

509 SENSORY IRRITATION (S), PULMONARY IRRITATION (P) AND AIRFLOW LIMITATION ALONG THE CONDUCTING AIRWAYS OF THE LUNG (A) IN GUINEA PIGS USING DIGITIZATION OF AIRFLOW (V) DURING INSPIRATION (VI) AND EXPIRATION (VE) OBTAINED FROM A BODY PLETHYSMOGRAPH

M F Stock, J E Luo, L A Boylstein, R D Thompson, Y Alarie. *University of Pittsburgh, Pittsburgh, PA*

A computer program is available to analyze the breathing pattern of unanesthetized mice held in a body plethysmograph, to recognize S on the basis of duration of breaking at the beginning of expiration (TB), P on the basis of duration of a pause at the end of expiration (TP) and A on the basis of a decrease in VE at 0.5VTE (VD) (Vijayaraghavan et al., *Arch. Toxicol.* 68: 490, 1994). This computer program is being modified to process data with guinea pigs. In this species there is a strong first phase of pulmonary irritation (P1) which is characterized by a shorter duration of inspiration (TI), shorter duration of expiration (TE) and lower VT, i.e., rapid, shallow breathing, before A or P occur. Recognition of P1 is important in this species since it occurs during immediate pulmonary hypersensitivity reactions (Alarie et al., *Am. Coll. Toxicol.* 9: 407, 1990). Each breath of each animal was collected for a period of 15 min to establish control values for TB, TP, VD, TI, TE and VT and increases or decreases in these values were then used to classify each breath as normal (N), or S, A, P1 or P during exposure. The results indicate that a P1 effect can be easily detected, as induced by low exposure concentrations of histamine or propranolol aerosols. An S effect was also easily recognized during exposure to chlorobenzylchloride (CBC). However, guinea pigs were about 7-10 times less sensitive than mice to the effect of CBC. For A effects the program does not yet appropriately recognize this pattern. Similarly the program overclassifies the P effects. Thus, so far, only P1 and S effects can be detected. Supported by RO1-ESO2747, NIEHS.

510 INHALATION TOXICITY IN RATS EXPOSED TO p-PHENYLENE DIISOCYANATE AND CYCLOHEXANE DIISOCYANATE FOR TWO WEEKS

J C Stadler, G S Elliot, K P Lee. *E.I. duPont de Nemours and Co, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE*

Isocyanates have numerous industrial uses and are also noted respiratory tract irritants. Two diisocyanates with ring structures, p-phenylene diisocyanate (PPDI), an aromatic, and cyclohexane diisocyanate (CHDI), an aliphatic, were examined in 2-wk (6 hrs/day; 5 days/wk) studies with rats. The solid test materials were heated, and vapor sublimation produced mixed particulate/vapor exposure atmospheres. Design concentrations were 0, 0.5, 2, or 8 mg/m³ PPDI and 0, 1, 3, or 10 mg/m³ CHDI. Reduced body weight gains, lung noise and/or nasal discharge were observed. Respiratory tract irritation was noted microscopically after the last exposure. At the lowest levels, lesions were limited to the anterior nasal cavity; at the intermediate and high levels, lesions extended into the lower airways. Anterior nasal lesions from both isocyanates included rhinitis and hyperplasia, metaplasia and/or denudation of epithelial cells. Lower airways had inflammation and hyperplasia from both compounds; metaplasia and epithelial cell denudation with CHDI. After a 2-wk recovery, PPDI-exposed rats were free of lesions; CHDI-exposed rats (3 or 10 mg/m³) had mild lesions in the nasal cavity. Under study conditions there was no observed-adverse-effect level for either isocyanate; however, irritant effects were slightly more severe with CHDI than with PPDI.

511 FORMALIN INDUCES SPONTANEOUS OSCILLATIONS OF MEMBRANE POTENTIAL IN HUMAN AIRWAY SMOOTH MUSCLE TO SUBSTANCE P

I S Richards, G D Leikauf. *Department of Environmental and Occupational Health, College of Public Health, University of South Florida, Tampa, FL; Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH*

Previous studies from our laboratory have shown that formaldehyde, a ubiquitous indoor environmental contaminant and respiratory irritant, produces alterations in several aspects of the electromechanical properties of human airway smooth muscle (ASM) including: 1. the production of transient contractions, 2. depolarisations of ASM cell membranes over the concentration range of 0.1-10 ppm formalin, and 3. an apparent increase in sensitivity to the contractile agonist, acetylcholine. The present study was conducted to determine if acute formaldehyde exposure of human ASM *in vitro* altered the transmembrane resting potential during the subsequent exposure to the neurotransmitter Substance P. Preparations were studied at 37°C using a specially constructed superfusion system and 3 M KCl-filled microelectrodes. We ob-

served that 2 hours of exposure to 1 ppm formaldehyde (as formalin), produced spontaneous electrical oscillations of membrane depolarizations and repolarizations in the presence of 1.0×10^{-12} M Substance P. At this concentration of Substance P we were unable to demonstrate any changes in membrane potential in the absence of formalin. These results suggest that increased sensitivity to multiple neural contractile agonists may result from short-term exposures to moderate levels of formaldehyde. (Supported in part by a grant from The Center for Indoor Air Research, Inc.).

512 ASSESSING THE PENETRATION OF INHALED NITRIC ACID VAPOR IN THE RESPIRATORY TRACT

L C Chen, R B Schlessinger. *NYU Medical Center, Tuxedo, NY*

Nitric acid (HNO₃) vapor is a component of ambient photochemical pollution. Because of its high water solubility and reactivity, it would be anticipated to undergo significant removal within the upper respiratory tract (URT). However recent studies show that inhaled vapor can alter bronchial responsiveness and other functions of the lower respiratory tract (LRT). The penetration of HNO₃ into the lungs was examined using a physical model which mimicked the URT of the animal used in this laboratory for toxicologic studies, namely the rabbit. The system allowed for mixing of precisely metered HNO₃ with ammonia (NH₃) at concentrations present in the URT, under conditions of controlled relative humidity (RH). The penetration of HNO₃ is determined by measuring the concentration of particles and vapor downstream from the mixing port. The penetration of HNO₃ through the URT increased with increasing relative humidity and NH₃ concentration. The portion of HNO₃ that penetrated was found to be present as particles. In an NH₃-free atmosphere at 77% RH, ultrafine particles at 0.003 μm were formed. When NH₃ was added, the particle size increased to 0.15 μm. While there was greater production of particles when NH₃ was present at various levels of RH, even in the absence of NH₃, almost 50% of HNO₃ formed particles at high RH. We also examined the ability of other particles (saline) to act as vectors for adsorbed HNO₃, which could then be carried into the LRT. The results indicate that HNO₃ vapor is likely transformed into particle form at some point following inhalation. Endogenous ammonia may react with inhaled HNO₃, producing particulate ammonium nitrate. Once formed, these particles may then also serve as absorption surfaces, and additional vectors, for HNO₃ delivery to the LRT. Supported by CARB.

513 MOLECULAR AND MORPHOLOGIC DETERMINANTS OF ORGANIC DUST EXPOSURES IN ALVEOLAR MACROPHAGE (AM) CELLS

G N Cosma, W F Davis, D J Ufferfilge, S A Olenchok¹, M L Beard. *Dept. Env. Health, Colo. St. Univ., Ft. Collins, CO; ¹ NIOSH, Morgantown, WV*

To understand the pathology of pulmonary diseases after exposures to airborne dusts, we have previously measured acute-phase gene induction in rat/mouse lung after inhalation of respirable particulates. We have now measured *in vitro* responses of target AM cells to grain dust (GD) extracts and specific etiologic agents (bacterial endotoxin and fungal mycotoxins) found in elevator wheat samples. Area samples of respirable wheat dust were collected onto filters by personal pumps during routine elevator operations. Endotoxin levels were quantitated by chromogenic LAL assay, and fungi identified by standard mycologic culture. Rat AM cell line NR8383 displayed greatly reduced cell growth and elevated toxicity in response to purified endotoxin vs. *Alternaria* mycotoxins. When cells were exposed to GD extracts, dose-responses most closely resembled those of endotoxin alone, suggesting a pivotal role for this febrile agent in the pathophysiology of dust-related pulmonary diseases. Induction of the metallothionein gene was also detected by Northern blot analyses. Further acute-phase gene induction and oxidative burst analyses are in progress. Supported by NIOSH #U07/CCU807121-02.

514 BIOCHEMICAL RESPONSES OF INHALED CARBON BLACK IN RATS

J N Finkelstein, G Oberdörster, C Johnston, L Paulhamus. *University of Rochester, Dept. of Environmental Medicine, Rochester, NY, USA*

The objective of this study was to establish mechanisms of response of lung to low toxicity particles after subchronic inhalation. Fischer-344 rats were exposed to carbon black for 3 months at 6h/day, 5 days/week at concentrations of 1.7 and 50 mg/m³. At intervals during the exposure and up to 6 months post-exposure the pulmonary response was assessed by biochemical analysis of lavage fluids for pulmonary surfactant and fibrogenic growth factors. In addition, cells recovered from lavage were assayed *in vitro* for production

SOCIETY OF TOXICOLOGY

34th Annual Meeting



THE TOXICOLOGIST

Volume 15, No. 1, March 95

FUNDAMENTAL AND APPLIED TOXICOLOGY