

*Minutes from the June 2005 Meeting of the NTP Board of Scientific Counselors  
Nanotechnology Working Group (NWG)*

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## I. ATTENDEES

The National Toxicology Program (NTP) Board of Scientific Counselors Nanotechnology Working Group (NWG) met on June 24, 2005, at Rodbell Auditorium, Rall Building, National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive Research Triangle Park, North Carolina. The following individuals attended this meeting.

### NWG Members

John Balbus, M.D., M.P.H.

Mark Lafranconi, Ph.D.

Martin Philbert, Ph.D.

James Platner, Ph.D.

Steven Roberts, Ph.D.

Mary Vore, Ph.D.

\*Kristen Kulinowski, Ph.D., joined by phone to represent Vicki Colvin, Ph.D.

### NIEHS Staff

David Balshaw, Ph.D.

Amy Brix, Ph.D.

John Bucher, Ph.D.

Raj Chhabra, Ph.D.

Dori Germolec, Ph.D.

Chris Portier, Ph.D.

Kris Thayer, Ph.D.

Cynthia Smith, Ph.D.

Molly Vallant, Ph.D.

Allison Veit

Nigel Walker, Ph.D.

Mary Wolfe, Ph.D.

### Other Federal Staff

Norris Alderson, Ph.D. (FDA)

Clayton Teague, Ph.D. (National Nanotechnology Initiative)

Mary Lynn Woebkenberg, Ph.D. (NIOSH/CDC)

Steve Stern, Ph.D. (National Cancer Institute-Frederick, Inc.)

### Public

Mohammad Ali

Piotr Grodzinski, Ph.D.

Rodney Miller, Ph.D.

Morando Soffritti, M.D.

*Background materials and presentations for NWG meetings are available on the NTP web site (<http://ntp.niehs.nih.gov/> see "Advisory Boards & Committees"). The meeting was broadcast through the Internet and the public was provided opportunity to comment in person. The meeting was taped for preparation of summary minutes.*

## II. STRUCTURE AND GOALS OF THE WORKING GROUP

Dr. John Bucher briefly reviewed the charge and function of the NWG (see Attachment 1). Dr. John Balbus asked for background on the extent to which the NTP Board of Scientific Counselors ("the Board") has discussed nanotechnology. Dr. Steven Roberts, Chair of the NWG, said the Board strongly supports the NTP testing program on nanomaterials and recognizes the challenges of this research. In fact, the Board's discussions on research challenges provided an impetus for organizing the "Developing Experimental Approaches for Evaluation of Toxicological Interactions of Nanoscale Materials" workshop. This workshop was co-sponsored by the University of Florida in conjunction with multiple federal agencies including NIEHS/NTP and held November 3-4, 2004, at the University of Florida Hotel and Conference Center, Gainesville, Florida. The purpose of the workshop was to discuss experimental challenges in nanomaterial research. The workshop report and recommendations are available at <http://ntp.niehs.nih.gov/> (see "Meetings & Workshops"). One recommendation is to urge journal editors to require proper physical and chemical characterization of nanoscale materials in submitted manuscripts that investigate biological/toxicological interactions or effects of nanotechnology-derived products.

In response to this recommendation, Dr. Bucher sent a letter outlining this issue to editors of journals that publish articles on the biological effects of nanotechnology (a sample letter and list of relevant journals was included as background materials for the NWG meeting). Dr. Clayton Teague asked how keywords to identify the journals were selected. Dr. Bucher was not aware of the complete list of specific terms used as the search was conducted by staff in the NIEHS library. Dr. Bucher said he would send the search strategy to Dr. Teague.

Dr. Kristen Kulinowski discussed activities of the International Council for Nanotechnology (ICON) relevant to the NWG. ICON is developing “standards of care” that will include guidance on nanotechnology toxicology test methods. In addition, ICON is maintaining a database of nanotechnology literature expected to be publicly available by Fall 2005. The database was established at Oak Ridge National Laboratory and now has over 1300 records dating back to the 1980s.

Dr. Balbus asked for additional detail on the NWG charge. He interpreted the charge to include (1) providing general input on nanotechnology research needs, (2) advising on NTP research activities in light of federal agency needs, and (3) reviewing NTP research agendas and protocols. Dr. Bucher said reviewing specific research protocols is beyond the scope of the NWG, but discussing the NTP research agenda for nanotechnology is appropriate.

Dr. Mary Vore asked whether the NTP research program will address interactions between nanoparticles and other environmental exposures or compromised health status. Dr. Bucher said there is no specific program addressing combined exposure at this time although this is an important issue. Dr. Nigel Walker added that the NWG should feel free to comment on general research gaps including those that may be better addressed by non-NTP mechanisms such as extramural funding. Also, the scope of what NTP considers to be a nanomaterial is very broad and can include particles and devices, although less complex agents will be evaluated initially.

Dr. Roberts noted that a written public comment from Dr. Sherry Ward was received.

### **III. OVERVIEW OF THE NATIONAL NANOTECHNOLOGY INITIATIVE (NNI)**

Dr. Clayton Teague, Director, National Nanotechnology Coordination Office (NNCO), discussed the NNI, a federal research and development program established to coordinate the multiagency efforts in nanoscale science, engineering, and technology. Major topics covered by Dr. Teague included:

- Nanotechnology development, applications, and target industries
- U.S. nanotechnology research and development spending (1997 – 2005)
- Interagency management of the NNI within the framework of the National Science and Technology Council (NSTC) Committee on Technology
  - The NSTC is a Cabinet-level body and the principal means by which the President coordinates science and technology programs across the federal government
- Roles of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee and the Nanotechnology Environmental and Health Implications (NEHI) Working Group
- The 21<sup>st</sup> Century Nanotechnology Research and Development Act of 2003
- NNI vision and goals and the “NNI Strategic Plan” document released December 2004
- Roles, research and development priorities, and fiscal year 2006 budget request for NNI participating agencies

- Application of existing regulations to nanotechnology

A NWG member asked how the NNCO is funded. Dr. Teague replied that the NNCO is funded through a tax on agencies that participate in the NSET subcommittee and the current budget is approximately two million dollars. Most of the funding for the NNCO is used to support the triennial review of the NNI conducted by the National Research Council of the National Academies. A considerable portion of funding is also used to support coordination of workshops and publication preparation.

Dr. Balbus asked whether it is possible to get a breakdown of funded projects included in the \$38.5 million directed towards Environment, Health, and Safety (EHS) research for fiscal year 2006. Dr. Teague said yes for the National Science Foundation (NSF), but not necessarily for other agencies. Dr. Vore asked whether the NSF money would address human health issues. Dr. Teague replied that most of the funding is likely focused on environmental research with some directed to research on basic cellular mechanisms. Dr. Martin Philbert asked what proportion of the EHS money is directed towards understanding potential impacts of nanomaterials in workers. Dr. Teague replied that the \$3.1 million slated for NIOSH would represent the majority of this work. Although NIOSH has ongoing activities to address nanomaterials in the context of ultrafine particles generated from mining and other processes, the \$3.1 million represents new money to address engineered nanomaterials.

#### **IV. U.S. FEDERAL AGENCY EFFORTS IN NANOTECHNOLOGY<sup>1</sup>**

##### **A. Food and Drug Administration (FDA)**

Dr. Norris Alderson, Associate Commissioner for Science at the FDA, provided an overview of FDA considerations for nanotechnology in public health. In brief, Dr. Alderson discussed:

- The types of products FDA regulates, regulatory issues specific to nanomaterials, and nanotechnology approvals
- The FDA risk management approach for nanomaterials
- FDA research on nanotechnology
  - FDA does not conduct research in support of any product except under the orphan products program
  - The FDA National Center for Toxicological Research (NCTR) is conducting skin absorption and phototoxicity studies of titanium dioxide (TiO<sub>2</sub>), zinc oxide (ZnO), and quantum dots
- FDA nanotechnology policy coordination

Dr. Philbert said one of the most challenging issues for understanding distribution of nanomaterials in the body is that the labeling of nanomaterials can fundamentally change their chemistry. Dr. Alderson agreed this is an important issue and said the imaging capabilities of nanomaterials could be a valuable tool in this respect. Dr. Philbert agreed but radionucleotides may exert biological effects also and it will be difficult to discern effects due to the nanomaterial, its components, or the radionucleotide.

Dr. Balbus asked for clarification on the two nanotechnology devices approved by FDA (Synthetic bone made from calcium phosphate nanocrystals produced by Angstrom Medica, Inc and Supreme Universal Restorative based on nanomers and nanoclusters manufactured by 3M).

Dr. Alderson said these two devices met a standard that already existed for these types of products and size was not considered in the approvals. Within the device law, high risk products require pre-clearance evaluation of safety and low risk devices, such as the ones presented, are approved based on a standard that has been approved for those types of products. New products meeting these standards are approved without any evaluation. The concern is whether FDA has the appropriate tools for evaluation. Dr. Balbus asked about nanomaterials used in cosmetics. With respect to nanomaterials in cosmetics, the FDA does not approve cosmetics and it is up to the manufacturer to assure safety. The FDA may regulate cosmetics if adverse events are reported once a cosmetic is in use. The burden of proof to demonstrate harm lies with the FDA. It would be helpful in the area of cosmetics to have validated protocols for assessing the toxicity of nanoparticles for use by the cosmetic industry. Dr. Mark Lafranconi said it is important to be able to follow the physical state of the nanomaterial (i.e., solid state or solution) in addition to the chemical signal. He believes this sort of fundamental analytical work is best conducted by the government and industry has the responsibility to apply the work to specific applications.

#### **B. National Institute for Occupational Safety and Health (NIOSH)**

Dr. Mary Lynn Wuebkenberg, Director of the NIOSH Division of Applied Research and Technology (DART), reviewed NIOSH activities related to nanotechnology. Dr. Wuebkenberg's presentation described:

- The newly established NIOSH Nanotechnology Research Center
- Critical occupational health and safety issues related to nanotechnology
  - Exposure and dose, communication and education, epidemiology and surveillance, recommendations and regulations, sampling, toxicity, controls, risk assessment, and safety
- NIOSH intramural and extramural research projects related to nanotechnology

Dr. James Platner said one of his concerns with nanotechnology is the safety of production operations. He believes NIOSH should address hazards in the work process (importance of engineering controls, waste streams, etc.) and not just the product. Dr. Wuebkenberg said NIOSH does not have the resources to evaluate total life cycle, but NIOSH is looking at different jobs within certain production processes.

#### **C. National Institute of Environmental Health Sciences (NIEHS)**

Dr. Sally Tinkle, Program Administrator, Division of Extramural Research and Training (DERT) at NIEHS, discussed:

- NIEHS coordination with other federal agencies on nanotechnology
- How NIEHS efforts fit into the NNI Strategic Plan
- The NIEHS Nanoscale Science Initiative which will involve a request for applications (RFA – R01/R21), program announcement(s), and an interagency agreement
  - to address dose; response; determinants of biological compatibility or toxicity; technologies to support exposure or risk assessment, biologic mechanism or therapeutic intervention; exposure and risk assessment; and interagency activities on societal impact, education, and training
- NIEHS's participation in an interagency RFA on environmental and human health effects of manufactured nanomaterials with the Environmental Protection Agency (EPA), NSF, and NIOSH

- to support research on the toxicology of manufactured nanomaterials; environmental and biological fate, transport and transformation; and exposure and bioavailability of nanomaterials

Dr. Philbert asked whether any of this research will address the ability of nanoparticles to sequester and concentrate other chemicals in the environment. Dr. Tinkle said this is an important area and NIEHS has already fielded an inquiry about interactions between nanoparticles and air pollution. Dr. Alderson asked about the funding levels of the agencies in the interagency RFA. Dr. Tinkle believed the total would be \$8 million (\$7 million from EPA, NSF, and NIOSH and \$1 million from NIEHS).

#### **D. National Toxicology Program (NTP)**

Dr. Nigel Walker, Project Leader for the NTP Nanotechnology Safety Initiative, discussed NTP's efforts in nanotechnology research. He reviewed:

- The testing nomination from Dr. Vicki Colvin, Director Center for Biological & Environmental Nanotechnology at Rice University, and rationales for need to assess safety
- Research needs and questions (e.g., exposure, pharmacokinetics, toxicity evaluations)
- Current and future challenges NTP faces in addressing nanotechnology (e.g., selecting specific nanomaterials for study, procurement and characterization of nanomaterials, strategy for evaluation, and communication)
- Initial NTP focus areas: single and multi-walled nanotubes, fullerene C60, titanium dioxide/metal oxides, and quantum dots
- Ongoing and planned skin absorption and phototoxicity studies of nanomaterials at the NTP Center for Phototoxicity (directed by Dr. Paul Howard and housed at the NCTR)
- NIOHS activities on single walled carbon nanotubes

One of the meeting participants asked how the 100 g quantity of nanomaterial required for subchronic testing was derived. Dr. Walker said it was based on number of animals being tested and a top estimated dose of 400 mg/kg for a proposed low toxicity material. Dr. Christopher Portier added that the required amounts change dramatically depending on toxicity (more toxic agents require less) and NTP has conducted studies requiring kg amounts for relatively non-hazardous materials. Dr. Tinkle commented that the nanomaterials for which this type of quantity would be a problem in procuring may also be those for which there is limited human exposure and thus less need to conduct animal studies. Dr. Philbert asked about species selection. Dr. Walker replied that NTP animal studies are generally conducted in rodents, although non-rodent species are used on occasion. Dr. Vore asked for clarification on the issue of expressing dose on a mass basis (e.g., mg/kg) rather another metric. Dr. Walker said expressing dose on a mass basis rather than a surface area per unit exposure basis may dramatically change the dose. Also, different aspects of surface area can be expressed, such as total or functional surface area. Dr. Tinkle commented that the smaller materials are not necessarily more toxic and that a recent study shows toxicity is material and composition specific.

Dr. Portier said development of physiologically based pharmacokinetic (PBPK) models will not wait until the pharmacokinetic studies have been started and this effort will have an intramural component. Dr. Balbus asked for more information on PBPK efforts. Dr. Portier said the advantage of doing PBPK studies early is it allows the model to evaluate "what if" scenarios to anticipate what experimental concerns might arise so that these issues can be addressed experimentally to get answers to shape the model. Dr. Lafranconi asked if the NTP research program would have both *in vitro* and *in vivo* components to allow screening level predictions.

Dr. Walker replied that *in vivo* studies are the initial focus and they would be followed by *in vitro* studies that target effects observed *in vivo*. Dr. Platner asked how NTP tracks which nanomaterials are being produced and thus most relevant for testing. Dr. Walker said it's a real challenge to find the information and then identify nanomaterials with near market applications. He uses interactions within the NEHI to help identify relevant companies and then he reads the company websites and other trade literature to see what is being produced. Dr. Teague added that there is a study underway to estimate total international production of single and double walled nanotubes. He was concerned that although C60 is one of the more characterized nanomaterials, it is not likely to enter the marketplace in the same quantities as other nanomaterials such as quantum dots. Dr. Walker replied that from his background research he has learned C60 is likely to have a bigger market than other nanomaterials such as nanotubes.

## **V. CONCLUDING REMARKS**

Dr. Bucher said the intent of the current meeting was mostly to provide information on federal activities in nanotechnology and future NWG meetings will be more evenly balanced between discussion time and presentations. He proposed that appropriate topics for the next meeting are characterization and measurement to include presentations from the National Institute of Standards and Technology (NIST) and the National Characterization Laboratory located at the National Cancer Institute in Frederick, MD. In addition, he anticipates a presentation by EPA on their nanotechnology activities.

Dr. Bucher said advice provided at the next meeting will be useful since it is taking some time to develop the research program. Dr. Bucher asked if there were suggestions for other topics. Dr. Balbus asked for a more detailed discussion on the *in vitro* methods for novel mechanisms mentioned in Dr. Walker's talk.

Dr. Portier thanked everyone for attending and the meeting adjourned at 4:45 PM.