PS 2079 INHIBITORY EFFECTS OF SILVER NANOPARTICLES ON RECOMBINANT CYTOCHROME P450 ENZYMES AND HUMAN LIVER MICROSOMES.

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Silver nanoparticles have been used in numerous biomedical applications including wound dressing, catheter coating, and bone cement for the purpose of bacterial growth inhibition. Meanwhile, there is an increasing concern in that exposure to these nanoparticles may cause a potential adverse effect to human. Several investigations showed that silver nanoparticles are able to interfere with cellular functions and cause cytotoxicity. In animals, liver is one of the main target organs where silver can be accumulated after exposure. However, there is still lack of data regarding potential effects of silver nanoparticles on cytochrome P450 (CYP), a major drug metabolizing enzyme system in the liver. Changes in CYP activity will be particularly relevant to the toxicity and the therapeutic effect of drugs or xenobiotics. In this study, we investigated effects of silver nanoparticles on CYP inhibition using recombinant CYP enzymes, CYP1A2, CYP2E1, CYP2C9, CYP2D6, and CYP3A4, as well as human liver microsomes (HLM). The specific probe substrates of each CYP isoform were used. The enzyme catalytic activities were measured by HPLC. Physicochemical properties of silver nanoparticles (Sigma 576832) including morphology, size and size distribution, and trace metal contaminants were also analyzed by TEM, DLS, and ICP, respectively. The results showed that silver nanoparticles predominantly inhibited CYP3A4 and CYP2C9, but demonstrated weak affects on CYP1A2 in recombinant CYPs and HLM. For CYP2E1 and CYP2D6, the particles showed stronger inhibitory effects in recombinant CYPs than in HLM. This study suggested that silver nanoparticles can inhibit some of the major CYP isoforms in vitro which might be a useful information for predicting adverse effects of silver nanoparticles in human.

PS 2080 EFFECT OF ORALLY EXPOSURED AMORPHOUS NANOSILICA ON ANTIGEN-SPECIFIC IMMUNE RESPONSES.

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Ultrafine amorphous nanosilica (nSPs) have already been available as a substitute for larger-size silica particles. However, the biological activity of nSPs remains undefined. Although the biological properties of nSPs may be limited, combined effects by food antigens may enhance food allergy. In the present study, we investigated the effect of repeated oral exposure of nSPs on antigen-specific immune responses in the presence of chicken egg ovalbumin (OVA) as model allergen. nSPs with diameter 30 nm (nSP30) as well as silica with diameter 300 or 1000 nm (nSP300 and mSP1000, respectively) were given orally with 1 mg of OVA. We evaluated in vivo distribution of nSPs by transmission electron microscopy, OVA-specific Immunoglobulin (Ig) E. Results suggested that only nSP30 migrated to blood through gut and reached spleen, although absorption of nSP300 and mSP1000 were not detected, suggesting that nSP30 influence immune system. Next, mice were orally exposed to OVA plus nSPs for four times at weekly interval, and the levels of OVA-specific IgE were determined. We found that oral exposure of OVA plus nSP30 tended to induce higher level of OVA-specific IgE causing type 1 allergy. These results indicate that migration of nSPs below 100 nm to spleen could induce immune-modulating effect. To create safe and effective forms of nSPs, we investigate information about immune response related to physicochemical examination. We believe that these data provide basic information that should help risk analysis of nanomaterials.

PS 2081 MATRIX METALLOPROTEINASES 2 AND 9 AND TISSUE INHIBITORS OF METALLOPROTEINASE 1 IN CERIUM OXIDE INDUCED PULMONARY FIBROSIS.

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Cerium compounds have been used as a diesel engine catalyst to lower the mass of diesel exhaust particles, but are emitted as cerium oxide nanoparticles (CeO_2) in the diesel exhaust. Our previous studies have shown that CeO_2 induced pulmonary inflammation, air/capillary injury, M2 AM differentiation and lung fibrosis. In this study, we investigated the mechanisms involved in CeO_2-induced pulmonary fibrosis. Male Sprague Dawley rats were exposed to CeO_2 (0.15 to 7 mg/kg) by a single intratracheal instillation and sacrificed at 1, 10, 28 and 84 days after exposure. Alveolar macrophages (AM) were isolated by bronchial alveolar lavage (BAL) and the first BAL fluid was saved for further analysis. The activity of osteopontin (OPN), a multifunctional matricellular protein expressed during inflammation and repair, in AM cultured media was significantly increased at 10 and 28 days post exposure. Collagen degradation enzymes, matrix metalloproteinases (MMPs)-2 and -9 and tissue inhibitor of MMP-1 (TIMP-1), in first lavage fluid were markedly induced by CeO_2 at 1 day- and subsequently declined to a lower level at 28 days-post exposure but remained significantly higher than the controls. Hydroxyproline content in lung tissues, a measure for fibrosis, was significantly elevated in the CeO_2-exposed lung tissues in a dose- and time-dependent manner. Morphological analysis showed enhanced collagen fibers in CeO_2 (3.5 mg/kg)-exposed lungs at 28 days post-exposure. In addition, CeO_2 particles were detected in lung tissue and fibroblasts isolated from CeO_2 (3.5 mg/kg)-exposed rats at 28 days after exposure using CytoViva's illumination technology. These results demonstrate that exposure of rats to CeO_2 induced fibrotic lung injury through induction of OPN and the imbalance of MMPs and TIMP in extracellular matrix remodeling. These findings suggest potential health effects of CeO_2 exposure.

PS 2082 PULMONARY TOXICITY OF CRYSTALLINE SILICA AFTER A SINGLE INTRATRACHEAL INSTILLATION IN RATS.

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Pulmonary toxicity induced by crystalline silica particles, micron and nano size, was assessed in rat intratracheal studies. The average primary size of micron and nano size particles was approximately 2.3 μm and 128 nm, respectively. Groups of male Crl:CD (SD) rats were intratracheally instilled with 5 mg/kg of the crystalline silica particles. Following the instillations, the bronchoalveolar lavage fluid (BALF) biomarkers such as the numbers of white blood cells and neutrophils, levels of lactate dehydrogenase (LDH), protein, and cytokines, and histopathological evaluation of lung, liver, spleen, and cerebrum at 1 week, 4 weeks, 3 months, and 6 months (micron-silica group only) after a single instillation was examined. In all crystalline silica groups, toxicological effects were observed only in the lung but not in the liver, spleen, or cerebrum. In the micron-silica-instilled group, the BALF revealed a significant increase in total cell and neutrophil numbers, LDH and protein concentrations, and TNF-α activities. In the histopathological examination, macrophage accumulation and in inflammatory-cell infiltration in the alveoli, and hypertrophy of the alveolar epithelium cells were observed in the micron-silica group up to 6 months after instillation. In the nano-silica-instilled group, the inflammatory responses were less than that of micron-sized groups at any time points after instillation. These findings indicate that the pulmonary inflammatory responses in the group of micron-silica were severe than that of nano-silica group.

PS 2083 SIZE-DEPENDENT IMMUNE-MODULATING EFFECT OF AMORPHOUS NANOSILICA.

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Recently, practical uses of Nanomaterials (NMs) are rapidly spreading to a wide variety of fields, such as cosmetics, foods, and medicine. However, potential harmful effects of nanomaterials on humans are raising concerns about their safety, because nanomaterials may possess novel properties different from micro-sized materials. Despite intensive research efforts, relationships between the biological responses and properties of NMs are not well understood. Using amorphous nanosilicas (nSPs) of different sizes, we have systematically investigated the influence of nSP properties on the distribution and immunue-modulating effect. Firstly, we applied silica particles in diameter of 70, 300 and 1000 nm (designated nSP70, nSP300 and mSP1000, respectively) on the ears of BALB/c mice. Transmission electron mi-

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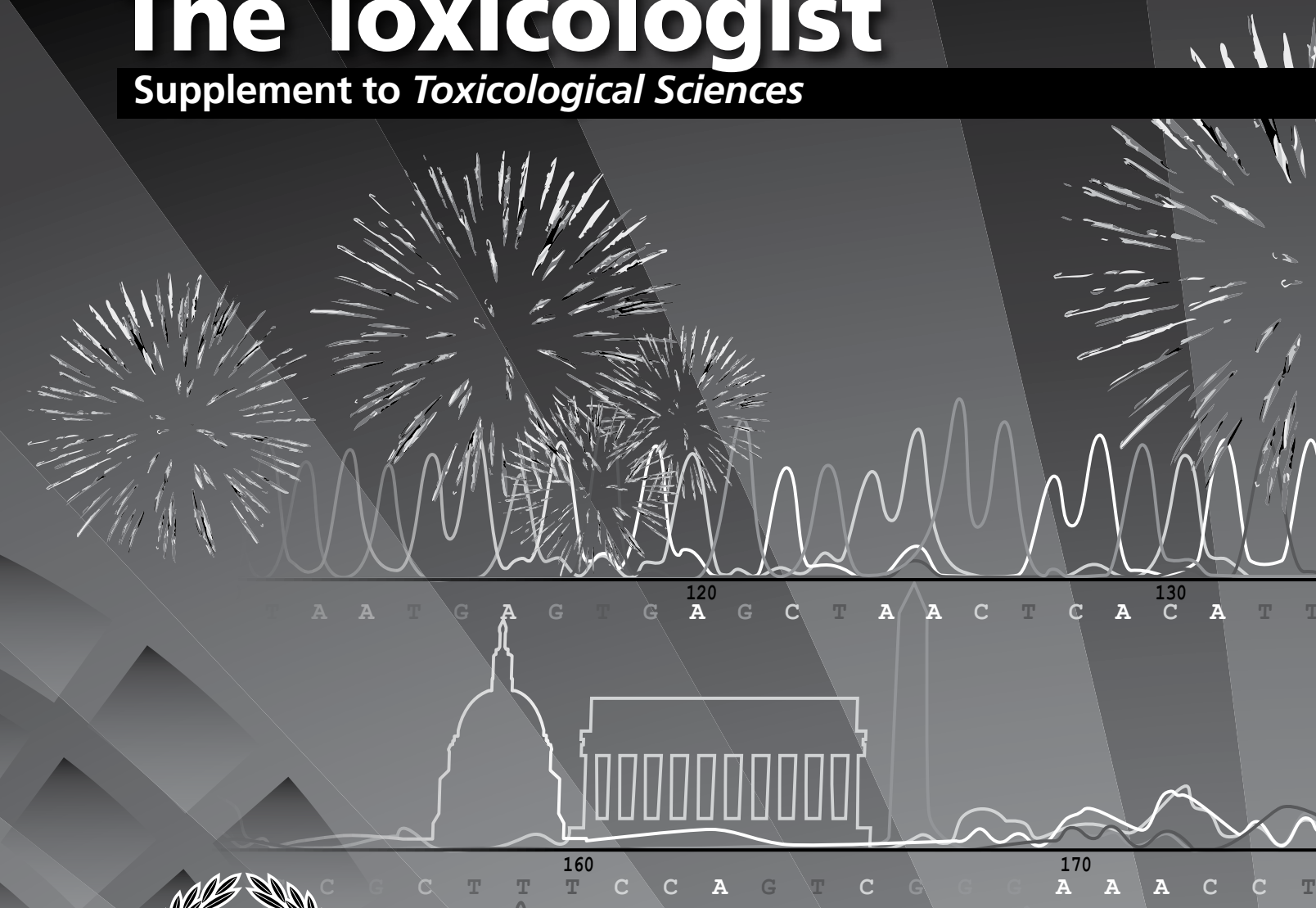

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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