aim of this study was to examine levels of P4501A1 and P4501B1 expression in human lung samples from smokers, non-smokers and ex-smokers. Using highly specific polyclonal IgG and immunoblot analysis of microsomes from lung tissues, we determined the specific content for P4501A1 and 1B1. P4501A1 was determined to have mean levels of 53.3 pmols/mg microsomal protein (n=12) in smokers, 7.5 pmols/mg microsomal protein (n=4) in non-smokers, and 32.9 pmols/mg microsomal protein (n=6) in ex-smokers. P4501B1 was determined to have mean levels of 4.2 pmols/mg microsomal protein (n=12) in smokers, 1.4 pmols/mg microsomal protein (n=4) in non-smokers, and 4.3 pmols/mg microsomal protein (n=6) in ex-smokers. These results indicate that both P4501A1 and P4501B1 are at higher levels of expression in lung tissues from smokers and ex-smokers when compared with non-smokers. In conclusion, induced expression levels for P4501A1 and P4501B1 may be due to smoking and exposure to PAHs present in cigarette smoke, such that smokers may be more susceptible to chemical carcinogenesis. Additional studies are underway to determine the variance, activity and cellular localization of these proteins.

453 CYTOCHROME P450 1A1 AND 2B1 IN THE RAT LUNG: EXPOSURE TO SILICA AND INDUCERS OF XENOBIOTIC METABOLISM.

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Pulmonary exposure to respirable silica causes alveolar type 2 cell proliferation. Cytochrome P450 (CYP) is present in type 2 cells and increased levels of CYP1A1 are reported in silicotic rats. Because carcinogen activation by CYP1A1 may contribute to human lung cancer and because silica is often present in occupational mixed dust exposures, we hypothesized that new type 2 cells in silicosis are potential sites of CYP1A1 induction and carcinogen activation. Male, Sprague-Dawley rats received intratracheal silica (20mg) or vehicle (saline). The silicotic and control rats were then exposed to inducers of xenobiotic metabolism by the intraperitoneal injection of phenobarbital (PB), β-naphthoflavone (NF), NF and PB, or vehicle (corn oil). 7-ethoxyresorufin (ER)-O-deethylase (EROD) and 7-ethoxycoumarin (EC)-O-deethylase (ECOD) activities were increased by NF but unaffected by PB. Morphometrically, the number of cells expressing immunoreactive CYP2B1 was not significantly affected by silica, NF, and/or PB. CYP 1A1 positive airway and alveolar epithelial cells were absent in controls, present after NF exposure but not significantly increased by PB or silica. Although we had hypothesized that induction of type 2 cells would lead to more xenobiotically active cells in silicotic rats, NF-exposed silicotic rats had significantly less EROD activity than NF-exposed control rats. We conclude that the new type 2 cells of silicosis were not a major site of 1A1 induction in combined exposures in this rat model.

454 REGULATION OF CYP1A EXPRESSION BY NICOTINE IN THE RAT: DOSE- AND ROUTE OF EXPOSURE-DEPENDENCE.

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The induction of pulmonary, renal and hepatic CYP1A expression by the major tobacco constituent nicotine was examined in rats administered either a single subcutaneous (SC, 2.5 mg/kg) dose, a vapor (VP, 200 μ g/m^3) dose or a 30-day, low (20 mg/kg), medium (60 mg/kg) or high (200 mg/kg) dietary dose of the alkaloid. SC nicotine caused a lung-specific but transient upregulation of CYP1A1 mRNA, protein and catalytic activity, as did VP nicotine, with the induction peaking (15-fold) 12 h post exposure. Dietary nicotine caused a dose-dependent induction of pulmonary, renal and hepatic CYP1A1 and of hepatic and renal CYP1A2. The hepatic CYP1A1 induction was not accompanied by elevated mRNA abundance and occurred only at the high nicotine dose, at which the pulmonary and renal induction was 21-fold and 55-fold, respectively. Nicotine bound weakly to the Ah receptor in a gel shift assay, suggesting some involvement of transcriptional mechanisms in the induction. Nicotine-fed rats had plasma levels of nicotine and cotinine comparable to those reported in heavy smokers. However, administered cotinine did not induce CYP1A1. The findings suggest that CYP1A induction by cigarette smoke may be contributed by nicotine. (Supported by ES06414 and DK43135.)

455 COMPARISON OF LOW-OXYGEN MEDIATED CYP1A1 INDUCTION IN 3 HEPATOMA CELL LINES.

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Hepatoma cell lines are useful *in vitro* models for understanding liver metabolism of xenobiotics. However, when standard cell-culture incubation conditions (5%CO2/95% air) are used, oxygen concentrations are generally higher than the physio-logical range. This may have an impact on the responsiveness of cells and general applicability for toxicological testing. When oxygen was lowered to 10%, we found that 3-methyl-cholanthrene (3-MC)-mediated induction of ethoxyresorufin O-dealkylase (EROD) activity in human HepG2 cells was significantly enhanced (14-fold). Immunoprecipitation studies using specific antibodies showed that the low-oxygen effect was mediated primarily by the CYP1A1 isoform. Interestingly, the specific CYP1A1-specific inducer, 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) did not show a similar enhancement in EROD activity, but may have been more acutely toxic to the cells. The low-oxygen effect was also tested in hepatoma cell lines derived from mouse (1c1c7) and rat (H4IIE). The mouse cell line showed a similar response but it was much less pronounced than in the human HepG2 cell line. The rat-derived cell line was totally unresponsive. These results indicate that physiological oxygen tension may be an important regulator of inducer-mediated drug metabolism in cultured hepatoma cell lines; however, the response is inducer- and species-specific.

456 INDUCTION OF CYP1A1, CYP1A2, AND CYP1B1 IN PRECISION-CUT HUMAN LIVER SLICES BY 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN AND OMEPRAZOLE.

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Precision-cut human liver slices incubated in dynamic organ culture were utilized as an *in vitro* model to investigate the ability of the environmental pollutant TCDD and the clinically relevant proton pump inhibitor omeprazole to modulate the cytochrome P450s 1A1 (CYP1A1, 1A2 (CYP1A2), and 1B1 (CYP1B1). These cytochrome P450s have been specifically implicated in the metabolic activation of compounds, such as the polycyclic aromatic hydrocarbons and heterocyclic aromatic amimes, into carcinogenic species. Liver slices were incubated in dynamic organ culture for up to 96 hours in Waymouth's medium (supplemented with 25 mM HEPES, 25 mM glucose, 5% horse serum, 5% fetal calf serum, and penicillin and streptomycin) containing either 10 nM TCDD (initial 24 hr), 50 μM omeprazole, or vehicle alone (0.1% DMSO). The slices remained viable throughout the incubation period maintaining an intracellular potassium content of 40 μmoles/g liver or greater. The levels of CYP1A1, CYP1A2, and CYP1B1 proteins and corresponding activities were measured in microsomal preparations from the human liver slices and the levels of CYP1A1 and CYP1B1 mRNA were quantitated by reverse transcriptase-polymerase chain reaction. Induction of CYP1A1, CYP1A2, and CYP1B1 was observed following exposure to either TCDD or omeprazole. Interestingly, variability in responsiveness was observed between different individual liver specimens. For example, the fold induction of CYP1B1 mRNA following exposure to 50 μM omeprazole for 48 hours ranged from ≈5 to 18, compared to control. Likewise, the same liver specimens displayed a ≈7 to 41 fold induction of CYP1A1 mRNA following omeprazole (50 μM) treatment for 48 hours, compared to control. The present study demonstrates the utility of precision-cut human liver slices as *in vitro* model for studying the modulation of cytochrome P450s by xenobiotics. Furthermore, the ability of omeprazole to induce the recently identified CYP1B1 is a novel observation which warrants further investigation.

457 SEA OTTER (*ENHYDRA LUTRIS*) CYTOCHROME P450 1A GENE EXPRESSION IN PERIPHERAL BLOOD MONO-NUCLEAR CELLS AS A BIOMARKER OF EXPOSURE TO CRUDE OIL.

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The nearshore ecosystem of the Prince William Sound (PWS) serves as a

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