1143 RELATING MOLECULAR MECHANISMS TO PATHOPHYSIOLOGICAL EFFECTS: FUMONISIN AS A CASE STUDY.

P. D. Constable[1], L. A. Gumprecht[1], G. W. Smith[1], M. E. Tumbleson[1], R. M. Eppley[2], S. Mathur[1] and W. M. Haschek[1]. [1]*University of Illinois, Urbana, IL and* [2]*USFDA, Washington, DC.*

Fumonisins, mycotoxins produced by *Fusarium verticillioides* (= *F. moniliforme*) and *F. proliferatum*, inhibit sphingosine N- acyltransferase, a key enzyme in the pathway of *de novo* sphingolipid biosynthesis, resulting in increased concentrations of sphingosine (So) and sphinganine (Sa) in serum and tissues of all species. Fumonisins cause lethal pulmonary edema in pigs and leukoencephalomalacia in horses; renal injury in rabbits, sheep, and rats; and liver injury in all species. Our recent studies have focused on the pathogenesis of fumonisin B_1 induced pulmonary edema, which is unique to swine, taking into consideration pathological, physiological and biochemical alterations. Interstitial pulmonary edema was accompanied by membranous accumulations in the pulmonary capillary endothelial cells which appear specific to this cell type and to swine. Fumonisin B_1 increased mean pulmonary arterial pressure and decreased heart rate, cardiac output and mixed venous oxygen tension. Additionally fumonisin B_1 decreased cardiac contractility as assessed by left ventricular end-systolic elastance and maximal rate of change of pressure. However, the permeability of the alveolar-capillary membrane was not altered. Fumonisin increased the concentrations of So and Sa in the kidney>liver>lung>heart, as well as in serum. Neither pulmonary edema nor cardiovascular physiologic alterations occurred in calves given purified fumonisin B_1 intravenously at the same dose; however, the increases in serum Sa and So in calves were much lower than in pigs. The changes in pigs are compatible with the inhibition of L-type calcium channels by increased So and/or Sa concentration. Therefore, fumonisin-induced pulmonary edema in swine presumably results from acute left-sided heart failure mediated by inhibition of sphingolipid biosynthesis.

2003825

1144 THE INFLUENCE OF CO-POLLUTANTS ON THE TOXICITY OF AIRBORNE PARTICULATE MATTER.

M. C. Madden[1] and K. E. Pinkerton[2]. [1]*USEPA, Research Triangle Park, NC and* [2]*University of California, Davis, CA.*

Recent epidemiological reports have shown an association between ambient air particulate matter (PM) concentrations and human mortality and morbidity, such as increased hospitalizations. PM coexists in the ambient air with many other pollutants, and therefore complicates the assessment of the contribution of PM to the affected health endpoints. In the National Research Council's Report in 1998 that concerned Airborne PM Research Priorities, one of the research aspects emphasized was performance of controlled toxicological studies and epidemiological studies related to examining effects of co-pollutants on possible PM-induced health endpoints. In this session, evidence of the support for co-pollutant influences on PM-associated health effects will be examined from epidemiological studies. Evidence of co-pollutants affecting PM-induced responses will be will drawn from findings of controlled *in vivo* and *in vitro* exposure studies that examine cardiopulmonary effects of PM. These controlled co-pollutant studies can potentially suggest which pollutants are likely to influence PM-induced lung and extrapulmonary toxicity, and potential mechanisms for these interactions. Additionally, the characteristics and components of PM likely to be influenced by other ambient pollutants can be identified in these studies. Oxidants including ozone, inorganic components such as sulfates, organic constituents such as aromatic compounds, and biological substances (i.e., endotoxin) can all play an important role in modifying PM-induced effects by allowing co-pollutant interactions. Data presented from gaseous pollutant interaction with cigarette smoke, more typically an indoor pollutant, will compliment the understanding of outdoor PM toxicology.

1145 EPIDEMIOLOGIC EVIDENCE OF CO-POLLUTANT INFLUENCE ON PARTICULATE-INDUCED TOXICITY.

C. A. Pope. *Brigham Young University, Provo, UT.* Sponsor: M. C. Madden.

Epidemiologic evidence suggests that airborne particulate matter (PM), especially primary and secondary combustion-related PM, is a risk factor for cardiopulmonary disease and mortality. Most epidemiological studies have focused on effects of acute exposure. Chronic exposure, however, may be more important in terms of overall public health relevance. Chronic exposure likely increases the risk of cardiopulmonary disease and mortality. Acute exposure can exacerbate existing cardiopulmonary disease and increase the number of persons in a population who become symptomatic, require medical attention, or die. There is also evidence of health effects due to exposure to other air pollutants-including O_3, CO, SO_2, and NO_2. Basic approaches to evaluating the contributions of co-pollutants to PM-induced toxicity include: 1) estimate regression models with multiple pollutants as covariates and use statistical criteria such as significance levels or coefficient size and stability to evaluate the relative impact; 2) evaluate estimated pollution effects in areas with different levels and combinations of co-pollutants. These epidemiologic approaches reveal evidence of combustion-source PM toxicity that is independent of co-exposure to SO_2, NO_1, or O_3. It remains unclear if the relative toxicity of combustion-related PM is due to the relative small size of the particles, their chemical composition, or their associations with other combustion related pollutants. Epidemiologic studies are limited due to the use of people living in uncontrolled environments with complex mixtures of air pollution. An improved understanding of the influence of co-pollutants on PM-toxicity requires continued contributions from toxicological studies.

1146 EFFECT OF CO-POLLUTANTS (SO_2, NO_2, AND NH_3) ON THE ACUTE PULMONARY TOXICITY OF PARTICLES AND PARTICULATE MATTER (PM)—ASSOCIATED METALS.

K. L. Dreher. *USEPA, Research Triangle Park, NC.* Sponsor: D. L. Costa.

Exposure to ambient air PM occurs in the presence of a complex and dynamic mixture of gaseous air pollutants. The ability of co-pollutants to influence the adverse health effects associated with ambient air PM exposure represents a critical risk assessment issue. Toxicology studies have employed surrogate aerosols and mixtures to examined the extent to which co-pollutants (SO_2, NO_2, and NH_3) may influence the ability of particles to alter lung physiology, immune function and injury or modulate the toxicities of causal PM components. Exposure of animals to aerosol mixtures containing SO_2 and soluble metal salts or insoluble metal oxides was found to enhance the ability of SO_2 to induce alterations in pulmonary function through the formation of H_2SO_4. Additional studies involving the exposure of animals to carbon black (CB) particles in the presence of sulfuric acid or SO_2 with high relative humidity were found to produce immunotoxic and cellular cytotoxic effects that were not induced by individual exposures to these substances. Similar studies have detected increased cell proliferation in epithelial cells at airway bifurcations in rats exposed to a mixture of NH_4NO_3 and CB particles. Surrogate mixture studies have examined the potential interactions between PM-associated metals (Fe and Zn) and other PM co-constituents (H_2SO_4, NO_3-, and NH_4+) resulting from the transformation of gaseous air pollutants (SO_2, NO_2 and NH_3). Dilute sulfuric acid was found to dramatically increase ZnO bioavailability and pulmonary toxicity. Nitrate and ammonium were found to enhance Fe and attenuate Zn pulmonary toxicities. Metal bioavailability could account for some but not all of the observed effects of NO_3-, and NH_4+ on either Fe or Zn pulmonary toxicities. These results demonstrate the ability of SO_2, NO_2 and NH_3 co-pollutants to influence PM toxicity through: (i) the surface formation and/or deposition and enhanced pulmonary delivery of toxic substances such as acids; and (ii) the surface formation and/or deposition of acids, NO_3-, and/or NH_4+ which can modify the toxicity of other PM constituents such as metals by enhancing their bioavailability or biopotency, and/or altering their cellular specificity.

1147 EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS) ENHANCES THE SENSITIVITY OF THE LUNGS TO OZONE-INDUCED INJURY.

K. E. Pinkerton, M. Yu and H. P. Witschi. *University of California, Davis, CA.*

To examine the effects of ETS on the sensitivity of the lungs to ozone, A/J and B6C3F1 mice were exposed to filtered air, ETS, ozone or ETS followed by ozone. ETS exposure was for 6 hr/day for 3 days at a total particulate concentration of 30 mg/m³; ozone exposure was for 24 hrs at 0.5 ppm. Proliferating cells were identified by bromodeoxyuridine (BrdU) immunolabeling. The percent of BrdU labeled cells within the centriacinar regions of the lungs was found to be significantly elevated in both strains of mice following exposure to ozone (3-fold above control) and further augmented in mice exposed to ETS and ozone (4-fold above control). In contrast, exposure to ETS alone did not change BrdU labeling compared with filtered air control mice. Cytokine release *in vitro* from alveolar macrophages obtained from the lungs by bronchoalveolar lavage was also examined. In both strains of mice, there was a significant decrease in IL-6 production with or without

407-CC4-90662