Bronchoalveolar lavage was performed and pulmonary eosinophils assessed. The application area appeared normal, without any sign of inflammation examined grossly or microscopically. Immunohistochemical study (with one exposure only) found TMA-adduct staining in the stratum corneum and hair follicle. Specific IgE was noted by day 14 and levels were TMA dose-dependent. Eosinophilic inflammation and both early (EAR) and late airway response (LAR), were observed after airway challenge. EAR subsided within 30 min following challenge. LAR typically began 2 or more hours following challenge and persisted longer than 8 hours. TMA specific IgE and airway responses occurred in both occluded and non-occluded dermally exposed rats. Dermal exposure to dry TMA powder can induce specific-IgE and subsequent asthmatic-like EAR and LAR following TMA aerosol challenge. This model may be useful for mechanism study of dermal exposure and asthma from low-molecular-weight chemicals.

293 THE ROLE OF DERMAL EXPOSURE IN THE DEVELOPMENT OF LATEX ALLERGY.

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Latex allergy remains a serious risk for health care workers with past prevalence rates reported to range from 2.7-12%. Exposure may occur through inhalation as latex proteins bind to glove powders and are aerosolized during donning and removing gloves or through dermal exposure. Although hand dermatitis has been accepted as a risk factor, little is known of the relative contribution of the two routes of exposure to the development of sensitization. Animal models (BALB/c mice and hairless guinea pigs) have been used to evaluate the role of dermal exposure in the development of latex sensitization and to compare the potential for sensitization by the two routes. *In vitro* penetration studies using human surgical specimens and hairless guinea pig skin have demonstrated the importance of skin condition in the penetration of latex proteins with less than 1% of the applied dose of non-ammoniated latex (NAL) penetrating intact skin while as much as 30% penetrated through abraded skin. Exposure of BALB/c mice to 25µg NAL every 5th day by the dermal or intratracheal (i.t.) routes resulted in similar levels of latex specific IgE as measured by ELISA. A robust latex specific IgA response was seen in animals exposed by the i.t. route as compared to the dermal route. Upon respiratory challenge with methacholine, non-specific airway hyper-reactivity was dose-responsively increased and positively correlated with total IgE levels in animals exposed to latex proteins by either the i.t. or dermal routes. Immunoblot analysis revealed a different spectrum of sero-recognition of individual latex protein when exposure was *via* the i.t. versus the dermal route. Intervention strategies have been aimed at reducing the powder and latex protein content of gloves. Although these efforts have been observed to reduce the prevalence of symptoms in sensitized individuals, these data raise concerns regarding dermal exposure resulting from the continued use of low protein latex gloves. This work was supported in part by NIEHS interagency agreement #Y1-ES-0049-03.

294 INCLUSION OF SKIN EXPOSURE REDUCTION IN A TOTAL HYGIENE PROGRAM TO REDUCE EXPOSURE TO BERYLLIUM: BACKGROUND AND RESULTS.

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Recent epidemiological studies show no or very weak association between the mass concentration of beryllium in air, the traditional metric of exposure, and the prevalence of sensitization to beryllium or chronic beryllium disease. In general in the USA beryllium workplaces have permitted unlimited skin contact with beryllium solutions or particulate. In 1998 the possibility that sensitization to beryllium might occur *via* the skin was raised. Since then measures have been introduced to reduce skin exposure to beryllium solutions and particulate. Also taken were measures to reduce lung exposure to beryllium as well as dispersion of beryllium by various pathways within the workplace. Early data suggests these measures together reduce sensitization to beryllium.

295 GENOMIC MARKERS OF NEPHROTOXICITY IN FEMALE CYNOMOLGUS MONKEYS.

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The emergence of genomic technologies has led to a focused effort to identify early predictive markers of target organ toxicity. We define gene expression changes that correlate with the onset of histopathlogical lesions as genomic indicators of toxicity. For a genomic target to be considered an early predictive marker its expression pattern must quantitatively change before the development of the lesion, and the magnitude of change should intensify with the detection of histopathology. We have studied quantitative gene expression changes in the kidneys of female cynomolgus monkeys dosed with gentamicin (10 mg/kg) and/or everninomicin (30 or 60 mg/kg), an experimental oligosaccharide antibiotic, for seven days. Both drugs have been demonstrated to cause renal tubular necrosis and degeneration in rodents and non-human primates. Monkeys receiving both drugs showed renal lesions as early as day 1, consistent with a potentiation mechanism of gentamicin on everninomicin toxicity. By day 7 monkeys dosed with 60 mg/kg everninomicin alone also developed renal lesions, while the group exposed to both compounds had more extensive renal damage. The modulation of several genes previously identified to be associated with nephrotoxicity in rodent models was confirmed using quantitative real-time PCR. Among these, c-myc, c-jun, and MMP-9 exhibited changes consistent with the definition of a genomic marker of toxicity. Logistic regression modeling demonstrated a high degree of correlation between changes in gene expression and the development of histopathology. In addition, we identified a candidate early marker of toxicity. The expression of clusterin, a protein previously associated with renal necrosis, was significantly different from control levels (≥2-fold change) on day 1, and its level of expression was greater on day 7. These results provide the first data confirming gene expression changes associated with rodent nephrotoxicity in a non-human primate model, and are the first step in the validation of clusterin as an early marker for nephrotoxicity.

296 EXPRESSION OF GENES ASSOCIATED WITH DRUG-INDUCED BILIARY HYPERPLASIA AND CELL PROLIFERATION IN CYNOMOLGUS MONKEYS.

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Bile duct hyperplasia (BDH) can develop following administration of certain drugs. It is an important health concern because there are no predictive biomarkers for BDH that would allow adequate patient monitoring in the early stages. BDH arises as a consequence of cell proliferation within the hepatobiliary tree. We have investigated gene expression changes associated with BDH and cell proliferation in Cynomolgus monkeys treated with an experimental S-P compound. Histopathological evaluation of the livers and determination of a BrdU labeling index (BrdU-LI) for the biliary epithelium were used to separate the treated monkeys into good responders (BDH and high BrdU-LI), poor responders (BDH and low BrdU-LI) and non-responders (no BDH and no change in BrdU-LI). RNA isolated from the livers of these monkeys was hybridized on the Affymetrix U133 human genome chip. Analysis of this data with the GeneLogic Gene Express software revealed gene expression changes associated exclusively with monkeys in each of the good-, poor- and non-responder groups. There was limited overlap between the histopathological results for individual monkeys in each of these groups and between gene sets in these groups. Some of the genes that overlap include cyclins and other genes associated with cell proliferation. We identified 13 gene expression changes that discriminate between good- and non-responders, 63 for discrimination between good- and poor responders, and 23 for discrimination between poor- and non-responders. We also identified 5 gene expression changes that would discriminate between groups of monkeys with hyperplasia and those with no hyperplasia, 7 for high BrdU and low BrdU, and 2 for both of these effects. The predictive value of these changes will be evaluated further with quantitative PCR.

297 GENE EXPRESSION PROFILING OF NORMAL MAMMARY TISSUES FROM RAT STRAINS SENSITIVE AND RESISTANT TO MAMMARY CARCINOGENESIS.

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While human genetic linkage analyses have identified tumor suppressors that are responsible for familial breast cancer, many susceptibility genes are likely to be partially penetrant, due to the modifying effects of diverse genetic backgrounds and gene-environmental interactions. The advantage of using animal models to study inherited cancer susceptibility genes is the ability to use carefully controlled carcinogen exposure in highly inbred strains of animals. Consequently, breast cancer suppressor mutations that would have low penetrance in the human population may present as highly penetrant phenotypes in experimental tumor models. To gain insight into gene-environmental interactions in mammary carcinogenesis, we compared gene expression profiles in normal mammary glands from the sensitive Fisher 344 and resistant Copenhagen rat strains. Gene expression profiles were compared