2031 AN INVESTIGATION OF C-*JUN* AND TGF-β_1 GENE EXPRESSION IN FISCHER 344 RATS DURING AMIODARONE-INDUCED PULMONARY FIBROSIS.

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Amiodarone (AM) is an effective antidysrhythmic agent, the use of which is restricted because of its propensity to cause potentially fatal pulmonary toxicity. Initial cytotoxic insult of AM to the lung causes release of inflammatory and fibrogenic mediators. Evidence suggests that downstream signalling pathways of some of these mediators are dependent on the nuclear transcription factor, c-jun. One mediator that has been implicated in the development of various models of pulmonary fibrosis is the growth factor, TGF-β_1. In the present study, c-*jun* and TGF-β_1 gene expression was examined following AM administration to male Fischer 344 rats. Rats were treated with AM intratracheally (1.83 µmol/day on days 0 and 2) or an equivalent volume (400 µl) of distilled water. At 4 weeks (n=6 (vehicle), n=8 (AM)) and 5 weeks (n=6 (vehicle), n=9 (AM)) post-treatment, AM increased lung hydroxyproline content by 30% compared to control. Lungs from AM-treated animals demonstrated marked septal thickening and cellular infiltration of the interstitium and alveolar spaces at 4 and 5 weeks post-treatment. Northern blot analysis demonstrated a 1.6 ± 0.7 and 1.8 ± 0.7 (mean ± SD) fold increase in lung TGF-β_1 mRNA 1 and 2 weeks post-AM treatment, respectively, while lung c-*jun* mRNA was increased 1.7 ± 0.5 fold 5 weeks post-AM treatment relative to control (n=6-9). Immunoblot analysis demonstrated a 1.5 ± 0.5 and 1.5 ± 0.4 (mean ± SD) fold increase in lung TGF-β_1 protein 1 and 2 weeks post-AM treatment, respectively, and lung c-jun protein was increased 1.6 ± 0.5 and 3.3 ± 1.4 (mean ± SD) fold 4 and 5 weeks post-AM treatment, respectively, relative to control (n=6-9). These results indicate that induction of c-*jun* and TGF-β_1 expression may play a role in the development of AM-induced pulmonary fibrosis. (Supported by the Canadian Institutes of Health Research Grant No. MT-13257)

2032 EFFECTS OF ASPHALT FUME EXPOSURE ON THE PULMONARY CYTOCHROME P450 SYSTEMS.

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Asphalt fumes are complex mixtures of aerosols and vapors containing various organic compounds, including polycyclic aromatic hydrocarbons (PAHs). The present study was carried out to determine the acute pulmonary inflammatory responses and the alteration of cytochrome P450 (P450) metabolism in rats exposed to asphalt fume by inhalation. Rats were exposed to air or asphalt fume generated at paving temperature (~150°C, ~15mg/m^3, 5 days, for either 3.5h/day or 6h/day). To assess the inflammatory responses, differential cell counts, acellular LDH and protein content of the lavage fluid were determined. Chemiluminescence generation and the secretion of TNF-α and IL-1 were monitored to assess alveolar macrophage (AM) function. Microsomes were isolated by differential centrifugation of lung homogenate. The protein level and activity of P450 isozymes, CYP1A1 and CYP2B1, were determined to assess the effect of asphalt fume exposure on P450 systems. CYP2B1 and CYP1A1 activities were monitored by measuring O-dealkylation of 7-pentoxyresorufin and 7-ethoxyresorufin, respectively. The data show that asphalt fume exposure did not cause neutrophil infiltration, alter LDH and protein content, or affect AM function. These results suggest that asphalt fume exposure did not induce acute pulmonary inflammation. However, asphalt fume exposure significantly altered pulmonary P450 activity. Microsomes isolated from asphalt fume-exposed rats exhibited a concentration-dependent increase in CYP1A1 activity, while CYP2B1 activity was not significantly affected. Western-blot analysis shows that exposure of rats to asphalt fume reduced microsomal CYP2B1 level, but significantly increased CYP1A1 level in comparison to the control. These results demonstrate that exposure of rats to paving asphalt fume significantly induced CYP1A1 activity and protein level in the lung. Such changes may alter PAH metabolism and lead to increased pulmonary susceptibility to potential toxic effects of PAHs.

2033 ROLE OF CYTOCHROME P450 ISOZYMES IN THE METABOLISM OF METHYL *tert*-BUTYL ETHER IN RAT NASAL MUCOSA.

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Methyl tert-butyl ether (MTBE), a fuel oxygenate, is blended into gasoline at concentrations of 11-15% by volume. Health complaints suggestive of respiratory effects have been reported in areas where gasoline formulated with MTBE has been introduced. It is thought that the toxicity of MTBE may be related to differences in metabolism. Cytochrome P450s demethylate MTBE to tert-butyl alcohol (TBA) and formaldehyde. The nasal mucosa has a high level of these enzymes, and genetic polymorphisms of some cytochrome P450 isoforms are known to exist, possibly underlying the increased sensitivity of some individuals to MTBE. The purpose of this study was to assess the role of various isoforms (CYP 2A3, CYP 2B1, and CYP 2E1) on the metabolism of MTBE to TBA in rat nasal mucosa. Coumarin, a competitive substrate for CYP 2A3, and 4-methylpyrazole, a specific inhibitor of CYP 2E1, both inhibited the metabolism of MTBE in a concentration-dependent manner. The IC50s were approximately 50 µM and 250 µM for coumarin and 4-methylpyrazole, respectively. Orphenadrine, a specific inhibitor of CYP 2B1, showed only slight inhibition of MTBE metabolism. These results suggest that CYP 2A3 plays a major role in the metabolism of MTBE, with a lesser role played by CYP 2E1. Exposure to o-xylene (300 ppm for 6 hours by inhalation) inhibited CYP 2A3, CYP 2B1, and CYP 2E1 in nasal mucosa. Inhibition of enzyme activities was greatest immediately following exposure, but CYP 2A3 and CYP 2E1 remained significantly inhibited 24 hours following cessation of exposure albeit not as extensively. Metabolism of MTBE to TBA was inhibited in nasal microsomes from rats previously treated with o-xylene and sacrificed immediately following exposure, with some recovery 24-hours following o-xylene exposure, thereby mirroring effects on CYP 2A3 and CYP 2E1. Therefore, the metabolism and possibly the toxicity of MTBE could be modulated by previous exposure to compounds that either inhibit or induce cytochrome P450 isoforms, notably CYP 2A3 and CYP 2E1.

2034 THE EFFECT OF THERMAL DEGRADATION PRODUCTS FROM TDI- AND MDI-FORMS ON ISOLATED PERFUSED GUINEA PIG LUNG.

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Isocyanates are irritating to the respiratory tract and in the most common reason for occupational asthma. When polyurethanes (PUR:s) are heated, isocyanates are released. We compared the acute toxic lung effects of thermal degradation products from of polyurethane foams, one containing toluene diisocyanate (TDI) and the other diphenylmethane diisocyanate (MDI). The polyurethane foams were burned in a furnace under controlled conditions, the one containing TDI at 300°C and the one with MDI at 350 or 450°C. From the MDI-foam, MDI, phenyl isocyanate (PhI) and methyl isocyanate (MIC) were released. An isolated, perfused and ventilated guinea pig lung was exposed to air containing the thermal degradation products for 30 min. In the recirculating perfusion medium (Krebs-Hepes buffer with 2% albumin), the concentration of toluenediamine and diphenylmethandiamine were increased during the experiment, indicating that TDI and MDI are metabolised in the lung and that the hydrolysed products are released in the perfusion medium. Thermal degradation products from MDI-foam caused a dose dependent decrease in conductance and compliance. Thermal degradation products from TDI-foam did not cause any decrease in the lung function in spite of that. The released concentration of TDI was 150 times higher than the concentration of released MDI. However, TDI from TDI-based PUR was particle associated to a much less degree than MDI emitted from MDI-based PUR. Lungs were also exposed to pure PhI in order to investigate if PhI caused the decreased lung-function after exposure to the MDI degradation products. PhI failed to decrease conductance and compliance. As many different compounds are formed from heated MDI-foam, including different MDI-metabolites, carbon monoxide, cyanide and particles, we cannot assess which particular compound(s) that caused the decrease in lung-function.

2035 TWO-WEEK INHALATION TOXICITY OF N-PROPYL PROPIONATE IN RATS.

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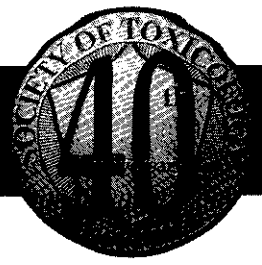
n-Propyl Propionate(nPP) is a solvent and a component in paint finishes. Groups of 10 male Crl:CD ® (SD)IGS BR rats were exposed 6 hours/day, for 9 exposures over a 2 week period, to 0, 50, 250, or 2000 ppm of nPP vapor. Five rats/group were necropsied after the 2 week exposure period and the remaining rats necropsied after a 3 week recovery period. At 2000 ppm there was a diminished or absent alerting response during the daily exposures. These effects were considered reversible and were not observed in the other test groups. Body weight depression was also observed in the 2000 ppm group and this was reversible after the 3-week recovery



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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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