## 1185 A Short-Term Whole-Body Inhalation Study of Potassium Titanate Whisker in Mice with an Improved Dispersion and Inhalation System

Y. Taquahashi[1], K. Morita[1], M. Tsuji[1], Y. Hirabayashi[1], A. Hirose[1], and J. Kanno[1,2]. [1]*National Institute of Health Sciences, Kawasaki, Japan; and* [2]*Japan Organization of Occupational Health and Safety, Hadano, Japan.*

Potassium titanate whisker (PTW) is one of the man-made mineral fibers and used for an alternative to asbestos. There is a report that a certain type of PTW was positive for mesotheliomagenesis in intraperitoneal injection study. As the particles of PTW are respirable in size, inhalation study is essential for the assessment of its respiratory toxicity. A rat study has been reported with a low lung burden for a mass concentration of the aerosol, suggesting the presence of a large proportion of non-respirable agglomerates in the aerosol. In order to establish an inhalation exposure condition of PTW for a precise hazard assessment with better dosimetry, we conducted a mouse short-term whole-body inhalation study of a commercially available PTW in Japan, using our dispersion method and inhalation system designated as Taquann Method and Taquann Direct-Injection Whole Body Inhalation System (J Tox. Sci. 2013). In our study, the mass concentration was 4.1 mg/m$^3$, and relative concentration was 7,575/mL measured by condensation particle counter (Model 3776, TSI). MMAD on aerosol in the chamber was 1,348 nm measured by MOUDI (Model125, Kanomax). The fiber length of PTW aerosol was 4.3±3.7 micrometer (max. 23.8), and the fiber diameter was 338±171 nm (max. 990), observed by scanning electron microscopy (VE-9800, Keyence). Male C57BL/6 mice, 12 weeks old, were exposed for two hours per day for five consecutive days. Mice in control group inhaled clean air in the same manner. The lung burden of mice immediately after the last exposure (Day 0) was 15 micrograms per animal, and the length distribution of PTW recovered from the lung was virtually identical to that in the aerosol. Histologically, single fibers were found in the alveolar spaces, and there were no epithelioid cell granulomas in the lung at Day 0. The observation is ongoing to investigate long-term effects of PTW. It is concluded that the study enabled to expose well-dispersed PTW fibers with high concentration of respirable fraction down to alveolar region of mice. *This work was supported by the Health and Labour Sciences Research Grant, Japan.*

## 1186 Silica-Triggered Ectopic Lymphoneogenesis in the Lungs of Lupus-Prone Mice Is Suppressed by the Omega-3 Docosahexaenoic Acid

P. Akbari, M. A. Bates, K. N. Gilley, E. A. Eldridge, J. J. Pestka, and J. R. Harkema. *Michigan State University, East Lansing, MI.*

Pulmonary exposure to crystalline silica dust ($cSiO_2$) has been implicated as an environmental trigger of autoimmune disease. Previously, we found that intranasal $cSiO_2$ instillation triggers systemic manifestations of autoimmunity (glomerulonephritis, proteinuria) and the perivascular formation of ectopic lymphoid structures (ELS) in the lungs of mice genetically prone to develop lupus. ELS are tertiary lymphoid organs, associated with autoimmunity, that develop in areas of chronic inflammation and are characterized by the formation of organized B cell and T cell aggregates and germinal centers with follicular dendritic cell networks. The goal of this study was to 1) determine the kinetics of $cSiO_2$-induced ELS development in the lungs of lupus-prone mice and 2) assess the impact of the dietary ω-3 polyunsaturated fatty acid docosahexaenoic acid (DHA) on $cSiO_2$ triggering of ectopic lymphoneogenesis. Cohorts of 6-week-old lupus-prone female NZBWF1 mice were fed diets supplemented with 0%, 0.4%, or 1% DHA and maintained on assigned diet until sacrifice. Beginning at 8 wks of age, mice were intranasally instilled with 1 mg $cSiO_2$, or saline vehicle alone, once per wk, for 4 consecutive wks. Animals were sacrificed 1, 5, 9, or 13 wks after the last $cSiO_2$ instillation. Pulmonary densities of B (CD45R+), T (CD3+) and follicular dendritic (CD21+/CD35+) cells were immunohistochemically and morphometrically determined. Lymphoid cell densities significantly increased over time in the lungs of $cSiO_2$-treated mice. DHA supplementation markedly attenuated $cSiO_2$-triggered B and T cell, but not follicular dendritic cell, infiltration over the entire 13-wk post-exposure period. These results suggest that the development of ELS in the lung may be an early indicator of $cSiO_2$-induced autoimmunity and that dietary DHA may effectively prevent development of these aberrant structures. *Research funded in part by NIH grant ES027353, Lupus Foundation of America grant 362470, and the Dr. Robert and Carol Diebel Family Endowment.*

## 1187 Modifications of Silica-Induced Pulmonary Toxicity by Diet-Induced Obesity

T. M. Sager, C. M. Umbright, B. L. Frye, W. McKinney, T. Chen, M. Orandle, M. Kashon, and P. Joseph. *NIOSH, Morgantown, WV.*

From an occupational standpoint, exposure to silica can have devastating consequences. An estimated 2.3 million workers in the US are exposed to dust containing crystalline silica, annually. In addition, of the 140 million people over the age of 20 employed in the US, 30% are obese. If and how diet-induced obesity modifies silica-induced pulmonary toxicity is unknown. Therefore, the objective of this study was to determine the effect of diet-induced obesity, if any, on silica-induced pulmonary toxicity. Rats (Fischer 344, male) were fed either a regular-fat diet (RFD; 18% kcal as fat) or a high-fat diet (HFD; 60% kcal as fat) and exposed by whole-body inhalation to either air or crystalline silica (15 mg/m$^3$, 6 hours/day, 5 days). At designated post-exposure time intervals (1, 3, 6, and 9 months), pulmonary toxicity was determined. Toxicity parameters including lactate dehydrogenase (LDH) activity, oxidant production, cell counts (including infiltrating neutrophils and alveolar macrophages), inflammatory cytokine levels (IL-1β, IL-10, TNF-α, MCP-1, and MIP-2), and lung histopathology were assessed. Body weights and serum triglyceride levels, indicators of diet-induced obesity, in the HFD rats were higher compared to those in RFD rats. The results showed that silica particles were seen in lung sections from the exposed animals. Silica inhalation resulted in pulmonary toxicity, which progressed across all post-exposure time points, as evidenced by enhanced neutrophil infiltration, increased LDH levels, enhanced oxidant production, and increased inflammatory cytokine levels. The incidence and severity of silica-induced lung pathology was similar between the two diet groups up to 6 months post-exposure. However, by 9 months post-exposure, silica-induced pathology tended to be slightly more severe in animals fed a RFD compared to those fed a HFD. In summary, our results indicated that certain pulmonary toxicity parameters induced by silica inhalation were modified by diet-induced obesity in rats.

## 1188 Characterization of Pulmonary Responses in Mice to Asbestos/Asbestiform Fibers Using Gene Expression Profiles

N. Yanamala[1], A. A. Shvedova[1,2], E. R. Kisin[1], D. W. Gutkin[3], and M. R. Shurin[3]. [1]*NIOSH, Morgantown, WV;* [2]*West Virginia University, Morgantown, WV; and* [3]*University of Pittsburgh, Pittsburgh, PA.*

Humans exposed to asbestos and/or asbestiform fibers are at high risk of developing many lung diseases, including asbestosis, lung cancer, and malignant mesothelioma. However, the disease-causing potential and related processes associated with various asbestos/asbestiform fiber exposures in triggering the different (non-)carcinogenic outcomes is still largely unknown. In this study, we investigated whether exposure to different asbestos/asbestiform fibers leads to differences in inflammatory responses and gene expression profiles at acute/subacute phases that can be related to pathological outcomes observed at extended time points of post-exposure. We exposed mice to asbestos (crocidolite, tremolite asbestos), asbestiform fibers (erionite), and a low-pathogenicity mineral fiber (wollastonite) using oropharyngeal aspiration. We observed some shared inflammatory and tissue damage responses, albeit to different extents, at day 1 and 7 post-exposure. In addition, exposure to different fibers also exhibited distinct changes in the regulation and release of a number of inflammatory mediators. Further, a detailed comparison of gene regulation changes in the lungs on day 7 post-exposure also suggested differential biological responses that were consistent with histopathological changes at day 7 and 56 post-exposure. Taken together, these results suggest clear differences in the magnitude of various pulmonary responses and gene regulation that were consistent with pathological alterations upon exposure to the four asbestos/asbestiform fibers studied. Further mechanistic studies focusing on long-term endpoints are critical for understanding how early biological responses are associated with pulmonary exposures to asbestos/asbestiform materials and their ability in triggering different carcinogenic outcomes, i.e., lung cancer versus mesothelioma.

# The Toxicologist

Supplement to
*Toxicological Sciences*

## 57th Annual Meeting and ToxExpo™

San Antonio, Texas
March 11–15, 2018

OXFORD
UNIVERSITY PRESS

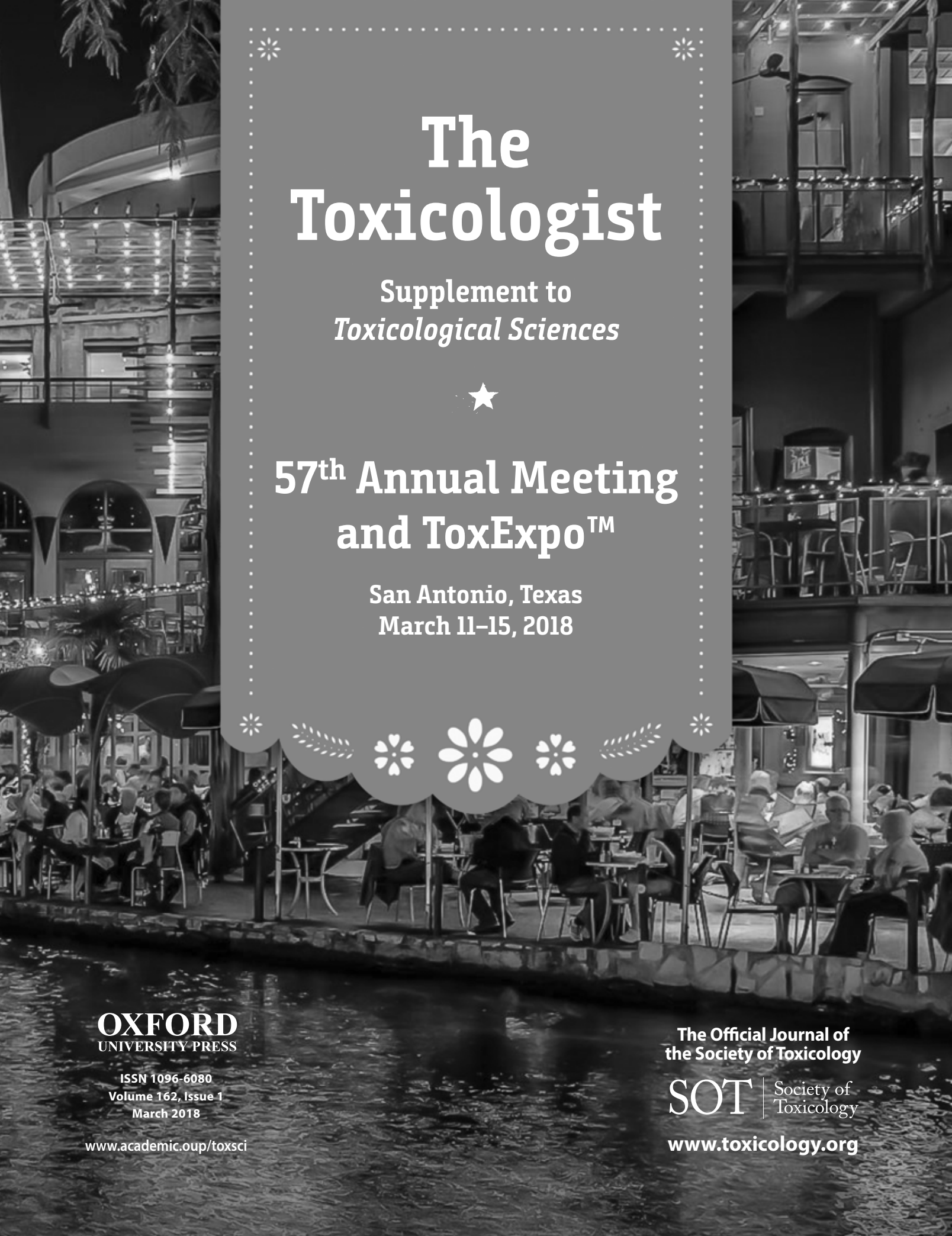
ISSN 1096-6080
Volume 162, Issue 1
March 2018

www.academic.oup/toxsci

The Official Journal of
the Society of Toxicology

SOT | Society of Toxicology

www.toxicology.org



# The Toxicologist

Supplement to
*Toxicological Sciences*

## 57th Annual Meeting and ToxExpo™

San Antonio, Texas
March 11–15, 2018

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 162, Issue 1
March 2018

www.academic.oup/toxsci

The Official Journal of
the Society of Toxicology

SOT | Society of Toxicology

www.toxicology.org