1326 Pulmonary Exposure to Respirable Cellulose Nanocrystals Caused Sustained Lung Damage and Male Reproductive Toxicity

A. A. Shvedova[1,4], M. T. Farcas[1], A. L. Menas[1], D. W. Gutkin[3], A. Star[2], N. Yanamala[1], E. R. Kisin[1], and V. E. Kagan[2,2]. *[1]NIOSH, Morgantown, WV; [2]University of Pittsburgh, Pittsburgh, PA; [3]University of Pittsburgh Medical Center, Pittsburgh, PA; and [4]West Virginia University, Morgantown, WV.*

Cellulose nanocrystals (CNC) unveil an interesting combination of properties (e.g. mechanical, thermal, rheological and optical) and produced in large scale as nanofillers in polymer composites, building materials, cosmetics, food, and the drug industry. To date, there are only few studies investigating the potential adverse effects of nanocellulose materials. The present study was undertaken to investigate the pulmonary outcomes as well as alterations of the male reproductive system induced by repeated exposure to respirable CNC. C57BL6 male mice were treated by pharyngeal aspiration with CNC (40 µg/mouse) twice a week for 3 weeks. Three months after the last administration, exposure to respirable CNC resulted in pulmonary inflammation and damage, oxidative stress, elevated TGF-β and collagen in the lung. Additionally, CNC exposure significantly altered sperm concentration, motility, cell morphology, and sperm DNA integrity. These parameters correlated with elevated pro-inflammatory cytokines and myeloperoxidase activity in testes, as well as increase in oxidative stress in both testes and epididymis. Exposure to CNC also induced damage to testicular structure and imbalance in levels of testosterone and luteinizing hormone. Taken together, these results demonstrate that exposure to respirable CNC not only lead to pulmonary toxicity but also induces sustained adverse effects in spermatocytes/spermatozoa indicating male reproductive toxicity.

1327 Histological and Immunohistochemical Studies of a Nanocellulose Diester from Cotton Seeds in Rats

C. A. Otuechere, A. Adewuyi, O. Adebayo, and I. Ebigwei. *Redeemer's University, Ede Town, Nigeria.*

Chemical modification of cellulose nanofibers is currently attracting attention as researchers attempt to take advantage of the abundance of hydroxyl groups on its surface to introduce extra biological functionality. However, the toxicity profile of this esterified nanocellulose has not been established in animal models. Thus, a 7-day repeated oral toxicity study of cotton seed nanocellulose diester (NCD) was conducted in male Wistar rats. A total of three groups (5 rats per group) were compared: (1) Control (normal saline), (2) 50 mg/kg NCD and (3) 100 mg/kg NCD. The effects of NCD in rats were investigated by assaying oxidative stress biomarkers, lipid peroxidation, plasma toxicity markers, nitric oxide and myeloperoxidase levels. The expressions of cyclo-oxygenase-2 and inducible nitric oxide synthase were also evaluated by immunohistochemical staining. Acute treatment of NCD had no adverse effect on enzymatic antioxidant status but significantly elevated the aminotransferases activities when compared with controls. Improvement in reduced glutathione levels was accompanied by a decrease in myeloperoxidase activity. Histological observations did not reveal any adverse effects on the liver at the lower concentration dose when compared with control. Treatment with NCD elicited a reduction in the expressions of cyclo-oxygenase-2 and inducible nitric oxide synthase when compared with controls. The present findings suggest that NCD appears to have minimal adverse oral toxicity effect on animals.

1328 Long-Term Inhalation Study with Nano Barium Sulfate: Unexpected Morphological Findings and Lung-Burden after 12 Months of Exposure

S. Groeters[1], L. Ma-Hock[1], H. Ernst[2], J. Keller[1], V. Strauss[1], K. Wiench[1], B. van Ravenzwaay[1], and R. Landsiedel[1]. *[1]BASF SE, Ludwigshafen am Rhein, Germany; and [2]Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany.*

Lung carcinogenicity and putative systemic effects of low-dose lifetime inhalation exposure to biopersistent nanoparticles were examined in a combined chronic/carcinogenicity inhalation study performed according to OECD test guideline no. 453 with several protocol extensions. Female rats were exposed to barium sulfate (NM-220; 50 mg/m^3) for 12 month (interim sacrifice, 10 animals), 24 month (final sacrifice, 50 animals) and 24 month plus 6 month exposure-free period (50 animals). A control group was exposed to clean air. Lung burdens and burdens in extrapulmonary tissues were measured at various time-point. In parallel, bronchioalveolar lavage fluid (BALF) was investigated and histopathology was performed. Range finding studies with 5d and 28d of inhalative exposure to Barium Sulfate (BaSO4; 50mg/m^3) revealed no histopathological findings in the lungs, low lung burden concentrations and no signs of inflammation in BALF examination. BaSO4 lung burdens were comparatively low (1 mg/g) within the first 13 weeks of exposure and steeply increased to > 10 mg/g lung tissue after one year, accompanied by severe inflammatory changes in the lung detected by BALF and histopathology. Whereas the excretion of BaSO4, after 13 weeks was comparable to control, a significant increase in feces after 12 and 24 months was measured. Histological examination of lungs revealed several adverse and non-adverse effects in the lung. The non-adverse effects comprised accumulation of particle-laden macrophages in alveolar/interstitial areas and in the BALT with an accentuation on interstitial accumulation and bronchiolo-alveolar hyperplasia (alveolar bronchiolization). The adverse effects included (mixed) alveolar/interstitial inflammatory cell infiltration without granulomatous inflammation, minimal interstitial fibrosis and alveolar lipoproteinosis. Neither pre-neoplastic nor neoplastic changes were observed after 12-months exposure. A no observed adverse effect concentration could not be established in this study. The comprehensive histopathological examinations of lungs and other tissues after 24 and 30 months of exposure will be finalized in 2017.

1329 Food Grade Titanium Dioxide (E171) Consumption in Diet Induces Higher DNA Damage in Colon than in Spleen and Liver of Mice

C. Rodríguez-Ibarra, L. G. Garduño-Balderas, N. L. Delgado-Buenrostro, and I. Chirino. *Universidad Nacional Autónoma de México, Tlalnepantla de Baz, Mexico.*

Food grade titanium dioxide, known as E171, is used as a food additive and in personal care products. The Food and Drug Administration allows the use of E171 in up to 1% of the final product weight. However, the IARC has classified TiO_2 as a posible carcinogen to humans by inhalation but the oral route has been poorly investigated. It is known that after oral administration, TiO_2 can be absorbed into blood stream and can be taken up by different organs such as colon, liver and spleen. However, the toxic efects in these organs are still unknown. Here we investigated the potential genotoxic effect of E171 in colon, liver and spleen after oral administration to mice in the diet. For this purpose, Balb/C mice were fed with 0.5% E171 through diet during 4 and 10 weeks and DNA damage in these organs was measured using the γ-H2AX immuno-staining assay. We found that 0.5% E171 in the diet induced a 1.5-fold of increase of fluorescence in liver, 2-fold in spleen and 3-fold in colon after 4 weeks and the DNA damage was sustained at least until 10 weeks. Also, two of the mice treated for 10 weeks developed adenomas in the distal colon. These results suggest that oral consumption of 0.5% E171 in the diet caused DNA double strand breaks in these organs, but also, that probably colon tissue could have higher susceptibility followed by spleen and liver.

1330 Differences in Nickel Oxide Nanoparticle-Induced Pulmonary Toxicity and Exacerbated Allergic Response following Acute Respiratory Exposure

K. A. Roach[1,2], S. E. Anderson[1,2], A. B. Stefaniak[1], C. E. McLoughlin[1], D. Schwegler-Berry[1], and J. R. Roberts[1,2]. *[1]CDC/NIOSH, Morgantown, WV; and [2]West Virginia University, Morgantown, WV.*

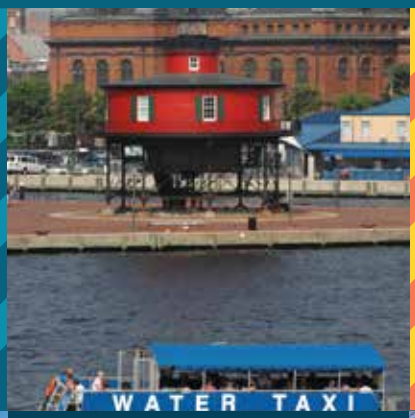
Particle size and morphology play critical roles in nanomaterial-induced lung inflammation, but the relationship of these factors to augmentation of allergic response in the respiratory tract is largely unknown. To address this concept, two different sizes of nickel oxide (NiO) particles were characterized and investigated *in vivo*. Dynamic light scattering showed the average particle sizes (APS) were 27 nm for NiO-1 and 190 nm for NiO-2. NiO-1 particles were spherical while NiO-2 particles were more irregular and plate-like. The goal of the study was to assess effects of the different NiO particles on augmentation of allergic response using an ovalbumin (OVA) model. Effects of NiO on the lung were also assessed at critical time points correlating to the OVA model in the absence of OVA. Female BALB/c mice were given a single dose of 40 micrograms of NiO-1, NiO-2, or dispersion medium (DM; vehicle control) by oropharyngeal aspiration (OPA) and euthanized at 1, 10, 19, and 29 d post-exposure in the absence of OVA. In the OVA allergy model, mice were similarly exposed to particles or DM on day 0, sensitized to OVA via i.p. injection at 1 and 10 d, challenged with OVA at 19 and 28 d via OPA, and euthanized at 29 d. In the absence of OVA, only NiO-2 induced significant and persistent increases in lung injury and inflammation in the lung, but both NiO-1 and NiO-2 increased mediastinal lymph node


The Toxicologist

Supplement to *Toxicological Sciences*

56th Annual Meeting and ToxExpo™

Baltimore, Maryland | March 12–16, 2017

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 156, Issue 1
March 2017

www.toxsci.oxfordjournals.org

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

www.toxicology.org