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Recent Government Briefs

EPA States Carbon Nanotubes Will Be Regulated Case-by-Case

<http://www.epa.gov/fedrgstr/EPA-TOX/2009/June/Day-24/t14780.pdf>

On June 24, 2009, the US EPA promulgated significant new use rules (SNUR) under Section 5(a)(2) of the Toxic Substances Control Act (TSCA) for 23 chemical substances, including single- and multi-walled carbon nanotubes (CNTs) which were the subject of premanufacture notices (PMN). According to the decision, there is concern that CNTs will have lung health effects based upon data for poorly soluble particulates and that there may be lung irritation based on particle size. Under a SNUR, persons who intend to manufacture, import, or process any of these substances for an activity designated as a significant new use must notify US EPA at least 90 days before commencing that activity. US EPA will then have an opportunity to review and evaluate the data submitted prior to the manufacturing, importing, or processing of a listed chemical substance for the described use. Following the results of the evaluation, US EPA may then regulate the prospective manufacturers, importers, or processors before the new use occurs. Any potential regulation will be only that which is warranted pursuant to TSCA. The final rule describes how a "significant new use" is defined as the absence of wearing NIOSH-approved full-face respirators with N-100 cartridges, impervious gloves, and protective clothing when workers are handling the CNTs, including both multi- and single-walled carbon nanotubes. The specific respirator cartridge that is required filters 99.97 percent of airborne particles 0.3 millionths of a meter

(μm) in diameter. US EPA states that the issuance of the SNUR for CNTs does not signify that the chemical substance is listed on the TSCA. Guidance on how to determine if a chemical substance is on the TSCA Inventory is available at the link below.

Information about the TSCA Inventory can be found at:

<http://www.epa.gov/opptintr/newchems/pubs/invntory.htm>

Reports, Reviews, White Papers, and Books

Safety of Manufactured Nanomaterials

By Organisation for Economic Co-operation and Development

<http://www.oecd.org/dataoecd/15/25/43290538.pdf>

The Organisation for Economic Co-operation and Development (OECD), an inter-governmental organization, has published a new report on exposure assessment and exposure mitigation for manufactured nanomaterials from a workshop held in October 2008 in Frankfurt, Germany. This document provides information on the outcomes of discussions related to the safety of manufactured nanomaterials, and it includes a summary of the plenary presentations that were given at the Workshop on Exposure Assessment and Exposure Mitigation [ENV/JM/MONO(2009)18]. The report reviews exposure measurement techniques and discusses how standard measurement processes have to be both agreed upon and calibrated. Sections of the report also review safety measures and control strategies specific to nanomaterial manufacturing. Participants concluded that the OECD should consider establishing a database with information on exposure measurement and exposure mitigation measures for nanomaterials.

This document is one of over a dozen reports in the series of [Safety of Manufactured Nanomaterials](#) documents published by the OECD.

Nanotechnology and *In Situ* Remediation: A Review of the Benefits and Potential Risks

By B. Karn, T. Kuiken, M. Otto

<http://www.ehponline.org/members/2009/0900793/0900793.pdf>

A paper on the use of nanoparticles for *in situ* remediation, written by Barbara Karn and Martha Otto (both affiliated with the US EPA) and Todd Kuiken (a research associate at

the Project on Emerging Nanotechnology), discusses the potential benefits and risk of such activities. The paper reviews current practices; research findings; societal issues; potential environment, health, and safety implications; and possible future directions for nanoparticle remediation. The authors conclude that *in situ* nanoparticle remediation has the potential to reduce the overall costs of cleaning up large scale contaminated sites by reducing cleanup times, eliminating the need for treatment and disposal of contaminated soil, and potentially reducing contaminant concentrations. The authors also note that the potential risks of nanoparticle remediation remain poorly understood. The article will appear in an upcoming issue of *Environmental Health Perspectives*.

New European Union Repository of Nanotoxicology Information

<http://ec.europa.eu/research/infocentre>

The European Union is developing an open-access repository of published data on health and environment effects following exposure to nanoparticles. The Nano Health Environment Commented Database (NHECD) project, funded under the EU's Seventh Framework Programme (FP7), is planned to be compatible with existing databases and capable of analysis at the metadata level. According to the project coordinator, Professor Oded Maimon from Tel Aviv University, both private industry and public institutions will be able to access data on understanding the impact of nanoparticles on health and the environment. The project aim is to create a novel layer of information for every paper in the database, which includes metadata and scientific information that is extracted from each paper using the developed mining algorithms, and subsequent rating of the paper using a specific algorithms.

Upcoming Meetings and Conferences

4th International Conference on Nanotechnology – Occupational and Environmental Health

<http://www.ttl.fi/Internet/English/Information/International+meetings+and+symposia/Nanoeh2009/>

August 26-29, Helsinki, Finland

Hosted by the Finnish Institute of Occupational Health, in collaboration with several other European organizations, the International Conference on Nanotechnology – Occupational and Environmental Health (NanoEH2009) will consider the global health and safety issues of engineered nanoparticles, focusing on occupational and environmental health. NanoEH2009 will bring together scientists and other experts interested in the safety and health implications of nanoparticles – occupational and environmental health experts; leaders in the industry of nanotechnology; employers in the field of nanotechnology; national, regional, and international policy-makers; and organizations funding

nanoparticle research. Presentations, posters, and educational sessions will cover many topics, including the commercial applications of nanomaterials; nanoparticles in the ecosystem; research breakthroughs; exposure assessment and characterization; policy; occupational exposure; and toxicology.

Nanocarbons: From Physicochemical and Biological Properties to Biomedical and Environmental Effects

<http://www.esf.org/index.php?id=5254>

September 8-13, Acquafredda di Maratea, Italy

This conference, sponsored by the European Science Foundation, will convene scientists of diverse backgrounds who work with carbon nanotubes (CNT), including physicists, chemists, and biologists. The first part of the conference will focus on the properties of CNT: synthesis and characterization, chemistry, and biomedical applications. The second part will focus on the biological and environmental effects of CNT: toxicity, ecotoxicity, and the life cycles of nanoparticles.

Nanotech Europe 2009

<http://www.nanotech.net/>

September 28-30, Berlin, Germany

Nanotech Europe 2009, formally called Nanotech Northern Europe, encompasses a conference and exhibition of 36 sessions and 180 speakers, the Lux Research Executive Research Forum, and matchmaking meetings. Attendees will include researchers, industry representatives, policy-makers, and investors. The broad scope of the conference includes sessions on electronics, photonics, materials and functional surfaces, health and biomedicine, energy, safety (*i.e.*, toxicology, risk management, and regulatory issues), and public and private investment opportunities. Nanotech Europe is organized by Agent-D, a consortium of Nanotechnology Competence Centers in Germany; Technische Universität Berlin; and the German Federal Ministry of Education and Research.

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

1. Kreyling, WG; Semmler-Behnke, M; Seitz, J; Scymczak, W; Wenk, A; Mayer, P; Takenaka, S; Oberdörster, G. 2009. "Size dependence of the translocation of inhaled iridium and carbon nanoparticles from the lung of rats to the blood and secondary target organs." *Inhal. Toxicol.* 21(S1):55-60.

Abstract: <http://www.ncbi.nlm.nih.gov/pubmed/19558234>

Synopsis:

- Although many studies have demonstrated that some nanoparticles (NP) have the potential to cause adverse health effects, the mechanisms underlying these effects are not yet understood. While many effects are observed at the point of entry, most commonly the tracheobronchial region, systemic effects have also been observed. A critical component for evaluating potential cause-effect relationships for systemic effects is understanding extrapulmonary distribution of NPs. The aim of the study by Kreyling *et al.* was to evaluate extrapulmonary distribution of NPs, using chain-type aggregates of iridium (Ir) and elemental carbon (EC), using Ir-NPs with count median diameter (CMD) between 15-20 nm and 70-80 nm, and EC-NPs with CMD between 22-25 nm.
- ¹⁹²Ir radiolabeled aerosols of iridium and elemental carbon NPs were generated using a spark generator. The NP aerosols were administered by ventilating young adult, male WKY/Kyo@Rj rats (four rats for each aerosol type) *via* an endotracheal tube for one hour. An endotracheal tube was used to administer the NP aerosols in order to avoid deposition of the NPs in the extrathoracic region or on the animals' fur, both of which could result in gastrointestinal exposures that could complicate understanding systemic distribution of NPs deposited in the pulmonary region. Following NP exposure, rats were housed in metabolic cages for 24 hours in order to quantify NPs in the urine and feces. Prior to being sacrificed, bronchoalveolar lavage (BAL) fluid was collected from the rats to quantify NPs. Rats were then anesthetized and sacrificed by exhaustive exsanguination. The portion of blood removed by exsanguination was estimated according to body weight, and the portion of blood remaining in the organs and tissues was estimated based on both body weight and residual blood volume following exsanguination. Radioactivity was quantified for the BAL, blood, secondary target organs, muscles, bone and skin. The secondary target organs included the lungs, liver, spleen, kidneys, heart, and brain.
- The majority of NPs deposited in the tracheobronchiole region were cleared into the GI tract within 24 hours. For NPs deposited in the lung, more than 90% of the 20 nm Ir-NPs were retained in the lung, and more than 95% of the 80 nm Ir-NPs and 25 nm EC-NPs were retained in the lung. For the NPs distributed outside the lung, the majority were in the soft tissues other than the secondary target organs. The 20 nm Ir-NPs were distributed fairly evenly among the individual secondary target organs (*i.e.*, lungs, liver, spleen, etc.) – each containing approximately 0.5% of the total deposited in the lung, with approximately 2% remaining in the blood. Less than 0.1% of the total 80 nm Ir-NPs deposited in the lung distributed to the secondary target organs, with about 0.1 remaining in the blood. The fraction of 80 nm Ir-NPs distributed to the brain was smaller than for other secondary target organs. For the EC-NPs deposited in the lungs, approximately

0.2% distributed to the liver, and less than 0.1% distributed to each of the other secondary target organs and the blood.

Implications:

- For NPs deposited in the lung, only a very small fraction distributed to the secondary target organs – less than 0.5% for the 20 nm Ir-NPs and less than 0.1 % for the 80 nm Ir-NPs and the 25 nm EC-NPs. Moreover, the results from this study indicate that uptake and distribution of NPs from the lung is a function of both size and particle type. Whereas uptake and distribution of the 20 nm Ir-NPs was greater than for the 80 nm Ir-NPs, uptake and distribution of the 25 nm EC-NPs was more comparable to that of the 80 nm Ir-NPs. That uptake from the lungs decreases with size is significant in that, under actual inhalation exposure conditions, aerosolized NPs may aggregate to larger sized particles before reaching the distal lung, which would hence reduce their ability to translocate from the lungs to secondary target organs.
- The results from this study, which used a radio-isotope with no natural background in biological systems, indicates that a much smaller fraction of NPs translocates from the lung than what the researchers of this study estimated previously using ¹³C-labeled carbon NPs. Considering that only a portion of inhaled NPs would reach the distal lung, uptake, distribution, and subsequent exposure of secondary target organs to certain types of inhaled NPs may be minimal. Although NPs cleared from the tracheobronchiole region could potentially be absorbed from the GI tract, previous studies by these researchers indicate that GI absorption of NPs is negligible.
- This study demonstrated that certain types of NPs can translocate from the lung to secondary target organs, such as the liver, heart, kidney, and brain. What remains to be determined is whether presence of NPs in these secondary target organs is associated with adverse health effects, and if so, at what concentrations.

2. Bello, D; Hsieh, SF; Schmidt, D; Rogers, E. 2009. “Nanomaterials properties vs. biological oxidative change: Implications for toxicity screening and exposure assessment.” *Nanotoxicology*. DOI: 10.1080/17435390902989270

Abstract: <http://www.informaworld.com/smpp/content~content=a911901403~db=all~jumptype=rss>

Synopsis:

- Given the large variety of engineered nanomaterials (ENMs) that are commercially available and pose challenges to the capacity of current toxicity testing approaches, there is a critical need for the development and validation of robust, inexpensive, and high-throughput methods for screening ENM toxicity. A number of investigators have proposed biological oxidative demand (BOD) as a possible screening metric, given that BOD is well recognized as a key mechanism of toxicity for particulate matter. In this study, Bello *et al.* evaluate the utility of the “Ferric reducing ability of serum (FRAS)” assay

as a screening tool for quantifying BOD and for assessing ENM exposure. Using a diverse set of 19 commercially important ENMs, analyses were conducted to investigate the relationship between specific ENM physico-chemical properties and FRAS-measured BOD.

- As described by the investigators of the study, the FRAS assay is responsive to multiple oxidative reaction mechanisms, and thus quantifies BOD potential by measuring total changes in the antioxidant pool of human serum. The FRAS assay was applied to 19 different ENMs that included a series of carbon blacks differing in primary particle sizes and surface areas; a series of fullerenes differing in purity; a series of titanium dioxides that included nano- and micron-sized anatase and rutile; a series of single and multi-wall carbon nanotubes (SWCNTs and MWCNTs, respectively) varying in length and purity; H₂O₂-oxidized single wall carbon nanohorns (SWCNHs-ox); nano alumina; nano silver; and micron-sized crystalline silica. Extensive material characterization data were collected on the ENMs, with measurement of specific surface area (SSA), transition metals content, organic carbon content, surface charge, and crystallinity. BOD was calculated as the difference in total antioxidant capacity (expressed in trolox equivalent units, or TEUs) for unexposed versus ENM-exposed serum, with authors classifying ENMs into three categories: no activity (FRAS value 8.6-20.2 $\mu\text{m TEUs}$), moderate activity (FRAS value 31.1-165.7 $\mu\text{m TEUs}$), and high activity (FRAS value 706.2-1,725.4 $\mu\text{m TEUs}$).
- The study reported a dramatic range in FRAS results that spanned over two orders of magnitude, with the oxidized SWCNHs-ox and two SWCNTs (long and short) having the highest BOD values (1,725, 1,376, and 1,236 $\mu\text{m TEUs}$, respectively). In contrast, several ENMs were found to have negligible BOD values, including three out of the four TiO₂ samples, two out of the three fullerene samples (the refined and purified samples, but not the high-soot fullerene sample), and the nano-alumina and crystalline silica samples, indicating low toxic potential of these ENMs *via* oxidative mechanisms.
- Within the various ENM series, distinct trends in FRAS BOD responses were observed. For example, the two SWCNTs and the SWCNHs-ox were found to elicit statistically greater BOD responses than the MWCNT samples. Within the tested MWCNTs, the short MWCNT sample was found to have a BOD response more than four times greater than its long MWCNT counterpart, while the industrial-grade MWCNT sample was found to have a BOD response that was approximately two to 16 times less than all other CNTs. Among the carbon black samples, there was a linear relationship between BOD and primary particle size/specific surface area.
- Correlational and multivariate analyses showed two ENM properties, namely specific surface area (SSA) and transition metals content, to be the strongest predictors of FRAS-measured BOD, explaining 93% of observed BOD. The relationship between SSA and BOD was found to be especially strong within the C-based series of ENMs (e.g., CNTs, carbon black, and fullerenes), while no association between BOD

and SSA was found for the TiO₂ series. Several properties, including surface charge and organic carbon content, were not found to be associated with BOD.

Implications:

- As emphasized by the authors, acellular FRAS BOD should be viewed as an indicator of the oxidative damage potential of ENMs, with higher FRAS BOD responses indicating a greater potential for toxicity. The validity of FRAS BOD as a screening tool for ENM toxicity is supported by observations in the literature, given that all of the ENMs showing positive FRAS results in this study have also been shown to exhibit toxic responses in published *in vitro* and animal studies. While the authors demonstrate how FRAS testing has utility for placing ENMs into broad tiers of materials corresponding to different levels of priority for further evaluation and testing, further research is needed to characterize the nature of the relationship between FRAS BOD and the degree of toxicity in organisms.
- Because ENMs can potentially cause adverse health effects *via* other non-oxidative mechanisms, it is important to keep in mind that a negative FRAS BOD result does not necessarily equate to low *in vivo* toxicity. Similarly a high FRAS BOD does not necessarily mean high *in vivo* toxicity, because of the possible role of anti-oxidant mechanisms in limiting toxicity. Therefore, it is important that the FRAS BOD assay be used as one of a battery of screening tools and that additional validation be conducted on the method.
- Consistent with other recent studies that provide evidence for a threshold of effects for ENMs, these study findings, and specifically the minimal BOD findings for ENMs with low specific surface area (<300 m²/g) and transition metal contents (<100 ppm), are suggestive of a possible biological threshold. Additional research is needed to determine the broader significance of these findings.
- By highlighting findings that provide support for FRAS BOD as providing an “integrated response to several physico-chemical parameters, including specific surface area, transition metals, redox-active organics, etc.,” the study investigators propose BOD as a potential exposure metric, among others, for characterizing airborne ENM exposures.

Coming In the Next Issue

A review of nanomaterial case studies, including nanoscale titanium dioxide in water treatment and topical sunscreen.

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