1464 SUPPLEMENTAL DOSING IN PRECLINICAL INHALATION STUDIES INCREASES SYSTEMIC EXPOSURES.

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Limitations of the exposure generation apparatus and physicochemical properties of the test article can restrict the maximum dose generated by the inhaled route of exposure for preclinical studies. Resultant inhaled doses oftentimes do not achieve adequate systemic exposure to permit the identification of potential extra-pulmonary target organ(s) of toxicity. To optimize systemic exposure and thus help establish target organ toxicity, we have implemented adjunct dosing for preclinical inhalation studies. For two inhaled asthma programs, in which the top inhaled dose was limited due to exposure generation (VLA4 and IL-4 targets), rats and dogs were exposed in 13-week toxicity studies by dry powder inhalation and an adjunctive route (either subcutaneous or oral, based on solubility of test article and oral bioavailability). The studies consisted of an air-sham control and a vehicle control (i.e. received inhaled lactose powder and the adjunct dosing vehicle via subcutaneous or oral route), and a low-, mid- and high-dose inhalation group. An additional high-dose inhalation group received adjunct compound (by the oral route for the IL-4 program and the subcutaneous route for the VLA4 program), at the maximally feasible dose, 1-hour following the daily inhalation session. Results of these studies indicate supplementing compound by the oral or subcutaneous route to the high-dose inhaled group can increase systemic exposures by 2 to13-fold (Day 90 AUC) over the high-dose dry powder only group. Moreover, dosing dogs and rats to the adjunct vehicle had no deleterious effects on the vehicle control group as compared to the air-sham control group (based on clinical signs, food intake, and body weight). In conclusion, supplemental dosing offers an advantageous method of augmenting systemic exposure when limitations have been imposed by the inhalation exposure system and/or physicochemical properties of the test compound. Achieving higher systemic exposures increases the probability of establishing target organ toxicity.

1465 APPLICATION OF THE AERONEB® PROFESSIONAL NEBULISER TO INHALATION DOSING SYSTEMS FOR DOGS AND PRIMATES.

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The compact, single-pass nebuliser was mounted close to the breathing zone in face masks and oropharyngeal dosing apparatus for inhalation exposure. No animals were used in this study, which was a system characterisation using aqueous Salbutamol. Delivery to the animal airways via a facemask was modeled by sampling from within a manikin head into a filter with a respiratory pump to simulate the animal breathing. Deposition was also measured in the mask and the exhaust system. Deposition in the dog manikin airway was ca 37%, while into the primate manikin airway this was ca 30%. In a similar experiment modeling delivery to a dog via an oropharyngeal tube, 45% of the generated Salbutamol was drawn into filters by the respiratory pump. The delivered aerosols were highly respirable aerosol, with average Mass Median Aerodynamic Diameter 1.8 micron. Used in conjunction with dog and primate inhalation dosing apparatus, the Aeroneb® Pro delivered respirable aerosols with good efficiency, offering advantages for inhalation toxicology studies.

1466 PERFORMANCE OF FLOW-PAST AND CONVENTIONAL NOSE-ONLY INHALATION EXPOSURE SYSTEMS WITH POWDER AND DROPLET AEROSOLS.

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For snout-only exposure of rodents, two types of inhalation chamber are commonly used: a simple 30-cm cylinder with breathing ports in the side (ADG-type) and a "flow-past" system that delivers fresh aerosol to each animal individually via a manifold. We have evaluated both types of chamber equipped for the exposure of 120 and 128 animals respectively. Nominal aerosol concentrations were between 0.3 and 12 mg/L with 80 L/min air flow rate. Kaolin aerosol from a Rotating Brush Generator was delivered via the flow-past and ADG chambers with ca 25% and 35% efficiency respectively. The delivered Particle Sizes were ca 2.0 and 2.5µm Mass Median Aerodynamic Diameter (MMAD). Consistency of delivered aerosol concentration across all animal ports was e.g. 13% and 7% respectively at the high concentration. Greater variability of Kaolin concentration was observed with the flow-past chamber, possibly due to re-dispersal of impacted powder. An aqueous aerosol of 1% Sunset Yellow in buffer was generated from 1 to 4 Parry LC+ nebulisers. Efficiency of delivery via the flow-past and ADG chambers was ca 60% and 75% respectively at high concentration and a similar 90% efficiency at low concentration. The delivered Particle Size was similar at ca 1.1 µm MMAD. Consistency of delivered aerosol concentration was typically ca 10% for both chambers. It was concluded that while either chamber design can give consistent results with liquid aerosols, the advantages of the Flow

1467 ANALYSIS OF UNRESTRAINED WHOLE-BODY PLETHYSMOGRAPHY (WBP) DATA BY SIGNAL PROCESSING AND MECHANISTIC MODELING.

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Unrestrained WBP provides a measure of respiratory response to irritant gases. We first used WBP and BioSystem XA software (Buxco Electronics, Inc., Wilmington, NC) to collect and analyze respiratory data from rats. The software menu provides the model of "Drorbaugh and Fenn" (Pediatrics, 16:81-87, 1955; D&F) as one option but that model was derived for a completely sealed chamber and the current WPB has continual flow-through of air or exposure atmosphere. Since the software is proprietary, details of the data analysis code are unavailable. Therefore we re-derived the D&F model to include flow and created a program in Matlab (Mathworks, Inc., Natick, MA) to implement the model. Due to high noise in the raw data we also performed a spectrographic analysis to identify the frequency range of primary interest as well as persistent interference from mechanical or electrical noise. Visual investigation of the spectrogram allows for quick identification of periods of high vs. low noise, the general trend of the primary breathing frequency, and constant background noise. A low-pass digital filter was used to remove high-frequency noise from the data before respiration analysis. Criteria for breath length, volume, and volume balance were then applied to identify acceptable breaths, which were analyzed for breathing parameters. BioSystems output and our values for peak inspiratory flow and tidal volume compared well (e.g., 5.7 vs. 5.1 ml/s and 0.90 vs. 0.96 ml, respectively), but our estimated frequencies (e.g., 82 vs. 100 bpm) were substantially lower. Our model derivation for the flow-through WPB uses the same basic assumptions as D&F, is implemented in Matlab, and allows modification of the assumptions and equations as needed for subsequent research.

1468 DESIGN AND CHARACTERIZATION OF A NOVEL ROBOTIC WELDING FUME INHALATION AND EXPOSURE SYSTEM FOR LABORATORY ANIMALS.

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Respiratory effects observed in welders have included lung function changes, metal fume fever, bronchitis, and a possible increase in the incidence of lung cancer. Many questions remain unanswered regarding the causality and possible underlying mechanisms associated with the potential toxic effects of welding fume inhalation. The objective was to construct a completely automated, computer-controlled welding fume generation and exposure system to simulate real workplace conditions. The system was comprised of a programmable six-axis robotic welding arm, a water-cooled arc welding torch, and a wire feeder that supplied the wire to the torch at a programmed rate up to 300 in/min. For the initial studies, gas metal arc welding was performed using a stainless steel electrode. A flexible trunk was attached to the robotic arm of the welder and was used to collect and transport fume from the vicinity of the arc to the animal exposure chamber. Undiluted fume concentrations consistently ranged from 90-150 mg/m^3 in the animal chamber during welding. Temperature and humidity remained constant in the chamber during the welding operation. The welding particles were comprised of (from highest to lowest concentration) Fe, Cr, Mn, and Ni as measured by inductively coupled plasma atomic emission spectroscopy. Size distribution analysis indicated the mass median aerodynamic diameter of the generated particles to be approximately 0.24 µm with a geometric standard deviation of 1.39. As determined by scanning electron microscopy, the generated aerosols were mostly arranged as chain-like agglomerates of primary particles. These characterization studies of the generated welding aerosol have indicated that particle morphology, size, and chemical composition are comparable to stainless steel welding fume generated in the workplace. With the development of this novel system, it will be possible to establish an animal model using controlled welding exposures to investigate how welding fumes affect health.

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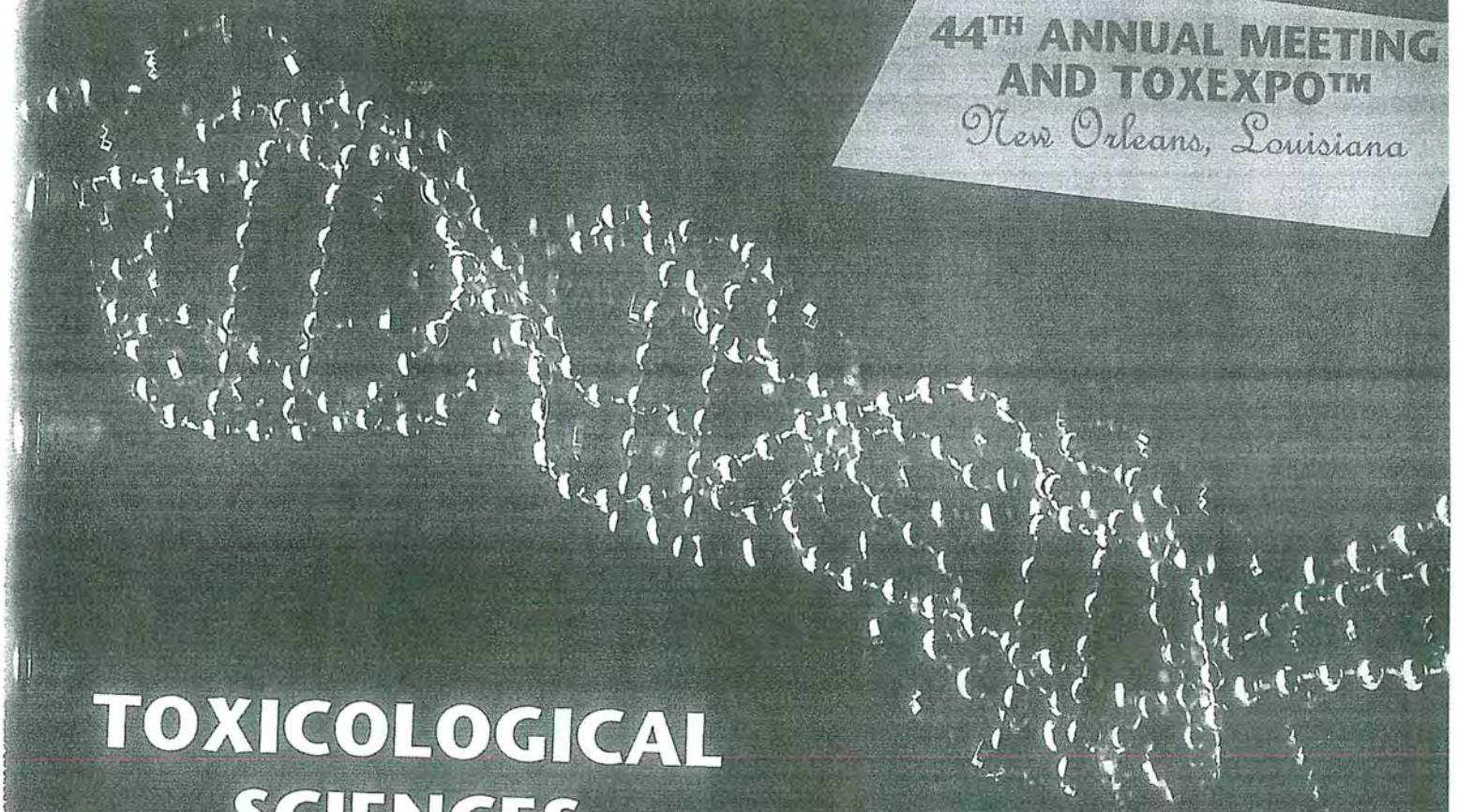

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