

tify airway resistance has gained widespread use as a technique to determine airway responses to aerosol challenge with bronchoconstrictive agents. However, results generated with the unrestrained WBP have come under increased scrutiny because airflow in the lung is indirectly measured. To address this problem, mice with known interstrain differences in bronchial reactivity (A/J, BALB/c, CD-1, and B6C3F1) were subject to methacholine challenge while unrestrained in a WBP and while restrained with a rubber neck collar in the widely accepted noninvasive airway mechanics (NAM) plethysmograph for measurement of Penh and specific airway resistance (SRaw), respectively. Animals were placed into the plethysmographs and were then subject to challenge with aerosols generated from isotonic saline (control) and methacholine solutions of increasing concentration (2.5 to 320mg/ml) for 3min. Measurements of airway resistance were recorded and averaged for 3min following each concentration. Methacholine challenge data for the unrestrained WBP confirmed the previously reported observation that A/J mice have enhanced airway responses to cholinergic challenge, demonstrated by a concentration of methacholine required to induce a 200% increase in airway resistance (PC<sub>200</sub>) that was at least 4-fold lower than that observed in the CD-1, BALB/c, and B6C3F1 strains. In contrast, mice restrained in the NAM did not differentiate this strain difference in airway reactivity, with A/J mice demonstrating PC<sub>200</sub> values were indistinguishable from those observed in the CD-1 and BALB/c mice. Thus the unrestrained WBP is a more sensitive tool than the restrained NAM in assessing airway resistance and responsiveness to bronchoconstrictive agents.

#### 482 ADAPTATION TO STRESS INDUCED BY RESTRAINING RATS IN NOSE-ONLY INHALATION HOLDERS.

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Nose-only inhalation studies involve restraining rodents in nose-only inhalation holders. Protocols for adapting rodents to restraint are used to minimize the stressful effects but there is limited data on the efficacy of adaptation procedures. We examined 1) whether a gradual increase in the duration of restraint facilitates adaptation, 2) how much time is needed for full adaptation when restraint is repeated daily for 4 hrs/day, and 3) whether adaptation persists when restraint is interrupted for several days. Experiments were done in 3 groups of male Sprague-Dawley rats (n = 5/group) as shown in the Table. Heart rate and body temperature were monitored as measures of stress using ECG transmitters. Restraint of rats in nose only holders caused an increase in heart rate (approx. 40 BPM, p <0.05) with no significant change in temperature compared to cage controls. After the first 4 days, the restraint-induced increase in heart rate was the same in rats that were gradually exposed to restraint compared to rats restrained for 4 hours per day. There was a gradual decrease in the effect of restraint on heart rate. Full adaptation to restraint required 14 days of repeated daily restraint. Adaptation persisted even after an interruption of 4 days. In conclusion, nose only restraint for 4 hours caused a modest increase in heart rate. The rats slowly adapted to the stress of restraint with repeated daily exposure indicating that adaptation to nose-only inhalation holders is not necessary for short term exposures except when heart rate is an important factor. A gradual increase in the duration of restraint does not facilitate the adaptation process. Supported in part by EPA R827351.

Purpose	Day	Group 1	Group 2	Group 3
Gradual vs repeated restraint	1-4	cage only	increase restraint by 1 hr per day	4 hrs restraint/day
Fully adapt groups 2 + 3	5-9	cage only	4 hrs restraint/day	4 hrs restraint/day
Interrupt repeated restraint	10-13	cage only	cage only	4 hrs restraint/day
Test effect of interruption	14	cage only	4 hrs restraint	4 hours restraint

#### 483 A METHOD TO CHARACTERIZE AEROSOLS PRODUCED BY VOLUNTARY RESPIRATORY MANEUVERS.

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Many respiratory diseases are associated with changes in the composition and balance of fluids within the airways. The purpose of this study was to develop a system to measure the production of aerosols generated while performing a variety of respiratory maneuvers. Results of these measurements will be used to determine if aerosol generation is associated with airway fluid composition and the development of airway diseases. The system was designed to measure airflow, expired gas volume, and aerosols generated during a variety of ventilatory procedures. It featured a small dead space and was housed in a chamber held at body temperature to reduce the ef-

fects of evaporation and condensation. The temperature and humidity of the collected gas was recorded during the course of each experiment. Prior to each measurement, the test subject breathed HEPA filtered air for two minutes to reduce the contribution of inhaled ambient particulates. The subject then voluntarily coughed or performed an exhalation procedure into a mouthpiece attached to a spirometer. The spirometer was used to characterize the airflow pattern while collecting the exhaled air and aerosol. Three types of particle analyzers (APS, GRIMM, SMPS) were used to characterize aerosol size over a range between 10 nm and 10 µm. Results show that aerosol characteristics were consistent for each test subject but varied widely between subjects. This method has potential in evaluating the toxicological effects of substances that alter airway integrity. This project is supported in part by FAA IAG 97-11.

#### 484 CHARACTERIZATION OF RESIDENCE TIMES FOR GASES AND AEROSOLS FLOWING THROUGH CHAMBERS USED TO MEASURE RESPIRATORY PARAMETERS OF RODENTS.

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Inhalation studies commonly use two basic systems to provide respiratory information for mice and rats used in pulmonary toxicity research on airborne agents. Bronchoconstrictive agents can be characterized by measuring the enhanced pause (Penh) in the breathing pattern of an unrestrained rodent in a whole body plethysmograph (WBP). Direct measurements of airflow and volume may be made on a rodent restrained by a rubber neck collar in a noninvasive airway mechanics (NAM) plethysmograph. However, variations in aerosol concentrations in a plethysmograph were observed in a recent study [Bowen, L.E. et al., 2001. *Toxicologist*, 60]. This variation in aerosol concentration could be due to nonideal air flow patterns in the chamber. The uniformity of flow distribution within a chamber was characterized by the mean residence time for a step change in gas or aerosol concentration. A rat and a mouse WBP, and a rat and a mouse NAM (Buxco Electronics, Inc.) were evaluated. An atmosphere of the airborne material was introduced into the plethysmograph chamber, allowed to reach equilibrium, and then flushed out with clean air. The mean residence time for mixing and clearance of nitrogen, ultra fine carbon black and latex particles were evaluated for the WBP and NAM chambers and compared with the mean residence times of ideal exposure units of the same volume. Results showed that nitrogen gas diffused in the rat WBP within 17.5 % and the rat NAM within 1 % of the ideal mean residence time. Introduction of ultrafine carbon black or latex particle aerosols resulted in a shorter mean residence time by more than 31 %. These shorter experimental times indicated that the aerosols were, in effect, mixing in a smaller volume of the inhalation chambers, supporting the possibility of non-uniform distribution of particles in the inhalation chambers. Similar results were obtained for the mouse WBP and NAM. Thus, the uniformity of distribution within a plethysmograph should be characterized, especially for short duration inhalation tests.

#### 485 AIR-LIQUID INTERFACE CULTURE FOR EVALUATION OF CELLULAR EFFECTS OF COMBUSTION EMISSIONS.

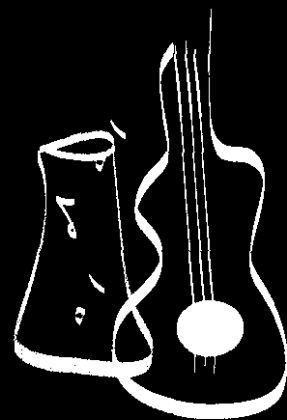
J. C. Seagrave, J. D. McDonald and J. L. Mauderly. *Lovelace Respiratory Research Institute, Albuquerque, NM.*

Combustion products from mobile sources contribute to a particulate material fraction of air pollution implicated in adverse effects on human health (PM<sub>2.5</sub>). In these studies, we have examined the effects of a major constituent of PM<sub>2.5</sub>, diesel exhaust emissions, on cells in culture under conditions more closely representing the physiology of the intact lung than conventional submersion culture. The Cultex system allows cell exposure to a continuous flow of material at an air-liquid interface in a controlled manner. Prior to this work, no known study of the dose of material deposited from an atmosphere onto the Transwell membrane surface had been conducted. Here we present the deposition dose and deposition homogeneity for a delivered amount of PM and gases to the Cultex system. PM deposition was studied using fluorescent microspheres ranging in size from 50 nm to 5 microns. Gas deposition was measured using NO<sub>2</sub> and the Salzmann method. Both PM (all investigated particle sizes) and gases were homogeneously distributed throughout the system. To test the biological effects of diesel exhaust on lung epithelial cells, A549 human type II-like cells were grown to confluence on Transwells and exposed to diesel exhaust at an air-liquid interface using this system. The exhaust was diluted to 1000 mg/m<sup>3</sup> total PM and passed over the cell surface at a flow rate of 8.3 ml/minute per Transwell. Cells were exposed to the exhaust for 1 hr, or to whole exhaust or filtered exhaust for 3 hr. The cells were then returned to conventional submersion culture conditions for 1 or 24 hr, and overt toxicity (LDH release, loss of ATP or changes in mitochondrial tetrazolium salt cleavage), oxidant stress (glutathione content), epithelial integrity (diffusion of Evans Blue-labeled BSA across

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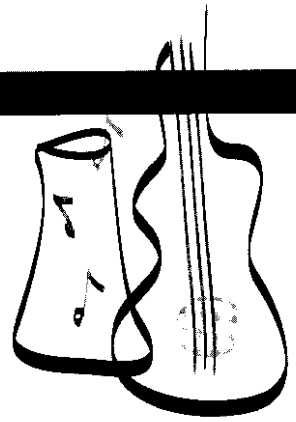


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## *Preface*

**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 41<sup>st</sup> 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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