there is an acute need for assessing nanotoxicity. Nanoparticle size, surface functionalization, and chemical composition are but three critical nanotoxic metrics. Zebrafish (*Danio rerio*) embryo exposures with non-functionalized, colloidal silver (cAg) and gold nanoparticles (cAu) in an array of sizes (3, 10, 50, and 100 nm) produced a range of toxic effects. Using a semi-quantitative scoring system, cAg3, 10, 50, and 100 elicited nearly 100% embryonic mortality 120 h post-fertilization (hpf); cAu3, 10, 50, and 100 exposures resulted in less than 3% mortality 120 hpf. While cAu induced minimal sublethal toxic effects, cAg exposures generated various embryonic and morphological malformations including stunted growth, opaque and non-depleted yolks, circulatory malformations, and jaw defects amongst others at 120 hpf. Both cAg and cAu were taken up by the embryos and results from vector control experiments suggest cAg sublethal toxicity and mortality were a result of the nanoparticles themselves or Ag^+ ions formed either during *in vivo* nanoparticle destabilization or as a residual synthetic contaminant. Although cAg toxicity was size-dependent at specific concentrations and time points, the most striking result is that parallel sizes of cAg and cAu induced significantly divergent toxic profiles, with the former being toxic and the latter inert at all sizes tested. Thus, we propose that nanoparticle chemistry is as, if not more, important than specific nanosizes at inducing toxicity *in vivo*. Ultimately, nanotoxicity assessments using the zebrafish embryo model should identify nanomaterial physicochemical characteristics that yield minimal or no toxicity for improved rational designs of nanomaterials.

PS 237 EXAMINATION OF POTENTIAL DERMAL IRRITATION FOR DIFFERENT SIZES OF METAL NANOPARTICLES.

D. R. Mattie, R. J. Godfrey, T. A. Bausman, M. J. Wagner, L. N. Talton, P. Gunasekar, K. Prabhakaran, N. M. Schaeublin and S. M. Hussain. *711 HPW/RHPB, Air Force Research Labs, Wright Patterson, OH.*

Nanoparticles can have properties different than larger sizes of the same material. Knowledge about potential health effects is limited. Exposure of skin to nanoparticles is possibly and could result in dermal irritation. In an effort to test nanoparticles in vivo while minimizing the number of rabbits used, nine nanoparticles were placed on the backs of 4 rabbits to determine if they cause skin irritation. The study followed the Environmental Protection Agency Health Effects Test Guidelines, Office of Prevention, Pesticides and Toxic Substances 870.2500, Acute Dermal Irritation, as the basic procedure. We determined the ideal number of sites when placing Hilltop Chambers on the skin is 8 sites per rabbit. Three other sites are used as a control with no chamber at all. Four rabbits were used to expose 9 nanoparticles, three times for each nanoparticle. A randomized rotation was employed to blind those reading the sites. Each of the 4 rabbits had at least one negative control site with a Hilltop Chamber only and seven sites with nanoparticles (six for one rabbit with two negative controls). Each nanoparticle site on each rabbit was a different nanoparticle so that each nanoparticle was still placed on 3 different rabbits. Nanoparticles used were suspended in 0.5 ml of saline: Aluminum (50, 80 nm); Silver with proprietary organic coating (10 and 80 nm); Silver without coating (10, 25, 80 nm); Tungsten (60 nm); and Aluminum Oxide (30 nm). After the 72 hour observation, skin was collected for histopathology. The results demonstrated that none of the nanoparticles tested produced skin irritation.

PS 238 LACK OF DERMAL PENETRATION FOLLOWING TOPICAL APPLICATION OF COATED AND UNCOATED NANO- AND MICRON-SIZED TITANIUM DIOXIDE TO INTACT AND DERMABRADED SKIN IN MICE.

N. V. Gopee[1], C. Cozart[1], P. Siitonen[1], C. S. Smith[2], N. J. Walker[2] and P. C. Howard[1]. *[1]National Center for Toxicological Research, Jefferson, AR and [2]National Institute for Environmental Health Sciences, RTP, NC.*

Dermal transport and possible toxicity of nanoscale metal oxides used in cosmetic and personal care products are relatively unexplored and is the focus of this study. We previously reported that ~10% and 6% of intradermally injected PEG-coated quantum dots (QDs) bioaccumulate in the liver and lymph nodes. The topical application of QDs to dermabraded skin resulted in accumulation of ~1% and ~0.1 % of the applied dose in the liver and lymph nodes, respectively. We also demonstrated that following intradermal injection, the biodistribution of three different types of TiO_2, uncoated nano, coated nano and micron, depended upon the size and coating properties. In that study an increase in titanium (Ti) in liver accounted for ~10% of injected dose of all three TiO_2, in lymph nodes the Ti accounted for ~1% of injected dose seen with coated nano and micron TiO_2, and Ti accumulated in kidneys exclusively with micron TiO_2 (~16% of dose). In the present study, emulsions containing 5% of either nanoscale (25 nm primary particle size) uncoated anatase TiO_2, micronscale anatase TiO_2 and nanoscale (14 x 79 nm rods) polystearate/alumina-coated TiO_2 were topically applied to intact dorsal or inguinal and axillary regions or to dermabraded skin of hairless mice. Lymph nodes, liver, spleen, kidneys and blood were collected at 6 and 24 hours post application and Ti levels were quantified by ICP-MS. No significant elevations in Ti levels were observed in all the organs analyzed for the three different TiO_2 formulations when applied to intact and dermabraded skin. The results suggest that both intact and compromised skin of hairless mice may be an effective barrier in preventing dermal penetration and subsequent organ bioaccumulation of topically applied nano-and micron-sized TiO_2 of different surface coatings.

These studies were supported by an IAG between the National Toxicology Program and FDA (IAG# 244-07-0007).

PS 239 PULMONARY RESPONSES TO DIESEL FUEL CATALYST CERIUM OXIDE NANOPARTICLES.

J. Y. Ma[1], H. Zhao[1], M. Barger[1], M. Rao[1], T. Meighan[1], V. Castranova[1] and J. Ma[2]. *[1]HELD, NIOSH, Morgantown, WV and [2]School of Pharmacy, West Virginia University, Morgantown, WV.*

Cerium oxide has been used as a fuel-borne catalyst to lower the mass of diesel exhaust particles (DEP), but is emitted as nanoparticles in the diesel exhaust. While the health effects of DEP have been investigated for decades, the potential pulmonary toxicity of cerium oxide nanoparticles has not been characterized. The objectives of this study were to investigate the effects of cerium oxide on the pulmonary immune/inflammatory responses. Rats (Sprague Dawley) were exposed to cerium oxide (0.5 to 20 mg/kg) by intratracheal instillation. Alveolar macrophages (AM) were isolated via bronchoalveolar lavage (BAL) the next day. Cerium oxide exposure was found to induce significant neutrophil infiltration and elevate lactate dehydrogenase activity and albumin content in the BAL fluid, suggesting that these particles induced inflammation, cytotoxicity and epithelial damage. The results also show a direct interaction of cerium oxide with AM, resulting in elevated AM phagocytic activity as monitored using confocal microscopy, increased reactive oxygen species production in response to zymosan challenge as indicated by enhanced chemiluminscence generation, and increased production of the pro-inflammatory cytokines IL-12 and TNF-α. However, cerium oxide significantly reduced nitric oxide production by AM in response to ex vivo LPS challenge, demonstrating that these particles may modify AM host defense capability. Analysis of mRNA levels of several genes using real time RT-PCR indicate that cerium oxide significantly increased suppressor of cytokine signaling and osteopontin (OPN) in BAL cells, while OPN was also increased in the lung tissue. When OPN was analyzed at 28 days post exposure, there was a further increase of mRNA in lung tissue. These results show that cerium oxide-mediated lung toxicity includes pulmonary inflammation and lung injury, and a persistent induction of OPN in lung tissue, which has been associated with lung fibrosis.

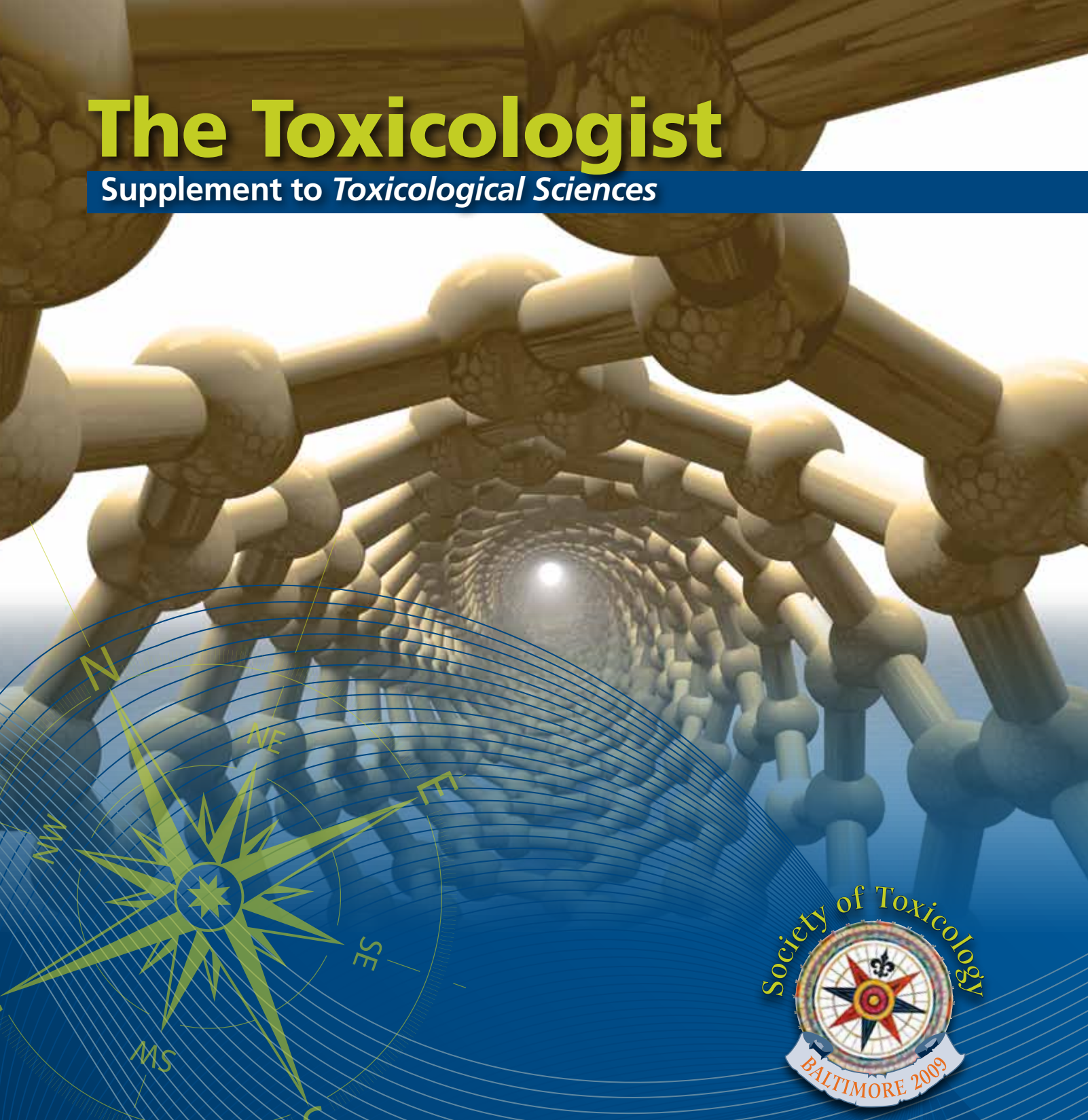
PS 240 BIODISTRIBUTION OF QUANTUM DOTS AFTER PULMONARY EXPOSURE IN RATS.

J. R. Roberts, D. Schwegler-Berry, R. Chapman, J. M. Antonini, J. Scabilloni, V. Castranova and R. R. Mercer. *HELD/PPRB, NIOSH, Morgantown, WV.*

The potential use of quantum dots (QD) as a medical diagnostic tool, as well as in other biomedical applications, has led to concern regarding their toxicity, potential systemic distribution, and biopersistence. In addition, little is known about workplace exposure to QD, such as research, manufacturing, or medical settings. We have shown that pulmonary exposure to functionalized QD caused a dose-dependent increase in lung injury and inflammation which persisted up to 28 days. The goal of the present study was to assess the biodistribution of QD in rats after pulmonary exposure. QD were composed of a cadmium-selenium (CdSe) core (~5nm) with a zinc sulfide (ZnS) shell functionalized with carboxyl (COOH-QD) or amine (NH_2-QD) terminal groups Male Sprague-Dawley rats were intratracheally-instilled (IT) with saline, COOH-QD, or NH_2-QD (12.5 μg/rat). On days 0, 1, 3, 7, 14, and 28 post-IT, the left lung, lung-associated lymph nodes (LALN), heart, kidneys, spleen, liver, brain, and blood were collected for metal analysis of Cd content by neutron activation. Right lungs from rats in each group were either subjected to bronchoalveolar lavage (BAL) to retrieve BAL fluid and cells for analysis of damage, or were preserved and sectioned for histopathology, confocal imaging, and autometallographic silver enhancement of Cd. No Cd was detected in the liver, spleen, heart, brain, or blood at any time point. At days 7 and 14, when lung injury and inflammation were at their greatest, approximately 3-5 % of the total Cd instilled was detected in the LALN of rats treated with COOH-QD, and approximately 10-20% was located in the kidney in these rats. By day 14, Cd was also found to be present in the kidneys of rats treated with NH_2-QD. Both forms of QD caused significant lung injury and inflammation, with particles present in alveolar macrophages, on epithelial surfaces, and in the interstitium, which persisted in the lungs up to 28 days post-exposure. QD are not readily cleared from the lungs after IT and translocation to other organs appears to be related to damage to the air-blood barrier.

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