genic phenotypes by allylamine. (Supported in part by NIH Grant ES 09106 and a TAMU Interdisciplinary Grant.)

## 1192 ACTIVATION OF HEPATIC NF-κB BY POLYCHLORINATED BIPHENYLS (PCBS) *IN VIVO* AND IN CULTURED RAT HEPATOCYTES.

Z. Lu, B. T. Spear, L. W. Robertson and H. P. Glauert. *University of Kentucky, Lexington, KY.*

Polychlorinated biphenyls (PCBs) are environmental pollutants that, due to their persistence and biomagnification, raise concerns about the health consequences of long-term exposure. The mechanism of the promoting activity of PCBs has not yet been determined. Previous studies show that oxidative stress occurs during metabolism of PCBs, with the formation of free radicals and oxidative DNA damage, which may contribute to their promoting activity. In this study, we examined whether oxidative stress-sensitive transcription factors NF-κB or AP-1 would be induced by PCBs *in vivo* or in primary hepatocyte culture. Male Sprague-Dawley rats were injected i.p. with corn oil, 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153, 30, 150 or 300 umol/kg), 3,3',4,4'-tetrachloro-biphenyl (PCB-77, 30, 150 or 300 umol/kg) or both PCBs (30 or 150 umol/kg each). Rats were killed 2, 6, or 24 hours, or 2, 6, and 10 days after the PCB injection. Electrophoretic mobility shift assays were performed to determine the DNA binding activities of NF-κB and AP-1. The highest NF-κB DNA binding activity was observed in rats receiving higher doses of PCB-153 (150 and 300 umol/kg), with a peak occurring 2 days after injection. NF-κB activity was also increased in rats receiving both PCBs to a lesser extent, but no effect was seen in rats treated with PCB-77. Primary rat hepatocytes were cultured on collagen gels in serum-free L-15 medium with or without PCBs. NF-κB binding activity in hepatocytes culture was increased after a 48 hour exposure to PCB-153 (20 μM). These results show that hepatic NF-κB binding activity can be activated by specific PCBs *in vivo* and in cultured rat hepatocyte culture, indicating hepatic oxidative stress induced by PCBs. (Supported by ES 07380.)

## 1193 BCL-X1 AND BCL-2 EXPRESSION IN RAT VESTIBULAR AND AUDITORY BRAINSTEM NUCLEI FOLLOWING *IN VIVO* EXPOSURE TO *m*-DINITROBENZENE.

M. L. Hann and M. A. Philbert. *University of Michigan, Ann Arbor, MI.*

m-Dinitrobenzene (DNB) induces dose-dependent gliovascular lesions in auditory and vestibular brainstem nuclei with secondary damage to neurons. This study investigates Bcl-2 and Bcl-$X_L$ expression in rat brainstem nuclei during DNB-induced neurotoxicity *in vivo*. Male Fisher 344 rats were given either 7 mg/kg (mild lesion) or 10 mg/kg (severe lesion) DNB in DMSO twice daily via intraperitoneal injection for 1-3 days and sacrificed at 24, 48, 54 and 72 h after the first dose. Immunohistochemistry and western immunoblotting were used to examine expression of Bcl-$X_L$ and Bcl-2 in affected regions such as inferior colliculi, deep cerebellar roof, vestibular, and cochlear nuclei. Regions resistant to DNB-induced neurotoxicity, such as cerebellum and hippocampus, were also examined. Positive staining for Bcl-$X_L$ and Bcl-2 was noted in neuronal somata, dendrites and proximal axons of brainstem neurons in rats given 60 mg/kg DNB at 10 mg/kg twice daily for three days. No expression of Bcl-$X_L$ and Bcl-2 was observed in neurons and astrocytes of control brains. Western blotting revealed moderate basal expression of Bcl-$X_L$ and Bcl-2 in the inferior colliculi, deep cerebellar roof and cochlear nuclei of all control and DNB-exposed animals. A time-dependent increase in Bcl-$X_L$ and Bcl-2 expression was observed in cerebellum and hippocampus in animals exposed to 10 mg/kg DNB, but not in controls at any timepoint. DNB-related induction of both proteins began at 24 h and was maximal at 72 h. Increased levels of Bcl-$X_L$ and Bcl-2 were observed by immunohistochemical analysis in all brainstem nuclei examined from animals exposed to 7 mg/kg DNB twice daily for three days. No increase in expression of Bcl-$X_L$ and Bcl-2 was observed by western blot analysis with the 7 mg/kg DNB dosing regimen. These results suggest that differential expression of Bcl-$X_L$ and Bcl-2 correlates with lack of susceptibility to DNB neurotoxicity. (This research is supported by PHS-NIH Grants ES08846 & ES06103.)

## 1194 DIFFERENTIAL EXPRESSION AND ACTIVITY OF *Nrf2* IN LUNGS OF HYPEROXIA-SUSCEPTIBLE AND -RESISTANT MICE.

H. Cho, S. P. M. Reddy, L. Zhang, A. E. Jedlicka and S. R. Kleeberger. *Johns Hopkins University, Baltimore, MD.*

Acute respiratory distress syndrome (ARDS) is a major lung disease mediated by reactive oxygen species. An *in vivo* model of acute lung injury with similar features of ARDS has been produced by administration of hyperoxia (>95% oxygen) to animals. Among inbred mouse strains mice, C57BL/6J (B6) have greater sensitivity to hyperoxia than other inbred strains, including C3H/HeJ (C3). We recently identified significant hyperoxia-susceptibility quantitative trait locus (QTL) on mouse chromosome 2. A strong candidate gene within this QTL is *Nrf2*, an essential transcriptional regulator of antioxidant enzymes that play key roles in protecting cells against carcinogenicity and oxidative stress. To test the hypothesis that *Nrf2* confers differential susceptibility to oxygen toxicity, *Nrf2* mRNA expression (by reverse transcriptase-polymerase chain reaction) and DNA binding activity (by gel shift/supershift analyses) were evaluated in the lungs of C3 and B6 mice exposed to hyperoxia. Exposure markedly and similarly induced *Nrf2* mRNA expression at 90 min and 6 hr in both strains, compared to strain-matched air-controls. The mRNA levels returned to basal levels at 24 hr in both strains. A second increase in *Nrf2* mRNA expression occurred after 48 hr in C3 mice; in B6 mice, the mRNA level did not increase again until after 72 hr. The basal NRF-2 activity was greater in B6 mice compared to C3. After 90 min exposure, NRF-2 activity increased in C3 mice proportional to gene expression and remained elevated until 48 hr. In contrast, NRF-2 activity was markedly decreased in B6 mice by 6 hr and continued to decrease during the exposure. These results indicate that there is a significant strain-specific variation in *Nrf2* expression and activity after hyperoxia exposure. The results also suggest the early increase in NRF-2 activity conferred greater protection against oxidant injury in resistant C3 mice, while decreased NRF-2 activity may enhance susceptibility in B6 mice. (Support: ES 09606, HL 57142.)

## 1195 ACTIVATION OF ACTIVATOR PROTEIN-1 BY REACTIVE OXYGEN SPECIES ASSOCIATED WITH ASBESTOS.

V. Vallyathan, M. Ding, X. Shi and V. Castranova. *NIOSH, Morgantown, WV.* Sponsor: D. Jones.

Inhalation of asbestos causes alterations in cell signaling cascades, gene expression, cell injury and cell proliferation which may lead to pulmonary fibrosis, lung cancer, or mesothelioma. Asbestos-mediated free radical reactions are believed to trigger a number of cellular and molecular events that may promote fibrogenesis and carcinogenesis. Because activator protein 1 (AP-1) plays an important role in pre-neoplastic-to-neoplastic transformation, tumor promotion and metastasis, we studied the possible activation of AP-1 *in vitro* in cultured JB6 cells and *in vivo* using transgenic mice after exposure to crocidolite asbestos. *In vitro* exposure to asbestos, caused a dose- and time-dependent activation of AP-1 in cultured JB6 cells. Exposure of mice to crocidolite asbestos caused a significant (22-fold) activation of AP-1 in bronchiolar tissue compared to a moderate 10-fold increase in the lung tissue. The induction of AP-1 in asbestos exposure appears to be mediated through the phosphorylation of mitogen-activated protein kinases, Erk 1 and Erk2. Hydroxyl radical scavengers inhibited asbestos-induced AP-1 activation. These data support the hypothesis that oxygen radical mechanisms may be associated with pulmonary fibrosis and carcinogenesis.

## 1196 METHODS FOR MEASURING EXPRESSION OF IL-1 ALPHA, NITRIC OXIDE SYNTHASE, AND NITRIC OXIDE IN F-344 RAT SKIN IN RESPONSE TO DERMAL EXPOSURES TO FUELS OR SOLVENTS.

M. Kabbur[1], C. Garrett[2], K. Geiss[2], W. Brinkley[1] and J. McDougal[2]. [1]*AFRL/HEST, Wright-Patterson AFB, OH and* [2]*Geo-Centers, Inc., Dayton, OH.*

Organic chemicals such as jet fuels and solvents are recognized to cause skin irritation after dermal exposures. The molecular responses to these chemicals that result in acute irritation are not understood well enough to allow the establishment and choice of safe exposure limits. We conducted studies to determine the feasibility of measuring various inflammatory factors, including IL-1 alpha, nitric oxide synthase, and nitric oxide. Male F-344 rats were exposed to organic chemicals for one hour using Hill Top Chambers®. Three hours after the exposures treated and control skin samples (1 to 1.5g) were collected. Light microscopy evaluation was performed on formalin-fixed and


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