of MM, caused mRNA increase and activation of NLRP3 as measured by caspase-1 activation and IL-1β release. Inhibition of NLRP3 by siRNA caused significant decreases in NLRP3 mRNA levels as well as asbestos-induced IL-1β release in medium. On the other hand, human MM lines and tumor tissues showed significantly decreased levels of NLRP3 and caspase-1 as compared to LP9 or matching normal tissues respectively. Our findings suggest that initial exposure to asbestos causes increased mRNA levels and activity of NLRP3, which may help in MM development by promoting mesothelial cell transformation. However, tumor development culminates in MM with decreased NLRP3 protein and increased drug resistance which may be due to caspase-1 inactivation. Thus NLRP3 may be an appropriate target for therapy of MM, especially in combination with cytotoxic chemotherapeutic drugs and IL-1 receptor antagonists. This study is supported by a Meothelioma Applied Research Foundation (MARF) grant (AS) and by NIEHS grants T32 ES07122 (BM).

#5462 Single dose dermal irritation study of apaziquone in rabbits. Guru Reddy, Shanta Chawla, Steven Fruchtman. *Spectrum Pharmaceuticals, Irvine, CA.*

Introduction and Objectives: Apaziquone is a novel bioreductive alkylating agent in development for intravesical therapy of nonmuscle invasive bladder cancer (NMIBC). The standard dose of apaziquone in all ongoing clinical studies is 4 mg/40 mL (0.1mg/mL). For clinical use, lyophilized apaziquone is reconstituted with diluent and instilled in the bladder. During the preparation and handling of the product, there is a possibility of accidental dermal contact for the healthcare professionals. To date, dermal irritation potential of apaziquone has not been investigated. The purpose of this study was to evaluate the dermal irritation potential of apaziquone in rabbits. Materials & Methods: Apaziquone was administered topically on the skin (non-occlusive) to New Zealand White (NZW) rabbits as a single dose for 4 hours followed by removal of excess material, and skin examination for up to 72 hours after removal of excess material. Each male NZW rabbits (3/group; one group) had three identified treatment sites on the back: (1) untreated (2) vehicle (diluent for apaziquone) and (3) apaziquone (0.1 mg/mL). Animals were treated with a single non-occlusive dermal dose of apaziquone (0.5 mL of 0.1 mg/mL) and vehicle for 4 hours followed by removal of excess material. No test material or vehicle was applied to the site designated as untreated. The treatment sites were observed and scored at baseline and at various times (4, 24, 48, and 72 hours) after removal of excess test article and vehicle. The following parameters were evaluated: viability, clinical observations, and dermal observations/scoring by modified Draize method. Results: No clinical signs of toxicity were observed during the study and no signs of dermal irritation related to test article or vehicle/diluent were observed at any of the dose sites in any of animals. The Primary Dermal Irritation Index for apaziquone, administered at clinically relevant exposures, had a value of zero (0) indicating no irritation at the concentration and for the duration of exposure. Conclusion: Apaziquone did not cause any dermal irritation in rabbits at a clinically relevant concentration.

#5463 Serum aminotransferases and alkaline phosphatases as biomarkers of hepatotoxicity in sprague-dawley rats exposed to silver nanoparticles. Anita K. Patlolla, Paul B. Tchounwou. *Jackson State University, Jackson, MS.*

Nanoparticles are small scale substances (<100 nm) used in biomedical applications, electronics, and energy producrion. Increased exposure to nanoparticles being produced in large scale industry facilities elicits concerns for the toxicity of certain classes of nanoparticles. In particular, the oral toxicity of silver nanoparticles is of concern to ensure public and consumer health. Due to the intensive commercial application of silver nanoparticles (Ag-NPs), health risk assessment of this nanoparticle is of great importance. The previous in vitro studies demonstrated that Ag-NPs caused toxicity in various cell-lines. However, toxicity of Ag NPs in vivo is largely lacking. This study evaluated the effect of Ag-NPs on the activities of specific liver enzymes such as aminotransferases (GOT/GPT), and alkaline phosphatases (ALP) which may be useful as biomarkers of hepatotoxicity. Four groups of five male rats each weighing approximately 80 + 2 g were orally administered once a day for five days with doses of 5, 25, 50 and 100 mg/kg BW of silver nanoparticles. A control group was also made of 5 rats. At the end of the experiment, serum samples were collected following standard protocols. The data obtained from the hepatotoxicity study clearly show that highest two dose 50 and 100 mg/kg of silver nanoparticles has statistically significantly increased the activity of serum aminotransferases (GOT and GPT) and alkaline phosphatases (ALP) when compared to control. The results demonstrate that Ag-NPs have the potential to induce hepatotoxicity in Sprague-Dawley rats. Our result does not imply that silver nanoparticles should be banned from use but more in vivo studies with histopathological characterization should be designed to confirm the results of this study.

#5464 Genotoxicity of multi-walled carbon nanotubes at occupationally relevant doses. Linda M. Sargent,[1] Steven H. Reynolds,[1] David Lowry,[1] Michael L. Kashon,[1] Stanley A. Benkovic,[2] Jeffery L. Salisbury,[3] Ann F. Hubbs,[1] Shih-Houng Young,[1] Katelyn J. Siegrist,[1] Michael J. Keane,[1] John Mastovich,[4] Kristin Bunker,[4] Jacqueline Sturgeon,[4] Lorenzo Cena,[1] Cerasela-Zoica Dinu[1]. *[1]CDC/NIOSH, Morgantown, WV; [2]NeuroScience Associates, Knoxville, TN; [3]Mayo Clinic, Rochester, MN; [4]RJ Lee Group, Monroeville, PA.*

Carbon nanotubes represent a creative alternative for applications in medicine as therapeutic vectors, imaging and controlled release of active molecules. Although the low density and small size of carbon nanotubes makes respiratory exposures to workers likely during the production or use of commercial products, the potential genotoxicity of multi-walled carbon nanotubes has not been investigated. We have previously shown mitotic spindle aberrations in cultured primary and immortalized human airway epithelial cells exposed to single-walled carbon nanotubes (SWCNT). In order to investigate whether genetic damage was unique to SWCNT, we examined mitotic spindle aberrations following dosing of cells to multi-walled carbon nanotubes (MWCNT) at concentrations anticipated in the workplace. Immortalized and primary respiratory epithelial cells were exposed to 0.024, 0.24, 2.4, and 24μg/cm^2 carbon nanotubes. The minimal dose of MWCNT considered for this research was based on the permissible exposure limit for particles with an aerodynamic diameter of less than 5 microns (Occupation Safety and Health Administration). MWCNT induced a dose response of disrupted centrosomes, mitotic spindles and aneuploid chromosome number. The data further showed that monopolar mitotic spindles comprised 95% of the disrupted mitoses. The monopolar phenotype of the disrupted mitotic spindles is in sharp contrast to the multipolar spindle of SWCNT-induced disruption. Three-dimensional reconstructions showed carbon nanotubes integrated with the microtubules, the DNA and within the centrosome structure. The lower doses did not cause cytotoxicity or apoptosis 24 hours after exposure; however, after 72 hours, significant cytotoxicity was observed in the MWCNT-exposed cells. Disruption of the centrosome is common in many solid tumors including lung cancer. The resulting aneuploidy is a key event in the progression of cancer and is correlated with tumor stage. Our results demonstrate significant disruption of the mitotic spindle by MWCNT at occupationally relevant doses. These results suggest caution should be used in the handling and processing of carbon nanotubes.

#5465 Role of CYP2A13 in NNK bioactivation and lung tumorigenesis: *In vivo* studies using a CYP2A13-humanized mouse model. Vandana Megaraj, Xin Zhou, Zhihua Liu, Fang Xie, Jaime D'Agostino, Weizhu Yang, Xinxin Ding. *Wadsworth Center, New York State Department of Health, and School of Public Health, State University of New York at Albany, Albany, NY.*

The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent lung procarcinogen. Previously, we have demonstrated that NNK-induced lung tumorigenesis depends on target tissue bioactivation by pulmonary P450 enzymes (Weng et al., 2007, Cancer Res 67:7825–7832). However, the specific P450 enzyme(s) responsible for NNK bioactivation in the lung have not been identified. The aim of the present study was to test the hypotheses that 1) mouse CYP2A5 plays an essential role in NNK bioactivation and tumorigenesis in mouse lung, and 2) transgenic expression of human CYP2A13, known to be selectively expressed in the respiratory tract and be the most efficient enzyme for NNK bioactivation in vitro, can increase the rates of NNK bioactivation and incidence of tumorigenesis in the mouse lung. Kinetic parameters of microsomal NNK bioactivation in vitro, tissue levels of O^6-methylguanine (O^6-mG) DNA adducts formed in vivo, and incidence of NNK-induced lung tumors were determined for wild-type, Cyp2a5-null, and CYP2A13-humanized (CYP2A13-transgenic/Cyp2a5-null) mice. The results indicated that, in both liver and lung microsomes, the loss of CYP2A5 resulted in significant increases in the Km value for the formation of 4-oxo-4-(3-pyridyl)-butanal (OPB), which represents the reactive intermediate that can lead to the formation of O^6-mG DNA adducts; but, the gain of CYP2A13 led to recovery of the activity in the lung, but not in the liver. The levels of O^6-mG, the DNA adduct highly correlated with lung tumorigenesis, were significantly higher in the lungs of the wild-type mice and CYP2A13-humanized mice, than in the Cyp2a5-null mice. Furthermore, lung tumor bioassays, performed for the three mouse strains on A/J background, and using NNK at various doses (30 -200 mg/kg; single i.p. dose), revealed that lung tumor multiplicity determined at 4 months post-treatment was significantly greater in wild-type and CYP2A13-humanized mice than in Cyp2a5-null mice, for all NNK doses tested. The difference in lung tumor multiplicity between CYP2A13-humanized mice and Cyp2a5-null mice was greater at low (30 mg/kg) NNK dose (~70%) than at high (200 mg/kg) NNK dose (~30%). In control experiments, rates of systemic clearance of NNK and its major circulating metabolite, NNAL, were confirmed to be not different among the three mouse strains. These results indicated that CYP2A13 is a low-Km enzyme in catalyzing NNK bioactivation in vivo, and they provide

Proceedings

Volume 53 | 2012

Continuing Medical Education Activity – *AMA PRA Category 1 Credit(s)™ Available*

2012

Accelerating Science:
Concept to Clinic

AACR ANNUAL MEETING

March 31 - April 4
McCormick Place West
Chicago, IL

AACR American Association for Cancer Research www.aacr.org