



Gradient CORPORATION EH&S Nano News

Volume 2, No. 07

www.ehsnanonews.com

October 2007

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

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Recent Government Briefs

Nanosciences and Nanotechnologies: An Action Plan for Europe 2005-2009, First Implementation

<http://cordis.europa.eu/nanotechnology/actionplan.htm>

The European Commission (EC) is among the world's largest public investors in nanotechnology and is making efforts to retain a strong presence in this sector. To preserve this status, the EC has issued a progress report on its nanoscience policy making and funding initiatives from 2005 to 2007. This is part of an effort to increase private investment of nanotechnology in its member states. The report highlights funding increases to various research projects and nanotechnology-dependant infrastructure. It also details the EU's efforts to increase nanotechnology programs in academia, address knowledge gaps related to human health and safety, and develop initiatives to increase public awareness and acceptance of nanotechnology. The report also addresses weaknesses, such as a shortage of private investment in research and industrial innovation, lack of leading interdisciplinary structures, and risks of duplication and fragmentation in current research efforts. The EC also calls for proposals for the establishment of a central location that will provide decision-makers with dynamic assessments of scientific and market developments.

Review of the Office of Research and Review of the Office of Research and Development's Safe Pesticides/Safe Products Research at the US Environmental Protection Agency

<http://www.epa.gov/osp/bosc/pdf/sp2072307rpt.pdf>

The Board of Scientific Counselors (BOSC), an advisory body that reviews and advises US EPA's major research programs, has issued a report recommending that the Agency strengthen its coordination with other key agency science programs to improve its research on nanotechnology exposure and health impacts. BOSC describes US nanotechnology research as being in a category of "high priority that exceeds resources available," meaning that nanotechnology research requires immediate additional funding. It calls on US EPA to rapidly develop its own research program in nanotechnology and encourage other funding organizations internationally to work in this area. BOSC also notes that nanotechnology receives little mention in US EPA's multi-year plan, even though other government reports describe the implications of nanotechnology as "virtually unknown." Last, BOSC describes US EPA's nanotechnology budget (US\$8 million) as inadequate, since it cannot address research issues described in a previous agency white paper.

Reports, Reviews, White Papers, and Books

Where Does the Nano Go? End-of-Life Regulation of Nanotechnologies

By Linda K. Brigglin and John Pendergrass, of the Project on Emerging Technologies, Woodrow Wilson Center for International Scholars

http://www.wilsoncenter.org/index.cfm?topic_id=166192&fuseaction=topics.event_summary&event_id=267182

This article addresses the regulatory aspects of nanomaterials entering the waste stream or at the end of their life cycle. The authors state that the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) is broad enough to give US EPA authority to regulate potential releases of nanoparticles into the environment, and that the cleanup standards and processes in the statute are broad enough to apply to cleanups of nanomaterials. They also note, however, US EPA would be limited to cleanup and could not recover costs from responsible parties. The authors also found that the current Resource Conservation and Recovery Act (RCRA) regulations cover potential nanowastes, even though using mass as a determinant of regulatory coverage is not

necessarily appropriate for nanomaterials. They conclude that both RCRA and CERCLA, in their current state, are broad enough to be used to regulate nanomaterial waste and products at the end of their life cycle. They recommend US EPA further invest in researching nanomaterial fate and transport, conduct outreach and education with the private sector on how current laws apply to nanomaterials, and conduct wider research to determine if existing nanomaterials could be considered hazardous wastes. They also advise the private sector to apply current RCRA regulations to nanomaterial production, take steps to avoid future liability, and collaborate with government and academia to promote future research of nanomaterial fate and transport.

Formulating the Problems for Environmental Risk Assessment of Nanomaterials

Owen, R, Handy, R. 2007. "Formulating the Problems for Environmental Risk Assessment of Nanomaterials." *Environmental Science and Technology* 41(16):5582-5588. http://pubs.acs.org/subscribe/journals/esthag/41/i16/html/081507viewpoint_owen.html

This viewpoint article discusses the potential strategies for identifying problems in nanoparticle risk, and how those problems should be addressed. The authors note that while exposure to and risk of nanomaterials is actively being researched, formulation of future problems posed by nanomaterials and research prioritization is sometimes overlooked. Owen and Handy observe that even over a small span of time, scientists' concerns have shifted from more far-fetched concerns (e.g., self-replication of nano-robots) to the potential toxicological issues discussed today. They state the need for how future problem formulation should proceed. The authors discuss which environmental media should receive research priority. They stress that even though nanomaterials are recognized as a potential source of biological exposure, there may be other exposure scenarios that may be either critical or irrelevant. Last, the authors indicate that a coordinated, worldwide initiative is required to properly set up a framework for nanoparticle risk assessment. They note that several initiatives and programs have become available for policy makers, but also point out there are still several lingering questions on how to prioritize and standardize nanoparticle risk assessment.

Upcoming Meetings and Conferences

Nanotechnology and Health: Evidence and Impact
<http://www.sph.umich.edu/riskcenter/2007%20Symposium.htm>
Ann Arbor, Michigan; Oct. 25-26, 2007

Presented by the University of Michigan Center for Risk Science and Communication, this conference will bring together leading scientists and policymakers to examine the emerging field of nanotechnology, its potential impact on human health, and the growing debate over whether

to regulate nanotechnology products. Keynote speaker Christine Todd Whitman, former Governor of New Jersey and Administrator of the US Environmental Protection Agency (2001-2003), will examine nanotechnology through her address, "Risky, Riskier, Riskiest: The Pitfalls, Perils, and Possibilities for Policymakers." Other national and international scientific and policy experts, including Gradient Principal Perti (Bert) Hakkinen, will explore the implications, challenges, and opportunities provided by this emerging technology; Dr. Hakkinen will examine nanotechnology through his address, "The European Perspective on Risk, Science, Policy, and Practice."

Nanoparticles for European Industry II

London, United Kingdom, October 24-25, 2007
<http://nano.org.uk/conferences/nanoparticles2007/prog.htm>

Presented by the UK-based Institute of Nanotechnology, this conference brings together corporate, academic, and private research interests active in the responsible development and use of nanoparticles for industrial uses. Speakers and discussion panels will cover topics such as nanoscale manufacturing, nanoparticle measurement and standardization, regulatory considerations, and toxicological issues.

2nd Annual Nanotech World Conference

Boston, Massachusetts, USA, November 13-14, 2007
<http://www.selectbiosciences.com/conferences/nanobiotech2007/>

Select Biosciences is sponsoring the Nanotech World Conference, which covers topics such as drug discovery, drug delivery, and commercial aspects of nanobiotechnology. Features will include contributions from invited distinguished faculty, an exhibition workshop, and exhibitions by nanotech suppliers.

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

Yang, R.S.H., et al. 2007. Persistent tissue kinetics and redistribution of nanoparticles, quantum dot 705, in mice: icp-ms quantitative assessment. *Environmental Health Perspectives* 115(9): 1339-1343. Abstract: <http://www.ehponline.org/docs/2007/10290/abstract.html>

Synopsis

- Due to their unique properties such as autofluorescence, Quantum Dots (QD) show great potential for medical applications including in vivo biomedical imaging; however, little is known about their disposition, elimination, or health consequences in the human body.
- This study was conducted to assess the tissue disposition and pharmacokinetics in mice of QD705, a commercially

available QD with a diameter of about 13 nm, consisting of a cadmium-tellurium (CdTe) core, a zinc sulfide (ZnS) shell, and an inert biologically-compatible polymer coating. The methodology involved a single IV injection and estimation of blood and tissue kinetics up to 28 days post-exposure, determination of mass balance at 1 and 28 days post-exposure, and localization in major target organs based on fluorescence microscopy and inductively coupled plasma-mass spectrometry (ICP-MS).

- The authors found that the plasma half-life of QD705 was short (18.5 hrs), but that QD705 accumulated and even continued to increase through the study period in the spleen (4.8-5.2% of the administered dose), liver (29-42% of the administered dose), and kidney (1.5-9.2% of the administered dose).
- Mass balance recoveries at both the 1- and 28-day periods were near 100%, indicating that all QD705s remained in the body and that excretion in the urine or feces was practically non-existent.

Implications

- Based on the study findings that indicate that QDs may have a very long biological half-life on the order of weeks or even months and the known mammalian toxicity of common metalloid core materials such as cadmium, lead, and selenium, there is the potential for toxicity from the QD metalloid cores following degradation of the QD coatings. Given remaining uncertainties regarding the potential toxicity of various QD types, additional research is needed to better understand the potential release of metals from QD metalloid cores and dependence of QD toxicity on physicochemical properties such as size, charge, concentration, outer coating, and mechanical stability.
- These findings suggest that precautionary measures, including thorough safety evaluations, should be exercised prior to widespread medical use of QDs. Although caution is advised based on these findings, further study is needed to improve our understanding of the mechanisms underlying the observed accumulation of QD705 in the spleen, liver, and kidneys and to confirm these findings for other QD types and animal species.
- Given the direct injection of QDs in these experiments, their relevance to other exposure routes, such as inhalation of QDs or dermal contact with QDs in the workplace, is very uncertain. However, these findings suggest that additional study is needed to understand the kinetics and tissue distribution of QDs for other potential exposure routes, such as inhalation.
- As suggested by the authors, it may be beneficial for researchers of the synthesis and formulation of QDs to investigate possible modifications to QD physicochemical properties that enhance their excretion.

Sayes, C. M., et al. 2007. "Comparative

pulmonary toxicity assessments of C60 water suspensions in rats: few differences in fullerene toxicity in vivo in contrast to in vitro profiles." Nano Letters 7 (8): 2399-2406.

Abstract: <http://pubs.acs.org/cgi-bin/abstract.cgi/nalefd/2007/7/i08/abs/nl0710710.html>

Synopsis:

- The cytotoxic effects of water-soluble fullerenes have previously been shown to depend on their surface derivatization status. In vitro testing showed a much greater toxicity of underivatized C₆₀ (nono-C₆₀) as compared to fully derivatized C₆₀(OH)₂₄. The aim of the present study was to determine the toxicities of aqueous solutions of these two species in vivo.
- Rats were given intratracheal instillations of nano-C₆₀, C₆₀(OH)₂₄, or alpha-quartz particles (positive control) at doses of 0.2, 0.4, 1.5, or 3.0 mg/kg, in aqueous suspension. Toxicity endpoints were measured at 1 day, 1 week, 1 month, or 3 months post-exposure, and included the following: pulmonary cytotoxicity and inflammation, oxidative stress, airway and lung parenchymal cell proliferation, and histopathology of lung tissue.
- Cytotoxicity of either fullerene water suspension (FWS) was not different from controls (vehicle alone) as measured by the presence of lactate dehydrogenase, micro-total protein, and alkaline phosphatase in the bronchoalveolar lavage fluids (BALF) of treated rats. All cytotoxicity parameters were significantly higher in the alpha-quartz -treated rats. Pulmonary inflammation, as measured by the number of neutrophils in BALF, increased in both FWS groups at day one only, then returned to control values. Values for the positive controls remained significantly higher throughout the time course. Some oxidative stress was evident in the nano-C₆₀ group at 1.5 and 3.0 mg/kg at 1 day and three months, as measured by lipid peroxidation in BALF. No other treatment groups had increased lipid peroxidation values, and none of the groups had increased concentrations of glutathione in BALF.
- Proliferation of airway and lung cells, as measured by the percent of immunostained cells taking up BrdU, was increased only in the positive controls. In the histopathological studies, no adverse effects of either FWS were noted, whereas the positive controls exhibited signs of dose-dependent inflammation, including increased numbers of neutrophils, foamy alveolar macrophage accumulation, and lung tissue thickening.

Implications:

- In contrast to the results of in vitro toxicity studies by the same authors, FWS caused little significant adverse effects to lung tissue when administered to rats in vivo. Inflammation was transient and reversible, and there was no evidence of altered histopathology. Some lipid

peroxidation was noted in the nano-C₆₀ group, but this did not correlate with any increase in glutathione production, another indicator of oxidative stress.

- There was very little difference in the effects of the nonderivatized fullerene, nano-C₆₀, and the hydroxylated fullerene, C₆₀(OH)₂₄. This is also in contrast to previous investigations in which C60(OH) was far less toxic than nano-C₆₀ as measured in vitro.
- The authors note that in vitro assays for toxicity of nanoparticles will need to be further developed in order to correlate more closely with toxicity resulting from in vivo exposures.
- It has been proposed that nanomaterials may be engineered for safety based on toxicity data. The authors note that this concept may be premature based on the discrepancies between in vitro and in vivo exposure outcomes.

Guest Contributor

By Dr. Wolfgang G. Kreyling and Dr. Manuela Semmler- Behnke

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Do Nanoparticles Stay Where They Got Into the Body?

Novel nanomaterials are finding a wide variety of environmental, consumer, and technical (including medical) applications, leading to increased intended and incidental human and environmental exposure. Many reports world-wide have recommended the need for proactive risk management able to define exposure risks of nanomaterials and guide regulatory policy. As nanotechnologies will play an important role in the growth of the European economy and application of nanoscience has the potential to bring significant societal benefits (e.g. nanomedicine), it is imperative to develop validated tools that will enable nanotechnology competitiveness while protecting the health and safety of the society and the environment.

In fact, materials at the nano-scale exhibit new physical and chemical characteristics which can be very different from those of bulk material; this opens wide horizons for new development and many new applications that principally create sustainability because they are saving of energy and material resources. Nanotechnology involves the design and production of nanomaterials, i.e. having nano-scale size at least in one dimension (< 100 nm). Nanomaterials are now being used for, or being developed for, a variety of environmental, medical, cosmetic, food, electronic, energy, and other technological applications. Clearly, nanotechnology will play an important part in the growth of the future economy. Globally, nanotechnology funding in 2006 was approximately US\$ 12.4 billion. Although the current market for nanotechnology products is less than \$500 billion, it is estimated to reach a market size of \$2.9 trillion across the value chain by 2014.

Due to this exponentially growing use of nanomaterials, both

increasing intended and incidental human and environmental exposure will be inevitable. As for any other new material, there are potential risks of exposure to nanomaterials during their entire life cycle; production, distribution, use and application, consumer safety, and waste disposal. The potential adverse effects from exposure at any stage of the life cycle are still largely unknown (Maynard *et al.* (2006) *Nature*, 444, 267; Barnard (2006) *Nature Materials*, 5, 245).

It is clear that the explosion of interest in nanotechnology is leading to the production of many novel nanosized particles and nanomaterials, which could potentially lead to a dramatic increase in human and environmental exposure. Historically, epidemiology and then subsequent experimental observations have shown a correlation between PM2.5 including ultrafine particles (diameter less than 100 nm when present as environmental pollutants such as traffic derived particulate air pollution) and adverse reactions that lead to poor health (WHO Air Quality Guidelines 2007). Toxicology studies using model carbon, TiO₂, or polystyrene ultrafine particles clearly demonstrated that smaller particles have more potential to induce disease mechanisms including oxidative stress and inflammation that can cause or exacerbate pre-existing illness not only in the respiratory tract but also in other organ systems, e.g. cardio-vascular and central nervous system (Oberdörster *et al.*, 2005; Donaldson *et al.*, 2005a+b).

Effects of inhaled ultrafine particles on non-respiratory organs raises the question about possible mechanisms. One would be that nanoparticles (NP) can cross the respiratory barrier and enter blood circulation, thus having access to secondary target organs. Indeed, while a growing body of reports confirms that there is translocation of NP into blood circulation not only across the lung membrane but also across the gastro-intestinal epithelium and possibly across the skin, the amount of the translocated fraction, the transport mechanisms and the rate-determining parameters are under current debate. There is agreement that, under normal conditions – excluding high dose exposure or toxic particle exposure or pharmacologically tailored particles - micron-sized particles are not likely to be translocated towards the systemic circulation – as was reviewed earlier by us (Kreyling & Scheuch, 2000). More recently others and we have reviewed the translocation data of NP (Oberdörster *et al.*, 2005; Kreyling *et al.*, 2006a+b) and emphasized that quantitative determination of translocation requires a full account of the biokinetics of sufficiently stable NP. These data suggest that a small fraction (usually < 1% and only for very small NP < 10%) of the NP delivered to the lungs or gut is translocated into circulation and accumulated subsequently in secondary target organs such as liver, spleen, kidneys, brain, and heart. Data also indicate higher translocation rates for smaller NP, and they show a dependence on different surface coatings. Currently we are systematically varying a number of these nanoparticle parameters to obtain a quantitative understanding of their role on translocation. Interestingly even six months after a single one-hour inhalation exposure,

the NP were still detectable in secondary target organs (Semmler et al., 2004), which raises the question as to the extent to which extent NP can accumulate in secondary target organs during chronic exposure. Another question relates to the underlying mechanisms driving translocation and accumulation: it is very likely that NP rapidly form complexes with biomolecules and proteins immediately after incorporation rather than persisting as single entities; the biological compounds of these complexes may determine the rate of membrane crossing, circulation time and accumulation in secondary target organs and the biological compounds may change dynamically such that NP may not only use one biological ferry boat but also change them in different milieus.

The dramatically increasing multitude of next generation NP with very specific properties, multiple functionalities, and re-assembling features will present challenges to understanding the role of such properties on the biokinetic behaviour of NP and to the selection of NP with properties which are more advantageous in terms of lower doses to target organs and less adverse reactions than other NP. This biokinetic information will be the rational base for realistic dose-response relationships, for biological mechanistic analyses and for integral risk assessment of newly emerging NP in order to select safe NP.

This note on current knowledge and open questions on the biokinetics of incorporated NP illustrates both the urgent need for, and the potential future benefits of, bringing together all international expertise - across all disciplines relating to nanomaterials. Only in this way will it be possible to provide effective risk assessment and define validated tools for nanomaterial risk management for all those important societal nanotechnology applications foreseen in the future. The tailored design of new nanomaterials requires building in safety based on a sound scientific background from the very first design sketch, since this will prevent undesirable development and eventually necessary costly remediation efforts.

Coming In the Next Issue

New research on the effectiveness of different techniques to disperse nanoparticles for toxicity testing.

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