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Nanotechnology Law Report

Legal Issues Surrounding Nanotechnology & General Nanotechnology News & Events

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INSIDE THIS ISSUE

EPA Office of Inspector General to Evaluate Agency's Nanotechnology Efforts

The U.S. Environmental Protection Agency's Office of Inspector General (OIG) "helps the Agency protect the environment in a more efficient and cost effective manner. [It] consist[s] of auditors, program analysts, investigators, and others with extensive expertise" who are tasked with evaluating EPA's ability to deliver on key Agency policies. Risk Policy Report ran an article in October indicating that EPA's OIG intended to assess EPA's nanotechnology efforts in FY 2009.

We tracked down the underlying document ,which indicates that EPA OIG intends to conduct an "[a] ssessment of EPA's Efforts to Monitor, Evaluate, and Act on Threats from the Production, Use and Disposal of Nanotechnology Products/Nanomaterials."

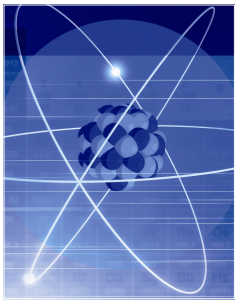
Nano-Mesothelioma False Alarm

For those who are interested, below is the abstract of our new article published in the fall edition of NANOTECHNOLOGY LAW & BUSINESS. *You can find the full article at: www.nanolabweb.com.*

A Nano-Mesothelioma False Alarm

In May 2008, a scientific study (the "Poland Study") was published in Nature Nanotechnology—which sparked a rash of popular media claims that like asbestos, exposure to carbon nanotubes may cause mesothelioma. In this article, a team led by lawyer John Monica evaluates the Poland Study in a potential litigation context to determine its significance, if any, in legally establishing that the inhalation of multiwalled carbon nanotubes ("MWCNTs") causes mesothelioma. After first considering the reliability of the Poland Study's design and execution, they conclude that it would not be admissible in a court of law because it fails Daubert standards. Specifically, they argue that: (i) the design and execution of the Poland Study are not generally accepted in the scientific community for the purposes offered; (ii) in order to reach the conclusion that inhalation of MWCNTs may cause mesothelioma, an expert would have to use the Poland Study in such a manner as to extrapolate from an accepted premise to an unfounded conclusion; and, (iii) the Study's authors failed to adequately account for obvious alternative explanations (confounders), including surface chemistry, sample contamination, sample commingling, spontaneous formation of granulomas, and possible mouse colony infections.

For Good Measure: Standards for Nanotechnology Measurement and Characterization



This fourth article in a series contributed by ANSI on standards for the nanotechnology community addresses the development of specifications for measurement, characterization, and test methods that will provide a common reference point for material manufacturers and their customers.

Measurement and characterization standards fly under the radar, affecting our lives in innumerable ways – from the number of miles driven to work to the paper loaded in the office printer. To imagine daily activities without these concepts would be nearly impossible, but that is exactly the challenge faced by scientists and manufacturers in the nanotechnology community.

For the growing number of industries that work with or are affected by nano-materials, consistent and globally accepted methods for testing, measurement, and characterization will provide a common reference point. By establishing a baseline to determine the starting properties of materials, these standards can facilitate meaningful comparisons of manufacturing and research results from different organizations and labs, and help to form a basis for the measurement of additional material properties.

When the American National Standards Institute (ANSI) Nanotechnology Standards Panel (NSP) first convened in September of 2004 to discuss priority recommendations for nanotechnology standardization, participants earmarked metrology, methods of analysis, and test methods as areas needing urgent attention. In particular, guidelines for particle size and shape, as well as particle number and distribution, were considered critical.

These needs are being addressed by the International Organization for Standardization (ISO) through its Technical Committee (TC) 229, Nanotechnologies, Working Group (WG) 2, Measurement and Characterization. Convened by Japan under the Japanese Industrial Standards Committee (JISC), WG 2 focuses on the development of standards for consistent descriptions, assessment, and test methods for nanotechnologies, taking into consideration the need for metrology and reference materials.

U.S. participation in ISO/TC 229 WG 2

U.S. participation in ISO/TC 229 and its Working Groups is centered in the U.S. Technical Advisory Group (TAG) to ISO/TC 229, chaired by Clayton Teague, director of the National Nanotechnology Coordination Office. The TAG, which is administered by ANSI, is organized into Working Groups that mirror their efforts on the scope of each TC 229 WG.

The U.S. mirror group for WG 2 is led by Dr. Ray Tsui of Motorola. The TAG WG plays an important role in establishing ANSI's positions on the issues addressed in the group with the help of experts from the industry, government, and academia.

Several other U.S. organizations actively participate in the both the international and domestic WG 2 work efforts, including the National Institute of Standards and Technology (NIST) and the National Aeronautics and Space Administration (NASA), as well as Honeywell, Hyperion Catalysis, and others.

Guidance Documents in Progress

Representative of its efforts over the past three years, WG 2 is currently developing 10 work items; most involve single-walled or multi-walled carbon nanotubes, and how to characterize them using specific instrumentation methods. Four of these work items are led or co-led by the United States:

- ISO/Approved Work Item (AWI) Technical Specification (TS) 10797, Nanotubes – Use of transmission electron microscopy in walled carbon nanotubes (co-led by the U.S. and Japan)
- ISO/AWI TS 10798, Nanotubes – Scanning electron microscopy and energy dispersive X-ray analysis in the characterization of single walled carbon nanotubes (led by the U.S.)
- ISO/New Work Item Proposal (NP) TS 10812, Nanotechnologies – Use of Raman spectroscopy in the characterization of single-walled carbon nanotubes (led by the U.S.)
- ISO/AWI TS 11308, Nanotechnologies – Use of thermo gravimetric analysis in the purity evaluation of single-walled nanotubes (co-led by the U.S. and Korea)

"The activities in WG 2 are strongly coupled to the other efforts within ISO/TC 229," said Dr. Tsui. "The work of WG 1, Terminology and Nomenclature, defines the materials being measured, while the output from WG2 provides im-

portant information regarding intrinsic material properties and measurement methods that can be used by WG 3, Health, Safety, and Environment, and WG 4, Material Specifications."

This overlap is apparent in one work item that is currently in the domain of WG 3: Guidance on physico-chemical characterization of engineered nano-objects for toxicologic assessment. This document, being developed under U.S. leadership, will serve as a reference for characterizing nano-objects to be used in toxicology testing. WG 3 is presently creating toxicology guidelines as they relate to health and safety; WG 2 may join the effort to assist in the development of methods used to characterize toxicity.

Getting Involved in ISO/TC 229 WG 2

Participation in the U.S. TAG ISO/TC 229 Working Group is open to all nationally interested stakeholders. The TAG actively seeks participants who have expert knowledge in all aspects of nanotechnology measurement and characterization. To join the ANSI-accredited U.S. TAG for ISO/TC 229 or any of its WGs, contact Heather Benko (hbenko@ansi.org; 212.642.4912).

For more information on the U.S. TAG for ISO/TC 229, visit http://www.ansi.org/isotc229tag.

Stay Tuned: The last article in this series will introduce ISO/TC 229/WG 4, Material Specifications.

Massachusetts Interagency Nanotechnology Committee

Inside EPA is reporting that the Massachusetts Interagency Nanotechnology Committee is developing a set of "best practices" for labs and companies working with materials to protect nano-sector workers, the public, and the environment from potentially harmful exposures.

The interagency group was formed in April 2007, held one workshop on nanotechnology risks in November 2007, and announced plans to create a website as an information clearinghouse for nanotechnology. The proceedings have been published and are available for review, however, the on-line clearinghouse could not be located.

The best management practices are reportedly going through "internal review" and then will be revealed to "stakeholders" before full publication. The group plans to build its best management practices on knowledge gained from prior attempts, such as by NIOSH and the Nano Risk Framework.

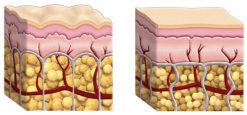
Another set of best management practices is another example of the level of attention nanotechnology continues to generate in state and local governments. These new publications also serve as an iterative process for the prior versions that may or may not be continually revised. By using prior attempts at developing best management practices, current versions can revise the information, and maintain developed institutional knowledge, in an effort to reach better sets of principles.

Nano EHS Database

The International Council on Nanotechnology (ICON) just released its newest project/tool, the Nano-EHS Database Analysis Tool. To quote ICON, "This web tool allows you to obtain a quick and thorough synopsis of our Environment, Health and Safety Database using two types of analysis. The first is a Simple Distribution Analysis (pie chart) which compares categories within a specified time range. The second type is a Time Progressive Distribution Analysis (histogram) which compares categories over a specified overall time range and data grouping period." The report will generate data in pdf or xls format as well as a report on available publications based on search categories, such as material studied, target receptors, and type of publication.

While the Tool only tracks ICON's database, it will likely become a valuable resource for literature searches. With the increased importance of regulatory schemes such as TSCA registrations, literature reviews will become more critical, even to smaller operations. ICON's Tool will assist those entities, and others seeking wide ranging topics addressing nanotechnology or nanomaterials.

Quantum Dot Skin Penetration Study



A recent *in vivo* study published in NanoLetters focuses on the impact of ultraviolet radiation on the ability of Quantum Dots (QD) to penetrate skin.

> *L. Mortensen, et al., "In Vivo Skin Penetration of Quantum Dot Nanoparticles in the Murine Model: The Effect of UVR," NanoLetters, Vol. 8, No. 9, pp. 2779-2787 (August 2008).*

The article begins by noting that "[n]anoparticles (NP) are commonly used in sunscreens and other cosmetics, and since consumer use of sunscreen is often applied to sun damaged skin, the effect of UVR on NP skin penetration is a concern due to potential toxicity;" and "[t]he question of whether or not NP can penetrate the healthy stratum corneum skin barrier *in vivo* remains largely unanswered."

The authors acknowledge that there are conflicting results from recent studies in this area, which they attribute to different researchers using different nanoscale materials with different sizes/diameters. The authors point out that the inconsistent results of prior studies "highlight the need for standardization of experimental techniques if ex vivo skin models are to be useful."

Despite the authors' stated concern with possible dermal penetration of NP contained in cosmetics and sunscreens, they chose to test a nanoscale material that is not used in any cosmetic or sunscreen – Quantum Dots.

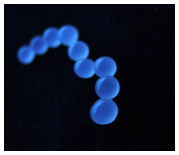
The authors explain:

> We selected to investigate QD, as they posses ideal characteristics for in vivo experimentation including broad excitability, narrow emission bandwidth, high fluorescence quantum yield, photostability, and ease of surface functionalization. Moreover, QD are of a similar size to TiO2 NP used in sunscreen applications, they intrinsically generate ROS species, and the carboxyl terminated QD have a similar negative oxide surface chemistry to the TiO_2 and ZnO raw materials often used in sunscreen applications.

Critics of the study point out that there are no lack of manufacturers selling the very type of nanoscale zinc oxide and titanium oxide used in consumer cosmetics and sunscreens. Quantum dots are very remote cousins to these particles. Why not test the substances themselves rather than a surrogate?

Regarding the animals used in the experiment, the researchers selected 6-7 week old SKH-1 hairless, albino mice. The QD mouse application vehicle was a solution of 75% glycerol/25% carboxyl QD Stock Solution (pH=9.0 borate buffer, 8µm QD). One half of the mice received an acute single UVR dose, which was administered using UVA Sun 340 lamps (320-400 nm (UVA)) (290-320 nm (UVB)).

The scientists found increased QD penetration for 8-hour and 24-hour treatment conditions after UVR exposure. However, "[m]ost strikingly, under no circumstances is there evidence for massive QD penetration, even for UVR exposed mice 24 [hours] after QD application."…"[N]one of the penetration observed was at a very high level."



The scientists conclude that "[t]hese studies demonstrate the importance of skin condition to effect the penetration of QD nanoparticles…in the…mouse model. We have shown that QD work their way between corneocytes of the stratum corneum and penetrate deep in the epidermis and dermis of an *in vivo* model with UVR penetration exacerbation….The minimal QD penetration observed in our study on barrier intact (non-UVR exposed) skin suggests the preponderance of current literature suggesting TiO_2 and ZnO NP used in commercial sunscreens exhibit limited penetration in layers below the lower SC."

Registration of Carbon Nanoscale Materials Required Under REACH

The EC's 2006 Registration, Evaluation, Authorisation and Registration of Chemicals ("REACH") regulations place "the responsibility for the management of the risks of [chemical] substances with. . .[the companies that] manufacture, import, place on the market or use [the] substances in the context of their professional activities." Guidance on Registration, Guidance for the Implementation of REACH, European Chemicals Agency, Version 1.3, May 2008, at p. 12.

To this end, REACH requires companies manufacturing or importing chemical substances in quantities greater than one ton per year to register those substances before they "can be manufactured, imported or placed on the market." As part of these requirements, "manufacturers and importers need to collect or generate data on the substances

and assess how risks to human health and environment can be controlled by applying suitable risk management measures." This can often be an expensive and time consuming process.

Providing some relief in certain circumstances, Article 2(7)(a) of Regulation (EC) No. 1907/2006 provides that certain substances are exempt from registration under REACH because "sufficient information is known about these substances [such] that they are considered to cause minimum risk because of their intrinsic properties." These substances are listed in REACH Annex IV.

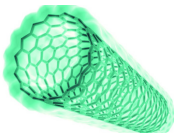
On October 8, 2008, the EC removed carbon and graphite from Annex IV "due to the fact that the concerned Einecs and/or CAS numbers are used to identify forms of carbon or graphite at the nano-scale, which do not meet the criteria for inclusion in" Annex IV. We first posted on this possibility last June.

Commission Regulation (EC) No. 987/2008 of 8 October 2008 Amending Regulation (EC) No. 1907/2006 of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annexes IV and V.

This decision is consistent with the U.S. Environmental Protection Agency's reasoning that nanoscale substances with new molecular identities -- such as fullerenes and carbon nanotubes -- are considered new chemical substances for purposes of premanufacturing notice submissions under the Toxic Substances Control Act.

Carbon Nanotubes and TSCA Registrations

US EPA issued a Federal Register notice stating that the Toxic Substances Control Act (TSCA) registration requirements are "potentially applicable to carbon nanotubes." EPA confirmed its position that CNTs are "chemical substances distinct from graphite or other allotropes of carbon listed on the TSCA inventory." The bottom line is stated succinctly by EPA: "Many CNTs may therefore be new chemicals under TSCA Section 5."



Consequently, those companies that use or import CNTs will have to ensure that such materials are registered on the TSCA inventory before manufacturing commences or importation occurs. To determine if a particular type of CNT is already on the inventory, manufacturers and importers can submit a bona fide intent to manufacture or import letter to EPA under 40 CFR 720.25, and EPA will respond as to the particular listing. Further, "sometime after March 1, 2009, EPA anticipates focusing its compliance monitoring efforts to determine if companies are complying with TSCA section 5 requirements for carbon nanotubes."

The message here could not be clearer: if you are manufacturing or using CNTs, you must comply with TSCA. EPA admits that some of the confusion over listing/not listing may be due to prior communications, but this notice removes all confusion. EPA indicates that it is reviewing "several" premanufacture notices for carbon nanotubes, so it is likely many of the "common" CNTs will be registered soon. In the meantime, expect CNTs to be treated as "new" chemicals under TSCA.

New Communication from the EU Concerning Nanomaterials

The following was provided by Luca Escoffier, a PhD student at Queen Mary, University of London, a Transatlantic Technology Law Forum (TTLF) fellow at Stanford writing his dissertation on patenting medical nanotechnology inventions, and currently a visiting fellow at the University of Washington. He is also the author of the Nanomedicine and IP Blog and watches European developments for us.

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE - REGULATORY ASPECTS OF NANOMATERIALS

In June 2008, the European Commission, in light of the aims and principles contained in the Communication "Nanosciences and nanotechnologies: an action plan for Europe 2005 – 2009," which asked for a full compliance when using and applying nanosciences and nanotechnologies with all existing and future rules on health, safety, workers' protection, and environment, adopted a Communication also reflecting the commitment to adapt the current regulation to such current and future uses and applications. The Communication is a document covering nanomaterials currently in production and/or placed on the market. The Communication does not regard naturally occurring or unintentionally produced nanomaterials or nanoparticles. Please see the text of the Communication and accompanying document for more information.

EPA Consent Order for Multi-Walled Carbon Nanotubes

We previously reported on a press release by Thomas Swan & Co. Ltd. of the United Kingdom indicating that the company had recently entered into a PMN consent order with the EPA under the Toxic Substances Control Act ("TSCA") concerning one of its multi-walled carbon nanotube (MWCNT) products. Barring an unusual coincidence, it appears that EPA has recently published a redacted version of the Swan Consent order.

The order makes it clear that the PMN was submitted pursuant to § 5(a)(1) of TSCA and that it covers a MWCNT product. A dditionally, the consent order places several requirements on the manufacturer. Specifically, the manufacturer is required to:

1. Deliver 1 gram of the MWCNTs to EPA with a copy of MSDS for the product;
2. Conduct "90 day inhalation toxicity study in rats with a post exposure observation period of up to 3 months, including bronchoalveolar lavage fluid ("BALF") analysis (OPPTS 870.3465 or OECD 413);
3. Submit material characterization data within six months (see below);
4. Ensure that employees "use gloves impervious to nanoscale particles and chemical protective clothing;" and
5. Ensure that employees "use a NIOSH-approved full-face respirator with an N-100 cartridge while exposed by inhalation in the work area."

Regarding the second requirement, the consent order also provides the manufacturer with an opportunity to submit toxicity testing data under the Agency's new Nanoscale Material Stewardship Program as an alternative to the 90-day mouse inhalation test: "If, for example, a consortium of companies commit to testing a representative set of MWCNT for subchronic mammalian toxicity, EPA may consider waiving the triggered testing requirement. EPA would be willing to facilitate the process in coordination with other ongoing health effects testing for MWCNT nationally and internationally. EPA would consider accepting the results of such testing in lieu of triggered testing in this order."

Regarding material characterization information, EPA is requiring the manufacturer to submit the following within six months:

- Type of multi-walled carbon nanotube (concentric cylinders or scrolled tubes; number of walls/tubes);
- Configuration of nanotube ends (e.g., open, capped);
- Description of any branching;
- Width/diameter of inner most wall/tube (average and range);
- Carbon unit cell ring size and connectivity;
- Alignment of nanotube along long axis (straight, bent, buckled);
- Hexagonal array orientation used in the manufacture of the nanotube;
- Particle size of catalyst used in the manufacture of the nanotube;
- Molecular weight (average and range); and
- Particle properties: shape, size (average and distribution), weight (average and distribution), count, surface area (average and distribution), surface-to-volume ratio, aggregation/agglomeration.

Finally, manufacturers of MWCNTs (other than Thomas Swan) will be interested in two of EPA's general legal conclusions expressed in the consent order:

> "EPA is unable to determine the potential for human health effects from exposure to the PMN substance. EPA therefore concludes, pursuant to § 5(e)(1)(A)(i) of TSCA, that the information available to the Agency is insufficient to permit a reasoned evaluation of the human health effects of the PMN substance."
>
> "In light of the potential risk to human health posed by the uncontrolled manufacture, import, processing, distribution in commerce, use, and disposal of the PMN substance, EPA has concluded, pursuant to § 5 (e)(1)(A)(ii)(I) of TSCA, that uncontrolled manufacture, import, processing, distribution in commerce, use, and disposal of the PMN substance may present an unreasonable risk of injury to human health."

No doubt other MWCNT manufacturers will feel the need to file PMN's for their products similar to Thomas Swan given the language of the consent order.

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