ICON NanoEHS Research Needs Assessment
Toward Nanomaterial Classes
Workshop 1 Report

January 9-10, 2007
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Executive Summary

Nanomaterial risk assessment is currently hampered by a lack of information regarding nanomaterial hazard and exposure potentials. Given the near-limitless variety of nanomaterial types that can be synthesized for applications, it is necessary to develop a more predictive framework that would enable assessment of nanomaterials based on understanding of properties that contribute to expected hazards and risks. The International Council on Nanotechnology has designed a two-workshop series to develop a research framework that will enable the development of predictive models of engineered nanoparticles’ interactions with biological systems. This document summarizes the outcomes of the first workshop.

The goals of the first ICON Research Needs Assessment workshop (Workshop 1) were to identify preliminary classes of nanomaterials with common properties and to identify for these classes potential “hot spots” in their lifecycle. The results from Workshop 1 will be used in the second ICON Research Needs Assessment Workshop (Workshop 2) to define research strategies for developing predictive models of engineered nanoparticles’ interactions with biological systems.

Workshop 1 included sixty five participants from broad international stakeholder groups in academia, government, industry, and non-governmental organizations (NGOs). Workgroups were organized to discuss six types of nanomaterials: oxide, metal, semiconductor, carbon, macromolecules, and self assembled materials. Emerging from the work groups was a set of common “hot spots” for nanomaterials in “dry” powder form and a different set identified for those in liquid form. While an understanding of properties that affect bio-interaction is emerging from research, these properties are not unique to any of the materials types. Physical, chemical, and in vitro screening methodologies need to be developed to determine the bio-interaction class of the materials.

For nanomaterials in a dry powder form, the primary potential “hot spots” were in the cleaning of synthesis reactors, bagging operations, surface functionalization and formulation areas of manufacturing, and in applications where materials are topically applied or formulated in aerosol delivery systems. Similarly, nanomaterials in liquid form had potential “hot spots” when the material was topically applied or aerosolized in manufacturing or product applications. Research is clearly needed into the 1) bio-activity of nanomaterials in their native form, 2) stability and mobility of nanoparticles in different formulations, and 3) bio-interactions of aerosolized formulations and liquids. Furthermore, research is needed into the effectiveness of filters and engineering controls in reducing exposure to nanoparticles whether in dry or wet form.

From preliminary research, properties that affect transport of nanomaterials may include size, shape, surface charge, surface chemical reactivity, and concentration. Properties that affect bio-interaction may include size, shape, intrinsic chemical toxicity, solubility, surface charge, chemical reactivity, and surface chemistry. Since many of these properties, including size, shape, and chemical reactivity, can be dramatically altered during the synthesis of the material, and since the surface charge, surface chemical reactivity, and surface chemistry can be modified during the functionalization and formulation of these materials, classes of nanomaterials need to be established around the functional properties of the materials. The best potential mechanism to characterize these properties would be by physical/chemical screens and select in vitro tests to determine chemical reactivity, surface charge, surface composition, and solubility. These screens
would need to be correlated to transport properties in full biological tests to enable identifying nanomaterials that need detailed testing. Finally, research is needed to establish predictive models that correlate nanomaterial structure, composition and properties to transport and bio-interactions.

Next Steps: Workshop 2: Towards Predicting Nano-Bio Interactions will be held at the Swiss Re Centre for Global Dialogue outside Zurich, Switzerland on June 5-7, 2007 to identify research needed to develop predictive models of nano-bio interactions. The workshop will produce a document with recommendations on research strategies for developing models to predict adverse or desirable effects of engineered nanoparticles upon interaction with biological systems. This will include detailed discussions on nano-biological interaction mechanisms including oxidative stress, inflammation and immune response, protein misfolding, apoptosis and necrosis, genotoxicity and mutagenicity, and developmental effects at cell-free, cellular, tissue and whole-animal levels. The strategies will identify short-, medium- and long-term research objectives with achievable milestones and a timeline for their accomplishment.

Workshop 1 was jointly sponsored by the US National Science Foundation (NSF) [BES-0646107], the International Council on Nanotechnology (ICON) and the US National Institutes of Health (NIH).

a. A hot spot is defined as a process or application in which there is a potential for direct exposure high-concentration, or prolonged exposure to moderate concentrations.
Introduction

The first ICON, NSF, NIH sponsored NanoEHS Research Needs Assessment Workshop brought together a broad stakeholder group to identify potential “hot spots” in the life of nanomaterials, identify common properties that affect bio-interaction and establish a draft of nanomaterial classes based on the properties that affect bio-interaction.

The meeting started with a number of presentations to set the stage for the workgroup discussions. Steve Brown identified the importance of establishing principles of interaction for different “classes” of nanomaterials with biological organisms to enable development of improved practices for assessing the risk of new nanomaterials. Andrew Maynard presented an overview of nanomaterial properties that may be important in bio-interaction based on early research results. Dr. Maynard’s presentation highlighted the potential importance of size, shape, nanostructure, composition, surface charge, chemical reactivity, and other properties in bio-transport and reactions with biological organisms. He also identified the need for establishing definitions for nanomaterial classifications based on physical, structural and physical properties of nanomaterials. Vicki Colvin presented a review of unique nanomaterial properties that arise as a result of their size and structure. Mike Holman identified the range of applications for a number of materials and the volume of these materials used. His presentation highlighted that oxide-based materials are in high volume in a broad range of applications and that the other nanomaterials were used in more specialized applications with generally lower volume.

The participants then broke up into six workgroups to identify nanomaterials, their common applications, potential “hot spots” in the life of nanomaterials, and properties that would be important to their bio-interaction. These groups were 1) Oxide, 2) Metal, Semiconductor (or Nanodots), 4) Carbon, 5) Macromolecule, and 6) Self Assembling Materials. These groups were arbitrarily established and were not meant to identify these materials as “Classes”. The range of nanomaterial applications in the different workgroups was very different and this will be discussed in the summary that follows after the individual reports.
Oxide Group Summary

Steve Brown Facilitator
Mike Holman Facilitator
Richard Canady Scribe

Introduction:
The meeting started with presentations by Barry Park and Fred Klaessig, who provided the background required for understanding the physical properties of the materials and applications. Then the team reviewed the nano oxide materials and their applications. It was agreed that these oxide materials have a wide variety of properties that may make classification challenging. In many cases, materials are being doped with other metal oxides to change properties. Also, the properties are often dependent on the synthesis technique and post synthesis thermal treatment. Thus, it may be very difficult to identify nanomaterials classes based on composition. It was proposed that a number of chemical screens and in vitro test be developed to determine potential for biological interaction and correlate these to physical and chemical properties. Since the applications for different oxide particles is very diverse, it difficult to assess for potential hot spots in the applications. It was felt that exposure to high concentrations of nanoparticles in dry form was a potential hot spot and this could occur in cleaning dry synthesis reactors and in handling powders in bagging and formulation.

Common Oxide Particles
Titanium oxide
Zinc oxide
Cerium oxide
Iron Oxide
Silicon Oxide (Silica)
Copper Oxide
Zirconia
Alumina
Nickel oxide
Antimony pentoxide
Yttria
Barium sulphate
Hydroxyapatite
Calcium carbonate (paper mills, filler, probably in the nanoscale)
Pigment that include particles in nanoscale – manganese oxide, etc, pigments used in inkjets
Nano-clays (including talc)

Nanomaterial Properties and Bio-interaction
The properties affecting bio-interaction include size, shape, intrinsic chemical toxicity, chemical reactivity and solubility and surface charge of the nanomaterial. While many of these factors can be characterized, the chemical reactivity can be dramatically changed by introducing chemical impurities or changing the surface nanostructure and surface charge can be changed by multiple factors. Since these chemical reactivity and surface can be dramatically changed by synthesis and in some cases, which may be difficult to detect with structure and composition, test may need to be developed to determine the relative magnitude of these properties for nanomaterials.
Chemical Reactivity: While different chemical reactions can occur, the electrons in the highest occupied states in one material must have sufficient energy to either transfer electrons to an unoccupied excited state in a molecule or form a bond with a molecule. In nanomaterials, a material must have electrons at the surface with adequate energy and introduction of impurities on the surface of an oxide may dramatically change the availability of electrons with energies capable of either transferring an electron or forming a bond. Similarly, the nanostructure of a surface may change the electron energy levels and concentration electron concentration on a surface. So, subtle changes in composition may have dramatic affect on chemical reactivity. Thus, developing a test of the functional ability of a nanomaterial to either transfer electrons or form a chemical bond with biological molecules may better establish the potential for a nanomaterial to interact with biological organisms.

Surface charge can be established by the chemical functionalization of the surface, by defects in the surface or near the surface, or by impurities introduced on the surface. Furthermore, exposure to light can generate electrons and holes and either of these could migrate to the surface of the material. Also, changing the pH of a solution may also change the surface charge of the material. So, it will be important to have a monitor that determines the surface charge over a range of pH that would be common in a biological organism in light and dark conditions.

**Synthesis, Formulation & Manufacture**

Synthesis Techniques include:
- Combustion synthesis
- Plasma synthesis
- Wet phase processing
- Chemical precipitation
- Sol-gel processing
- Mechanical processing
- Mechano-chemical processing
- High energy ball-milling
- Chemical vapor deposition
- Laser ablation
- Plasma synthesis or arc methods

**Formulation**

Almost all applications are placed in a liquid or polymer with surfactants or coupling agents. The range of chemistries is quite broad. Common matrices include water, silicone, rubber, plastics and oils.

**Potential Hot Spots in the Nanomaterial Life**

The highest risk areas in the life of these materials is in the handling of powders, bagging and un-bagging and maintenance of pyrolysis reactors, cleaning bagging houses and accidental spills.

Since these materials are used in such diverse applications, it was difficult in a short time to assess the potential hot spots in applications and disposal.

- Precipitated materials processes are likely to predominate for synthesis (Sol-gel, chemical precipitation, arc, etc)
- Flame pyrolysis is used for SiO2 TiO2 so data from “incidental” nanoparticles in soot may provide information useful to, e.g., fumed silica

**Research Priorities:**
The oxide nanomaterials group established priorities based on:
Intrinsic chemical toxicity
Chemical reactivity (and factors that control) for generation of oxygen radicals
Charge State
Other…

Applications Research Priorities
Applications where the nanoparticles may be released from the matrix
Dispersed applications (sunscreens, etc.)
Application formulations with human exposure potential (e.g. paints, etc)

The highest research priority issues were to:
1. Establish a suite of validated test to determine potential bio activity response of different nanomaterials and correlate to physical properties.
2. Establish test methodologies to assess the potential for release of nanoparticles from different matrixes.

General Comments of Concerns:
1. Can we identify a list of likely and less likely physical/chemical properties that correlate to bio activity?
2. Is it appropriate to have an arbitrary threshold for nanotechnology of 100nm?
3. It is hard to identify where in the life of nanomaterials primary particles will arise when they are placed in complex matrices that will involve agglomerates.
4. We should also consider the benefits of nanotechnology in assessment.

Back-up information:
Establishment of a Validated Suite of Bioactivity Test and correlation to physical properties
• Arrive at and test standard set of assays
• Independent confirmation of assay (oxidative stress, etc.) in different labs
• Standard reference materials to compare against – tested in assays
• Compare and validate by in vivo results
• Correlate assay results with physical characteristics, esp. dynamic characteristics (towards structure activity relationships)
• Design modification of assays

Materials characterization should comprise the following as appropriate:-
• Chemical composition
• Aggregation/agglomeration state
• Number of particles per unit mass
• Physical form
• Median size and size distribution
• Surface area
• Surface charge
• Solubility/miscibility
• Rate of dissolution
• Partition coefficient
Metals Work Group Summary

Andre Nel, Co-Chair
Mbhuti Hlophe, Co-Chair
Jennifer Sass, Scribe

Introduction:
The meeting started with presentations by Frank DiStefano and Michael Thompson, who provided the background required for understanding the physical properties of the materials and applications. Then the team reviewed the common nanometals, their applications and potential hot spots in the life of these nanomaterials and the properties that could contribute to bio interaction. After the first day, the team recommended that they be integrated into the oxide nanomaterials group since most metals would oxidize, be used in nanotube synthesis or embedded catalyst applications (catalytic converters, fuel cells, etc.).

Nanomaterial Applications
Common materials in this class and their applications include:

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Nanomaterial Properties and Bio-interaction
The most common applications of nanometals are for catalysis or antimicrobial applications for silver.
For silver, the most important properties are electrochemical potential, surface area, surface texture, edge texture, size and size distribution. These properties may be applicable to other metals. Surface or edge texture has been demonstrated to dramatically increase the catalytic properties of silver and this highlights the critical importance of surface structure. Research needs to be directed to the property relationship between catalytic activity and surface topography at the atomic level, and developing metrology to characterize catalytic activity. Surface properties may be important to the activity of other metals in generating oxygen radicals, but the relationship is not clear.

The metals used for growth of nanoparticles properties that could affect bio-interaction include chemical composition, surface chemistry, valence of the charge states, electrochemical potential, redox cycling potential. For nano-catalyst incorporated with nanotubes, the bonding of the carbon to the surface may affect the combined bio activity potential. Research is therefore needed to distinguish between the bio-activity arising from the nanotubes themselves and that arising from the presence of the embedded, cobalt, nickel and iron catalyst particles.

For catalytic converters, the catalyst is inert to adiabatic reactions, but the potential for bio-reactions is unknown. With the number of applications for catalyst rapidly increasing, there is a critical need to develop catalyst from new materials which are not resource limited such as platinum and rhodium. As the range of materials used in this field may increase so will the need to predict and monitor their potential bio-activity.

Synthesis, Formulation & Manufacture
Synthesis
The most common synthesis technique for Nano silver and Nano catalyst for use in catalytic converters is wet chemical precipitation and the group felt that this should have a low risk for human exposure.

Nan catalyst used to grow carbon nanomaterials are used in many forms that are usually in a closed reactor. This issue should be addressed by the carbon nanomaterial WG.

**Formulation (applies to most nanoparticles):**
The steps after synthesis include functionalisation, dispersion, and formulation.

- **Functionalisation is done to:**
  - Enable dispersion
  - Improve matrix compatibility
  - Passivate the nanomaterial
  - Reduce particle solubility
  - Introduce reactive sites
  - Minimize photocatalysis
  - Improve biocompatibility

- **Common functionalisation methods include:**
  - Organic carboxylic acids, amines, phosphonates, mercaptans, etc.
  - Organosilanies and siloxanes
  - Depositing inorganic oxide coatings: SiO2 and Al2O3

- **Dispersion Mechanisms include:**
  - Direct Charging (MOH+) Electrostatic
  - Silane treatment (M-OSiR)
  - Polymeric dispersants (Steric)
  - Surfactant bilayers

  The direct charging and surfactant layers may introduce particle charging.

- **Formulation:**
The functionalized nanoparticles are mixed with multiple materials depending on the application and examples of these are:
  - Architectural coatings include anionic materials, wetting agents, surfactants and thickeners.
  - Personal Care: Oils, thickeners, emollients, emulsifiers, polymers, and amines
  - Plastics and elastomers: Polymers, antioxidants, curing agents, plasticizers, pigments and fillers, thermal stabilizers and flame retardants.

  The chemistry of these formulations is quite complex, so risk assessment must consider the specific formulation and application. In most applications, the goal is to keep the particles in the formulation matrix.

- **Potential Hot Spots in the Nanomaterial Life**
The workgroup felt that metals for application in embedded catalytic applications were low risk though their life cycle.

  Nano-silver and Nano-copper may have risk as ecotoxins in the disposal of waste.
Most metal nanoparticles will form oxides and the potential hot spots for these will be addressed in the Oxide WG.

**Research Priorities:**
Significant research is needed in materials to correlate properties including electrochemical potential, surface area, surface structure, oxidation state, and surface composition with chemical reactivity, and catalytic properties. It is also important to determine which of these properties may correlate with the ability to generate oxygen radicals or other bio-interactions. New parameters may need to capture the bio-activity of surfaces as there may be no direct correlation between chemically active sites and surface area.
Semiconductor Nanoparticle Work Group Summary

Facilitator: Vicki Colvin
Scribe: Amy Cannon

Summary
Fluorescent crystalline semiconductor nanoparticles, also known as quantum dots (QDs), are being developed for use in biolabels and in vitro diagnostics; optoelectronic applications such as LEDs, displays, solar cells; inks and paints for identification or brand protection. [ref Lux] Lux Research estimates the 2005 market for quantum dots to be approximately $4.3 million, growing to $38 million by 2010. Given the small market volume and relatively high cost of production, QDs can be fairly characterized as boutique nanomaterials.

Synthesis
The synthesis and processing of QDs is done primarily in solution phase and is to a great extent performed manually rather than through automated processes, especially in the purification stage. Therefore the primary route of exposure is expected to be dermal, although inhalation exposure should be ruled out definitively through testing of ambient air around the breathing zone, particularly for those QDs that are generated as powders after undergoing a coating process.

QDs have shown the ability to dissolve and release their constituent components into solution over time. [ref] Therefore, any assessment of potential hazard from QD exposure should distinguish between QDs whose constituents are known to be highly toxic, e.g., cadmium, and those with lower intrinsic toxicity, e.g., [selenium, zinc- are essential metals]. In addition, the bioavailability and distribution of the constituents should be considered.

Synthesis and processing of QDs generally involves the use of organic solvents, highly volatile metal precursors, e.g., dimethyl cadmium, and temperatures between 100-400°C. Under these conditions, explosion presents a possible hazard though new processing techniques are beginning to utilize salts of metals rather than the highly volatile precursors. The formation of aerosols or sublimed metals should be ruled out by sampling the breathing zone during a typical synthesis and processing procedure. Current techniques generate significant volumes of waste solvent contaminated with heavy metals.

Purification of QD solutions generally involves centrifugation, phase transfer with an amphiphilic polymer and sedimentation. Large volumes of solvent are used, posing an explosion hazard and resulting in the generation of hazardous waste requiring special handling. Since these processes are still done manually, effectiveness of personal protective equipment, particularly gloves, should be validated.

Key point was scale of material- biomarker synthesis was 100 milligram quantities, whereas solar cells was in the 10g-Kg quantities

Applications
Two of the primary applications of QDs are solar cells and biomarkers. Each raises different questions with respect to possible hazards during their intended use. QDs in solar cells will generally be encapsulated and thus not offer a high exposure potential despite their much greater volume. QDs used in biomarkers pose the possibility of bioaccumulation which has not been explored in great depth in the technical literature.
At the end of life, QDs in solar cells will likely not be recovered from the product and will therefore become part of the waste stream with unknown long-term consequences. QDs used as biomarkers would be used in extremely small quantities and the extremely small quantities used are unlikely to pose a great exposure potential in the long-term.

Measuring exposure to workers could involve periodic (e.g., six month) serum tests for high heavy metal concentration or the use of fluorescence techniques to detect the QDs themselves though it remains unknown whether the QD fluorescence will persist long enough in the body to render this an effective technique.

“Hot Spots”
The primary “hot spots” for QDs occur during synthesis and processing through the potential for explosion and dermal exposure, which is related to the use of high temperature solvents, not the nanomaterials. Therefore the emphasis should be on developing engineering controls that limit personal exposure and the risk of explosion from the use of volatile materials.

If the volume of materials increases dramatically long term, controls may need to be established for handling and disposal of materials at end of life (solar panels, etc).

Critical Material Properties
Chemical Toxicity: Many of the elements used in these materials (e.g. Cd, Hg, Se, etc) have inherent chemical toxicity.

Energy Levels: These materials have a ground state (valence band) and an excited state (conduction band).

Direct Bandgap Materials: As the size of the semiconductor nanoparticles decreases, the energy levels in both the bands become split and usually the separation between the conduction and valence band increased (Band Gap Increases). For luminescence, “direct bandgap”, materials the wavelength of light shifts to shorter wavelength (higher energy) as the particle size decreases.

Indirect Bandgap Materials: These materials are generally not luminescent, but absorb energy above the bandgap and create an electron (negative charge) and hole (positive charge). If the energy of electrons at or close to the surface is higher than the energy to excite oxygen, they could create some level of oxygen radicals.

Work function: The work function of the material is the energy required to excite an electron from the Fermi level to vacuum and this depends on the dopant levels in the semiconductor.
Carbon Nanomaterial Work Group Summary

Facilitator: Vicki Stone
Scribe: David Berube

Introduction
It is worth noting that Risk = Hazard x Exposure
This document refers to exposure (hot spots) and to the intrinsic properties of the carbon nanomaterials that might influence hazard. Hazard per se will be considered in the next workshop.

Carbon nanomaterials
Common carbon nanomaterials identified included carbon nanotubes (single, double and multiwalled), fullerenes, carbon nanofibres, graphene sheets and carbon black. Most of the discussion focused on carbon nanotubes/nanofibres and fullerenes since these are produced in relatively large quantities and have many applications. Carbon black was recognised as a useful reference material for which toxicology and epidemiology data is available.

Carbon nanotube production requires the use of a metal catalyst and an organic carbon source either (i) floating in a reaction fluid, (ii) in a porous microparticle or (iii) on a surface. Fullerene production involves either (i) Arc method, or (ii) combustion method. The former is primarily conducted in a University setting, and the latter is an enclosed system that can be used in a commercial environment.

Exposure scenarios during manufacture/synthesis
A number of activities were considered to have the potential to result in relatively high exposure. During manufacturing and synthesis of nanomaterials processes considered to be able to generate high exposure included anything which disrupts the normal process, maintenance, cleaning, vacuuming and failure of personal protective equipment (PPE). Following manufacture, transport and transfer from transport vessels into a subsequent product were also both considered to potentially generate high exposure. Waste disposal and unintended use were also considered to be potentially high exposure scenarios.

By-products and contaminants
It is likely that CNT and fullerene samples will generate by-products as well as a product that contains contaminants unless specifically purified/cleaned. Since the CNT and fullerenes are made by combustion processes, contamination with carcinogenic polyaromatic hydrocarbons (PAH) is likely. The metal catalysts are also contaminants of unpurified CNT. Amorphous carbon is found in many fullerene and CNT samples. Fullerene production also produces polymer C60 and oxidised products. CNT purification requires acids, and so acid waste containing trace amounts of CNT occurs.

Applications and uses for carbon nanomaterials
Uses for carbon nanotubes and nanofibres are diverse including high performance light weight fibres, high thermal conductivity fibres, wires of low-loss electricity transmission over 1000s kw, multifunction fibers and materials (enhance polymers), imaging of diseases, treatment of diseases (ablation), scaffolds for biological applications, lithium ion batteries, IT devices and display technologies, sensors (e.g., environmental monitoring), food packaging (smart packaging), and even a space elevator. Some of these were identified as potentially generating a high exposure to either the consumer (especially those used in medical applications) or environment.
Uses for fullerenes overlap with those of nanotubes and nanofibres with respect to lithium ion batteries, IT and medical applications, but also includes coatings and cosmetics.

**Exposure scenarios during use of carbon nanomaterials**

Exposure of humans and the environment during use can be broken down into the occupational scenario, where raw nanomaterials are used and incorporated into products, and a consumer scenario, where the general public use a product containing nanomaterials. Most exposure scenarios have already been covered in an occupational setting in relation to manufacture and synthesis, with the exception of exposure during unloading of nanomaterials from storage vessels. For consumers, exposure is likely to occur via multiple routes including examples such as use of personal care products, ingestion of food, wearing of clothes and through medical treatment. Consideration of the wide range of uses lead the group that exposure via ingestion, inhalation and dermal absorption (as well as injection for medical applications) were all conceivable.

Accidents are also provide a risk for high exposure (e.g. fires, traffic accidents…). The risks during disposal are multiple including comminution (cutting, grinding), incineration/burning, changing filters, waste handling, cleaning of reactors, accidents at reactor/manufacturing sites (e.g., fires, spillages and uncontrolled removal of materials). During disposal aerosol, liquid, powder and solid materials were all considered. Aerosolisation of carbon nanoparticles could occur due to accidental release, but during controlled processes could be minimized by filtration. Liquids containing carbon nanoparticles could gain access to landfill, potable and waste water (shower, drugs), marine environments, estuarine environments. Release into these environments could be via spills and transport accidents, as well as purposeful disposal. Powders are most likely to be recycled during the production process, but cleaning (leading to release into waste water), scraping, filtering and vacuuming could all lead to human and environmental exposure. Vacuumed product has the potential to be contaminanted. Powders are likely to be disposed of via landfill and incineration and via waste disposal companies that are not well regulated. Finally there are additional risks that are difficult to quantify such as terrorism.

**Improving exposure assessment**

In order to understand exposure and risk more adequately a variety of information is required. For example, we require exposure assessment in the workplace linked to hazard assessment. An understanding of the carbon nanomaterials during uncontrolled combustion and incineration for different media (powder, liquid, composites) is required. An understanding of whether nanoparticles can be released from composites by comminution is required. The ability of maintenance and cleaning procedures to release nanoparticles into the air is currently not understood. Little is known with respect to human and environmental exposure through release during degradation of products or during the transportation of raw materials and products. the environmental fate of consumer products is also poorly understood. There is very little information on the behavior in waste water or groundwater.

**Prioritization of research needs**

- Data relating to the quantity carbon nanomaterials made over time is required.
- E.g. CNTs – 1750 metric tons (2005). C60 - specific data 40 tons per year (FCC).
- Information relating to potential applications is required.
- Improved assessment of workplace and consumer exposure.
- High hazard materials should be prioritized as well as high volume materials.
- The role of contaminants in influencing hazard.
- Structure function relationships.
- Occupational health screening (registries) linked to epidemiology studies.
Carbon nanoparticle hazard
The intrinsic toxicity of carbon was recognised as being low, but factors considered to be responsible for enhancing toxicity include particle size (small being more toxic) and contamination with other materials (e.g. metal contamination of carbon nanotubes). Metals, fullerenes and carbon nanotubes have all been shown to be redox active, with the suggestion that metals are more potent than fullerenes, that are more potent than nanotubes, although this requires further investigation. Due to their large surface area these particles were proposed to be potential carriers of other materials that may influence toxicity. The charge of carbon nanomaterials varies according to the media in which they are dispersed, e.g in water nano-C60 is negatively charged, and with functionalisation.

The group conducted a survey of which particle properties need to be characterised as part of the EHS process. Each member had 3 votes, the number of votes were then used to rank the characteristics in terms of importance.

1. Particle surface area. (7)
2. Redox activity. (6)
3. Composition/contamination (metals, organics, etc.). (6)
4. Solubility (water and organics). (3)
5. Durability (biopersistence) (3)
6. Particle count. (2)
7. Particle size distribution. (2)
8. Defect density. (1)
9. General characteristics from material science. (1)
10. Length (aspect ratio) of CNT affecting inhalation, transport, filtering, and toxicity.
11. Charge.
12. Degree of agglomeration.
Introduction:
The Macromolecules group focused on nanomaterials generally engineered from organic molecules to have a precise size, shape, and surface functionality. Such materials include dendrimers, dendrons, and dendrigrafts of various generations, hyperbranched polymers and nano-engineered classical polymers. Naturally occurring macromolecules such as DNA constructs, peptides/peptoids/proteins, carbohydrates, and biopolymer/synthetic polymer constructs were also discussed because of their similarities to the engineered macromolecules.

The group included technical experts in the field, such as Donald Tomalia and Mark Banaszak Holl, who were able to provide the background required for understanding the physical properties of the materials.

Nanomaterial Properties and Bio-interaction
The group identified a number of critical properties that are engineered into the design of macromolecules that may lead to increased environmental health and safety risks and that can be measured including:

- Intrinsic chemical toxicity of monomers (ex: acrylates as neurotoxins)
- Shape
- Size/Molecular weight
- Surface area
- Surface chemistry
  - Charge, intermolecular forces, Chemical Reactivity (ex: redox chemistry)

Cationic macromolecules have been observed to bind to the negatively charged heparin sulfate proteoglycan molecules on the surface of cells through electrostatic interactions leading to the rapid uptake of the macromolecules by the cells through an actin filament-mediated endocytosis process (Kopaz, Remy, Behr, J. Gene Med. 2004, 6, 769). Similarly, amine-terminated dendrimers have been observed to generate holes in lipid bilayers leading to disruption of membrane functions and leaking of cytosolic enzymes out of the cells (Langmuir, 2005, 21, 10348; Hong et. al., Bioconjugate Chemistry, 2004, 15, 774-782). This research also suggested that larger G7 dendrimers had a greater effect on membrane disruption than smaller G5 dendrimers. Although amine terminated dendrimers show greater association with tissue, anionic dendrimers functionalized with carboxylic moieties have been observed to rapidly cross the intestinal membrane of adult rats (Wiwattanapatapee et. al., Pharm. Res., 2000, 17, 991).

Other physical properties discussed that may contribute to transport and toxic response in biological systems that warranted capturing include:

- Primary sequence (base structure)
- Secondary structure (internal structure built off the base)
- Tertiary structure (external structure the interacts with environment)
  - Crystallinity
- Topology/architecture
- Branching
- Amphoterism
- Alteration of transport properties of other materials (i.e. serve as delivery systems)
- Dynamics – ability to rearrange to change structural characteristics
Synthesis, Formulation & Manufacture, and Application & Use

Synthetic techniques for the synthesis of macromolecules include:
- Step-growth / chain polymerization (liquid phase)
- Gas phase polymerization
- Grafting
- Reactive co-extrusion
- Electrospinning

Common formulation processes include:
- Batch mixing
- Ultrafiltration
- Ball milling / jet milling
- Extrusion / thermoforming
- Coating (spin, spray, dip. Etc.…)
- Microfluidics

Common formulation chemistries include:
- Surfactants
- Additives (stabilizers, inhibitors, antioxidants, etc…)

Common matrixes in which the macromolecules can be found include:
- Aqueous/solvent solutions
- Creams / gels
- Solids / Powders

Potential applications for macromolecules include:
- Delivery systems (Drugs, platforms, therapeutics, nutraceuticals)
- Bioassays
- Image contrast agents
- Transfection polymers
- Ink jet printers
- Ion exchange resins / metal chelation
- Coatings
- Cosmetics
- Engineering materials
- Formulation viscosity modifier
- Environmental remediation

Potential Hot Spots in the Nanomaterial Life

For potential near term commercial applications of macromolecules, the liquid phase step-growth/chain polymerization technique is the most commonly employed synthetic technique. Within this process, the greatest potential activities of high exposure include synthetic steps in the purification of the materials when they are at their highest concentration. However greatest exposure potential to free nanomaterials will occur with synthetic techniques and applications in which the materials are aerosolized. Examples of these techniques include spray drying and ball or jet milling. Unexpected hotspots for exposure potential may occur from degradation byproducts of these materials resulting from temperature, oxidative, or photochemical degradation.
Applications with the greatest potential for intentional human exposure include their uses as delivery agents for pharmaceuticals, nutraceuticals, contrast agents, and cosmetics.

There is less of a concern around potential for high exposure at the end of life of products containing macromolecules due to their high propensity for degradation in the environment. The greatest concern addressed was the difficulty in removing these materials at waste treatment plants.

**Hot Spots Summary**

<table>
<thead>
<tr>
<th>Nanomaterial</th>
<th>Synthesis</th>
<th>Formulation</th>
<th>Application</th>
<th>Disposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macromolecule</td>
<td>Purification</td>
<td>Milling, spraying &amp; aerosolizing</td>
<td>Cosmetics Delivery systems Inkjet printing</td>
<td>Remove at treatment plants</td>
</tr>
</tbody>
</table>

In order to isolate and identify macromolecules at these hotspots for high exposure potentials, the characteristics of the materials that need to be understood include:

- Material size and shape (includes molecular weight)
- Polyvalency / dynamics
- Amphiphilic character
- Charge state
- Monomer chemistry
- Surface functional groups
- Formulation chemistry (accompanying compounds)

The size of the material includes the nanometrics, hydrodynamic diameter, and radius of gyration of the particles. The functional groups on the material surface influence the charge, hydrophobicity/hydrophilicity, and receptor specific characteristics of the material. The architecture of the material is the shape of the material as defined by topology, primary, secondary and tertiary structure, aggregation, and dynamic characteristics of the material. Understanding these physical properties of the materials will help develop appropriate metrology protocols for detecting these materials in the environment.

**Prioritized Research Needs Recommendation**

The criteria for prioritizing research needs to understand the environmental, health, and safety impact of these materials include understanding the association of the physical properties of the materials to their biointeraction and the facilitation of the development of metrology, standards, and data to correlate the structure activity relationship of the materials. The recommended research priorities are focused on the pharmacological and environmental impact of the physical properties of the materials and the manufacturing processes. These research priorities include:

- SAR of size, topology/architecture, and functional groups to pharmacokinetics, pharmacodynamics, and pharmacology
  - Size* – Nanometrics, hydrodynamic diameter, radius of gyration
  - Functional groups* – Charge, receptor specific, hydrophobicity/hydrophilicity
  - Architecture* – Shape as defined by topology, primary, secondary, tertiary structure, aggregation, and dynamics
  - Pharmacology/Pharmacodynamics§ – Toxicology and therapeutics
  - Pharmacokinetics§ – Absorption, distribution, metabolism, excretion
• SAR of size, topology/architecture, and functional groups to environmental fate and transport
  • Size* – Nanometrics, hydrodynamic diameter, radius of gyration
  • Functional groups* – Charge, receptor specific, hydrophobicity/hydrophilicity
  • Architecture* – Shape as defined by topology, primary, secondary, tertiary structure, aggregation, and dynamics
  • Environmental fate and transport - Diffusion, degradation, persistence, bioaccumulation
• Toxicological and environmental impacts of manufacturing processes (green chemistry).

Where * represents the potential for interactions among combinations of these properties and § represents the potential for synergies of macromolecules changing the pharmacological properties of other small or biomolecules.

In addition, it is recognized that these studies need to be conducted across a wide range of organisms since the response to these materials may differ across organisms.
Self Assembly Group Summary

Team Leader: Kenneth Dawson
Scribe: Sally Tinkle

**Introduction:**
The Self Assembly Group was charged with identifying potential physical, chemical, and biological properties of engineered, self assembling nanostructures and conceptualizing the points in their production, use, and disposal that might merit special attention to hazard.

Self assembled nanomaterials are composed of even smaller nanoscale building blocks such as lipids and metal oxide nanoparticles and may include modifying components such as surfactants, inorganic materials, and organic molecules. Self organizing nanostructures are designed to assemble into ordered functional or structural units by maximizing colloidal, electrostatic and noncovalent properties and minimizing human intervention. Self assembling nanoscale structures display interesting and potentially useful properties, such as optical transparency, enhanced diffusive transport, structural flexibility and improved stability of nanoemulsions. Examples of self assembling nanomaterials include nanoemulsions, lattices, hollow spheres, tubes and capsules.

This team started with presentations by Tom Mason, UCLA; Mike Wong, Rice University. Two major categories of self assembled nanomaterials were discussed, lipid assemblies and nanocomposite assemblies, and these will be reviewed separately.

**Lipid Assemblies**

**Synthesis & Formulation**
Common formulation process:
- Emulsification with sufficient shear to produce nanoscale assemblies

Common formulation chemistries may include:
- Surfactants
- Additives (stabilizers, inhibitors, antioxidants, etc…)

Common matrixes in which lipid assemblies can be found include:
- Aerosol
- Solution
- Cream / gel

**Potential Applications**
Primarily as delivery systems
- therapeutics, contrast agents and neutraceuticals
- cosmetics and personal care products
- advanced research and development

**Properties and Bio-interaction**
Critical characteristics
- size and morphology are dependent of conditions of synthesis
  - primary particle size: 10 – 1000nm
  - agglomerate size: nanoscale to macroscale
- shape: compact, fibrous, tubular and multi-lamellar
• surface chemistry
  o charge state: positive, negative or neutral
  o surface can be functionalized for specific application, e.g. targeting to a cell type or organ system
  o surface may abstract molecules from the environment non-specifically
• permeable

Biological interactions
• lipids, the primary building block, are biocompatible
• toxicity may derive from non-specific adsorption of molecules from the microenvironment or inappropriate functionalization
• primary routes of exposure: lung and skin, although ingestion and ocular uptake are possible
• uptake is dependent on the biological context
• response to stimuli can be simple or complex

Dose metric should consider 3 parameters:
• particle number per cell
• volume fraction of the contents (that is, the concentration of molecular species per vesicle)
• concentration of liposomes in the delivery system

Potential Hot Spots in Lipid Assembly Life Cycle
• Exposure to materials over their life cycle- manufacture, use and disposal- all present different issues for safety assessment and are largely unknown.
• Lipid assemblies have high potential for environmental transformation. They may bind non-specifically to entities in the environment that would change their shape, chemistry, and propensity for environmental transport. Inaccurate assembly could permit inappropriate systemic transport, e.g., across Blood-Brain Barrier, or through the environment.
• The potential for and consequences of disassembly and inappropriate reassembly, especially in post-use, is unknown. This could occur in the body or in the environment and lead to inappropriate structures, unanticipated uptake and transport.
• Increased potential for stealth entry into undesirable locations in the body and inappropriate reassembly represents a significant concern.

Nanocomposite Assemblies
Two forms discussed: nanoparticle polymer assemblies and organic-inorganic hybrid assemblies

Synthesis & Formulation
Common formulation process:
• Self assembly driven by thermodynamics and/or kinetics
  o Evaporative self assembly
  o Electrostatic assembly
    ▪ nanoparticle assembly
    ▪ layer by layer assembly
• Aggregation prevented by charge repulsion and steric repulsion (e.g., polymer and surfactant coating)

Common formulation chemistries may include:
• Surfactants, polymers
• Organic molecules

Common matrixes in which nanocomposite assemblies can be found include:
• Aerosol
• Solution
• Cream / gel
• Solid organic composites
• Ceramics

Potential Applications
Delivery systems
• therapeutics, contrast agents and neutraceuticals
• cosmetics and personal care products
• advanced research and development

Environmental applications:
• energy harvesting
• catalysis
• structural materials and nanoceramics
• rheological modifiers for nanocomposites

Properties and Bio-interaction
Critical characteristics
• size and morphology are dependent of conditions of synthesis
  o primary particle size: 1 – 100nm
  o assembly size: 10 - >1000nm
  o agglomerate size: morphology is condition dependent and size is microenvironment dependent
• shape: compact, fibrous (e.g., self assembling polypeptides), capsular structures, 2-dimensional sheets, hollow spheres, crystals, wires
• crystal structure: higher order crystallinity
• functionalized surface chemistry
  o charge state: positive, negative or neutral
  o coating composition: organic (surfactant), polymers (PEG, polylysine), inorganic (native nanoparticle)
  o surface coating can be functionalized for specific application
  o surface may abstract molecules from the environment non-specifically
• porous and permeable

Biological interactions
• toxicity may derive from toxicity of components in the assembly and from non-specific adsorption of molecules from the microenvironment onto the assembly or inappropriate functionalization
• primary routes of exposure: lung and skin, although ingestion and ocular uptake are possible
• uptake is dependent on the biological context
• response to stimuli can be simple (disassembly: pH, temperature, pressure, ionic strength) or complex

Dose metric should consider 3 parameters:
• assembly units number per cell
• volume fraction of the contents (that is, the concentration of molecular species in each assembly)
• concentration of assemblies in the delivery system

Potential Hot Spots in Nanocomposite Assembly Life Cycle
• Toxicity of the nanocomposite assembly components during manufacture
• Toxicity and potential transformation of components during degradation and disassembly
• Assemblies may be inappropriate carriers of manufacturing byproducts, e.g., solvents, that are toxic.
• Inaccurate assembly may inappropriately enhance systemic transport, e.g., across Blood-Brain Barrier, or through the environment.
• Exposure to materials over their life cycle- manufacture, use and disposal- all present different issues for safety assessment and are largely unknown.
• Nanocomposite assemblies may bind non-specifically to entities in the environment that would change their shape, chemistry, and propensity for environmental transport.
• The potential for and consequences of disassembly and inappropriate reassembly, especially in post-use, is unknown. This could occur in the body or in the environment and lead to inappropriate structures, unanticipated uptake and transport.
• Increased potential for stealth entry into undesirable locations in the body and inappropriate reassembly represents a significant concern.
• Use of nanocomposite assemblies in industry may lead to an industry sector mismatch between the required material science expertise to create the nanocomposite assemblies and the applications expertise, e.g., material scientists making drug delivery systems.

Prioritized Research Needs Recommendation
The criteria for prioritizing research needs to understand the environmental, health, and safety impact of these materials are similar to other categories of nanomaterials and include understanding the association of the physical properties of the materials to their biointeraction and the facilitation of the development of metrology, standards, and data to correlate the structure activity relationship of the materials. Additionally, self assembly imposes additional critical research needs to address the potential for inappropriate assembly and inappropriate disassembly and reassembly.
Summary

As can be seen in the workgroup reports, the applications of the nanomaterials covered by each work group were very different. One of our goals was to identify classes of materials based on common properties that affected bio-interaction, but the oxide and metal work groups highlighted that subtle changes in surface structure or composition could produce dramatic changes in chemical reactivity and possibly other properties. The oxide workgroup proposed that a set of tests be established to measure the functional properties of nanomaterials that may affect bio-interaction. The properties included size, shape, composition, chemical reactivity, surface charge, and others. The macromolecule and semiconductor workgroup identified potential applications of their materials to medical diagnostics and treatment, so research in these areas may provide more insight into nano-bio-interaction mechanisms.

The oxide and carbon nanomaterials workgroups identified a number of “hot spots” in the life of their materials that included maintenance of the nanomaterial synthesis and process equipment, in bagging, and mixing operations for powders. For macromolecules, the maintenance of equipment and operations that involve spray or aerosol formation were identified as potential “hot spots.”

Since the applications of the materials in each workgroup were so diverse, each team was often studying different properties that potentially affect bio-interaction. As a whole, properties that may be important in bio-interaction include size, shape, composition (intrinsic chemical toxicity), chemical reactivity (including the ability to generate oxygen radicals), solubility and surface charge/chemical functional groups. During the discussions, it became apparent that adding a small amount of dopant to an oxide, placement of ligands on the surface of C60, or increasing surface step density on a metal nanoparticle, can dramatically change their chemical reactivity. Since subtle changes in nanostructure and composition can produce dramatic changes of properties in some nanomaterials, it would be very difficult to fully characterize nanostructure and then predict properties, so it may be best to assess physical/chemical functional performance and correlate these to bio-interactions.

This workshop was successful in identifying potential “hot spots” in nanomaterial life, but consensus was that it was premature to establish classes of nanomaterials based on properties that will affect bio-interactions. The results of this meeting will be used to identify where additional materials property understanding is needed and existing knowledge will be consolidated prior to the second workshop. The results from Workshop 1 will be used as input to the second workshop, which will be more focused on biological interactions.

Based on discussions on macromolecules and self assembled materials, future nanomaterials will be more complex and the potential for unplanned assembly should be explored as these and all nanomaterials are placed in complex environments. It is important to develop an understanding of the principles that govern bio-interactions with exiting and future nanomaterials.

Research needs of the work groups are very different and are included in each of the individual summaries. Efforts should be established to coordinate the collection and dissemination of bio-interaction knowledge from research in such diverse areas as medical diagnostics and treatment application to interactions studies for consumer applications.

Next Steps

As has been identified in this discussion, nanomaterial bio-interactions have been identified to be dependent on some combination of size, shape, surface charge, chemical reactivity, chemical
toxicity, surface composition, and concentration that may change depending on the type of material involved. Many of these properties can be designed into the material and changed by synthesis and formulation, so it will not be possible to establish classes of nanomaterials based on composition or a limited set of structural properties. Rather, establishing a set of screens that determine in addition to size, shape, and composition, and also measure the functional performance of the nanomaterials that indicate the relative chemical reactivity, surface charge, solubility, and surface composition.

The next steps are to 1) review the individual workgroup research priorities and assess their broader applicability, 2) identify screening strategies to measure physical (size, shape, nanostructure) and chemical properties including composition, chemical reactivity, particle surface charge, solubility, and surface composition, 3) establish agreement on a set of functional screens and identify test to determine whether these properties correlate to bio-interaction potential, 4) assess potential for nano-interactions with a wider range of biological systems, and 5) identify research needed to develop predictive models of nano-bio interaction.

ICON will hold Workshop 2 at the Swiss Re Centre for Global Dialogue outside Zurich, Switzerland on June 5-7, 2007 to identify research needed to develop predictive models of nano-bio interactions. The workshop will produce a document with recommendations on research strategies for developing models to predict adverse or desirable effects of engineered nanoparticles upon interaction with biological systems. This will include detailed discussions on nano-biological interaction mechanisms including oxidative stress, protein misfolding, inflammation and immune response, apoptosis and necrosis, genotoxicity and mutagenicity, and developmental effects at cell-free, cellular, tissue and whole-animal levels. The strategies will identify short-, medium- and long-term research objectives with achievable milestones and a timeline for their accomplishment.

After this, ICON will write a report summarizing the results of both workshops.
# ICON Research Needs Assessment Workshop 1

## Monday, January 9, 2007

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>ICON (Executive) Director’s Welcome and Overview</td>
</tr>
<tr>
<td>8:45</td>
<td>Physical Properties of Nanomaterials – TBD</td>
</tr>
<tr>
<td>9:15</td>
<td>Current Understanding of NanoEHS of Nanomaterials – Andrew Maynard</td>
</tr>
<tr>
<td>9:45</td>
<td>International Common Research Objectives – Mike Garner</td>
</tr>
<tr>
<td>10:15</td>
<td>Nanomaterial Classification, Research Prioritization Process &amp; Charge to Workgroups</td>
</tr>
<tr>
<td>10:45</td>
<td>Break</td>
</tr>
<tr>
<td>11:00</td>
<td>Work Groups Convene (Work Groups: Oxide, Metal, Semiconductor, Carbon, Macromolecules, Emerging Nanomaterials)</td>
</tr>
<tr>
<td>12:00</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:00</td>
<td>Work Groups Convene</td>
</tr>
<tr>
<td>4:30</td>
<td>Reconvene for Report Backs</td>
</tr>
<tr>
<td>6:00</td>
<td>Adjourn</td>
</tr>
<tr>
<td>6:30</td>
<td>Dinner (at hotel)</td>
</tr>
</tbody>
</table>

## Tuesday, January 10, 2007

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>Introduction</td>
</tr>
<tr>
<td>8:15</td>
<td>Workgroup Breakout Sessions</td>
</tr>
<tr>
<td>11:00</td>
<td>Reconvene for Report Backs</td>
</tr>
<tr>
<td>12:00</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:00</td>
<td>Report Outs, Summary, and Next Steps</td>
</tr>
<tr>
<td>2:00</td>
<td>Adjourn</td>
</tr>
</tbody>
</table>
Attendees

ICON Staff: Vicki Colvin, Executive Director (Rice University - USA)
            Kristen Kulinowski, Director (Rice University - USA)
            David Johnson, Operations Manager (Rice University - USA)
            David Berube, Communications Director (U South Carolina - USA)

Eric Amis (National Institutes of Standards and Technology – USA)
John Balbus (Environmental Defense – USA)
Bob Bronaugh (Food and Drug Administration – USA)
Steven Brown (Intel – USA)
Richard Canady (Food and Drug Administration – USA)
Amy Cannon (Center for Green Chemistry – University of Massachusetts – USA)
Vince Castronova (National Institute for Occupational Health and Safety – USA)
Wei Chen (Chinese Academy of Science – China)
Scott Cumberland (Clorox – USA)
Ken Dawson (University College Dublin – Ireland)
Frank Distefano (Air Products – USA)
Thomas Epprecht (Swiss Reinsurance Company – Switzerland)
Mike Garner (Intel – USA)
Robert Glenn (Crowell & Moring LLP – USA)
Mbhuti Hlophe (North West University – South Africa)
Mark Banaszak Holl (University of Michigan - USA)
Mike Holman (Lux Reseach Inc. – USA)
Matthew Jaffe (Crowell & Moring LLP – USA)
Guibin Jiang (Chinese Academy of Sciences – China)
Fred Klaessig (Degussa – USA)
Bill Kojola (AFL-CIO – USA)
Stephen Lehrman (ASME Fellow – Senator Mark Pryor – USA)
Thomas Mason (University of California – Los Angeles – USA)
Andrew Maynard (Wilson Center – USA)
Scott McNeil (NCI Nano Characterization Lab – USA)
Cyrus Mody (Chemical Heritage Foundation – USA)
Hideki Murayama (Frontier Carbon Corp. – Japan)
Chris Murray (IBM – USA)
Imad Naasani (Invitrogen – USA)
Andre Nel (University of California, Los Angeles – USA)
Gunter Oberdorster (University of Rochester – USA)
Barry Park – (Oxonica – UK)
Matteo Pasquali (Rice University – USA)
Juergen Pauluhn (Bayer Health Care – Germany)
Francis Quinn (L’Oreal – France)
John Randall (Zyvex Corporation – USA)
Mike Roco (National Science Foundation – USA)
Marc Saner (Council of Canadian Academies – Canada)
Jennifer Sass (Natural Defense Resource Council – USA)
Ted Schettler (Greater Boston Physicians for Social Responsibility – USA)
Jo Anne Shatkin (Cadmus Group – USA)
Attendees (Cont)

John Small (National Institutes of Standards and Technology – USA)
Vicki Stone (Napier University – UK)
Robert Tanguay (Oregon State University – USA)
Clayton Teague (NNCO – USA)
Adam Teepe (ICF International – USA)
Trevey Thomas (Consumer Product Safety Commission – USA)
Mike Thompson (FEI Company – USA)
Sally Tinkle (National Institute for Occupational Safety and Health – USA)
Donald Tomalia (Dendritic Nanotechnologies – USA)
Nigel Walker (National Institute of Environmental Health Sciences – USA)
David Warheit (DuPont – USA)
John Warner (Center for Green Chemistry, University of Massachusetts – USA)
Michael Wong (Rice University – USA)
Yuliang Zhao (Chinese Academy of Sciences – China)