TOXICOLOGICAL SCIENCES 77, 3–5 (2004)
DOI: 10.1093/toxsci/kfh041

TOXICOLOGICAL HIGHLIGHT

Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles

Kevin L. Dreher[1]

National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC 27711

The articles highlighted in this issue are "Pulmonary Toxicity of Single-Wall Carbon Nanotubes in Mice 7 and 90 Days after Intratracheal Instillation" by Chiu-Wing Lam, John T. James, Richard McCluskey, and Robert L. Hunter (pp. 126–134) and "Comparative Pulmonary Toxicity Assessment of Single-Wall Carbon Nanotubes in Rats" by D. B. Warheit, B. R. Laurence, K. L. Reed, D. H. Roach, G. A. M. Reynolds, and T. R. Webb (pp. 117–125).

The microtechnology of the second half of the 20th century has produced a technical revolution that has led to the production of computers and the Internet and taken us into a dynamic emerging era of nanotechnology. This issue of *Toxicological Sciences* includes two articles, "Pulmonary Toxicity of Single-Wall Carbon Nanotubes in Mice 7 and 90 Days after Intratracheal Instillation" by Chiu-Wing Lam, John T. James, Richard McCluskey, and Robert L. Hunter (pp. 126–134) and "Comparative Pulmonary Toxicity Assessment of Single-Wall Carbon Nanotubes in Rats" by D. B. Warheit, B. R. Laurence, K. L. Reed, D. H. Roach, G. A. M. Reynolds, and T. R. Webb (pp. 117–125), related to a newly emerging area in toxicology. The studies by Lam *et al.* and Warheit *et al.* represent the first peer-reviewed comparative toxicological assessments of a specific type of manufactured nanoparticle called single-wall carbon nanotubes (SWCNTs). This highlight provides a brief overview of the emerging issue of manufactured nanoparticle risk assessment, highlights the results and contributions to this area by these companion articles, and places their contributions into perspective regarding the emerging issue of manufactured nanomaterial toxicology.

Nanotechnology has been defined by the interagency Subcommittee on Nanoscale Science, Engineering and Technology of the Office of Science and Technology as follows:

> Research and technology development at the atomic, molecular, or macromolecular levels, in the length of approximately 1–100 nm range, to provide a fundamental understanding of phenomena and materials at the nanoscale, and to create and use structures, devices, and systems that have novel properties and functions because of their small size. The novel and differentiating properties and functions are developed at a critical length scale of matter typically under 100 nm. Nanotechnology research and development includes integration of nanoscale structure into larger material components, systems, and architectures. Within these larger scale assemblies, the control and construction of their structures and component devices remain at the nanoscale. (National Research Council, 2002)

In an effort to coordinate nanotechnology and nanoscience research and application activities at the federal, academic, and private sectors, the National Nanotechnology Initiative was created in 2001 (National Research Council, 2002). In theory nanoparticles can be produced from nearly any chemical; however, most nanoparticles that are currently in use today have been made from transition metals, silicon, carbon (single-walled carbon nanotubes; fullerenes), and metal oxides (zinc dioxide and titanium dioxide). In many cases engineered nanoparticles exist as nanocrystals composed of a number of compounds such as silicon and metals (quantum dots) (Murray *et al.* 2000).

Manufactured nanoparticles display physicochemical characteristics and coatings that impart upon them unique electrical, thermal, mechanical, and imaging properties that are highly desirable for applications within the commercial, medical and environmental sectors (National Research Council, 2002; US Environmental Protection Agency, 2003; Masciangioli and Zhang, 2003). Potential occupational and public exposure to manufactured nanoparticles will increase dramatically in the near future due to the ability of nanomaterial to

Disclaimer: Information presented in this article has been reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and has been approved for publication. Approval does not indicate that the contents necessarily reflect the views and policy of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

[1] To whom correspondence should be addressed at MC B143-01, Pulmonary Toxicology Branch, Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, US EPA, 109 TW Alexander Drive, Research Triangle Park, NC 27711. Tel.: (919) 541-3691. Fax: (919) 541-0026. E-mail: Dreher.Kevin@epa.gov.

improve the quality and performance of many consumer products the public employs daily as well as the development of medical therapies and tests which will use manufactured nanoparticles. Currently, information describing the relative health and environmental risk assessment of manufactured nanoparticles or nanomaterials is severely lacking. Only recently have critical questions regarding the potential human health and environmental impact of manufactured nanoparticles or nanomaterials been raised (Dagani 2003; Colvin, 2003; National Science Foundation and US Environmental Protection Agency, 2003). A recent workshop cosponsored by the National Science Foundation and the US Environmental Protection Agency has identified a number of critical risk assessment issues regarding manufactured nanoparticles, such as

1. exposure assessment of manufactured nanoparticles;
2. toxicology of manufactured nanoparticles;
3. ability to extrapolate manufactured nanoparticle toxicity using existing particle and fiber toxicological databases;
4. environmental and biological fate, transport, persistence, and transformation of manufactured nanoparticles; and
5. recyclability and overall sustainability of manufactured nanomaterials.

The studies by Lam *et al.* and Warheit *et al.* highlighted in this issue of *Toxicological Sciences* are the first peer-reviewed comparative toxicological assessments of SWCNTs. SWCNTs have a very broad commercial application potential due to their superior mechanical, electrical, and magnetic properties. Both studies employ a comparative toxicological approach and intratracheal instillation route of exposure to examine the pulmonary toxicity of SWCNT in rodents. Lam *et al.* examined histopathological alterations in mice at 7 and 90 days following exposure to SWCNTs manufactured by different methods and containing varying amounts of residual catalytic metals. Carbon black and quartz particles were employed as low and high pulmonary toxicity particle controls, respectively. Lam *et al.* demonstrated that all three types of SWCNTs products induced dose-dependent lung lesions that were characterized by granulomas. Purified SWCNTs containing relatively low amounts of metal were able to induce pulmonary granulomas suggesting that metal contaminants alone were not causal. Close histological evaluation of the lung tissues suggested different fates and reactions of carbon black particles and SWCNTs following their pulmonary deposition. Carbon black–laden macrophages were found scattered in the alveolar space, while SWCNT-laden macrophages moved to centrilobular locations where they entered the alveolar septa with resulting epithelioid granuloma formation. Lam *et al.* concluded that under their test conditions and on an equal-weight basis that SWCNTs can be more toxic than quartz, a particle with recognized occupational health hazards associated with chronic inhalation exposures. The ability to extrapolate the pulmonary toxicity of SWCNTs using existing particle toxicity databases is questioned by the results of Lam *et al.* In current practice SWCNTs are classified as a new form of graphite on material safety data sheets provided by manufacturers of these nanoparticles. However, the data presented by Lam *et al.* suggest that extrapolations from graphite-based permissible exposure limits, set by the National Occupational Safety and Health Administration, may not be protective for exposure to SWCNTs due to their unique physicochemical properties and pulmonary toxicity.

Warheit *et al.* performed a more comprehensive comparative toxicity assessment of SWCNTs in rats by examining the ability of these nanoparticles to induce pulmonary inflammation as well as alter lung cellular proliferation, and pathology following intratracheal instillation of SWCNTs. Pulmonary granuloma formation was also observed by Warheit *et al.* following SWCNT exposure. In contrast to quartz particles, SWCNT-induced multifocal pulmonary granuloma formation occurred without evidence of ongoing pulmonary inflammation or cellular proliferation. The formation of pulmonary granuloamatus lesions appears to occur as a result of the lung's immune response to removal of foreign substances that are not easily degraded. Pulmonary granulomas have been observed in chronic beryllium disease, sarcoidosis, and hypersensitive pneumonitis (Du Bois *et al.* 1991). As noted by Warheit *et al.,* the finding of granulomas in the absence of pulmonary biomarkers of ongoing inflammation, cell proliferation, or cytotoxicity does not appear to follow the normal paradigm of toxic dusts such as quartz and silica suggesting a potentially new mechanism of pulmonary toxicity and injury induced by SWCNTs. The ability of SWCNTs to induce granulomatus lesions by a unique mechanism within the lung may be consistent with their physicochemical properties which impart to them enhanced structural properties but may also make them more persistent in biological and ecological systems. The bio-persistence of SWCNTs may be a significant occupational safety issue since chronic exposures to low levels of SWCNTs could be associated with adverse health effects (Maynard *et al.*, 2003).

At the present time products derived from emerging technologies are viewed by the public in a more demanding perspective from the standpoint of safety and environmental impact. In the case of nanotechnology, the potential for exposure to nanoparticles will increase as the quantity and types of nanoparticles used in society grow. The studies reported by Lam *et al.* and Warheit *et al.* in this issue of *Toxicological Sciences* provide our first insight into the *in vivo* toxicity of a specific type of manufactured nanoparticle, SWCNTs. These studies' results highlight several key health risk assessment issues associated with manufactured nanomaterial, such as the paucity of information on nanoparticle toxicology and exposure assessments as well as the extent to which nanoparticle toxicity can be extrapolated from existing particle and fiber toxicology databases. Recently, proactive multidisciplinary research initiatives have been initiated by the National Center for Environmental Research of the US Environmental Protection Agency and the National Toxicology Program, National Institute of Environmental Health, National Institutes of Health, to address the impact of nanoparticles on human health and the environment (National Center for Environmental Research, 2003; National Institute of Environment and Health, 2003). Hopefully these and other efforts will allow nanotechnology and nanomaterials to develop responsibly with a full appreciation of their health and environmental impacts.

REFERENCES

Colvin, V. L. (2003). The Potential Environmental Impact of Engineered Nanomaterials. *Nature Biotechnology*, 21(10):1166–1170.

Dagani, R. Nanomaterials: Safe or Unsafe? *Chem. & Eng. News*, April 28, 2003, pp. 30 – 33. http://www.cen-online.org or http://pubs.acs.org.

Du Bois, R. M., Holroyd, K. J., Saltini, C., and Crystal, R. G. (1991). Granulomas Process. pp 1925 – 1938. In The Lung, ed. R.G. Crystal, J. B. West, P. J. Barnes, N. S. Cherniack, E. R. Weibel. Published by Raven Press, NY.

Masciangioli, T. and Zhang W-X. (March 1, 2003). Environmental Technologies and the Nanoscale. American Chemical Society. *Envrionmental Science & Technology.* 102A – 108A.

Maynard, A.D., Baron, P.A., Shvedova, A.A., Kisin, E.R., and Catranva, V. (2003). Exposure to carbon nanotube material 1: Aerosol release during the handling of unrefined single walled carbon nanotube material. *Jour. Toxicology and Environmental Health*. In press.

Murray, C.B., Kagan, C.R., and Bawendi, M.G. (2000). Synthesis and characterization of monodisperse nanocrystals and close-packed nanocrystal assemblies. *Annu. Rev. Mater. Sci*. 30:545–610.

National Center for Environmental Research. (July 2003). Science to Achieve Results Program, "Impacts of Manufactured Nanomaterials on Human Health and the Environment. US Environmental Protection Agency. http://es.epa.gov/ncer/rfa/current/2003_nano.html

National Research Council (2002). Small Wonders, Endless Frontiers: A Review of the National Nanotechnology Initiative. pp. 12. Washington, DC, National Academy Press. www.nano.gov

National Science Foundation and U.S. Environmental Protection Agency (May 2003). Nanotechnology Grand Challenge in the Environment Research Planning Workshop, Session E: "Nanotechnology Implications in Health and the Environment". In press.

National Institute of Environment and Health, National Institutes of Health. Substances Nominated to the NTP for Toxicological Studies and Testing Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) on June 10, 2003. http://ntp-server.niehs.nih.gov/NomPage/2003Noms.html. http://ntp-server.niehs.nih.gov/htdocs/liason/Factsheets/FactsheetList.html.

US Environmental Protection Agency. (February 2003). Proceedings: EPA Nanotechnology and the Environmental: Applications and Implications STAR Progress Review Workshop. EPA Document Number: EPA/600/R-02/080.