



Gradient CORPORATION

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Editor:

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Gradient Nanotechnology Presentations

Cambridge, MA. April 24-25, 2006. **Peter A. Valberg, Christopher M. Long, and Sonja N. Sax.** "Inhalation Health Risk Assessment: Extrapolating from Macromaterials to Nanomaterials."

Cambridge, MA. April 24-25, 2006. **Noelle M. Cocoros and Barbara D. Beck.** "A Qualitative Risk Assessment to Evaluate the Remediation of Trichloroethylene by Nanoscale Zero-Valent Iron Particles."

Poster presentations at the Overcoming Obstacles to Effective Research Design in Nanotoxicology conference. See "Upcoming Meetings and Conferences" section (p. 2) for more information.

In This Issue

- Recent Government Briefs
- Reports, Reviews, White Papers, and Books
- Upcoming Meetings and Conferences
- Hot-off-the-Presses Peer-Reviewed Research Articles of Note
- Guest Contributor

Recent Government Briefs

United States Environmental Protection Agency (EPA)

On February 16, EPA launched the GreenNano series, a series of meetings on "green" nanotechnology lead by Dr. Barbara Karn, manager of EPA's nanotechnology research program. The series is intended to highlight research on green nanotechnology applications and smart engineering and business practices, as well as to promote examination of governmental incentives for developing low-risk practices. For a listing of scheduled events in the GreenNano series, see: <http://www.nanotechproject.org/index.php?id=41>.

The National Institute for Occupational Safety and Health (NIOSH)

NIOSH recently announced the development of the web-based Nanoparticle Information Library (NIL). As summarized by NIOSH, the goal of this tool is to help organize and share information on nanoparticles, including their health and safety-associated properties. Users will have the capability to submit data for inclusion in the database, such as data on material properties, origin/synthesis methods, and contact information for people developing nanomaterials. This resource, which is to include searchable online databases, is currently available in prototype form for public review and comment. For more information, see: <http://www2a.cdc.gov/niosh-nil/index.asp>.

German Federal Ministry of Education (BMBF)

The German Federal Ministry of Education (BMBF) announced on February 17 the funding of a three-year, government-industry initiative to investigate nanoparticle properties and their health and environmental effects. This

approximate \$9 million study, known as the NanoCare project, is scheduled to begin March 1, with funding and participants drawn from 13 companies, universities, and research institutes. One of the anticipated products of this project is a publicly accessible database of nanoparticle physical and chemical properties and other pertinent findings. For more information, see: <http://www.bmbf.de/en/nanotechnologie.php>.

Reports, Reviews, White Papers, and Books

Nanomaterials Handbook - Edited by Yury Gogotski

Taylor & Francis, CRC Press; January 2006
<http://www.crcpress.com>

The Nanomaterials Handbook is a brand new collection of review chapters written by internationally recognized experts in the field of nanotechnology and is intended for both scientists and engineers. It includes important new information on nano-structured semiconductors, ceramics, biomaterials, and drug delivery systems. This book provides an overview of the current state of knowledge on nanomaterials and can serve as a gateway to more in-depth work on specific topics covered in the collection.

The Nanotechnology-Biology Interface: Exploring Models for Oversight

The Center for Science, Technology and Public Policy (CSTPP)
University of Minnesota Humphrey Institute of Public Affairs
http://www.hhh.umn.edu/img/assets/9685/nanotech_jan06.pdf

This report reviews the key discussions held at the September 2005 CSTPP workshop on the interface of nanotechnology and biology. The themes of the workshop were the following: science and applications at the nano-bio interface, health and

environmental safety concerns, regulatory and non-regulatory approaches to governance, striking an appropriate balance for governance in a societal context, and far-future applications and how governance systems can account for them. The report provides the recommendations made and conclusions drawn from the various sessions, and offers a full view of the current thinking on governance among experts in the field.

Upcoming Meetings and Conferences

Overcoming Obstacles to Effective Research Design in Nanotoxicology - Cambridge, MA: April 24-25, 2006

Overcoming Obstacles to Effective Research Design in Nanotoxicology

<http://www.tfilearning.com>

This conference will focus on the challenges in conducting nanotoxicology research and ways to address such challenges. Topics covered during the two-day conference will include nanoparticle transfer across biological barriers, and anticipated environmental routes and exposure levels associated with use of nanoparticles for environmental remediation.

Nanoparticles for European Industry – London, UK: May 2-3, 2006

Manufacture, Scale-Up, Stabilization, Characterization, and Toxicology

<http://www.nano.org.uk>

This two-day meeting will cover a broad range of current topics applicable to the use of nanoparticles in Europe. Policy issues, manufacturing concerns, societal impacts, topics in toxicology, and clinical trials of nanoparticles are among the many subjects addressed by the talks at this conference.

NanoBusiness 2006 – New York, NY: May 17-19, 2006

The Official Conference of the NanoBusiness Alliance

<http://www.nanobusiness2006.com>

The fifth annual NanoBusiness Alliance Conference will explore issues in nanotechnology such as investing, commercialization, as well as current and future global opportunities. This gathering is attended by international business leaders, investors, venture capitalists, scientists, engineers, legal professionals, and government officials.

For the first time, this year, the Converging Technologies Bar Association (CTBA) is sponsoring *Protecting Your Nano Assets: A Legal Tutorial* the afternoon of May 18th. One not-to-miss session will be *The Nano Chase: NYS v. The Nano Company* - a mock hearing on environment, health and safety involving a nano-manufacturing facility, led by the CTBA EHS Committee. Dr. Peter Valberg of Gradient Corporation will be participating as the technical expert on potential

health risks associated with nanomaterials. Another session of interest will be *Four Angry Men: Converging Technologies vs the Patent System* - a corporate roundtable on intellectual property, led by the CTBA IP Committee.

Members of the CTBA receive a discounted rate at registration. To learn more about membership and committee opportunities in the CTBA or receive a membership application, and obtain your member passcode for registration, call: (212) 591-CTBA or email: info@convergingtechnologies.org. Membership in the CTBA is open to attorneys as well as non-attorney professionals interested in the area of nanotechnology and converging technologies. Complete conference information and registration can be obtained by visiting www.nanobusiness2006.com.

Hot-off-the-Presses Peer-Reviewed Research Articles of Note

Nel A, Xia T, Madler L, Li N. 2006. "Toxic potential of materials at the nanolevel." *Science*. 311(5761):622-7.

Synopsis:

- This article summarizes the state of the knowledge regarding the toxic potential of engineered nanomaterials (NM), and proposes a rational, science-based approach to nanotoxicology.
- Although the authors highlight size as the main characteristic of NM affecting their physicochemical properties and toxic potential, they discuss several other unique NM properties such as shape, aggregation, surface coating, and solubility that can modify the effects of particle size.
- The authors propose that generation of reactive oxygen species (ROS) and oxidative stress is currently the best-developed paradigm for nanoparticle toxicity.
- The authors discuss the necessary components of a toxicity screening strategy for engineered nanoparticles, including three key elements: (1) physicochemical characterization of NM, (2) *in vitro* assays (cellular and noncellular), and (3) *in vivo* studies.
- Overall, the authors conclude that although there are no clinically relevant findings of NM toxicity to date, it is still too early to draw any far-reaching conclusions regarding the emergence of major toxicological problems. They recommend a proactive approach to addressing the toxic potential of NMs that includes conducting safety evaluations now, developing testing tools and assays, and open communication with the public.

Implications:

- As discussed by the authors, particle toxicology is a mature science, with an abundance of available research findings and methodologies that can be applied to the case of engineered nanoparticles. Specifically, both *in vivo* assays of oxidative stress and *in vitro* assays for ROS and oxidative stress comprise a currently available predictive paradigm for toxicity screening of ambient PM that can inform the development of a similar paradigm for engineered NM.
- Given the growing body of evidence linking toxic potential of NMs with physicochemical characteristics, the authors emphasize that toxicity screening studies of NM must attempt to characterize test materials for a diverse number of properties, including size (surface area, size distribution), chemical composition (purity, crystallinity, electronic properties, etc.), surface structure (surface reactivity, surface groups, inorganic/organic coatings, etc.), solubility, shape, and aggregation.
- Recognizing the outstanding questions regarding the best metric for evaluating exposure-dose-response relationships, the authors suggest the calculation of NM dose based on three relevant metrics- mass concentration, number concentration, and surface area. The authors suggest that research be dedicated to the development of detection methods for exposure assessment and dosimetry calculation.
- Due to the remaining uncertainty regarding real-life NM hazards, the authors conclude that NMs be considered to be potentially toxic when handled (*i.e.*, use standard hygiene procedures and move ahead as new information comes to light) and that their waste be considered to be potentially hazardous until proven otherwise.

Hardman R. 2006. "A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors." *Environ. Health Perspect.* 114(2):165-72.

Synopsis:

- This article summarizes the toxicological literature on engineered quantum dots (QDs), a class of engineered nanoparticles with current applications in biomedical imaging and electronics industries.
- The author emphasizes that not all QDs are alike, that engineered QDs cannot be considered to be a uniform group of nanomaterials, and that it is the unique physicochemical properties of QDs that determine potential toxicity or lack thereof.

- As discussed by Hardman, the potential toxicity of QDs has been shown to be related to QD size, charge, concentration, metalloid core structure/composition, outer coating bioactivity (capping material, functional groups), and oxidative, photolytic, and mechanical stability.
- The author concludes that the findings of their literature review (consisting primarily of rodent animal models and *in vitro* cell cultures) are suggestive of potential environmental and human health risks from elevated exposures to certain types of quantum dots under certain conditions.

Implications:

- Given that quantum dots have widely varying physicochemical properties that affect their absorption, distribution, metabolism, excretion, and toxicity, toxicity screening for QDs will likely need to be done on an individual basis rather than by classification or grouping based on shared properties.
- Recognizing that many of the available studies addressing the toxicity of quantum dots have been conducted by nanotechnology researchers rather than toxicologists or health scientists, well-designed toxicological studies (*e.g.*, dose, duration, frequency of exposure, mechanisms of action) are needed to resolve some discrepancies in the available data.
- As discussed by Hardman, the fate of QDs in products and the environment is a major data gap, as little is currently known regarding stability of QDs in the environment, product lifetimes, and how these materials partition into environmental media.
- Although available data indicate that all exposure routes are of potential concern for QDs due to their ability to enter a variety of different cell types via endocytotic mechanisms, research is needed to identify the most likely routes of exposure, and also to investigate hypotheses that QDs pose a risk of bioaccumulation.

Guest Contributor: Lynn L. Bergeson

Nanotechnologies and FIFRA

Nanotechnology regulatory mavens would agree that a good number of articles have been written about the Toxic Substances Control Act's (TSCA) adequacy in assessing the risks posed by existing and new engineered nanoscale materials. The United States Environmental Protection Agency's (EPA) Office of Pollution Prevention and Toxics is well along in tackling the tough issues that these emerging technologies pose in terms of risk assessment challenges and related matters, and EPA leadership is to be commended for its pioneering work in this regard. Less has been written about nanotechnologies

and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which is curious since the regulatory hurdles and opportunities nanotechnologies pose for EPA's Office of Pesticide Programs (OPP), pesticide manufacturers, formulators, and other FIFRA stakeholders are every bit as challenging. This column explores applications of nanotechnologies in the agricultural sector, and a few of the issues OPP is now considering.

There are many promising agricultural applications of nanotechnologies. Nanosensors offer the promise of real-time pathogen detection/location reporting using nanotechnologies in micro electromechanical system (MEMS) technology. Increased biological efficiency could result in diminished amounts of pesticides being applied. Similarly, nanodevices used for "smart" treatment delivery systems hold promise. Smart field systems detect, locate, and report/apply, as needed, pesticide and fertilizers prior to the onset of symptoms. Nanopesticide delivery systems, including nanocapsules, nanocapsules, and nanocages, could replace conventional emulsifiable concentrates, thus reducing organic solvent content in agricultural formulations, and enhancing dispersity, wettability, and the penetration strength of the droplets. Enhanced use of smart systems could also diminish run off and avert unwanted movement of pesticides. These are only a few of the innovations nanotechnologies offer in the food and agriculture areas.

OPP is working with other EPA program offices to consider how best to address the growing number of issues engineered nanoscale materials pose. EPA's Science Policy Council Nanotechnology White Paper includes a brief discussion of FIFRA. EPA notes its expectation "that pesticide products containing nanomaterials will come under FIFRA review and registration." EPA also observes that nanotechnologies may produce "[m]ore-targeted fertilizers and pesticides that result in less agricultural and lawn/garden runoff of nitrogen, phosphorous, and toxic substances is potentially an important emerging application for nanotechnolog[ies] that can contribute to sustainability." Finally, EPA notes that until adequate nomenclature conventions are developed, it will be difficult to delineate in some instances "if reporting to EPA is required because the nanomaterials are not contained on the TSCA Inventory, or if use of a nanoscale material results in a change to a pesticide product already registered under FIFRA."

Key issues OPP can be expected to tackle include:

Registration Issues – How will OPP review and approve a new nanopesticide, will OPP consider a nanoscale version of a conventional pesticide a new pesticide, what will inform OPP's registration decision logic, what are the data needs and how will they be satisfied given test protocols and/or methods do not in all cases exist, and where will the resources come from to undertake this work? The inclusion of nanoscale materials as inert ingredients in pesticide formulations also raises vexing issues. It is not clear what the review process will be for a new inert and/or nanoscale version of an existing inert ingredient, what data requirements might apply, and what process OPP will use to review these matters.

Label Claims – How will EPA approach and monitor the growing number of claims being made by product manufacturers regarding the antimicrobial properties of certain engineered nanoscale substances (e.g., silver nanoparticles)?

Reporting Implications – Will existing guidelines under FIFRA Section 6(a)(2) and the requirements set forth at 40 C.F.R. Sections

156.10 and 168.22 be adequate to inform the regulated community's understanding of what EPA believes is reportable under FIFRA with respect to engineered nanoscale materials?

New agricultural/antimicrobial products and application techniques are likely to revolutionize these markets, and there are many commercial opportunities to promote sustainable agricultural and pollution prevention through nanotechnologies. Industry stakeholders and others must engage with EPA and the United States Department of Agriculture early, openly, and regularly to ensure nanotechnologies fulfill their promise as pollution prevention and sustainable agricultural tools.

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Coming Next Month

- US EPA Update with the latest on TSCA implications
- Research summary of the second published, peer-reviewed aquatic toxicology study of nanoparticles

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