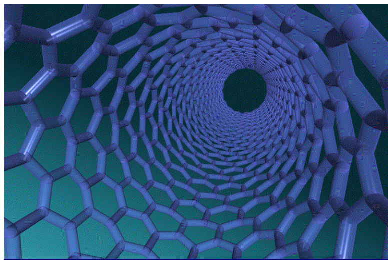

Gradient CORPORATION

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In This Issue

Recent Government Briefs

US EPA Considers Carbon Nanotubes as New Substances under Toxic Substances Control Act (TSCA)

http://edocket.access.gpo.gov/2008/pdf/E8-26026.pdf

On October 31, 2008, the US Environmental Protection Agency (US EPA) published a notice in the *Federal Register* (Volume 73, Number 212) indicating that the Toxic Substances Control Act (TSCA), the law that regulates introduction of new chemicals, is applicable to carbon nanotubes (CNTs). This clarifies the US EPA's 2007 position on CNTs. US EPA stated that it considers CNTs as chemical substances distinct from other carbon compounds already listed in the TSCA inventory (*e.g.*, graphite). Therefore, CNTs may be considered as new chemicals under Section 5 of TSCA. This will require entities that use, make, or import CNTs to ensure their materials are already on the TSCA inventory. If a particular CNT is not in the inventory, anyone who intends to use, make, or import this material needs to make a TSCA notification at least 90 days before use.

Petition Presented to US EPA Calls for Nanoscale Silver to be Classified as a Pesticide

http://edocket.access.gpo.gov/2008/pdf/E8-27204.pdf

Earlier this year, the US Environmental Protection Agency (US EPA) received a petition asking the agency to regulate engineered nanoscale silver particles (nanosilver) and nanosilver-containing products, as well as to classify nanosilver as a pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Nanosilver is currently the most common engineered nanomaterial in nanotechnology-based commercial products, and it has been the focus of numerous analyses and regulatory actions. The petition was presented by several non-governmental organizations, including the International Center for Technology Assessment, Center for Food Safety, Friends of the Earth, Greenpeace, and the Center for Environmental Health. The petition specifies that US EPA should take significant action regulating nanosilver and nanosilver-containing products, including classifying nanosilver as a pesticide; requiring registration of all nanosilver-containing products under FIFRA; clarifying the regulatory definition of "pesticidal intent;" evaluating potential human and ecological risks of nanosilver under other federal laws such as the Food Quality Protection Act and National Environmental Policy Act; and taking immediate regulatory action against entities that currently have nanosilver products in the marketplace. The comment period will be open until January 20, after which US EPA will publicly respond to the petition and comments.

Reports, Reviews, White Papers, and Books

Nanotechnology Oversight: An Agenda for the New Administration

By Dr. J. Clarence Davies, Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies

http://207.58.186.238/process/assets/files/6709/pen13.pdf

The administration of President-Elect Obama will face several headline-generating challenges, such as the economy and health care. Nanotechnology, though less frequently mentioned, has the potential to affect energy use, military technology, the environment, consumer products, and the workplace. Dr. Davies' report highlights several nanotechnology policy issues that he feels require immediate attention by the next President's administration. He identifies the Food and Drug Administration (FDA), US Environmental

Protection Agency (US EPA), Consumer Product Safety Commission (CPSC), and Occupational Health and Safety Administration (OSHA) as the primary bodies with authority to regulate nanomaterials. He indicates that progress has been stalled in these agencies towards making proactive steps in the oversight of nanomaterials. Davies recommends that involved agencies conduct more research, further coordinate with each other, and receive more funding; he also gives several agency-specific recommendations such as developing nanotechnology plans and recommending that agencies show strong links between research and regulatory functions. He suggests actions taken by the government should be supplemented by voluntary industry efforts and public participation. Last, he emphasizes the importance of potential long-term actions, such as clear definitional language in the Toxic Substances Control Act, changes to the regulation of cosmetics and dietary supplements that claim to contain engineered nanomaterials, and providing regular updates to the federal government as new forms of engineered nanoparticles are created.

Genotoxicity of Engineered Nanomaterials: A Critical Review.

By Laetitia Gonzalez, Dominique Lison, and Micheline Kirsch-Volders

http://www.informaworld.com/smpp/content~content=a905749655~db=all

In this paper, the authors evaluated and compared data from 19 *in vitro* and four *in vivo* nanoparticle genotoxicity studies, in an effort to propose "minimal criteria for conducting nano-genotoxicity assays." Proposed genotoxic modes of action of engineered nanomaterials include generation of reactive oxygen species and mechanical interference with cellular components (*e.g.*, interference with microtubules or centrosomes). Based on an evaluation of available nanomaterials genotoxicity studies, the authors determined that general conclusions could not be made regarding the genotoxicity of the nanomaterials. Key limitations in experimental design in the *in vitro* studies that hindered interpretation included incomplete nanomaterial characterization, the lack of repeated experiments, the lack of uniform use of similar positive controls, and the common use of inadequate maximum doses. No general conclusions could be drawn from *in vivo* studies, since all experiments involved different nanomaterials, exposure routes, and animal species. Based on the overall lack of standardization, the study authors proposed several prerequisites for every nanotoxicology study, including specifying the method and synthesis of preparation, measuring particle size and distribution, reporting the specific surface area, and ascertaining aggregation status in the nanoparticle exposure media.

Upcoming Meetings and Conferences

2nd Annual Massachusetts Nano Technology Workshop: Promoting the Safe Development of Nanotechnology in Massachusetts

January 28, 2009, Boston, MA (USA)

http://www.mass.gov/dep/service/outreach/nano_workshop.htm

Hosted by the Massachusetts Interagency Nanotechnology Committee (which includes Departments of Environmental Protection and Public Health, Division of Occupational Safety, and Office of Business Development), this day-long workshop aims to attract nanotechnology experts from industry, government, research, and academia to discuss approaches for protecting workers, public health, and the environment from the impacts of engineered nanoparticles. Topics will include nanomaterial life-cycle case studies, feasible protection strategies, and the future of safe nanotechnology development in Massachusetts. This forum will focus on existing Best Practices and Good Current Practices and will also present techniques to measure airborne nanoparticle releases. Speakers will include representatives from the Nanotechnology Research Center, National Institute for Occupational Safety and Health (NIOSH), and University of Massachusetts.

Nanotoxicology: Health & Environmental Impacts

February 27, 2009, Welwyn Garden City, Hertfordshire (UK)

https://www.regonline.co.uk/builder/site/Default.aspx?eventid=161852

This event, organized by European Scientific Conferences (EuroSciCon), aims to bring together toxicologists, nanotechnology engineers, industry representatives, and governmental regulatory officials. This one-day symposium will allow nano-scientists to present their current research findings and discuss the potential impact of nanomaterials on human health and the environment. Scheduled presentations cover topics such as health implications of nanoparticles, the potential hazards of carbon nanotubes, ecotoxicology of nanoparticles, and the effects of silver nanoparticles in the environment.

NanoImpactNet: For a Healthy Environment in a Future with Nanotechnology

March 23-27, 2009, Lausanne, Switzerland

http://www.nanoimpactnet.eu/object_binary/o2841_Handout_NanoImpactNet-Event_Lausanne%202009%20print.pdf

NanoImpactNet, a European network that focuses on the health and environmental impact of nanomaterials, is hosting this platform to exchange ideas about nanotechnology research and to discuss its safe and responsible development. The target audience includes experts and other interested researchers who are developing, testing, or contributing to methods that investigate the health effects and environmental impact of nanomaterials. This three-day conference will include nanotechnology training seminars, workshops, and talks. Topics will include testing strategies, protocols for assessing hazards, environmental dispersion, exposure assessment, life cycle analysis, and nanomaterial standardization.

International Conference on the Environmental Implications and Applications of Nanotechnology

June 9-11, 2009, Amherst, MA (USA)

http://www.umass.edu/tei/conferences/NanoConference/index.html

Hosted by the University of Massachusetts Environmental Institute and sponsored by the US Environmental Protection Agency (US EPA), National Institute of Environmental Health Sciences (NIEHS), Golder Associates, Environ, and Gradient Corporation, this conference will bring together researchers and practitioners to address the environmental implications and applications of nanotechnology. The three-day program will include poster galleries, plenary sessions, platform sessions, and an exhibitor hall. Topics to be covered at the conference include materials characterization, green nanotechnology, regulatory issues, environmental fate and transport, toxicology, and pollution control. The deadline for poster abstracts is April 30; all conference papers will be considered for publication in the UMass open access online journal, International Journal for Soil, Sediment and Water. Registration is open until May 26.

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

1. Ryman-Rasmussen, JP; Tewksbury, EW; Moss, OR; Cesta, MF; Wong, BA; Bonner, JC. 2008. "Inhaled Multi-walled Carbon Nanotubes Potentiate Airway Fibrosis in Murine Allergic Asthma." *Am. J. Respir. Cell. Mol. Biol.* Sept. 11.

Abstract: http://www.ncbi.nlm.nih.gov/pubmed/18787175

Synopsis:

- Carbon nanotubes can be manufactured and used as either single-walled carbon nanotubes (SWCNT) – comprised of a single layered graphite sheet rolled into a cylinder; or multi-walled carbon nanotubes (MWCNT) – comprised of several layers of graphite sheets rolled into a cylinder. Due to their ability to conduct electricity and mechanical strength, carbon nanotubes (CNT) have applications in electronics, structural engineering, and in medicine. Because CNTs have a length-to-width (*i.e.*, aspect) ratio similar to asbestos, there is some concern that CNTs could cause injuries similar to those caused by asbestos, such as pulmonary fibrosis and lung cancer. When administered *via* intratracheal instillation, in an aqueous media, CNTs aggregate into micron-sized bundles that can cause granulomas and fibrosis at the deposition site. Compared with intratracheal instillation, deposition of MWCNTs following inhalation is much more diffuse, with minimal inflammation and fibrosis. Ryman-Rasmussen and colleagues conducted this study to evaluate whether MWCNTs exacerbate pre-existing inflammation, using a mouse model of asthma.
- In order to establish pulmonary inflammation characteristic of asthma, pathogen-free, adult, male C57Bl/6 mice were sensitized to ovalbumin adsorbed onto alum, administered *via* intraperitoneal injection at 14 and 7 days prior to exposure. At 1 day prior to exposure, mice were challenged with ovalbumin, administered intranasally. Control, unsensitized mice were administered saline at 14, 7 and 1 day prior to exposure. Control and sensitized mice were then exposed for 6 hours, via nose only, to either aerosolized saline, or autoclaved, high purity aerosolized MWCNTs, at a concentration of 100 μg/m^3. This concentration was chosen to deliver a dose comparable to that delivered in studies that administered CNTs *via* intratracheal instillation. MWCNTs were 0.5 – 40 μm in length, with a mean mass aerodynamic diameter of 714 + 328 nm, and a particle size distribution of 160 + 38.9 nm. Distribution of MWCNTs within the lungs was assessed on post-exposure days 1 and 14, using both light microscopy and transmission electron microscopy. At 1 day post-exposure, bronchoalveolar lavage fluid (BALF) was assayed for transforming growth factor-β 1 (TGF-β 1), platelet derived growth factor (PDGF), interleukin-13 (IL-13), macrophage chemo-attractant protein-1/JE (MCP-1/JE) and eotaxin. mRNA for these growth factors and cytokines was also assessed in lung tissue on post-exposure days 1 and 14, in addition to mRNA for IL-5, the chemokines CXCL9 and CXCL10, pro-collagen type 1, α2 and connective tissue growth factor. Fibrosis was assessed by assaying for soluble collagen in lung tissue, and by using quantitative morphometry to determine thickness of collagen surrounding the bronchioles. Lung tissues were also evaluated using transmission electron microscopy.
- MWCNTs retained their tube-like structure in the exposed mice, and were distributed homogeneously throughout the lung, occurring primarily as large agglomerates within alveolar macrophages, with some agglomerates deposited on the surface of the alveolar ducts and the alveoli, and some smaller aggregates and individual MWCNTs within the alveolar macrophages. MWCNTs were detected in the alveolar macrophages at both 1 and 14 days post exposure, with approximately 80% of macrophages containing MWCNTs on both days. Some MWCNTs were also taken up by lung epithelial cells.
- The most remarkable finding from this study was a statistically significant increase in thickness of collagen surrounding the bronchioles, at 14-days post exposure, in the ovalbumin-sensitized mice that were exposed to MWCNTs. However, there was no increase in soluble collagen in any of the ovalbumin-sensitized, MWCNT-exposed mice. PDFG, which is a potent fibroblast mitogen, was increased in BALF of animals exposed to MWCNTs, in both unsensitized and ovalbumin-sensitized

animals. In contrast, TGF-β1, which stimulates collagen production in fibroblasts, was increased in BALF of animals sensitized to ovalbumin, either with or without exposure to MWCNTs. IL-13, which is a mediator of allergic asthma, was also increased in BALF of animals sensitized to ovalbumin, and IL-13 mRNA was increased in lung tissue of animals sensitized to ovalbumin. mRNA for the interferon-inducible chemokine CXL9 was increased in animals sensitized with ovalbumin; MCP mRNA was increased in animals exposed to MWCNTs; mRNA for the chemokine eotaxin was increased in animals sensitized to ovalbumin as well as in animals exposed to MWCNTs, and IL-5 mRNA was increased only in animals both sensitized with ovalbumin and exposed to MWCNTs. All mRNA levels had returned to basal expression levels by post-exposure day 14.

Implications:

- In contrast to intracheal instillation of MWCNTs, inhalation exposures, at comparable doses, do not elicit an inflammatory or fibrotic response in healthy, adult mice. However, results from this study demonstrate that sensitization with ovalbumin, followed by exposure to MWCNTs, can act in concert to increase thickness of collagen surrounding bronchioles. The results from this study further suggest that the increase in collagen thickness might be related to the coordinated expression of PDGF, which stimulates fibroblast growth, and TGF-β1, which stimulates fibroblasts to produce collagen, along with expression of other cytokines, such as IL-5. That exposure to MWCNTs increased collagen thickness only in mice that were sensitized to ovalbumin suggests that individuals with pre-existing inflammation, such as those with asthma, may have enhanced susceptibility to inflammation and fibrosis subsequent to MWCNT exposure.
- Because this study evaluated only one exposure concentration, it does not provide information regarding the nature of the concentration-response relationship, and whether there is a threshold for the observed collagen response. The MWCNT concentration used in this study - 100 μg/m^3, is approximately 2000-fold greater than concentrations of SWCNTs estimated during handling in occupational exposure scenarios (0.053 μg/m^3) and 20-fold greater than the NIOSH occupational exposure standard for unregulated particles, of 5 μg/m^3. It would be of interest to determine whether exposure to lower concentrations of MWCNTs, more representative of those expected in occupational or environmental settings, would result in a similar collagen response. In addition, because exposures in occupational or environmental settings could occur on an ongoing basis, it would also be important to evaluate effects of repeated exposure to lower concentrations of MWCNTs.
- Although the results from this study highlight the possibility that individuals with underlying pulmonary inflammation may be particularly susceptible to pulmonary effects of MWCNT, it is not possible to evaluate whether the observed response is specific to MWCNTs, or is a more generalized response to high particle concentrations. Studies using other types of nanoparticles, as well as larger-sized particles present in ambient air, would provide useful information regarding whether the observed effects are related to MWCNT-specific properties.

2. Jaisi, DP; Blake, RE; Elimelech, M. 2008. "Transport of Single-Walled Carbon Nanotubes in Porous Media: Filtration Mechanisms and Reversibility." *Environ. Sci. Technol.* 42(22):8317-8323. Abstract: http://pubs.acs.org/doi/abs/10.1021/es801641v

Synopsis:

- Carbon nanotubes (CNTs) possess unique characteristics such as small size, large surface to volume ratio, chemical reactivity and biocompatible surface properties. Despite their emerging use in a variety of technological applications, CNTs are recognized to be materials of low biodegradability, suggesting the potential for release and accumulation in the environment. Compared to the large number of studies on the environmental fate and transport of nanomaterials such as zerovalent iron (ZVI), silica and iron oxide, very few studies have investigated the fate and transport of CNTs. In this work, the transport behavior and filtration mechanism of single walled carbon nanotubes (SWCNTs) were investigated in packed porous columns.
- Functionalized single walled carbon nanotubes (SWCNTs) were selected for this study and clean quartz sand was used as the porous medium for the column experiments. The diameter of the SWCNT particles ranged from 0.9 to 1.6 nm, while the average grain size of sand was in the range of 225-300 μm. The deposition of SWCNT on porous sand was determined by feeding a saturated solution of SWCNTs to the column. Following a rinsing step, the release of SWCNT from the porous sand was determined by flushing the sand columns with de-ionized water. The attachment efficiency of the SWCNT was then determined based on the influent and effluent concentrations. The influence of pore water chemistry, with varying ionic strengths, natural organic matter content (as humic acids), and levels of calcium ions, on SWCNT deposition/retention and release behavior was also studied.
- Transport experiments indicated that the deposition and retention of SWCNT on porous sand increased with ionic strength of the solution and decreased significantly in the presence of organic matter. The deposition of nanomaterials on solid surfaces occurs primarily due to electrostatic interactions between the solids surfaces. At low ionic strengths, deposition of SWCNT was slower due to repulsive electrostatic interactions at the surface. Higher ionic strengths resulted in the suppression of electrostatic repulsion, thereby increasing deposition rates. The authors also determined that the shape and size of SWCNT particles influenced their deposition rates, due to their trapping in the pores of the porous media (*i.e.*, filtration).

- Results from previous studies on ZVI and C_{60} fullerenes have shown that hydrodynamic particle size increases significantly in the effluent stream as compared to the influent stream, due to agglomeration of the nanoparticles. However, in this study, the hydrodynamic particle size was observed to be lower in the effluent stream and was also observed to be constant with time. This suggests the possibility of breakage of bundled SWCNT particles, which could result in greater transport of the particles over long distances. The breakage of bundles of SWCNTs observed in this study is in contrast to the agglomeration usually observed in nanoparticles behavior in aqueous environments and merits further investigation.
- Columns containing the deposited SWCNTs were used to determine the nanomaterial release profiles. SWCNT release profiles were similar to those observed in the deposition experiments. The amount of SWCNT released increased with ionic strength. The presence of calcium ions in the solution increased the stability of the deposited SWCNT in the solid, thereby reducing their release.

Implications:

- With increasing manufacture and use of carbon nanotubes, their mobility, fate and transport in the environment is of great interest. This study highlights the effects of environmentally relevant conditions on the mobility of SWCNTs, providing information on the mechanisms controlling their retention in porous medium. Pore water chemistry and nanomaterial characteristics both appeared to influence nanomaterial transport significantly. This study also indicated that the presence of natural organic matter could enhance SWCNT transport, while metal cations can decrease it. The determination of the transport and release mechanisms in this study could be useful in the development of source control treatment technologies that act to prevent release of CNTs into the environment.
- The transport of SWCNT in soils and the subsurface is expected to be limited due to the heterogeneity of the medium and increased deposition/filtration of the particles. However, despite high rates of SWCNT deposition in most transport experiments, subsequent release of the deposited SWCNT even with low ionic strength solutions indicated reduced particle stability in the porous media which would result in particle mobilization. Localized accumulation of SWCNTs in environmental media near the release sites could be a cause of concern, as flood or rain events could result in potential transport of the SWCNTs over large distances.

Guest Contributor

By Louis A. Chiafullo, Esq.
Partner, McCarter & English, LLP

Insurance Industry Reactions to Nanotechnology

Nanotechnology. Many believe that it will revolutionize many sectors of commerce and industry. Others believe that nanoparticles could cause widespread environmental damage and bodily injury. There is no question of the benefits flowing from the use of this technology. Yet, with benefits, there often come risks. The same properties that make these materials useful and appealing could pose risks to human health and to the environment. Because these risks are currently unknown, insurance companies are concerned, and some – most often plaintiff's trial lawyers – suggest the possibility that nanoparticles are the "new asbestos." Insurance companies clearly have taken notice of this emerging field. Several have even assigned "risk teams" to evaluate the potential risks associated with the use of nanoparticles in a variety of products. For instance, Lloyd's of London's Emerging Risks Team recently published a report entitled "Nanotechnology – Recent Developments, Risks and Opportunities." In the report, Lloyd's even analogizes carbon nanotubes to asbestos fibers, and suggests that nano-sized objects "tend to be more toxic than their large scale form."

Although the Lloyd's Report recognizes that nanotechnology could have tremendous societal benefits, it cautions other insurers that "this is perhaps one of the great dangers; because the benefits are so seductive society may rush to capitalize on them before adequately assessing safety." There is no question that insurance companies will begin analyzing and assessing their insured's risks with respect to the use of nanoparticles in their products. Insurers tend to approach risks with a broad brushstroke, evidenced by the absolute pollution exclusion that became de rigueur in the mid- to late 1980s, and is still a fixture in many types of insurance policies today. For a policyholder who uses nanoparticles in its business, there is no question that insurance policies will need to be examined, and upon renewal those policies or any other offered policies will need to be analyzed and perhaps modified, to ensure that the coverage provided matches the risks inherent in the policyholder's business.

Until recently, general liability policies covering third-party damage did not contain any specific exclusions for bodily injury or property damage relating to nanoparticles. That has just changed. A new exclusion has been developed by Continental Western Insurance Company, and there is a concern that other insurers will seek to use it as well. The exclusion removes from the scope of coverage any defense or indemnity costs associated with claims relating to bodily injury, property damage, or personal and advertising liability related to the "actual, alleged, or threatened presence of or exposure to 'nanotubes' or 'nanotechnology' in any form, or to harmful substances emanating from 'nanotubes' or 'nanotechnology.'"

Given this new nanotechnology exclusion – essentially a knee-jerk reaction by one insurer to the negative press generated by certain insurance companies – it is critical that businesses whose products use nanomaterials, or where R&D on nanomaterials is being performed, examine their insurance coverage program. Brokers are a good resource, and can look at the market to determine whether there are any insurers offering products that match the risk the business is seeking to insure, or whether there are insurers who will work with the policyholder to develop a manuscript policy tailored specifically to the policyholder's business. Policyholder-side insurance coverage lawyers can also assist in assessing a policyholder's risk, and provide some guidance on whether existing or contemplated insurance policies might adequately insure against a loss. Although there are many nanotechnology "unknowns," it is clear that businesses are getting ahead of the curve, ensuring that safety is paramount, working with scientists and consultants to analyze risks, and developing technologies that may have significant impacts on products and services. Hopefully, the insurance industry will do nothing to staunch any such impacts.

Louis Chiafullo, Esq., is a partner in the Insurance Coverage Group of McCarter & English, LLP, in its Newark, New Jersey office. He regularly litigates and arbitrates coverage claims on behalf of policyholders, and also counsels policyholders on various types of insurance issues.

Coming In the Next Issue

Research that examines the effects of diesel exhaust-derived and engineered nanoparticles on heart cells.

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