thereby triggering idiosyncratic toxicities. Because glucuronide conjugates are substrates for the hepatic basolateral transporter Mrp3, we investigated the potential of DG to induce liver, kidney, and intestinal toxicity in FVB wild-type (WT) and Mrp3-null (KO) mice. We postulated that a deficiency in hepatic Mrp3 should redirect DG from sinusoidal excretion towards biliary excretion. This shift in disposition could alter the susceptibility of key organs handling DG to diclofenac toxicity. In the present work, a single toxic dose of 90 mg/kg diclofenac was administered i.p., to WT and KO mice. Analytes of interest (diclofenac and its glucuronide) were previously quantified in bile, plasma, and tissue homogenate via LC/MS/MS in a separate study at non-toxic doses of diclofenac. Lower DG plasma concentrations in KO were detected, serving as evidence that in the absence of Mrp3 the basolateral excretion of DG is compromised. Several tissues were inspected for evidence of histopathological damage. Both WT and KO mice had ulceration in the pyloric region of the stomach, with the KO group having a higher incidence and severity of ulcers. Clinical chemistry and histopathology showed no evidence of liver or kidney toxicity in either genotype. Surprisingly, WT mice had multiple ulcers in their small intestines whereas the KO mice had none. The differential intestinal injury between WT and KO mice may indicate that the absence of Mrp3 stimulates cytoprotective compensatory changes that confer protection against ulceration. This work was supported by The National Institutes of Health Grant DK069557.

PS 1598 THE INTERACTION OF PLACENTAL EFFLUX TRANSPORTERS WITH XENOBIOTICS.

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The placenta plays an important role in normal foetal development, providing the conduit for nutrient and gaseous transport, removal of waste materials and a protective barrier for the foetus against exposure to exogenous agents. Active efflux transporter proteins, including P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) are known to be expressed in the placenta, and are thought to contribute to the barrier-like properties of this tissue. The aim of this project was to explore assays which may be useful in investigating the interaction of placental efflux transporters with xenobiotics. Two functional assays were evaluated, one ex vivo and one in vitro. P-gp function in fresh human placental fragments was assessed by measuring [3H]Taxol (a P-gp substrate) accumulation over time. There was a time dependent increase in [3H]Taxol accumulation in all placentae studied which was differentially sensitive to verapamil (a P-gp inhibitor). The in vitro model, using P-gp-expressing JAr placental choriocarcinoma cells (which mimic the trophoblast layer of the placenta), confirmed active extrusion of the P-gp substrate calcein acetoxymethylester (AM). This was inhibited by verapamil, demonstrating in vitro functional activity. The in vitro system was further characterised to assess the ability of a number of therapeutic agents (known to be P-gp substrates), to modulate P-gp activity. These compounds included the chemotherapeutic agents vinblastine, tamoxifen and cyclosporine A and quinidine, (an antiarrhythmic used in 2 % of pregnancies, Evseenko et al., 2006), and saquinavir (an antiretroviral drug used in 0.01-0.3 % of pregnancies, Evseenko et al., 2006). A 2-4.7 fold increase in calcein intracellular accumulation was observed, showing the assay is capable of measuring interaction of compounds with P-gp. Evseenko, D., Paxton, J. W. & Keelan, J. A. (2006) Active transport across the human placenta: impact on drug efficacy and toxicity. Expert Opin Drug Metab Toxicol, 2, 51-69.

PS 1599 THE IMPACT OF REPEATED NICOTINE AND ALCOHOL CO-EXPOSURE ON THE *IN VIVO* CHLORPYRIFOS PHARMACOKINETICS AND PHARMACODYNAMICS.

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Chlorpyrifos (CPF) is an organophosphorus insecticide widely used in agriculture. The neurotoxicity of CPF results from inhibition of cholinesterase (ChE) by its metabolite, chlorpyrifos-oxon (CPF-oxon), which subsequently leads to cholinergic hyperstimulation. The objective of this study was to evaluate the influence of repeated nicotine and ethanol co-exposure on in vivo CPF pharmacokinetics and pharmacodynamics. The routine consumption of tobacco products and alcoholic beverages may modify key metabolic and physiological processes. Blood and urine profiles of the non-toxic metabolite, 3,5,6-trichloro-2-pyridinol (TCPy) along with changes in plasma and brain ChE activities were measured in male S-D rats (~ 300 g). Animals were co-exposed to CPF (1 or 5 mg/kg/day, po), ethanol (1 g/kg/day, po) and nicotine (1 mg/kg/day, sc), for 7 days. Rats were sacrificed at times from 1 to 24 hr post-last dosing of CPF. There were apparent differences in blood TCPy pharmacokinetics following nicotine and ethanol pretreatment in both CPF dose groups, which showed higher TCPy peak concentrations and increased blood TCPy AUC (~2-fold) in ethanol/nicotine pretreated groups over saline pretreatment groups. Brain acetylcholinesterase (AChE) activities from ethanol and nicotine-treated groups showed substantially less inhibition following repeated 5 mg CPF/kg dosing compared to CPF-only controls (96 ± 13 and 66 ± 7% of naïve at 4 hr post-last dosing, respectively). Inhibition of brain AChE activities was minimal in both 1 mg CPF/kg dosing groups, but a similar trend indicating less inhibition following ethanol/nicotine pretreatment was apparent. No alcohol/nicotine treatment effects were observed in plasma ChE activities. This study shows that repeated exposure to alcohol and nicotine (i.e., from smoking) could alter the pharmacokinetics and pharmacodynamics of CPF [Supported by CDC/NIOSH grant R01-OH003629].

PS 1600 THE DEVELOPMENTAL EFFECTS OF LEAD, MANGANESE, AND CHRONIC STRESS ON RAT BEHAVIOR.

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Exposure to metals such as lead (Pb) and manganese (Mn) results in neurocognitive deficits in humans and laboratory animals. Children of lower socioeconomic status (SES) are particularly susceptible, as they are more likely to live in homes that contain Pb paint and to be fed soy formula, which contains high levels of Mn. Additionally, these children are also exposed to higher levels of chronic stress, such as neglect, impoverished conditions, or lack of resources. The purpose of this study was to determine the long-term behavioral effects in rats exposed to low-level Pb and/or Mn and chronic stress (i.e., reduced cage bedding) during critical stages of development. It was hypothesized that the concurrent administration of Pb and Mn with the chronic stressor would interact to produce behavioral deficits. On postnatal day (P)4, Sprague-Dawley rat pups were housed in cages containing either no woodchip bedding (paper towel only) or normal woodchip bedding. Pups were gavaged every other day with 10 mg/kg Pb, 100 mg/kg Mn, both Pb and Mn, or an appropriate control from P4-P28, at which time animals were weaned and housed in cages with standard woodchip bedding until the start of behavioral testing on P60. Mn, Pb+Mn, and reduced bedding conditions each resulted in significantly decreased body weights relative to controls, while Pb alone had no effect. Animals raised without bedding also exhibited increased latencies in the Cincinnati water maze, a navigational test of egocentric learning, while metal treatment had little effect on this test. During light-dark exploration, rats raised with reduced bedding demonstrated increased anxiety as they had shorter latencies to dark entry. Animals treated with Mn or Pb+Mn entered the dark more frequently than Pb- or vehicle-treated rats, signifying elevated anxiety. These results suggest that chronic developmental stress and Mn exposure result in behavioral deficits. Ongoing tests will determine whether Pb interacts with Mn and/or developmental stress. Support: RO1ES015689 & T32ES07051

PS 1601 FETAL OXIDATIVE DNA DAMAGE AND REPAIR IN METHYLMERCURY NEURODEVELOPMENTAL DEFICITS.

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Reactive oxygen species (ROS)-mediated oxidative damage to cellular macromolecules has been implicated in embryopathies caused by several xenobiotics including methylmercury (MeHg), an important environmental toxin that causes neurodevelopmental deficits in infants. We previously found that CD-1 fetuses exposed to a maternal dose of 8 mg/kg MeHg chloride exhibited a dose-dependent increase in oxidative DNA damage by 4 hr post-treatment, measured as 8-oxo-2'-deoxyguanosine (8-oxodG), using high-performance liquid chromatography with electrochemical detection ($p<0.05$), suggesting that oxidative DNA damage may play a role in the mechanism of MeHg-initiated neurodevelopmental deficits. The studies herein determined the time of peak levels of DNA oxidation in fetal brain and the neurodevelopmental consequences after maternal exposure to MeHg. Pregnant CD-1 dams were injected on gestational day (GD) 17 with either MeHg (4 or 8 mg/kg i.p.) or the phosphate-buffered saline vehicle, sacrificed 2, 6 or 12 hr post-injection, and the fetal brains were collected. Fetal brain levels of 8-oxodG continued to increase at 6 ($p<0.05$) and 12 hr following the 8 mg/kg MeHg dose, and peaked at 6 hr following the 4 mg/kg dose ($p<0.05$). In complementary behavioural studies, the offspring of dams treated with 4 mg/kg MeHg on GD 17 were tested for cognitive impairment using an object recognition test at 4 and 6 weeks of age. The 8 mg/kg dose was abandoned due to maternal toxicity. Both genders exposed to MeHg exhibited postnatal cognitive impairment by 6 weeks of age ($p<0.05$), and males appeared to show cognitive deficits as early as 4 weeks of age. These results show that a dose of MeHg that increases fetal DNA oxidation can also cause postnatal cogni-

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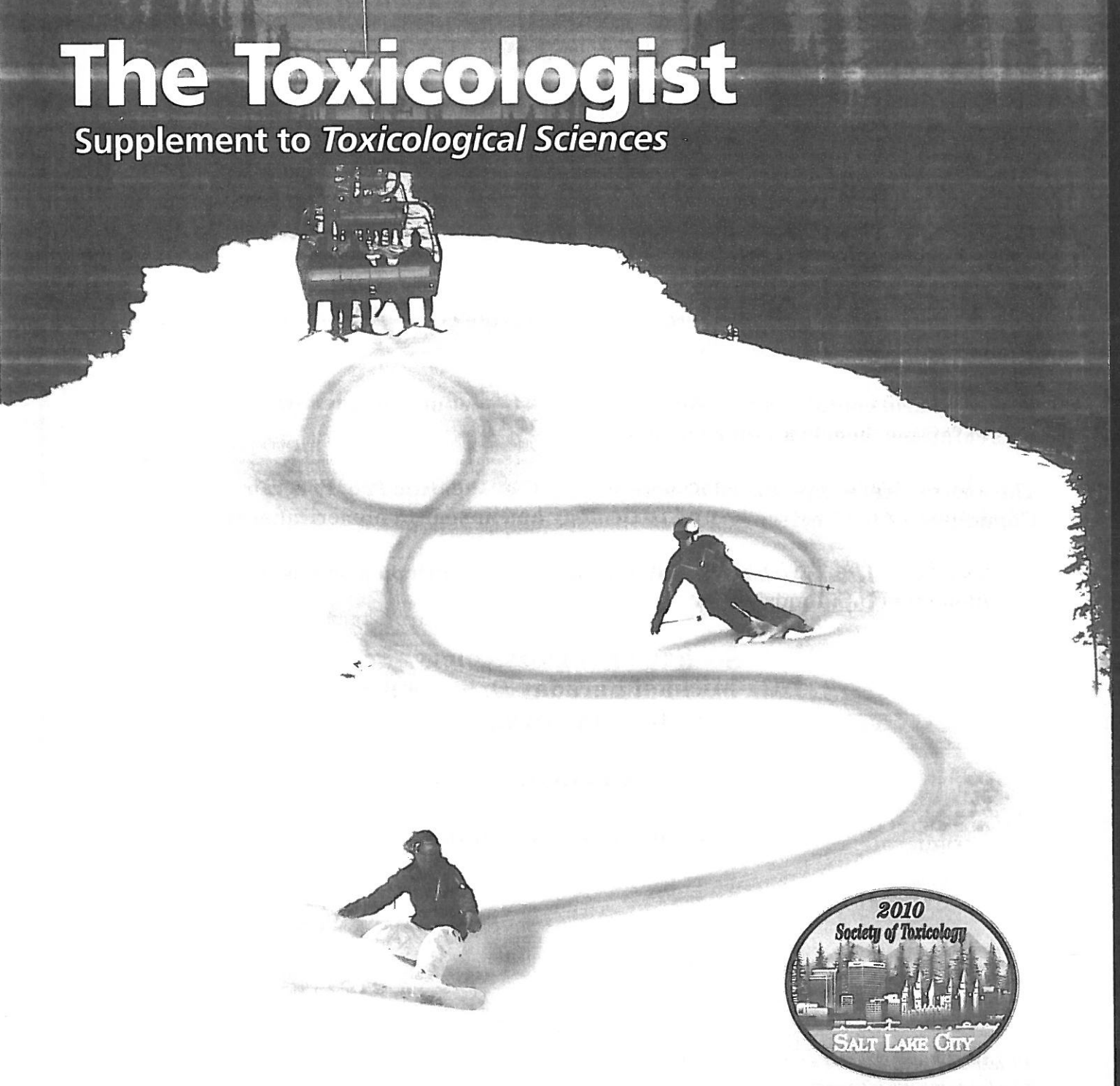

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 49th Annual Meeting of the Society of Toxicology, held at the Salt Palace Convention Center, March 7–11, 2010.

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.

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

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