metabolism of NN and the possible involvement of glutathione (GSH) in the detoxification in highly susceptible (lung) and less susceptible (liver) tissues in rat. Microsomes were prepared from liver and different subcompartments of the lung. Dihydroxy-1-nitronaphthalene, identified by mass spectrometry and NMR spectroscopy, was a major metabolite generated in both liver and airway microsomes incubated with NN. The rates of dihydroxy-NN formation varied with airway level and were 10 to 20% that observed in the liver. Preincubation of liver microsomes with 2EN decreased the formation of dihydroxy-NN to 25% of control; the rates of metabolism of pentoxyresorufin, a selective CYP2B substrate, were decreased similarly to 25% control. Significant depletion of GSH was observed in distal airways and parenchyma but not in other airways of rats treated with 200 mg/kg NN, ip. This is consistent with radioprofiles demonstrating putative GSH conjugates isolated from microsomal incubations with GSH transferase and GSH. These data suggest the involvement of CYP2B in both liver and lung metabolism of NN and that GSH derived metabolites are generated during NN metabolism. Supported by NIEHS 00628, 04699 and 05707; NIH 1S10-RR04795; NSF BBS88-04739.

1721 ROLE OF THE MAJOR HISTOCOMPATABILITY II COMPLEX IN MEDIATING BERYLLIUM-INDUCED PULMONARY LESIONS IN MICE.

J M Benson, EB Barr, and K J Nikula. *Lovelace Respiratory Research Institute, Albuquerque NM.*

The lesions in human chronic beryllium disease are induced by a cell mediated immune response in the lung and Be stimulates proliferation of sensitized CD4+ T cells in a MHC class II-restricted manner. C3H mice inhaling Be metal develop pulmonary lesions suggesting a CD4+-dependent, cell-mediated immune response. Carefully selected wild-type, congenic, and knockout mouse strains were used in these studies to test the hypothesis that components of the Be-induced pulmonary histopathology are a result of a cell-mediated immune response and that the magnitude of the response is influenced by the IA region of the MHC II complex. Female C3H/HeJ [haplotype at H-2 Allele IA/IE = k/k] B10.A(4R) [k /-] and B10.A(5R) [b/b], C57BL/6 [b/-], and A^b_β, knockout [CD4+ lymphocyte depleted], mice were exposed nose-only to 30 mg Be metal/m^3 to provide lung burdens of 20 and 45 μg Be/lung. Subgroups of 12 mice/strain/Be lung burden were sacrificed 6 and 9 mo after exposures for evaluation of histopathological changes characteristic of immune (peribronchial and septal lymphocytic aggregates, lymphocytic infiltrates, and microgranulomas), inflammatory (alveolar macrophage hyperplasia and alveolar neutrophils), and nonspecific responses (alveolar epithelial hyperplasia and alveolar proteinosis). Preliminary ranking of strains, in order of magnitude of both immune and inflammatory components of the response was C3H/HeJ > C57BL/6, B10.A(4R) > A^b_β. Alveolar proteinosis and alveolar epithelial hyperplasia occurred chiefly in the C57BL/6, B10.A(4R), B10.A(5R) and A^b_β strains. Comparison of lesions between the C3H/HeJ and A^b_β strains indicate that lesions in the former strain are due to a cell-mediated immune response. The greater cellular response in the C3H/HeJ strain compared to the other strains indicate the importance of haplotype k/k in determining the magnitude and nature of the response. [Research supported by the Office of Health and Environmental Research, U.S. department of Energy, under Contract No. DE-AC04-76EV01013.]

1722 DEVELOPMENT OF TOLERANCE TO CLARA CELL NECROSIS FOLLOWING REPEATED DOSING OF COUMARIN.

A S Fix[1], S L Born[2], L D Lehman-McKeeman[2]. [1]*Procter and Gamble Co., Cincinnati, OH and* [2]*Research Institute for Fragrance Materials, Hackensack, NJ.*

Coumarin, a fragrance ingredient, causes acute Clara cell necrosis in B6C3F1 mouse lung and hepatic necrosis in the F344 rat. Toxicity is thought to result from cytochrome P450-mediated bioactivation of coumarin to form coumarin 3,4-epoxide (CE). In the mouse lung, coumarin induces selective swelling, necrosis and sloughing of Clara cells in terminal bronchioles 24 hr following a single oral dose (200 mg/kg). These data correlate with the formation of alveolar/bronchiolar adenomas and carcinomas in mice following chronic coumarin (200 mg/kg) administration (NTP 422), suggesting that acute lung damage may play a role in the carcinogenicity of coumarin. In the current study, the effects of repeated coumarin administration in mice were examined using a dosing regimen similar to that of the bioassay. Female B6C3F1 mice were administered 200 mg/kg coumarin via oral gavage for up to 2 weeks (5 doses/week). After a single dose, Clara cell necrosis was observed histologically and immunoblotting indicated that P450 abundance was decreased in whole lung. In contrast, Clara cell necrosis was not evident following 5 consecutive doses of coumarin, and after 10 doses, the bronchiolar epithelium was normal, suggesting that the cells had become tolerant to the toxic effects of coumarin. Based on qualitative observations, Clara cells from mice receiving 10 doses appeared histologically normal but their number was diminished. Tolerance was further demonstrated biochemically as Western blots indicated that cytochromes P450 2A, 2B, 2C, 2E and 2F had returned to control levels. Thus, Clara cells become tolerant to coumarin-induced toxicity. However, tolerance does not result from altered P450 levels.

1723 EXTENDED EXPOSURE TO AGED AND DILUTED SIDESTREAM CIGARETTE SMOKE (ADSS) ALTERS PULMONARY NEUROENDOCRINE CELLS (PNECS) IN NEONATAL RATS.

K P Avadhanam, C G Plopper and K E Pinkerton. *School of Veterinary Medicine and Institute of Toxicology and Environmental Health, University of California, Davis, CA.*

Previous work in our laboratory has demonstrated significant increases in fetal neuroendocrine cells following maternal exposure to ADSS. Epidemiological studies report neuroendocrine cell modifications associated with cigarette smoke-related airway disorders such as asthma. The main objective of this study has been to determine developmental and morphometric changes in single neuroendocrine cells (NECs) as well as neuroepithelial bodies (NEBs), following perinatal ADSS exposure. Sprague-Dawley rats were exposed both *in utero* and postnatally to filtered air (FA) or ADSS and their lungs examined at 1, 7, and 21 days postnatal age (DPN) for calcitonin gene-related peptide (CGRP) positive NECs and NEBs. A distinct age effect on the frequency of NECs, NEBs and total sites was observed. NEC, NEB, and total site frequency as well as the size of NEBs declined with age. Perinatal ADSS exposure did not significantly affect the frequency of NECs or NEBs at 1, 7, or 21 DPN. However, the combined effect of age and exposure on the size of NEBs was significant. NEBs of the ADSS group had significantly more cells per NEB than those of the FA group (2-way ANOVA $P<0.05$), predominantly at 1 DPN (ADSS 7.7 ± 0.74 vs. FA 5.3 ± 0.32; mean cells/NEB ± SEM). We conclude that *in utero* and early postnatal ADSS exposure affects the size of NEBs of the developing rat lung in an age-dependent manner.
Funded by the California Tobacco-Related Disease Research Program 4RT-0213 and 6RT-0327

1724 SILICA-INDUCED PULMONARY INFLAMMATION IN RATS: ACTIVATION OF NF KAPPA B AND ITS SUPPRESSION BY DEXAMETHASONE.

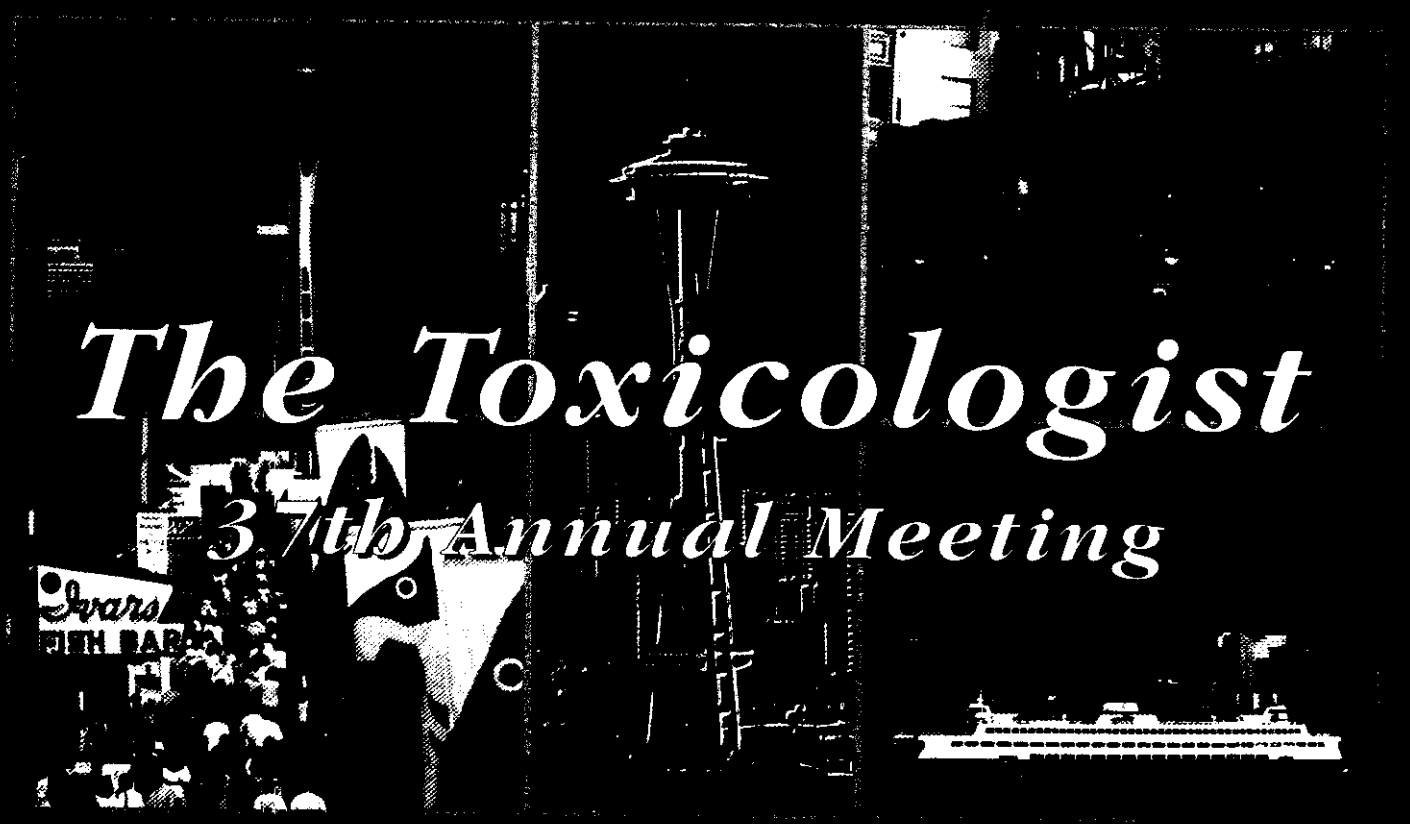
M Sacks[1], J Gordon[1], J Bylander[1], D Porter[2], X L Shi[2], V Castranova[2], W Kazmarczyk[1], M J Reasor[1] and K Van Dyke[1]. [1]*West Virginia University, and* [2]*National Institute of Occupational Safety and Health, Morgantown, WV.*

Inhalation of silica is characterized by initial pulmonary inflammation leading to fibrosis. The goal of this study was to determine the relationship of the transcriptional regulatory factor, nuclear factor kappa B (NFkB) to the early inflammatory events involved with silica exposure. Male F-344 rats received an intratracheal of silica (20mg/0.5ml) or saline. At 1, 3, 6 and 18 hours post-installation, the rats underwent broncheoalveolar lavage (BAL) for analysis of inflammation. From 3 hours post-instillation and onward, the silica-instilled (SI) rats showed significant increases in BAL fluid neutrophil and lymphocyte counts as compared to the saline controls. BAL fluid cells from the SI group also showed a significant increase in luminol-dependent chemiluminescence (LDCL) as compared to the controls. NFkB was present at 3 hours post-instillation and continued throughout the 18 hour time course. Dexamethasone (Dex) has been shown to inhibit NFkB expression invitro, but this has not been examined in the lung in-vivo. Treatment with Dex (5mg/kg) at −3 and 0 hours prior to silica instillation and +1.5 hour post instillation resulted in both a reduction in NFkB expression (by 70%) at 3 hours post-instillation as well as corresponding reductions in LDCL, BAL fluid cell count and BAL fluid inflammatory cells. These results show silica-induced pulmonary inflammation is associated with activation of NFkB and the inhibition of its activation correlates with suppression of inflammation.

An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology



The Toxicologist

37th Annual Meeting

AP

Academic Press

Volume 42, Number 1-s, March 1998

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology
Published by Academic Press, Inc.

Abstracts of the
37th Annual Meeting
Volume 42, Number 1-S
March 1998

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 37th Annual Meeting of the Society of Toxicology, held at the Washington State Convention Center, Seattle, Washington, March 1-5, 1998.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 407.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 433.

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

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332