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## ABSTRACTS OF THE 1985 ANNUAL MEETING

285 MODULATION OF ACUTE $NO_2$ TOXICITY BY VITAMIN E IN THE RAT LUNG. D.J. Guth and R.D. Mavis, Division of Toxicology, University of Rochester Medical Center, Rochester, New York 04642.

The role of lipid peroxidation in acute $NO_2$ toxicity was studied in rat lung. After 4 hr exposure to 40 ppm $NO_2$ there was no increase in lipid conjugated dienes in lung homogenate, lavage, or free cells. Thiobarbituric acid reactive materials were not increased in lung homogenate or lavage and slightly increased in free cells. In rats maintained on a semipurified diet with 0, 10 or 1000 ppm Vitamin E (VE) for 11 weeks, the lung content of VE was 3.6, 17.4 and 87.7 μg VE/lung, respectively. Groups of 5 or 6 rats were exposed to 0, 10, 20, 30 or 40 ppm $NO_2$ for 4 hr and $NO_2$ toxicity was measured by increase in lavagable protein, sialic acid, lactate dehydrogenase (LDH), malate dehydrogenase (MDH), glucose-6-phosphate dehydrogenase (GDH), acid phosphatase (AP), and aryl sulfatase (AS). Increases in lavagable protein, sialic acid, AP and AS were not affected by VE ($p > .05$). Increases in lavagable LDH, MDH, and GDH after $NO_2$ exposure were significantly attenuated by 1000 ppm VE ($p > .05$), consistent with a lipoperoxidative mechanism. (Supported by US DOE contract no. DE-AC02-76EV03490 and NIH Training Grant No. 5 T32-HL07216-08).

286 TOLUENE DIISOCYANATE (TDI) INDUCED AIRWAY HYPERRESPONSIVENESS AND INFLAMMATION IN GUINEA PIGS. T. Gordon, D. Sheppard, D.M. McDonald, S. Distefano, and L.A. Scypinski. Cardiovascular Research Institute, UCSF, San Francisco, CA

We examined the changes in airway responsiveness to increasing doses of an acetylcholine (Ach) aerosol in anesthetized and ventilated guinea pigs 2, 6, or 24h after exposure to 2ppm TDI or 2h after exposure to air or 1ppm TDI. The concentration of Ach calculated to cause a 200% increase in pulmonary resistance was significantly lower for animals studied 2h (6.8mg/ml) or 6h (7.7mg/ml), but not 24h (23.9mg/ml), after TDI than for air animals (30.7mg/ml). Exposure to 2ppm TDI caused a patchy loss of cilia, shedding of epithelial cells into the lumen, and an influx of inflammatory cells into the trachea and other airways. In the lamina propria of the trachea, the concentration of extravascular polymorphonuclear leukocytes (PMN's) was 13 to 26 fold greater in animals studied 2 or 6h after exposure to 2ppm TDI or 2h after 1ppm TDI than in animals exposed to air. The concentration of PMN's in the epithelium was significantly increased only in animals examined 2h after 2ppm TDI. Exposure to TDI also caused an influx of eosinophils into the tracheal mucosa. This influx occurred later and was more persistent than the influx of PMN's. These results indicate that a single exposure to TDI can cause an increase in airway responsiveness that is associated with epithelial injury and acute airway inflammation.

287 EVALUATION OF THE PULMONARY EFFECTS OF HDI TRIMER AEROSOLS IN GUINEA PIGS. Ferguson, J.S., Schaper, M.M. and Alarie, Y., Dept. Ind. Env. Hlth. Sci., Univ. of Pittsburgh, Pittsburgh, PA

Hexamethylene diisocyanate trimer (HDIt) is a viscous liquid and used in spraying operations for durable coatings. It has been shown to be a pulmonary irritant following a single exposure. A group of guinea pigs was exposed to 65 to 74 $mg/m^3$ for 3 hour/day on 11 consecutive days to establish if a cumulative pulmonary toxic effect would occur. The particle size was around 0.7 μm MMD. Prior to and following exposure, each animal was exposed to 10% $CO_2$ in 20% $O_2$ and 70% $N_2$ to evaluate their pulmonary performance. Following the first exposure, the respiratory frequency of these animals was increased and frequent apneic periods were observed as well as coughing. Also their ventilatory response to 10% $CO_2$ was highly abnormal. However, with repeated exposures a tolerance began to develop as indicated by a return toward normal of their ventilatory response to 10% $CO_2$. The tolerance occurred within the first 5 days of exposure. From day 6 to 11 there was a demonstrable effect but the level of effect was much less than following the first exposure. Supported by NIEHS Grant 1 R01-ES02747.

288 A PHYSIOLOGICALLY-BASED KINETIC MODEL (PB-KM) FOR INHALED $CCl_4$ IN THE RAT. D. J. Paustenbach, H. J. Clewell, M. L. Gargas, and M. E. Andersen, Syntex Corporation, Palo Alto, CA, and Air Force Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH

The disposition of inhaled $^{14}C$-$CCl_4$ described by Paustenbach (1985) included measurement of radiolabel excreted in the breath ($CO_2$ and $CCl_4$) and unspecified metabolites excreted in urine and feces after multiple daily exposures to 100 ppm. We have developed a PB-KM for $CCl_4$ to describe these data. Partition coefficients (PC) were measured by vial equilibration and kinetic constants by gas uptake. PC for blood and fat were, respectively, 4.52 and 359. Vmax and Km were 0.4 mg/kg/hr and 0.25 mg/L. Metabolism is saturated at 100 ppm and is inhibited by pyrazole. The PB-KM was used to describe elimination in multiday exposures (either 8 or 11.5 hr/day for 10 to 14 days of exposure). The models either assumed first order elimination of metabolites or included delays for fecal elimination before the first order phase. With suitably adjusted elimination rate constants, the predictions were in good agreement with data. Most inhaled $CCl_4$ was metabolized; the fat is an important depot supplying $CCl_4$ for post exposure metabolism even at 100 ppm; and the mass balance suggests that fecal radioactivity is primarily associated with metabolites.