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Robert Clear, Ph.D.

Chair of Berkeley California's Community Environmental Advisory Commission (CEAC)

Recent Government Briefs

(Cambridge, MA). Following recent actions in Berkeley, California, the Cambridge (Massachusetts) City Council recently announced their intentions to consider enactment of a law regulating use of nanoparticles in research and manufacturing. The Cambridge City Council decided on January 8, 2007, to request that the Cambridge Director of Environmental Health study the Berkeley law and recommend whether Cambridge should pursue a similar statute. One month earlier, Berkeley became the first US city to regulate nanoparticles, with the Berkeley City Council voting to amend its hazardous materials law to require researchers and manufacturers to disclose their use and/or manufacture of nanoparticles. The Berkeley ordinance requires disclosure of "the current toxicology of the materials reported, to the extent known, and how the facility will handle, monitor, contain, dispose, track inventory, prevent releases and mitigate such materials." Cambridge, which has a strong high-tech community, was the first city to regulate recombinant DNA research over three decades ago. For more information, see http://www.cambridgema.gov/cityclerk/PolicyOrder.cfm?item_id=16916.

(UNEP). On February 5, the United Nations Environment Programme (UNEP) released its annual report of the global environment, the Global Environment Outlook (GEO) Year Book 2007, which highlighted the need for assessment of potential nanotechnology risks and "swift action" by policy makers given the current mass-production of some nanomaterials. Although the GEO Year Book emphasized

the far-reaching societal, economic, and environmental benefits of nanotechnology, UNEP stressed the need for more research, and greater cooperation between public and private sectors, to identify potential environmental, health, and socio-economic hazards and develop science-based frameworks to manage the risks and uncertainties. The report cautioned that "It is not clear whether current regulatory frameworks are adequate to deal with the special characteristics of nanotechnology... A balanced approach is required to maximize benefits while minimizing risks." For more information, see www.unep.org/geo/yearbook/yb2007/

Reports, Reviews, White Papers, and Books

Opinion on the Ethical Aspects of Nanomedicine

(Opinion No. 21) European Group on Ethics in Science and New Technologies to the European Commission (EGE)

http://ec.europa.eu/european_group_ethics/publications/index_en.htm

In its Opinion on the Ethical Aspects of Nanomedicine, the EGE acknowledges the vast potential for nanotech in medicine and human health, while also identifying numerous actions that must be taken on the national and EU level that pertain to this topic. For example, the EGE calls for the establishment by institutions that already evaluate the safety of medical and other products of similar measures and assessments to confirm the safety of nanomedical products and devices. In addition, the EGE asserts the need for transparency with the public. The authors suggest that surveys be conducted to understand the public's perception of the benefits and risks of nanotech applications in medicine. The expansive Opinion also addresses legal and legislative issues in nanomedicine and the need for interdisciplinary research in this field.

Addressing Potential Environmental and Occupational Health and Safety Risks of Nanotechnology

American Public Health Association, Policy Statement

<http://www.apha.org/advocacy/policy/policysearch/default.htm?id=1329>

At the end of last year, the APHA published its policy statement on nanotechnology. The Statement reviews the need for a better understanding of the potential health and safety implications of nanotech in the context of recent toxicologic and environmental research, products already on the market in the US, governmental funding of nanotech, and recent publications from regulatory bodies such as EPA and NIOSH. The APHA makes three specific requests. First, the authors urge that federal funding be increased in order to study such areas as interventions to prevent

exposures to nanomaterials. They also call for the adoption of manufacturing practices to protect human and environmental health from exposures to nanomaterials, unless there are data to show the releases/exposures are safe; the authors indicate the usefulness of a voluntary program similar to the High Production Voluntary Program. Finally, APHA requests that federal agencies do the following: require the generation/submission of data to assess the safety of nanomaterials in the environment and workplace; recommend “protective interim risk management measures” until a better understanding of the potential risks of nanomaterials is available; and assure the health, safety, and education of workers, consumers, and the public through regulatory actions.

Upcoming Meetings and Conferences

Nanotoxicology 2007 – 2nd Informa Conference

Venice, Italy; April 19-21, 2007

<http://www.informaworld.com/smpp/nanotoxconference>

The theme of Informa’s 2nd conference on nanotoxicology is “Progress and Future Perspectives.” This meeting will cover recent scientific findings and cutting-edge ideas in nanotech – and their potential societal impacts. The target audience includes toxicologists, risk and exposure assessors, nanotech scientists, and those in industry and government agencies. Attendees can anticipate keynote speeches from renowned scientists as well as oral and poster presentations.

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. 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 nanoparticles dosimetry in the lung and exposure assessments of nanoparticles.

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

1. Magrez, A., et al. 2006. “Cellular toxicity of carbon-based nanomaterials.” *Nano Letters* 6(6): 1121-1125. Abstract: <http://pubs.acs.org/cgi-bin/abstract.cgi/nalefd/2006/6/i06/abs/nl060162e.html>

Synopsis:

- Despite recent progress in their synthesis and incorporation into potential applications such as advanced drug delivery systems and nanocomposites, relatively little remains known regarding the potential

health hazards of carbon-based nanomaterials (CBNs) such as carbon nanotubes. To help address these data gaps, this study investigated the cellular toxicity of three CBN types (carbon nanotubes, carbon fibers, and carbon nanoparticles) as a function of their morphology (*e.g.*, shape, size, and aspect ratio) and surface chemistry.

- *In vitro* tests, and specifically the mitochondrial function (MTT) assay, were performed using human lung-tumor cell lines to evaluate the effect on cell proliferation and cytotoxicity of three CBNs with different morphological properties, namely (1) multiwalled carbon nanotubes (MWCNTs), with an average diameter of 20 nm and aspect ratios (length: width) ranging from 80 to 90; (2) carbon nanofibers (CNFs), with a mean diameter of 150 nm and aspect ratios of 30 to 40; and (3) flakelike-shaped carbon nanoparticles (carbon black, obtained after grinding graphite) with aspect ratios of about 1 and size distributions ranging in the submicrometer range. CBNs were suspended in a strongly diluted gelatin solution to avoid aggregation at concentrations ranging from 0.002 to 0.2 mg/mL. In addition, a second set of experiments was conducted where the surface chemistry of the MWCNTs and CNFs was modified through the addition of carbonyl (C=O), carboxyl (COOH), and/or hydroxyl (OH) groups.
- The study investigators observed a dose-dependent cytotoxic response, with the number of viable cells decreasing as a function of the CBN dose for all CBNs tested. At the lower CBN doses (0.002 and 0.02 mg/mL), a clear CBN morphological dependence on cell toxicity was observed, with the number of viable cells decreasing according to the following pattern: carbon black > CNF > carbon nanotubes. These differences were found to diminish at higher doses (*e.g.*, 0.2 mg/mL).
- Significant reductions in numbers of viable cells were observed for the surface treated MWCNTs and CNFs, indicating the increased cytotoxicity of these modified CBNs. This effect of chemical surface treatment was observed to be larger for MWCNTs than CNFs.

Implications:

- These experiments showed that CBNs can cause cell proliferation inhibition and cell death at the tested concentrations, with the hazardous effect showing a morphological (*e.g.*, size and shape) dependence. In general, MWCNTs were found to be of lesser toxicity than the other two materials, namely carbon black and nanofilaments.
- Although these findings provide support for the toxicity of CBNs, further *in vitro* and *in vivo* research is needed to confirm these findings, to identify the mechanisms by which CBNs may cause cell death, and to help relate the concentrations in the cell line to human exposure conditions.
- These findings suggest that the toxicity of MWCNTs and CNFs can be enhanced through the addition of putatively “toxic” chemical groups to the particle surfaces. This is in

contrast to a previously published *in vitro* study of human dermal fibroblasts that reported reductions in cytotoxic responses and little change in mitochondrial activity with greater degrees of surface functionalization of single-walled carbon nanotubes.

- The authors concluded based on their findings that the health concerns of CBNs merit additional close scrutiny prior to pushing forward on their potential applications, such as advanced drug delivery.

2. Kandlikar, M., et al. 2007. "Health risk assessment for nanoparticles: a case for using expert judgment." *Journal of Nanoparticle Research* 9: 137-156. Abstract: <http://www.springerlink.com/content/d501p0520038t051/>

Synopsis:

- Risk assessment has proven to be a highly useful, objective tool for integrating exposure and health effects information and characterizing the potential for human health risk from toxic substances. Nanoparticles pose a significant challenge to risk assessment through the presence of both parametric uncertainties (*e.g.*, how precisely parameter or observational values are known) as well as major "structural" or "model" uncertainties involving the relationships between variables and the causal mechanisms themselves. This paper discusses tools that risk analysts can use to handle the large uncertainties inherent in today's nanoparticle risk calculations.
- The study authors classify the model uncertainties for risk assessments of nanoparticles into three general categories: (1) those resulting from physical and chemical characterization of nanoparticles including the choice of an appropriate exposure metric (*e.g.*, mass, surface area, number concentration); (2) those resulting from uncertainty in dose and health endpoints from different exposure routes; and (3) those resulting from a lack of understanding of toxicity mechanisms.
- As an example of a significant model uncertainty, the study authors highlight research that has demonstrated the potential importance of several exposure routes (*i.e.*, not only inhalation but also dermal uptake and ingestion) and the ability of nanoparticles to translocate to parts of the body (*e.g.*, from the alveolar region deep in the lungs into the interstitium, to the local and regional lymph nodes, into the circulatory system, into the central nervous system) that are not accessible to larger particle types and other well-studied toxic chemicals and carcinogens, thus effectively rendering existing physiological models of exposure and movement of particles within the human body insufficient and highly uncertain for nanoparticles. Furthermore, nanoparticles may thus have multiple health endpoints.
- The study authors present professional or expert

judgment as a useful tool for assessing relevant variables, characterizing model forms, and estimating model parameters. As discussed by the study authors, expert assessment can be useful for structuring problems, identifying key variables, assessing the sufficiency of the current level of expertise for calculating health risks, and examining relationships and influences between variables for piecing together the risk causal chain. In contrast to consensus committees, expert assessments can be useful for highlighting the degree of consensus and/or disagreement along different steps of the exposure-response paradigm, and quantifying the degree of scientific uncertainty at each step of risk causal chain.

Implications:

- As discussed extensively by the study authors, there are a number of major uncertainties that pervade each element of the exposure-response-risk paradigm for nanoparticles. The authors emphasize the need to grapple with these uncertainties, and offer expert assessment as a tool for risk assessors to handle and reduce levels of uncertainty.
- Risk assessments are frequently conducted in the absence of complete information, and the authors note the value of qualitative risk assessments in situations where it is not possible to conduct fully quantitative risk assessments.
- Although there will be uncertainties in their extrapolation to other types of nanoparticles and exposure scenarios, the authors highlight the need for epidemiological studies of occupational environments to provide quantitative health risk data for engineered nanoparticles.
- Since engineered nanoparticles can widely differ in a large variety of key properties such as morphology, chemical composition, and surface coatings, risk assessment methods will need to be developed to allow for extrapolation of findings for certain nanoparticle types and applications to other situations.
- Expert judgment on the level of consensus/disagreement for different parts of the exposure-response paradigm can help in research prioritization and budget allocation exercises.

Guest Author

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The right time is now.

Nuclear power? No. Genetically modified crops? Still no. How about nanotechnology? If recent history is any guide, it would not take much to get a "no" to nanotechnology too. When there are fortunes to be made, there is an incentive to view environmental protection, and health and safety issues, as costs to be avoided if at all possible. However, it might not take a very big incident to get a public backlash that could stall or hinder the development of nanotechnology.

Although it may seem to be a radical idea, early adoption of safety and environmental regulations that are recognized as effective by the public may actually be beneficial to the development of a nanotechnology industry.

Berkeley, California, is the home of the Lawrence Berkeley National Laboratory (LBNL), which is positioned to be a national center for the study of nanotechnology. The lab's Molecular Foundry is due to be available for research this year. LBNL will be doing basic research, which may inspire or draw start-up companies to the area. Berkeley's Community Environmental Advisory Commission (CEAC) has been in discussion with LBNL for the past two years, both with regards to the general issue of safety, and the more specific issue of the lab's plans with regards to nanotechnology. The CEAC has also attempted to keep abreast of national and state activity with regards to nanotechnology. There is still a lot that is unknown about nanoparticle properties and toxicity, and to a large extent this appears to be driving the state and national response, or rather the lack thereof. With the Molecular Foundry about to become operational, the CEAC was in a position analogous to contractors who have to install portapotties, because they cannot wait for the indoor plumbing. The environmental community has long proposed that the precautionary principle be used whenever knowledge about environmental impacts is incomplete. The city of Berkeley has in the past regulated hazardous materials based on the known chemical and toxicological properties of the material. The whole point of nanotechnology is that nanoparticles behave differently than bulk materials. The CEAC therefore proposed that nanoparticles be treated as new materials, whose toxicity and properties need to be established. Until their properties are established, the materials have to be treated as potentially toxic. Because we really don't know how toxic these new materials might be, the CEAC also eliminated the lower limit with regards to the quantity of material that triggers regulation. The city of Berkeley passed the CEAC's recommended ordinance, and the City's toxics manager is now soliciting input on minimally acceptable safe handling practices, and how to best structure reporting requirements.

The goal of Berkeley's nanoparticle ordinance is to provide health and environmental protection at a reasonable cost given our current incomplete knowledge about nanoparticles. Time may lead to a more refined ordinance, but for now the Berkeley ordinance provides a model for jurisdictions which probably have less access to expert knowledge about nanoparticles, yet suddenly are faced with an institutional or industrial desire to experiment with or produce them.

(Disclaimer: The above material is the personal opinion of the author, and not an official statement of opinion for CEAC, or the city of Berkeley.)

Coming Next Month

- Findings of fine & nanoparticle toxicity using *in vitro* vs. *in vivo* techniques

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