



# Gradient CORPORATION

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Editor: Barbara D. Beck, Ph.D., DABT

Dr. Beck directs Gradient's nanotechnology, toxicology, and risk assessment practices.

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## Recent Government Briefs

### **US Executive Office Memorandum on Principles for Nanotechnology Environmental, Health, and Safety Oversight**

[http://www.ostp.gov/html/Nano%20EHS%20Principles%20Memo\\_OSTP-CEQ\\_FINAL.pdf](http://www.ostp.gov/html/Nano%20EHS%20Principles%20Memo_OSTP-CEQ_FINAL.pdf)

In November 2007, the White House Council on Environmental Quality and Office of Science and Technology Policy issued a memorandum outlining “generally applicable principles” to government departments and agencies that have federal oversight of nanotechnology. This memorandum instructs federal agencies such as USEPA, FDA, and OSHA to consider several criteria when issuing nanotechnology regulations or drafting nanotechnology policy. Examples of these principles include: recognition of benefits of nanotechnology, awareness of the adequacy of the current regulatory structure, application of risk assessment and risk management, development of nanotechnology information resources, and international cooperation in the nanotechnology arena. The memo concludes that these principles should be weighted when drafting future regulations to help ensure transparency, justification of costs, sound scientific judgment, and economic feasibility.

### **ATSDR Proposal to Write a Toxicological Profile for Nanomaterials**

[http://www.ehsnanonews.com/register\\_vol72no206.pdf](http://www.ehsnanonews.com/register_vol72no206.pdf)

The Agency for Toxic Substances and Disease Registry (ATSDR) recently proposed a list of chemical substances

for potential Toxicological Profile development; included in this proposed list of 73 substances were nanomaterials. Toxicological Profiles evaluate the relevance of available scientific literature in order to determine measurable toxicological standards and gauge potential public health implications of the substances in question. ATSDR Toxicological Profiles are normally published for substances commonly found at National Priorities List (NPL) sites (e.g., benzene or lead). ATSDR noted that, although comprised of various compounds, the unique nature of nanomaterials gives them properties not seen in a compound's native state. This is the basis of ATSDR's proposal to evaluate nanomaterials in a separate category. Although Toxicological Profiles have no regulatory impact, they can serve to increase pressure on regulatory agencies such as USEPA, FDA, and OSHA to promulgate new regulations. Currently, these regulatory agencies have issued no regulations covering the nanotechnology industry.

## Reports, Reviews, White Papers, and Books

### **Nanotechnology applications and implications research supported by the US Environmental Protection Agency STAR grants program**

By Nora Savage (Environmental Engineer, US EPA), Treye Thomas (Toxicologist, Consumer Product Safety Commission), and Jeremiah S. Duncan (Nanotechnology Scholar, Georgetown University)

<http://www.rsc.org/publishing/journals/EM/article.asp?doi=b704002d>

This article provides an overview of federal grants under USEPA's “Science-To-Achieve-Results” (STAR) program, which was implemented in 2002. The objective of STAR is to meet USEPA's nanotechnology data needs, as well as those of other government agencies, the scientific community, and the general public. Grants funded through the STAR program focus on both the applications-based and implications-based fields of nanotechnology research. Applications-based studies include potentially beneficial uses for nanotechnology, such as environmentally-friendly (“green”) and remediation/treatment applications. Implications-based studies examine potential health effects to humans and the environment, exposure pathways, fate and transport of nanomaterials in the environment, and life cycle analysis. Although STAR grants total \$25 million in both of these areas, significant data gaps remain, especially in determining which types of nanomaterials are currently being produced in the highest quantities, and which types of nanomaterials are of greatest

concern for human and environmental exposure. Research performed by STAR grantees is beginning to address these gaps. For more information on USEPA's STAR grants, see <http://www.epa.gov/ncer/nano>.

### Review of the First Annual Nanotechnology Safety for Success Dialogue, Held October 2007, Brussels, Belgium

Hosted by the EU Health and Consumer Directorate-General [http://ec.europa.eu/health/ph\\_risk/ev\\_20071025\\_en.htm](http://ec.europa.eu/health/ph_risk/ev_20071025_en.htm)

The Safety for Success Dialogue was held to initiate discussion of relevant nanotechnology developments, examine the aspects of risk assessment in the nanotechnology area, discuss the policy and regulatory aspects in the EU and its major trading partners, and establish an understanding of the priorities for future action. Participants represented the regional European governments, the US Food and Drug Administration (FDA), non-governmental organizations (NGOs) such as the Natural Resources Defense Council, academic institutions such as Cambridge University, and private entities such as Lux Research and Nestlé. Presentations on applications of nanomaterials examined current and potential uses in the food, health, and consumer products industries. Other discussions examined the state of knowledge of nanoparticle risk assessment and toxicology. Last, speakers presented regulatory and policy perspectives of European and other national government agencies, such as the FDA. Break-out groups were also conducted to discuss viewpoints among scientists, industry, non-governmental organizations, and public authorities.

## Upcoming Meetings and Conferences

### International Symposium on Nanotechnology in Environmental Protection and Pollution

December 11-13, 2007, Fort Lauderdale, Florida  
<http://www.isnepp.org/ISNEPP07/front1.htm>

The Asia Pacific Nanotechnology Forum is sponsoring the first annual International Symposium on Nanotechnology in Environmental Protection and Pollution, addressing the areas of environmental protection, remediation, public health, energy production, and environmental regulation. This forum will provide a platform for researchers and industry to highlight new developments and research needs on these topics. Discussion rounds and panel sessions will include nanomaterial life cycle assessment, detection and remediation, toxicity and exposure assessment, and development of standards.

### Risk, Uncertainty and Decision Analysis for Nanomaterials: Environmental Risks and Benefits and Emerging Consumer Products

April 27-30, 2008, Lisbon, Portugal  
<http://www.risk-trace.com/portugal2008/>

Presented by the North Atlantic Treaty Organization (NATO), the Society for Risk Analysis (SRA), and other trade and government groups, this conference aims to identify issues in emerging nanotechnology applications that may have environmental and health implications. The workshop will examine the decision analyses used to weigh benefits and risks of nanotechnology, discuss future research options of emerging nano-enabled products, and ascertain nanomaterial management strategies for developing countries.

### 2nd International Conference on Nanotoxicology

September 7-10, 2008 Zurich, Switzerland.  
<http://www.nanotox2008.ch>

Hosted by the University of Zurich and the Swiss Federal Institute of Technology, this conference aims to address the hazards of and exposure to nanomaterials, in an open dialog with the public and stakeholders. Participants will have the chance to attend panels on the biological effects of nanomaterials and learn about the development of new methods and standardization processes. The conference program will cover topics such as nanomaterial mechanisms of action, exposure and uptake of nanomaterials, inhalation of nanomaterials, and properties of special materials associated with nanotechnology.

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

### Sager, T. M., et al. 2007. "Improved method to disperse nanoparticles for in vitro and in vivo investigation of toxicity." *Nanotoxicology 1 (2):*

**118-129.** Abstract: <http://www.informaworld.com/smpp/content~content=a778819428~db=all~jumptype=rss>

#### Synopsis

- Particle size and surface area are important factors in the toxicity of nanoparticles. Previous studies have shown that surface area may be a better dose metric than mass in the assessment of toxicity. Thus, ensuring that nanoparticles remain suspended as individual particles to maintain the original surface area is relevant to toxicity testing. This study investigates the effectiveness of different media in the suspension and dispersion of nanoparticles for use in toxicity testing.
- Ultrafine and fine carbon black and titanium dioxide (TiO<sub>2</sub>) were suspended in phosphate-buffered saline (PBS), PBS plus dipalmitoyl phosphatidylcholine (DPPC), PBS plus DPPC and albumin, rat bronchoalveolar lavage fluid (BALF), or mouse BALF. Images of the nanoparticles

in suspension were taken using light microscopy, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) to assess dispersion.

- To determine whether BALF alters the toxicity of nanoparticles, *in vivo* and *in vitro* tests were performed using silica suspended in either BALF or PBS. Intratracheal instillation of silica suspensions in rats were followed by bronchoalveolar lavage at 24 hours. Lavage fluid was tested for evidence of inflammation and cytotoxicity. In addition, an alveolar type II cell line, A549, was incubated with the silica suspensions, and the media were tested at 18 hours for the presence of lactate dehydrogenase (LDH), an indicator of cytotoxicity.
- Both carbon black and TiO<sub>2</sub> were more uniformly dispersed, with fewer and smaller agglomerates, in rat or mouse BALF than in PBS alone or PBS plus DPPC, as viewed by light microscopy, TEM, and SEM. A mixture of PBS with DPPC and bovine serum albumin, at concentrations found in BALF, was almost as effective as BALF in dispersion of carbon black.
- The presence of BALF or DPPC did not affect the toxicity of silica as compared to suspension in PBS alone, as measured by *in vivo* and *in vitro* assays described above. Silica was used for these assays because it disperses well in PBS.

### Implications

- Because nanoparticle toxicity is, in part, dependent on surface area, effective dispersion of particles in suspension media is important for accuracy in toxicity assays. The authors show that PBS may not be a satisfactory suspension medium for nanoparticles because agglomeration can lead to inaccurate dose estimations.
- The use of BALF as a suspension medium can greatly reduce agglomeration and lead to more accurate dosing. PBS plus DPPC and protein can be used as an alternative to BALF, being only slightly less effective at dispersion.
- Previous studies have shown that dispersion of nanoparticles can affect the potency of the toxic response. The use a suspension medium that reduces agglomeration may lead to more accurate dose estimations and evaluations of nanoparticle toxicity.

### **Mitchell, L. A., et al. 2007. Pulmonary and systemic immune response to inhaled multiwalled carbon nanotubes. *Toxicological Sciences* 100 (1): 203-214.**

**Abstract:** <http://toxsci.oxfordjournals.org/cgi/content/abstract/100/1/203>

#### Synopsis:

- Since *in vivo* pulmonary toxicity studies of carbon nanotubes (CNTs) have employed non-physiological

exposure techniques (e.g., either intratracheal instillation or pharyngeal aspiration), this study was conducted to assess the short-term pulmonary and systemic immune responses of mice to multi-walled carbon nanotubes (CNTs) under more realistic inhalation exposure scenarios.

- Following development of an aerosol delivery system designed to generate respirable MWCNT aggregates with similar properties to resuspended CNT powders in the workplace, adult mice (C57BL/6, 10-12 weeks) were exposed in whole-body inhalation chambers to either control air or 0.3, 1.0, or 5.0 mg/m<sup>3</sup> MWCNTs for 7 or 14 consecutive days (6 hours/day). Pulmonary and systemic immunological responses were then assessed in a battery of tests, including a number of standard measurements of pulmonary injury (e.g., histopathology, white blood cell count in bronchial alveolar lavage fluid, and some measurements of oxidative stress and cytokine induction) and immune function measurements on spleen-derived cells.
- Although histopathology of lungs of exposed animals revealed alveolar macrophages containing black particles, no inflammation or tissue damage was observed. Furthermore, no increases in white blood cell counts were observed in bronchial alveolar lavage fluid despite observation of particle-laden macrophages.
- All MWCNT exposures caused nonmonotonic systemic immunosuppression after 14 days, but not after 7 days. Indicators of systemic immune suppression included suppressed T-cell-dependent antibody response, decreased proliferation of T cells following mitogen stimulation, and altered NK cell killing in spleen-derived cells.

### Implications:

- These findings of a lack of lung damage of inhaled MWCNTs call into question the toxicological relevance of previous findings for instilled or aspirated CNTs that demonstrated significant pulmonary effects, including inflammation, evidence of oxidative stress, fibrosis, and granuloma formation.
- Although for only very short exposure durations, study findings do not provide support for significant fibrogenic effects of MWCNTs. Additional studies are needed to confirm these findings for longer duration exposures and for other CNT forms and compositions, including single-walled carbon nanotubes (SWCNTs).
- Additional study is needed to understand the potential health implications of the findings of immune function responses in the spleen. As discussed by the study authors, work is needed to elucidate the mechanism underlying these findings and to investigate whether similar immune function responses occur in other parts of the body, such as in the lymph nodes or immune cells in the lung.

## Guest Contributor

**By Joe Clark**

Counsel for Day Pitney Hardin LLP, Florham Park, New Jersey

### **Regulatory Uncertainty, the Precautionary Principle and Nanotechnology – Towards A New Paradigm of Cooperation?**

As the prevalence of nanoenabled products increases, so too does concern over a lack of industry regulation, particularly relating to the environment and human health and safety. Of the many regulatory approaches that exist, one of the most controversial, at least in this country, is the Precautionary Principle. At its most basic, it is a dressed up version of the old adage “better safe than sorry.” Although no one can fault this sentiment, it is the perceived potential for heavy-handed application by the government, without regard to public benefit, that has some parties worried.

So the question then becomes: is there a way that the Precautionary Principle can be modified so that the government does not act unilaterally when regulating nanotechnology? The answer is that the traditional method of regulation at the federal level must be supplemented with additional methods of sharing information between regulatory bodies and interested parties. This is not a new idea, and back in 2004, insurance giant Swiss Re’s Centre for Global Dialogue published a report entitled “Nanotechnology: Small Matter, Many Unknowns.” Of all the points made in the report, the most important is that a “risk dialogue” involving scientists, businesses, regulatory authorities, consumers and the insurance industry is a necessity.

Given that nanotechnology is in its infancy, the time for such a dialogue is now. A solicitation of views from a wide variety of interests, combined with a recognition by stakeholders that the current lack of toxicological data counsels in favor of temporary self-restraint in terms of R&D and product launches, is an iteration of the Precautionary Principle that is far more palatable than unilateral governmental interference, which is the Precautionary Principle at its most draconian.

Admittedly, this may have the effect of slowing business and research efforts, at least while a regulatory scheme is being formulated. However, the alternatives are much worse. Decades of toxic tort litigation indicate that when risk is not properly accounted for, bad things can happen to the public, businesses, and insurance companies, among others. Not only can damage claims be staggering, but the government’s response to an industry perceived as ignoring risk can be severe. Even absent litigation, nanotechnology, which holds so much promise, can face a tremendous uphill battle for acceptance if the court of public opinion judges nanotechnology to be too dangerous. The “Frankenfood” label attached to genetically modified food, and the Alar scare immediately come to mind.

Consequently, the early days of nanotechnology must be defined by a transparent and well-informed regulatory process that encourages participation throughout the regulatory lifecycle, not just at the beginning, when the first wave of regulations is being developed. Many government agencies including EPA and FDA have been active in that regard, and are more than willing to hold public meetings to address various concerns. Interested parties should

avail themselves of every opportunity to advance nanotechnology by participating in the regulatory process so that risk can be addressed in a rational and intelligent manner.

*Joseph A. Clark, Counsel, Day Pitney Hardin LLP – Mr. Clark practices in the areas of complex commercial and corporate litigation, insurance and reinsurance disputes, intellectual property litigation, and emerging technologies. He is a U.S. Delegate to ISO Technical Committee 229 – Nanotechnologies, and a Participating Member of ASTM International, Committee E56 – Nanotechnology.*

## Coming In the Next Issue

Findings from the first in vivo inhalation study of C60 fullerene nanoparticles and microparticles.

## Publication Staff

### **Editorial**

Barbara D. Beck, Ph.D., DABT  
Christopher M. Long, Sc.D.  
Noelle M. Cocoros, M.P.H.  
Todd C. Hudson, M.S.P.H

### **Production**

Elizabeth Allen  
Janelle Forbes  
Matthew Braman  
Ruth Buchman



### **Contact Us**

Gradient Corporation  
20 University Rd  
Cambridge, MA 02138

t: 617.395.5000  
f: 617.395.5001

email: [ehsnanonews@gradientcorp.com](mailto:ehsnanonews@gradientcorp.com)  
website: [www.gradientcorp.com](http://www.gradientcorp.com)

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