PS 1571 Development of an Inhalation Exposure System for Resistance Spot Welding Using an Anti-Spatter Spray

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A common metal joining process is resistance spot welding (RSW). In RSW, two copper alloy electrodes squeeze pieces of sheet metal together and pass high levels of current through the metals to create a weld. The process generates a complex aerosol. The chemical properties of the aerosol are dependent on the metal profile of the welded sheet metal as well as the composition of anti-spatter agents used during the process. Anti-spatter treatment protects the electrodes and improves the welding surface finish. However, anti-spatter chemicals contain ingredients known to be harmful to health. Respiratory disease has been observed in RSW welders. The goal was to design an RSW inhalation exposure system that includes an anti-spatter spray system and determine if the anti-spatter agent contributes to lung responses associated with RSW fume. This system will be used for animal toxicology studies. The system is divided into different areas: (1) enclosed automated spot welder; (2) exposure chamber with aerosol characterization equipment; (3) sheet metal driving system; (4) computer control room and (5) anti-spatter spray unit. The anti-spatter agent was sprayed before welding on the surface of two strips of low carbon steel. A fume injector was used that is controlled by a data acquisition system. Generated RSW fume was delivered to the animal exposure chamber. A real-time aerosol monitor was used to measure and maintain a RSW particle mass concentration of 25 mg/m^3. SEM/EDX revealed the RSW aerosols to be primarily composed of iron and arranged as chain-like agglomerates. Analysis of the size distribution indicated the MMAD of the generated particles was approximately 0.258 μm. Two distinct particle morphologies were observed; a reddish-brown metal particle (likely iron) observed in the nanometer size range and a yellowish particle in the larger micron/submicron range (likely from anti-spatter agent). The exposure system has been designed to assess the potential toxicity of anti-spatter spray used in RSW.

PS 1572 Acetaminophen Potentiates Acute Respiratory Responses to Oxidants and Environmental Tobacco Smoke

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Epidemiological evidence suggests that acetaminophen (N-acetyl-para-aminophenol, APAP) may play a role in the pathogenesis of asthma, likely through pro-oxidant mechanisms. However, direct data on the pro-oxidant effects of APAP in the airways is absent. To determine if APAP acts as a pro-oxidant in the airways, we administered APAP (100mg/kg, ip) to female C57Bl/6J mice and measured tissue non-protein sulfhydryl (NPSH), and antioxidant response element (ARE)-dependent gene induction by qRT-PCR. APAP caused a 20% NPSH loss and significant ARE gene induction within 2hrs throughout the airways. An attenuated ARE response in Nrf2 null mice confirmed a role for the Nrf2 pathway in this response. We hypothesized that as a pro-oxidant, APAP may enhance the airway response to known pro-oxidant asthma causative factors such as environmental tobacco smoke (ETS). Therefore, we measured the effect of the combination of ETS and APAP pretreatment on airway NPSH, ARE gene expression, and sensory irritation. APAP and ETS caused greater NPSH loss (-40%) than either treatment alone, and potentiated the ARE gene response. The ETS induced irritation response was greatly enhanced by pretreatment with APAP. APAP enhanced the response to the pure-oxidant acrolein, but not to the non-oxidant cyclohexanone suggesting that this is not a generalized pro-irritant phenomenon, but rather specific to oxidants. The increased acrolein response was blocked by giving a cytochrome p450 2E1 inhibitor, 5-phenyl-1-pentyne, indicating an APAP metabolite was responsible for the response. Taken together these data demonstrate that APAP, at moderate doses, acts a pro-oxidant in the airways and enhances the airways response to ETS. Furthermore, our results support the novel concept that APAP may influence the pathogenesis of asthma by potentiating the effects of other oxidants such as ETS. (Supported by the University of Connecticut President's Research Award and NIH RO1HL105365)

PS 1573 Preclinical Nebuliser Comparisons to Allow More Effective Decision-Making on Device Selection

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The generation output comparison of the 15 most common pneumatic or jet nebulisers was undertaken to assist in formulating a more informed decision on device selection and compound requirements when provided information on the disease target, test article and formulation properties, study design and dose levels. Each nebuliser was primed with 0.9% Phosphate buffered saline and the generation output (g/min) determined for a period of 10mins. The airflow through each device was then increased in 2L/min increments from 3 to 27L/min. The generation rate at 3L/min was <0.05g/min for the Wright and EVO nebulisers but was over 5 times higher at 0.25g/min for the Pari LC nebuliser. All nebulisers apart from the Wright gave a linear increase in output from 3 to 7L/min. The Wright nebuliser gave an exponential increase in generation output over this range. At airflows between 7 and 12L/min, the outputs from several devices either did not increase proportionately or gave no increase in output irrespective of the increase in airflow. This was particularly apparent for the AeroEclipse, Hudson 2, Pari LC plus and EVO devices. At airflows between 12 and 20L/min, there were several devices that still gave a proportionate increase in output with increased with airflow. These included the HEART, AeroMist, Pari LC D and Wright nebulisers. No increase in output was observed for the EVO nebuliser at airflows >9L/min. In summary, the mini-Heart gave the most consistent output over the airflow range evaluated. The Wright nebuliser gave the lowest output from those tested. The Pari LC plus gave the highest output over the manufacturers recommended working range for the device. In conclusion, this data has allowed improved prediction with greater accuracy of the formulation requirements and help make a more informed decision on device selection recommendations for a given study design. This is of particular importance when active drug is very expensive and non-clinical programme time lines are critical.

PS 1574 A Controlled Human Exposure System for Di-(n)-Butyl Phthalate (DBP) in the Vapor Phase

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Phthalates are commonly used as plasticizers and are ubiquitous contaminants in indoor environments. Epidemiological studies have linked phthalates to development and exacerbation of asthma and allergy, but the contribution of the inhalation exposure route remains unclear. To perform a controlled human exposure study and assess the pulmonary and systemic effects due to phthalate inhalation, we have designed and built an exposure system to deliver a known concentration of DBP in vapor phase to the study participants through a facemask. DBP was chosen as a model phthalate since some of the highest indoor air levels have been reported for this phthalate. The target DBP concentration, to be inhaled for 3 hours by study participants, is 4 times the maximal reported concentration within homes, i.e. 60 μg/m^3. The DBP is contained in a flask, immersed in a temperature-controlled water bath where the temperature determines the DBP vapor concentration. A photo ionization detector (PID) monitors the level of total volatile organic compounds (TVOC) in the system. The major determinants for the measured TVOC levels are temperature, DBP volume and airflow through the flask. The desired TVOC level, calculated to correspond to 60 +/- 10 μg/m^3, is reached within 90 minutes and kept stable for a 3 hour period, when applying the developed experimental procedure. However, since the PID provides a non-specific TVOC measurement, these levels are now calibrated by collecting air samples in Tenax tubes for measurement of the corresponding DBP concentration by thermal desorption GC-MS. Prior to initiating the main study for investigating pulmonary and systemic effects, the anticipated pulmonary DBP absorption due to the phthalate inhalation will be verified in a sub-study by determining the urinary concentrations of the primary DBP metabolite.

PS 1575 Precision-Cut Lung Slices As an Alternative Model for Repeated-Dose Inhalation Toxicity

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There is a growing need for appropriate alternatives for animal inhalation studies in order to test respiratory adverse effects of inhalable substances. These alternatives should comply with the three R principles. In this regard Precision-cut lung slices (PCLS) are a prevalent used *ex vivo* alternative reflecting the respiratory tract. However, most studies using PCLS have been conducted within a 72 h time window to investigate acute respiratory toxicity. In order to evaluate the feasibility of long-term PCLS cultivation to test e.g. toxicity of slowly metabolized substances, rat PCLS were cultivated for more than 14 days. Additionally, triple Triton X-100 treated rat PCLS were compared to single and double exposed PCLS in order to investigate their suitability for repetitive exposure studies. Markers for slice vitality

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