



Gradient CORPORATION

EH&S Nano News

Volume 1, No. 5

www.ehsnanonews.com

June 2006

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Recent Government Briefs

The Food and Drug Administration (FDA)

FDA announced plans to hold a public meeting in Fall 2006 to further their understanding of current developments in the use of nanomaterials in FDA-regulated products. FDA is particularly interested in nanotechnology applications in the areas of foods (including dietary supplements), food and color additives, animal feeds, cosmetics, drugs and biologics, and medical devices. In addition to scientific and other issues involving the use of nanotechnology materials in FDA-regulated products, FDA specifically noted its interest in learning about opportunities where FDA could assist in overcoming scientific obstacles inhibiting the use of nanotechnology in medical product development. In preparation for this meeting, FDA is currently asking for parties interested in presenting at or attending the meeting to inform the Agency of their interest. For more information, see: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01356.html>.

Germany's Federal Institute of Risk Assessment (BfR)

Following a formal investigation, Germany's Federal Institute of Risk Assessment (BfR) has concluded that nanoparticles are not to blame for the more than 100 reported respiratory complaints associated with use of the "Magic Nano" sealing spray in Germany. "Magic Nano," an aerosol spray that is marketed as a sealing spray for making glass and ceramic surfaces such as bathtubs and mirrors water- and dirt-repellant, was withdrawn from the market on March 28th due to consumer reports of respiratory problems that included severe respiratory disorders and a few cases of pulmonary edema. Based on information provided by the manufacturers to BfR at a May 23rd meeting, as well as confirmatory chemical analyses conducted by two specialist laboratories, the sealing sprays do not actually contain any nano-sized particles. The cause of the intoxications remains unclear, and BfR has plans to hold another expert meeting to discuss results from several ongoing studies aimed at elucidating the toxic mechanisms underlying the health disorders. For more information, see: <http://www.bfr.bund.de/cms5w/sixcms/detail.php/7842>.

Reports, Reviews, White Papers, and Books

Identification & Assessment of the Effects of Engineered Nanoparticles on Human & Environmental Health

<http://www.ufz.de/index.php?en=7157>

In Germany, a consortium has formed with the intent to create a database of information about the possible risks associated with nanoparticles. The German Ministry of Research has funded the 3-year project, called Identification & Assessment of the Effects of Engineered Nanoparticles on Human & Environmental Health, and the consortium is comprised of both research institutes and companies from Dresden and Leipzig that do work in materials and environmental sciences and medicine. The press release describing this project indicates that a certified lab will be created specifically for this project. The group will begin with assessment of *in vitro* testing and the results will be available free to the public *via* the database.

Nanomaterials in the Workplace – Policy and Planning Workshop on Occupational Safety and Health

By James T. Bartis and Eric Landree

http://www.rand.org/pubs/conf_proceedings/CF227/

This report on the workshop held in October reviews the day's proceedings and may be of particular interest to those in industry focused on planning for the development and use of nanomaterials and products. One of the key topics the group addressed was how to reconcile private and public funding and support for worker safety research with the speed of technological development and research in the field. The report is available for free *via* the link provided.

Upcoming Meetings and Conferences

Nano Regulation

NanoEurope 2006 - St. Gallen, Switzerland, Sept. 12-14, 2006

http://www.olma-messen.ch/wEnglisch/messen/nanoeurope/01_besucher/home/home.php

Within this three-day fair and conference on medical devices, plastics, and textiles, is a two-day conference on Nano Regula-

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

tion. This second international meeting on nano regulation will focus on practical safety, risk, and research trends—from best practices for handling of materials to nano-communication with customers and the public.

International Conference on Nanotechnology Occupational and Environmental Health and Safety: Research to Practice

Cincinnati, OH Dec. 3-8, 2006

<http://www.uc.edu/noehs/>

NIOSH, the University of Cincinnati, US EPA, and others are the co-sponsors of this conference that will address the future of nanotechnology from two distinct perspectives of health and safety: the promotion and protection of worker safety throughout the life cycle of nano products, and the use of nanotech to prevent, detect, and treat occupational and environmental diseases.

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

D.B. Warheit *et al.* 2006. “Pulmonary instillation studies with nanoscale TiO₂ rods and dots in rats: toxicity is not dependent upon particle size and surface area.” *Toxicological Sciences*. 91 (1): 227-236. [Abstract](#).

Synopsis:

- This article summarizes acute toxicity tests conducted to test the hypothesis that nanoscale TiO₂ particulates, in the form of nanoscale dots or rods, elicit greater pulmonary inflammation and cytotoxicity as compared to equivalent mass dose concentrations of fine-sized TiO₂ particle types.
- In a series of acute lung toxicity tests, rats were intratracheally instilled with doses of 1 or 5 mg/kg of solutions of either pigment-grade fine-sized TiO₂ particles (rutile-type particle size = ~200 nm), nanoscale TiO₂ rods (anatase= 200 nm x 35 nm), nanoscale TiO₂ dots (anatase= ~10 nm), or a positive control type, quartz. Lung responses were assessed using bronchoalveolar lavage fluid biomarkers, cell proliferation methods, and histopathological evaluation of lung tissue at 24 hours, 1 week, 1 month, and 3 months post-instillation exposure.
- No significant adverse pulmonary effects were observed for the pulmonary instillation exposures to TiO₂ nanoscale rods or dots, with experiments yielding only transient inflammation and cell injury effects at 24 hours post-exposure that were not sustained and did not differ from the pulmonary effects of the larger-sized TiO₂ particle exposures.
- In contrast to the fine and nanoscale TiO₂ exposures, pulmonary exposures to quartz particles produced dose-dependent lung inflammatory responses in the rats that were characterized by neutrophils and foamy lipid-containing alveolar macrophage accumulation as well as evidence of early lung tissue thickening consistent with development of pulmonary fibrosis.

Implications:

- As discussed by the authors, this study is the first to report results for a nanoscale particle type that does not appear to be more cytotoxic or inflammatory to the lung compared to larger-sized particles of similar composition.
- These findings thus run counter to the “conventional wisdom” that surface area is a major factor associated with the pulmonary toxicity of nanoscale particle types.
- Relevance to other types of exposures (*i.e.*, *via* inhalation) is currently uncertain, and additional study is needed to investigate whether *in vivo* conditions yield similar results.
- The authors acknowledge that additional research is also necessary to investigate the role of particle aggregation as a mitigating factor for the presumed effects of particle size.

T.J. Brunner *et al.* 2006. “In vitro cytotoxicity of oxide nanoparticles: comparison of asbestos, silica, and the effect of particle solubility.” *Environ. Sci. & Technol.* ASAP Article. [Abstract](#).

Synopsis:

- This article summarizes experiments conducted to evaluate the use of an *in vitro* setup based on well-established lines of rodent or human cells (mesothelioma MSTO-211H and rodent 3T3 fibroblast cells) to provide possible early toxicity indicators for nanoparticles.
- *In vitro* cytotoxicity tests were conducted for a number of industrially important nanoparticles (highly insoluble ceramic materials such as ceria, titania, and zirconia; slightly soluble materials such as zinc or iron oxides; and tricalcium phosphate nanoparticles), as well as a positive control (crocidolite asbestos) and a negative control (amorphous silica). Cultures were exposed to physiologically relevant 0-30 ppm nanoparticle dispersions in aqueous solution, and measures of metabolic activity and cell proliferation were used as indicators of cytotoxicity.
- *In vitro* toxicity tests demonstrated that solubility was a key factor affecting the cell culture response to the nanoparticles, with the more soluble zinc oxide and iron oxide test species showing greater cytotoxic effects than the insoluble nanomaterials.
- Zinc oxide nanoparticles, which are now used as ingredients in sunscreens, were found to cause the death of virtually all MSTO or 3T3 cells for exposure concentrations above 15 ppm.
- Insoluble zirconia, ceria, and titania nanoparticles elicited a clear cytotoxic effect for short exposure times, with partial detoxification or recovery after 6 days.

Implications:

- Although this study indicates the promise of simple pre-screening tests for providing early indicators of nanoparticle-derived adverse health effects, animal studies are needed to verify these *in vitro* findings and additional

experiments are also needed to address potential long-term effects that could result from translocation and uptake of the more persistent insoluble materials into cells.

- Study findings for a range of different nanoparticle types, similar in size to silica and asbestos, showed that cytotoxic responses result from the complex interplay of a number of important factors including measurement parameters, duration of treatment, and cells types.
- For iron oxide particles, observed cytotoxic responses were found to be greater than those associated with chemical toxicity of completely dissolved iron ions, indicating the presence of an additional nanoparticle specific cytotoxic effect. Based on these findings, the authors hypothesized that iron oxide nanoparticles may be rapidly taken up into different compartments of the cell not normally accessed by aqueous iron ions.
- Through the use of a combination of quantitative analytical methods, the authors demonstrated the need for careful physical analysis of dispersions and delivery of reliable size data.

Guest Contributor W. Tyler Beaty

Communicating Potential Hazards of Nanoparticles and Raw Nanomaterials

The National Science Foundation estimates that by 2015 the United States will employ one million workers in nanotechnology. Although the nanotechnology industry is still in its infancy, as more nanotechnology applications are commercialized, the potential for human exposure to nanoparticles and raw nanomaterials will continue to increase. The greatest likelihood of human exposure to raw nanomaterials is during research and manufacturing phases when nanoparticles and raw nanomaterials are not yet infused in a final application. This type of exposure is expected to be similar to that of conventional industrial operations producing ultra-fine particles that could be absorbed or inhaled into the body; questions regarding the impact of such exposure are still open.

Employers that work with nanoparticles and raw nanomaterials face increasing risk from regulatory uncertainty as growing numbers of employees are exposed to potentially hazardous nanomaterials. Nanomaterial researchers and manufacturers have (or should have) many questions about how to limit their risks and exposures and ensure the safety of their employees. One broad question involves how nanotechnology will or will not fit within the current regulatory regime. By way of example, the Occupational Safety and Health Act of 1970 (OSHA) is one such area of the law that challenges nanomaterial researchers and manufacturers operating in the U.S. to comply with regulations that seem to be outpaced by nanotechnology innovation.

OSHA requires employers maintain a safe and healthful workplace, “free from recognized hazards likely to cause death or serious physical harm.” Among the duties that OSHA imposes on employers is compliance with the Hazard Commu-

nication Standard (HCS). The HCS is designed to ensure that hazards of all chemicals produced or imported are evaluated, and that information concerning their hazards is transmitted to employers, employees, and contractors. Employers must comply with the HCS by communicating the risks of workplace hazards through comprehensive hazard communication programs which include three components: labeling, material safety data sheets (MSDS), and employee training.

Compliance with the HCS may prove to be a daunting task for nanomaterial researchers and manufacturers. The reason for this is that potential hazards and risks of nanoparticles and raw nanomaterials are largely unknown. Moreover, widely accepted risk and toxicity assessment protocols remain nonexistent. Thus, nanomaterial researchers and manufacturers will struggle to develop hazard communication programs for substances where risks are not completely understood.

The good news is that the void of information concerning nanoparticle and nanomaterial risks is being addressed by many organizations that may eventually result in guidance for nanomaterial manufacturers. The National Institute for Occupational Health and Safety (NIOSH) has identified the goal of developing “Best Practices” for working with nanomaterials. The first draft of the “Best Practices” document is called “Approaches to Safe Nanotechnology: An Information Exchange with NIOSH.” This draft document suggests some exposure control strategies that would be helpful in developing hazard communication programs for nanomaterial researchers and manufacturers, but is incomplete in critical areas such as procedures for cleaning up nanomaterial spills.

It must be noted that until a final version of the “Best Practices” documentation is formally released by NIOSH, it should not be construed to represent any agency determination or policy. However, in spite of the lack of guidance in this area thus far, nanomaterial researchers and manufacturers should consider the draft versions of the “Best Practices” document when crafting hazard communication and other safety programs to address OSHA compliance.

According to NIOSH, drafting “Best Practices” documentation is a dynamic process because knowledge regarding nanoparticles continues to grow and change. So much has been learned since the last draft’s release that another draft is anticipated for release this summer. NIOSH anticipates releasing a finalized “Best Practices” for working with nanomaterials once the underlying research is concrete enough to do so.

Until a finalized “Best Practices” document is released, nanomaterial researchers and manufacturers must evaluate their operations on their own. First, they should consider any existing toxicology studies for specific nanoparticles that they work with. Second, nanomaterial manufacturers should consider the potential for exposure with their production processes. Third, any existing hazard communication programs should be evaluated with respect to adequacy in the event that risks are not completely understood for a given nanoparticle or raw nanomaterial. Fourth, nanomaterial researchers and manufacturers should remain alert for new guidance from regulators and research studies that may affect safety policies and operations. Finally, nanomaterial researchers and manufacturers need to weigh the value of operating without finalized

guidance against the potential for regulator enforcement actions, and even worse, product liability lawsuits resulting from human exposures to hazardous nanoparticles.

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For more information, see: <http://www.jpm-law.com>

Coming Next Month

- Summary of emerging research on coating technologies used to render carbon nanotubes non-toxic and expand their potential for biological use.
- An update on the Organisation for Economic Cooperation and Development (OECD) workshop on the safety of manufactured nanomaterials.

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