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**1661** USE OF PHARMACOKINETIC AND LUNG DEPOSITION MODELING IN A CANCER RISK ASSESSMENT FOR CADMIUM.

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Cadmium has been shown to be a carcinogen in both animals and humans. The strongest evidence for cadmium carcinogenicity is from inhalation studies where rats were exposed to aerosols of different cadmium compounds for two years and then followed for the 18 months to determine the incidence of lung tumors. These inhalation studies have shown cadmium to produce a dose-responsive increase in tumor incidence with increasing inhalation concentration. Epidemiological studies of workers exposed to cadmium aerosols have also shown evidence of cadmium being a lung carcinogen in humans. We have employed kinetic models of cadmium to assist in the analysis of the dose-response for lung tumors in rats and humans after inhalation exposure. The lung tumor dose-response data from animal studies by Takenake et al. (1983) were analysed using the lung deposition model developed by the EPA and animal clearance data from studies by Oberdorster. Extrapolation of the rat inhalation lung tumor response data to the human exposure situation was accomplished using the EPA deposition model. These animal based estimates of lung cancer risk to human exposed by inhalation to cadmium were compared to risks determined from epidemiological studies. As a comparison, the inhalation cancer slope factor based on the epidemiological data from occupational exposures (Thun et al., 1985, Stayner et al., 1992) were adjusted for an ambient aerosol size and distribution, to account for the differences in deposition between an occupational versus an environmental aerosol. Recently, Waalkes and Rehn (1991,1992) have found that rats dosed orally with Cd develop testicular tumors. A kinetic model developed for cadmium was also used to provide dose-metric estimates for testicular tumors in rats.

**1662** APPLICATION OF A CLOSED INHALATION EXPOSURE SYSTEM FOR SIMULTANEOUS MEASUREMENT OF METABOLIC AND PHYSIOLOGICAL VARIABLES DURING CHLOROFORM (CHCl<sub>3</sub>) EXPOSURE IN RATS.

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In the past, physiologically based pharmacokinetic (PBPK) models for volatiles have relied upon averaged physiological data from the literature. Direct measurement and use of individual physiological parameters such as heart rate (HR), core temperature (T<sub>co</sub>), and indices of pulmonary function may lead to improved models for use in the risk assessment process. Telemetry transducers were surgically implanted in male F344 rats to monitor HR and T<sub>co</sub>. Eight days after surgery, the rats were exposed to initial concentrations of 500, 1000 and 3000 ppm CHCl<sub>3</sub>. The closed response system functioned as a whole body plethysmograph and used a pressure transducer to provide the signals from which ventilation frequency, tidal volume and minute volume were derived. In addition, an automated closed-loop oxygen control system allowed real time measurement of minute oxygen uptake. T<sub>co</sub> and HR showed a substantial decrease: Δ1.5°C and Δ125 beats per minute (bpm) for 500 ppm (n = 1), Δ1.0°C and Δ65 bpm for 1000 ppm (n = 2) and Δ2.5°C and Δ150 bpm for 3000 ppm CHCl<sub>3</sub>, respectively (n = 2). At the highest concentration, ventilation frequency decreased 33% relative to controls, tidal volume increased 45%, and oxygen uptake decreased 20%. In summary, CHCl<sub>3</sub> exposure in a closed inhalation system showed important changes in physiological parameters which may lead to improved PBPK models. (This abstract does not necessarily reflect EPA policy).

**1663** SIMULATION AEROSOL MODEL STUDIES WITH PERYLENE CONDENSED ONTO CARBON BLACK PARTICLES.

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Continued improvement of aerosol generation systems is imperative as attempts are made to develop meaningful dose-response relationships for

various classes of chemicals. Here we report the characterization of an improved, large volume, aerosol generation system that is described in terms of simulations with the polycyclic hydrocarbon fluorescent dye, perylene. The efficiency of perylene vaporization and condensation onto ultrafine carbon black particles was quantified as a function of its temperature of vaporization (T<sub>vap</sub>) at a total system flow rate of 40 liters per minute representing 39 liters per minute of carbon black to 1 liter per minute of perylene vapor. Aerosol size distribution measurements of the resulting carbon black:perylene particulate aerosol revealed an average mass median aerodynamic diameter of 2.313 μm over a three point temperature range with 65 percent of the carbon black particles being 2.5 μm or less. These simulations predict that significant deposition within all regions of the rat respiratory tract can be achieved in future toxicity testing with genotoxic polycyclic aromatic hydrocarbons.

**1664** INFLUENCE OF ORGANIC FILMS ON REACTIVITY AND HYGROSCOPICITY OF SULFURIC ACID AEROSOL.

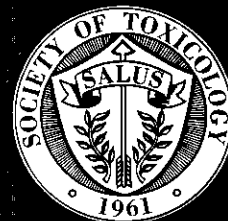
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In the atmosphere, gaseous ammonia (NH<sub>3</sub>) is an important neutralizing substance for acidic aerosols. The kinetic data shows that pure H<sub>2</sub>SO<sub>4</sub> aerosol can react rapidly with NH<sub>3</sub>. This reaction is also important in the human airways, where endogenous NH<sub>3</sub> concentrations are much higher than atmospheric levels. In ambient air, organic chemicals, natural as well as man-made origins, are common constituents of aerosol particles. If these compounds are present as surface films, mass transfer of gaseous molecules into the particles could be impeded and the chemical reaction kinetics as well as the hygroscopic growth of the H<sub>2</sub>SO<sub>4</sub> acid aerosol could be reduced. In this study, we focused on the investigation of the influence of organic films on hygroscopic growth rate of ultrafine monodispersed (20, 40, and 100 nm) sulfuric aerosols. We found that 1) The presence of monolayer films of fatty acids retards the hygroscopic growth rate of H<sub>2</sub>SO<sub>4</sub> aerosols due to obstructive effect of the films on the permeation of gaseous water. 2) The retardation effects depend on the original film coating thickness, but not on the particle sizes. 3) Linear molecules, such as, lauric acid (C<sub>12</sub>) and stearic acid (C<sub>18</sub>), has stronger effects than those nonlinear molecules, such as oleic acid (C<sub>18</sub>). Therefore, it is possible that organic films may protect ambient acidic aerosols from being neutralized by ammonia (ambient and respiratory tract) and allowing them to retain their acidity to produce biological effect in the deep lung (Sponsored by EPA R822476).

**1665** THE USE OF PRECISION-CUT RAT LUNG SLICES AS AN *IN VITRO* TOOL IN TOXICOLOGY: EFFECTS OF DIESEL EXHAUST.

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The aim of this study was 1) the characterization of an *in vitro* model of precision-cut rat lung slices in a gas/liquid biphasic exposure system and 2) its application to the evaluation diesel exhaust toxicity. Evaluations were performed 1h or 24h following a 1h exposure to pollutants. Continuous flow rotating chambers with controlled pO<sub>2</sub>, pCO<sub>2</sub> and hygrometry have been designed in which slices are positioned on rolling insert placed into vials with opened caps to allow free access to the gaseous phase. In the control slices, viability was preserved up to 48h, as assessed by the intracellular ATP and K<sup>+</sup> contents, the respiratory activity and protein synthesis. Histological examinations revealed the preservation of the alveolar architecture. Moreover, the study of the pulmonary specific functions allowed to prove the *in vitro* cellular differentiation: 1) polyamine transport is preserved and exhibited kinetic properties similar to those observed in lung *in vivo*, 2) the surfactant synthesis is preserved and 3) the study of the antioxidative detoxication pathway indicated that catalase, superoxide dismutase and selenium dependent glutathione peroxidase are stable in this system over the experimental period. Diesel exhaust exposure induced decreased cellular respiration and intracellular ATP concentrations. Inhibition of super oxide dismutase activity and decreased total intracellular glutathione rates were observed 1h after the end of the exposure. 24h after the exposure, these 2 markers recovered values similar to those observed in control slices. Increased specific activity of selenium dependent glutathione peroxidase was observed. This antioxidative response points out the occurrence of peroxidative stress which is an important intermediate of Diesel exhaust cellular toxic injury. We concluded that the *in vitro* precision-cut rat lung slices in a biphasic gas/liquid system can be



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# Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshops, roundtables, and poster sessions of the 36<sup>th</sup> Annual Meeting of the Society of Toxicology, held at the Cincinnati Convention Center, Cincinnati, Ohio, March 9-13, 1997.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 371.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 395.

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

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