I. LOCATION OF BACKGROUND MATERIALS/PRESENTATIONS AND FREQUENTLY USED ABBREVIATIONS

Background materials and presentations for NWG meetings are available on the NTP website at *http://ntp.niehs.nih.gov/go/430.*

EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
NIEHS	National Institute of Environmental Health Sciences
NCI	National Cancer Institute
NCL	Nananotechnology Characterization Laboratory
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NSF	National Science Foundation
NTP	National Toxicology Program
OECD	Organization for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy
ARDEC	U.S. Army Armament Research, Development and Engineering Center

II. ATTENDEES

The NTP Board of Scientific Counselors Nanotechnology Working Group (NWG) met on March 15, 2006, at the Holiday Inn-Rosslyn at Key Bridge, 1900 N. Fort Myer Drive, Arlington, VA. The following individuals attended this meeting.

NWG Members
John Balbus, M.D., M.P.H. (Environmental Defense)
Vicki Colvin, Ph.D. (Rice University)
Mark Lafranconi, Ph.D. (Procter & Gamble)
Martin Philbert, Ph.D. (Univesity of Michigan)
James Platner, Ph.D. (Center to Protect Workers' Rights)
Steven Roberts, Ph.D. (University of Florida)
Jennifer Sass, Ph.D. (Natural Resource Defense Council)
David Warheit, Ph.D. (DuPont Haskell Laboratories)
Maria Morandi, Ph.D. (University of Texas Health Science Center at Houston)

NIEHS Staff
John Bucher, Ph.D.
Allen Dearry, Ph.D.
Sally Fields
Barbara Shane, Ph.D.
Sally Tinkle, Ph.D.
Nigel Walker, Ph.D.

Other Federal Staff
Norris Alderson, Ph.D. (FDA)
Richard Canady, Ph.D. (FDA)
Vincent Castranova, Ph.D. (NIOSH)
Mengdawn Cheng, Ph.D. (Oak Ridge National Laboratory)

Public
Jean Chun (PPG Industries, Inc)
Carol Eisenman (Cosmetic, Toiletry, and Fragrance Association)
John Festa, Ph.D. (American Forrest & Paper Association)

Other Federal Staff continued

Public continued

Gregory Downing (NCI)
Kyle Elliott (ARDEC)
Karen Hamernik, Ph.D. (EPA)
Kimberly Hogrelius (ARDEC)
Paul Howard, Ph.D. (FDA)
Steve Lingle (EPA)
Scott McNeil, Ph.D. (NCI)
Celia Merzbacher, Ph.D. (OSTP)
Greg Miller (EPA)
Nancy Miller, Ph.D. (NIH)
Jeffrey Morris (EPA)
Vladimir Murashov, Ph.D. (NIOSH)
Vivian Ota Wang, (NIH)
Diane Poster, Ph.D. (NIST)
Nora Savage, Ph.D. (EPA)
Philip Sayre, Ph.D. (EPA)
Loretta Schuman, Ph D. (OSHA)
Kristina Thiagarajan, Ph.D. (Oak Ridge National Laboratory
Treye Thomas, Ph.D. (EPA)
Thane Thurman, Ph.D. (FDA)
Dennis Utterback (EPA)
Colin Finan (Inside Washington Publishers)
Martha Marrgsese (Keller & Heckman)
Tyler Laner (Environ Corporation)
Steve Mann, Ph.D. (Johnson & Johnson)
Brian Mayes, Ph.D. (General Electric)
Kristin Marano (Environ Corporation)
Larry Pearl (Aara Informa)
Kevin Reinhert, Ph.D. (AMEC Earth & Environmental)
Takahiko Suwa (Shiseido)

III. WELCOME AND OPENING REMARKS

Dr. Steven Roberts, Chair, called the meeting to order at 9:00 a.m. and asked individuals in the room to introduce themselves. Dr. Barbara Shane, NIEHS/NIH, read the conflict of interest statement. Dr. Roberts noted receipt of a written public comment submitted by Dr. Samantha Dozier on behalf of People for the Ethical Treatment of Animals. Dr. Allen Dearry, Interim Associate Director of the NTP, welcomed those in attendance.

Dr. John Bucher, NIEHS/NIH, briefly reviewed the topics discussed at the last NWG meeting (June 24, 2005) and agenda items scheduled for the present meeting. He noted several recent nanotechnology related events: (1) the House Committee on Science meeting to discuss environmental and safety impacts (November 17, 2005), (2) an NTP briefing with the staff of this committee to discuss the NTP Nanotechnology Safety Initiative (December 13, 2005), and (3) the OECD Workshop "Safety of Manufactured Nanomaterials: Building Cooperation, Coordination, and Communication" (December 7-9, 2005). The NTP participated in the OEDC workshop.

IV. NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY (NIST)

Dr. Dianne Poster, NIST, summarized the nanotechnology activities at NIST, a non-regulatory agency located with the U.S. Department of Commerce. The mission of NIST is to develop and promote measurement, standards, and technology to enhance and improve the quality of life. Major topics covered by Dr. Poster included:

- NIST organization, facilities, products, and services.
- NIST contributions to the NNI:
  - NIST serves as the lead agency for instrumentation research, metrology, and standards for nanotechnology.
  - NIST is the co-lead agency with NSF for nanomanufacturing.

- NIST nanotechnology research areas: (1) characterization of materials, (2) science and measurement research, (3) development of nanoscale electronics, (4) nanochemistry and nanobiotechnology, and (5) quantum computing and communications.
  - Approximately 15% of the NIST budget is devoted to nanotechnology-related research. During fiscal year 2005, the financial investment by NIST toward nanotechnology was $61.1 million.
  - A report summarizing NIST accomplishments in nanotechnology during fiscal years 2004-2005 is in the final stages of review and will be available soon.
- Current NIST particle size standards for standard reference materials.
- NIST strategy for characterizing nanoparticles with respect to size, images (surface characteristics), and chemistry.
- NIST communications on nanotechnology (e.g., workshops and reports) and interactions with the NNI.
- NIST's role in developing measurement technologies.
- Overview of the NIST Advanced Measurement Laboratory.
  - Developed for advanced nanometrology and designed to be the most environmentally stable laboratory in the world.
- Mechanisms to collaborate with NIST.

Discussion

Dr. David Warheit asked whether NIST is doing research in the area of nanoparticle aerosols. Dr. Poster said this research is being undertaken within the Building and Fire Research Laboratory. The research is primarily focused on combustion processes, generation of ultrafine particles, and measurement accuracy. In reference to NIST's research on nanoparticles in wastewater, Dr. John Balbus asked if NIST is considering the issue of pre-existing "natural background" levels. Dr. Poster said this area of research is in the early stages of development and she is confident that the issue of background levels will be considered. Dr. Vicki Colvin asked for additional information on the particle size standards that NIST is developing. Dr. Poster responded that NIST is working to develop standards as quickly as possible, but it is too early to outline a specific timeframe. Dr. Jennifer Sass asked if NIST is also working to characterize nanoparticles in living biological systems, such as cells and tissues. Dr. Poster replied that research of this type is conducted within the Biochemical Science Division at NIST. Specific research projects include improving metrology to increase sensitivity/selectivity for measurement and characterizing quantum dots in tissues. Dr. Sass asked if NIST focuses on purified isolates or particles as found in products. Dr. Poster said in most cases, especially for studies conducted in conjunction with the NCI, both are evaluated to see if they differ. Results from NIST studies can be found on the website or by contacting specific researchers. Dr. Bucher asked Dr. Poster to comment on discussions of NIST serving as the national repository of characterized materials for researchers and on the throughput of material characterization. Dr. Poster said the concept of NIST functioning as a national repository has not advanced past the discussion stage. The coordinator of nanotechnology at NIST, Dr. Michael Postek, may have more information. In terms of throughput, she said the time frame depends upon the nature of the collaboration and project.

Dr. Bucher asked if any working group members had opinions on nanomaterial nomenclature in terms of consistency of descriptions. Dr. Colvin believes the definitions of nanotechnology and nanoparticles found in U.S. government documents are fairly consistent. There are a couple of mechanisms to address terminology and nomenclature standards internationally. For U.S. citizens, the best way to participate is through the American Society for Testing and Materials (ASTM). This society develops consensus-based standards. The American National Standards Institute (ANSI) has developed a terminology standard focused on nanoparticles. There is an effort to harmonize definitions for a set of 15 nanotechnology-

related terms between the ASTM and ANSI within the next few years. Dr. Bucher commented that the lack of precision in the descriptions of nanomaterials presents a significant challenge to regulatory agencies. Dr. Colvin added that although members of the regulatory community are involved in the ASTM, terms with regulatory implications tend to be more contentious and are proving difficult to define using a consensus-based approach. Nanoparticle is one such term. She foresees the need for regulatory agencies to develop more specific and elaborate definitions specific to their needs for some terms. Developing a consistent nomenclature is more challenging and may require workshops. Dr. Bucher asked if NIST has plans to address the creation of a descriptive terminology. Dr. Poster said NIST is involved with the ASTM and is having ongoing internal discussions on this topic. Dr. Nigel Walker asked how NIST communicates with the broader scientific community on standardization issues. Dr. Poster said the goal is to disseminate metrology information as a standard. In the long-term, the process of refining methods and comparing performance across laboratories should help standardization efforts. Dr. Walker agrees, but based on the published literature sees the need to standardize the way different laboratories characterize materials. Dr. Colvin said one critical need is to have standards available commercially for use in calibrating equipment. Dr. Mark Lafranconi asked whether NIST will develop the methodology and techniques to characterize once the the nomenclature issues are more resolved. Dr. Poster believes NIST will be very involved once a nomenclature issue is defined, for example, when a primary critical size is specified. She also believes development of standard reference materials will help address this issue.

Dr. Paul Howard asked if the methods that NIST is developing allow measurement of the distribution of contaminants within a particle size, for example, a 40 nm particle among 60 nm particles. Dr. Poster said the methods can characterize chemical composition and impurities. NIST is using field flow fractionation techniques and spectrometry. Dr. Martin Philbert commented that current efforts are directed toward characterizing a material prior to contact with biological systems. However, properties of biological systems (e.g., complex protein mixtures, changes in ionic strength) may impact particle characteristics. He asked if NIST or others are characterizing the way nanoparticles agglomerate in biological media. Dr. Poster said this is an ongoing area of research, especially in the context of collaborations with NCI. Dr. Sally Tinkle asked if there is sufficient instrumentation to conduct this work or whether it is a research need. Dr. Colvin believes the instrumentation is a research need. Dr. Walker asked if there are any standards for polydispersed solutions. Dr. Poster said some of the particle size standards are characterized for a range of sizes (e.g., TiO2) and might be relevant; however, she is not aware of any specfic examples of polydispersed material standards. Dr. Roberts emphasized the need for NIST to take an active role in developing standard materials and methods, especially for use in biological environments.

V. NATIONAL CANCER INSTITUTE (NCI) AT FREDERICK

Dr. Gregory Downing, Director of the Office of Technology and Industrial Relations at the NCI, summarized activities at the Nananotechnology Characterization Laboratory (NCL). In general, the NCL is directed towards supporting medical product development for cancer diagnostic and therapeutic applications. Major topics in Dr. Downing's presentation include:

- A critical mass of private, federal, state, and regional investments into nanotechnology make goals feasible.
- Nanoparticles have multiple functions in biomedical applications: tissue targeting, sensing or imaging capability, disease prevention/treatment (e.g., VivaGel), drug delivery (e.g., Abraxane™-paclitaxel), high-throughput screening, and non-invasive treatment.
- Types of nanoparticles being investigated in biomedical research include quantum dots, polymer particles, dendrimers, magnetic particles, nanoshells, nanotubes, and virus engineered particles.
- NCI Alliance for Nanotechnology in Cancer (launched in September 2004).

  - Activities involves both public and private sectors and emphasizes cross-disciplinary collaborations.
  - Four major programs: centers of cancer nanotechnology excellence, multidisciplinary research teams, nanotechnology platforms for cancer research, and the NCL.
- Key features of the NCL establishment, program development, scientific oversight, partnerships, and outreach.
- The cancer Biomedical Informatics Grid (caBIG).
- Approaches to understanding potential toxicity from both a medical product and environmental health perspectives.

Dr. Scott McNeil, NCL Director, discussed the characterization of nanoparticles for use in cancer therapy and diagnosis:

- By increasing the solubility, stability, and specificity of a therapeutic, nanomaterials may decrease toxicity and increase efficacy.
- The NCI Alliance for Nanotechnology in Cancer.
  - Major hurdles to the transitioning of nanomaterials to the clinical realm are a lack of available standards, characterization, and regulatory uncertainty.
- NCL objectives:
  - Identify and characterize critical parameters related to nanomaterial biocompatibility.
  - Establish and standardize an assay cascade for characterization.
  - Examine the biological characteristics of multi-component/combinatorial platforms.
  - Engage and facilitate academic and industrial-based education and knowledge sharing.
- NCL receives nanomaterials from a variety of sources (i.e., federal agencies, academia, industry) and then works to characterize the material (in conjunction with NIST) prior to conducting *in vitro* and *in vivo* studies to assess the utility of the material for detection, diagnosis, and therapeutics.
  - These studies are collectively referred to as the NCL Assay Cascade.
  - NCL conducts pre-clinical characterization for investigative new drug submissions to the FDA.
- NCL also develops and validates protocols that can be reviewed to establish a method as a Voluntary Consensus Standard (VCS).

Discussion

Dr. Warheit asked for more detail on NCL's efforts to characterize particles in the biological matrix. At this point, Dr. McNeil said they can only make general trend statements; for example, on how particle size relates to elimination. However, they cannot say what exact size a particle needs to be to target a specific tissue. He believes predictive modeling approaches will be needed to make more specific statements. Dr. Bucher asked if the NCL will be able to release the data that underlie early trend conclusions. Dr. McNeil said the information would be publicly available through the caBIG and also through reports. Dr. Balbus asked for more information on what is meant by stability. Dr. McNeil said stability could include shelf life, pH, and stability in serum. Currently, these assessments are not made in the context of behavior in environmental media. Dr. Philbert asked how long it takes for the NCL to characterize materials. Dr. McNeil replied that the physical and *in vitro* characterization take approximately 4-5 months. The *in vivo* portion takes about 3 months. Dr. Philbert commented that this is not a high throughput process that lends itself to characterizing a large number of environmental samples. Dr. Philbert asked if NCL is developing pharmacokinetic models to address some of the unanticipated interactions between compartments of the body. Dr. McNeil said they are using the *in vitro* studies as indicators of what to look for in the *in vivo* studies. However, the *in vivo* models are not designed to look at compartmentalization or interactions. Dr. Philbert asked the NTP to take note that this is a very

expensive and resource intensive process that stands in contrast to the extraordinary amount of data being published. Dr. Colvin suggested that the NCL consider characterizing sample library datasets in order to test hypotheses and generate more definitive trend statements. She also wondered the extent to which the work being conducted at the NCL can be adapted to address environmental questions. Dr. Colvin suggested the NCL consider exploring the Department of Energy (DOE) model of using user groups at its nanocenters. In this case, the user groups are closely related collaborators. This allows the DOE to engage and take advantage of the academic community. Dr. Downing said the NCL is exploring mechanisms to better engage scientists working on nanotechnology. Dr. Sass endorsed creation of a searchable database. Also, she suggested the NTP begin to group materials by their properties and characteristics as an aid to regulatory agencies. She asked what type of worker protection precautions the NCL utilizes given that workers are exposed to uncharacterized materials. Dr. McNeil said the NCL presumes the materials are hazardous in the absence of any information. For example, dry materials are handled in a chemical fume hood with HEPA filters. Any materials generated at the NCL are incinerated.

Dr. Philip Sayre asked about the overall scope of the types of materials that the NCL is investigating. The NCL is interested in *in vivo* applications. Dr. Sayre asked how much it costs to obtain the 12 measures that NCL uses to physically characterize a material and whether the suppliers of the material undertake any of this work. Dr. Downing did not have specific cost estimates, but noted that it would cost millions of dollars to recreate the NCL facilities. Dr. Sayre asked how much material vendors are asked to supply and if it needs to be in a particular form. The NCL will take any form and vendors are asked to provide 1 gram of pooled batches. The NCL is often contacted when vendors have 50 mg and will work with the vendors to create a larger amount. Approximately 1 kg is required for clinical trials.

VI. ENVIRONMENTAL PROTECTION AGENCY (EPA)

Dr. Philip Sayre, Risk Assessment Division of the Office of Pollution Prevention and Toxics (OPPT), presented EPA's perspective on nanoscale materials. Major points included:

- EPA's role: (1) to provide leadership, (2) support research, (3) use EPA's statutes to protect human health and the environment, and (4) work with industry and NGOs to ensure responsible development and realize potential benefits of nanotechnology.
- Some of the biological effects of nanomaterials that raise concern for toxicity.
- EPA Nanotechnology White Paper (*http://www.epa.gov/osa/nanotech.htm*) developed by a workgroup established under the EPA Science Policy Council (SPC).
  - The white paper discusses the applications and implications of nanotechnology for EPA risk managers.
- EPA Nanotechnology STAR Grants (*http://es.epa.gov/ncer/nano/*).
- EPA's fiscal year proposal for 2007 includes $8.6 million for nanotechnology research.
- Approaches for regulating nanoscale materials under the Toxic Substances Control Act (TSCA).
- OPPT risk screening evaluation process.
- International Life Sciences Institute (ILSI) tiered testing framework.
- A stewardship program under consideration by the National Pollution Prevention and Toxics Advisory Committee (NPPTAC).
- OECD and other European activities.

Discussion

Dr. Lafranconi asked how EPA will disseminate information on nanotechnology research. Dr. Sayre replied that the STAR grants program is accessible on the web. He believes that the Office of Research and Development will be preparing more detailed summaries to convey the results of health- and

environmental-associated research. In terms of OPPT activities, the EPA is faced with issues about confidential business information that limit the release of much information. Dr. Lafranconi commented that it would be extremely useful to have all the disparate information in one database. Dr. Sayre is aware of a proposal for the OECD to assume control of database that would contain both federal or literature references.

Dr. Balbus commented that the NTP may be able to play a role in creating a more integrative, tiered strategy for safety screening. Dr. Sayre agrees and said the ILSI project discussed in his presentation is a framework and represents more of a starting point than an actual tiered testing strategy. Dr. Warheit asked if the EPA intends to formalize a tiered testing strategy. Dr. Sayre said the EPA is at the beginning of this process. The white paper identifies a tiered strategy as a reasonable option to work toward. It may be premature and perhaps not feasible at the current time. Dr. Maria Morandi questioned whether EPA is doing any life cycle analyses to better understand releases to the environment from production versus use in consumer products. Dr. Sayre said EPA does this for review of premanufacture notices (PMN). The EPA Office of Research and Development (ORD) also has life cycle built into the STAR program. Dr. Morandi also asked whether an effort like the NCI on biomedical applications could be undertaken to characterize materials from a more "health safety" perspective. Dr. Walker said the NTP is focused on non-biomedical materials; however, there is no central toxicological characterization lab that fulfills a function like the NCI does for biomedical materials. The NTP is trying to facilitate this process by procuring enough materials to be able to provide samples to other researchers. Dr. Sayre said Rice University is also supportive of providing materials. Dr. Tinkle said consolidating databases could also help inform a very directed research effort.

VII. NANOTECHNOLOGY ENVIRONMENTAL AND HEALTH IMPLICATIONS WORKING GROUP UPDATE

Dr. Celia Merzbacher provided an overview of the Nanotechnology Environmental and Health Implications (NEHI) Working Group:

- Structure and organizational placement of the NEHI, which was established in 2003.
- The purposes of the NEHI are to (1) exchange information between research and regulatory agencies; (2) facilitate identification, prioritization, and implementation of research directed towards responsible development of nanotechnology; and (3) promote communication about research results to the research community, federal agencies, and nanotechnology stakeholders.
- NEHI member agencies: Consumer Product Safety Commission, Department of Agriculture, Department of Commerce, Department of Energy, EPA, FDA, NIEHS, NNCO, National Science Foundation, OSHA, OSTP, and the Office of Management and Budget.
- NEHI Research Needs document:
  - Outlines research needed to support regulatory needs.
  - Considers other research needs documents and input from nanotechnology stakeholders.
  - Expected release in Spring 2006.

Discussion

Dr. Warheit asked if research needs discussed at other meetings, such as those convened by the National Academy of Sciences (NAS), impacted development of the NEHI Research Needs document. Dr. Merzbacher said the NAS meetings are a separate effort. Those meetings are organized to allow the NAS to review the NNI as required. Dr. Sass asked for more information on NEHI communications with nanotechnology stakeholders. Dr. Merzbacher said the primary route of communication is electronically through NEHI members. In terms of formal activities, the NNCO serves as point of contact. NEHI's primary function is to support government agency needs and communication efforts are not intended to be

comprehensive. Dr. Sass confirmed that there is no strategy to communicate with stakeholders outside of the federal government. Dr. Walker clarified that scientific discussions among NEHI members focus on published rather than unpublished data. Dr. Sass suggested that the NTP and NEHI work together to classify broad groups of nanomaterials.

VIII. NTP UPDATE

Dr. Walker provided an update of the NTP Nanotechnology Safety Initiative:

- Purposes are to (1) identify key components that govern nanomaterial safety and (2) examine how nanomaterials enter, travel through, and deposit in the body.
- Initial "classes" under study are: (1) metal oxides, (2) fullerenes, (3) core shells, and (4) nanotubes.
- Project goals:
    - Investigate physicochemical parameters of quantum dots that impact dermal penetration and pharmacokinetics.
    - Evaluate physicochemical characteristics of metals oxides in sunscreens.
    - Evaluate dermal penetration of metal oxides in sunscreens.
    - Evaluate photocarcinogenicity of titanium oxide.
- Experimental strategy requires physical/chemical characterization and will use both *in vitro* and *in vivo* methods.
- Updates on specific studies (see presentation for more details).
- Impediments to progress and areas under development.

Discussion

Dr. Warheit wondered whether NTP is devoting too many resources towards characterization of nanoscale materials at the expense of initiating experimental studies. Dr. Walker agreed that it is possible to "over-characterize," but believed that the NTP is striking the correct balance, focusing on critical factors such as size, surface area, and aggregation potential. Dr. Warheit also asked if there is a representative fullerene. Dr. Walker said the fullerene soot mixture is produced in the largest quantities. The soot is approximately 65% C60 and 25% C70. The difficulty for characterization will be to differentiate the effects of the soot versus the pure C60 and C70.

Dr. Sass commented that nanomaterials likely differ in their isolated form compared to the application or product form. Some people claim that nanomaterials should be considered "safe" for consumers if they are part of the surface coating or otherwise bound. She asked whether the NTP intends to test formulations from actual products in addition to isolated forms. Dr. Walker acknowledged that this is a major research issue. The NTP tries to address the issue in the context of specific studies, but not in a broad-based manner. For example, for the TiO2 studies, the TiO2 is a material that is found in sunscreens, but NTP is not testing a specific sunscreen product.

Dr. Philbert had several questions. First, he asked for additional information on the excipients used in the dermal exposure studies. Dr. Walker said that acetone, oil-water emulsions, and potentially alcoholic gels are being used as vehicles to assess their impact on penetration. Second, Dr. Philbert wondered whether the data would also be expressed in terms of surface area in addition to mass concentration. Dr. Walker said yes for the TiO2 and other bulk materials, but the situation is different for wet systems. Dr. Colvin added that quantum dots are made in such small quantities that it's difficult to obtain enough raw powder to obtain surface area. Estimates of surface area can be obtained by measuring hydrodynamic diameter and then back calculating with information on the geometry of the system. Data based on the dried down

version is not necessarily relevant to the aqueous or oil-water emulsion systems. Dr. Philbert asked whether the hydrodynamic radius depends upon the vehicle. Dr. Colvin said the effect of the vehicle is very small (~ 2 nanometer effect on a 30-40 nanometer size). Dr. Philbert asked if NTP is considering possible effects on solubility when metals and metalloids get into phagolysosomes and are exposed to pH values below 5. Dr. Howard replied that with respect to cadmium and quantum dots, the data from intradermal injection studies indicate that a large portion of the dots are intact. Dr. Philbert noted the importance of understanding the behavior of these materials in tissues so that effects can be appropriately ascribed to the nanoparticle. Dr. Colvin commented that *ex vivo* studies with quantum dots in a buffered pH solution indicate that the dots do not dissolve. Her research group is attempting to address this issue and she invited suggestions on how it might be best addressed. Dr. Philbert commented that a buffered solution doesn't provide a "sink" for liberated ions and suggested trying to model ion transport and storage processes, for example, by adding metallothionein. Dr. Walker said some researchers are characterizing the fractionation gradients after ultracentrifugation to see whether the cadmium is solubilized or pelleted. He recalled that cadmium pellets and is therefore assumed to be part of something that has more mass than a soluble form. However, there are many caveats that complicate interpretation.

Dr. Morandi had some concern about the practice of grinding materials to create uniform size because it may change the properties of the material. Dr. Walker said the rationale for grinding the fullerenes is that the materials are very large (~ 100 μm) and need to be in the 1 – 10 μm range to be more representative. The NTP has not yet evaluated the extent to which grinding changes the properties of the materials. Dr. Bucher added that the design team believes the best way to address the nomination is to test the purest form possible. Although it is important to understand nanomaterials as used in products, characterizing one product may have limited applicability to other products. The NTP is also considering the synthesis of nanomaterials for testing. For example, in the fullerene inhalation study, the NTP may use fullerenes generated in the air stream that goes into the inhalation chamber. The question of applicability to relevant exposures remains regardless of whether the NTP synthesizes a material or modifies an existing formulation. Dr. Morandi also questioned the wisdom of using cerium oxide as a diesel additive to improve the efficiency of diesel and reduce particulate emissions from diesel given that it appears to create chemicals that are not currently present in exhaust. Dr. Walker said one of the major reasons why NTP is studying cerium oxide is because of concern for possible increases in nanosized cerium oxide resulting from this use. Dr. Morandi asked who is providing the C^{13} labeled C60. Dr. Walker said the MER Corporation was identified as a commercial source an enriched sample of labeled C60.

Dr. Lafranconi asked if the liver would be used for the TiO2 studies as an indicator organ. Dr. Walker said it would probably be used and noted that the liver, spleen, and regional lymph nodes are commonly used as indicator tissues for a variety of nanoparticles. Dr. Lafranconi also commented that the increased solubility of zinc oxide in biological systems might lead to decreased detection in tissues such as the liver. Dr. Bucher added that the background levels of zinc in the body would also complicate the analysis.

IX. NIEHS UPDATE

Dr. Tinkle, Nanotoxicology Program Administrator at NIEHS, provided an update on NIEHS activities. Major points included:

- NIEHS/Division of Extramural Research and Training initiatives.
  - Second Interagency Research Solicitation (joint solicitation by EPA, NSF, NIOSH, and NIEHS).
    - Announced in December 2005.
    - Research areas: (1) toxicology of manufactured nanomaterials, (2) environmental and biological fate, transport, and transformation, and (3) exposure and bioavailability.

  - Third Interagency Research Solicitation (joint solicitation by EPA, NSF, NIOSH, NIEHS, and the European Union).
- NIEHS/DERT collaborative activities.
- Recent meetings and workshops.

Discussion

Dr. Philbert asked if the RFAs would require applicants to provide a minimal set of characterization data on the materials used. Dr. Tinkle said RFA does require physical characterization, but does not prescribe specific characterization activities. The RFA requires characterization upon arrival at the research facility or after synthesis in the medium in which the materials are suspended. Also, if the exposure occurs over time the materials will need to be characterized when the biological response is assessed. The question is whether sufficient technology exists to make this a requirement.

Dr. Walker asked if the RFA could specify that data should meet certain guidelines for characterization prior to publication, similar to the Minimum Information About a Microarray Experiment (MIAME) guidelines. Dr. Tinkle said the RFA could do this if guidelines exist. However, such guidelines can take a long time to be developed and finalized. Dr. Lafranconi asked if the NEHI document on research priorities would be used to evaluate proposals received in response to the second research solicitation. Dr. Tinkle said the research needs identified in the NEHI document will likely be very similar to those identified in other research needs documents. For this reason, evaluation of the proposals does not need to be constrained by the NEHI document. The goal of the NEHI document is to facilitate research undertaken to meet the needs of regulatory agencies, but it is the responsibility of individual research agencies to conduct the research. Dr. Colvin wondered how the NIEHS determines what research is conducted intramurally and extramurally. Dr. Tinkle said intramural and extramural research activities at most NIH institutes are separate. They do not share the same pool of money. Intramural identifies its own mission-related research and priorities and these may be very different from extramural needs. There may be areas of similarity, but they are not intentionally coordinated.

Dr. Sass was appreciative of the research efforts, but commented that regulatory statutes are not currently adequate to ensure that nanomaterials are tested for safety prior to use. These materials are already being used in consumer products and can be released into the environment. She believes some relatively simple changes to the Toxic Substances Control Act (TSCA) could be helpful; for example, creating an inventory for nanomaterials and requiring PMNs.

X. PUBLIC COMMENTS

Dr. Mengdawn Cheng, Oak Ridge National Laboratory, said the Oak Ridge Center for Nanophase Materials Sciences studies nanomaterials for all types of applications. This center has the ability to generate and characterize the materials as well as evaluate some biological effects (i.e., genomic array). This is the first fully operational DOE center. In terms of characterization, he suggested that characterizing a few key parameters might be sufficient for toxicological research. He also noted the importance of knowing how materials are prepared. For example, a material produced in the gasous phase suggests that workers would be primarily exposed via inhalation. Materials prepared through the wet route might result in exposure by ingestion. Dr. James Platner asked Dr. Cheng to identify the primary objective of the research conducted at the center. Dr. Cheng said the center investigates the use of nanomaterials for energy production purposes as well as for other purposes.

XI. CONCLUDING REMARKS

Dr. Bucher said the working group has heard from most of the federal agencies engaged in nanotechnology research. He asked NWG members to consider what research gaps the NTP could

address. It was noted that since the NTP program is still in its infancy, it is a difficult question to answer. Dr. Bucher asked if there are projects NWG members believe the NTP should not be doing. Dr. Philbert said the NTP efforts are scientifically critical and will set the standard as to how health effects are addressed. In this respect, the NTP program needs to be very thorough. Therefore, while complete characterization of physical properties may not be required to conduct toxicology studies, the time NTP is devoting to obtaining characterized materials is worth it. One major gap is characterizing materials *in situ*. He is eager to see data from chronic studies that use real world exposure levels.

Dr. Bucher said one of the NTP's goals is to conduct studies that others cannot, such as chronic inhalation bioassays. Dr. Warheit commented that early data may surprise and change the course of subsequent research; for example, we may learn that surface area is more important than size. Dr. Balbus also endorsed the NTP's strategy even if it is slow as a result of the material characterization issues noted by Dr Warheit. He also supported the strategy of establishing fundamental structure activity relationships that are followed-up with hypothesis-testing studies. He believed the NTP/NIEHS may need to become more involved in understanding environmental fate and transport issues (i.e., persistence in environmental media, impact of conditions such as acidity and UV light changes). His interpretation is that efforts in this area appear disconnected across the agencies. Finally, he would like to see hypothesis-generating efforts on novel mechanisms, because these materials can access parts of the cell that other substance do not. Dr. Lafranconi said the role of government research is to conduct high risk expensive studies, such as analytical characterization, and establish fundamental characteristic of nanoscale materials that can be used to build structure activity predictions, etc. Dr. Sass reiterated the benefits of NTP spearheading an effort to categorize the behavior of classes of nanomaterials. Dr. Platner thought the focus on engineered materials is probably appropriate given resources. He thought, however, that there could be more interaction with those who work on non-engineered nanomaterials (e.g., welding fumes) because this is where the information will be applied most quickly. In addition, there may be some very simple efforts that could be undertaken to provide some reassurance about worker protection, such as the recent NIOSH National Personal Protective Technology Laboratory assessment of respirators. Dr. Colvin commented that it is critical that NTP work with NIST and NSF on characterization because this falls outside of NTP's traditional areas of expertise.

Dr. Dearry thanked everyone for attending.