PS 241 INVESTIGATION OF NANOPARTICLES-INDUCED TOXICITY USING CAENORHABDITIS ELEGANS FUNCTIONAL GENOMICS.

J. Choi and J. Roh. *Environmental Engineering, University of Seoul, Seoul, Korea, South.* Sponsor: D. Ryu.

In the present study, toxicity of nanoparticles (i.e. silver nanoparticle, fullerene, carbon nanotube) was investigated in Caenorhabditis elegans using functional genomic tools. Whole genome microarrays were used to screen for global changes in C. elegans transcription profiles following nanoparticle exposure and with subsequent quantitative analysis conducted on selected genes. The integration of gene expression with organism and population level endpoints was investigated using C. elegans functional genomics tool, to test the physiological relevance of nanoparticle-induced gene expression. Silver nanoparticle exerted considerable toxicity in C. elegans, observed most clearly as a dramatic decrease in reproduction potential after silver nanoparticle exposure. Significant decreases in reproduction parameter concomitantly occurred in silver nanoparticle exposed C.elegans. Overall results of functional genomic using mutant analysis suggested that the sod-3 and daf-12 genes may be related to silver nanoparticle -induced reproductive failure in C. elegans and that oxidative stress may be an important mechanism in nanoparticle -induced toxicity. This study also suggested that the interpretation of microarray and subsequent quantitative gene expression data was greatly strengthened by linking them with organism and population level experiments and functional genomics using mutant strains appears to be an ideal tool for biomarker discovery in toxicological research as it can reveal the physiological meaning or function of observed altered gene expressions. Acknowledgment: This work was accomplished through the supports of the Ministry of Environment as "The Eco-technopia 21 project"

PS 242 INVESTIGATION OF THE ROLE OF AIRWAY INFLAMMATION BY NANOPARTICLES IN RESPIRATORY ALLERGY INDUCED BY TMA.

H. Muijser[1], Y. Staal[1], J. van Triel[1], J. Arts[2] and F. Kuper[1]. *[1]Quality of Life, TNO, Zeist, Netherlands and [2]AkzoNobel T&E, Arnhem, Netherlands.* Sponsor: B. Blaauboer.

Nanoparticles are increasingly used in a wide range of applications, and may have a higher toxic potential than similar particles of larger sizes. Nanoparticles can induce inflammatory reactions in the lung and may thus interfere with existing allergic inflammation. Our study aimed to assess whether inhalation exposure to nanoparticles aggravated a respiratory allergic response in Brown Norway (BN) rats. The rats were topically sensitized to trimellitic anhydride (TMA) and were challenged by inhalation to TMA 14 days later. Next, animals were exposed by inhalation to carbon nanoparticles (about 30nm), aggregated carbon nanoparticles, fine carbon nanoparticles (about 300nm), multi-walled carbon nanotubes (MWCNT) or clean air 5 hours/day, 2 days/week during 3 weeks, and thereafter challenged with TMA again. The allergic rats exhibited an altered breathing pattern (apnoeas), and a slightly increased breathing frequency during challenge, allergic laryngitis and increased granulomatous inflammation in the lungs. Exposure to nanoparticle aggregates and fine particles induced accumulation of black particles in the larynx, lungs and mediastinal lymph nodes. Exposure to nanotubules induced black granula, tubules and tubular aggregates in the lungs only. Exposure to carbon nanoparticles or carbon particles did not aggravate the TMA-induced allergy. Therefore, it was concluded that nanoparticles or nanoparticle aggregates did not alter the allergic response against TMA in BN rats, despite the presence of distinct particle accumulation in case of the nanoparticle aggregates.

PS 243 PBPK MODELING OF MICRO AND NANO SIZED FLUORESCENT POLYSTYRENE SPHERES.

X. Chang[1], K. Sarlo[2], N. J. Walker[1], K. Blackburn[2], E. Clark[2], J. Chaney[2], J. Grothaus[2] and C. J. Portier[1]. *[1]NIEHS, Reseach Triangle Park, NC and [2]Miami Valley Laboratories, Procter & Gamble, Cincinnati, OH.*

To understand the kinetics of nanoparticles in comparison to that of chemically-identical larger particles, we developed a physiologically-based pharmacokinetic (PBPK) model for micro and nano sized fluorescent polystyrene spheres using distribution data in rats. Four differently sized spheres (1000, 100, 40, 20nm) were dosed to rats as a single intravenous (IV) injection or pharyngeal aspiration into the airways, and the subsequent tissue distribution was assessed. Using these data, a full tissue compartment model was constructed consisting of blood, lymphatic system and twelve tissue blocks, each described using diffusion-limited kinetics. The model was initially fit to the IV data on 1000nm spheres and applied to predict kinetics of the 3 nanosized spheres with same exposure route. The model successfully simulated the kinetics of 1000nm spheres. It also predicted tissue kinetics well from micro to nano in several major organs such as liver, lung, and heart. The model prediction suggested that compared to microspheres, the 40 and 20 nm spheres had a reduced distribution to the spleen and bone marrow and an increased distribution to the brain. However, it is unclear whether the slight increase in distribution to the brain for the small particles is real because the particle concentration in brain samples was near or below the limit of detection (<0.04% of total spheres). By re-optimizing certain parameters, we also fit the model to IV data on each of the 3 nanosized spheres respectively. The resulting model fit well for 100nm spheres, but was inadequate for 40 and 20nm spheres, for which further modifications of model structure may be needed. A comparison of model parameters optimized specifically for each sized particle indicated that the smaller particles tend to stay longer in blood circulation. Regardless of particle size, the estimated partition coefficients are always high for spleen and liver, but low for brain, suggesting a common kinetic mechanism of these particles in major organs.

PS 244 ALTERED GENE EXPRESSION PROFILES IN MURINE BRAINS FOLLOWING EXPOSURE TO INHALED NICKEL NANOPARTICLES.

P. Gillespie, G. Kang, T. Gordon and L. Chen. *New York University School of Medicine, Tuxedo, NY.*

The respiratory tract is the primary target for inhaled nanoparticles (NPs). However, there is evidence that once deposition occurs, these particles can escape clearance mechanisms and target secondary organs like the brain. The aim of this study was to examine the transcriptional response of three regions (olfactory bulb, midbrain, and cerebellum) in the mouse brain following exposures to inhaled nickel nanoparticles (Ni NPs). Utilizing a whole-body exposure system, C57 male mice inhaled either 100 μg/m3 of spark generated Ni NPs or filtered air for 5h/d, 5d/w, for up to 5m. The three regions were collected 1w, 3m, and 5m, post exposure (24h) for gene expression analyses (n=4/group). Since studies suggest that NPs damage tissue through oxidative stress and inflammatory mediated pathways, PCR profiling systems for both pathways were used to evaluate the change in expression of 168 genes in each region as compared to controls. A change of 3-fold or higher was considered important. After 1w of exposure, the expression of approximately 50 oxidative stress and inflammation related genes were altered in all regions. Following 3 and 5m of exposure, more changes in gene expression were observed in the olfactory bulb (85 and 72, respectively) followed by the cerebellum (35 and 45, respectively) and the midbrain (21 and 28, respectively). To confirm these results, individual real time RT-PCR was performed on selected genes: Mcp-1, Tnfα, Il-1b, Ho-1, and Gpx-1. Brain deposition of inhaled Ni NPs was determined for all regions, using graphite furnace atomic absorption spectroscopy. A significant difference was only observed for the olfactory bulb (n=8, $P<0.05$). These results suggest that all three regions are affected by exposures of inhaled Ni NPs via oxidative stress- inflammatory mediated pathways; but, the olfactory bulb may be a more sensitive target to adverse effects. Additional studies are needed to link the changes in gene expression to mechanisms of toxicity.

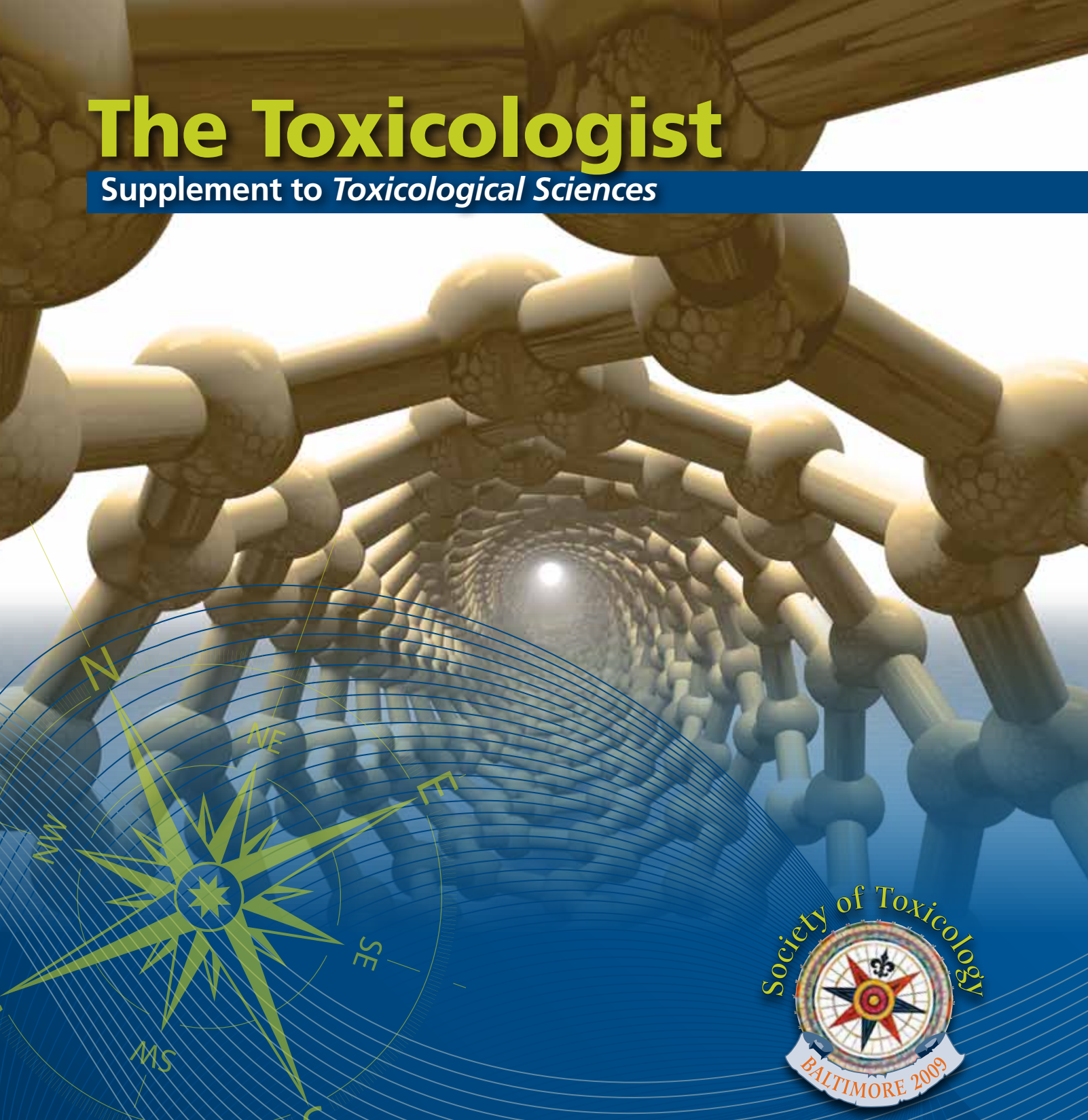
PS 245 POTENTIAL CARDIOVASCULAR EFFECTS OF FULLERENE C60 INHALATION EXPOSURE.

P. P. Simeonova[1], A. Erdely[1], A. Liston[1], M. I. Luster[1], J. Roycroft[2], D. Germolec[2] and N. J. Walker[2]. *[1]NIOSH, CDC, Morgantown, WV and [2]NIEHS, Research Triangle Park, NC.*

Fullerenes are forms of carbon nanomaterials used in a wide variety of commercial applications and have the potential for significant human exposure. Based on ambient ultrafine particle research, it is predicted that small particles may have systemic toxicity related to cardiovascular outcomes. This study evaluates the cardiovascular effects of subchronic inhalation exposure of B6C3F1 mice to C60 particles (diameter 1 and 0.05 μm). The initial screening for cardiovascular toxicity was conducted applying a custom-designed TaqMan array for genes known to play an important role in the mechanisms of atherosclerosis such as inflammation, oxidative stress, and coagulation. We observed changes on expression of several genes related to stress response, including c-fos, and heat shock protein (hsps) 25, 70, and 90 in the aortas of the exposed mice independent of the size of the particles. These findings were confirmed by a real-time RT-PCR. Hsps are incremental in triggering many autoimmune/chronic inflammatory diseases. In this regard, it has been suggested a multifaceted role for hsps in atherosclerosis. For example, it has been reported that the expression of hsps is upregulated very early at lesion-prone sites in the aortas of young apoE-/- mice. Thus, fullerene exposure of wild type mice, not prone to develop atherosclerosis, resulted in a cardiovascular stress response which may provide a predisposition to atherogenesis. **Disclaimer:** The findings and conclusions in this abstract are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

The Toxicologist

Supplement to *Toxicological Sciences*



Society of Toxicology
BALTIMORE 2009

An Official Journal of the Society of Toxicology

SOT | Society of Toxicology

48th Annual Meeting and ToxExpo™

Baltimore, Maryland

www.toxsci.oxfordjournals.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 108, Number 1, March 2009