cells to secrete chemokines such as interluekin-8 (IL-8) and monocyte chemotatic protein (MCP-1) to recruit inflammatory macrophages and neutrophils to the lung. Inflammatory cells can then release proteases and reactive oxygen species, initiating apoptosis of pulmonary cells, resulting in the destruction of alveolar structure. CS also activates nuclear Nrf2-dependent pathways in pulmonary epithelial cells that increase the expression of cytoprotective enzymes providing a protective mechanism against CS-induced lung inflammation and injury. We hypothesize that activating Nrf2 with sulforaphane (SFN) will afford protection against CS-induce lung damage by increasing Nrf2-dependent gene expression thereby inhibiting chemokine production. Results: Our results indicate that 10 μM SFN does not induce apoptosis in the human epithelial cell line, BEAS-2B cells. SFN triggers Nrf2 translocation to the nucleus after 6 hours as determined by immunoblotting and significantly increases the expression of Nrf2-dependent genes such as NADPH quinone oxidoreductase-1, heme oxygenase-1, and glutamate cysteine ligase modulatory subunit as determined by real-time PCR. BEAS-2B cells exposed to cigarette smoke extract (CSE) lead to a significant increased in IL-8 and MCP-1 levels. BEAS-2B cells pretreated with SFN for 24 hours and then exposed to CSE significantly decreased IL-8 and MCP-1 chemokine production. Conclusions: Our results indicate that activating Nrf2 pathways with SFN inhibits CSE-induced chemokine production in human epithelial cells. However, the mechanism by which the production of chemokines is inhibited through SFN still remains to be elucidated. Moreover, it is unclear whether Nrf2-dependent gene expression induced by SFN is necessary to inhibit chemokines produced by CSE

PS 733 REFERENCE SMOKELESS TOBACCO EXTRACT INDUCED INFLAMMATORY GENE EXPRESSION *IN VITRO*.

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The use of smokeless tobacco products at the same oral site may result in an acute injury characterized by ulceration and inflammation that is reversible upon elimination of same site use. However, little research has been conducted on in vitro models that mimic the human oral cavity response to smokeless tobacco exposure. In the current study, we used the HET-1A cell line to investigate the role of short term repeated exposures to reference smokeless tobacco extracts similar to product usage in humans. The total exposure lasted for 3 to 5 hours and consisted of 1hr of exposure followed by 1 hr of recovery followed by 1hr of exposure (3hrs) followed by 1hr of recovery followed by 1 hr of exposure (5hrs). Results from this exposure method were compared to those from the cells exposed for the entire 3 to 5hrs. The use of the repeated dosing in vitro model resulted in reduced cytotoxicity as detected by Calcien AM staining, yet augmented the inflammatory gene expression of IL-6, IL-8, Cox-2, and TNF-alpha detected by RT-PCR. To investigate the smokeless tobacco components that may be involved in the cytotoxicity and inflammatory gene expression, nicotine and hyperosmolarity were investigated using this model. Our findings indicate that exposure to nicotine alone, at the levels in smokeless tobacco extracts used in these studies, did not cause cytotoxicity or inflammatory gene induction in this in vitro model. However, HET-1A cells exposed to hyperosmotic solutions at levels similar to smokeless tobacco extracts demonstrated cytotoxicity and induction of inflammatory gene expression. In conclusion, repeated exposures of smokeless tobacco extracts in short term in vitro cultures of HET-1A enhance inflammatory gene expression and hyperosmolarity appears to play a role in this process.

PS 734 EFFECT OF INHALATION OF GAS METAL ARC STAINLESS STEEL WELDING FUME ON MOUSE LUNG INFLAMMATION AND TUMORIGENESIS.

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Previously, we found strain dependent differences in the degree and resolution of the lung response in tumor susceptible (A/J) and resistant (C57BL/6J) mice exposed by pharyngeal aspiration to stainless steel (SS) welding fumes. We also found a borderline significant tumorigenic effect of gas metal arc (GMA)-SS fume. In this study, our objective was to further examine the inflammatory and potential carcinogenic effects of GMA-SS fume in mice via an inhalation exposure route. Male A/J and C57BL/6J mice were exposed to GMA-SS welding fume (40 mg/m3 x 3 hr/day x 6 or 10 days) or filtered air. At day 1, 4, 7, 10, 14 and 28 after the last exposure day, bronchoalveolar lavage (BAL) was done postmortem. Lung cytotoxicity (lactate dehydrogenase activity), air-blood barrier damage (albumin), inflammatory cytokines (IFN-γ, IL-6, IL-10, IL-12p70, MCP-1, MIP-2, TNF-α), total BAL cell counts and differentials (≥300 cells identified) were analyzed. Gross tumor counts and sizes were assessed in A/J mice at 78 weeks post-exposure. In both strains, inhalation of SS fume caused significant cytotoxicity and damage at all time points compared to air. Also, an early sustained macrophage and lymphocyte influx was found followed by a gradual neutrophil accumulation with no resolution of the response at 28 days post-exposure. MCP-1, MIP-2 and TNF-α were increased in both strains while the C57BL/6J also had increased IL-6 BAL protein. Tumor incidence and multiplicity in the 6 and 10 day GMA-SS-exposed groups were not significantly different from the corresponding air control groups. Furthermore, no tumor size differences were found in this study. Overall, inhalation of GMA-SS welding fume caused a similar lung inflammatory response in both mouse strains that was unresolved at 28 days post-exposure. Additionally, under the experimental conditions, GMA-SS welding fume did not significantly affect tumor development in A/J mice.

PS 735 IL-17 MEDIATED INFLAMMATORY RESPONSE INDUCES POLYMERIC IG RECEPTOR AND ELEVATED IGA LEVELS *IN SILICA* EXPOSED RAG1-/- MICE.

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Prolonged exposure to crystalline silica (SiO2) in occupational and environmental settings induces an inflammatory lung disease (known as silicosis) characterized by a diffuse mononuclear cell infiltrate in the lung that can progress to pulmonary fibrosis with chronic exposure. Insufficient information on the pathophysiological mechanisms of silicosis has severely limited the development of effective therapeutic strategies. Because conventional anti-inflammatory agents do not control SiO2-induced inflammation, much less cure the disease, more effective therapeutic alternatives must be developed. IL-17 plays a prominent role in the pathogenesis of lung inflammatory diseases such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis, by promoting the recruitment and survival of neutrophils, as well as the establishment of chronic inflammation. However, it remains unclear whether IL-17 contributes to SiO2-induced neutrophilia and chronic inflammation. In the current study, we investigated the inflamed airways of SiO2 exposed lymphopenic Rag1-/- and C57Bl/6 wild-type mice. SiO2 exposure results in enhanced neutrophil-dominated inflammation associated with elevated levels of IL-17 in the lavage. Coincident with this inflammatory response, was a striking induction of pIgR expression by SiO2-activated epithelium and a subsequent increase in IgA and secretory component levels in the lavage. These responses were exacerbated in Rag1-/- mice demonstrating that the generation of IL-17 mediated inflammation can occur independently of lymphocytes.

PS 736 DIFFERENTIAL EFFECTS OF 1-NITROPYRENE AND 1-AMINOPYRENE ON CXCL8 (IL-8) AND CCL5 (RANTES) IN BEAS-2B CELLS: ROLE OF AHR, ARNT, NF-κB AND AP-1.

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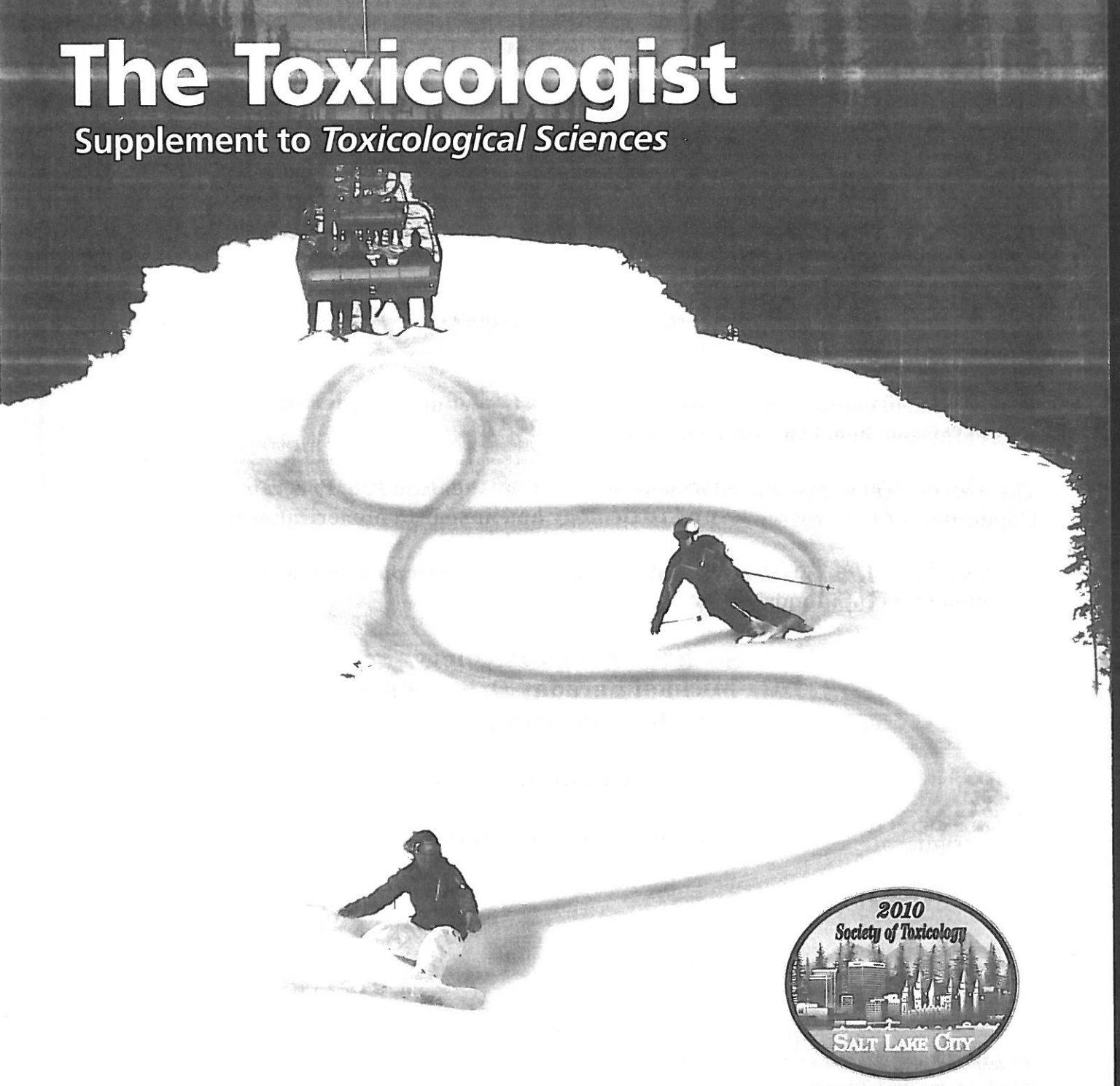
1-Nitropyrene (1-NP) is an abundant PAH in diesel exhaust particles (DEPs) and has been reported to be among the main contributors to the mutagenicity of DEPs. The nitro group on 1-NP can be reduced by cytosolic nitroreductases, giving rise to 1-aminopyrene (1-AP) through a process that may cause formation of reactive oxygen species. We have recently shown that 1-NP may be a potent inducer of cytokine and chemokine responses in human bronchial epithelial BEAS-2B cells. In the present study we further examined the effects of 1-NP and 1-AP on 17 cytokine and chemokine genes in BEAS-2B cells by real-time PCR. While the 1-NP-induced response was characterized by maximum effects on CXCL8 (IL-8) and TNF-α expression, 1-AP induced a completely different gene expression pattern dominated by CCL5 (RANTES) and CXCL10 (IP-10). This marked difference in response pattern following 1-NP and 1-AP exposure was confirmed by ELISA on CXCL8 and CCL5. Real time-PCR further showed that the two compounds did not induce expression of aryl hydrocarbon receptor (AhR)-regulated genes, such as CYP1A1 and CYP1B1. In spite of this, silencing of AhR and the AhR nuclear transporter (ARNT) by siRNA increased the release of CCL5 and CXCL8, respectively. Preliminary findings by "transcription factor ELISA" suggest that 1-NP induced a stronger activation of activator protein-1 (AP-1) than 1-AP, while 1-AP induced the

The Toxicologist

Supplement to *Toxicological Sciences*



An Official Journal of the Society of Toxicology

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Creating a Safer and Healthier World by Advancing the Science of Toxicology

49th Annual Meeting and ToxExpo™

Salt Lake City, Utah

www.toxsci.oxfordjournals.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 114, Number 1, March 2010

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.

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