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Smaller is not always better: nanotechnology yields nanotoxicology

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FORMER CALIFORNIA GOVERNOR Jerry Brown advocated the mantra that "small is beautiful." The paper by Shvedova et al., the current article in focus (Ref. [15](#), see p. L698 in this issue), suggests some less-attractive perspectives of this vision. Nanomaterials are receiving increasing attention for their promise as engineering and biomedical miracles. Unfortunately, their use may ultimately be limited because of concerns about toxicity ([14](#)). The fact that their size overlaps with the ultrafine particles (<0.1 μm) characteristic of urban air pollution confirms a basis for this concern. It has been well established that air pollution, in particular fine particles, can increase morbidity and mortality from pulmonary and cardiovascular causes with both long-term and immediate effects ([10–12](#)). Mechanistic studies in

rodents have demonstrated that inhaled ultrafine (nanometer range) particles distribute beyond the lung and can cause both pulmonary and systemic inflammation and promote blood coagulation within minutes to days of exposure (6–9). To date, human studies, limited to acute exposures, measuring both pulmonary and systemic inflammatory endpoints, have been inconsistent, perhaps in part attributable to variable particle sources (1–3, 13). None of these fine or ultrafine aerosols has previously been associated with the development of pulmonary fibrosis in either short or long-term studies. In this issue, Shvedova and colleagues (15) verify and expand upon preliminary reports (4, 16) to document substantial pulmonary toxicity, including fibrosis, from single-walled carbon nanotubes (SWCNT) in mice and go further to provide clues toward underlying mechanisms of toxicity.

The authors used a pharyngeal aspiration model and significantly lower doses of SWCNT (10–40 $\mu\text{g}/\text{mouse}$, ~ 0.5 mg/kg) compared with 5 mg/kg in rats or 500 $\mu\text{g}/\text{mouse}$ in previous studies (4, 16). The maximum dose used in this study extrapolates to 20 days' exposure at the current Occupational Safety and Health Administration (OSHA) standard. This standard is based on OSHA's existing graphite (same pure carbon composition but much larger molecules than the SWCNT) standard of 5 mg/kg respirable particles, the same as the standard for nuisance dust. In contrast to control materials of silica particles and ultrafine carbon black, the authors report that C57BL/6 mice developed significant early inflammation characterized by a dose-dependent increase in protein, lactate dehydrogenase, and γ -glutamyl transferase in bronchoalveolar lavage fluid, along with evidence of oxidative stress. A dose-dependent accumulation of neutrophils (*day 1*), lymphocytes (peak on *day 3*), and macrophages (peak at 7 days) was also observed, along with elevated levels of the proinflammatory cytokines $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ (*day 1*) and the fibrogenic mediator transforming growth factor ($\text{TGF-}\beta$) 1 (peak on *day 7*). Macrophage cell culture studies of SWCNT showed significant stimulation of $\text{TGF-}\beta$ 1 production with smaller effects on production of $\text{TNF-}\alpha$ and $\text{IL-1}\beta$, but no oxidative burst, nitric oxide production, engulfment of SWCNT, or apoptosis. A dose-dependent increase in airway resistance persisting for the length of the experiment (60 days) and reduced clearance of bacteria from the lungs of treated animals were also observed, suggesting clinically meaningful health effects. Of greatest concern, and consistent with prior studies, both granulomas, surrounding aggregates of SWCNT, and diffuse interstitial fibrosis, seemingly associated with more dispersed SWCNT, were identified, along with the lung function changes.

Granulomas formed within 7 days at sites of deposition

of the micrometer-sized SWCNT aggregates. This evidence of physiologically significant histopathological changes clearly indicates the potential of these nanomaterials for human toxicity at realistic doses. The OSHA standard described above must be reviewed in light of this accumulating evidence of mammalian pulmonary toxicity.

Granulomatous domination of diffuse interstitial pneumonia is uncommon, and once berylliosis, misattributed sarcoidosis, and the overwhelmingly biogenic, and uncommon, hypersensitivity pneumotitides are accounted for, it is distinctly uncommon. Although the differential diagnosis for granulomas is potentially long, foreign body reactions, uncommon as they are in occupational settings, seem more likely than a true hypersensitivity response in this case. However, the present studies also showed nongranulomatous interstitial fibrosis at sites distant from the aggregates, seemingly associated with dispersed SWCNT. This is highly novel since this fibrosis appears to result from mechanisms distinct from the chronic inflammation and alveolar macrophage activation typically associated with the development of such pulmonary fibrosis, as in the case of asbestos. That neither type of fibrosis was induced by the carbon black or the fine silica suggests that the changes, at least in this model, are specific to the SWCNT. Absent a true positive control, inflammation but no fibrosis from the silica exposure suggests the need for confirmation in an inhalation model.

On the basis of the data obtained with other nanomaterials, cardiovascular and coagulation endpoints should be sought in the next series of studies, ideally using inhalation rather than aspiration as the exposure route and also varying the chemical composition of the nanomaterials. As stated by the authors, the present studies suggest that workers exposed at the current permissible exposure level may be at risk of developing pulmonary fibrosis. Although worker exposure to SWCNT has not yet been demonstrated, a recent report of low overall exposure described more significant exposure associated with vortexing of SWCNT in a laboratory (5). Clinical surveillance of exposed workers for lung fibrosis should certainly be a present consideration.

In the earlier study by Warheit et al. (16), the effects of nanotubes were described as transient, nondose dependent, not progressive past 1 mo, associated with negative lavage and cell proliferation results, and characterized by nonuniform lesions with possible regression. The current study has resolved all of these concerns, concluding that there is significant toxicity at lower, and currently permissible, exposure levels. Although additional studies, particularly inhalation, are certainly indicated, the regulatory community needs to update their current assessment of these materials given the important new data presented in this paper.

▶ FOOTNOTES

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