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

In This Issue

Recent Government Briefs

(Berkeley, CA). In late April, the City of Berkeley released its "Manufactured Nanoscale Material Disclosure Guidelines". These guidelines are a follow up to Berkeley's manufactured nanoscale material disclosure ordinance that was adopted in December 2006. These disclosure requirements, which are intended to cover the period of June 1, 2007-June 2, 2008, require facilities that produce or handle manufactured nanoscale materials to report such information as the average and maximum daily amount of the material stored onsite at any time during the year; the source of the material if it is not produced on site; data on the physicochemical properties of the material; available toxicological data regarding inhalation toxicity, dermal penetration and/or toxicity, oral toxicity, mutagenicity/genotoxicity, and reproductive toxicity; ecotoxicity and environmental fate data; and extensive information regarding occupational safe handling practices. The Berkeley guidelines propose a risk-based approach, and specifically the use of control band measures, for prioritizing high-risk activities and identifying the appropriate control measures that should be taken to protect workers and the environment. Reports are due to be filed with Berkeley's Toxics Management Division (DMD) by June 1, 2007. For more information, see http://www.ci.berkeley.ca.us/toxics/Manufactured Nanoparticle Reporting Final.pdf.

(NTP). With the May 10 closing of the public comment period for the 2007 toxicological study nominations to the National Toxicology Program (NTP), NTP is moving closer to its final recommendations regarding the nominated materials that include both nanoscale gold and nanoscale silver. Nanoscale gold and nanoscale silver were nominated to the NTP for toxicological study by the U.S. Food and Drug Administration in late 2006 based on "(a) increasing widespread use in drug, food and cosmetic products, and (b) the general lack of data on the toxicology and pharmacokinetics of these materials." Few toxicity data are available for either of these materials, which, due to their antibacterial properties, are gaining widespread usage in a variety of consumer products. Preliminary study recommendations for both nanoscale gold and silver include nanoscale materials characterization and metabolism and pharmacokinetic studies, as well as acute, subacute, and subchronic toxicity studies and mechanistic studies. For more information, see http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=B88594DB-F1F6-975E-78457F2FC85C50AD.

Reports, Reviews, White Papers, and Books

Green Nanotechnology: It's Easier Than You Think

US EPA, Science Policy Council, Nanotechnology Workgroup
By Karen Schmidt
http://www.nanotechproject.org/116/4262007-green-nanotechnology-its-easier-than-you-think

In the spring of 2006, meetings were held at the Woodrow Wilson International Center for Scholars, Project on Emerging Nanotechnologies, which were aimed at the responsible, or 'green,' development and use of nanotechnologies. This paper by science writer Karen Schmidt reports on the work and views of scientists, policymakers, and others in the field of green nanotechnology that participated in those meetings. The report includes a summary of some of the current research on "clean and green nanotechnology," such as a green method for synthesizing carbon nanotubes and a "greener" method for making microchips using semiconductor materials. Green nano policies and green applications for nanotech are also reviewed by the author. In all, the paper provides a brief, but substantial, overview of current work and thought in this field.

Quantifying the Effect of Nanotech on Carbon Emissions

Cientifica Limited
http://www.cientifica.eu/

This white paper from Cientifica Ltd. is based on the firm's report entitled, "Nanotechnologies for Sustainable Energy: Reducing Carbon Emissions Through Clean Technologies

and Renewable Energy Sources." The paper summarizes the key aspects of the model used by Cientifica to quantify the effect nanotechnologies will have on CO_2 emissions. The authors explain that nanotechnologies will affect three key aspects of emission reduction: reduction of transportation emissions (*e.g.*, through weight reduction); reduction in energy use by buildings via improved insulation; and renewable energy using thin film solar panels. The estimates in CO_2 emission reductions generated by the model are provided and discussed for each of these three areas. The overall conclusion is that while developments in nanotech for emission reduction are perhaps a decade or more away, such nano applications will have an impact on current and future energy technologies. Importantly, nanotech's role in the reduction of CO_2 emissions will apparently - and not surprisingly - be just one part of the larger resolution to the problem of CO_2 emissions.

Upcoming Meetings and Conferences

3rd International Symposium on Nanotechnology, Occupational and Environmental Health

Taipei, Taiwan; Aug. 29 – Sept. 1, 2007
http://nano-taiwan.sinica.edu.tw/EHS2007/index.htm

This symposium will bring together international nanotech experts with a variety of backgrounds to discuss how to identify, assess, and manage/govern risks associated with nanotech in both occupational and environmental health settings. Topics that will be addressed at the meeting include environmental and exposure monitoring, environmental applications of nanotech, and good working practices. In addition to keynote lectures and research presentations, there will be tutorials that provide basic training in areas such as nanoparticle dosimetry in the lung and exposure assessment of nanoparticles.

2nd Advanced Course on Public Communication & Applied Ethics of Nanotechnology

Oxford, England; Sept. 23 – 28, 2007
http://nanobio-raise.org/

Advertised as an intensive course for those working in nanobiotechnology with an interest in its public communication and ethical implications, the course consists of an alternating program of expert lectures, case studies, media training, role play, group discussions and debate. It is being organized by Nanobio-RAISE, a European Coordination Action bringing together nanotechnologists, ethicists and communication specialists with the aim of anticipating the societal and ethical issues likely to arise as nanotechnologies develop. Course participants are expected to gain knowledge relevant to the ethical, legal, and social aspects of nanobiotechnology, as well as skills for communicating effectively with the media and the public

2nd International Conference on the Environmental Effects of Nanoparticles and Nanomaterials

London, England; Sept. 24 – 25, 2007
http://www.sebiology.org/Meetings/pageview.asp?S=2&mid=107

The UK branch of the Society of Environmental Toxicology and Chemistry (SETAC) and the Society for Experimental Biology (SEB) are organizing the 2nd international meeting on the potential biological and environmental effects of nanoparticles and materials. The meeting will cover a range of themes on this topic such as ecotoxicology, life cycle analysis, environmental applications of nanomaterials, and regulatory and policy issues. Abstract submission is now open for oral and poster presentations.

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

1. **Li, Zheng, et al. 2007. "Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes." Environmental Health Perspectives 115(3): 377-382.** Abstract: http://www.ehponline.org/docs/2006/9688/abstract.html

Synopsis:

- Building upon previous research that demonstrated persistent accumulation of carbon nanotube aggregates in the lung and rapid formation of pulmonary granulomatous and fibrotic tissues following intratracheal or pharyngeal instillation of single-wall carbon nanotube (SWCNT) suspensions, this study is one of the first investigations of the potential cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes.
- Two sets of animal experiments were conducted, the first involving screening for systemic oxidative effects in two mice strains (HO-1 reporter transgenic mice and C57BL/6 mice) exposed to SWCNT (or ultrafine carbon black particles as a control material) in doses of 10-40 µg/mouse by single intrapharyngeal instillation (*i.e.*, pipetting of 60-µL SWCNT suspensions onto the base of the tongue of anesthetized mice). In these experiments, several markers for oxidative stress were measured, including activation of heme oxygenase-1 in lung, aorta, and heart tissue, aortic mitochondrial DNA damage, and aortic mitochondrial glutathione and protein carbonyl levels. In the second set of experiments, which were designed to evaluate the effects of chronic SWCNT exposures on atherosclerosis progression, apolipoprotein E knockout (APOE-/-) mice (i.e., mice prone to development of spontaneous hypercholesterolemia and atherosclerosis) were exposed by pharyngeal aspiration to a medium dose of SWCNT (20 µg/mouse) via multiple exposures (once every other week for 8 weeks). Two dietary regimens were employed in these experiments, one in which mice were

fed a regular chow diet and a second in which they were fed a high-fat chow diet.

- The study investigators observed a dose-dependent increase in oxidative vascular damage among SWCNT-exposed mice, as demonstrated by increased heme oxygenase (HO)-1 gene activation and mitochondrial alterations including mitochondrial DNA damage in the aortic tissue. In comparison, mice exposed to the ultrafine carbon black control particles did not show evidence of mitochondrial DNA damage in aortic tissue at comparable doses.
- Although SWCNT exposures did not modify the lipid profiles of the exposed APOE-/- mice and plasma levels of several inflammatory mediators known to play a role in atherosclerosis were not found to be elevated in SWCNT-exposed mice, the study investigators observed evidence of atherosclerosis progression, and specifically accelerated plaque formation in the aorta and brachiocephalic artery, in the mice fed the high-fat (*i.e.*, atherogenic) diet.

Implications:

- These study findings demonstrate the potential for SWCNTs, under certain conditions, to have the potential to influence cardiovascular disease progression. The study authors concluded that "Taken together, the findings are of sufficient significance to warrant further studies to evaluate the systemic effects of SWCNT under workplace or environmental exposure paradigms."
- These study findings for SWCNT are consistent with findings from epidemiologic and experimental studies of ambient particulate matter (PM) that have reported positive associations between ambient PM, and ambient ultrafine particles specifically, and adverse cardiovascular outcomes, as well as evidence of atherosclerosis in PM-exposed test animals.
- Although these findings are suggestive of the systemic toxicity of SWCNTs, the extrapolation of these study results to actual human exposures remains unclear at this point. Uncertainties involve not only animal-to-human extrapolations but also the use of intrapharyngeal instillation rather than inhalation exposures, the tendency of the SWCNTs to agglomerate, and the relationship of the dosing levels to potential inhalation levels.
- As discussed by the study authors, there remains uncertainty regarding the mechanism for the observed atherosclerosis progression, but study findings suggest that mitochondrial distress rather than inflammation may play a likely role. There remain outstanding questions as to whether SWCNTs are translocating from the lung into the systemic circulation and are causing direct cardiovascular endothelial dysfunction, or are instead indirectly inducing cardiovascular effects, such as through release of mediators in the lung into the systemic circulation or through platelet activation in the lung circulation. The study authors indicate that studies in progress, including those involving labeled SWCNTs as well as a detailed analysis of lung platelet activation, may provide further mechanistic information.

2. Maynard, AD and Aitken, RJ. 2007. "Assessing exposures to airborne nanomaterials: current abilities and future requirements." Nanotoxicology 1(1): 26-41.

Abstract: http://www.informaworld.com/smpp/content~content=a776419006~db=all~order=page

Synopsis:

- Given research findings on the toxicity of nanoscale materials that indicate that the hazard potential of these materials may not be best-represented by mass concentration measurements alone (*i.e.*, the "mass paradigm"), the study authors explore the applicability of different physical exposure metrics to a range of particle class/attribute combinations for both airborne nanometer-scale particles (nanoparticles) and nanometer-structured particles (nanostructured particles). Following this assessment, they review currently available techniques to measure exposures against three relevant metrics (particle number, surface area, and mass concentration), and, given the inability of existing techniques to effectively make routine personal exposure measurements of engineered nanomaterials, propose an approach to developing new exposure monitoring instruments.
- Through a systematic analysis whereby the utility of various exposure metrics are assessed for combinations of particle classes (*e.g.*, spherical or compact particles, high aspect ratio particles, complex non-spherical particles, compositionally heterogeneous particles, homogeneous aggregates, heterogeneous aggregates, *etc.*) and attributes thought to be relevant to determining potential health impact (*e.g.*, size, shape, surface area, surface chemistry, composition, solubility, *etc.*), the study authors demonstrate how the traditional mass-based measurement approach to health-related aerosol exposure measurements will not be appropriate in all exposure situations for airborne nanomaterials. Further, by highlighting circumstances where such exposure metrics as particle number, surface area, and mass concentration measurements will be of high utility, Maynard and Aitken show that there is no single method for monitoring nanoaerosol exposures that is universally relevant to all nanomaterials.
- The study authors review available techniques for measuring nanostructured aerosols, focusing on devices capable of measuring particle number, size distributions, surface area, and mass concentration. Although the study authors show that there already exist a range of sophisticated tools capable of measuring nanostructured aerosols exposures against these key exposure metrics,

they highlight the limitations of available techniques, most notably their general lack of applicability for making the routine personal exposure measurements necessary to ensure workplace safety.

- To meet the pressing need for a device capable of making routine personal exposure measurements, the study authors propose the development of a universal aerosol monitor capable of making simultaneous personal measurements for particle number, surface area, and mass concentration that is sufficiently inexpensive to support widespread use. The study authors discuss desirable attributes of such a device, including simultaneous measurement and data logging of particle number, surface-area, and mass concentration, size-selective aerosol sampling, personal exposure monitoring, real-time and time-averaged exposure capabilities, and low cost.

Implications:

- Although available toxicity and exposure data are limited in nature, there is a growing body of evidence that indicates that no single exposure metric, including the traditional mass-based paradigm for measuring airborne particle exposure, is likely to be universally applicable to assessing exposures and the potential for harm of the wide range of nanomaterial classes and particle types.
- As discussed by the study authors, there remains uncertainty regarding the most appropriate strategy for assessing nanoaerosol exposures, but there is evidence that measurements of aerosol number, surface area, and mass concentration will provide useful information for characterizing exposure to a wide range of nanomaterials. The study authors highlight the benefits of techniques capable of making combined measurements of two or three of these exposure metrics.
- While the authors propose the development of a universal aerosol monitor, the technical feasibility of such a device, the time to develop a reliable, well-validated product, and its costs remain uncertain. Thus, it is likely that scientists and regulators will continue to rely on existing methodologies for perhaps several years.
- In addition to their proposal that a universal aerosol monitor be developed, the study authors also suggest modifications to existing techniques and instruments to refine their capabilities for measurement of nanoaerosol exposures. In particular, although recognizing uncertainties associated with the sensitivity of these methods for measurements of nanoaerosol exposure, Maynard and Aitken suggest that particle size selective inlets could be developed for existing mass concentration techniques, including filter-based personal samplers and the real-time, static Tapered Element Oscillating Microbalance (TEOM®), to restrict sampling and measurement to only particles less than 100 nm.
- Although Maynard and Aitken conclude that "the current state-of-the-art of aerosol science is sufficient to provide solutions for developing a universal aerosol monitor," they emphasize that targeted research and method development is critical for converting this potential into commercially viable instruments.

In Other News

Nanosafe2

http://www.nanosafe.org/

Nanosafe2 is a project funded by the European Commission. It is aimed at the safe and sustainable production and use of nanomaterials. There are four subproject areas and the primary deliverables of these areas include the development of methods for nanotoxicity evaluation, the development of monitoring devices and personal protective equipment, and analysis of regulatory issues. The project is also publishing a semi-annual newsletter, which can be found at its website, on the work being done through the project

Coming In the Next Issue

- An update on the City of Cambridge's (Massachusetts) activities pertaining to potential nanotech regulation
- Review of a new research study investigating the role of nanoparticles in contributing to cellular heavy metal uptake

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