proactive approach to enhance the safety of materials, inform hazard assessment upstream, and move nanotechnology toward sustainability based on green chemistry principles. This abstract may not necessarily reflect US EPA policy.

PS 317 EFFECTS OF CERIUM OXIDE NANOPARTICLES ON DIESEL EXHAUST PARTICLES—INDUCED PULMONARY RESPONSES.

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Diesel exhaust particles (DEP) are the major constituent of ambient particulate that are known to induce lung inflammation and injury. When using cerium compounds as diesel engine catalyst to lower DEP emission, cerium oxide nanoparticles (CeO_2) were detected in the exhaust. Our previous studies have shown that CeO_2 not only induces pulmonary inflammation, but also lung fibrosis. In this study, we investigated the effects of CeO_2, DEP and their combination on pulmonary responses pertaining to lung inflammation and fibrosis. Male Sprague Dawley rats were exposed to DEP with or without CeO_2 (20% w/w) by a single intratracheal instillation and sacrificed at 1, 10 and 28 days after exposure. Bronchial alveolar lavage (BAL) was performed; cellular and acellular fractions of BAL fluid were obtained; and particle-induced lung inflammation, cellular toxicity, and alveolar air/blood barrier damage were determined through monitoring PMN infiltration, LDH activity, and albumin content in the first BAL fluid. The DEP-induced responses were acute and transient, peaked at 1-day after exposure, but significantly declined at 10- and 28-day post exposure. However, CeO_2+DEP induced inflammatory responses were found persistent throughout the 28-day exposure period. DEP-exposed alveolar macrophages induced oxidant and nitric oxide generation and proinflammatory cytokine, TNF-α and IL-12, production. The presence of CeO_2 markedly reduced DEP-induced cellular responses. At 28 days post exposure, CeO_2- and CeO_2+DEP-exposed lungs showed significantly induced phospholipidosis and hydroxyproline content in lung tissues. Morphological analysis showed that both DEP and CeO_2+DEP demonstrated granulomatos lesions. However, there were more cells and collagen in CeO_2+DEP- than DEP-exposed lungs. These results suggest that exposure of rats to CeO_2+DEP induced sustained inflammatory lung injury and enhanced fibrotic development compared to exposure to DEP alone. These findings suggest potential health effects of CeO_2 when used as diesel engine catalyst are of concern.

PS 318 COMPARISON OF THE GLOBAL GENE EXPRESSION OF RAT LUNG INHALED MANUFACTURED NANOMATERIALS: ULTRAFINE NICKEL OXIDE, C_{60} FULLERENE, AND CARBON NANOTUBES.

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In tis study, comparative analyses of gene expression profiling of the rat lung after whole-body inhalation exposure to ultrafine nickel oxide (Uf-NiO), C_{60} fullerene, multi or singlewall carbon nanotubes (MWCNTs or SWCNTs) for 6 h a day, for 4 weeks were performed to gain insights into the influence of MNs on the pulmonary system at a molecular level. DNA microarray analysis revealed that high expression of genes associated with chemokines and response to oxidative stress were induced by Uf-NiO at both 3 days and 1 month post-exposure. Mmp12 (macrophage metalloelastase) were significantly upregulated at both 3 days and 1 month post-exposure. The results suggest that Uf-NiO lead to acute inflammation for the exposure period, and the damaged tissues are repaired in the post-exposure period. Few genes involved in the inflammatory response, response to oxidative stress, apoptosis, and metalloendopeptidase activity were upregulated by C_{60} fullerene or SWCNTs at both 3 days and 1 month post-exposure. C_{60} fullerene or SWCNTs might not have a severe pulmonary toxicity under the inhalation exposure condition. Meanwhile, MWCNTs induced high expression of genes involved in chemokines, Mmp12 and Mmp7 (matrilysin) at 3 days post-exposure. The expression levels of genes involved in inflammatory chemokines were significantly higher than those of SWCNT or C_{60} fullerene exposure under the conditions. These results were consistent with neutrophil count or chemokine levels in bronchoalveolar lavage fluid (BALF). Hierarchical clustering of gene expression associated with chemokines revealed that candidate MNs-induced genes (i.e., Ccl2, Ccl3, Ccl7, Ccl22, Cxcl1, Cxcl2, and Cxcl6) were identified as potential acute-phase inflammatory biomarkers in the lung tissue.

PS 319 LONG-TERM PHARMACOKINETICS AND BIODISTRIBUTION OF SILICA NANOPARTICLES USING ACCELERATOR MASS SPECTROMETRY *IN VIVO.*

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Nanoparticles and their use for commercial applications are continuing to increase, especially for diagnostic and therapeutic purposes in the biomedical field. However, to date, the toxicity and biological fate of nanoparticles have not been thoroughly investigated; this information is critical for translation of nanoparticles for clinical use. Silica nanoparticles are used for many biological applications including imaging and as drug delivery vehicles. In this work, Accelerator Mass Spectrometry (AMS), an ultrasensitive technique for quantifying long-lived radioisotopes, is used to measure the long-term biodistribution and pharmacokinetic properties of silica nanoparticles after administration *in vivo.* ^{14}C-Labeled ($t_{1/2}$=5730 yrs) carboxylated silica nanoparticles (33nm) were administered as a single bolus i.v. dose to male mice. AMS was used to quantify the tissue distribution and pharmacokinetic parameters over an eight week period. Within eight hours after dosing, nanoparticles were cleared rapidly from the bloodstream, but were retained in organs of the reticuloendothelial system, including the liver, spleen, bone marrow and lymphatic tissue. Small amounts of nanoparticles were also observed in other peripheral organs and in excreta. These results demonstrate that silica nanoparticles can accumulate in organs upon entering the blood stream and that AMS is a powerful tool to assess the long-term pharmacokinetics and biodistribution of nanomaterials *in vivo*. This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344 and supported by LLNL CRADA No. PNNL/284.
LLNL-ABS-500511

PS 320 TISSUE-SPECIFIC GENOTOXICITY OF TITANIUM DIOXIDE NANOPARTICLES EVALUATED USING THE *IN VIVO* COMET ASSAY.

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Nanosized titanium dioxide (nanoTiO2) is one of the most widely used nanomaterials. Although TiO2 is chemically inert, it can cause lung cancer in rats. The International Agency for Research on Cancer (IARC) recently classified TiO2 as possibly carcinogenic to humans (class 2B), based on sufficient evidence in experimental animals. Considering that nanosized TiO2 materials are much more reactive than its bulk materials, a genotoxic evaluation of nano-TiO2 is necessary because the genotoxicity data are required for the cancer risk assessment. In the current study, we evaluated the tissue-specific genotoxicity of 10 nm TiO2 nanoparticles and the possible mechanisms for their genotoxicity using in vivo Comet assay. B6C3F1 (1H) male mice were treated by intraperitoneal injection with 50 mg TiO2 nanoparticles /kg body weight daily for three days and sacrificed 4 and 24 hr after the last treatment. Liver, bone marrow, spleen and lung were collected for the evaluation. The standard Comet assay was performed to detect DNA breaks induced by the nanoparticles; and the enzyme-modified Comet assays by addition of human 8-oxo-guanine DNA glycosylase (hOGG1) and endonuclease III (Endo III) were conducted to measure the oxidative DNA adducts due to the treatment. The study revealed that the treatment significantly resulted in DNA strand breaks in liver at both the 4 and 24 hr sampling times and in spleen at the 4 hr time point, but not in other tissues. Statistically significant ($p \leq 0.05$) increases of oxidative DNA adducts were observed in all tissue samples at all time points. The results suggest that the 10 nm TiO2 nanoparticles can induce DNA damage including DNA breakage and DNA adducts tissue-specifically; and that the possible mechanism for the induction is the oxidative stress caused by the treatment of the nanoparticles.

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