the susceptibility to Parkinson's disease, possibly by altering accumulation of environmental neurotoxicants in the brain. However, evidence is missing as to whether these neurotoxicants are P-gp substrates and if P-gp alters their ability to cross the BBB. Our goal is to measure P-gp transport of neurotoxicants and determine if *ABCB1* genetic variation changes transport across the BBB. Our initial studies focused on the neurotoxicant paraquat. We utilized two cell lines: MES-SA cells that express no P-gp and MES-SA-DX5 cells that overexpress P-gp. In these cells we measured intracellular paraquat accumulation by HPLC detection and paraquat-induced cytotoxicty. After incubation with 500 μM paraquat, we observed higher intracellular paraquat accumulation in MES-SA cells compared to MES-SA-DX5 cells (18.2+1.3 and 1.22+0.31 pmol/1x106cells/hr, respectively; p<0.0001) indicating that P-gp is mediating the transport of paraquat. To confirm this, we utilized a P-gp inhibitor (GF120918) and observed a significant increase in paraquat accumulation in MES-SA-DX5 cells. We observed an approximately 10-fold increase in resistance to paraquat cytotoxicity in MES-SA-DX5 cells compared to MES-SA cells, providing further evidence that paraquat is a P-gp substrate. Alteration in P-gp transport due to *ABCB1* genetic variation has been proposed to play a role in the development of Parkinson's disease. Therefore, our future studies will examine how *ABCB1* genetic variation alters neurotoxicant transport utilizing a lentivirus expression system in LLC-PK1 epithelial cells. This study will provide the missing data to measure P-gp-mediated transport of neurotoxicants involved in the susceptibility to Parkinson's disease and the influence of *ABCB1* genetic variation.

PS 359 STYRENE INDUCED HEALTH EFFECTS RELATED TO ALDH2 POLYMORPHISMS IN CHINESE WORKERS.

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Styrene is an important industrial chemical used worldwide. Styrene-exposed workers have been studied extensively for the induction of various types of genotoxic effects in relation to genetic polymorphisms, and the results remained conflicting. One important cause is that most of the studies performed thus far included only relatively small subjects, making it more difficult to detect possible associations and possibly suggesting false associations. To further clarify genetic modification of DNA damage levels following exposed to styrene, we recruited a relatively larger sample (more than 400 workers including styrene-exposed and non-exposed control subjects). In addition, we also evaluated the effect of aldehyde dehydrogenase 2 (ALDH2) gene polymorphisms on styrene-induced DNA damage. Owing to that not only ALDH2 is involved in the metabolism of styrene, but also approximately over 40% of the population in East Asia lacks the enzyme activity due to mutant alleles of ALDH2 gene. DNA damage was measured by the FPG-modified comet assay. ALDH2 genotypes were determined by PCR-RFLP. Styrene exposure levels were estimated by the urinary concentrations of its metabolites (mandelic acid and phenyglyoxylic acid). We found no effect of styrene exposure on red blood cell count, but the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were significantly lower in styrene-exposed workers, and these effects were found in both genders. Other detailed results will be presented. To our knowledge, this is the first investigation that ALDH2 polymorphisms may have an effect on DNA damage in leucocytes caused by styrene.

PS 360 INDIVIDUAL VARIATION IN PARAOXONASE 1 ACTIVITY IN HUMAN SERUM OVER TIME.

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Paraoxonase 1 (PON1) is a serum glycoprotein capable of hydrolyzing many pesticides. There is a substantial variation among individuals within a population due to genetic and environmental factors, including the Q192R polymorphism, which affect the efficiency of substrate hydrolysis. Low PON1 activity levels have been associated with increased risk for atherosclerosis and other disorders. It has been shown that PON1 levels appear to be lower in older populations, but no known study has measured serum PON1 activity levels in the same individuals over time. A prospective study is underway to determine if individual serum PON1 levels vary significantly over a time span of about 15 years and which changes in lifestyle, diet, or occupational exposure factors may influence PON1 levels. In a pilot study, 30 rural Iowan males ages 44-73 at the study onset, about half farmers, were evaluated. Serum samples had been taken since 1994 roughly every 5 years and stored at -80°C, making three samples available from each individual. PON1 activity and Q192R phenotype were determined using phenyl acetate and CMPA [4-(Chloromethyl)phenyl acetate] as substrates. Based on the assay results, all three phenotypes are represented in the cohort. With phenyl acetate and CMPA, 53% and 43% of subjects, respectively, did not show the expected decreased PON1 levels with age. This difference in substrate sensitivity may be due to the lower enzyme specificity of phenyl acetate. This pilot study did not conclusively confirm the assumed age-related decrease in PON1 levels at the individual level. Increasing the number of participants and including dietary, health, and pesticide exposure data from the accompanying questionnaires of this ongoing large population study will allow us to identify genetic and environmental risk factors for low PON1 status, the role of pesticide exposure, and allow us to counsel the most at-risk subgroup about their individual pesticide vulnerability. (NIEHS P42ES013661 and U07/CCU706145 from CDC/NIOSH)

PS 361 MODULATION OF GENETIC DAMAGE AND DNA REPAIR CAPACITY BY GENETIC VARIATIONS IN THE NUCLEOTIDE EXCISION REPAIR GENE XPC.

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Xeroderma pigmentosum complementation group C protein, encoded by the XPC gene, plays a key role in DNA nucleotide excision repair (NER). XPC is highly polymorphic, with over 90 single nucleotide polymorphisms (SNPs). A few were evaluated as potential modifiers of cancer risk, however, a comprehensive evaluation of all common XPC SNPs on DNA damage-response and DNA repair capacity (DRC) has not been performed. We constructed a comprehensive haplotype map encompassing all XPC SNPs, and evaluated the relationship between DNA damage associated with smoking, using chromosome aberrations (CA) as a biomarker, and these haplotypes. We identified 21 haplotypes that segregated into 6 phylogenetic haplotype groups (PGHs A-F). Our data indicate significant interaction between PGH-C and smoking for baseline CA (P=0.046). Using the mutagen-sensitivity assay (a biomarker that serves as an intermediate phenotype for cancer risk), we also observed significant interaction between smoking and PGH-D (P=0.023) and PGH-F (P=0.007) for mutagen-induced CA. To provide mechanistic explanations to our findings, we exposed human lymphoblastoid cells, with different XPC haplotypes, to UV radiation, which generates classical NER substrates (cyclobutane pyrimidine dimers and 6-4 photoproducts). Using the UVDE FLARE assay, which quantitates UV-induced DNA damage, we determined the relationship between XPC haplotypes and DRC. We hypothesized that if XPC haplotypes have functional effects, there would be a correlation between these haplotypes and DRC, and levels of UV-induced genetic damage. Our preliminary results suggest a relationship between XPC haplotypes and DRC, and provide initial mechanistic explanations to the biological effects we observed in smokers and to the reported association between XPC SNPs and cancer risk.

PS 362 GENETIC VARIATION IN ISOGENIC STRAINS OF FEMALE MICE ALTERS THE DISPOSITION AFTER ACUTE EXPOSURE TO [14C] BENZENE.

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Many variations in human susceptibility to chemically-induced toxicities are linked to alterations in phenotype/genotype. Such genetic diversity may influence the disposition/metabolism of a chemical. Genetically diverse murine strains were selected from the NTP-Perlegen Mouse Genome Resequencing Project (Tier 1) to examine differences in systemic exposure and/or metabolite formation and clearance following a single benzene exposure. Using 18 strains of male mice, genetic diversity appears to alter the disposition of benzene and/or its metabolites as assessed by the AUC, Cmax or Tmax of [14C] benzene equivalents in whole-blood. Current studies have focused on searching for corresponding differences in female mice from these same strains. Female mice (5 per time point) were administered a single oral dose of [14C] benzene, (0.1 mg/kg, 75 μCi/kg). Blood and urine (from bladder) were obtained at 5-120 min post dose for analysis of total [14C] content. The AUC, Cmax and Tmax of [14C] equivalents in blood ranged from 34 to 119 min*μmol/mL, 0.2-0.6 μmol-eq/mL and 11-38 min, respectively. Small but notable differences were observed in the qualitative profile of benzene metabolites present in bladder urine among the various mouse strains. These results indicate the inter-strain differences in benzene metabolism and disposition are less variable in females that those seen in males of the same strains. Based on these results, strains showing notable differences in these parameters will be selected for detailed pharmacokinetic/metabolic studies. This research was supported in part by the NIEHS NTP Grant No. N01-ES-45529 and NIEHS-sponsored Southwest Environmental Science Center Grant Number P3-ES-06694.

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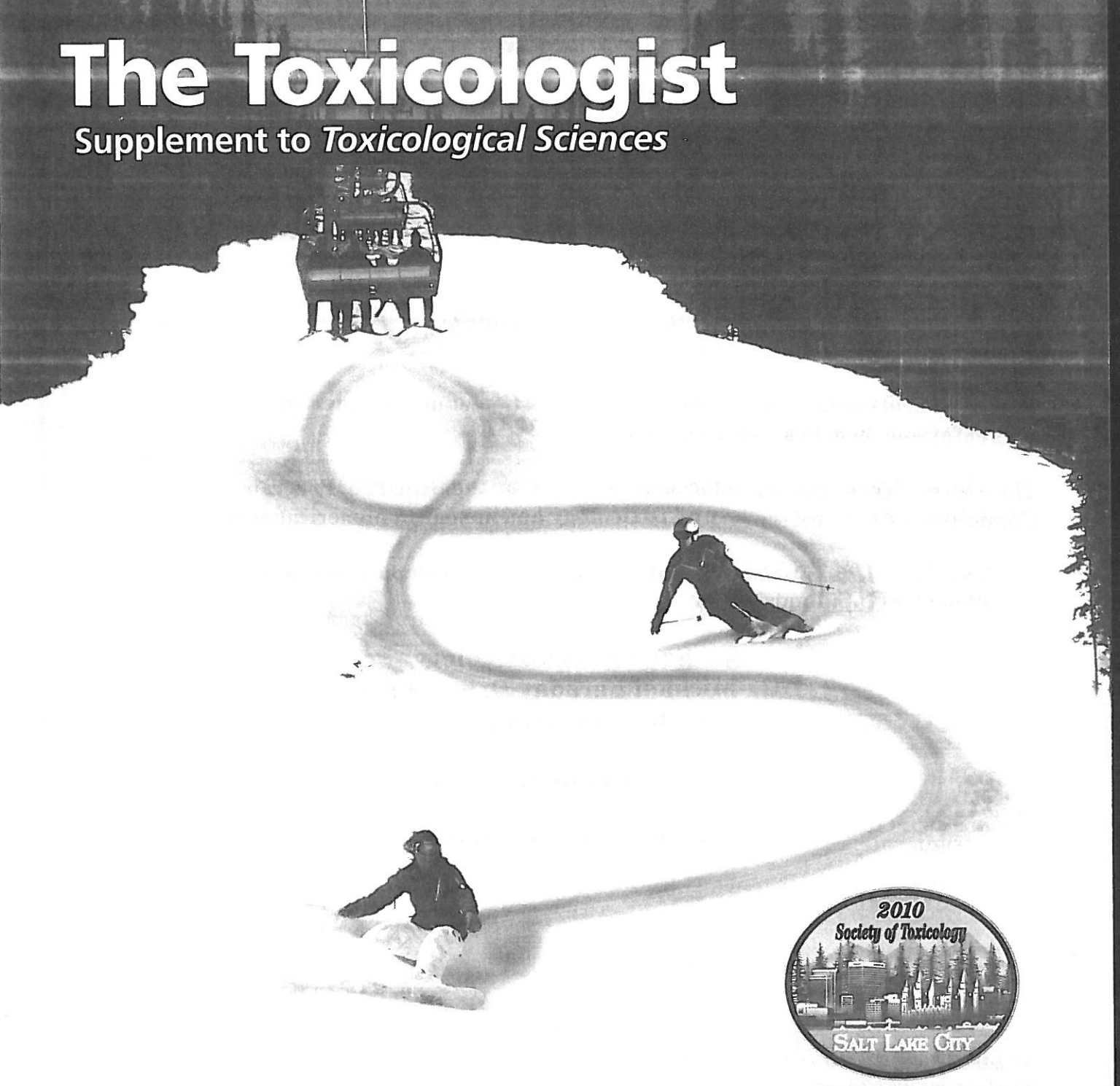

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

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