QRS (5) duration. However, variability (calculated as %relative standard deviation) over the entire collection was comparable for PR (3.3%, JET; 2.6%, ImpTLM), QT (5.7%, 6.1%), QTc (3.5%, 3.0%), and QRS (2.0%, 1.9%). Bland-Altman and regression analyses showed no consistent bias for data collected using JET or ImpTLM. Discussion: Data collected using JET or ImpTLM was of sufficient quantity and quality for analysis. While the absolute quantitative values varied minimally, both methods had near-equal variances. Taken together, these data suggest that both JET and ImpTLM have a similar ability to detect potential changes in quantitative ECG data and statistical sensitivity when compared in identical study designs and environments.

PS 559 MINIMALLY-INVASIVE TELEMETRIC MEASUREMENT OF ARTERIAL BLOOD PRESSURE IN THE FREELY MOVING MINIPIG. ISOPRENALINE VALIDATION.

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Methods for arterial blood pressure (ABP) measurement by non invasive, Bluetooth-based telemetry in toxicology studies are not as well advanced in comparison to ECG capture. Additional difficulties arise when automated tail cuff measurements of ABP are foreseen in the Göttigen minipig, a species with unsuitable tail conformation and sensitive to stress generated by cuff inflation. We have thus assessed whether ABP signals could be collected in freely moving minipigs by ambulatory telemetry. In particular, we have focused on limiting surgical invasiveness by selecting more readily accessible arteries, by selecting two sizes of telemetry implant device and by assessing signal quality. Isoprenaline (ISO) was subcutaneously administered at the dose level of 30 µg/kg to induce acute hemodynamic changes. The DSI telemetry implants PA-C10-TOX-LA ("C10-Tox") and PA-C40 ("C40") were used. In one animal, the catheter from a C40 and a C10-Tox implant was inserted respectively in the left sub-clavian (SCL) and femoral (FEM) artery. In a second animal, each pressure catheter from two C40 implants was placed in the left SCL and a collateral of the FEM artery (FEMcoll). The best quality signal was obtained with the FEM catheter. Baseline fluctuations and spikes were observed in the FEMcoll signal. Finally the SCL signal presented a more irregular pattern possibly related to kinking or pinching of the catheter. ISO induced a prompt and maximal fall in ABP versus control (~20 mmHg) and a concomitant tachycardia (~90 bpm). The amplitude and time-course of the hemodynamic effects were similar with either implant. ABP can be reliably measured in the minipig with minimal surgery with the pressure catheter from the PA C10 TOX-LA implant inserted in the femoral artery. The resources involved by this approach must be balanced with the ability to continuously and reliably record hemodynamic signals in a species with notoriously variable blood pressure parameters.

PS 560 CLINICAL AND HISTOPATHOLOGICAL OUTCOMES FOLLOWING AMBULATORY INTRAVENOUS INFUSION FOR USE IN PRECLINICAL STUDIES IN THE BEAGLE DOG.

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A feasibility study was performed to assess the suitability of an ambulatory method of intravenous infusion for use in preclinical studies in the dog and to provide background histopathology data. Five male and 5 female beagle dogs were infused for 2 hours per day with sterile physiological saline at a rate of 10 mL/kg/day for one (4 animals) or four weeks (6 animals). A polyurethane catheter was surgically implanted into the jugular vein with the tip protruding into the anterior vena cava. The distal portion of the catheter was tunneled subcutaneously to exit at the nape of the neck and was connected to a peristaltic pump (Pegasus Light, LAB). The total weight of the pump was approximately 200 g. The pump and 150-mL plastic pouch filled with saline were protected by a polystyrene case contained within a jacket worn by the dog. Standard observations and measurements were performed as in a routine toxicology study including tissue sampling of selected regions of the catheter implantation and injection sites, as well as lungs, liver, spleen, heart and kidneys. The dogs were allowed to socialize in groups of the same sex for 2 hours per day (except during weekends and public holidays), under constant supervision by a technician. There were no adverse findings on ophthalmology electrocardiography, hematology and serum clinical chemistry parameters. The histopathological lesions were considered to be those normally encountered with this route of administration and comparable with in house data generated from the tethered dog model. This experiment demonstrated the feasibility and advantages in terms of socialization of the ambulatory method of intravenous infusion for use in safety studies in dogs.

PS 561 HIGH DEFINITION OSCILLOMETRY (HDO) IN MONKEYS: ACCLIMATION REQUIREMENTS AND SENSITIVITY ASSESSMENT OF HDO *VERSUS* TELEMETRY.

A. Mitchell, A. Lee and T. W. Beck. *Safety Pharmacology, Covance Laboratories Inc., Madison, WI.* Sponsor: P. Kruzich.

Monkeys are commonly used in toxicological research to evaluate drug effects on the cardiovascular system. Obtaining meaningful estimates of blood pressure (BP) and pulse rate (RATE) from conscious, manually restrained monkeys remains a challenge. Animals should be acclimated to the measurement procedure to ensure that unperturbed measurements of BP and RATE are recorded. Eight monkeys implanted with telemetry transmitters (DSI) were acclimated to restraint and HDO measurements (at least 5 readings per animal) on 5 consecutive days. Four days after the last acclimation, 4 animals received L-NAME at 10 mg/kg i.v. and 7 days later clonidine at 0.05 mg/kg i.m. to elevate or lower BP, respectively. The 4 control animals received saline at the respective route. At least 5 HDO readings were obtained for each animal before and at 4 intervals after each drug. The precision and reliability of HDO measurements were compared to simultaneously recorded direct blood pressure data from telemetry implants. Systolic, diastolic, mean arterial pressure (MAP), and RATE were determined. Acclimation data for all parameters were comparable for HDO and telemetry and suggest that animals should be acclimated to the procedure on at least two occasions. Animal remained acclimated to the HDO recording procedure for up to 11 days after the last acclimation session. HDO and telemetry were both able to detect drug induced changes in BP and RATE. Compared to predose values, L-NAME increased MAP by 29 (HDO) vs 19 mmHg (telemetry) four hours postdose, while RATE decreased by 98 (HDO) vs 90 beats per min (bpm) (telemetry). Clonidine decreased MAP by 31 (HDO) vs 27 mmHg (telemetry) one hour postdose, and RATE was decreased by 111 (HDO) vs 101 bpm (telemetry). In conclusion, HDO provides an alternative BP and RATE measurement technique in conscious, manually restraint monkeys when invasive techniques are not warranted.

PS 562 TELEMETRY ECG LEAD PLACEMENT IN CYNOMOLGUS MONKEYS (*MACACA FASCICULARIS*): METHOD TO MAXIMIZE SIGNAL QUALITY.

S. Authier[1, 4], M. Stonerook[2], S. Fournier[1], B. Moon[3] and E. Troncy[3]. *[1]Lab. Research Inc., Laval, QC, Canada, [2]Vertex Pharmaceuticals, Cambridge, MA, [3]Data Science International, St. Paul, MN and [4]Faculty of Veterinary Medicine, University of Montreal, St. Hyacinthe, QC, Canada.* Sponsor: K. Draper.

Electrocardiograms (ECG) in cynomolgus monkeys are required safety pharmacology investigations. Telemetry enables continuous ECG monitoring and is considered the gold standard to meet regulatory requirements for safety assessments in non human primates. In recent years, different ECG leads have been used with mixed results: Derivation II (DII) subcutaneous ECG leads (significant electromyogram artifacts and low p-wave amplitude); Intracardiac leads (various complications including cardiac chamber perforation); DII ECG leads placement (+) apex of the heart, (-) 4th intercostals space (low P-wave amplitude); Pericardiac ECG lead placement associated with adequate ECG morphology and amplitude with minimal EMG interferences but requires an invasive thoracotomy. The current study evaluated a DII telemetry ECG lead placement with the positive lead sutured to the diaphragm at the level of the heart apex and the negative lead inserted through the jugular vein and advanced to ¾ inch above the right atria as confirmed with fluoroscopy imaging during surgery. This telemetry ECG lead implantation technique resulted in high amplitude QRS complexes (mean R-wave amplitude of 3.5 mV) and P-waves (mean P-wave amplitude of 0.8 mV) which facilitated computerized interval measurements. Average signal to noise ratio was 279.5 for R-wave and 64.0 for P-wave. The technique also provided stable ECG complex morphology with minimally invasive surgical procedures.

PS 563 CHARACTERIZATION OF WELDING AEROSOLS GENERATED BY RESISTANCE SPOT WELDING.

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Resistance spot welding (RSW) is effective for fabricating sheet metal articles when high rates of production are necessary. RSW is commonly used in the automotive, aircraft, and appliance industries where high speed, repetitive welding is needed and relatively thin section sizes are welded. Decreased lung function, metal fume fever, and chronic bronchitis have been observed after exposure to the complex fumes produced by RSW. The goals of the study were to develop a RSW generation

and inhalation exposure system that will be used for future animal toxicology investigations and to characterize the aerosols and vapors formed during RSW. The system is divided into three different areas: (1) enclosed spot welder, (2) animal exposure chamber including aerosol/vapor characterization equipment, and (3) computer control room. RSW was performed inside of an enclosure as two strips of low carbon steel (1/32 in. thick, 1 in. wide) were continually fed between two copper alloy electrodes and spot welded every 45 sec at a setting of 760 lbs force and 5000 amps. A real-time aerosol monitor (Data RAM) was used to monitor and maintain a particle mass concentration at 1.4 mg/m^3. Particle size distribution and mass median aerodynamic diameter (MMAD) were determined using a Micro-Orifice Uniform Deposit Impactor (MOUDI). Particle morphology and elemental composition were determined by scanning electron microscopy and energy dispersive X-ray analysis (SEM/EDX). Analysis of the size distribution indicated the MMAD of the generated particles was approximately 0.94 μm with a geometric standard deviation of 2.0. SEM/EDX revealed the RSW aerosol particles to be primarily composed of iron and arranged as chain-like agglomerates that resembled the morphology of typical arc welding fume. Larger, more amorphous particles also were observed among the agglomerates. With the development of this novel RSW system, the potential toxic lung effects of spot welding fume can be examined in an animal model.

PS 564 ACUTE INHALATION STUDY OF ALLYL ALCOHOL FOR DERIVATION OF ACUTE EXPOSURE GUIDELINE LEVELS (AEGL).

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An acute whole-body inhalation study for allyl alcohol in Crl:CD(SD) rats was designed to support derivation of AEGL values, with emphasis on establishing NOAEL's for irreversible effects of different exposure concentrations(C)and durations(T). This study also illustrates a practical approach to enhancing the design of acute studies for improved derivation of AEGL values. Groups of 10 rats (5 per sex) were exposed for 1 hr (0, 50, 200 or 400 ppm), 4 hrs (0, 20, 50 or 100 ppm) or 8 hrs (0, 10, 20 or 50 ppm). Clinical examinations were performed by one technician 30 min, 1 and 4 hr into exposure (depending on duration of exposure),and near the end of exposure (including ranked response to a novel noise stimulus). Clinical observations in an open field were made on all animals in random order within 22-71 minutes after exposure was terminated. Clinical pathology, gross necropsy, and histopathology (nasal tissues-6 levels, larynx, trachea, lungs/bronchi, liver, kidneys) were evaluated 14 days after exposure. Mortality was limited to 1 male exposed for 8 hrs to 50 ppm. Clinical findings of gasping, rales, increased respiration, or flushing noted during or 1 hr after exposure were rapidly reversed for all groups. Histopathology in the nasal cavity, which is considered reversible, was noted at all exposure levels following 1,4 or 8 hrs of exposure, with increased incidence at mid and high-dose levels. Severe, irreversible lesions were only present in 50 ppm/8-hr males. No treatment-related findings were observed in the liver and kidneys, or in the lungs of surviving animals. The NOAEL for reversible effects was <50, <20 and <10 ppm for 1, 4 and 8 hrs, respectively. The NOAEL for irreversible effects was >400, >100 and 20 ppm for 1, 4 and 8 hrs, respectively. In comparing treatment levels with same C X T products, the incidence and/or severity of olfactory epithelial degeneration appeared to be positively dependent on the exposure duration.

PS 565 COMPARING ELECTROSTATIC AEROSOL *IN VITRO* EXPOSURE SYSTEM (EAVES) TO TRADITIONAL PARTICULATE MATTER EXPOSURE TECHNIQUE.

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The majority of *in vitro* studies examining the effects of particulate matter (PM) use techniques involving ambient PM collected on filters, which are subsequently resuspended in a liquid medium and then added to the cell culture. Major shortcomings of such filter collection methods include the potential loss of volatile organic compounds from the PM, agglomeration of particles during collection, and the possible alteration of the particles during the recovery process and while in the liquid medium. To overcome this issue, the Electrostatic Aerosol *in vitro* Exposure System (EAVES), was developed to expose human lung cells directly to particles without prior collection in media. The goal of the study described here is to compare published methods using resuspension of particles collected on filters (~80 μg per cm2) to exposures using the EAVES device (~3.0 μg per insert). Diesel exhaust (DE) was used to determine the efficiency and sensitivity of the respective methods. The DE PM used during these experiments was collected with an outdoor smog chamber capable of mimicking the ambient atmosphere. All emissions were injected directly from either a 1980 Mercedes Benz or a 2006 Volkswagen Beetle and combined with a background of synthetic urban atmosphere. Human respiratory epithelial cells (A549) were exposed to PM in EAVES and filters were collected simultaneously for later resuspended exposures. Following exposures, the toxicological response from the two methods were compared by analyzing IL-8 cytokine production. The data suggest that exposing cells to resuspended PM requires 20x the amount of PM material used in the EAVES device to get similar IL-8 responses. Taken together these results further support the use of the EAVES device and direct exposure of target cells to PM, as it provides an efficient and effective alternative to the more conventional particle *in vitro* exposure methods.

PS 566 VITAMIN C YELLOWING ASSAY STUDIES WITH TITANIUM DIOXIDE AND NONFIBROUS POTASSIUM TITANATE SAMPLES.

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Using animal alternative methodologies for screening lung toxicity of particles is a significant goal. Previously, we assessed the role that particle physicochemical characteristics might play in producing lung toxicity in vivo. Groups of rats were intratracheally exposed to different compositions of nanoscale and fine TiO2 particulates and conventional lung biomarkers were measured over a 3-month postexposure period. It was concluded that particle surface reactivity indices of the TiO2 particulates correlated better with lung toxicity endpoints when compared to other factors such as particle size or surface area measurements. In that study, particle surface reactivity endpoints were measured using the Vitamin C yellowing assay as an indicator of chemical reactivity. Subsequently, it has been proposed that this screening in silico tool might be useful for predicting in vivo pulmonary hazard effects of other titanium containing compounds, such as nonfibrous potassium titanate particulates. Accordingly, the surface reactivity of four different potassium titanate test particulate samples were measured using the Vitamin C yellowing assay; and were compared to previously assessed in vivo pulmonary toxicity effects following short or long-term pulmonary exposures to these test substances in rats. Using Vitamin C yellowing assay methodology, the results demonstrated moderate chemical reactivity for the Terracess TF-S and JS compounds (delta-b values of 8.9 and 9.0, respectively vs. a positive control ultrafine TiO2 value of 28.2), and low delta-b activity for the Terracess LS (0.55) and PS (1.1) particle-types. The finding of moderate delta-b activity for the Terracess TF-S and JS particle samples did not correlate with the finding of very low in vivo pulmonary activity for these particle-types in the lungs of rats. Based upon these results, it seems reasonable to conclude that the Vitamin C yellowing assay may not be an appropriate in silico screening tool for predicting the effects of potassium titanate compounds following pulmonary exposures in rats.

PS 567 SUSTAINED TRANSCRIPTIONAL RESPONSES ACCOMPANY PULMONARY ACROLEIN EXPOSURE IN MICE.

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P. Burcham, B. Lauder, A. Raso and P. Henry. Pharmacology Unit, University of Western Australia, Perth, Australia.
Acrolein is a noxious 3-carbon electrophile that readily attacks cell macromolecules in exposed tissues. Its presence in smoke produced during the combustion of diverse organic matter ensures acrolein plays an important pathogenetic role in the life-threatening lung oedema that afflicts victims of smoke inhalation injury (SII). Since the transcriptional responses that accompany pulmonary exposure to odedatomatogenic doses of acrolein are poorly characterized, we used Agilent microarrays to monitor time-dependent changes in the levels of 15,000 gene transcripts in mouse lung at various times (0, 2, 4, 8 and 24 h) after the administration of a pneumotoxic dose of acrolein (12 mg/kg). Acrolein was administered via oropharyngeal instillation in a small volume of isotonic saline. Acrolein exposure significantly increased lung wet/dry ratios and protein content in bronchoalveolar fluid after 24 h. RNA was extracted from the lungs of 3 animals per time point. Microarray analysis revealed maximum gene dysregulation occurred 2 h after acrolein dosing, with 565 transcripts altered more than 2-fold at this time relative to controls (315 upregulated and 250 downregulated). Gene upregulation also dominated transcriptional responses at the subsequent time points (71% of 242 responsive genes at 4 h, 62% of 357 altered genes at 8 h, and 67% of 249 responsive genes at 24 h). The transcriptional response to acrolein was very stable, with a

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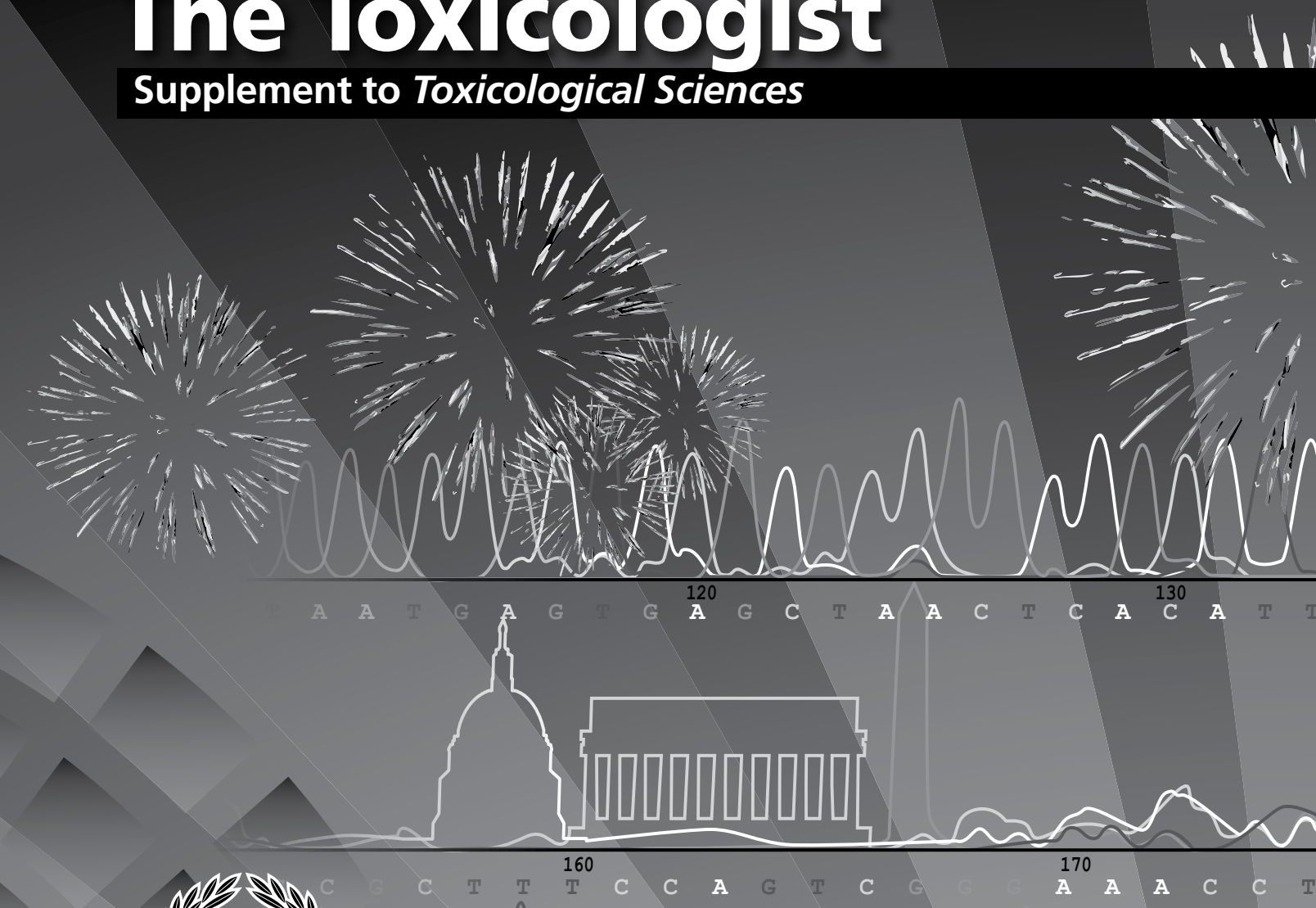

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

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