prior to kainic acid-induced seizures were recently reported (Bragin et al., 2009). In contrast, increases in lower frequency bands delta-theta, which are typically elicited by many anticonvulsants, may prevent generalized seizures from occurring following ketamine treatment. Our data suggest quantitative EEG analysis is a promising approach to assess the seizuregenic potential of CNS active compounds.

PS 1325 RAT SKELETAL MUSCLE TOXICITY MEDIATED BY A PPAR-DELTA AGONIST: EVALUATION OF BIOMARKERS.

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Peroxisome proliferator-activated receptor delta (PPARδ) agonists are attractive targets for metabolic syndrome, but concerns about skeletal and cardiac toxicity have been impediments to successful drug development. A 14-Day rat study was performed to evaluate the toxicity of a novel mixed PPARδ/α agonist (Compound X) and to evaluate the performance of previously suggested and novel biomarkers of muscle toxicity. Male Sprague-Dawley rats were orally treated with Compound X at 10, 100, or 300 mg/kg/day for 1, 6, or 14 days. There were no compound-related clinical observations and changes in clinical chemistry were limited to small increases in triglycerides and transaminases. Degeneration/regeneration of quadriceps was observed at the mid and high doses on Day 14. The appearance of the lesion was not fiber-type specific based on glycogen staining. Additional findings were hepatic hypertrophy and hyperkeratosis in the stomach and esophagus. Previously reported potential biomarkers of muscle toxicity evaluated in this study included serum h-FABP, skeletal muscle troponin I, and cardiac troponin and urinary myoglobin. Serum skeletal muscle troponin I and urinary myoglobin showed the best correlation with histopathology scores for myotoxicity. Transcriptional profiling indicated increased expression of genes associated with fatty acid β-oxidation in muscle tissue with accompanying regulation of genes involved in oxidative stress. Based on lesion-associated expression changes and tissue distribution, Ankrd1 (Ankyrin repeated domain 1) and Rrad (Ras-related associated with diabetes) were investigated further. Ankrd1 and Rrad protein expression in skeletal muscle tissue demonstrated a pattern similar to that of mRNA expression and correlated well with lesion occurrence. Evaluation of Ankrd1 and Rrad as biomarkers of skeletal muscle toxicity in other biological matrices (plasma and urine) is ongoing.

PS 1326 QUANTIFICATION OF TETRAHYDROPHTHALIMIDE AND PHTHALIMIDE BIOMARKERS OF EXPOSURE TO CAPTAN AND FOLPET BY LIQUID CHROMATOGRAPHY - ATMOSPHERIC PRESSURE CHEMICAL IONIZATION-TANDEM MASS SPECTROMETRY (LC-APCI-MS).

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Captan and folpet are thiophthalimide fungicides largely used to treat fungal diseases. They have similar chemical structures, except that folpet has an aromatic ring unlike captan. Their half-lives in blood are very short, given that they are readily metabolized, in particular to tetrahydrophthalimide (THPI) or phthalimide, respectively. To our knowledge, few authors measured these two biomarkers in urine or blood and analysis was conducted either by gas chromatography with mass-spectrometry (GC-MS) or liquid chromatography with UV detection (LC-UV). The objective of this study was to develop a more sensitive and specific liquid chromatography - atmospheric pressure chemical ionization-tandem mass spectrometry (LC-APCI-MS) method to quantify THPI and phthalimide in human blood and in urine. Briefly, deutered THPI was added as an internal standard and purification was performed by solid phase extraction followed by LC-APCI-MS analysis in negative ion mode. Validation of the method was conducted using spiked blank urine and blood samples at concentrations ranging from 0.5 to 2 000 µg/L along with urine and blood samples of workers or volunteers exposed to captan or folpet. The calibration curves for the two compounds showed a good linearity, with a correlation coefficient >0.99. The limit of detection was 3 pmol/L for THPI and 34 pmol/L for phthalimide. The coefficient of variation was less than 10% for repeatability and reproducibility. The described method is rapid, simple, accurate, sensitive and specific, and it proved useful to quantify THPI and phthalimide in human biological samples.

PS 1327 SUSCEPTIBILITY FACTORS FOR PULMONARY INFECTION DURING DIET-INDUCED OBESITY FROM GENOMICS ANALYSIS OF MICE EXPOSED TO LIPOPOLYSACCHARIDE.

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The systemic effects of obesity on the immune system are poorly understood, but often associated with increased susceptibility to bacterial infections and increased risk for chronic pulmonary disease. Obesity is known to increase sensitivity to endotoxin-induced liver injury, but effects on the lung are uncharacterized. To identify the key biological pathways that define susceptibility factors for pulmonary infection during obesity, we performed parallel exposures of normal weight (NW) and diet-induced obese (DIO) C57BL/6 mice to 0.5ug/L lipopolysaccharide (LPS) by inhalation for 1hr/d for 4 days over a period of 2 weeks. Bronchoalveolar (BAL) cytology indicated a strong macrophage response with LPS exposure, which was 50% higher in DIO mice compared to NW, while neutrophil infiltration was comparable in NW and DIO mice. Likewise, levels of inflammatory cytokines in BAL fluid also increased after LPS exposure in NW and DIO mice (MDC-1, MIP-1g), however a couple cytokines displayed some suppression of the immune response in DIO mice (IL-12, TARC) compared to NW mice. Microarray analysis revealed that DIO reprograms the lung's transcriptional response, altering both the number of genes and the specific molecular pathways induced or suppressed by LPS exposure. Comparison with microarray data from DIO mice exposed to cigarette smoke indicates both overlapping and unique toxicity pathways, which could be used to link exposure to outcome data. In addition, we identified genes whose expression levels are significantly different between regular and DIO sham control animals, indicating an overall suppression of the immune system and induction of heat shock proteins in the lung during DIO. These results demonstrate biosignatures of systemic inflammation and oxidative stress in obese mice, which may make them more sensitive to environmental lung toxicants. Supported by U54 ES016015.

PS 1328 HEMOGLOBIN ADDUCTS AND PLASMA METABOLITES AS BIOMARKERS OF EXPOSURE TO 1, 6–HEXAMETHYLENE DIISOCYANATE.

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Diisocyanates (dNCO) are considered a major cause of occupational asthma. The mechanisms of toxic reactions, type and yield of various dNCO metabolites, and their relationship with exposure have not been adequately addressed in exposure assessment. We investigated the utility of 1,6–hexamethylene diamine (HDA) hemoglobin adducts and plasma HDA as internal dosimeters of exposure to 1,6–hexamethylene diisocyanate (HDI). We quantified levels of HDA hemoglobin (Hb) adducts, as well as HDA in hydrolyzed plasma among 15 spray painters (N=36) applying HDI-containing paint and investigated their relationship with HDI air exposure or urinary HDA levels. HDA–Hb adducts were detected by GC-MS as heptafluorobutyryl derivatives (1.2–37.2 ng/g Hb). The correlation between HDA–Hb adducts and HDI air exposure was strongest when exposures were measured 2–5 months before blood collection (r^2=0.40, P=0.019). However, the correlation between plasma HDA and HDI air exposure was strongest when exposures were measured 0.5–2 months before blood collection (r^2=0.28, P=0.010). Urinary HDA was most strongly associated with plasma HDA collected on the same day or within the previous 2 months (r^2=0.12–0.86, P<0.10), whereas urinary HDA was most strongly correlated with Hb–HDA adducts in blood collected 2–5 months prior (r^2=0.16, P=0.11). These findings indicate different elimination kinetics of plasma and Hb–adduct metabolites, and their application as biomarkers of cumulative exposure to HDI monomer. Such information on the type and yield of different metabolites and their relationship with cumulative HDI air exposure levels may be used in retrospective studies and to promote further research into susceptibility factors related to disease development. Supported by NIOSH R01-OH007598, T42/CCT422952, and T42 OH008673; NIEHS P30ES10126 and T32 ES007018; American Chemistry Council RSK0015-01.

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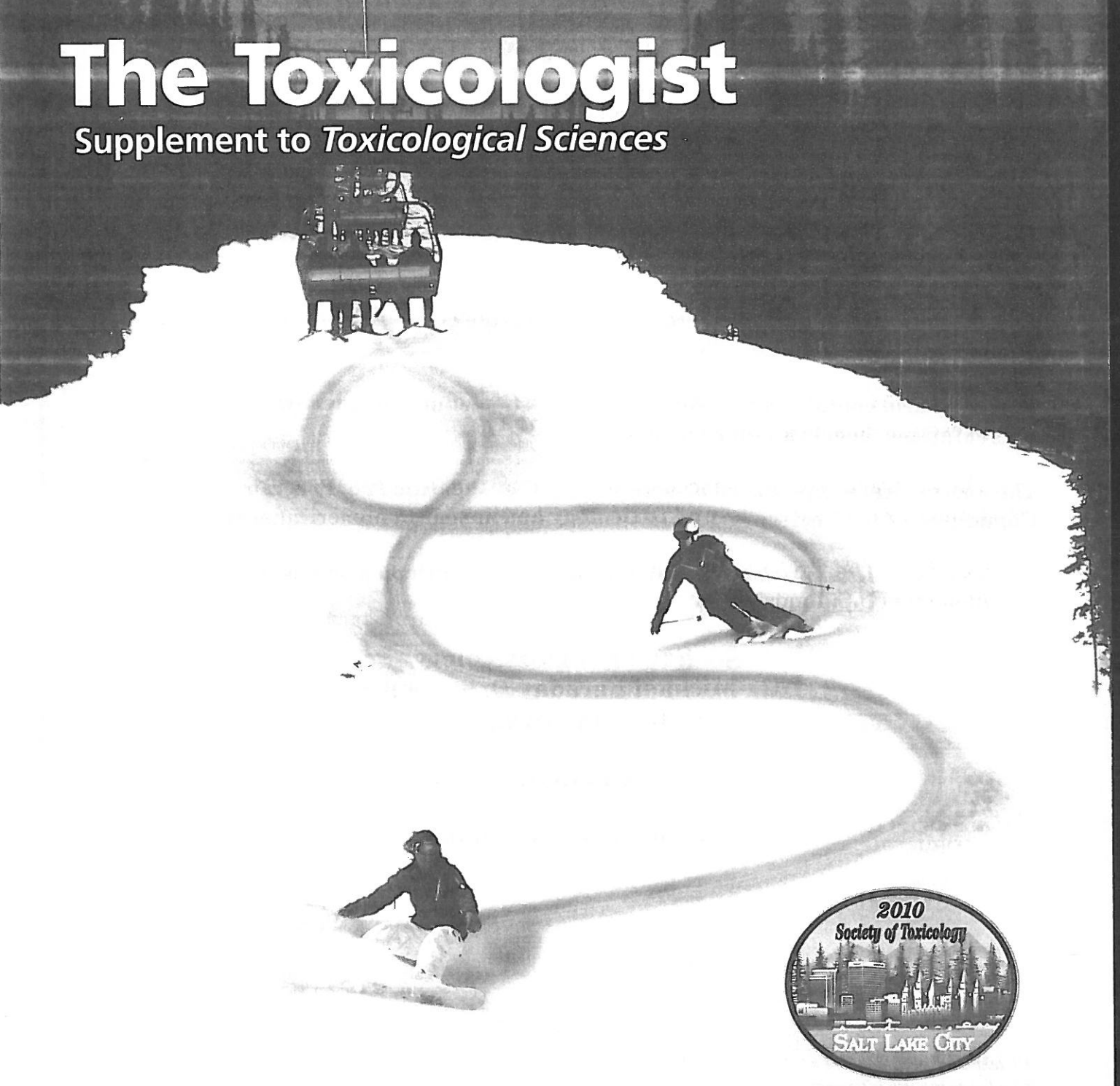

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Preface

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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