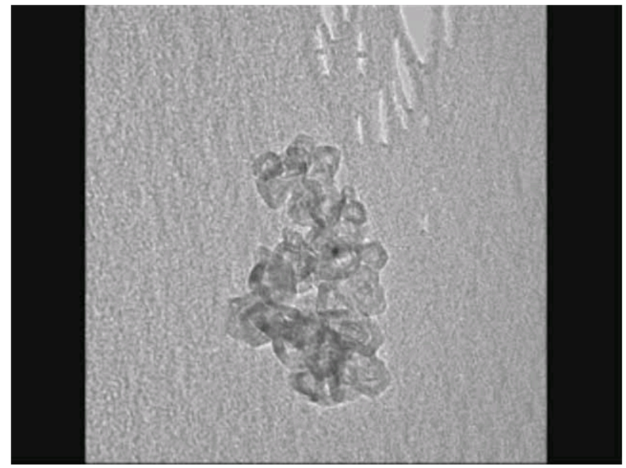
5 µm



- cut with ion beam
- image/X-ray map with SEM
- repeat…

Serial Focused Ion Beam (3D FIB)

TEM tilt series



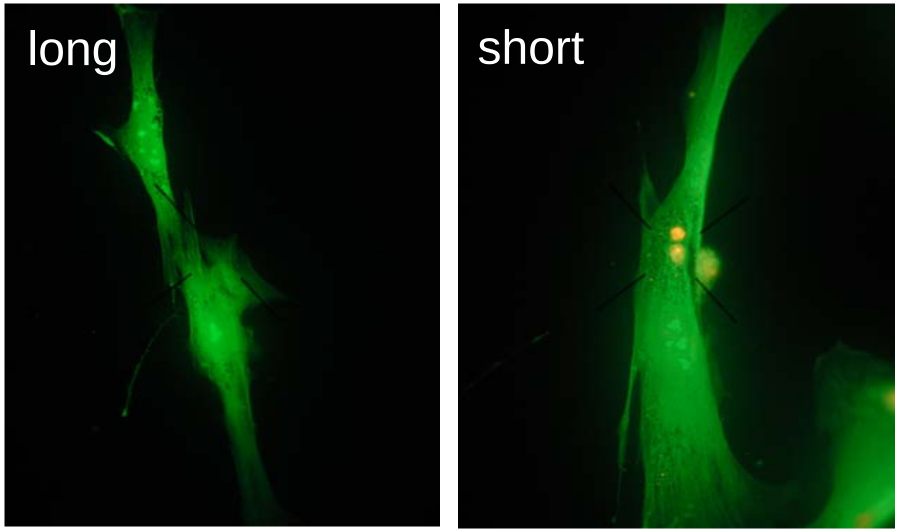
50 nm

- TEM based
- tilt sample
- ~ 160 projections
- chemistry by EELS
- 3D reconstruction

TEM nanotomography

Validation of Toxicological Methods: Support Understanding Environmental and Health Impacts

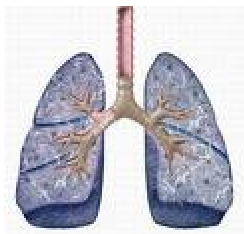
Evaluating cellular uptake, fate

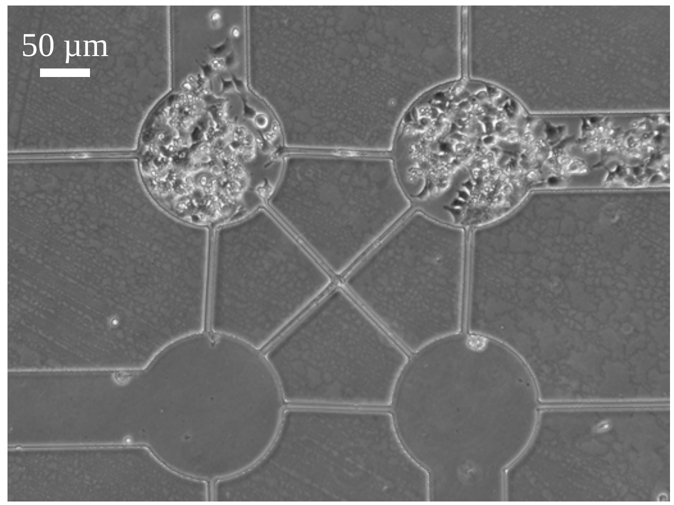


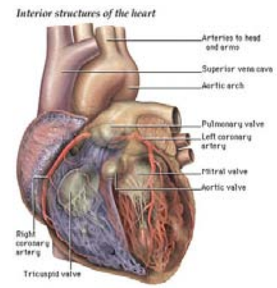
DNA-wrapped single-walled carbon nanotubes (SWCNTs) shorter than about 200 nanometers readily enter into human lung cells and may pose increase health risk.

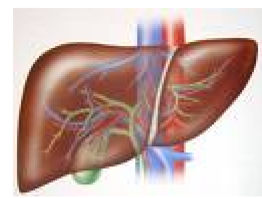
*M.L. Becker, J.A. Fagan, N.D. Gallant, B.J. Bauer, V. Bajpai, E.K. Hobbie, S.H. Lacerda, K. B. Migler and Jakupciak. Length-dependent uptake of DNA-wrapped single-walled carbon nanotubes. *Advanced Materials*, published on-line : 20 March 2007

In vitro systems approach





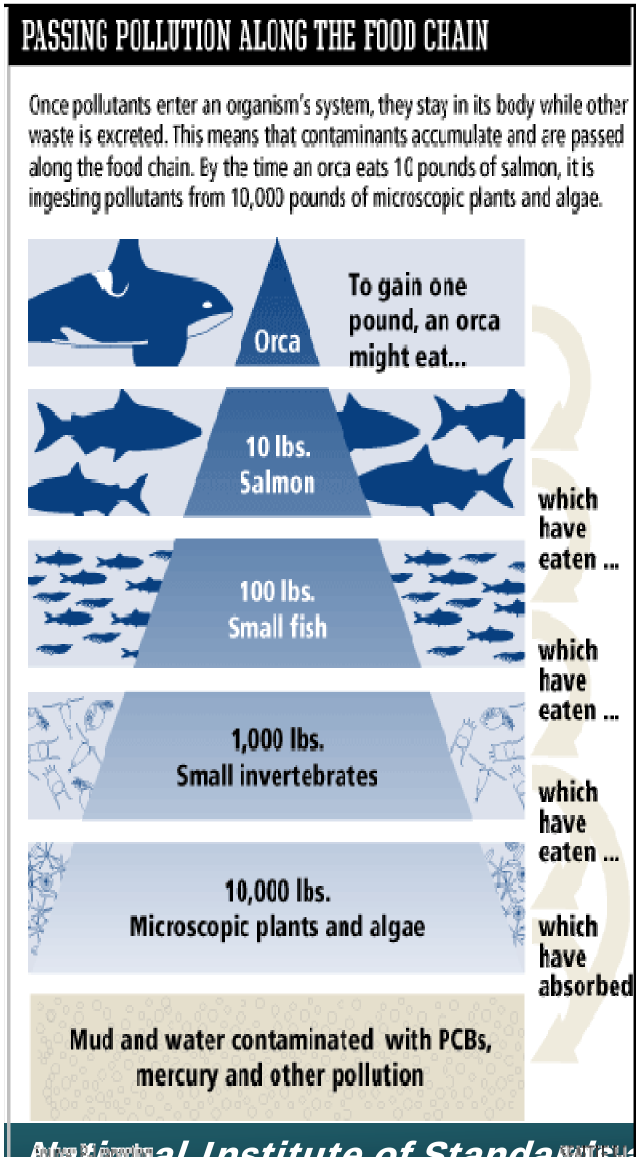




Microfluidic models of in vivo systems can be used to study ‘downstream’ toxic effects of nanoparticles

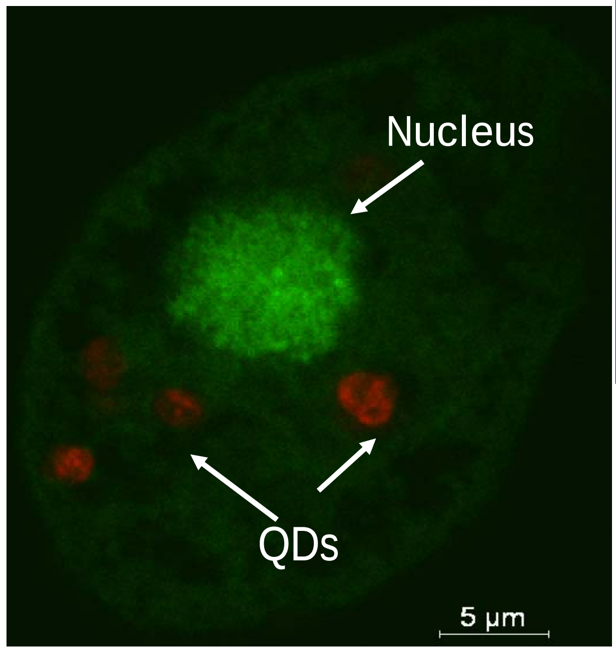
Validation of Toxicological Methods: Support Understanding Environmental and Health Impacts

Nanomaterials in the Food Chain



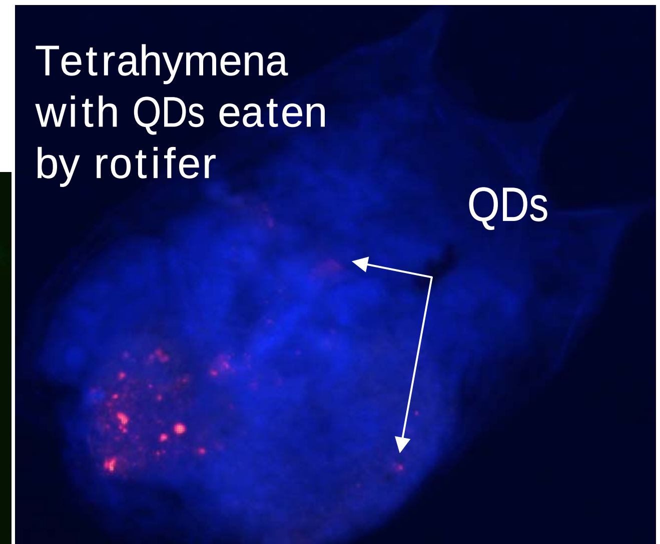
Tetrahymena (single cell eukaryote)

Passed up food chain



QDs internalized in vesicles

Tetrahymena eaten by rotifers (freshwater microorganisms)



QDs in undigested tetrahymena but also found distributed in rotifer