and 3 A4 polyclonal antibodies . *Helicobacter pylori* status, drug intake and smoking habit information were collected. The results were assessed according to the presence or absence of immunostaining using standard light microscope. Differences in staining proportions were tested with square χ test. Briefly, we found 2E1 and 3A4 CYP expression in normal tissues. This expression decreases in active and inactive chronic gastritis. A 95% of intestinal metaplasia analysed tissued exhibited 2E1 CYP expression while only 23% was found in GC specimens. CYP 2E1 and 3A4 is inversely correlated to *Helicobacter pylori* infection.

612 CYP1B mRNA EXPRESSION IN TWO RELATED CATFISH SPECIES.

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CYP1B1 is a P450 gene that in mammals is involved in the metabolism of polycyclic aromatic hydrocarbons (PAHs) and estradiol to potentially toxic intermediates. This gene was recently cloned in fish (scup and plaice). The objective of our study is to characterize CYP1B in channel catfish (*Ictaluras punctatus*, CC) and brown bullhead (*Ameriurus nebulosus*, BB). These species were selected because of their established differences in sensitivity to PAH-induced carcinogenesis; BB is the more sensitive species. An 861 nucleotide sequence to the polyA tail was cloned from CC liver that was 67% similar to the human and plaice CYP1B1 protein sequences (104 of the 183 residues were shared by all 3 species). In a 459 nt sequence spanning two exons, there was only one amino acid residue different between the two catfish species. Tissue distribution was investigated in fish exposed to control and 20 mg/kg benzo(a)pyrene (BaP). RT-PCR analysis indicated a 207 nt CYP1B band in gill, blood, gonad, kidney, and liver of BB and CC. When standardized against beta-actin, there appeared to be an induction by BaP in some CC tissues but not liver where CYP1B was lowest. Complete Dose-Response curves for CYP1B mRNA induction by BaP and TCDD exposure of primary hepatocytes and gill cells are being established with real time quantitative PCR. Using semiquantitive RT-PCR, neither TCDD nor BaP caused significant induction in BB hepatocytes, however BaP caused CYP1B some induction in CC hepatocytes. Ultimately, we will compare CYP1B induction responses in BB and CC to determine if differential CYP1B activity could have a role in species differences in PAH susceptibility.

613 ASSESSING THE ROLE OF CYP3A5 AND CYP3A7 IN DRUG-DRUG INTERACTIONS.

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CYP3A5 is present in significant quantities in 20-60% of human livers, whereas CYP3A7 is most abundant in fetal liver. The role of these enzymes in drug interactions is not well understood. A panel of 16 compounds was tested for potential to inhibit dealkylation of 7-benzyloxy-4-trifluoromethylcoumarin (BFC) catalyzed by cDNA-expressed CYP3A5, CYP3A7, CYP3A4 and human liver microsomes (HLM). CYP1A2 was used as a non-CYP3A comparator. Three of 16 compounds exhibited 50% inhibition of CYP1A2 activity (IC50) whereas at least 13 of 16 compounds exhibited 50% inhibition of CYP3A4, CYP3A5, CYP3A7 and HLM activity. α-Naphthoflavone inhibited CYP1A2, but activated all CYP3A enzymes as well as HLM catalysis. The IC50 values for all CYP3A enzymes and HLM correlated well with each other ($r > 0.77$). We show that inhibitor specificity for CYP3A5 and CYP3A7 is similar to CYP3A4 but inhibitor potency for these enzymes is on average, 45-fold less than with CYP3A4. Since HLM is a mixture that includes at least two CYP3A enzymes, expect intermediate potency when using HLM as an enzyme source in CYP3A4 inhibition assays. Indeed, this was observed. Because of similarities in inhibitor specificity between CYP3A4 and CYP3A7, CYP3A7-mediated drug-drug interactions and/or drug-endobiotic interactions in fetus may exhibit a specificity profile similar to that of CYP3A4 in adults, however, inhibition potency appears to be at least an order of magnitude less with CYP3A7.

614 DIESEL EXHAUST PARTICLE-INDUCED ALTERATIONS OF PULMONARY PHASE I AND PHASE II ENZYME SYSTEMS.

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Several environmental pollutants including polycyclic aromatic compounds induce carcinogenesis through the activation of xenobiotic metabolic pathways. The xenobiotics require bioactivation by phase I enzymes to induce carcinogenicity, while phase II enzymes contribute to resistance to chemical toxicity. The purpose of this study was to investigate the effects of diesel exhaust particle (Department) on phase I and phase II enzymes. Male rats were intratracheally instilled with saline (vehicle control) or a single dose of Department or carbon black (CB) at 5, 15, or 35 mg/kg body weight. CB was used as a control for the particulate carbon core of Department. At 1, 3, or 7 days post-exposure, lung microsomes and cytosol were prepared. The activities of CYP1A1 and CYP2B1 (Phase I enzymes) in microsomes and GST and catalase (phase II enzymes) in the cytosol were determined. Enzyme protein levels were determined by Western blot analysis. Department exposure at 5, 15, or 35 mg/kg, but not CB, significantly elevated CYP1A1 protein levels at 1 and 3 days post-exposure compared to the control. CYP1A1 activity was also increased with 15 and 35 mg/kg Department at 1 day post-exposure. On the other hand, both Department and CB exposures caused a significant decrease in CYP2B1 protein levels at 15 and 35 mg/kg with a concomitant attenuation of CYP2B1 enzyme activity. At 1 day post-exposure, both Department and CB significantly decreased the GST-Pi protein level at all doses tested with a significant attenuation in GST activity at 15 and 35 mg/kg. Catalase activity was significantly decreased by Department or CB (35 mg/kg) exposure at 1 and 7 days. These data suggest that the organic components of Department induce CYP1A1, while the carbon core attenuates CYP2B1, GST and catalase activities. The Department-induced alterations in the phase I and phase II enzyme pathways may play a significant role in pulmonary toxicity/carcinogenicity.

615 METABOLISM AND TOXICITY OF THE FUNGICIDE THIRAM AND ITS METABOLITES IN RATS.

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Thiram (tetramethylthiuram disulfide) is a dithiocarbamate compound widely used as an agricultural fungicide, antioxidant in rubber/rayon industry and antibacterial agent in medicine. The objective of this study was to examine whether thiram and its two metabolites, dimethyldithiocarbamate (DMDC) and carbon disulfide, interact with hepatic cytochrome P450 (CYP) isozymes and cause hepatic damage in rats. These compounds were individually administered i.p. to rats at two equimolar doses (0.1 and 0.5 mmol/kg) and the animals were sacrificed 3 and 24 hr afrer treatment. At 3 hr, there was a significant inhibition of CYP1A1 caused by only the higher dose of thiram and DMDC whereas the inhibitory effect was seen with both doses of carbon disulfide. On the other hand, CYP2E1 was inhibited by all doses of all compounds. CYP2B1 was not affected by DMDC, but was inhibited by higher dose of thiram and both doses of carbon disulfide. The activity of CYP3A2 was decreased by only the higher dose of carbon disulfide and not by others. The results of 24 hr treatment indicated that CYP 1A1 and 2E1 were inhibited only by higher dose of thiram, CYP 2B1 and 2E1 were induced by higher dose of carbon disulfide and CYP3A2 remained unaffected by all doses of all three compounds. The higher dose of thiram elevated the levels of serum SDH and ALT at 24 hr. Further assessment of liver damage was done histopathologically, and only the higher dose of thiram produced mild to moderate hepatic cell necrosis 24 hr after treatment. In summary, the results suggest that these compounds are metabolized by CYP 1A1, 2B1 and 2E1, but not by 3A2, and only thiram is hepatotoxic. Supported by NIH/MBRS S06GM08091.

616 INCREASED CYP2E1 ACTIVITY AND ENHANCED SYSTEMIC OXIDATIVE STRESS AFTER ENDOTOXIN IN HUMANS.

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Reactive oxygen species (ROS) are important toxic mediators in the pathophysiology of systemic inflammation. Previous studies have shown systemic oxidative stress in animal models of inflammation. Usually activities of hepatic P450s are decreased. However, we previously reported that CYP2E1, a P450 that leaks ROS, is not decreased in humans afrer LPS. To further evaluate CYP2E1 and oxidative stress in the human LPS model, human volunteers were given LPS. Methods: Six healthy, non-smoking men were given two consecutive daily injections of E. coli lipopolysaccharide (LPS) as a safe reproducible model of inflammation. In a control study each subject was monitored after saline injection. Oral and formation clearances of chlorzoxazone (CZX) as a measure of hepatic activity of CYP2E1 were assayed. Urinary F2-isoprostanes, whole blood GSH, peripheral blood leukocyte NF-κB activation, and plasma nitrate/nitrite concentration were measured as markers of systemic oxidative stress, as well as plasma TGF-*beta*1 and hyaluronic acid concentration. Results: Pharmacokinetic data of CZX clearance showed increases in the activities of CYP2E1 after LPS administration. Statistically significant two to three fold increases in urinary F2-isoprostanes were found between 0-6 hr after each dose of LPS. Plasma nitrate/nitrite concentration reached peak values of 86.0 ±36uM and 70.8 ±18uM between 3 and 6hr after first and second LPS dose respectively, while the control value was 40.1 ± 18uM. The profiles of changes in leukocyte NF-κB (p50 and p65), human plasma TGF-*beta*1 and plasma

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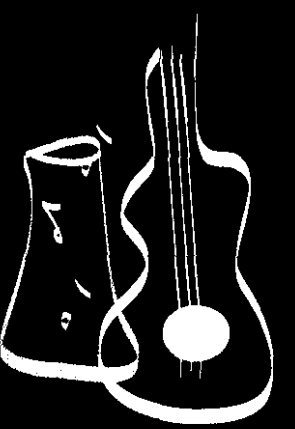

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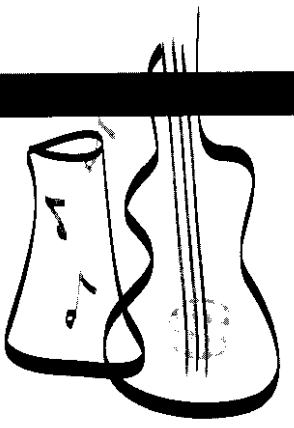

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Additional Late-Breaking Abstracts are issued in a supplement to this publication and are available at the 41st Annual Meeting and through the Society of Toxicology Headquarters office.

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