protein kinase C translocation, due to a reduction in its anchoring protein RACK-1 in old rats. Use of RACK-1 antisense oligonucleotide reduced the response of young macrophages to silica, supporting the idea that age-associated alterations in AM signal transduction pathways contribute to decreased sensitivity to silica-induced lung fibrosis.

## 373 THIOL ANTIOXIDANTS INHIBIT THE ADJUVANT EFFECTS OF AEROSOLIZED DIESEL EXHAUST PARTICLES IN A MURINE MODEL FOR OVALBUMIN SENSITIZATION.

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Although several epidemiological studies indicate a correlation between exposure to ambient particulate matter (PM) and adverse health effects in humans, there is still a fundamental lack of understanding of the mechanisms involved. We set out to test the hypothesis that reactive oxygen species are involved in the adjuvant effects of diesel exhaust particles (Department) in a murine ovalbumin (OVA) sensitization model. First, we tested six different antioxidants, N-acetylcysteine (NAC), bucillamine (BUC), silibinin, luteolin, trolox (vitamin E) and ascorbic acid, for their ability to interfere in Department-mediated oxidative stress *in vitro*. Of the six agents tested only the thiol antioxidants, BUC and NAC, were effective at preventing a decrease in intracellular GSH/GSSG ratios, protecting cells from protein and lipid oxidation, and interfering with HO-1 expression. We therefore selected the thiol antioxidants for testing in the murine OVA inhalation exposure model. Our data demonstrate that NAC and BUC effectively inhibited the adjuvant effects of Department in the induction of OVA-specific IgE and IgG1 production. Furthermore, NAC and BUC prevented the generation of lipid peroxidation and protein oxidation in the lungs of OVA + Department exposed animals. These findings indicate that NAC and BUC are capable of preventing the adjuvant effects of inhaled Department, and suggest that oxidative stress is a key mechanistic component in the adjuvant effect of Department. Antioxidant treatment strategies may therefore serve to alleviate allergic inflammation and may provide a rational basis for treating the contribution of PM to asthmatic disease. (Supported by US Public Health Service Grant AI34567, EPA Southern California Particle Center, and by NIAID AI07126).

## 374 THIOL AND IMMUNE EXPOSURE DEPENDENT RESPONSE TO OVALBUMIN IN SENSITIZED RATS.

N. H. Al-Humadi[1,2], P. D. Siegel[1], D. M. Lewis[1], M. W. Barger[1], J. Y. Ma[1], D. N. Weissman[1] and J. K. Ma[2]. *[1]ASB, NIOSH, Morgantown, WV and [2]School of Pharmacy, West Virginia University, Morgantown, WV.*

Brown Norway rats were exposed 30 min to the antigen, ovalbumin (OVA) at 7.2, 68, 93, 111 or 156 mg/m3 on days 1, 8, 15, and 29. Tissue was collected one day after the last exposure. Cysteine (CYSH), glutathione (GSH), and markers of inflammation in bronchioalveolar lavage fluid (BALF) were measured. Alveolar macrophage (AM) and pulmonary associated lymph node lymphocyte (PALNL) were isolated and assessed for CYSH and GSH concentrations. Specific IgG and IgE, and lung tissue IFN-gamma, IL-4, and TNF-alpha mRNA levels (standardized with G3PDH) were the immunological endpoints studied. Rats were immunologically sensitized as evident by exposure related increases in all immunological parameters and OVA challenge induced increases in BALF albumin, protein and lactate dehydrogenase. In addition, OVA caused a modest elevation at low OVA challenges, but sharp reduction in AM thiols at higher OVA challenges. Concomitantly, OVA exposure dependent increases in BALF CYSH and GSH were observed. CYSH, but not GSH was elevated in PALNL of OVA challenged rats. In summary, antigen exposure dose dependent alteration of thiol and immune parameters were demonstrated *in ova* sensitized and challenged rats.

## 375 PROTEASE ENHANCEMENT OF IGG1 AND IGE ANTIBODY RESPONSE TO HEMICELLULASE IN MOUSE MODELS OF ALLERGY.

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The mouse intranasal (MINT) and mouse aspiration (MaspT) tests are being developed as replacements to the guinea pig intratracheal (GPIT) test used to assess the allergenic potential of protein allergens. Protease enzymes have been shown to enhance the IgG1 antibody response to non-protease enzymes in guinea pigs exposed to mixtures of protease and non-protease enzymes (Sarlo, et.al. JACI, 1997, 100:480). The shift in the antibody response to enzyme mixtures in the GPIT test is used to adjust occupational exposure guidelines. To replace the GPIT test, we must show similar shifts in antibody responses to enzyme mixtures in the mouse models. BDF1 mice were exposed *via* intranasal (IN) instillation to protease, hemicellulase or a mixture of protease + hemicellulase on days 1, 3, 10, 17 and 24; sera were collected on day 29. Similarly, mice were exposed to the same enzymes *via* aspiration (ASP) instillation on days 1, 3 and 10; sera were collected on day 15. IgG1 and IgE antibody to each enzyme were measured by ELISA. IgE titers were randomly confirmed by the rat passive cutaneous anaphylaxis (PCA) test. The protease shifted the IgG1 antibody response to the hemicellulase ~3x in IN and ASP dosed mice. The shift was dependent upon the amount of protease in the mixture - the lower the protease levels in the mixture, the smaller the shift. The protease also shifted the IgE antibody response to the hemicellulase in IN and ASP dosed mice. The enhancement was greater for IgE than for IgG1. The antibody response to protease was not altered by the presence of the hemicellulase. Testing of the protease + hemicellulase mixture in the GPIT test also showed a 3x to 4x shift in IgG1 antibody to the hemicellulase. Therefore, there is consistency between the guinea pig and mouse models. Continued work with mixtures of enzyme allergens is needed to develop the mouse model as a full replacement to the GPIT test.

## 376 RESPIRATORY PHYSIOLOGICAL RESPONSES TO AN EXTRACT OF *Stachybotrys chartarum* IN BALB/C MICE.

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Exposure to *Stachybotrys chartarum* has been associated with the development of serious health problems in humans, including asthma. Previous studies by our group demonstrated respiratory exposure to a pool of *S. chartarum* extracts caused biochemical and immunological responses indicative of a respiratory allergic response. The goal of this study was to assess the abiliry of this extract to cause alterations in respiratory physiological responses similar to those observed in human allergic asthma. Five isolates of *S. chartarum* obtained from wallboards in water-damaged houses were grown and combined in approximately equal weight amounts, extracted using Hanks' Balanced Salt Solution (HBSS) + Tween-80, and filter sterilized to form a crude antigen preparation (SCE-1). Female BALB/C mice were anesthetized and exposed to 4 aspirations of 50 µl volume containing 10 mg of SCE-1, BSA as a non-allergenic protein, or HBSS over a 4-week period. Barometric whole-body plethysmography was performed to measure enhanced pause (PenH) 10 minutes prior to (baseline) and 1 hour following each aspiration exposure to assess immediate respiratory responses. Additionally, airway hyperresponsiveness to nebulized methacholine (MCh) was assessed on days 1 and 3 following the 4th aspiration exposure. Exposure to HBSS or BSA did not alter baseline PenH values, PenH following the aspiration exposures, or airway responsiveness to MCh. Exposure to SCE-1 resulted in a 4.7-fold increase in PenH over baseline after the 3rd exposure, increasing to 5.6-fold after the final exposure, and increased responsiveness to a 32 mg/ml MCh aerosol challenge. We conclude respiratory SCE-1 exposure causes respiratory physiological responses similar to those observed in human allergic asthma. However, BSA does not generate the respiratory physiological responses expected of an allergenic protein when administered by aspiration. (Supported by NCSU/EPA Cooperative Training Agreement CT826512010.) (This abstract does not reflect EPA policy.)

## 377 PATHOLOGIC AND CYTOKINE RESPONSES IN THE RESPIRATORY TRACT OF A/J MICE AFTER INTRANASAL SENSITIZATION AND CHALLENGE TO TOLUENE DIISOCYANATE.

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Occupational asthma is the most frequently diagnosed respiratory disease in the workplace and is often linked to low molecular weight chemicals (LMWC) such as toluene diisocyanate (TDI) that sensitize the respiratory tract. Occupational asthma is characterized by smooth muscle hypertrophy, mucus hypersecretion, epithelial desquamation and an inflammatory influx consisting of lymphocytes, eosinophils, and neutrophils in the airways. Many experimental models have linked the Th2 phenotype to LMWC-induced occupational asthma. Most murine models of occupational asthma, however, use systemic administration (e.g., dermal) to sensitize mice. The present study was designed to test the hypothesis that intranasal sensitization and challenge to TDI will induce the immunologic (cytokine and IgE) and pathologic responses in the lung that are characteristic of LMWC-induced occupational asthma. Only mice that were intranasally sensitized and challenged to TDI exhibited an increase in lung derived IL-4 mRNA. IL-4 mRNA expression in these animals reached 8-fold the level of control 24 hours after exposure and waned to 4-fold the control levels by 96 hours. In addition, only TDI sensitized and challenged animals exhibited an increase in total serum IgE. The total serum IgE levels

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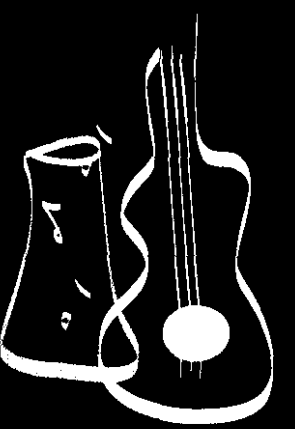

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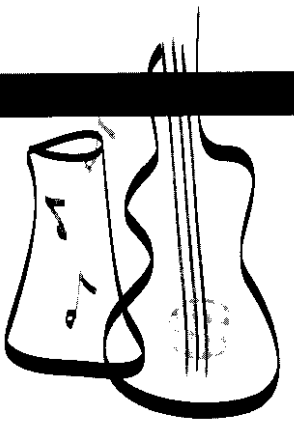

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# *Preface*

**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 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.**

**An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.**

**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.**

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

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