broad variety of inorganic fibrous materials: fiber glass, mineral wool, and refractory ceramic fiber. Ongoing epidemiology studies of SVF manufacturing workers have provided very little evidence of harmful effects in humans. Research using rodents exposed by inhalation have confirmed that SVF pulmonary effects are determined by fiber dose (to the lung), dimension, and durability. Fiber dose over time is determined by fiber deposition and biopersistence in the lung. Deposition is inversely related to fiber diameter. Biopersistence is directly related to fiber length and inversely related to fiber dissolution and fragmentation rates. Inhaled short fibers (< 5μm) are cleared from the lung relatively quickly by mobile phagocytic cells, but long fibers (> 20 μm) persist until they dissolve or fragment. In contrast to asbestos, most of the SVFs tested in rodent inhalation studies are cleared rapidly from the lung and were innocuous. However, several biopersistent SVFs induced chronic inflammation, lung scarring (fibrosis), and thoracic neoplasms. Thus, biopersistence of fibers is now generally recognized as a key determinant of the toxicologic potential of SVFs. In vitro dissolution of fibers in simulated extracellular fluid correlates fairly well with fiber biopersistence in the lung and pulmonary toxicity, but several exceptions suggest that biopersistence involves more than dissolution rate. In vitro cell culture studies indicate that the biological effects of fibers are coordinated by a complex system of inter-cellular messengers and cytotoxic cell products; phagocytic lung cells appear to be central players. Research demonstrating the relationship between biopersistence and SVF toxicity has provided a scientific basis for hazard classification and regulation of SVFs. It is unclear whether the mechanisms of SVF lung clearance and toxicity apply to carbon nanotubes.

## 38 HOW THE PROGRESSION OF PULMONARY TOXICITY RESEARCH IS INFORMING COMPARISONS OF CNT WITH MINERAL FIBERS.

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Previously we reported that intratracheal instillation exposures to laser ablation-type single wall carbon nanotubes (SWCNT) in rats produced a non-dose-dependent series of multifocal granulomas; evidence of a foreign tissue body reaction. In addition, instillation of high-dose SWCNT produced some mortality, resulting from mechanical blockage of the upper airways by the agglomerated instillate. Other investigators have demonstrated similar granulomatous lesions in mice exposed to a variety of SWCNT-types. In our study in rats, we have noted that the development of these granulomatous lesions is not consistent with a normal dust-related paradigm, including adverse pulmonary reactions caused by cytotoxic dusts such as quartz particles or asbestos fibers. These lesions generally develop following lung inflammatory responses at the anatomical sites of bronchoalveolar junctions. In contrast, we observed the presence of SWCNT-nanorope-induced multifocal granulomas located primarily in the distal airways. As a consequence, we have questioned the physiological relevance of our findings following instillation exposures. Moreover, it is conceivable that due to the electrostatic nature and tendency of SWCNT to agglomerate into nanorope structures, instillation of SWCNT may produce very different pathological results when compared to exposures via the inhalation route. In contrast to SWCNT, chrysotile asbestos fibers are highly respirable, tend to fibrillate, and produce similar lung pathological responses following either inhalation or instillation exposures. The main criteria for the pathogenicity of chrysotile asbestos fibers is biopersistence concomitant with the length dimension, with chrysotile fibrils greater than 10 microns producing lung inflammation, fibrosis and tumors in rats. Indeed, the pathological sequelae of these pulmonary lesions are very different from those reported thusfar with exposures to SWCNT. This issue of similarities or differences in responses to SWCNT vs. asbestos can be reconciled following the implementation of inhalation toxicity studies in rats with aerosolized SWCNT samples.

## 39 COMPARISON OF PULMONARY RESPONSES TO SINGLE-WALLED *VS.* MULTI-WALLED CARBON NANOTUBES.

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Exposure of mice to purified single-walled carbon nanotubes (<0.25% iron) by pharyngeal aspiration resulted in a rapid but transient inflammatory response as well as an early onset and progressive fibrotic reaction. Labeling of single-walled carbon nanotubes with gold nanoparticles indicated that granulomas occurred at deposition sites of large agglomerates, while interstitial fibrosis was associated with deposition of more dispersed nanotube structures. Techniques were developed to improve the dispersion of single-walled nanotubes. Aspiration of this dispersed single-walled carbon nanotube sample resulted in greater interstitial fibrosis in the absence of granulomas. Aspiration of a dispersed preparation of gold-labeled single-walled carbon nanotubes resulted in rapid movement of nanotube structures into the alveolar interstitium and measurable translocation to systemic organs. Mice are currently being exposed by pharyngeal aspiration to a dispersed preparation of purified multi-walled carbon nanotubes. Results of these studies will be compared to those of single-walled carbon nanotubes to evaluate the effect of nanotube dimension (diameter) on pulmonary response. Single-walled carbon nanotubes were also evaluated in vitro to determine their ability to generate reactive species and stimulate oxidant production from macrophages. In vitro assays were not very good predictors of the in vivo fibrogenic potential of single-walled carbon nanotubes. In conclusion, results indicate that it would be prudent to implement strategies to limit exposure to carbon nanotubes in the workplace.

## 40 TOXICITY OF CARBON NANOTUBES AND ITS IMPLICATIONS FOR OCCUPATIONAL AND ENVIRONMENTAL HEALTH.

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Carbon nanotubes (CNTs), which possess desirable electrical and mechanical properties, potentially have wide industrial applications. CNTs exist in two forms, single-wall (SW) and multi-wall (MW). There has been great concern that if CNTs enter the work environment as suspended respirable particulate matter (PM), they could pose an inhalation hazard. The results of recent rodent studies have collectively shown that CNTs can produce inflammation, epithelioid granulomas, fibrosis, and biochemical changes in the lungs. Studies in mice given equal amounts of test dusts showed that CNTs were more toxic than quartz and produced lesions that became progressively more pronounced. These results have led us to recommend that respirable CNT dust be considered a serious occupational health hazard, and that exposure limits be established in the expectation of expanded industrial applications. CNTs, which are totally insoluble and fibrous, would be expected to be more biopersistent than mineral fibers. Biopersistence is the key factor determining the long-term toxicity of mineral fibers and certainly of CNTs too. We have postulated that the electrical and fibrous properties of CNTs also play important roles in the toxicity of CNTs in the lungs. Recently, MWCNTs have been found in ultrafine PM aggregates in combustion streams of methane, propane, and natural-gas flames of typical stoves; indoor and outdoor fine (< 2.5 micron) PM samples were reported to contain significant fractions of MWCNTs. Environmental fine PM is mainly formed from combustion of fuels, and fine PM has been reported to be a major contributor to the induction of cardiopulmonary diseases by pollutants. Given that manufactured SWCNTs and/or MWCNTs have elicited pathological changes in the lungs and heart, we have postulated that exposure to combustion-generated MWCNTs in fine PM in the air may play a significant role in air pollution-related cardiopulmonary diseases. Therefore, CNTs from manufacturing and combustion sources in the environment could have adverse effects on human health.

## 41 HEALTH RISKS OF CARBON NANOTUBES (CNTS): WHERE DO WE GO FROM HERE?

F. S. Mowat[1] and J. S. Tsuji[2]. *[1]Exponent, Menlo Park, CA and [2]Exponent, Bellevue, WA.*

Health concerns of CNTs are related to their 1) nano-size and hence high surface area and increased reactivity relative to mass, as has been shown for ultrafine particulates (UFPs); 2) fiber-like shape and potential for respiratory effects; 3) reported fibrosis, inflammation, granulomas, and other effects, 4) challenges for quantifying exposure; and 5) high biopersistence, like asbestos and synthetic vitreous fibers (SVFs). While research to date indicates similarities of CNTs with SVFs and UFPs, differences are also apparent and must be considered in drawing analogies between CNTs and more well-studied substances to assess health risks. Comparisons to UFPs, SVFs, and asbestos also raise interesting issues. For example, single-walled CNTs that agglomerate to larger bundles may have similar size and shape as SVFs that are retained in the lung. Mixtures of single and multi-walled CNTs may not agglomerate and could be cleared from the lung; however, although health risk is often discounted for SVFs that are not retained because of smaller size and aspect ratio, translocation to the heart (and other organs) or effects on cytokines affecting the heart is a concern for UFP with some similarities indicated for CNTs. Moving forward, testing and evaluation of CNT health effects should examine issues such as: particle size/number distribution; shape and surface area; type of administration/exposure; dose delivered to the target site; chemical composition, including metal content (intended and as impurities); structure, whether multi-walled or single-walled, and distribution of types; use of standard reference dusts (carbon black, quartz, and TiO2) to benchmark CNT toxicity; CNT properties, including surface treatments/charges, agglomeration, and characteristics of larger structures; biopersistence; and translocation and fate within the body and in the environment. As has been shown for asbestos, SVFs, and UFPs, characterization of each type of CNT will be imperative, as not all nanotubes are similar, and differences in the above properties can greatly affect exposure, target organ effects, and resulting health risk.

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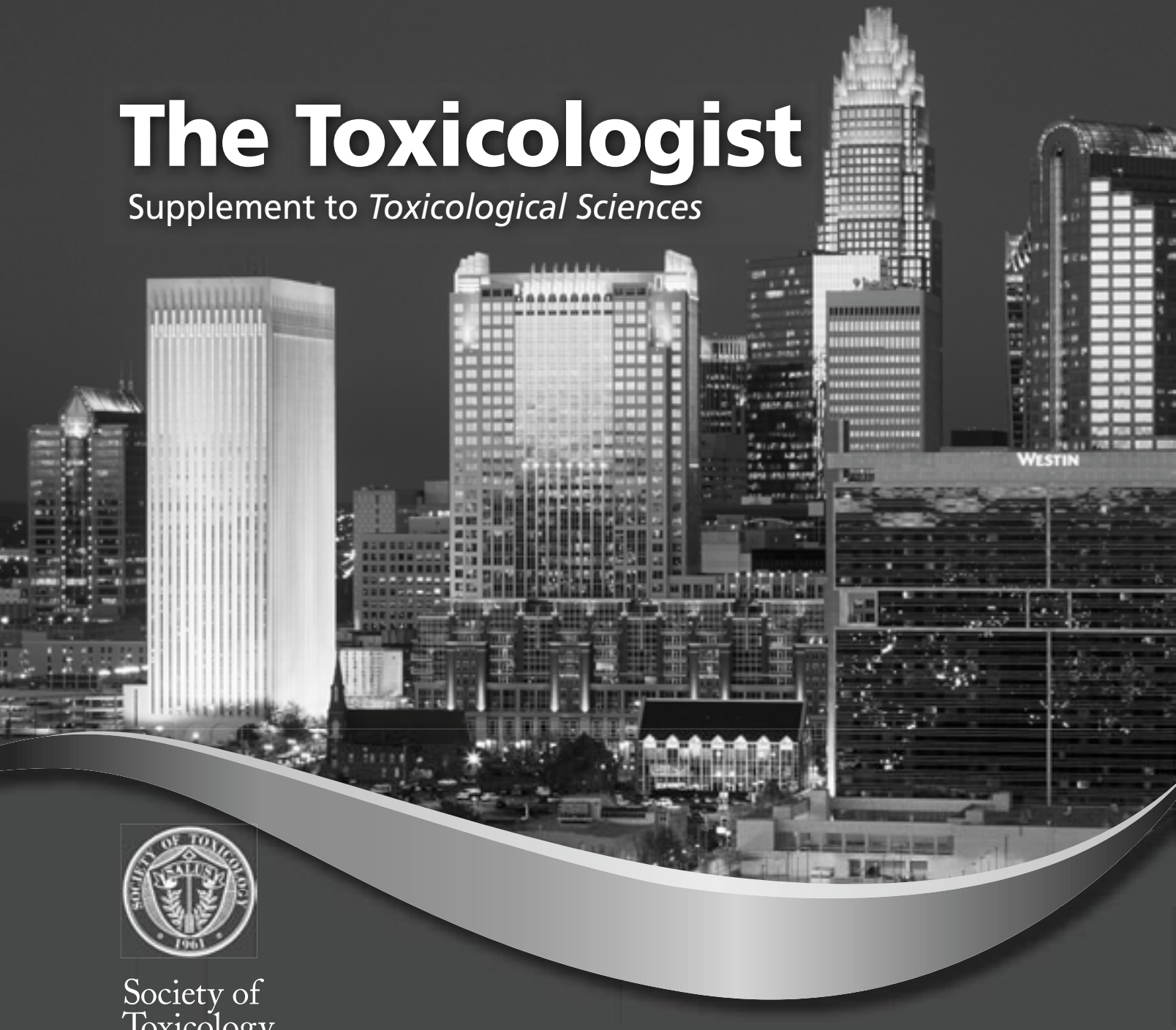


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# Preface

**This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.**

**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.**

**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.**

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