changes in EEGs observed at doses up to 1000 mg/kg even though the dose exceeded the maximum tolerated dose. The convulsions appear to be species specific for the rat since monkeys with plasma exposures similar to those associated with convulsions in rats were not observed to have any CNS related effects or convulsions following administration of LY for 1 year. The difference in incidence of convulsions between monkeys and rats is likely due to known anatomical and physiological differences between rodents and primates.

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PL **587** **DECREASED NEURONAL DAMAGE AND GLIAL REACTIVITY IN AN ANIMAL MODEL OF STRESS.**

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Neuronal damage elicits responses from glia that can be modulated by high levels of stress hormones. We evaluated neuronal damage and the glial response following treatment of C57BL/6J mice with corticosterone (CORT) and kainic acid (KA). Male mice were implanted with 100 mg/21 d release CORT pellets. After 7 d, mice received an intraperitoneal injection of saline or 25 mg/kg KA, were scored for seizures for 4 h, and were allowed to recover for 24 h. Brains were sectioned at 60 microns to allow 3-D evaluation of cellular morphology, and were analyzed for neurodegeneration by the cupric-silver stain, for microglia by Iba-1 and CD68 immunohistochemistry, and for astrocytes by GFAP immunohistochemistry. KA treatment caused neuronal damage that was especially evident in hippocampus, cortex, and thalamus. CORT pretreatment decreased argyrophilic staining. Iba-1 immunohistochemistry revealed microglial cells that were homogeneously dispersed throughout all brain regions including saline-injected controls. In 3-D space, ramified microglial cells occupied a specific volume that contained processes from that cell only. KA treatment caused activation of microglia and initiated a phenotypic transformation into amoeboid phagocytes that contained large vacuoles of ingested debris. In 3-D space, activated microglia were surrounded by a buffer space presumably formed as cellular processes retracted. Iba-1 staining was decreased in animals treated with CORT alone or with CORT + KA. CD68 immunostaining was not observed in control mice; however, KA treatment caused punctate immunoreactivity that was dispersed throughout the cell body and processes. In CORT-treated animals, CD68 immunostaining was virtually absent, and in co-treated mice, immunoreactivity was decreased. Basal GFAP immunoreactivity was observed in control mice where astrocytes displayed long, thin processes. KA treatment resulted in increased GFAP immunostaining that was prevented by CORT pretreatment. These data indicate high dosages of corticosteroids decrease neuronal damage caused by KA and subsequent astro- and microglial activation.

PL **588** **PROTEIN ARRAY METHODOLOGY IMPROVES THE DETECTION OF IMMUNE RESPONSE AGAINST PATHOGENS IN ANIMALS USED IN TOXICOLOGY STUDIES.**

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Testing new drugs in animal models is an integral component in pre-clinical and clinical studies. The toxicology data obtained from the animal could be tainted by the undetected presence of pathogens. Thus the data obtained from toxicology studies in animal models depend on the health status of the animals used. An animal whose health is compromised will generate data that are not related to the toxicity of the drug. This underscores the importance of knowing the health status of the animal before it is used in any toxicology study. A parameter used to decide if an animal can be used in a study is to determine if it is infected or has been infected by common species-specific pathogens. The assessment is done by detecting the presence of the pathogen or by detecting the animal's immune response to it. Due to the important role played by these assays in support of the drug development process, an improvement of detection level is always desired. In this abstract we report an improvement in the detection of immune response to pathogens by using a protein array based technology, as compared to a traditional and commonly accepted method. Serum samples were tested in the protein array to determine the limit of detection of a sample. Serum samples were prepared at several dilutions and tested by ELISA and protein array. Samples were tested for the detection of antibodies against several viruses, including Herpes B, Simian Immunodeficiency virus, Simian Retrovirus, and Simian T-Lymphotropic virus. Cut off values were determined by analysis of ROC curves from populations of positive and negative samples. Comparison of results between both assays showed an up to 32-fold improvement in antibody detection using the protein array. These results suggest that the protein array could detect antibodies against specific pathogens earlier than the ELISA, when the antibody levels are low. This is important because if infected animals are used in toxicology studies invalid data will be generated. This improvement increases the level of confidence in the observations obtained in toxicology studies.

PL **589** **EXPRESSION OF PHASE-I ENZYMES IN 17 MOUSE STRAINS – A TOOL FOR TOXICOLOGICAL RESEARCH.**

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The toxicity of many chemicals depends on their biotransformation by phase-I enzymes to more or less toxic metabolites. To determine the in vivo role of an enzymatic pathway in the toxicity of chemicals, inducers or inhibitors of a pathway, and/or genetically modified animals, are often used. Unfortunately, these models are often not ideal. It would be useful to have additional models which provide natural, reproducible variations in expression of an enzyme to understand its importance in the toxicity of a chemical. Therefore, the purpose of this study was to determine whether the mRNA expression of hepatic phase-I enzymes was variable enough in different mouse strains to alter the toxicity of chemicals. Livers of 9-week-old male and female mice were collected from 17 strains, and the mRNA expression of 5 cytochrome P450s (Cyp), cytochrome P450 reductase (CPR), 10 aldehyde dehydrogenases (Aldh), 8 carboxyesterases (Ces), and 2 paraoxonases were quantified. Five groups of genes could be distinguished based on their variance in 17 strains; such as genes which have 1.8 to 4-fold- (10 genes, e.g. Cyp2e1), 4 to 6-fold- (7 genes, e.g. Cy1a2, Cyp3a11, CPR), 8-fold- (2 genes), 20 to 30-fold- (4 genes), and more than 100-fold- (4 genes, e.g. Cyp2b10, Cyp4a14) variations. In the majority of strains, 7 genes were female-predominant (e.g. Cyp2b10, Cyp4a14, CPR), whereas 3 Ces genes were male-predominant. Some strains showed opposite gender differences from the majority of strains. For example, Cyp2b10 was female-predominant in 15 strains, but in the 129S1/SvImJ strain, Cyp2b10 was strongly male-predominant. In conclusion, for most phase-I enzymes, there is sufficient variation in expression so that low, medium, and high gene-expressing representative strains and/or genders could be selected, providing a natural in vivo model to determine the importance of a specific phase-I enzyme in the kinetics and toxicity of a chemical. (Supported by NIH grants ES009716, ES009649, ES013714, DK081461, RR021940.)

PL **590** **A MOUSE MODEL OF SEVERE HALOTHANE HEPATITIS BASED ON HUMAN RISK FACTORS.**

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Halothane is an inhaled anesthetic that induces severe hepatitis in approximately 1 in 20,000 patients. The known risk factors for the development of halothane hepatitis include female sex, mature age, genetics, and multiple exposures. The mechanism of the severe halothane hepatitis is not entirely understood. We examined human risk factors for the ability to alter the sensitivity of mice to halothane-induced liver injury. To evaluate the influence of sex and age on halothane sensitivity, 4, 8, and 10-12 week old (wo) female and male BALB/cJ mice were treated with halothane (15 mmol/kg, ip), and alanine aminotransferase (ALT) activity was evaluated 24hr later. The 8wo and 10-12wo female mice developed severe liver injury (ALT ~8000 and ~7000 U/L), whereas this response was milder (ALT<2000 U/L) in males of the same age and in younger mice of either sex. Livers from halothane-treated, 10-12wo female mice developed extensive centrilobular necrosis, inflammatory cell infiltrate, and steatosis within 12hr of halothane exposure. This is consistent with the histological findings in livers from human patients with halothane hepatitis. To examine the influence of genetics on the sensitivity to halothane, two inbred mouse strains (BALB/cJ and C57BL/6) were exposed to halothane (5, 15, 30 mmol/kg, ip), and ALT activity was evaluated 24hr later. There was no hepatotoxicity at any dose in the C57BL/6 mice, whereas dose-dependent hepatotoxicity developed in BALB/cJ mice. No liver injury developed when 10-12wo female mice were exposed to isoflurane (5, 15, 30mmol/kg), an inhaled anesthetic with less idiosyncratic hepatotoxicity liability than halothane in humans. Therefore, this animal model based on human risk factors is characterized by reproducible, severe hepatitis from halothane exposure and lesions characteristic of those seen in patients who died from halothane hepatitis. (Supported by NIH grant GM075865.)

PL **591** **EVALUATING THE SENSITIVITY OF 6 DIFFERENT F1 HYBRID MICE FOR GENETIC SUSCEPTIBILITY TO IONIZING RADIATION.**

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Heterozygous allelic variation introduced by outcross of female isogenic mice to B6.129-Trp53tm1Brd N12 deficient male mice was predicted to modify tumor phenotype, prevalence, and latency. To evaluate the effect of allelic variation intro-